Modern Meat

The Next Generation of Meat From Cells

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Modern Meat

First Edition

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Notes prior to reading Modern Meat

- This digital version of Modern Meat consists of submissions from 100+ experts on cultivated meat. While there may be some cross-referencing across chapters (one chapter referencing information about another chapter), please treat each chapter independently, including its individual content and citation structure. The Prologue & Preface excluded, all chapters ought to be seen as a unit unto themselves.

- As material is quickly developing in the cultivated meat space, the cutting edge of yesterday quickly becomes the outdated of tomorrow. Please view the "Last Updated" date at the beginning of this document to reference the current state of this living document.

- Parts of this text may be outdated, incomplete or incorrect; further copyediting and development will commence as the physical version of Modern Meat is created. If you discover any errors or would like to provide an update to information found within Modern Meat, please email us at info@cellag.org.

- You may come across various terms for **cultivated meat**; please advise that any of the following forms of nomenclature that authors used are synonymous in Modern Meat: cultured meat, cell-based meat, cell-cultured meat, clean meat, synthetic meat, lab-grown meat, in-vitro meat.

Table of Contents

P.8	SECTION I: CONTEXT
P.9	i. Prologue
P.18	ii. Preface
P.22	SECTION II: IMPACT OF CULTIVATED MEAT
P.24	Chapter 1: Humanity
P.51	Chapter 2: Animals
P.89	Chapter 3: Environment
P.117	SECTION III: SCIENCE OF CULTIVATED MEAT
P.118	Chapter 4: Cells
P.170	Chapter 5: Media
P. 209	Chapter 6: Bioprocess
P.243	Chapter 7: Automation
P.288	Chapter 8: Scaffolding
P.336	SECTION IV: CULTIVATED MEAT IN SOCIETY
P.337	Chapter 9: Consumers
P.371	Chapter 10: Youth
P.397	Chapter 11: Regulation
P.413	Chapter 12: Space
P.442	SECTION V: CULTIVATED MEAT AROUND THE WORLD
P.443	Chapter 13: North America
P.467	Chapter 14: South America
P.495	Chapter 15: Europe
P.538	Chapter 16: Africa
P.559	Chapter 17: Asia
P.583	Chapter 18: Australia

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CONTEXT

SECTION 1

Prologue

Kris Spiros

The year is 90,318 B.C.E.

A small group of hunters roam the plains of Africa. Having not eaten in days, they are as hungry as they are determined to track down a fitting prey. They carry spears and stones, crafted with precision for the task at hand. After a search, hours long, complete with life-dependent calculation, they scout a lone wildebeest. The animal is likely old or injured as it walks alone, far away from the pack, vulnerable. Tactically coordinated, the predators make their strike and kill the lone wildebeest.

This single animal and the meat that comes from it holds immeasurable value, but fundamentally, this successful hunt translates to survival for these early humans. They bring back the reward to their tribe, where this densely nutritious food is brought upon a fire, satiating ancestral appetites. That is, until they must go out to hunt again for their next meal.

This was meat. And the process of obtaining it. African hunters killing a wildebeest, representing the modern state of meat to pre-agricultural people.

This was modern meat 100,000 years ago.

The year is 9,318 B.C.E.

An Asian farmer named Buwei herds his livestock along the Yangtze River. His village recently experienced a devastating wildfire, and in the process, much of his community's agricultural supply has suffered. To accommodate and prevent a local famine, Buwei must select more animals than he planned for tomorrow's slaughter.

Little does he know, Buwei is one of the first farmers on Earth – one of the first humans to practice the techniques of animal rearing that will fuel civilization for millennia to come. He's also versatile with his agricultural skills, doubling as a cattle farmer and fisherman; he's refined his fishing and herding techniques over decades, leading to pivotal moments like this where his community depends on him.

The next morning, Buwei sets out early, patiently fishing on the Yangtze till noon; in the afternoon, after taking stock of his herd, he inspects those best suited and slaughters 3 cattle, a third of all his animals.

Buwei does not work alone; almost everyone in his community plays a role in the meat preparation process. Buwei and his fellow ancient farmers approach this early form of meat production with a variety of skills – they collectively contribute to each part of the preparatory process, including handling, slaughtering, skinning, washing, and eventual cooking of the bovine meat.

At this time, it really does takes a village to raise animals for food.

This version of meat & animal husbandry notably contrasts that of the African hunters; there was great distance between the hunters' homes and where they sought meat. But the advancements of agrarian society have brought animals into the villages themselves; this has meant closer quarters between the first animal farmers like Buwei and their livestock.

And this closer relationship with food comes as no surprise – the majority of humans on Earth, now totaling a population of almost 5 million, must take on agricultural-related work for collective survival.

Noteworthy too, farmers like Buwei are beginning to use tools such as ropes and fences to maintain his herd; indeed, the earliest roots of animal agriculture are sprouting.

This was meat. And the process of obtaining it. Buwei harvesting fish and slaughtering 3 cattle in his village in pre-historical China, representing the modern state of meat to early-agricultural people.

This was modern meat 10,000 years ago.

The year is 931 B.C.E.

It's the early summer in Attica, Greece, and on a sunny morning, a shepherd named Ophelos rounds up his herd. Kronia, a summer festival, nears and he's one of the main suppliers of lamb for the local market, the third-largest in Athens. He slaughters 18 sheep and prepares the meat with modern techniques he learned from his father.

After thousands of years, the domestication of animals has become commonplace; farming these sheep for meat is practiced generationally. Agricultural success comes easily to Ophelos and his fellow ancient Greek farmers, or at least as often as Demeter's blessings are accounted for.

Meanwhile, the human population on Earth has increased in magnitude, now over 50 million. While animal farming techniques have increased in complexity, efficiency has meant fewer and fewer people are needed for labor, the diversity of civilization a result.

Nevertheless, all conquer their carnivorous palates through the work of farmers like Ophelos, regardless of their increasingly unique lives in the arts and government. The amplified capacity for trade and transport have also made it possible for not only Ophelos' neighbors in his polis to be his customers, but also people in nearby regions, all get to experience his lamb.

This was meat. And the process of obtaining it. Ophelos slaughtering 18 sheep on his farm in Ancient Greece, representing the modern state of meat to ancient civilizations.

This was modern meat 1,000 years ago.

The year is 1923 C.E.

On a cold autumn morning in Los Andes, Chile, a farmer named Eduardo lets his pigs out of their stalls. With the help of his children, he then tends to his chickens. Eduardo's father taught him a crafty way to keep the local foxes from getting to the hens; today he's teaching his son and daughters. The expansiveness of his family farm allows Eduardo to manage a variety of livestock across his land. Even still, he holds less than a couple hundred animals total, not including the occasional fishing he enjoys in the Aconcagua River in his spare time.

Simply put, farming is Eduardo's heritage; this Chilean family farm has been passed down from generation to generation. He learned everything he knows from his parents, and he teaches his children on a daily basis about how to operate the farm to take care of their future families. Eduardo's farm provides meat not just to communities along the Aconcagua, but across the entirety of Chile. And while his method of pasture farming, animals grazing on the open Chilean plains, is representative of the norm for animal agriculture in 1922, meat demand is rising across South America.

Eduardo learns that some of his peers beginning to modify the organization of their farms into so-called feedlots and concentrated animal feeding operations. This effort is being led by once small family farms who have now merged into large, conglomerate meat companies. They offer help to small family farms like Eduardo's, to evolve and use their new methods, methods that will allow his farm to breed and manage many more farm animals. With their proposed breeding techniques, as well as moving his animals from the outdoors to indoors, his farm could go from a couple of hundred animals to thousands. This translates to higher rates of meat production to feed an exponentially growing continent and world, but for him, it could mean feeding more people and making more money to take care of his family.

This proposition from the meat company comes at a cost though, and Eduardo is conflicted. There's much tradition in his familiar operation of his farm. The practices he's followed his whole life, taught to him by his elders, are basically his pedigree. He's accustomed to being outdoors with his animals, and moving everything into buildings feels unconventionally confining, both literally and figuratively. But the promise of feeding more hungry people, as well as the financial incentive of industrializing his farm is becoming more difficult to turn down.

Over the years, Eduardo sees the meat landscape becoming more competitive because many of his peers are taking on the new methods. They produce more and more meat while his production remains stagnant. The larger meat companies have helped install their methods across small family farms, adjacent to Eduardo's. In exchange for farmers increasing their overall meat production using the innovative methods, the meat conglomerates have held true to their promises of increased distribution of the farmers' meat products, as well as higher incomes for them and their families.

With these innovations in animal agriculture becoming more popular and meat's demand continually rising, they begin to offer contracts to family farms, increasing competition. They promise good money if farms can match the capacity they're looking for, really only possible with their proposed industrialized methods. How can Eduardo supply hundreds of pounds of pork per week when he still only has a few dozen pigs? How can he match the prices of his counterparts while he still pasture-raises his animals? He's beginning to think he has no choice but to join the architecture of industrialized animal agriculture – for if he doesn't, his farm will die and his family will suffer.

This situation is not unique to Eduardo in the 20th century. It's becoming increasingly necessary to industrialize animal farming to maximize meat output; the global population is nearing 2 billion. And while traditions are being left to the wayside, a mass transition away from pastures indeed will help meet the rising demand for meat in Chile and beyond.

Nevertheless, for now, Eduardo must continue running his family farm the way he knows how. While the meat landscape is changing, they still have a lot of hungry customers, and a large order just came in for pork, chicken, and eggs. He'll discuss the farm restructuring with his wife over the upcoming weekend, but for now customers await. With the help of his wife and children, they follow the same farming practices of past generations to feed their community in Los Andes, and beyond.

This was meat. And the process of obtaining it. Eduardo processing meat from his farm animals; 3 cattle, 9 pigs, and 18 chickens harvested on his family farm in Los Andes, Chile. This represented the modern state of meat in early 20th century civilization.

This was modern meat 100 years ago.

The year is 2013

It's a spring afternoon at the Smithfield Hog Processing Plant in North Carolina, United States. Indeed, the inklings of industrialization that Eduardo saw the beginnings of have become mainstream. Conventional animal agriculture has undergone massive shifts. Animal farming has transitioned from individuals and family operations to that of corporations and shareholders. What was once 99% of the global population working in agriculture, has become less than 1%. Yet, meat demand is at an all-time high, globally.

At this particular plant in North Carolina, Smithfield Foods processes 32,000 pigs in a single day. The millions of pounds of meat produced here daily would have amazed the previous generations, especially the African hunters. What would have taken them a lifetime of strategy, life-risking brutality, and effort has been boiled down to a single slaughterhouse's hourly production capacity.

A global population of now over 7 billion and meat's popularity is continuing to rise – this means the millions of pounds of meat produced at this plant barely supply a percentage of the total meat demand for the residents of North Carolina alone. Indeed, Smithfield's distribution expands outside of North Carolina, and even the United States. This giant of the meat industry has customers spanning not just the North American continent, but the globe, exporting billions and billions of pounds of meat per year to consumers worldwide.

This was meat. And the process of obtaining it. Smithfield Foods processing 32,000 pigs in a single day in North Carolina, United States. This represented the modern state of meat to early 21st century civilization.

This was modern meat 10 years ago.

Meanwhile, a new concept for meat production is being imagined, one that involves harvesting meat from farm animals' cells instead of farm animals themselves. The pioneers of this idea, academics and soon to be Founders from around the world, are beginning to consider its potential for feeding an exponentially-growing world population. And just as Eduardo was forced to consider a century ago, the global meat industry of the early 21st century must consider if this re-envisioned production process for meat could eventually outdate its status quo of industrialized animal agriculture. They begin to rethink the use of animals to produce meat.

The year is 2023

Well, what ten years can bring...the developments of the last decade may pose a greater shift to the production of meat than the last 100,000 altogether. What was once science fiction is becoming reality, and making meat from mere cells is now forming into an entire industry. Not a single company just a decade ago and minimal financial support has evolved into a landscape of more than 100+ startups across the globe, with over $2B of investment. And while industrialized animal agriculture still reigns supreme, the embers of this new concept grow stronger by the day.

This is modern meat today...

Preface

Kris Spiros

The only constant about modernity is that it always changes in its definition.

What has been considered “modern” for meat has evolved alongside civilization for millennia – from hunting, to farming, to factories, meat’s increasing demand has called for agricultural innovation across the board. And with such history behind us, we now stand on the edge of monumental prospect.

Meat may be on the precipice of its most revolutionary leap yet, removing the animal as the instrument of production. This is what we will explore in this textbook - what could be the next step in our relationship with meat…growing it from cells.

It’s within this new relationship, that the farm animal, having always been so intimately involved as the functional unit from which meat was harvested, may largely be decoupled from the process. Instead, the cells of farm animals would be used to produce meat through **Cellular Agriculture**, the process of farming animal products from cells instead of animals. This meat, real meat produced from cells instead of animals, is called **Cultivated Meat**, and it will serve as the focus of this textbook. You may have heard of some other terms for this concept, including *cultured meat*, *clean meat*, *lab-grown meat*, or *cell-based meat* to name a few.

At a surface level, the prospects of cultivated meat may appear both malevolent and benevolent in nature. Humanity may never need to slaughter another animal for food, nor tax the environment in the process of doing so, but in turn, there exists real threats to job loss in the agricultural industry and potential negative impacts on traditions and culture for which livestock farming is still an integral component.

But for better or for worse, the magnitude of this moment remains the same – cultivated meat could usher in the most dramatic shift in agricultural history, and we may just be years away from its mainstream introduction.

In this textbook, we will hone in on where the young industry of cultivated meat stands today. We will undertake a deep dive into a variety of topics, detailing the Impact, Science, Economics, and Cultural ramifications that this new process of producing meat could bring unto the world.

As we peer into the potential horizon of cultivated meat, many critical questions remain in the outlook of meat’s future. This textbook was not developed to tell you what the future of meat will be, but simply what it could be. What will meat look like in 10 years from now or 100? Will people view animals, or perhaps cells, as the origin of meat?

But modernity knows no past or future. At present, cultivated meat resides in the hands of select people, from the scientists and business leaders of cultivated meat startups, to their funders on Wall Street and regulators in Washington. However, these groups tell but the opening to this story; it is the billions of consumers around the world who will determine the fate of modern meat this century.

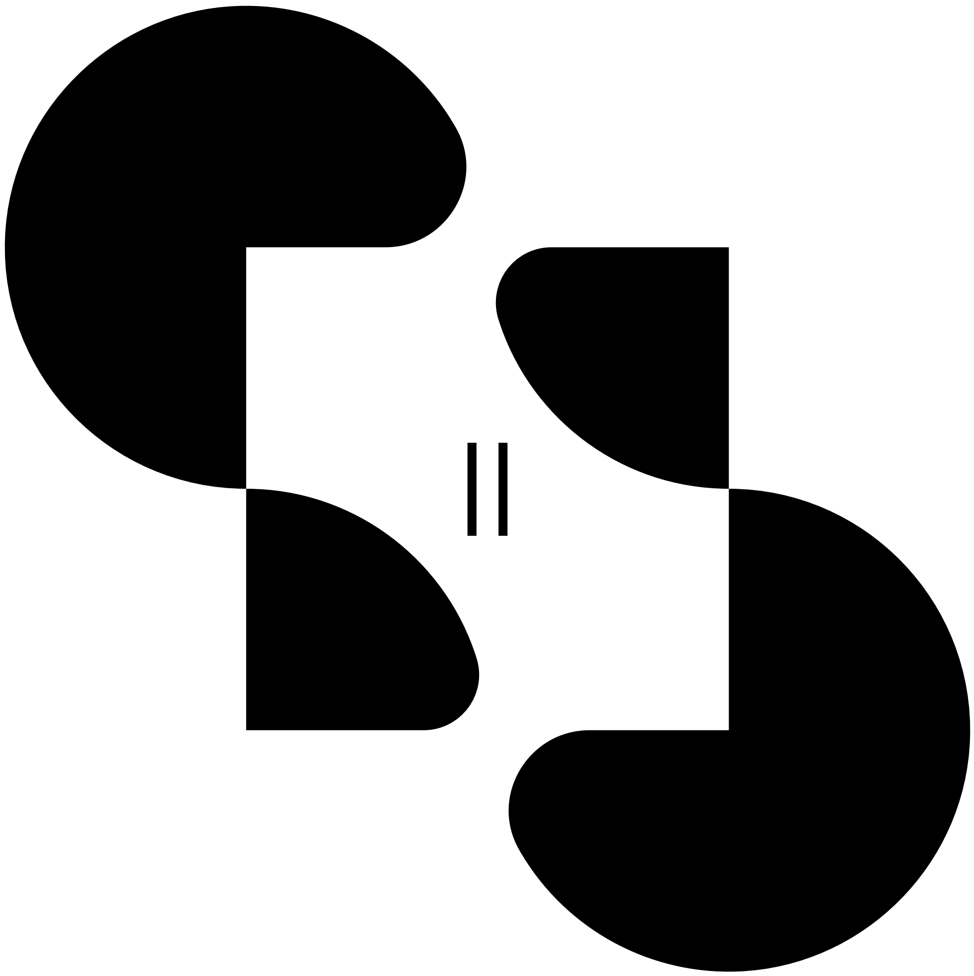
Within this textbook, you will learn about the concept of cultivated meat from a range of perspectives, including the world's top industry leaders and academics. The former, work on the cutting edge of cultivated meat daily, shortening the gap between rhetoric and reality, and the latter, have explored the intricacies of cultivated meat for decades, far before the world would know it. The authorship cast of this textbook consists of almost 100 members of the cultivated meat community, from 15+ countries. They gathered to contribute to this single text, mapping out the concept that unifies them all.

Deceptively so, it is this concept that embodies abundant diversity. Beyond its illusion as a seemingly simple food product, meat entangles itself in complex matters of the modern world. For discussions on the future of public health, animals, and the environment require its inclusion, and meat underwriting the entirety of the human story means it has profound roots in the full breadth of history's cultures and economies. It is these roots that elevate its status above a mere menu item and ultimately bring us back to the timeliness and history of meat.

The stories of the African hunters, Buwei, Ophelos, Eduardo, and Smithfield Foods illustrate that meat has indeed stood the test of time. All generations have experienced its service, regardless of the ways the process has evolved to harvest it. While the product has remained the same, how meat was prepared and brought to a tribe or a polis or a country has undergone much change. And now, the young concept of cultivated meat may be next in line to change the world. It makes the seemingly impossible possible: eating meat, without eating animals; a practice that may soon become synonymous with the modernity of meat.

We're pleased to share with you this outlook on what may become modern meat in the coming decades, and how meat made from cells could change the global landscape of agriculture forever.

We present to you the first edition of Modern Meat, the world's first textbook on cultivated meat.


II

IMPACT

SECTION 2

Prior to reading Modern Meat – Section 2

This section explores how cultivated meat may impact humanity, animals, and the environment. It explores this under the lens of the United Nations' Sustainable Development Goals.

Humanity

Impact of Cultivated Meat on Humanity

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Chapter Abstract

Cell-cultured meat presents an opportunity to reach several UN SDGs related to human well-being. In terms of Zero Hunger (SDG#2), cellular agriculture could improve different dimensions of food insecurity, production, distribution, utilization, and stability, but continues to face challenges in scaling and equal accessibility. Good Health and Well-Being (SDG #3) could be enhanced by cellular agriculture through physical health benefits, such as reduced antibiotic use and foodborne illnesses that continue to challenge traditional animal agriculture. Cell-cultured meat could create a shift in Decent Work and Economic Growth (SDG #8) from traditional blue-collar farming to white-collar food production, which may require a transfer in job skills, but could ultimately present physical and mental benefits as compared to conventional farming. As an emerging field, cellular agriculture offers substantial Industry, Innovation, and Infrastructure growth (SDG #9). Open access to cellular agriculture technology and its potential benefits could assist in Reducing Inequality (SDG #10) currently experienced by rural communities. Most funding for cell-cultured meat has stemmed from venture capitalists but calls for government funding are growing to increase the potential Partnerships to Achieve the Goals (SDG #17).

Keywords

Food Security
Health
Employment
Industry
Inequality
Partnership

Fundamental Questions

1. What are the four dimensions of food security and what are some examples of how cellular agriculture can improve these factors?

2. How does traditional animal farming affect the spread of disease and illness? What are some examples of how cell-cultured meat can change this?

3. What is one of the main concerns regarding cellular agriculture's impact on employment? What benefits could cell-cultured meat jobs bring?

4. Summarize the growth in cellular agriculture industry, innovation, and infrastructure. What advancements still need to be made?

5. How can cellular agriculture address inequality?

6. What type of funding has fueled cell-cultured meat research so far and what are some pros and cons to partnering with conventional meat companies?

Chapter Outline

1.1 Introduction

1.2 Zero Hunger
- 1.2.1 Food Security Dimensions
- 1.2.2 Challenges

1.3 Good Health and Well-Being
- 2.3.1 Antibiotic Use
- 2.3.2 Zoonotic Disease
- 2.3.3 Pollution
- 2.3.4 Meat-related Toxicity

1.4 Decent Work and Economic Growth
- 2.4.1 Employment
- 2.4.2 Occupational Physical Health
- 2.4.3 Mental Health

1.5 Industry, Innovation, and Infrastructure
- 2.5.1 Industry
- 2.5.2 Innovation and Biomedical Science
- 2.5.3 Infrastructure

1.6 Reduced Inequality

1.7 Partnerships to Achieve the Goals

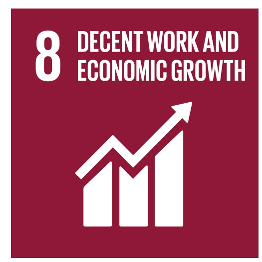
1.1 Introduction

Part II of this textbook discusses the potential effects of cell-cultured meat on people, animals, and the environmental state of the world with respect to the United Nations Sustainable Development Goals (UN SDG). The UN SDGs are a useful framework for assessing the impacts of new technologies on our global systems. There is overlap among the different UN SDG categories, so there will be cross references throughout the chapters. For example, a healthy ecosystem benefits both the environment and humanitarian public health through improved living conditions. This chapter will cover UN SDGs #2-3, 8-10, and 17, as these topics are most related to changes affecting people. Chapter 2, *Animals*, focuses on UN SDGs #14-16 associated with animal welfare, and Chapter 3, *Environment*, discusses UN SDGs #6, and 11-15, which are those most relevant to alterations in ecological systems.

The industrialization of meat production has huge impacts on consumers, laborers, and the global health system. This chapter explores how a future transition to cell-cultured meat production could transform these issue areas and bring structural changes to the global system. This chapter will discuss the six UN SDG tasks that most directly relate to human well-being.

(SDG #2) identifies opportunities for cell-cultured meat to mitigate world hunger.

(SDG #3) examines the ways the meat industry adversely affects our health, and this chapter discusses how cell-cultured meat could address these concerns.



(SDG #8) outlines the effects of conventional meat on workers' lives and economies.

(SDG #9) delineates opportunities for how cell-cultured meat could spark innovation in a variety of different sectors and transform the industrial landscape of nations.

(SDG #10) details ways in which conventional meat contributes to inequality on racial and socioeconomic lines and this chapter will discuss how cell-cultured meat could alleviate this burden.

(SDG #17) surveys corporate and national partnerships that could facilitate the growth of the cell-cultured meat sector.

1.2 Zero Hunger

The second UN SDG goal of "Zero Hunger" is a multifaceted problem with no single solution. Food insecurity and undernourishment are measurements to assess the risk of hunger. Food security is defined as "a situation that exists when all people, at all times, have physical, social and economic access to sufficient, safe and nutritious food that meets their dietary needs and food preferences for an active and healthy life". Food security consists of four main components: availability, access, utilization, and stability, which will be discussed in greater depth with respect to cell-cultured meat later in this section. In 2020, nearly 9 % of the world population, about 690 million people, many of whom were children, experienced hunger. The COVID-19 pandemic further worsened food security and is predicted to lead to 83-132 million more food-insecure people. Unfortunately, the world is not on track to achieve Zero Hunger by 2030 and an estimated 840 million people will face hunger by 2030.[1,2]

Food security remains to be investigated in the cell-cultured meat industry.[3,4] Malnourishment, one dimension of food insecurity, often involves a lack of protein rather than a lack of calories.[5] Once considered a luxury, the demand for meat is increasing as countries become more developed and as the human population grows. The world population is expected to increase to about 10 billion people by 2050. Conventional and sustainable farming will not be able to meet the future demand.[1,3] Cellular agriculture is a technology that could assist in addressing some of the challenges facing food security.

1.2.1 Food Security Dimensions

Cell-cultured meat's potential impact on food security is currently based upon projections as this technology is still in the research and development stage and is yet to be commercialized. As mentioned above, food security has many components, such as production and availability, distribution and access, economic affordability, utilization/nutrition, and stability.[1,3]

Production: The first aspect, production, is defined as securing the physical presence of food.[1] Cell-cultured meat production facilities could allow for an increase in the harvesting of sterile food, including in areas where such meat production could not otherwise occur. This could lower the global risk of famine and provide a sustainable way to generate food for the future.[6] Modern technology could also enable more efficient food production than conventional meat processes because traditional farming creates a system in which a majority of plant protein grown is fed to livestock, which are eventually killed for meat. The conversion of plant to meat protein is an inefficient biological process that results in higher food prices and could theoretically be solved through the implementation of cellular agriculture.[3,7,8] Furthermore, the increased availability of plant proteins could be directed to products for human consumption, improving efficiency and availability of healthy foods. [3,7] However, this will only be possible if cellular agriculture technology becomes much more efficient than it is currently. Although cell-cultured meat could benefit food security by increasing food availability and reducing waste, countries with food surpluses still report a high prevalence of food insecurity demonstrating that other components of food security need to be investigated.[3,9]

Distribution: The second dimension of food security is access to food,[1] which involves both geographic and economic factors. Cell-cultured meat is expected to have a longer shelf life than conventional meat, which could allow for cell-cultured products to be made farther away from consumers.[6,10] In addition, cellular agriculture technology could be used in locations that would otherwise depend on importing food, offering more geographical independence and simplifying supply chains.[6] Several futuristic food models have been proposed, such as a decentralized "pig in the backyard" production of cell-cultured meat with animals serving dual purposes as both samples for healthy cells and as companions to their owners [11] and another model of"Food-as-Software" in which molecular food formulas are "uploaded to databases" and accessed worldwide. [12] Cell-cultured meat may allow for easier physical access, especially in remote areas, as well as cheaper prices than conventional meat.[3,6] Price continues to be a challenge, and the future of cell-cultured meat may depend on which becomes a premium product: farmed meat or cell-cultured meat.[10,12]

Utilization: The third component of food security, utilization, is defined as the energy and nutrient input of food, its nutritional value. Global malnutrition is a persistent problem with low-income countries relying heavily on just one or two staple foods instead of a range of fruits, vegetables, and animal products. [1] Plant proteins generally offer fewer nutrients compared to animal proteins, and different scientific processes are being explored to improve the nutritional value of plant-based foods. Many plant-based meat substitutes also contain food allergens and sometimes have residual plant flavors that consumers find off-putting. Cell-cultured meat could possess identical or even enhanced nutritional values compared to conventional meat. Different aspects of cell-cultured meat, such as the quantity and type of fats, could be controlled and replaced with healthier options, such as omega 3 fatty acids.[6,7,10]

Stability: The final factor for food security is the stability and reliability of the food system.[1] Currently, the consistency of food supplies often overlaps with environmental stability. Cellular agriculture would be less dependent on natural resources and issues relating to climate change than conventional farming, which could enable stability during natural and man-made disasters.[3,6] Biodiversity is another key component of food security, which could be preserved through genetic storage of a wide variety of traditional livestock breeds in the form of cells that could be cultured to grow meat.[5,10,13] Public health concerns, such as foodborne illnesses and zoonotic diseases, could theoretically be diminished through cell-cultured meat's sterile environment, further contributing to a stable long-term food system; this is explained further in Section 2.3, *Good Health and Well-being*. While cell-cultured meat could enable more consistent access to protein for more of the world's population, high production demands could result in large energy requirements and additional threats to food security should also be considered.[13,14]

1.2.2 Challenges

It is likely that the potential for cell-cultured meat to have a positive impact on the UN SDG's second goal of Zero Hunger depends largely on access. The primary challenge of food security appears to be not a problem of resources, but one of resource allocation or distribution.[3,14] Geopolitical concerns surround the distribution of cell-cultured products and technology (see Section 2.6, *Reduced Inequality*). Some essential questions about the distribution of cell-cultured meat include:

Who will produce cell-cultured meat (meat industry, small farmers, scientists)?

Where will the production take place (only in developed countries)?

Who will profit from the technology?[13]

The main challenge to achieving equal access to cell-cultured meat seems to be whether urban areas will be the only places producing and benefiting from the technology. As mentioned earlier, other distribution models have been proposed, such as the "pig in the backyard" scenario and "Food-as-Software" model, which would reduce urban centralized production.[11,12] A portable cell-cultured meat production device would also assist in expanding the benefits of cellular agriculture, allowing greater access, and reducing food deserts[14]. Leveraging distribution management and operations from other sectors, such as food banks, disaster relief programs, the military, or even NASA, could assist in creating improved food distribution for cell-cultured meat.

In addition to the risk of cellular agriculture being abused for political power, other concerns may hinder cell-cultured meat's ability to aid with food security. The cost of cell-cultured meat will play a significant role in its economic accessibility, which will determine whether cellular agriculture will become a disruptive technology. Two possible outcomes are the "addition effect" in which cell-cultured meat offers another source of meat or the "substitution effect" where cell-cultured meat replaces conventional meat.[13] If cell-cultured meat prices remain high, the "addition effect" will prevail, catering only for a niche, wealthy market, but if costs are reduced a larger "substitution effect" may be achieved.

Cell-cultured meat might improve meat production as compared to conventional meat production with respect to some metrics, but at a cost to the environment and to small businesses if large corporations are allowed to monopolize the technology. If cell-cultured products impact the market, mass unemployment of farmers could lead to poverty and food insecurity for the very people who have supplied communities with food throughout history. Strict regulation and political solutions to prevent unemployment by transferring job skills could alleviate some of the negative aspects of disruptive technology (see Employment Section).[3] Alternatively, if cell-cultured meat becomes widely available, an increase in meat consumption may occur, along with the negative health effects of overconsumption.[3] Lastly, cell-cultured meat might present a risk of novel contamination routes, so production and distribution would need to be carefully monitored and regulated with the same rigor as current food production. If scaled and managed correctly, cellular agriculture offers an opportunity to address several aspects of food insecurity but is unlikely to be the sole solution.[3,13,14]

1.3 Good Health and Well-Being

The third UN SDG, “Good Health and Well-being,” can be related to the physical health benefits that cell-cultured meat could bring. As highlighted by the COVID-19 pandemic, food safety is essential and issues such as overabundant antibiotic use and zoonotic disease remain serious threats. Environmental factors like pollution are also linked to adverse effects on health and are closely related to the food industry. This section examines the ways the current conventional meat industry impacts health and well-being and how cell-cultured meat could address these issues.

1.3.1 Antibiotic Use

Although microbial resistance can occur naturally over time, antibiotic overuse in food production is a global concern for accelerating resistant disease strains. This overuse can have negative consequences for both human health (antibiotic resistant diseases) and the environment (farm runoff).[15] According to the Centers for Disease Control (CDC), at least 2 million people in the US get an antibiotic-resistant infection every year, and tens of thousands die as a result annually. Even when they are not lethal, antibiotic-resistant infections can cost people tens of thousands of dollars for health care in countries like the US and reduced productivity.[16] Animal agriculture plays a significant role in antimicrobial resistance. Animal food producers are encouraged to follow strict antibiotic use guidelines, and in the US, farmers can apply for the US Department of Agriculture (USDA)’s Process Verified Program to display their antimicrobial stewardship to consumers.[17]

> *“...Resistant bacteria can contaminate the foods that come from those animals, and people who consume these foods can develop antibiotic-resistant infections. Antibiotics must be used judiciously in humans and animals because both uses contribute to not only the emergence, but also the persistence and spread of antibiotic-resistant bacteria. Scientists around the world have provided strong evidence that antibiotic use in food-producing animals can harm public health...”* [18]
>
> \- *US Centers for Disease Control*

According to the Food and Drug Administration (FDA), nearly 80% of all antibiotics sold in the US are administered to farm animals to stimulate growth and to prevent diseases in often crowded, unsanitary living conditions.[19]

Because cell-cultured meat would be produced in sterile bioreactors, there would be little to no need for antibiotics (can we add this reference here please https://www.nature.com/articles/s43016-022-00602-y). Although some antibiotics may be used during the initial isolation of cells from host animals, this is not expected to continue long-term as advances in technology further reduce direct animal contact.

1.3.2 Zoonotic Disease

Illnesses transmitted to humans from animals are known as zoonotic diseases. Transmission is mainly bacterial, viral, or parasitic and can arise from vectors (e.g., mosquitos), infected air or water, direct or indirect contact with animals, or through consumption of raw or contaminated foods. Rural, agricultural, and lower income communities are at higher risk of contracting zoonotic disease. In the food industry, the risk of zoonotic disease is present during the rearing, transport, and slaughter of animals. There are over 200 types of known zoonoses – including SARS-CoV-1, salmonella, influenza (bird or swine), malaria, tuberculosis, rabies, HIV, Ebola, Listeria, Lyme disease, MRSA, and toxoplasmosis among others.[20]

EXAMPLE: HIV-1 is related to the similar chimpanzee disease, Simian Immunodeficiency Virus (SIV), which is believed to have been transmitted from chimps to humans in the Democratic Republic of Congo around the 1920s. Chimps carrying SIV were hunted and eaten by people, allowing for the virus to mutate within the human host to form different strains of HIV-1.[21]

Producing meat in a sterilized laboratory could reduce the risk of bacterial and viral contaminants from entering the human food system. The World Health Organization (WHO) states that one in ten people worldwide fall ill from contaminated food each year. The estimated global annual cost of foodborne diseases is US $110 billion, primarily affecting low-income countries.[22] In many developing countries, particularly in Africa and Asia, minimal regulation of food safety, such as wet markets, means zoonotic diseases pose a substantial and ongoing threat to human health and well-being. The “One Health” non-profit and associated initiative seeks to improve food biosecurity worldwide by addressing the connection between human and animal health.[23] In the US, food safety is regulated by the FDA, and zoonotic diseases are monitored by the CDC. The FDA also works to regulate food additives designed in laboratories, such as sweeteners, or other products listed under the Generally Recognized as Safe (GRAS) category.[24] Cell-cultured meat could minimize human contact with animals, thus decreasing the risk of food-related zoonotic disease. This has the potential to save lives, improve some people’s quality of life, and reduce healthcare economic costs in certain areas.[25]

1.3.3 Pollution

Pollution related to meat production affects both the natural environment and human well-being (for see Chapter 4, *Environment*). Both the people working on livestock farms and the surrounding community may be exposed to harmful pollutants. Although many technological advances have been made, many farmers continue to suffer from respiratory illnesses, such as asthma and bronchitis due to workplace exposure to harmful agents like microbials and endotoxins.[26] Examples of hazardous conditions resulting from animal agriculture pollutants include organic dust toxic syndrome (ODTS) from high concentrations of bioaerosols in livestock buildings and ambient fine particulate air pollution. Air pollution in general disproportionately affects people of color, but predominantly white agricultural farmers are also subjected to these toxins.[27,28,29] Local communities are also exposed to dangerous fertilizers and pesticides. Farmed animals in the US produce approximately 100 times the waste matter as humans, introducing a challenge as to its processing and sanitation. Animal manure is often disposed of in nearby low-income areas and can lead to health problems (see example box).[6] Concentrated animal feeding operations (CAFOs), where animals are raised to market size, are a major source of local environmental degradation often in impoverished areas of the US. Despite pushback, these facilities are generally placed in communities of color or low-income areas. Ongoing statistical analysis of North Carolina's hog industry—where the most thorough study of CAFOs' impacts on communities in the US has taken place—shows that nine times as many hog production operations are located in areas of eastern North Carolina where 12% or more of the population lives in poverty and 10% or more of the population is non-white.[30,31] The people in these locations are often subjected to periods of unpleasant odors including harmful emissions, such as ammonia, related to animal pollutants, which can lead to premature death.[27,32] Water sources are also at risk of pollution with nitrates and phosphates from animal operations, which poses a threat to both human and animal health.

EXAMPLE: In eastern North Carolina, hog operations spray liquefied feces into the air of local poor and disproportionately non-white communities; the proportion of the population living within three miles of an industrial hog operation is 2.14 times higher in areas with 80% or more people of color.[33] These pollutants are known to cause high blood pressure and asthma.[34] This is not an isolated case as tens of thousands of these hog operations release water and air pollutants across 43 US states for which data is collected.[35]

1.3.4 Meat-related Toxicity

Consumption of animal protein can add important nutrients to human diets, but red and processed meats have been shown in some studies to be carcinogenic.[36,37] Since cell-cultured red meat will likely be identical to traditionally produced red meat, it will also carry the same risk of carcinogenicity. The WHO classified processed meat as a carcinogen and red meat as a probable carcinogen with a meta-analysis of over 800 colon cancer studies.[36] Dioxins found in animal fat can be carcinogenic and toxic when consumed, and consumption adds up over time in a process called bioaccumulation.[38] Dietary recommendations from the Harvard T.H. Chan School of Public Health suggests that half of our plates be fruits and vegetables, with a quarter for grains, and a quarter for protein which includes legumes, nuts, fish, and poultry.[39] Men who adhered to these healthy eating guidelines reduced their risk of chronic illness, such as heart disease and cancer by 40%, and women reduced their risk by 30%.[40] Another seminal study found that adherence to these guidelines over the course of 18 years reduced mortality from all causes by 25% and mortality from heart disease by 42%.[41]

If cell-cultured meat production leads to high consumption of red and processed meats by making products more accessible, it may lead to an increase in the prevalence of cancers in the human population unless technological advances allow for enhanced nutritional value and lower carcinogenic risk of cell-cultured meat.

Aquaculture poses similar pollutant concerns as land animal agriculture with antibiotic overuse, harmful chemicals, and foodborne illnesses. Mercury and microplastics in fish products are another reason why cellular agriculture may offer a better alternative. Methylmercury is increasingly found in high levels among marine animals that humans eat, owing largely to emissions from coal power plants that accumulate in the oceans. Exposure to methylmercury, a neurotoxin, occurs primarily by consuming fish products, and can cause permanent neurodevelopmental damage. The Environmental Protection Agency (EPA) and FDA recommend that women of childbearing age and young children avoid eating many species of fish to minimize this risk.[42] Aquaculture that uses wild-caught fish as feed is also susceptible to carcinogenic pollutants. One to three million metric tons of plastic enter the ocean each year, and one study estimates that nearly half of the plastic entering the Pacific Ocean results from abandoned fishing gear from commercial trawlers.[43,44] This plastic is consumed by wild fish, which then concentrates plastic higher up the food chain through bioaccumulation. This can alter marine biological functions with uncertain impacts on human health.[45]

Transitioning aquaculture to a controlled laboratory environment not only has positive implications for environmental sustainability, but it can alleviate several human health and well-being concerns. Without commercialization of cell-cultured meat, however, the potential human health benefits are speculative. Research on the health effects of cell-cultured meat is needed, and careful design of cell-cultured meat production facilities will be required to ensure food safety.

1.4 Decent Work and Economic Growth

The UN has chosen “Decent Work and Economic Growth” as an SDG because labor enterprise empowers people to improve their standard of living. A shift away from conventional meat production could have at least three key implications for decent work and economic growth: employment, occupational health, and mental health.

1.4.1 Employment

A significant drawback for novel cell-cultured meat production is the potential displacement and unemployment of conventional farming and related animal byproduct industries. Since 2000, global employment in agriculture has fallen from 40% to 30% in 2017.[46] There are about 1.2 million jobs in US beef and dairy production, and one group estimates that, by 2030, half of those jobs could become obsolete if cell-cultured meat is scaled to become cheaper than traditionally farmed meat.[10,12] The industrialization of food production has had dramatic labor-reducing effects across history, and there is a well-established trend in global demographics linking decline in agricultural employment to urbanization.[47] The US is illustrative of this trend. USDA figures suggest that from about 1910 to 2000, employment on farms fell by nearly 70 % even as total production increased dramatically.[48] St. Louis Federal Reserve Data finds that, as a percentage of total employment, agriculture's share has fallen from about 4.5 % in 1960 to 1.5 % in 2012, as jobs continue to shift to other sectors.[49] A revolutionary change in the meat supply chain could create a ripple effect beyond agricultural industries with a "global-scale shift in livelihoods".[13,50] The labor involved in food production may change from primarily blue collar workers on farms to white collar scientists in laboratories.

Moreover, by disrupting an industry that employs hundreds of millions of people, directly in animal rearing and indirectly in crop cultivation for animal feed, cell-cultured meat could accelerate global trends toward urbanization. Since 2000, the share of the world's population living in rural areas has fallen from about 50 % to 45 %.[51] Meatpacking helped build the cities of Chicago and New York through European immigration in the 19th century, and similar recent effects have been seen in Nebraska and Kansas with immigrants from Central America. Given that roles in the cell-cultured meat sector would require a higher level of education and skill for initial production, it seems likely that the industry might locate its operations primarily in medium-sized to large urban centers, which already possess more of the scientific infrastructure, such as large bioreactors.[3,14,50,52] Some towns built around animal agriculture could experience a reduction in employment due to the rise of cell-cultured meat facilities, as they are likely to be highly automated. It is likely that cell-cultured meat could reduce demand for crops like corn, soy, sorghum, and hay, which compose most of the feed given to farm animals. USDA statistics for 2020-21 show that, of the major feed grains consumed by livestock in the US, corn accounts for more than 95 % of the total.[53] By reducing the number of farm animals and therefore also the amount of feed produced for them, cell-cultured meat could put conventional meat processing facilities and potentially grain farming operations out of business. The ensuing labor shock could displace hundreds of millions of people from rural communities and small urban areas, forcing them to seek work in larger urban centers, while reducing the quality of life for people who remain. While larger cities will likely survive a labor shock, many smaller urban areas centered around meatpacking plants may not persist through the disruption. Small cities may cease to thrive when an industry declines because they lack diversity of human capital.[54] If cell-cultured meat and conventional meat production require similar infrastructure, however, the corporations already mass-producing meat in rural population centers might purposefully locate cell-cultured meat facilities near infrastructure they already own in small cities (see Section 2.5, *Industry, Innovation, and Infrastructure*, below). In addition, factors such as vertical agriculture in the form of hydroponics and/ or aeroponics could also shift food production closer to urban centers. Ultimately, it is difficult to concretely predict the dynamic labor market effects of cell-cultured meat.

Cell-cultured meat production will likely require a transfer of skills and new job opportunities. The number of new jobs cellular agriculture will create is unknown, but government policy may assist in the transfer of skills.[10] Job retraining programs and financial support to farmers who want to transition to cell-cultured meat production could ease the transfer.[3,13] The theory that technology creates jobs by freeing up resources for deployment elsewhere in the economy has been in some ways undermined, as the employment system and government bodies often fail to retrain workers or create jobs in new sectors. Training for job opportunities in cellular agriculture could be part of a broad range of policies to address the perception that technological innovation has resulted in stagnant employment and median income levels, even as overall productivity has increased drastically. The Industrial Revolution was an example of an employment boom resulting from technological advances, but current innovation like artificial intelligence is already proving to be a disruptive force that is threatening the livelihoods of workers in certain industries.[55] Labor-saving technology is at odds with creating a direct substitution solution for displaced workers in the current market-based system in the US. The answer to this tricky problem could include increased redistribution, through a universal basic income, wage insurance regime, or a jobs guarantee. Additionally, a public jobs program could promote the arts or greening of the environment. It is unlikely that high-skilled molecular engineering jobs in the cell-cultured meat sector will replace all the jobs associated with animal agriculture. Some conventional farms could be repurposed for other products, such as the conversion of dairy farms to craft breweries.[56] Other farms may still be needed to provide raw ingredients for cell-cultured products and could be incorporated into cell-cultured meat production by supplying crops for cell media.[3,10] Further, partnerships like the RESPECT farm project between small-scale farmers and cell-cultured meat companies could forge mutual benefits by providing happy and healthy animals for tissue sampling for cell-cultured meat (https://www.respectfarms.com/?trk=public_post_share-update_update-text). More small business opportunities may arise with cellular agriculture.[11] It is also possible that a combination of traditional agriculture and cellular agriculture may forge a partnership instead of a direct replacement.[13]

1.4.2 Occupational Physical Health

The occupational health implications of the cellular agriculture industry is also unknown but may be less hazardous than conventional meat production conditions.[10] Injuries and illnesses related to the agricultural industry are higher than other industries, with one of the highest reported fatality rates in the US.[57] It is also known that the current fishing industry suffers from social welfare concerns like forced labor (https://onlinelibrary.wiley.com/doi/10.1111/faf.12152). Many farmers acquire non-fatal injuries and are subjected to dangers from machinery, livestock, chemicals, noise, and physical stress, which are worsened by limited access to medical care. Workplace accidents at slaughterhouses occur at more than twice the rate of other manufacturing jobs with similar hazardous conditions. Tractor-related injuries are one of the most common risks, and one in four people who work in indoor confined animal operations suffer from respiratory illness.[6,27,57] The confined workspaces and sanitation problems became especially apparent during COVID-19 when multiple meatpacking companies suffered from widespread workplace virus transmission.[58] Poultry workers are 14 times more likely to suffer debilitating injuries from repetitive trauma than workers in all other private industries.[59] Data from the Occupational Safety and Health Administration in 2014 reveals that repetitive motion injuries among beef and pork processing workers were nearly seven times that of other private industries. Additionally, nearly eight in every 10 workers in a standard processing plant in Maryland suffered from debilitating nerve damage in their hands.[60] These figures do not account for injuries that go unreported, as third-party contractors and undocumented workers may remain silent to avoid losing their jobs.[61] Many of the hazardous conditions described above are yet to be determined for commercialized cell-cultured meat. It is likely, however, that some degree of manufacturing-related injuries will occur in the operation of cell-cultured meat facilities. There is early evidence to show that there may be chemical exposure associated with cell-cultured meat production, such as from the neurotoxin, hexane, associated with soy production, and which is currently necessary for some cell-cultured meat production processes.[10]

1.4.3 Mental Health

In addition to physical risk, psychological hazards are evident in conventional farming. Mental health concerns among abattoir workers are common, owing to the conditions of the industry and the psychological impact of routine livestock slaughter. Studies show the violence required of kill-floor workers increases the probability of extra-institutional violence, similar to the psychological trauma experienced by police officers, prison guards, and military personnel.[62] The anxiety and depression exhibited by some farmers has been described as akin to post-traumatic stress disorder.[27] This stress and the additional agricultural economic decline have resulted in an increase in suicide among American farmers.[10,27] Across industries that have the same type of routinized labor and have similarly high injury rates, slaughterhouse work uniquely increases violent and sex-related crime, such as intimate partner violence.[63] Many of the stressors experienced by farmers extend further to their families and local communities.[57] The mental health implications for workers in commercial cellular agriculture have yet to be determined, but it may be assumed that transmission of violence would be reduced, if not eliminated, in production facilities absent of animal harm.

1.5 Industry, Innovation, and Infrastructure

The UN recognizes that human ingenuity and enterprise drives positive change in our society. Around the globe, more than two billion people still lack access to basic sanitation, electricity, and the internet. They do not have access to the modern technologies that connect people with information or the living standards conducive to revolutionary breakthroughs.[64]

1.5.1 Industry

Cellular agriculture is an emerging industry with substantial partnerships (see Section 2.7, *Partnerships to Achieve the Goals*). A rise in the cell-cultured meat industry will likely result in an increase in white collar jobs (see Section 2.4.1, *Employment*) and could result in new industrial hubs like Silicon Valley in other areas of the country and worldwide. Most cell-cultured meat companies are in the US, but there are more than 100 cell-cultured companies in 30 countries spanning six continents as of 2021. The number of companies have rapidly increased by 185% since 2018, where there were just 35 companies in the space.[65] In addition to the increase in the number of cell-cultured meat companies, there has been additional interest and funding from investors (see Section 2.7, *Partnerships to Achieve the Goals*). The focus of the cellular agriculture industry has expanded to include over 15 types of meat production and other animal products, such as eggs, dairy, leather, and collagen.[66,67] Growth is occurring in niche business-to-business companies working to solve the main challenges of the field, such as replacing fetal bovine serum in cell media with a non-animal alternative. An important component to this new industry will be its regulation. Singapore was the first country to approve a regulatory process for cultivated meat. In the US, the FDA and USDA agreed to work jointly: the FDA will oversee the cell culturing process while the USDA will regulate the cell harvesting and cultured product labeling.[10,66] More groundwork is needed, but some of the essential industrial components from the necessary corporate framework to physical factories have been formed and continue to grow.

1.5.2 Innovation and Biomedical Science

Cell-cultured meat technology has the potential to help both the cellular agriculture industry and biomedical technology. Historically, most of the technology that supports cellular agriculture was leveraged from biomedical research. With further advancements in cell-cultured meat production, cellular agriculture holds the potential to publish findings and create biotechnologies that also have implications for human health, including the ability to culture organ tissues or cells that can be used for transplants.[69] Researchers at cell-cultured meat accelerators are carefully considering how their technology can develop dual-technologies for regenerative medicine. Cell-cultured meat and regenerative medicine share similar goals, such as creating 3D, structured steaks or organs respectively. Technologies, such as tissue engineering, 3D printing with cells, scaffold development, and general cell culturing methodologies, such as maintaining different cell lines, have potential overlap in both cell-cultured meat production and the biomedical field. These two fields may use similar technologies, but a key difference will be the focus on the cells' taste and texture for cellular agriculture, whereas regenerative medicine requires cellular functionality.[70] Innovations in cellular agriculture have revolutionary potential for both food and regenerative medicine, underlining the need for private and public entities to invest resources in cell-cultured meat.[69]

1.5.3 Infrastructure

The increase in industry and cellular innovation may lead to increased urbanization (see Section 2.6, *Reduced Inequality*) and infrastructure related to cell-cultured meat. Many cellular agriculture companies in the US are based near San Francisco, providing access to Silicon Valley's infrastructure. A potential increase in urbanization and reduction in land needed for traditional agriculture could enable more infrastructure, such as transportation or housing projects. [71,72] Cell-cultured technologies may also expand upon the technology already in Silicon Valley and may lead to new infrastructure, such as the Cellular Agriculture Society's vision for a Cell-cultured Meat Facility (CMF) Project. Project CMF is a blueprint for what future cell-cultured meat facilities could achieve if scaled successfully. Currently the CMF design is described for an urban setting, but different adaptations could enable a CMF to be expanded and customized for various communities.[73] The commercialization strategy created by BlueNalu, a cell-cultured seafood company, predicts that a 4,600 square meter (150,000 square foot) food production facility would enable 8 million kilos (18 million pounds) of cell-cultured seafood to be produced annually.[66] A 300,000 liter bioreactor is estimated to provide enough meat production capacity to feed 75,000 people according to one computational model.[74] As noted earlier, some of the current meat production infrastructure might also provide crossover use for cell-cultured meat, which could allow for infrastructure in rural areas to be repurposed for cellular agriculture. As cities expand to greater scale, this promotes higher rates of invention, new patents, and employment in creative enterprise, likely owing to greater social opportunity and the concentration of human capital.[75] In general, urbanization is linked to improved sanitation, safe drinking water, and access to electricity and better nutrition.[47] Urbanization for cellular agriculture, however, may benefit more developed areas with the technological infrastructure already in place notably more than those cities and towns without existing resources. Nevertheless, cell-cultured meat's potential urbanization effects may also bring the world closer to the UN's Industry, Innovation, and Infrastructure goals for the world's poorest people.

1.6 Reduced Inequality

Inequality represents a failure of our global economic system to give everyone the chance to reach their full potential. The UN maintains that 40 % of global income is distributed among only the world's richest 10 %.[76] Unless accompanied by a strong public policy framework that ensures equitable access and distribution, technologies such as cell-cultured meat could accelerate global inequality by reorienting conventional farm incomes to the corporations that most successfully scale up the technology.

Cellular agriculture is predicted to impact urban and rural communities differently. If cell-cultured meat is produced in cities, urban areas may benefit from increased meat availability and health benefits as well as economic advantages from being a source of the technology. As noted earlier, rural regions could benefit from reduced climate pollution caused by conventional farming but may suffer from job and community loss related to the cell-cultured meat industry displacing local agriculture (also see Sections 2.3.3, *Pollution* and 2.4.1, *Employment*).[3,10] The disparity between urban and rural areas may also be extended to the development and wealth divisions globally. Cellular agriculture could increase economic and political power imbalance and allow developed countries to gain more power.[10,77] Investments from large meat companies have been helpful in accelerating cell-cultured meat research and development (R&D) and might assist in public consumer trust of cell-cultured products, but a monopoly of the technology by big companies could result in increased Western geopolitical power that disadvantages the developing world.[3]

Alternatively, a united goal to advance the potential benefits of cellular agriculture may provide opportunities for collaborations and a unified mission. Advances in the infrastructure surrounding cell-cultured meat may enable increased accessibility for rural communities. Also, projects such as producing meat for astronauts in outer space may accelerate the technology needed to create cell-cultured meat in remote areas on earth. This potential widespread sharing, democratization, of cellular agriculture could reduce the concern of equal distribution of the technology.[14,50,78] In the long term, cell-cultured protein could also contribute substantially to climate change mitigation. There is evidence that climate change disproportionately impacts low- and middle-income countries; therefore, technologies that combat climate change are also technologies that can fight inequality in this way. As the UN has described, climate change presents a “vicious cycle” for disadvantaged communities by leading to more exposure to climate hazards, more susceptibility to climate change-induced damage, and more difficulty recovering from the negative effects caused by climate change. Human inequality related to climate change is both an international and domestic problem. Climate change results in lower income populations suffering from reduced resources, such as access to food and water, and natural disasters. The risk of climate hazard exposure is greater for lower income populations partly due to their geographical location, as neighborhoods are often located in dangerous areas that are vulnerable to floods and erosion, and through occupational exposure. Because of these inequalities, disadvantaged communities are more likely to be exposed to natural disasters or workplace health risks, leading to loss of an already limited income and less ability for financial recovery. This cycle of disadvantage can be seen on both local and global scales.[79] If cell-cultured meat production can be designed to be environmentally friendly, then cellular agriculture may help reduce both climate change and the related worldwide social inequalities.

1.7 Partnerships to Achieve the Goals

Interest from investors in cell-cultured meats has spiked from about US $80 million in 2019 to US $366 million in 2020.[66,68] In 2021, the investment is expected to exceed two billion US dollars into cellular agriculture with funding supporting both acellular products, such as cell-cultured whey protein dairy products, and cell-cultured meats.[80,81] From 2016-2019, over half of the investments in cellular agriculture companies came from venture capitalists. Many investors are US-based and are also members of the GlassWall Syndicate, a group of venture capitalists, foundations, trusts, non-profits, and investors seeking to advance animal-free products that will also benefit people’s health.[66]

Conventional meat companies have begun to recognize shifting consumer preferences and the resource constraints of traditional meat production. Reinventing themselves as “protein” companies, food giants that have invested substantial funds in plant-based and cell-cultured meat include Kroger, Kellogg’s, Nestle, Nissin, Hormel, Perdue, and Smithfield (more are provided in the examples box).[67,82] Additionally, many fast food restaurant chains including Burger King, KFC, McDonald's, Del Taco, Pizza Hut, Qdoba, and Carl's Jr., have begun mainstreaming plant-based meat options on their menus, as early as 2018.[83] If cell-cultured meat reaches an affordable scale, there is reason to believe these restaurants will likely add these products to their menus, too.

Examples of conventional meat company investments in cellular agriculture	
Meat Company	**Cellular Agriculture Investment**
Tyson Foods	Future Meat Technologies Upside Foods
Cargill	Upside Foods
PHW-Gruppe	SuperMeat
Toriyama	Eat Just, Inc (JUST)
Bell Foods	Mosa Meats
JBS	BioTech Foods

These major corporate partners and investors pose both benefits and risks for cell-cultured meat startups conducting R&D. These partnerships provide cell-cultured meat entrepreneurs with valuable scientific resources and market insights, not just financial assistance. Billionaire philanthropists Bill Gates, Richard Branson, Li Ka-Shing, Sergey Brin, and Tom Steyer all hold stakes in cell-cultured meat companies, giving technology celebrity power, which raises cell-cultured meat's profile with popular media and in the minds of future consumers.[84,85]

Conventional meat companies, however, could possess biases and invest in alternative proteins only as an insurance policy against discoveries that could help the technology scale. Beyond Meat, a plant-based meat company that launched its initial public offering in 2019, serves as a potential example (see example box).

Tyson Foods and Beyond Meat Example
Prior to the IPO in 2019, Tyson sold its 6.5% ownership stake in Beyond Meat because of growing tension between the two companies. Beyond Meat likely believed Tyson was using inside information from board meetings to launch its own plant-based meats independent of Beyond Meat, demonstrating the potential for strain to develop between conventional meat companies and alternative protein companies.[86]

In addition to this potential conflict of interest, many traditional meat companies maintain close ties to lobbying organizations such as the North American Meat Institute (NAMI), National Cattlemen's Beef Association, and the National Pork Producers Council. These groups have pushed for legal barriers for plant-based and cell-cultured meat, including FDA standards for identity regulations that could have barred cell-cultured and plant-based meats from using the term "meat." One example of a conventional meat company and cellular agriculture company working together, however, is the joint letter the NAMI and Upside Foods wrote to the White House to request equal USDA regulation for cell-cultured meats.[87] Lastly, leaving this research to the private sector may pressure CEOs to put the concerns of investors over the long-term interests of the field, as they dedicate time and resources to creating samples for investors without first achieving scale.

The current lack of cell-cultured meat commercialization underscores the need for government-funded R&D for the field. Nobel-Prize winning economist Joseph Stiglitz compared the returns of government-supported and private R&D in 1999, finding that "primarily because of knowledge spillovers, profit-maximizing firms invest less than the socially optimal level of R&D. This disparity in the market creates the opportunity for governments to help mitigate the underinvestment problem."[88]

According to the Good Food Institute (GFI), a nonprofit accelerator for alternative proteins, global markets have expended about US $366 million in cell-cultured meat in 2020 and about US $114 million in cell-cultured seafood as of the first half of 2021.[66,68,89] New Harvest, another US-based nonprofit, also supplies some financial support for research related to cellular agriculture in academia and enables research that might not otherwise have sufficient funding to be performed.[90] Government-funded research could be possible if the USDA prioritizes grants to cell-cultured and plant-based meat researchers through its Agriculture and Food Research Initiative, the mechanism by which the USDA funded the Tufts University award, and small business grants. Governments around the world could benefit from funding open-access research that private companies can adapt to specific cell-cultured meat product lines in the future. The European Union Commission, Singapore, India, Japan, and local governments in Australia and Belgium have already provided financial support for cellular agriculture companies in their countries.[67] The US also awarded its first government grant to University of California, Davis through the National Science Foundation in 2020, and was quickly followed by the USDA-funded establishment of a National Institute for Cellular Agriculture at Tufts University in 2021.[91,92] Cell-cultured meat could become commercially viable if a broad cross-section of scientists is resourced to study scaling barriers, as has begun with increasing numbers of business-to-business companies. Attention and assistance from governments in advancing cellular agriculture, such as financial incentives for the creation of cost-effective cell mediums, currently one of the largest cost barriers to the technology's commercial viability, could accelerate progress in the field.[93] Cellular agriculture would greatly benefit from government support and could result in public benefits for the world's least fortunate people, global ecosystems, and the animals exploited in conventional animal agriculture. Diversity in investors through different avenues and with different backgrounds will facilitate cell-cultured meat innovation. Private investors and venture capitalists play an important role, but strategic government and large company investors will also be important to propel the field.

Much more work is needed for cellular agriculture products to reach mass commercialization, but the downstream opportunities for its incorporation into the food supply chain could provide some relief to current and future problems faced by humanity. Cell-cultured meat offers an opportunity to improve six UN SDGs associated with human well-being. Food security may be strengthened through additional food production, expanded distribution, enhanced utilization with nutritional fortifications, and improved stability with better food safety against natural disasters and food-borne illnesses. Good health and well-being can benefit from cell-cultured meat through less antibiotic use during food production and minimized risk of zoonotic disease. Environmental goals, such as decreased pollution and toxic bioaccumulation in meat, will likely also be impacted by cell-cultured meat and could benefit consumers. Cellular agriculture could develop to become an industry that provides new jobs and safer work environments compared to conventional meat production. In addition to new employment opportunities within a new industry, cell-cultured meat can facilitate innovation and supporting infrastructure and offers many possibilities for different partnerships and collaborations across industries. This societal transition from conventional meat towards cell-cultured meat, however, may come at a cost with a loss of jobs associated with the current meat industry and a shift to white collar workers. The spread of cellular agriculture and risk of industrial monopolies, however, will also depend on the development of partnerships associated with cell-cultured meat distribution. Equal distribution will be important for enabling the potential benefits of cellular agriculture to be shared across all communities, not only those in urban and wealthier areas. Cell-cultured meat holds promise to improve different aspects of human well-being, but only time will tell whether these speculative benefits can become reality.

Fundamental Questions – Answered

1. **What are the four dimensions of food security and what are some examples of how cellular agriculture can improve these factors?**
   The four aspects of food security are production, distribution, utilization, and stability. Cellular agriculture could increase food yield, enable decentralized distribution, increase nutritional content, and provide more food system resilience with less dependence on natural resources.

2. **How does traditional animal farming affect the spread of disease and illness? What are some examples of how cell-cultured meat can change this?**
   Conventional animal farming has been criticized for antibiotic overuse, increasing society's vulnerability to zoonotic disease, and environmental pollution. The production of cell-cultured meat in sterile environments could reduce the risk of foodborne illnesses, industry pollution, and limit the need for antibiotics.

3. **What is one of the main concerns regarding cellular agriculture's impact on employment? What benefits could cell-cultured meat jobs bring?**
   A major drawback for cellular agriculture is the potential displacement of traditional farming jobs. As a disruptive technology, cell-cultured meat may take jobs away from current farm owners but might provide safer physical and mental workplace environments instead.

4. **Summarize the growth in cellular agriculture industry, innovation, and infrastructure. What advancements still need to be made?**
   Cellular agriculture is an emerging industry that has received a lot of support in recent years. With over 200 companies as of 2023, companies continue to be established around the world with many different meat and animal product focuses and new pilot production plants. Advancements in commercial scaling and regulation continue to challenge the industry.

5. **How can cellular agriculture address inequality?**
   The potential for decentralized and democratized production and distribution of cell-cultured meat offers the chance to increase availability to more people. If cellular agriculture can contribute to reducing the effects of climate change, then disparities related to regions more affected by these environmental impacts may also benefit.

6. **What type of funding has fueled cell-cultured meat research so far and what are some pros and cons to partnering with conventional meat companies?**
   Thus far, the primary funding for cell-cultured meat has been through venture capitalists, but financial support from governments is increasing. Strategic partnerships with conventional meat companies offer a consumer base and resources such as funding but could introduce tension between industries and monopolization of the technology.

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Animals

Impact of Cultivated Meat on Land, Aquatic, and Wild Animals

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Chapter Abstract

There are over 100 billion animals in the food system today, more than 90% of which live on so-called “factory farms”. There is also a vast variety of wild-caught fish and other wildlife affected by animal agriculture. Cell-cultured meat could greatly reduce the role of animals in the food system, thus also limiting the impact on wildlife. Furthermore, widespread adoption of cell-cultured meat could also contribute to expanding humanity's moral circle to include animals to a greater degree.

Keywords

Factory farm
Gestation crates
Mollusks
Bivalves
Sentience
Donor herds
Moral circle

Fundamental Questions

1. What are the main concerns regarding the welfare of farmed terrestrial animals?

2. What are the most important issues around the welfare of farmed aquatic animals?

3. In what ways does animal agriculture impact the welfare of terrestrial and aquatic wild animals?

4. How might the growth of the cell-cultured meat industry affect the welfare of farmed animals, assuming that not all meat will be produced using cell-cultured technology?

5. What is humanity's moral circle, and how could the growth of the cell-cultured meat industry affect it?

Chapter Outline

2.1 Introduction

2.2 Life on Land
- 2.2.1 Chickens
- 2.2.2 Pigs
- 2.2.3 Cattle
- 2.2.4 Other Domestic Land Animals
- 2.2.5 Wildlife on Land

2.3 Life Below Water
- 2.3.1 Farmed Fish
- 2.3.2 Wild-caught Fish
- 2.3.3 Shellfish and Other Aquatic Animals
- 2.3.4 Indirect Effects on Ocean Life

2.4 Peace, Justice, and Strong Institutions
- 2.4.1 Recognition of Animal Sentience and Welfare
- 2.4.2 Future Herds
- 2.4.3 Extinction

2.1 Introduction

As cellular agriculture becomes more prevalent, the number of animals in the food system is predicted to decrease, perhaps leaving only donor herds. In addition to the removal of livestock, however, adoption of cellular agriculture may change the quality and quantity of life for a broad range of animals. Understanding the current state of animal agriculture is critical for projecting how this industry and its practices may change in the future as the result of cellular agriculture.

This chapter will take a close look at the impacts of cell-cultured meat production on animals, with a focus on those in the U.S. These impacts are not limited to farmed or hunted animals but apply also to wild animals that are indirectly affected by animal agriculture. Changes to the meat industry could also transform the fundamental human-animal relationship.

This chapter will cover three sections based on the United Nations' Sustainable Development Goals (UN SDG). "Life on Land" (SDG 15) examines the lives of chickens, pigs, cattle, and other land animals commonly raised and killed for food, as well as wild animals that live on land. "Life Below Water" (SDG 14) takes a closer look at various types of aquatic animals that are commonly farmed, as well as aquatic wild animals that are caught and harvested. "Peace, Justice, and Strong Institutions" (SDG 16) encompasses the philosophical and moral topics regarding animals, including animal sentience, humans' current views of animals, the use of donor herds in cell-cultured meat production, the potential extinction of farmed species, and the impact of cell-cultured meat on humanity's moral circle.

2.2 Life on Land

"Protect, restore and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss"

Several books and undercover investigations of industrial farms and slaughterhouses have documented concerning treatments of farmed animals. Much of the concern centers on "factory farms", which are referred to in some instances as concentrated animal feeding operations (CAFOs). A CAFO is defined by the U.S. Environmental

Protection Agency (EPA) as a facility that has been determined by a permitting authority to be “a significant contributor of pollutants,” to handle waste water in a certain way, and to meet certain size thresholds. A large CAFO will contain at least 1,000 cows, 2,500 large swine, 125,000 chickens, or a similar threshold for another farm animal species.[2] These CAFOs produce large amounts of food often at the expense of animal welfare. By maintaining large amounts of animals in close quarters, CAFOs prevent animals from moving and have led to the spread of disease. Mass animal culls from CAFOs have been required to attempt to stop the spread of disease such as COVID-19, mad cow disease, swine flu, and avian flu among animals in these concentrated operations.[3, 4, 5] In contrast, cell-cultured meat may require few or no animals as an isolated product grown in a bioreactor, and therefore has minimal possibility to spread disease, as pathogens in the culture could be identified and neutralized by producers before contact with consumers or animals.[6, 7]

Current estimates suggest that around 99% of all U.S. farmed animals are raised on factory farms (Table 1). Globally, this figure exceeds 90%, though there is limited data available for many countries.[8] More information on the current state of animal agriculture on different continents can be found in Part II, *The Impact of Cultivated Meat*.

Type of Farm Animal	Number of Animals Alive (approx.)	Percent Living on Factory Farms
Meat chickens	1,620,000,000	99.96%
Egg chickens	370,000,000	98.22%
Turkeys	105,000,000	99.85%
Pigs	72,000,000	98.27%
Cattle	94,000,000	70.36%

Table 1: U.S. animal agriculture statistics for 2019.[9]

2.2.1 Chickens

Chickens account for the vast majority of farmed land animals. This is due to rising chicken consumption, the ease with which chickens are factory farmed, and the fact that their small size means more animals must be raised to produce a given quantity of meat. It takes around 200 chickens to produce the equivalent amount of meat as a single cow (Figure 1).

Animal agriculture researchers have traced the first factory farm to the poultry industry, identifying it as the Mrs. Wilmer Steele's Broiler House in Delaware, which operated in the 1920s. During the early twentieth century, the U.S. was attempting to feed an increasingly urban population with small-scale farms and small-scale distribution systems. In 1923, Steele ordered 50 chicks for her small egg farm, but a delivery mistake resulted in her receiving 500. She capitalized on this opportunity, increasing production until 1926, by which time she was raising 10,000 chicks per flock for their meat and eggs.[10] Over time, demand for low-cost meat and the invention of facilitating technologies like subtherapeutic antibiotics encouraged the widespread implementation of factory farming (recall the discussion of antibiotic resistance outlined in Chapter 1, *Humanity*).

Today, there are two distinct populations of chickens. One is bred to optimize egg production, and the other for meat production. Domestic chickens have been deliberately selected for increased feed efficiency over the last century. Egg-producing hens or "layers" produce more than 300 eggs per year, while meat chickens or "broilers" have been selected for large body size, large chest muscles, and rapid growth. Selection of these traits and domestication has negative consequences on chicken welfare, notably, that broilers on certain factory farms have smaller leg bones and muscle, making them prone to break bones, as well as potentially higher rates of heart failure and susceptibility to other types of disease.[11, 12]

Over 99% of US chickens raised for meat live in factory farms.[8] There, they are confined to close quarters: each chicken has approximately 628-762 cm^2 of space, slightly more than a sheet of printer paper.[13] These birds usually live on the floors of large, crowded indoor sheds. Their fast growth and small legs cause 90% to experience trouble walking, with some collapsing under their own weight.[14,15] They can also suffer from dehydration, respiratory disease, heart attacks, and infections.[16]

Once a broiler is around 41 days old, it is sent to slaughter. A factory-sized chicken slaughterhouse in the U.S. generally operates as follows: workers gain control of a chicken from a transport crate by holding its legs, sometimes binding its ankles, and then hanging it along a conveyor belt. In some operations, the chicken is carried through a pool of electrified water, which is designed to render them immobile but not unconscious, and then its neck passes across an automated blade.[17] The final step before carving, at which point most chickens are now dead, is a hot water tank designed to defeather the bodies.

During the last several years, increased demand for chicken, combined with economic pressure, has encouraged slaughter lines to operate at faster rates. As speed increases, however, the likelihood of machine and processing errors increases, thus putting chickens at greater risk of injury and prolonged death. As of 2018, slaughter line speeds in the U.S. reach up to 175 birds per minute, leading to a larger fraction of birds having to endure broken limbs, electrocution, and submersion in hot water while still partially conscious.[18]

Although nearly all US broiler chickens are raised in factory farms, alternative raising methods are used to a larger extent in other countries. Free range farming is more common outside of the Western world. According to the Food and Agriculture Organization (FAO), 80% of farmers in Africa, Asia and Latin America raise poultry in fully or daily free-range conditions. Oftentimes, this poultry is kept for household consumption as well as commercial sale, with flocks ranging from 1-30 individuals. Cell-cultured meat will likely focus on replacing commercial factory farming rather than these small family farms. [19]

In systems where cell-cultured and farmed meat production coexist, the added supply of meat from cell-cultured production could ease economic pressure and demand by providing additional meat without the need to raise and process additional chickens. This has the potential to change the practices through which chickens are farmed, as the added supply of meat could allow for conventional chicken farming practices to become less intensive, thereby reducing possibility for error. Lower demand for farmed chicken meat could also change the selection traits for broiler chickens. However, both of these outcomes are purely speculative at this time.

In completely cell-cultured food systems, chickens would no longer be used to produce chicken meat. There is a possibility of “donor herds”, small populations of animals raised to provide cells for cell-cultured meat production. As discussed at the end of this chapter, the number of animals necessary for donor herds would probably only be in the hundreds. The welfare of these animals has yet to be determined, including whether new donation-optimal traits will be selected for, possibly creating new breeds or increasing the popularity of existing heritage breeds.

2.2.2 Pigs

Approximately 98.3% of pigs in the U.S. live on factory farms.[8] Left to their natural tendencies, some pigs will travel thousands of meters in a 24-hour period, spending much of their time exploring and foraging.[20] On many factory farms, however, pigs are often confined indoors to crates and crowded pens.

Female breeding pigs, or sows, are commonly kept in gestation crates for the majority of their lives. Only slightly larger than the animals’ bodies, the crates prevent sows from turning around or interacting with other pigs. Compared to the traditional alternative of communal pens, gestation crates allow pork producers to readily monitor each animal’s health and feed, as well as lessen aggression between pigs and prevent sows from crushing their piglets. Placed together in communal settings, sows can fight for food and establish pecking orders in which the weakest eat less, if at all, and most sows spend the majority amount of their time in individual small stalls if given the options of a communal pen and a stall. However, public sentiment is pressuring pork producers to transition away from gestation crates due to concern over the effects of long-term confinement, and several studies have documented the negative impact of confinement on sows’ physical and psychological welfare.[20,21] New automated individual rationing systems can allow each sow to receive adequate share of food in a communal setting. In these automated systems, each sow enters an automated feeding station sequentially where it is identified by a collar or ear tag or implant and given a precise ration that it eats in a specialised feeding stall that prevents other sows from entering. When the sow is finished eating, she can return to the communal setting. The transition from gestation crates to communal settings such as these, however, is expensive, and many suppliers have been reluctant to carry out their public promise to transition.[22]

Whether they live in gestation crates, stalls, or pens, both male and female factory farmed pigs are confined to a small area rather than being allowed to roam. The average space per pig is 0.7 m^2 for a pig with an average slaughter weight of 127.9 kg.[23,24] Concrete and/ or slatted floors of pens can prevent rooting, when a pig uses their nose to poke and explore, and digging. Deprived of the ability to engage in any natural behaviors, pigs on factory farms can show signs of apathy, boredom, and frustration. Researchers have observed that exploratory and foraging tendencies can be redirected into biting and in very rare conditions, cannibalism.[25]

Farmed pigs may experience violence for a variety of reasons in the pork industry. Sick or disabled piglets are often killed by "thumping," an industry term for knocking an animal unconscious or dead against the ground in order to reduce inefficiencies in resource costs. Male piglets are castrated, in some cases without anesthesia, as sexual maturation would produce an off odor to their pork. In addition, frustrated workers can occasionally inflict physical violence on the animals under their care to let off emotion.[26]

Farm alternatives to CAFOs alleviate some of the welfare challenges of CAFOs, but come with other welfare challenges. Farming that provides pigs access to a large outdoor space allows them to express a broader range of behaviors than they can in CAFOs, while bedding with straw mimics the type of bedding a pig would find in nature, reducing discomfort and injury compared to the slatted floors common in CAFOs. However, outdoor access and straw flooring complicates management of biosecurity, feeding, watering, temperature, and possibility of predators compared to CAFOs. Though pigs kept in these less restrictive farming systems seem to be less affected by respiratory diseases than those in CAFOs, parasitism and predation increases with outdoor access, and some parasites are more common in straw bedding compared to slatted floors. Biosafety measures are more difficult to implement in these environments. In addition, piglet crushing increases when the movement of sows is not restricted.[27] Each type of farming comes with its own welfare challenges.

Upon arrival at slaughterhouses, in most developed countries, pigs are rendered unconscious before slaughter.[28] This is often done with a stun bolt through the animal's head, which can involve minimal suffering if properly executed. Some operations in other nations use electrocution via two pieces of metal on the sides of their head, which can also be instantaneous, inducing minimal suffering. Sometimes pigs are stunned with carbon dioxide gas, but this method has been found to cause respiratory distress as evidenced by gasping, gagging, and thrashing behaviors. It takes an average of 60 seconds for a pig to begin losing consciousness in a 90% carbon dioxide mixture, as measured by brain activity in response to auditory stimuli.[29,30]

Pork, just like meat from chickens, can be made via cell culture. If widely adopted, cell-cultured pork may be an alternative to the transition from confined to communal pork farming that many suppliers have promised.[22] If so, pork may be produced without the violence expected of swine establishing a social order and living communally.

2.2.3 Cattle

It is more difficult to estimate at a given time the percentage of cattle living on factory farms compared to chickens or pigs, as calves raised for beef typically spend the first part of their lives on pasture and then are moved to feedlots. However, applying the same methodology used in determining the percentages of other populations living in industrialized agricultural environments, approximately 70% of cattle in the U.S. live on factory farms.[8]

Similar to the differences between “egg” and “meat” chickens, there are different traits and welfare issues for dairy and beef cattle, as well as for female and male cattle. In order for dairy cows to produce milk, they have to give birth. Usually after only a few hours from giving birth, the cow is removed from her calf. Female calves are raised in either the dairy farm in which they were born or are sold to another dairy farm, where they can produce milk once they reach breeding weight at about 15 months of age. Cows on average reproduce 2-3 times, resulting in 26 to 39 months of lactation, before they cease production and leave the herd. The leading reasons cows leave the dairy herd are low production, infertility, mastitis (inflammation of the udder), and lameness.[31] Once they leave, they are typically processed as low-quality ground beef.

Male calves are usually sold as veal calves or raised as steers (cattle grown for beef), though a small number of male calves may be used for natural breeding or for artificial insemination. Veal calves live in individual stalls to limit movement in order to make the flesh of these calves soft and suitable as a veal product.[32,33] This confinement, however, prevents calves from exhibiting natural exploration, foraging, and social behaviors. As a result, they are more likely to develop neurotic behavior, such as sucking on metal bars in lieu of their mother’s teats. In order to ensure their meat is still tender, veal calves are harvested at up to 18 weeks of age.[33]

The lives of beef cattle differ, especially in the degree of confinement. Beef cattle typically spend a majority of their life with open space to roam and exhibit natural behaviors on rangeland or pasture. During this time, they can be subject to painful procedures, sometimes without anesthesia, including castration, dehorning, and tail docking (though tail docking is more common for dairy cows than beef cows). After their time on pasture, they can be transported long distances by truck with limited food and water to be delivered to processing facilities. Upon reaching processing facilities, in the U.S., cattle are typically stunned before slaughter with a bolt through their head, an immediate and mostly painless procedure, although mistakes are possible.[34]

Meat from cows, just like chickens and pigs, can be produced with cell-cultured methods. It has been predicted that one 500 mg beef biopsy, if 35 cell doublings are achieved, could replace 20 cattle in beef production. If cell doubling improves to 50 doublings, a single biopsy could replace 13 million cattle.[35] As discussed for chickens, the added supply of beef from cell-cultured production could ease the burdens of economic pressure and demand, potentially allowing for more ethical treatment of beef cows in certain situations. No cell-cultured meat company has begun to pursue producing veal specifically, but if cell-cultured veal can eventually be produced at scale, this may reduce the use of male cattle in modern farming. Also, as is the case with chicken and pork, widespread adoption of cell-cultured meat may shift the traits selected for in cattle raised for meat. A number of cell-cultured meat companies are working with farmers of heritage cattle breeds to scale up production of these high value meats using donor samples. Future development in this area may cause promotion of more heritage breeds and other optimal donor traits over current industry-favored traits of rapid muscle growth and weight gain.

Although cell-cultured meat would not directly compete with dairy, the multiple ways in which dairy farming is interconnected with meat production will likely cause the dairy industry to be affected by cell-cultured meat production as well. There are also several cellular agriculture companies working to produce dairy products from cells.

The cell-cultured meat industry must, however, address their own reliance on cattle farming. Current research and production of cell-cultured meat often relies on including fetal bovine serum (FBS) as a component of the media fed to cells. FBS is a limited byproduct of the current cattle industry, harvested from the fetuses of cows pregnant during slaughter.[36] As cell-cultured meat increases production, perhaps resulting in reduction of farmed cattle and therefore FBS supply, media formulations without FBS will need to be a large area of research and development for the young industry.[37]

2.2.4 Other Domestic Land Animals

Though chicken, pigs, and cattle comprise the majority of farmed animals, the list of other land animals raised for food is extensive. Examples include sheep, turkeys, rabbits, goats, and ducks. The treatment of species varies widely, as does the popularity of food products derived from each animal, across various regions. As the majority of meat consumed today comes from chicken, pigs, and cattle, the focus of current cell-cultured meat research is mostly on these.[38] There are, however, a few companies working on other domestic animal products, such as duck foie gras. Foie gras is a high-value product that is facing several bans, as ducks must be force fed in order to develop the desired large, fatty liver.

2.2.5 Wildlife on Land

Animal agriculture has important direct and indirect consequences for biodiversity and the welfare of wild animals. First, conventional animal farming has a large carbon footprint contributing to climate change. Climate change will continue to affect ecosystems in terms of rainfall distribution, temperature, flooding, and sea level rise, forcing many species to either adapt or go extinct. Loss of Arctic sea ice in particular threatens biodiversity across an entire biome and beyond.[39,40,41,42,43] Animal agriculture is estimated to contribute to at least 14.5% of global greenhouse gas emissions alone.[44] Cell-cultured meat could dramatically reduce this contribution. More information on the effects of animal agriculture and cell-cultured meat on climate change, as well as other forms of pollution can be found in the *Environment and Ecological Sustainability* chapter.

Raising animals for food also displaces wild animals who would otherwise occupy the natural habitat. This is due not only to clearing of land for farm animals to occupy, but also the much larger expanses of land used to grow feed crops for farmed animals. It takes at least ten calories of plant-based food, often row crops such as corn and soy, to produce one calorie of animal-based meat.[45,46] A 2015 paper argued that, "livestock production is the predominant driver of natural habitat loss worldwide."[47] Deforestation of the Amazon Rainforest resulting from agricultural clearing is particularly concerning to biodiversity loss, threatening the 30 million animal species that live in the rainforest.[48,49,50] Theoretically, at scale, cell-cultured meat is estimated to use approximately 99% less land than conventionally produced meat.[46] Any land made available by a transition to cell-cultured meat could be used differently, or potentially left to rewild, thus repairing some of the damage to habitats.

Cell-cultured meat production may also address the UN SDG subgoal to "end poaching and trafficking of protected species" and "address both demand and supply of illegal wildlife products" by providing a sustainable and ethical source of meats that typically come from poached, trafficked, and otherwise illegal animal sources. However, the market effects of this are unclear. For example, the availability of cell-cultured products could help popularize or potentially enable poached animal products to be passed off as cell-cultured in order to avoid roadblocks of government regulation and consumer hesitation.

Legal animal hunting may also be affected by cell-cultured meat. Environmental philosopher Gary Varner identifies three types of hunting: therapeutic (hunting to secure the aggregate welfare of the target species and/or the integrity of its ecosystem by reducing overpopulation and damage the species causes to other animals, plants or elements of the environment), subsistence hunting (hunting to secure food for human beings), and sport hunting (hunting aimed at maintaining religious or cultural traditions, reenacting national or evolutionary history, honing certain skills, or pursuing a trophy animal).[51] Cell-cultured meat production may fulfill the motives of some types of hunting, most notably subsistence; a handful of cell-cultured meat companies are working towards producing wildlife meat, such as kangaroo and venison, that may allow for consumption of these meats without hunting.

In the case of commercial hunting, some animals may eventually reach live markets where they are contained in cages while waiting to be sold. Close contact between different wild species, livestock, and humans have originated several infectious diseases affecting multiple species, possibly including COVID-19. This contact is becoming increasingly common with encroachment on wildlife habitats as well as wet markets. In addition, when rare natural disasters occur, many farmers may leave their animals stranded during evacuations, with low chances of survival. In these situations, this can pose a public health threat since dead livestock, which attract pathogens and disease, can contaminate that area's water supply.[52,53,54] Cell-cultured meat, which requires little to no interspecies contact, may eliminate the risk of infectious disease spreading between species.

2.3 Life Below Water

"Conserve and sustainably use the oceans, seas and marine resources for sustainable development"

Globally, there are roughly 31 billion land animals living on farms. Although this is a huge figure, the numbers are even greater for life below water. There were between 51 and 167 billion farmed fish (finfish) slaughtered for food globally in 2017 alone, and between 0.79 and 2.3 trillion fish caught from the wild every year from 2007-2016.[55] These figures exclude shellfish like crabs and shrimp that are farmed and caught in even larger numbers.[55]

The welfare of aquatic animals is generally not as widely discussed, presumably because their physiology and behaviors compared to land animals are far less like those of humans. However, our oceans, seas and lakes contain vast numbers of animals that can feel pain and possibly emotion. For example, carp have been shown to avoid bait after being hooked previously, and other studies have revealed pain avoidance by fish. Despite this, aquatic animal welfare regulations are in general less strict than regulations for land animal welfare. The UK Animal Welfare Act, for instance, mentions aquatic animals only to say, "Nothing in this Act applies in relation to anything which occurs in the normal course of fishing."[56]

Until the 1990s, the annual global production of farmed fish was below 20 million tons, and annual wild fish capture had increased to almost 90 million tons. Since that time, however, annual farmed fish production has grown to 106 million tons in 2016, while annual wild fish capture has leveled out at between 80 to 90 million tons for three decades.[57,58,59]

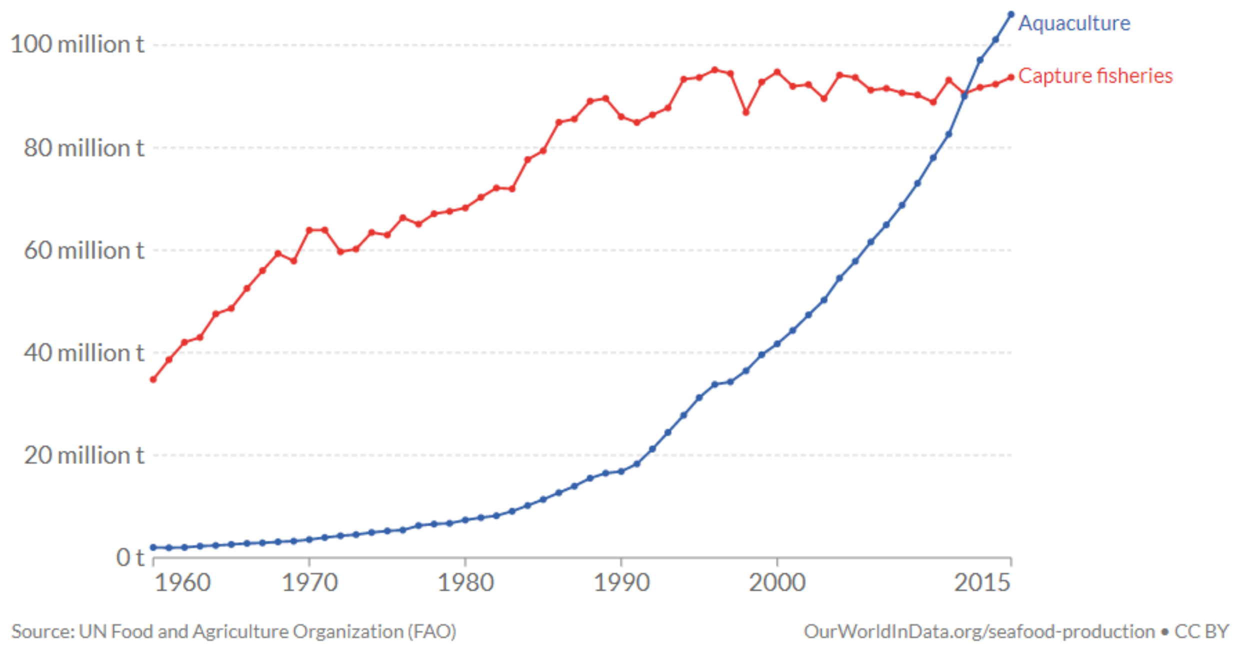

Figure 2. Annual productions by aquaculture and wild capture from 1960 to 2015, according to FAO data.[58,60]

Farmed fish production, also known as aquaculture, is increasing in proportion to wild capture because overfishing has depleted easily accessible wild fish stocks. The FAO estimated in 2015 that 33% of marine stocks were fished at biologically unsustainable levels (i.e., exploited beyond the limit at which there is a high risk of stock depletion and collapse), and 60% of marine stocks were fished at their maximum level.[61,62] This means that as the global human population increases to nine or ten billion by 2050, an animal-sourced seafood-based food system must continue to shift towards aquaculture if demand is to be met.

2.3.1 Farmed Fish

Evaluating the welfare of fish living in aquaculture is challenging. Much less data is available on the conditions, needs, and preferences of aquatic animals compared with land animals, though limited inferences can be made based on behavioral tendencies and similarities to land-animal physiology. There is also a wide variety of aquaculture businesses to consider, including at least 369 fish species and a range of farming methods based on species, location, and the animal's life cycle.[63] However, there are a number of welfare challenges common to aquaculture. Due to inbreeding, breeding for productive traits, and poor living conditions, harmful traits such as spinal curvature and other deformities, as well as increased mortality and decreased stress resilience, have become common in farmed species. High rearing densities can lead to poor water quality, aggressive behavior including cannibalism, reduced food availability, and higher disease, all of which contribute to fish stress and mortality. Fish vaccinations have decreased disease rates but can also be a welfare concern due to the stress a fish experiences while being handled, as well as potential inflammation and occasional subsequent deformations of the spine.[64] Adoption of cell-cultured seafood could relieve some of the economic pressure to farm fish intensively at high densities, decreasing the associated welfare challenges.

Fish can also be put under stress during the harvesting process. Capture from the growth pen and transfer from transport vehicle to holding pens are often stressful experiences for fish due to crowding, struggling, skin abrasions, and the poor water quality resulting from crowding. For some species, in order to avoid off-flavors and improve meat texture, fish may have restricted diets, which could result in further stress. Farmed fish are typically made unconscious in the harvesting process by suffocation (simply taking the fish out of the water, or in some cases, by adding carbon dioxide gas), hypothermia (moving the fish into ice water in order to freeze and preserve the fish meat), salt water bathing and gutting, or manual gill cutting or decapacitation, all of which are not the most efficient and painless methods of death for aquatic animals.[65] Relatively fast-working methods such as electrocution or precise blows to the head may be generally less stressful for the fish, though these methods are not always practical, for example with large numbers of small fish.[66,67]

2.3.2 Wild-caught Fish

Though aquaculture is on the rise, a large amount of seafood is still wild-caught. There are a variety of methods, nets, and apparatuses used to catch large numbers of fish. Depending on the target species, fishermen may use driftnets, which are carried across the surface using floats on top and weights on the bottom; purse seines, which are similar to driftnets, but drawn in a circle around a school of fish to trap them; pelagic trawls, which are carried through the middle of the water; bottom trawls, which are carried across the sea floor; or stationary traps. Fish may also be caught using long (up to 100 km) fishing lines with hooks, with smaller fish often being used as live bait.

Welfare challenges vary depending on the fishing method used. Fish and other aquatic animals caught in nets may be injured by being pressed against the net itself or against other caught animals. Fish and other aquatic animals caught in hooks inevitably sustain injuries from the hooks, though the frequency of more serious injury will vary depending on hook design. Fishing methods that keep the fish trapped for longer durations tend to cause more injury. When fish are captured at depths of 25 meters or deeper, the pressure and temperature change as the equipment is being pulled up can cause rupture of animals' internal organs, especially for animals who do not typically dwell near the surface.[66,67] Non-target animals that are captured usually die of physical injury or suffocation, either in the fishing equipment or on the boat. Other animals, like eels, which can survive for long periods out of water, die either from hypothermia if placed on ice or from being cut open by boat workers for meat processing.[68]

Large-scale fishing, especially trawling and bottom longlining, can capture, kill, and injure a number of wild aquatic animals other than the target species due to lack of selectivity in the fishing method. 'Bycatch' refers to the accidental capture of aquatic animals other than the target species. Bycatch species can include dolphins, turtles, other fish species, and more, and contributes to the endangerment of several species. In the US, the National Oceanic and Atmospheric Association (NOAA) has estimated that 17% of all catch is bycatch.[69] Scientists have noted that, "Fishing has accelerated and magnified natural declines in the abundance of many forage fishes and this has lead to reduced reproductive success and abundance in birds and marine mammals."[70]

Wild-capture fishing has led to the overfishing of numerous fish stocks, meaning that the amount of caught individuals from an isolated population exceeds the rate at which the population can reproduce and replenish, leading the population to decline over time. Approximately one-third of global fish stocks are now overfished. Some projections suggest that, on the current trend, 88% of fishing populations will be overfished and near depletion by 2050.[71,72] Overfishing and pollution from broken equipment on reefs also contributes to the deterioration of coral reef ecosystems, leading to further effects on species that live in the ecosystem, even if they are not overfished.[73,74,75,76] Aquaculture has decreased the rate at which stocks are overexploited by providing a different source of seafood. Further seafood production by cellular agriculture could contribute to a further decrease in overfishing.[77]

2.3.3 Shellfish and Other Aquatic Animals

Seafood consists of far more than fish. Shellfish includes crustaceans (e.g., crabs, crawfish, lobsters, shrimp) and mollusks, a group comprised of cephalopods (e.g., octopuses, squid); bivalves (e.g., clams, oysters, mussels); and gastropods (e.g., escargot, abalone). Other aquatic animals harvested for food include jellyfish, sea cucumbers, sea turtles, seals, starfish, and even dolphins and whales in rare situations. Worldwide, there were around 7.9 million tons of crustaceans produced on farms in 2016, compared to 6.7 million tons caught in the wild. The smallest crustaceans, shrimp, are also more frequently farmed than wild-caught.[78] In 2016, there were around 17.1 million tons of mollusks produced on farms and only 6.3 million tons wild-caught. However, cephalopods (squid, cuttlefish, and octopus) are almost exclusively wild-caught, totaling approximately 3.6 million tons.[78] Wild-caught crustaceans are typically caught in nets, bags, or traps. Unlike fish, crustaceans typically live for long periods after being taken out of the water. They usually only die once they are manually cut in a processing facility, or boiled in the case of lobsters.[79]

Farmed crustaceans can face similar welfare issues as farmed fish, including high stocking density and low water quality. In certain operations, they can also endure painful treatment such as eyestalk ablation, in which female shrimp have their eyestalks cut off or destroyed so they will reproduce more quickly.

The most commonly wild-caught class of mollusks are cephalopods.[77] Cephalopods are typically caught by trawling, though artisanal traps and 'jigging' (where a bait is put on a hook and the squid strikes at the 'prey' with its tentacles and becomes hooked) are also used.[80] Non-cephalopod mollusk capture involves dredge-harvesting, which may scrape the seafloor for mollusks and can damage habitats. Cephalopods, in particular octopi, have shown behaviors that suggest sentience and ability to feel pain, including tool use, complex problem-solving, and strong emotions. This has prompted objection to some current octopus harvesting techniques.[81,82] As cephalopod fishing rates continue to increase alongside fishing rates overall, the negative effects of this type of commerce will continue to grow.

Farmed bivalves, the most commonly farmed mollusk subgroup,[83] may be the animal-sourced protein with least animal welfare concerns. Bivalves display simpler behavioral patterns than almost any other animal, such as simple responses to specific stimuli, which some scientists argue puts them in the same tier as plants.[82] Unlike other farmed species, most bivalves do not require fishmeal feed and can instead benefit ecosystems by acting as filter feeders, feeding by straining suspended matter and food particles from water. Filter-feeding can counter the effects of eutrophication, which is excessive richness of nutrients in the water, frequently due to agricultural runoff from the land, causing a dense growth of plant life and death of animal life from lack of oxygen. They can also filter other materials and pollutants, thereby improving water quality and restoring shallow water ecosystems.[84,85] There is, however, a limit to how intensively bivalve farming can operate before biodeposition by the bivalves, food (plankton) depletion in the water column due to bivalve grazing, and alteration of nutrient and oxygen fluxes negatively affect other species in the habitat.[86] In addition, non-native farmed bivalves can introduce native species to new diseases and outcompete native species for resources.[87,88] An example of this is when Pacific oysters were brought to the U.S. East Coast, they brought the parasite *Haplosporidium nelsoni* (MSX), which causes minimal disease in adult Pacific oysters, but is fatal to the native Eastern oysters, contributing to population decline of Eastern oysters in many areas of the east coast.[89] Bivalves may be one of the least urgent targets for cellular agriculture due to their beneficial environmental impact in small numbers, but could become a more important target if there is demand beyond the carrying capacity or the native habitats of a species.

2.3.4 Indirect Effects on Ocean Life

Even when they are not directly captured or farmed, marine wildlife can be indirectly affected by changes in seafood demand and production caused by the adoption of cell-cultured seafood. Intensive fishing has far-reaching impacts on marine animals. Overfishing even one stock can disrupt the food chains it is a part of and empty its ecological niche. For example, recent studies suggest that overfishing of large shark species has had a ripple effect in the shark's food chain, increasing the number of species, such as rays, that are usual prey for large sharks, which in turn results in declining stocks of smaller fish and shellfish favored by these rays. With 33% of marine stocks fished at biologically unsustainable levels, and 60% of marine stocks fished at their maximum level in 2015, there are indirect effects on countless wildlife that interact with the fished stock throughout their various ecosystems.[59] Certain types of intensive fishing can also damage the habitats of marine life. Fishing by trawling destroyed approximately 454,000kg (1,000,000lb) of corals and sponges between 1997 and 1999 in Alaskan waters alone, affecting many animals that occupy those habitats.[89]

The fishing industry also loses or discards a large amount of equipment into the sea each year, much of it plastic.[89] A recent study has estimated that 5.7% of all fishing nets, 8.6% of all traps, and 29% of all lines are lost around the world each year, or 26 units of equipment per vessel each year.[90] This amount and type of waste has a large impact on marine life. Plastic debris can entangle or be ingested by wildlife, causing them to get sick and starve. Lost fishing equipment, however, has a disproportionately high impact on marine wildlife through "ghost fishing," capturing and injuring marine animals, which further contributes to overfishing.[89,91,92] In addition, fuel leaks and spills from fishing vessels can cause marine life to suffer endocrine/hormone disruptions, hypothermia, drowning, and death.[93]

While aquaculture relieves some of the pressures of wild capture, the rise of aquaculture has come at its own cost for marine wildlife. During the early days of aquaculture intensification, biodiverse but fragile mangrove habitats were converted into farms, threatening the many species that live in the mangroves and that use them as nursery grounds. Although the use of mangroves for aquaculture has since been largely banned, habitat loss is still a concern. Construction of ponds disrupt habitats in coasts, marshlands, and inner agricultural land by salinating the water and soil.[62,64,95,96,97]

Furthermore, animal agriculture, both marine and land, affects wild marine animals through the accidental release of pollutants and farmed fish. Outputs of agriculture include antibiotics, metabolic waste, such as ammonia, feces, urine, pesticides, and unused feed that cause eutrophication and subsequent algal blooms. These algal blooms limit light penetration, raise pH, produce toxins, and deplete oxygen, leading marine life, both farmed and wild, to starve and suffocate in marine dead zones.[98,99,100] For aquaculture in particular, antibiotic use is a concern. The combination of high density and poor water quality in aquaculture increases the likelihood of pathogen outbreaks, leading to reliance on antibiotics and other supplements. Depending on the type of aquaculture, antibiotics can move outside the farm and pose a toxicity risk to surrounding wildlife, while also possibly promoting selection of antibiotic-resistant bacteria.[101,102,103] In addition, escape of farmed fish in marine aquaculture poses a threat to native species. Tens of thousands to millions of farmed fish escape each year due to technical issues.[95] In rare cases, escaped farmed fish can upset balances in local food chains and transmit diseases and parasites such as sea lice. Non-native farmed fish may also compete with native species.[62,64,96,97] The probability of fish escapes at a regional scale increases with fish production intensity, either as a result of increases in farm fish density or in the number of farms.[104,105] Alternative methods of seafood production may decrease the risks of pollution and escaped fish from aquaculture by lessening the need for high-production intensification.

Animal agriculture currently relies on the fishing industry to supply the materials for animal feed. Farmed fish and land animals are often fed wild-caught smaller fish as direct feed, fish meal, and fish oil. Currently, 20% of the total quantity of fish caught around the world are rendered into fish meal and fish oil every year. Fish meal production is mainly sourced from forage fish species, which play a vital role in ecosystems by transferring energy from primary producers to higher trophic-level species including large fish, marine mammals and seabirds. Thus, the fish caught for fish meal production potentially represent a loss in production of higher trophic-level species.[106] Cell-cultured fish meal and fish oil could decrease this reliance on wild fish stocks while providing the same nutritional benefits.

Seafood is a promising target for cell-cultured meat production. As demand for many types of seafood is greater than the available supply and accelerating, there is reason to believe that the transition toward cell-cultured seafood may occur more rapidly than for meat, poultry, and dairy products, for which production has largely kept pace with increasing demand.[107] Several cell-cultured seafood companies are developing products from species that are on the brink of extinction due to overfishing, including bluefin tuna and fish maw. Other early targets are carnivorous fish that are commonly fed smaller fish in farms, such as salmon and trout. Cell-cultured seafood could replicate high-value products such as intact muscle tissue of fish, shellfish, mollusks, and crustaceans.[107] In the future, cell-cultured fish meal and oil could also decrease the dependence of aquaculture on wild-caught feed fish. Cell-cultured products could address rising demand without the need for overfishing or more intensive versions of aquaculture.

Cellular agriculture should also have a much-reduced impact on marine life due to pollution or habitat disturbance. It is unclear at this time whether production will use antibiotics that could pollute marine environments. However, unlike animal agriculture, cellular agriculture would not produce biowaste like manure, blood, pus, and mucus. In addition, a number of companies are working on media recycling to minimize the amount of unused feed that could pollute marine environments. For some cell-cultured meat production systems, for instance, nitrogen-fixing species of cyanobacteria could be selected as a nitrogen source to reduce the use of synthetic nitrogen fertilizer that contributes to eutrophication.[108]

In a broader context, research for cell-cultured seafood development may provide greater understanding of marine animal physiology to the benefit of individual species. Scientific knowledge of marine animal physiology is greatly lacking compared to that of land animals. As cell-cultured seafood provides new incentives to explore this area, it is likely that new strategies will arise for developing immortalized or long-term marine cell lines, as well as new knowledge on the fundamental metabolic and growth requirements of marine animal cells. This research could also have further applications in improving marine animal welfare, such as facilitating the study and treatment of diseases affecting them.[107,109]

2.4 Peace, Justice, and Strong Institutions

“Promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels”

Throughout history, societies have considered different groups to have varying degrees of rights to peace, justice, freedom, and equality. These groups have been defined based on gender, race, class, nationality, and other characteristics. Early in human history, humanity expanded their scope of moral concern from their families and clans to include other people in their nation-states. In the current century, people integrate morals, laws, and social norms into global societies. There is increasing concern for individuals with marginalized statuses within nation-states, including race, gender, class, age, and disability. Moreover, as discussed in this chapter, there is rapidly increasing concern for animals.[110]

Today, some believe that humanity should extend rights to nonhuman animals at varying degrees based on their sentience, or capacity to have feelings and to be aware of a variety of states and sensations such as pleasure and suffering. Cell-cultured meat could play a role in facilitating this extension of rights to other species.

2.4.1 Recognition of Animal Sentience and Welfare

Scientific recognition of animal sentience has been a complicated process involving thousands of years of research and debate. Over time most animals have become globally recognized by scientists as *sentient*, or having some capacity to have feelings and to be aware of a variety of states and sensations such as pleasure and suffering.

Philosophers since the Ancient Greeks have debated whether animals were sentient. Plutarch, Hippocrates and Pythagoras were all advocates for the fair treatment of animals based on their understanding of the capacity of animals to feel pain and suffer, but Aristotle asserted that only humans had rational souls and that nonhuman animals had only instincts. In the 18th and 19th centuries, a number of philosophers studied the ability of animals to suffer and reason. During this time, the English veterinarian William Youatt wrote of animals having senses, emotions and consciousness; he noted that various animals demonstrate sagacity, docility, memory, association of ideas, reason, imagination and the moral qualities of courage, friendship and loyalty.[112] Through much of the 20th century, however, the concept of sentience fell out of favor as behavioral scientists rejected any study of animal feelings as subjective, instead focusing on observable physical behaviors. When animal behaviorist Donald Griffin published his book *The Question of Animal Awareness* in 1976, he faced backlash for addressing the topic with a word like "awareness."[113] In 1992, biological psychologist Dr. Sonja Yoerg said that research on animal sentience "isn't a project I'd recommend to anyone without tenure." With rising interest in animal welfare in intensive farms, however, behavioral scientists gradually came to recognize welfare as a term that embraced both the physical and mental well-being of the animal. In 2009, the Lisbon Treaty, which amended the Treaty on the Functioning of the European Union (TFEU), introduced the recognition that animals are sentient beings.[113,114] Finally, in 2012, a prominent international group of neuroscientists authored the Cambridge Declaration on Consciousness, which declared that "the weight of evidence indicates that humans are not unique in possessing the neurological substrates that generate consciousness."[115] There is mounting evidence that animals other than humans exhibit varying degrees of sentience.

Cellular agriculture may facilitate a new step in the recognition of animal sentience and subsequent moral circle expansion. Eating meat can lead to feelings of cognitive dissonance, a psychological conflict resulting from incongruous beliefs and attitudes held simultaneously, resulting in inconsistency ("I eat meat; I don't like to hurt animals"), aversive consequences ("I eat meat; eating meat harms animals"), or threats to self image ("I eat meat; compassionate people don't hurt animals"). People typically work hard to avoid accepting things that cause them to question their actions, beliefs or attitudes.[116] Psychologists based in Australia conducted an experiment in 2011 with two groups of college students. Some students were told they would be eating beef or lamb, and the others were told they would be eating apples or nuts. Students who expected to eat animal products later tended to express the belief that farmed animals have fewer mental faculties such as intelligence and sentience.[117,118] This seems to be a mental defense mechanism. People recognize there is an issue with eating sentient beings, so adopting the belief that animals have fewer mental faculties helps them believe that their choice to eat meat is not wrong. Thus, people are held back from acting towards or caring about animal welfare when they rely on animals for food.

When it comes to farmed animals, a 2017 poll by the Sentience Institute found that 87% of Americans agree with the statement, "farmed animals have roughly the same ability to feel pain and discomfort as humans." The same poll found 69% in agreement with, "the factory farming of animals is one of the most important social issues in the world today." It also found large support for radical policy change, including 47% of U.S. adults supporting a ban on slaughterhouses and 33% supporting a ban on all animal farming.[119] Given these widespread beliefs, offering the option to eat meat without involving animals could play a role in causing widespread change around how people treat and think of animals.

Cell-cultured meat could thus encourage a society-wide psychological shift. There has historically been a relationship between technological progress and social change, such as the reduction of whaling by changes in how oil was sourced and progress in female empowerment through oral contraception development. If more people consume cell-cultured meat in place of animal-sourced meat in the future, this could reduce the need for us to engage in dissonance-reducing strategies, allowing humanity the freedom to more directly care about animals.

If cell-cultured meat plays a role in allowing this freedom and reduces the pressure to intensify animal agriculture, it could be easier to instate popularly supported agriculture reforms. For example, at least 76% of Americans support each of the following: switching to livestock breeds with higher welfare, ending live-shackle slaughter, ending extreme crowding, and improving chicken welfare, even if that increases chicken meat prices.[120] Ballot measures for welfare laws in various U.S. states consistently get majority votes, including a 78% approval for Massachusetts's 2016 cage-free law.[121] It is likely that many people would vote for a ban on CAFOs if cellular agriculture is eventually able to produce the same products at similar or lower prices.

A newfound freedom to care about animals may extend beyond those animals that humans consume. There is a growing movement of people curious about how to reduce the suffering of animals regardless of the source of that suffering. After the welfare of farmed animals is addressed, animal welfare efforts could expand towards reducing the suffering of wild animals, from birth control to disease management, or to expand our moral circle to care about all animals.[122] Humanity's moral circle, consideration of sentient beings, and animal welfare efforts may look very different if cell-cultured meat is one day widely adopted.

2.4.2 Future Herds

Cell-cultured meat production could theoretically render animal-sourcing of meat unnecessary through infinite cell replication. In a scenario where animals are no longer farmed for meat, a small number of animals could be kept for sourcing cells, research purposes, maintaining a healthy population of the species (both in terms of genetics and social dynamics), companionship, or separate production systems in regions without sufficient trade connections. In this scenario, the welfare of those animals will be an important moral consideration.

Companies may choose to use non-immortal cell lines rather than immortal cell lines due to concerns around the safety of immortal cell lines, which typically either come from tumors or are made using genetic engineering. If non-immortal cell lines are used for cell-cultured meat production, small donor herds that provide initial biopsies for cell-cultured meat will be required. Extracting cells from 'donor' animals may be relatively painless. It could involve subduing an animal, putting it under anesthesia, and taking a small biopsy.[33] Or, it could be as simple as a swab of saliva or using feathers that have fallen off an animal, depending on the capacity to differentiate sample cells into the desired cell type. Donor animals could live to their full lifespan and experience a natural death or may also be harvested for meat once they are unable to produce biopsies of a certain quality due to age or disease.[35,123] With fewer animals required, donor herds would likely receive more individualized care than in CAFOs. There may also be public viewings and tours of these herds so that the public can be knowledgeable about the conditions of the animals and the process in which their meat is made, a reversal of the current lack of closeness and knowledge allowing omnivores to eat animal-sourced meat with reduced cognitive dissonance.

Outside of donor animals, the transition of herds from current animal agriculture will need to be considered. If cell-cultured meat begins to replace animal-sourced meat rather than just addressing growing demand, farm animals may no longer be profitable to keep. In that case, farmers may choose to breed fewer animals each year, and (depending on the speed of this economic change) existing farm animals would be bought off, slaughtered for meat immediately, released, or put in rescues. Animal sanctuaries such as Farm Sanctuary and Animal Place already rescue and care for thousands of farmed animals, and could need to expand dramatically to facilitate a humane transition from animal agriculture to cellular agriculture. Even if it becomes unprofitable to continue slaughtering animals for meat, however, more animals than are required only for donor biopsies may still be farmed. At a minimum, to ensure the continued existence of a domestic species dependent on humans, it would be necessary to raise herds large enough such that inbreeding and limitations to evolutionary change are not concerns.[124] Further research is required, however, to determine this minimum viable population for livestock breeds.

Tomorrow's herds may look and grow very differently from those farmed today. It might not be desirable to perpetuate the existence of the most common breeds. Many current farm animals endure pain due not only to their treatment, but also because they have been bred to quickly produce extreme amounts of meat at the cost of their health. In a cell-cultured meat system, the concentration and quality of the target cell type, not fast growth, would be the traits for which the system is optimized.[123] Donor herds may therefore be optimized for their capacity to provide cell samples, which would have an unknown effect on their welfare. Reduced pressure on animal agriculture may also shift the breeds of animals kept in animal agriculture. Rather than being optimized for their food-production ability, these animals may be returned to heritage breeds or bred for optimal animal welfare, although all of this is still speculation. The characteristics of animal breeds used in the future will undoubtedly be affected by the evolving science and economics of cellular agriculture.

2.4.3 Extinction

While donor herds would likely still be maintained for large-scale cellular agriculture operations, the number of animals required could be a mere fraction of the

100 billion farmed animals required to produce food today. Depending on a few factors, such as whether cell-cultured meat ends up displacing all conventional meat production, whether donor herds are used, and whether people keep farmed animals for non-farming purposes, there is a possibility that farmed animal species could face extinction, which would have new ethical implications.

In part, these ethical implications will depend on the intrinsic value assigned to individuals or species. Intrinsic value is the value that an entity harbors within itself, for what it is. In comparison, instrumental value is the value that something has as a means to a desired or valued end, such as the value of farmed animals for providing meat. While some place intrinsic value on a species, meaning that they value the species itself rather than the individual animals who make up that species, others argue that what constitutes the good of species and ecosystems often is only a by-product or aggregate of that of individual organisms.[125] If domestic farm animals do not contribute value to other species or to ecosystems, there may be little intrinsic value in domestic farm species.

The ethical implications will additionally depend on whether it is considered that farm animals have, or are capable of having, lives worth living. Given the welfare issues that exist in current breeds, some may argue farmed animals' quality of life is less valuable than their nonexistence, even with significant improvements in farming practices. Of course, if farmed animals have lives worth living, then extinction or reduction as caused by cell-cultured meat could deny animals those lives. Thus, any value of the species needs to be weighed against the combination of suffering and pleasure an individual can experience throughout their life. It is unclear, currently, how to best simultaneously consider positive and negative experiences to determine whether a life is worth living.[126]

Matters get further complicated when the effects of the eradication of animal agriculture on other individuals are considered. Cell-cultured meat systems would probably use far less land (see Chapter 3), so what would happen to the land used now for farms and cropland to feed livestock? If humans live on that land, what kind of lives will they lead and how would other animals be affected by their settlement? If that land is rewilded, what kind of lives will wild animals gain access to? How will these land uses affect the economy and the land's ecological footprint? These are all important questions, and they are only a small sample of the complexity that comes with trying to estimate the long-term impacts of changes in the massive and interconnected industry of meat production.

Fundamental Questions – Answered

1. **What are the main concerns regarding the welfare of farmed terrestrial animals?**
   The most important issues regarding the welfare of farmed terrestrial animals are confinement in close quarters, artificial breeding at the expense of health, inhibition of natural behaviors, and infliction of pain, including slow slaughter methods. Confinement of large numbers of animals in close quarters, such as each chicken raised for meat having hardly more space than a piece of printer paper, limits animal movement and can facilitate the spread of disease. Artificial breeding that optimizes for high amounts of meat, milk, and eggs, will do so at the cost of other traits, in particular, heightening the risk of disease such as heart attacks and also make it difficult for individuals to move. The inability to move due to confinement and breeding inhibits natural behaviors in animals such as pigs who are not allowed to roam, explore, or forage. Finally, farmed animals experience pain throughout the growing process, from castration without anesthesia to inefficient and slow slaughter that can leave the animal alive until late in processing.

2. **What are the most important issues around the welfare of farmed aquatic animals?**
   The most important issues regarding the welfare of farmed aquatic animals are high stocking density that leads to poor water quality and aggressive behavior and disease, treatment and breeding that result in deformities, restrictive diets, and painful harvesting. Similar to terrestrial animal farming, the optimal practices for production tend to be at odds with what is best for animal welfare.

3. **In what ways does animal agriculture impact the welfare of terrestrial and aquatic wild animals?**
   The most important issues regarding the impact of animal agriculture on the welfare of wild animals are reduction in biodiversity, habitat loss, pollution, and painful hunting or fishing methods. Animal agriculture is a significant contributor to climate change, which is forcing species to either adapt or go extinct. Clearing habitats for agriculture puts additional stress on species, as does agricultural pollution of remaining habitat. Wild animals are also hunted or fished in ways that can cause stress and pain before death, and in some cases have been hunted to the point of endangering the survival of the population or species. Keeping wild animals in close contact with other species in markets, or due to the habitat encroachment of hunters or agriculture, can cause diseases that affect multiple species.

   Welfare challenges for aquatic animals include painful capture and death, unsustainable depletion of fishing stocks due to overfishing and bycatch, and indirect effects of biodiversity loss and pollution. Captive aquatic animals will experience pain from fishing hooks or extreme pressure changes from being pushed against the net and from being pulled from their high pressure environment to the low pressure surface. Captive aquatic animals usually die of physical injury or suffocation, either in the fishing equipment or on the boat. Other animals, like eels, who can survive for long periods out of water, die either from hypothermia if placed on ice or from being cut open by boat workers for meat processing. Depletion of fishing stocks due to overfishing and bycatch are also endangering species survival, lessening biodiversity. More than one-third of global fish stocks are now overfished. Overfishing even one population can disrupt the food chains it is a part of and deplete its ecological niche. Large-scale fishing can catch huge numbers of animals other than those intended for sale, with 17% of all U.S. catch being bycatch. Habitat pollution with lost or discarded fishing equipment also contributes to the deterioration of aquatic ecosystems, leading to further effects on species who live in the ecosystem. For example, animals can ingest or become entangled in the plastic debris. Escaped farmed fish, agriculture outputs, and fuel pollution from ships can also endanger aquatic animals and change their habitats. Aquatic wildlife therefore face welfare concerns directly through fishing, as well as more indirectly from aquaculture and terrestrial agriculture.

4. **How might the growth of the cell-cultured meat industry affect the welfare of farmed animals, assuming that not all meat will be produced using cell-cultured technology?**
   Technological advances in cellular agriculture, via research on animal physiology, cells, and more, could lead to advances in medical treatment for farmed animals.

   Cellular agriculture could meet some or all of the demand for animal products. If the pressure for animal agriculture is reduced, then fewer animals may be farmed, and animal agriculture could change to reprioritize the welfare of the remaining farmed animals. This is especially true if cell-cultured meat displaces intensive farming such as factory farms, which could mean that the animal agriculture that continues to exist is non-factory farm. A wider psychological shift could also occur: people may no longer feel cognitive dissonance between their care for animals and their desire for meat, and so our moral circles may expand to care more for all animals.

   Other impacts are more uncertain. Depending on whether immortalized cell lines are used, cellular agriculture may have its own need for small herds of donor animals. The welfare of animals in donor herds has yet to be determined, including whether new donation-optimal traits will be selected for, possibly creating new breeds or increasing the popularity of existing heritage breeds. In addition, it is unclear what might happen to the animals no longer needed if cellular agriculture becomes dominant. If the transition is fast, animals may be abandoned or culled, or farmers may give them to animal rescues or shelters. If the transition is slow, farmers may gradually raise smaller and smaller herds without much disruption to the lives of the animals farmed.

5. **What is humanity's moral circle, and how could the growth of the cell-cultured meat industry affect it?**
   The moral circle can be defined as the scope of living beings whose interests matter in our social structure. Over the past few centuries, Western society's moral circle has expanded to include people of different gender, race, nationality, and other demographics. If in the future people eat cell-cultured meat instead of conventional meat, then moral circles could widen to include animals that are no longer just seen as sources of food.

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Environment

Impact of Cultivated Meat on Ecological Sustainability

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Chapter Abstract

Agriculture and livestock production are major contributors to environmental change. This section discusses how cell-cultured meat could contribute to the United Nations' Sustainable Development Goals (SDGs) related to the environment. If cell-cultured meat replaces livestock production, especially beef, it has potential to reduce greenhouse gas emissions, land use, water use, and pollution of air and waterways. Due to the lower land use requirements compared to livestock production, cell-cultured meat could reduce deforestation and contribute to the conservation of biodiversity. As cell-cultured meat production technologies require further development before the products are widely available to consumers, it is questionable how much the technology will be able to contribute to the SDG targets set for 2030. While a complete reliance on cell-cultured meat to solve the environmental issues of food systems is not realistic, continuing to develop this technology to improve food system sustainability is a valuable step forward.

Keywords

Environment
Climate change
Biodiversity
Land use
Pollution
Emissions
Sustainability

Fundamental Questions

1. What are the possible environmental benefits of cell-cultured meat compared with conventional meat production?

2. Which SDGs associated with environmental issues can cellular agriculture help to tackle?

3. What are the potential downsides of cell-cultured meat regarding environmental issues?

4. Which are the main uncertainties regarding the impact of cellular agriculture?

5. How is waterway pollution impacted by livestock agriculture, and how could this be affected by adopting cellular agriculture?

6. How might cell-cultured meat production affect water resources?

7. How could cell-cultured meat contribute to achieving SDG 11, Sustainable Cities?

8. In which ways might cell-cultured meat affect mineral and fossil-fuel use?

9. How might cell-cultured meat affect food loss and waste?

10. How could cell-cultured meat production affect greenhouse gas (GHG) emissions compared to livestock meat?

11. How can cell-cultured meat impact SDG 14, Life Below Water?

12. What influence could cellular agriculture have on SDG 15, Life on Land?

Chapter Outline

3.1 Introduction

3.2 SDG 6: Clean Water and Sanitation

3.3 SDG 11: Sustainable Cities

3.4 SDG 12: Sustainable Consumption and Production

3.5 SDG 13: Climate Action

3.6 SDG 14: Life Below Water

3.7 SDG 15: Life on Land

3.8 Conclusion

3.1 Introduction

This chapter will discuss how cell-cultured meat could contribute to the environmental issues addressed in the United Nations' Sustainable Development Goals (SDG). The chapter is divided into six sections, each of which corresponds to one of the primary SDGs that are associated with the environment. The section on SDG 6, Clean Water and Sanitation, describes how cellular agriculture can curb water use and minimize waterway contamination as well as contribute to a sanitary food supply and healthy communities. The section corresponding to SDG 11, Sustainable Cities and Communities, discusses how cellular agriculture could impact air quality worldwide. The section on SDG 12, Sustainable Consumption and Production, describes how cellular agriculture could conserve natural resources and reduce food waste and demonstrates how integration of cellular agriculture technology can allow large companies to prioritize sustainability without threatening food production. The section on SDG 13, Climate Action, explains the potential of cell-cultured meat to contribute to the mitigation of climate change. The section discussing SDG 14, Life Below Water, describes how cell-cultured meat could contribute to conserving oceans, seas and marine resources. Finally, the section on SDG 15, "Life on Land" explains the potential contribution of cell-cultured meat to sustainable use of terrestrial ecosystems and conservation of biodiversity. As the directives of the SDGs overlap in some cases, a few of the environmental impact categories can be linked to more than one SDG. In order to avoid repetition, each environmental issue is discussed only in relation to the SDG to which it pertains most. The links between different environmental issues and SDGs are illustrated in Figure 1.

As cell-cultured meat production is still largely in the research and development stage, the current understanding of environmental impacts of the technology come from prospective modeling-based studies that have various degrees of uncertainty. The actual impacts will depend upon the types of systems developed for commercial scale production, ingredients used for the growth media, and the scale of adoption of the technologies. In this chapter, the possible environmental impacts of cell-cultured meat are discussed based on the assumption that the technology will be possible to scale up to commercial production in an economically feasible and resource-efficient way. Future research is key to reducing this uncertainty.

	Climate change	Ocean acidification	Nutrient emissions	Freshwater use	Land use	Energy use	Mineral resource use	Biodiversity	Food waste /loss	Air quality	Plastic waste
SDG6: Clean water and sanitation			x	x							
SDG11: Sustainable cities and communities					x					x	
SDG12: Sustainable consumption and production	x	x	x	x	x	x	x	x	x	x	
SDG13: Climate action	x				x						
SDG14: Life below water	x	x	x					x			x
SDG15: Life on land	x				x			x			

3.2 SDG 6: Clean Water and Sanitation

UN SDG Indicator 6.3 *"By 2030, improve water quality by reducing pollution, eliminating dumping and minimizing release of hazardous chemicals and materials, halving the proportion of untreated wastewater and substantially increasing recycling and safe reuse globally."*

UN SDG Indicator 6.4 *"By 2030, substantially increase water-use efficiency across all sectors and ensure sustainable withdrawals and supply of freshwater to address water scarcity and substantially reduce the number of people suffering from water scarcity."*

Fecal matter and chemical runoff from conventional animal agriculture are significant contributors to water pollution. In many places, the extent of this pollution is not only an environmental hazard but is also a threat to human and animal health. Livestock manure contains nutrients (nitrogen, phosphorus and potassium), residual antibiotics, heavy metals, and pathogens, which can leach into the environment and risk human health if they end up in waterways. The UN estimates that livestock are responsible for approximately 30% of nutrient emissions into freshwater resources globally, as well as 37% of pesticide and 50% of antibiotic emissions into waterways in the United States (US).[1]

Another major problem with animal agriculture is the large number of animals concentrated on relatively small areas of land. This is contrary to pre-industrial animal agriculture, during which, animals were not as tightly quartered, so there was sufficient feed on local grazing land. However, due to industrial trends to maximize animal quantity on modern farms, livestock feed must now be imported, as there is not sufficient feed onsite. Feed has to be transported long distances and is even imported from other countries in some cases. As the animals are not able to utilize all of the nutrients from feed, some portion of this

[1] Livestock's long shadow, http://www.fao.org/3/a0701e/a0701e04.pdf

ends up in the manure and urine. In smaller scale, mixed farming systems that are able to produce all feed for the on-farm animals, the excreta can be used as a fertilizer on the fields for the feed crops, allowing nutrients to cycle throughout the farm efficiently. Large livestock farms that import feed are not able to utilize manure as artificial fertilizer, as field areas near the farms are often not sufficient for spreading all of the manure without overloading the fields with nutrients. Therefore, in the worst cases, manure may be stored in open lagoons next to livestock farms or applied to fields in mismanaged, excess amounts. In both cases, the nutrients, chemicals, and pathogens may end up in waterways and disturb the chemical balances of the water ecosystems and/or contaminate surface and groundwater resources.

Furthermore, the excess nitrogen and phosphorus in waterways cause eutrophication, which is an increased growth of water plants and algae that can have detrimental impacts on certain fish species. In the US, for example, excess nitrogen from farms traveled from plainland rivers to the Gulf of Mexico. Once in the ocean, nitrogen causes algae to proliferate rapidly. These large algal blooms deprive other aquatic life of oxygen, creating annual "dead zones". At 8,776 square miles–approximately the size of New Jersey–the 2017 dead zone in the Gulf of Mexico was the largest ever recorded.[2]

Evaluations of private wells near large-scale livestock farms have found water contaminated with high levels of nitrates, which can be dangerous to consume, especially among vulnerable populations such as young children.[3] Similarly, fecal bacteria and pathogens from livestock units can cause contamination of drinking water.

Cell-cultured meat offers the potential to help eliminate the problems associated with excess animal manure, as manure would be produced only in small quantities by the donor herds. In cell-cultured meat, the main potential sources of water pollutants are related to the production of growth medium ingredients and the waste from the cell-cultured meat facilities. The water pollutants from making growth medium ingredients depend on the type and quantity of ingredients used. If agricultural crops, such as corn, are used as the glucose source for the cell-cultured cells, some eutrophication may result from the agricultural field sources. As the cell-cultivation processes are closed

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[2] "Gulf of Mexico Dead Zone is the largest Ever Measured." *National Oceanic and Atmospheric Administration.* https://www.noaa.gov/media-release/gulf-of-mexico-dead-zone-is-largest-ever-measured

[3] Hriber, C. (2010). *Understanding Concentrated Animal Feeding Operations and Their Impact on Communities*, National Association of Local Boards of Health, https://www.cdc.gov/nceh/ehs/docs/understanding_cafos_nalboh.pdf

systems, the nutrient emissions can be controlled by cleaning wastewater before it is released to waterways. A study estimated that cell-cultured meat could have 97% lower eutrophication impact compared to beef produced in the US, and 70% lower compared to pork, whereas, compared to poultry, this impact was roughly the same (Figure 1)[4].

In the 1800s, transportation was largely supplied by horses. The widespread use of these animals produced an enormous amount of feces, particularly in some of the most populated American cities. Waste commonly piled up in the streets without any easy way to remove it. At its peak, New York had approximately 100,000 to 200,000 horses. In addition to piles of excrement, the horse population also meant carcasses and flies, which, coupled with increasing population density, posed a risk for the spread of disease. In 1898, city planning experts gathered in New York City to figure out how to solve this problem. However, despite their effort, the experts were unable to come up with a solution, and the meeting disbanded after only three days, with no foreseeable steps forward. In 1908, Henry Ford introduced the Model T private automobile. As the price of horse feed rose, more and more people turned to this burgeoning new technology. Fast forward just a decade to the 1910s and cars powered by fossil fuels, rather than horses, were a faster, cheaper method of transportation for city dwellers (Figure 2). Today, horses and carriages are largely relegated to tourist attractions.[5] As a result of this sudden and transformative technological shift, the seemingly unsolvable feces problem that plagued American cities quickly dissipated.

In addition to minimizing water pollution, cell-cultured meat has the potential to reduce water use requirements for meat production globally. The World Health Organization (WHO) states that at least two billion people globally lack access to an uncontaminated drinking water source. They also predict that by the year 2025, half of the world's population will be living in a water-stressed area.[6] According to a 2010 report, animal agriculture consumes almost 2.5 billion cubic meters of water annually, with a third of this volume being used in the beef

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[4] Mattick, C.S., Landis, A.E., Allenby, B.R., and Genovese, N.J. (2015). Anticipatory life cycle analysis of in vitro biomass cultivation for cultured meat production in the United States. Environmental science & technology 49(19), 11941-11949.

[5] Doochin, D. (2016). *The First Global Urban Planning Conference was Mostly About Manure.* Atlas Obscura. https://www.atlasobscura.com/articles/the-first-global-urban-planning-conference-was-mostly-about-manure

[6] Drinking Water Key Facts (2019, June 19) *World Health Organization* https://www.who.int/news-room/fact-sheets/detail/drinking-water

cattle sector and nearly a fifth for the dairy cattle sector.[7] A corroborating 2013 study found that agriculture accounts for 92% of the freshwater footprint of humanity; almost one third relates to animal products.[8] Research suggests that it takes on average about 15,415 liters of water to produce one kilo of beef; for comparison, wheat production consumes 1,608 liters per kilo of wheat bread.[9]

Those estimates are based on a method that considers green, blue, and grey water footprint. Green water is rainwater, blue water is surface and groundwater (e.g., lakes, streams, oceans), and grey water is the quantity of fresh water needed to dilute polluted water to a level that meets the water quality standards of a certain water body (Figure 3). The water footprint of livestock production consists of 87% green, 6% blue and 7% grey water; 98% of this water footprint is associated with feed production.[10]

Some water footprint methods consider only blue water, and may even apply location specific scarcity factors based on the water resource availability of the region where water use takes place. If only blue water is considered, the contribution of livestock to global water use is 8%, of which 87% is used for feed production.[11] Due to the different water footprint analysis methods available, it is important to be cautious when interpreting results of water footprint studies.

The relative differences in water footprints of cell-cultured meat versus conventionally produced meat also depends on the method used. A study showed that if the analysis includes green, blue and grey water, cell-cultured meat could have 82 to 96% lower water footprint than meat from slaughter, depending on the product (Figure 2).[12] However, when a method including only blue water was used, cell-cultured meat had a higher water footprint compared to poultry and approximately 45% lower water footprint compared to beef and 30%

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[7] Mekonnen, M.M. and Hoekstra, A.Y. (2010) The green, blue and grey water footprint of farm animals and animal products, Value of Water Research Report Series No. 48, UNESCO-IHE, Delft, the Netherlands. https://waterfootprint.org/media/downloads/Report-48-WaterFootprint-AnimalProducts-Vol1_1.pdf

[8] Mekonnen, M.M. and Hoekstra, A.Y., Gerbens-Leenes P.W., (2013). The water footprint of poultry, pork and beef: A comparative study in different countries and production systems, Water Resources and Industry, Volumes 1-2 https://doi.org/10.1016/j.wri.2013.03.001

[9] Water Footprint Network (2019) https://waterfootprint.org/en/resources/interactive-tools/product-gallery/

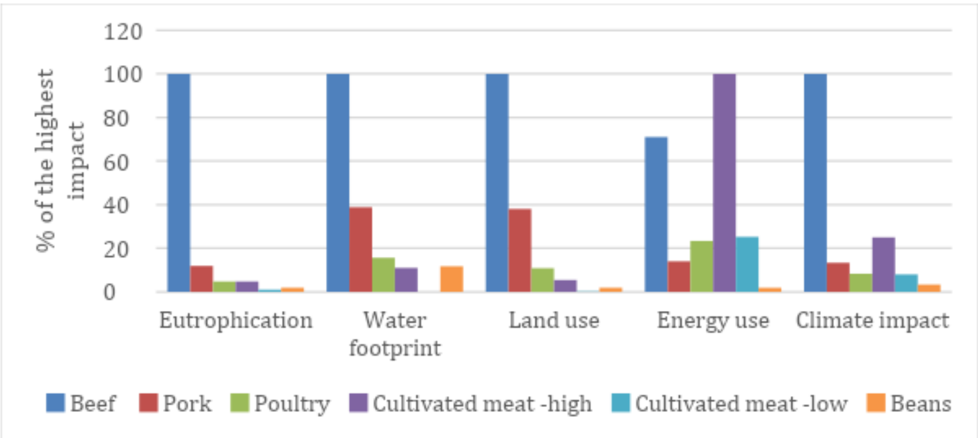
[10] Mekonnen, M.M., and Hoekstra, A.Y.J.E. (2012). A global assessment of the water footprint of farm animal products. 15(3), 401-415.

[11] Livestock's long shadow, http://www.fao.org/3/a0701e/a0701e04.pdf

[12] Tuomisto, H. L., & Teixeira de Mattos, M. J. (2011a). Environmental Impacts of Cultured Meat Production. *Environmental Science & Technology*, *45*(14), 6117–6123. https://doi.org/10.1021/es200130u

lower compared to pork.[13] Some of the differences in studies can be explained by differences in the assumptions of growth medium ingredients, but the main reason is that blue water use in livestock production is relatively low compared to green water. In cell-cultured meat production, water use consists of indirect water use required for production of energy and growth medium ingredients, and direct water used for the cell-cultivation medium, process water for cooling and heating, and water for cleaning the facilities. Therefore, the water footprint of cell-cultured meat depends on the type of energy and growth medium ingredients used, as well as on the water use efficiency in the production process.

In Figure 4, the large difference between the water footprint of various cell-cultured meat operations——high and low usages——is explained by different growth medium ingredients. In the *cell-cultured meat–high* scenario, it was assumed that corn was used as a source of glucose for the cell cultivation process and production of synthetic amino acids. In the *cell-cultured meat–low* scenario, it was assumed that cyanobacteria, a blue-green algae, produced in open ponds, was used as a main source of glucose and amino acids. This means that the *high* scenario also included green water use for the cultivation of corn, whereas the green water footprint of the *low* scenario was relatively low, as feedstock from agricultural origin was not used.



[13] Tuomisto, H.L., Ellis, M.J., and P., H. (Year). "Environmental impacts of cultured meat: alternative production scenarios ", in: 9th International Conference on Life Cycle Assessment in the Agri-Food Sector (LCA Food 2014), eds. R. Schenck & D. Huizenga: ACLCA), 1360-1366.

Figure 4: Comparison of environmental impacts of cell-cultured meat with livestock meat and bean production in the United States based on data from life cycle assessment studies of cell-cultured meat.[14,15]

Implementation of cellular agriculture could potentially reduce water usage and also could reduce water pollution stemming from conventional animal agriculture. This in turn has the ability to benefit communities and ecosystems, particularly those affected by polluted waterways or contaminated drinking water sources.

3.3 SDG 11: Sustainable Cities

UN SDG *Target 11.6* *— By 2030, reduce the adverse per capita environmental impact of cities, including by paying special attention to air quality and municipal and other waste management.*

There are two primary channels through which cell-cultured meat could improve air quality: first, by reducing air pollution related to agricultural production, and second, by minimizing the extent to which fossil fuel-based transportation is needed for supply chains.

The WHO estimates that nine out of ten people globally breathe polluted air, and approximately seven million people die annually due to air pollution.[16] While empirically analyzing the varied sources of air pollution is difficult, it is known that some portion is caused by global agricultural practices, such as burning forests to make way for animal feed crops, chemical-intensive production methods, farmed animals' digestive gases, and fossil-fuel intensive plowing.[17] Additionally, farm workers and residents near industrial farms breathe released

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[14] Tuomisto, H. L., & Teixeira de Mattos, M. J. (2011a). Environmental Impacts of Cultured Meat Production. *Environmental Science & Technology*, *45*(14), 6117–6123. https://doi.org/10.1021/es200130u

[15] Mattick, C.S., Landis, A.E., Allenby, B.R., and Genovese, N.J. (2015). Anticipatory life cycle analysis of in vitro biomass cultivation for cultured meat production in the United States. Environmental science & technology 49(19), 11941-11949.

[16] https://www.who.int/news-room/detail/02-05-2018-9-out-of-10-people-worldwide-breathe-polluted-air-but-more-countries-are-taking-action

[17] https://www.cdc.gov/nceh/ehs/docs/understanding_cafos_nalboh.pdf

particulate matter, which can cause severe respiratory problems in some cases.[18]

In North Carolina, air pollution from large-scale livestock farms is increasingly viewed as an issue of environmental justice. A 2018 study from Duke University found that residents living in areas surrounding livestock farms have higher all-cause and infant mortality, as well as above average mortality due to anemia, kidney disease, tuberculosis, and septicemia.[19] Residents have also documented throat and eye irritation and nausea due to the ever-present stench of manure, as well as increased incidence of asthma and a variety of other respiratory health ailments. A 2014 study conducted by researchers at the University of North Carolina found that the state's hog operations disproportionately affect people of color, a pattern referred to as environmental racism.[20] In 2018, several juries across North Carolina ruled in favor of residents who brought nuisance lawsuits against Murphy Brown LLC, a subsidiary of Smithfield Foods and the world's second largest pig producer, resulting in hundreds of millions of dollars in fines.[21] By producing meat through cell-cultivation, it would be possible to reduce the reliance on conventional agricultural practices that contribute to air pollution and environmental injustices.

Another way cell-cultured meat may improve air quality is by reducing the fossil fuel-based transportation used by supply chains that will be established to distribute cellular agriculture products. At scale, it is estimated that cell-cultured chicken products will use 35% to 67% less land than current chicken farms, and cell-cultured beef will reduce land use by over 95% (Figure 1). As a result, it is possible for meat cultivation to take place closer to cities. Although it is difficult to predict exactly what a future supply chain may look like, it is plausible that a decentralized production system could be developed (Figure 5). If this is eventually the case, meat products would have to travel shorter distances to get to consumers' plates. Even if our global energy infrastructure does not transition to more renewable sources, reducing the number of kilometers traveled per gram

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[18] https://www.cdc.gov/nceh/ehs/docs/understanding_cafos_nalboh.pdf

[19] Kravchenko, J. et al (2018). *Mortality and Health Outcomes in North Carolina Communities Located in Close Proximity to Hog Concentrated Animal Feeding Operations*, North Carolina Medical Journal, September-October 2018 vol. 79no. 5 278-288 http://www.ncmedicaljournal.com/content/79/5/278.full

[20] Hellerstein, E. and Ken Fine (2017). *A million tons of feces and an unbearable stench: life near industrial pig farms.* The Guardian. https://www.theguardian.com/us-news/2017/sep/20/north-carolina-hog-industry-pig-farms

[21] Brown, C. (2018). *North Carolina jury awards neighbors $473.5 million in Smithfield hog waste suit,* The New FoodEconomyhttps://newfoodeconomy.org/north-carolina-jury-fines-smithfield-foods-nuisance-lawsuit-hog-farm-manure/,

of animal protein would reduce air pollution caused by fossil-fuel-powered transportation.

A major challenge for improving air quality when switching to cell-cultured meat is to minimize the total energy requirements of the cell-cultured meat production process. The currently available estimates show that large-scale production of cell-cultured meat could require more industrial energy than conventionally produced meat.[22] In order to improve air quality, cell-cultured meat production must be optimized to consume less energy. Additionally, the adoption of clean energy sources will be an important factor for cell-cultured meat production to have minimal impact on air quality.

3.4 SDG 12: Sustainable Consumption and Production

UN SDG 12.2 *By 2030, achieve the sustainable management and efficient use of natural resources*

Switching from industrial animal agriculture to cell-cultured meat has the potential to conserve a wide array of natural resources including land, soil, water, forests, minerals, and potentially fossil fuels. Water use was discussed earlier in the context of SDG 6, and land, soil and forests will be discussed in the context of SDG 15. Therefore, this section concentrates on mineral and fossil fuel resources.

Phosphorus is an essential plant nutrient and agriculture uses more than 90% of global phosphorus resources as fertilizers.[23] However, as discussed in the context of SDG 6, the nutrient losses from agriculture to waterways are a major issue negatively impacting the environment. As phosphorus resources are finite, efficient use and recycling of phosphorus are essential for securing future food production. The phosphorus footprint of plant-based foods is lower compared to animal-based foods; for instance, the phosphorus footprint of 1 kg of beans is 99.4% lower than that of beef.[24]

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[22] Mattick, C.S., Landis, A.E., Allenby, B.R., and Genovese, N.J. (2015). Anticipatory life cycle analysis of in vitro biomass cultivation for cultured meat production in the United States. Environmental science & technology 49(19), 11941-11949.

[23] Reijnders, L. (2014). Phosphorus resources, their depletion and conservation, a review. Resources, Conservation and Recycling 93, 32-49. doi: https://doi.org/10.1016/j.resconrec.2014.09.006.

[24] Metson, G.S., Bennett, E.M., and Elser, J.J.J.E.R.L. (2012). The role of diet in phosphorus demand. 7(4), 044043.

It is likely that cell-cultured meat would have a lower phosphorus footprint compared to conventionally produced meat due to requiring less feedstock and the possibility to efficiently recycle nutrients. As cell-cultured meat production is a closed system, the unused phosphorus can be collected from the wastewater and reused as an input in the production system or alternatively, the nutrient-rich water could be used as a fertilizer for agricultural crops or algae. The phosphorus footprint of cell-cultured meat could be further reduced by utilizing recycled phosphorus in the production of growth medium ingredients.

The impact of cell-cultured meat production on fossil fuel depletion is unclear. Studies show that cell-cultured meat production may require more energy compared to farmed meat (Figure 2).[25] Therefore, the impact on fossil fuel resources depends on the source of energy used and the capacity to increase the supply of non-fossil fuel-based energy. Even though the cell-cultured meat industry could potentially use clean energy sources, at present, increasing the demand of energy would increase fossil fuel depletion unless the energy sector as a whole moves away from fossil fuels.

In cell-cultured meat production, the switch to non-fossil fuel-based energy sources may be easier than in conventional agriculture. In the bioreactor processes, the energy use consists mainly of electricity that is easier to produce from clean energy sources compared to fuel (currently diesel) for tractors. As discussed earlier, cell-cultured meat technology might also reduce transportation requirements, and therefore lessen the use of fossil fuels emitted across the supply chain.

The impact of cell-cultured meat production on the use of other mineral resources is uncertain. Further research is needed to quantify the resource requirements for cell-cultured meat production facilities and for the production of growth medium ingredients and energy inputs.

UN SDG 12.3 *By 2030, halve per capita global food waste at the retail and consumer levels and reduce food losses along production and supply chains, including post-harvest losses*

[25] Mattick, C.S., Landis, A.E., Allenby, B.R., and Genovese, N.J. (2015). Anticipatory life cycle analysis of in vitro biomass cultivation for cultured meat production in the United States. Environmental science & technology 49(19), 11941-11949.

According to estimates by the Food and Agriculture Organization (FAO), one third of all food produced globally is lost or wasted.[26] Food loss refers to the decrease in quantity or quality of food before reaching the retailer, whereas food waste means decrease in quantity of food at retail, food service provider, and consumer stages. It is estimated that, globally, 12% of livestock products are lost before retail.[26] According to the Natural Resources Defense Council of the US, 26.2% of all meat that enters the market is not eaten; 4.6% is wasted at the retail level, and 21.7% is wasted at the consumer level.[27]

Cell-cultured meat has the potential to reduce food loss and waste throughout the supply chain. Food losses in primary production would be reduced due to lower requirements of feedstock ingredients, and therefore, less overall losses would occur. If the cell-cultured meat production process could maximize efficiency while avoiding contamination, then feedstock waste would be reduced as a result of cells in a controlled environment having a much higher likelihood of reaching maturation. In contrast, in traditional animal agriculture, feedstock can go to waste through means such as animals dying prematurely from disease. Therefore, the feedstock investment in a cellular agriculture system will likely have higher net returns than an animal agriculture system.

A benefit of cell-cultured meat is that it is possible to produce only the part of the animal that is eaten. However, this means that if the co-products of meat production such as pet food, skins and hides are desired, they will have to be produced separately. In theory, the production of by-products only on-demand reduces losses, as only the required quantities can be produced, whereas in livestock production the quantities of by-products are directly proportional to the production of edible meat.

There is some speculation that cell-cultured meat might have a longer shelf-life than conventionally produced meat, thereby reducing food waste. However, this hypothesis has not been rigorously tested yet. The actual shelf-life of cell-cultured meat will depend on the characteristics of the product (e.g., pH, thickness) and how it is processed after cell-cultivation processes.[28]

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[26] http://www.fao.org/3/ca6030en/ca6030en.pdf

[27] Gunders, D. (2012). Wasted: How America Is Losing Up to 40 Percent of Its Food from Farm to Fork to Landfill *National Resources Defense Council* https://www.nrdc.org/sites/default/files/wasted-food-IP.pdf

[28] Miller, R.K. A 2020 synopsis of the cell-based animal industry. Animal frontiers : the review magazine of animal agriculture. , 2020, Vol.10(4), p.64-72. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7596797/pdf/vfaa031.pdf

UN SDG 12.6 *Encourage companies, especially large and transnational companies, to adopt sustainable practices and to integrate sustainability information into their reporting cycle*

Cellular agriculture presents an opportunity for large transnational companies to integrate sustainable practices into their business model. While cell-cultured meat is not yet on the market, many venture capitalists, including several of the world's largest global meat processors and producers, have invested in it. From 2016 to 2020, cell-cultured meat has garnered more than US $505 million in investments.[29]

For example, Cargill, the third-largest meat producer in the United States, invested in Aleph Farms, an Israeli cell-cultured meat company that debuted the world's first cell-cultured steak in 2018. Cargill was also an early investor in cultured chicken start-up Memphis Meats (now called Upside Foods). In describing their investment, Jon Nash, the president of Cargill Protein-North America, cited the need to address increasing protein demand globally and to consider all innovations that would help feed the planet.

Many other large meat companies have invested in cell-cultured meat, including PHW, a leading EU poultry producer; Bell Foods, Switzerland's largest meat producer; and Tyson, the second largest meat producer in the world. As cell-cultured meat nears mass market availability, other large companies may see this investment as an economic opportunity.[30] Whether or not sustainability is a primary motivator, investing in cell-cultured meat presents an opportunity for these companies to revisit their sustainability practices: such investments could move these companies toward integrating more sustainable practices into their business models and reporting cycles.

The development of cellular agriculture technology has the potential to contribute to sustainable consumption and production patterns. A study estimating the environmental impacts of cell-cultured meat based on data collected from start-up companies developing cell-cultured meat technology found that it could have a lower total environmental footprint than livestock meat when considering aggregated single-score impact consisting of a number of different environmental impacts (e.g., climate change, land use, water

[29] Byrne, B. (2020). 2020 State of the Industry Report: Cultivated Meat. *The Good Food Institute*. https://gfi.org/wp-content/uploads/2021/04/COR-SOTIR-Cultivated-Meat-2021-0429.pdf. Accessed November 7, 2021.
[30] Ibid.

consumption, fine particulate matter formation and human toxicity).[31] By incorporating cell-cultured meat into our food system, the pressure that our current food system is putting on natural resources could be alleviated, food waste could be reduced, and large companies could be encouraged to adopt more sustainable production methods.

3.5 SDG 13: Climate Action

UN SDG 13.2 *Integrate climate change measures into national policies, strategies and planning*

Tackling the climate crisis is perhaps the most pressing action item on the global environmental agenda. With 14.5% of human-induced greenhouse gas (GHG) emissions coming from livestock, our food system should be a critical piece of any climate plan.[32] A recent study demonstrated that major transformations in food systems in parallel with decarbonizing the economy are essential to avoid drastic consequences of climate change.[33]

In order to understand how animal agriculture contributes to climate change, it helps to break it down into subcategories: 44% of livestock GHG emissions come from methane, i.e., digestive gas of cattle and from manure lagoons, 29% from nitrous oxide, largely via synthetic fertilizers used for growing feed crops, and 27% from carbon dioxide, via a swath of actions, including tree clearing, land-use change for growing feed crops for livestock, and farm management.[34]

Most of these emission sources are avoided in cell-cultured meat production. As a result, some estimates suggest that GHG emissions would be greatly reduced by switching from conventional meat production to cell-cultured meat production. Although cell-cultured meat is not currently being produced at

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[31] Sinke, P. & Odegard, I. (2021) LCA of cell-based meat. Future projections for different scenarios. CE Delft. Delft. www.cedelft.eu.

[32] Gerber, P.J., Steinfeld, H., Henderson, B., Mottet, A., Opio, C., Dijkman, J., Falcucci, A. & Tempio, G. (2013). *Tackling climate change through livestock – A global assessment of emissions and mitigation opportunities*. Food and Agriculture Organization of the United Nations (FAO), Rome. http://www.fao.org/3/a-i3437e.pdf

[33] Clark, M.A., Domingo, N.G.G., Colgan, K., Thakrar, S.K., Tilman, D., Lynch, J., et al. (2020). Global food system emissions could preclude achieving the 1.5° and 2°C climate change targets. 370(6517), 705-708. doi: 10.1126/science.aba7357 %J Science.

[34] Gerber, P.J., Steinfeld, H., Henderson, B., Mottet, A., Opio, C., Dijkman, J., Falcucci, A. & Tempio, G. (2013). Tackling climate change through livestock – A global assessment of emissions and mitigation opportunities. Food and Agriculture Organization of the United Nations (FAO), Rome. http://www.fao.org/3/a-i3437e.pdf

an industrial scale, meaning that preliminary estimates must rely on a variety of assumptions, early research is promising. However, until industrial scale systems and production machines are put in place, it can only be an estimate.

According to an early Life Cycle Assessment (LCA) study published in 2011, cell-cultured meat could result in a 78-98% reduction in GHG emissions when compared to conventionally produced meat (*cell-cultured meat–low* scenario in Figure 4).[35] A later study found that cell-cultured meat could have higher GHG emissions when compared to pork and poultry, but 77% lower emissions compared to beef (as shown in the *cell-cultured meat–high* scenario in Figure 4).[36] The differences in the findings of these two studies can largely be explained by differences in the assumptions regarding the cell-cultured meat production systems and growth medium ingredients. A more recent study from 2021, showed that the GHG emissions of cell-cultured meat could be substantially reduced by using renewable energy sources in the production process.[37] While conventional meat production can implement renewable energy sources, it will be more difficult to incorporate into these established systems than cell-cultured meat processes, which are still under development.

The methods used for assessing the climate impacts can have an effect on the results. The LCA studies converted the GHG emissions to carbon dioxide equivalents that describe the impact of different gases during a 100-year timeframe (i.e., methane has 28 and nitrous oxide 265 times stronger impact than carbon dioxide). A study published in 2020, used the data from the two referenced LCA papers and applied a method that estimates the climate impact during a 1,000-year timeframe for comparing cell-cultured meat and beef.[38] The comparison showed that some of the most energy-intensive cell-cultured meat production scenarios that utilized fossil fuels had higher climate impact than beef in the longer term. This was explained by the fact that beef production emits more methane, whereas most of the GHG emissions of cell-cultured meat production consists of carbon dioxide. Even though methane is a stronger GHG emission in the short term, it remains in the atmosphere for only 12 years,

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[35] Tuomisto, H. L., & Teixeira de Mattos, M. J. (2011). Environmental Impacts of Cultured Meat Production. *Environmental Science & Technology*, *45*(14), 6117–6123. https://doi.org/10.1021/es200130u
[36] Mattick, C. S., A. E. Landis, B. R. Allenby, and N. J. Genovese. (2015). Anticipatory Life Cycle Analysis of In Vitro Biomass Cultivation for Cultured Meat Production in the United States. *Environmental Science & Technology 49 (19): 11941–49*.
[37] Sinke, P. & Odegard, I. (2021) LCA of cell-based meat. Future projections for different scenarios. CE Delft. Delft. www.cedelft.eu.
[38] Lynch, J., and Pierrehumbert, R. (2019). Climate Impacts of Cultured Meat and Beef Cattle. 3(5). doi: 10.3389/fsufs.2019.00005.

whereas carbon dioxide remains present infinitely, unless it is purposely removed. Therefore, when using a longer timeframe, the impact of methane becomes less significant than carbon dioxide.

Since carbon dioxide is used by plants, increasing the vegetation cover on Earth reduces atmospheric carbon dioxide. If cellular agriculture is widely adopted, agricultural land use could be reduced by up to 90%, freeing resources, which are otherwise involved in the production of traditional meat, for reforestation projects that could help combat any new carbon emissions released due to cell-cultured meat production. As the design of the cell-cultured meat production systems and the ingredients used for the growth medium will have a major impact on GHG emissions, more accurate estimations of any climate impacts will only be possible once these systems are in production.

Cellular agriculture also has the possibility to utilize clean energy sources that would help to cut the emissions even further, whereas in livestock production, the reduction of GHG emissions from all emission sources is not straightforward. For instance, the methane emissions from ruminants' digestive processes can be reduced to a certain extent by specific feed ingredients, but complete avoidance of those emissions is not possible.

3.6 SDG 14: Life Below Water

UN SDG 14.1 *By 2025, prevent and significantly reduce marine pollution of all kinds, in particular from land-based activities, including marine debris and nutrient pollution*

As previously discussed in relation to SDG 6, Clean Water and Sanitation, cell-cultured meat production could reduce harmful nutrient emissions to waterways, and therefore, also reduce the nutrient pollution of seas and oceans.

The impacts of macro-, micro- and nanoplastic pollution of seas and oceans are an increasing problem. Plastic pollution has a detrimental effect on marine fauna through ingestion and entanglement.[39] It has been estimated that agriculture accounts for approximately 4% of all plastics consumed in the US.[40]

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[39] Eriksen, M., Lebreton, L.C., Carson, H.S., Thiel, M., Moore, C.J., Borerro, J.C., et al. (2014). Plastic pollution in the world's oceans: more than 5 trillion plastic pieces weighing over 250,000 tons afloat at sea. 9(12), e111913.
[40] Briassoulis, D., Babou, E., Hiskakis, M., Scarascia, G., Picuno, P., Guarde, D., et al. (2013). Review, mapping and analysis of the agricultural plastic waste generation and consolidation in Europe. 31(12), 1262-1278.

The more plastic used, the more plastic debris ends up in the oceans. Therefore, reducing the overall use of plastics would also benefit marine ecosystems.

The impacts of cell-cultured meat production on plastic use is yet to be determined. It is likely that the need for agricultural plastics would be reduced. However, the use of plastics at the cell-cultured meat facilities would determine the total impact. For instance, if single-use bioreactors made of plastics were used, the use of plastics might be even higher than in livestock production. The benefit of cell-cultured meat production might allow for improved management of plastic waste compared to agriculture where plastics are often used outdoors, so the possibility of plastic debris ending up in the surrounding environment is higher.

UN SDG 14.3 *Minimize and address the impacts of ocean acidification, including through enhanced scientific cooperation at all levels*

Agriculture contributes to ocean acidification through carbon dioxide emissions to the atmosphere, which form carbonic acid when absorbed into seawater. Agriculture also causes acidifying emissions through nitrogen losses to waterways that drain to oceans. The contribution of agriculture on the acidification of oceans has been estimated to be approximately 25%.[41]

The impact of cell-cultured meat production on ocean acidification depends upon the level of carbon dioxide and nitrogen emissions of the production system. As discussed earlier, cell-cultured meat production is likely to have lower nutrient emissions compared to livestock farming. However, the level of carbon dioxide emissions is uncertain and dependent upon the type of energy used. If non-fossil fuel-based energy sources are used throughout the supply chain of cell-cultured meat, the carbon dioxide emissions are likely to be lower compared to livestock production.

UN SDG 14.4 *By 2020, effectively regulate harvesting and end overfishing, illegal, unreported and unregulated fishing and destructive fishing practices and implement science-based management plans, in order to restore fish stocks in the shortest time feasible, at least to levels that can produce maximum sustainable yield as determined by their biological characteristics*

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[41] Campbell, B.M., Beare, D.J., Bennett, E.M., Hall-Spencer, J.M., Ingram, J.S.I., Jaramillo, F., et al. (2017). Agriculture production as a major driver of the Earth system exceeding planetary boundaries. Ecology and Society 22(4). doi: 10.5751/ES-09595-220408.

Fish accounts for approximately 7% of global protein consumption and is an important source of protein for more than 50% of the population in the least developed countries.[42] It has been estimated that 35% of the global fish stocks are overfished and a further 60% are fished up to the maximum sustainable capacity.[43]

Cell-cultured meat production has the potential to indirectly contribute to the sustainable maintenance of fish stocks and reduction of overfishing by providing an alternative source of fish meat. The increased availability of fish in markets would reduce the pressure on overfishing the wild fish stocks.

3.7 SDG 15: Life on Land

UN SDG 15.1 *By 2020, ensure the conservation, restoration and sustainable use of terrestrial and inland freshwater ecosystems and their services, in particular forests, wetlands, mountains and drylands, in line with obligations under international agreements*

Agriculture accounts for approximately 40% of all global land use; 80% of this is used for livestock production.[44] The clearance of forests for pasture and livestock feed production is causing 67% of deforestation globally.[45] The deforestation of the Amazonian rainforest is largely driven by expansion of soybean feed production and pasture land for cattle. Soybean is a widely used protein feed especially for pigs and poultry. Over half of global soybean is produced in Latin America, while most of the consumption occurs in China, the United States, and the European Union.[46] Latin America is also a large exporter of beef, accounting for approximately 40% of all beef exports, with Brazil alone supplying 24%.[47] Due to the global feed and meat markets, it can be argued that all meat consumption has at least an indirect impact on deforestation of tropical forests.

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[42] Link, J.S., and Watson, R.A. (2019). Global ecosystem overfishing: Clear delineation within real limits to production. 5(6), eaav0474. doi: 10.1126/sciadv.aav0474 %J Science Advances.

[43] FAO (2020). The State of World Fisheries and Aquaculture 2020. Sustainability in action. Rome. http://www.fao.org/3/ca9229en/CA9229EN.pdf

[44] WRI (2019). Creating a sustainable food future. A Menu of Solutions to Feed Nearly 10 Billion People by 2050. World Resources Report. (Washington, DC, USA: World Resources Institute).

[45] Poore, J., and Nemecek, T.J.S. (2018). Reducing food's environmental impacts through producers and consumers. 360(6392), 987-992.

[46] https://www.foodsource.org.uk/building-blocks/soy-food-feed-and-land-use-change

[47] http://www.fao.org/faostat/

The current rate of biodiversity loss globally has been estimated to exceed safe levels by 100-1000 times.[48] Due to agriculturally driven deforestation and intensification of agriculture, it has been estimated that the contribution of agriculture to global biodiversity loss is around 80%. The deforestation of tropical forests is of particular concern, as they are a home for two-thirds of global terrestrial biodiversity.[49] The intensification of agriculture through increased use of agrochemicals, specialization in crop or livestock production, and reduced use of extensive grazing have all led to decreased agro-biodiversity. Mono-cropping systems and intensive tillage of soils have also led to declines in soil biodiversity, decreased soil quality, and increased soil erosion.

Soil is arguably one of earth's most valuable natural resources. Healthy soil is an integral part of any healthy ecosystem, providing the nutrients necessary for plant life to exist. Yet, current methods of agriculture tend to prioritize large short-term crop yields over preserving soil health. Farmers growing crops often till the soil, a method of intensive plowing used to turn over weeds and topsoil quickly. Over time, tilling can create infertile soil and lead to erosion and desertification. These poor soil management practices were part of the cause of the infamous Dust Bowl of the 1930s, a giant dust storm across the Midwestern US that dispossessed thousands of families and left the land virtually unusable for years.[50] Although the Dust Bowl was almost a century ago, challenges related to proper soil management remain ubiquitous in industrial agriculture today.

Cellular agriculture could contribute to the conservation of biodiversity and soils by reducing the pressure on land use. As cell-cultured meat production has been estimated to require 50-99% less land compared to conventionally produced meat, the need to convert forests into agricultural land would be

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48 Campbell, B.M., Beare, D.J., Bennett, E.M., Hall-Spencer, J.M., Ingram, J.S.I., Jaramillo, F., et al. (2017). Agriculture production as a major driver of the Earth system exceeding planetary boundaries. Ecology and Society 22(4). doi: 10.5751/ES-09595-220408.

49 Solar, R.R.d.C., Barlow, J., Andersen, A.N., Schoereder, J.H., Berenguer, E., Ferreira, J.N., et al. (2016). Biodiversity consequences of land-use change and forest disturbance in the Amazon: A multi-scale assessment using ant communities. Biological Conservation 197, 98-107. doi: https://doi.org/10.1016/j.biocon.2016.03.005.

50 McLeman, R. et al. (2013). What we learned from the Dust Bowl: lessons in science, policy and adaptation. *Population and Environment.* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4015056/

reduced, and it might be possible to reforest former agricultural land.[51, 52] Additionally, due to the decreased demand of crops for feed, it would be possible to use less intensive agricultural practices that would help to conserve agro-biodiversity and soils.

Extensive livestock grazing systems are essential for maintaining certain rare plant and insect species that have been adapted specifically for those environments. The species may, for instance, be dependent on manure deposited on land or require the type of vegetation that only extensive pastures provide. Therefore, a complete elimination of livestock production might not lead to the most desired outcome from the biodiversity conservation point of view. However, substantially fewer animals compared to the current levels would be sufficient for providing these biodiversity benefits.

3.8 Conclusion

The UN SDGs place an enormous challenge in front of humanity. For progress to be made, there must be action on a wide range of issues. This requires cross-cutting solutions that simultaneously address an array of SDGs. Cell-cultured meat production could contribute, both positively and negatively, to the environmental impacts addressed in the SDGs. However, as cell-cultured meat technologies are at a developmental stage, it is unlikely that the technology will be able to substantially contribute to the issues that require rapid transformative changes to achieve the targets set for 2030. In order to contribute to the SDG targets, the cell-cultured meat industry will need to commercialize and scale up the technology during the next few years and establish a substantial market share. In addition to the speed of technological development, the time requirements for legislative approval to sell the products as food and the subsequent time for consumers to adopt the products will affect the questions of when and how much cell-cultured meat could affect the sustainability of food systems.

In order to achieve the SDGs by 2030, major changes in the food systems must be implemented through currently available options. These include switching to plant-based diets consisting of seasonal and locally produced foods,

[51] Mattick, C.S., Landis, A.E., Allenby, B.R., and Genovese, N.J. (2015). Anticipatory life cycle analysis of in vitro biomass cultivation for cultured meat production in the United States. Environmental science & technology 49(19), 11941-11949.
[52] Tuomisto, H.L., and Teixeira de Mattos, M.J. (2011). Environmental impacts of cultured meat production. Environmental science & technology 45(14), 6117-6123.

reduction of food waste, improvement in the sustainability of agricultural practices, and halting expansion of agricultural land. At this point it is uncertain whether humanity will be able to reach the UN climate targets to avoid unfavorable environmental shifts; however, the development of cellular agriculture will be important for making progress towards these goals beyond 2030.

Fundamental Questions – Answered

1. **What are the possible environmental benefits of cell-cultured meat compared with conventional meat production?**
   Cell-cultured meat has potential to reduce greenhouse gas emissions, land use, water use and pollution of air and waterways. Due to the lower land use requirements compared to livestock production, cell-cultured meat could help reduce deforestation. Therefore, it could also contribute to the conservation of biodiversity.

2. **Which SDGs associated with environmental issues can cellular agriculture help to tackle?**
   Associated UN SDGs include: SDG 6, Clean Water and Sanitation; SDG 11, Sustainable Cities and Communities; SDG 12, Sustainable Consumption and Production; SDG 13, Climate Action; SDG 14, Life Below Water; and SDG 15, Life on Land.

3. **What are the potential downsides of cell-cultured meat regarding environmental issues?**
   Cell-cultured meat production may require more electricity than conventionally produced meat. This will increase the pressure on the supply of clean energy. Cell-cultured meat production could also have negative impacts on agro-biodiversity if it reduces extensive grazing-based livestock systems that have become integral parts of their surrounding ecosystems, and are key for supporting other animal, plant, or insect species.

4. **Which are the main uncertainties regarding the impact of cellular agriculture?**
   The ultimate impacts of cell-cultured meat will depend upon the types of systems developed for commercial production, ingredients used for the growth media, and the scale of adoption of the technologies.

5. **How is waterway pollution impacted by livestock agriculture, and how could this be affected by adopting cellular agriculture?**
   Livestock manure contains nutrients (nitrogen, phosphorus and potassium), residual antibiotics, heavy metals, and pathogens which can leach into the environment and risk human health if they end up in waterways. In the worst cases, manure may be stored in open lagoons next to livestock farms and may end up in waterways. With

cell-cultured meat, the main potential sources of water pollutants are related to the production of growth medium ingredients and the waste from the cell-cultured meat facilities. A study estimated that cell-cultured meat could have up to 97% lower eutrophication impact compared to beef produced in the US, and up to 70% lower compared to pork.

6. **How might cell-cultured meat production affect water resources?**
   In cell-cultured meat production, water use consists of indirect water use for production of energy and growth medium ingredients, and direct water used for the cell-cultivation medium, process water for cooling and heating, and water for cleaning the facilities. The water use of cell-cultured meat production could eventually be lower compared to conventionally produced meat due to efficiency of resource use and possibilities for recycling water.

7. **How could cell-cultured meat contribute to achieving SDG 11, Sustainable Cities?**
   There are two primary channels through which cell-cultured meat could improve air quality. First, it could reduce air pollution compared with agricultural production, and second, it could minimize the extent to which fossil fuel-based transportation is needed for food supply chains.

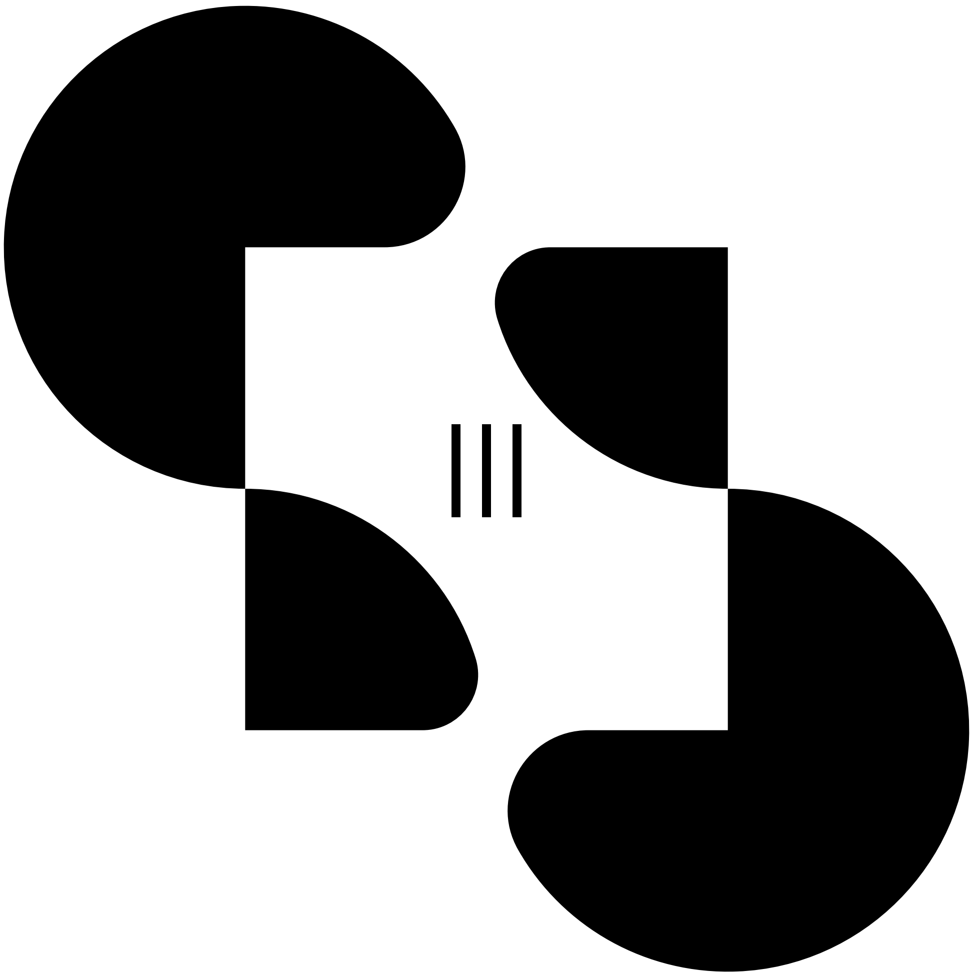
8. **In which ways might cell-cultured meat affect mineral and fossil-fuel use?**
   Cell-cultured meat could have a lower phosphorus footprint compared to conventionally produced meat, as it requires less feedstock and has options for efficiently recycling nutrients, because cell-cultured meat production is a closed system. The impact of cell-cultured meat production on fossil fuel use will depend on the source of energy used by cell-cultured meat operations and the capacity to increase the supply of non-fossil fuel-based energy.

9. **How might cell-cultured meat affect food loss and waste?**
   Cellular agriculture offers the possibility to cultivate cells to produce only the part of the animal that is eaten. Also, there are some preliminary scientific studies that suggest certain cell-cultured meat products could have longer shelf-lives.

10. **How could cell-cultured meat production affect greenhouse gas (GHG) emissions compared to livestock meat?**
    In livestock production, most GHG emissions originate from feed production, manure management, and feed digestion processes, especially enteric fermentation of ruminants. Cell-cultured meat production is likely to require less feed, and emissions from manure and enteric fermentation are completely avoided. If low-emission energy sources are used to power cell-cultured meat production, the GHG emissions can be substantially reduced when compared to livestock meat.

11. **How can cell-cultured meat impact SDG 14, Life Below Water?**
    Cell-cultured meat production can reduce water pollution from agricultural fields in the form of nutrient losses and micro/macro plastics. Cell-cultured meat can also help to reduce ocean acidification. Cell-cultured fish could replace the consumption of wild fish, and therefore, help to tackle issues associated with overfishing.

12. **What influence could cellular agriculture have on SDG 15, Life on Land?**
    Cellular agriculture could contribute to the conservation of biodiversity and soil health by reducing the pressure on land for agricultural purposes. The need to convert forests into agricultural land would be reduced, and it may be possible to reforest former agricultural land. Due to the decreased demand for feed crops, it should be possible to use less intensive agricultural practices that conserve agro-biodiversity and soils.


III

SCIENCE

SECTION 3

Cells

Introduction to Cellular Biology for Cultivated Meat

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Chapter Abstract

Biological cells are the main sources of proteins, lipids, minerals, and vitamins obtained from meat. Different cell types make up the muscles, fats, and other tissues that were originally part of the animal. Instead of growing an animal to create the muscle and fat found in various meat cuts, using cultured cells to recreate these components will take scientific collaborations between different fields of research. This chapter describes biological cells that are of interest to emerging industries in cellular agriculture, including cultivated meats. To introduce the reader to cell culture, the chapter begins with a brief description of its history both in food industries and in research laboratories. The chapter then describes the physical characteristics of muscle and fat cells, as well as methods used to culture and process these cells for cultivated meats. Other cell types, including stem cells and even microorganisms like yeasts are also covered in cases where they contribute to cultivated meat production. The chapter concludes with a note on safety considerations and future directions for cultivated meat research.

List of Tables

Table 1: Description and Classification of Key Muscle Fiber Types
Table 2: Physical Characteristics of Beef Muscle Fibers
Table 3: Composition of Beef Fat
Table 4: Physical Characteristics of Pig Muscle Fibers
Table 5: Physical Characteristics of Poultry Muscle Fibers
Table 6: Physical Characteristics of Fish Muscle Fibers
Table 7: Properties of Cultured Cow Muscle Cells
Table 8: Properties of Cultured Cow Fat Cells
Table 9: Properties of Cultured Pig Muscle Cells
Table 10: Properties of Cultured Pig Fat Cells
Table 11: Properties of Cultured Chicken Muscle Cells
Table 12: Properties of Cultured Chicken Fat Cells

Keywords

Muscle fiber
Myoblast
Myofiber
Adipose tissue
Adipocyte
Cultivated meat

Fundamental Questions

1) What is the definition of a cell, and how is this relevant for the development of cultured meats?

2) What type of materials can be used for the development of cells for cultured meat?

3) What type of cells and tissue architectures can be produced with the state-of-the-art technology?

4) How scalable is the preparation of cells, and are they cost-effective?

5) How can cells be integrated into a cell-cultured meat production process?

Chapter Outline

Background
4.1 Introduction
    4.1.1 An Overview of Topics Covered in this Chapter
    4.1.2 Cell Types Found in Meat: Mostly Muscle and Fat
        4.1.2.1 Background: Cell Types in Meats are Well-Studied and Provide Design Criteria
        4.1.2.2 Skeletal Muscle Cells
        4.1.2.3 Skeletal Muscle Fiber Types in Animals
        4.1.2.4 Skeletal Muscle Niche, Stem Cells, Satellite Cells, and Myoblasts
        4.1.2.5 Fat Adipocytes and Stem Cells

4.2 History of Cell Culture and Tissue Engineering
    4.2.1 History of Animal Cell Culture: Focus on Agricultural Species
    4.2.2 History of Cell Culture Scale-up: Bioreactors and Process Control
    4.2.3 History of Tissue Engineering: Form and Function

4.3 Designing Cultivated Meats
    4.3.1 Cell Line Development
    4.3.2 Culture Conditions
    4.3.3 Texture
    4.3.4 Nutrition

4.4 Building Cultivated Meats: Cell Culture and Tissue Engineering
    4.4.1 Culture Media and Growth Factors
    4.4.2 Growth Factors Produced in Cell Suspensions
    4.4.3 Bioreactors and Bioprocesses
    4.4.4 Post-Processing and Alternative Meat Architecture
    4.4.5 Increasing Complexity of the Technology

4.5 Converging Technologies with Relevance to Cultivated Meats
    4.5.1 Background: Cell Culture Needs to Grow Up
    4.5.2 Case Study of Technology I: Synthetic Biology and Suspension Cultures
    4.5.3 Case Study of Technology II: Animal Cell Culture
    4.5.4 Case Study of Technology III: Tissue Engineering
    4.5.5 From Lab Scale to Large Scale: Integration of Technology in Development and Manufacturing Processes

4.6 Limitations, Regulations, Cost Considerations, and Consumer Acceptance
    4.6.1 Limitations of Cultivated Meats
    4.6.2 Safety and Regulation
    4.6.3 Scale and Cost
    4.6.4 Consumer Acceptance

4.7 Conclusion

Background

The science of cell-cultured meats is multi-disciplinary, incorporating fundamental cell biology, food science and nutrition, material sciences and manufacturing, industrial bioprocessing and more. Motivated by the goal of recreating meat without the use of animals, cell-cultured meats aim to recreate the taste, texture, aroma, and nutrition of animal-based meats. Cell-cultured meats are expected to build on plant-based alternative meats by adding additional nutrition and flavor that cannot be achieved using plants alone.

Products based on plant proteins can contain all essential dietary amino acids, but they do not contain the same muscle- and fat-specific proteins, peptides, and lipids that are found in meats. One solution to this problem is the use of synthetic biology, where new strains of plants or microorganisms are genetically engineered to produce selected meat proteins. Several relevant (but relatively simple) molecules, such as the heme molecule, can be produced by microorganisms but the accurate reproduction of complex muscle proteins is not currently feasible using these methods. Synthetic biology is therefore expected to target high-value molecules rather than attempt to recreate the entire meat proteome (all the proteins found in meat).

Growing muscle and fat cells in cultures and using them in cell-cultured meat products is theorized to be the best way to approximate the protein composition found in meats. The main challenge with this approach is the large-scale industrial cell cultures required for food products. The low cost of existing meat products creates new challenges for bioprocess engineers that aim to scale-up cell production. There is also the challenge of wholly recreating the mature cell types found in meats, which is not yet possible using cell culture and tissue engineering methods. These challenges lead to interesting multidisciplinary questions that cover design criteria (how closely to we want to approximate a meat product?) to manufacturing methods (what cell culture media components will be used to expand large numbers of cells affordably?), and testing (what is the desired aroma, flavor, taste, texture, and nutritional profile?). To meet the goals of cell-cultured meats, we will need fruitful collaborations between cell biologists, material scientists, bioprocess engineers, food scientists, regulators, and consumers.

4.1 Introduction

4.1.1. An Overview of Topics Covered in this Chapter

The science of cultivated meat is supported by over 100 years of research and development in cell biology, industrial bioprocessing, and tissue engineering. From yeasts used in food and beverage industries, to pharmaceuticals produced by cultured mammalian cells, to tissue engineering practiced in academic laboratories, our acquired knowledge indicates that cultured cells can be used to produce meat products.

This chapter describes how cells are used to produce cultivated meat. Descriptions of skeletal muscle and fat cells present in animal meat are reviewed, including cell structures and proportions in specific species and meat cuts. Efforts to culture these cell types in the laboratory are then reviewed, including methods to produce them from stem cells. Under suitable conditions these cells can expand in number (proliferation) and be directed towards specific phenotypes (differentiation) that include skeletal muscle and fat. Using these methods, a large variety of meat-like tissues can be grown at small scales in the laboratory.

To produce large quantities of cultivated meats at costs that are acceptable for meat consumers, several obstacles need to be overcome. First, cells change slightly every time they divide, leading to genetic drift that needs to be managed during the long phases of expansion (proliferation) expected in cultivated meat scale-up. Second, the price of nutrients like growth factors contained in cell culture media needs to be reduced. Suspended cells like yeast are emerging as candidates for cost effective growth factor production. For this reason, we will also discuss cell types that can be grown at large scales in suspension and can be used as expression systems to produce valuable molecules like growth factors needed to culture skeletal, fat, and stem cells.

To focus this chapter, three categories are highlighted: muscle and fat cells, stem cells, and suspension cell lines. The structure and function of these cell types are reviewed, as well as the methods used to culture them in the laboratory. The supporting technologies that are used to grow and transform cells into tissues that look and feel like meat are then briefly defined. These include cell culture media and growth factors, bioreactors, automation, and scaffolds, all of which proceed as self-contained chapters following this one and play critical roles in cultivated meat production workflows (Figure 1).

4.1.2. Cell Types Found in Meat: Mostly Muscle and Fat

In this section, biological cells of interest to cell-cultured meats are defined and described, beginning with cell types found in meats. These include skeletal muscle myoblasts, fat adipocytes, connective tissues cells, and stem cells. The description of these cells is followed by a brief discussion of supporting materials used for cell culture and tissue engineering, and their influence over cells during culture. These include cell culture media, bioreactors, and associated microcarrier materials. This section concludes with an introduction to tissue-engineering and post-processing methods that give cell-cultured meat the texture and appearance of whole meat cuts.

4.1.2.1 Background: Cell Types in Meats are Well-Studied and Provide Design Criteria

The cell types most often associated with cell-cultured meats are found in skeletal muscle and fat, which account for most of meat's composition.[1] Extensive literature describes muscle biology as it applies to meat science,[2] meat biochemistry,[3] and muscle development in livestock animals.[4] The composition of muscle fibers found in meats is influenced by breed, gender, age, physical activity, environmental temperature, and feeding practices, which creates a challenge in recapitulating complex natural products.[5] Meat products also form a diverse group, ranging from processed meats such as sausage to whole cuts such as steak. These meat products have in common their derivation from livestock muscle, fat, and smaller amounts of other tissues. For this reason, muscle myoblasts found in skeletal tissues and adipocytes found in fat, as well as the stem cells that give rise to these cell types, are of key interest to cell-cultured cultured meats. The basic hypothesis is that if manufacturers can produce enough of these cell types at low costs, these cells can then be structured into pieces of tissue-like natural meat products. Each natural meat cut thus represents a different product objective, with specific design criteria based on the abundance of each cell type in the natural meat cut, as well as more detailed specific aspects of the cut's cellular phenotypes and organization. Currently, research has focused on reproducing processed meats, like ground beef and sausage, as these present easier initial targets for recreation as they lack higher levels of structural organization. However, in principle many of the techniques discussed in this chapter can be scaled to work on the more complex structures present in whole meat cuts.

4.1.2.2 Skeletal Muscle Cells

Skeletal muscle consists of approximately 90% muscle fibers and 10% of connective and fat tissues. Muscle fibers are elongated, multinucleated cells of approximately 10 to 100 μm in diameter with a length that ranges from a few millimeters to several centimeters depending on species and muscle type. In all species, the fiber size increases with animal age. More details about muscle structure are discussed in a 2016 review by Listrat et al.[5] Individual muscle fibers are classified according to their size, as well as their contractile and metabolic activities (Table 1). Muscle fiber structure and composition depend on species and on the specific muscle location in each meat cut (Tables 2 to 6). For example, pig Longissimus muscle contains approximately 10% type I fibers, 10% IIA, 25% IIX, and 55% IIB, whereas bovine Longissimus contains on average 30% type I fibers, 18% IIA, and 52% IIX.[5] These differences in muscle fiber composition contribute to differences in meat texture and composition. The following is a summary of key properties of livestock tissues and cells that have been studied during the last ~40 years *in vitro.* These provide cell-cultured meat researchers with design criteria based on livestock meats, as well as a reference point to compare cell-cultured or livestock-based meats.

4.1.2.3 Skeletal Muscle Fiber Types in Animals

The properties of livestock meats have been extensively studied to correlate animal genetics, feed, and growth conditions with meat quality.[6] For this reason, much more is known about livestock meat tissues than about recreating their properties in cell culture. The following is a review of the structure and function of skeletal muscle and fat from livestock animals including cow, pig, chicken, fish, and others. Descriptions and classifications of key muscle fiber types are provided in Table 1. Subsequent Tables 2 to 6 summarize physical characteristics of beef muscle fibers (Table 2) and beef fat (Table 3), pig muscle fibers (Table 4), poultry muscle fibers (Table 5), and fish muscle fibers (Table 6). The skeletal muscle *in vivo* microenvironment (the "niche") is then described, including how it promotes muscle regeneration and how muscle regeneration relates to muscle stem cells and their growth *in vitro*. Similarly, fat tissue and the stem cells used to produce it *in vitro* is also described. Key properties of cultured muscle and fat cells are summarized in Tables 7-12. This section concludes by discussing supporting materials like cell culture media and growth factors, bioreactors, and tissue engineering materials, which help transform cultured cells into functional tissues.

To design cultured meat products, manufacturers can use the properties of animal meat tissues as building standards. Each cut of meat has different proportions and types of muscle and fat tissues (Figure 2). For example, muscle fibers from specific cow breeds such as Blonde d'Aquitaine bulls[7] and Charolais cattle[8] have been analyzed and muscle fiber size correlates with lactation performance.[9] Similarly for pig, sensory properties of meat depend on the structure of specific muscles.[10] These include the Longissimus thoracis semitendinosus and masseter muscles,[11] as well as their constituent muscle fiber types.[12,13] Chicken myofibers have been studied *in vitro*,[14] and histological imaging techniques are used to correlate muscle structure and composition (such as chick breast pectoralis major muscle).[15] At a molecular level, these cell types produce muscle proteins such as fast myosin heavy chain[16] and assemble them into a sophisticated contractile architecture.[17] A large variety of muscle proteins are involved to produce functioning muscle tissue,[18] and their presence in cells or tissues can be observed using proteomic techniques[19] to examine protein composition, structure, and bioactivity.

4.1.2.4 Skeletal Muscle Niche, Stem Cells, Satellite Cells, and Myoblasts
Skeletal muscle can regenerate following injury and grow in response to exercise. The self-renewing proliferation of muscle stem cells, which are called satellite cells because they are located peripheral to muscle myofibers, gives muscle its regenerative capacity.[20,21] These cells provide a pool of muscle-producing myogenic cells, which proliferate, differentiate, fuse, and lead to new myofiber formation.[22] More specifically, in response to cues provided by damage or mechanical strain, quiescent satellite cells localized outside the sarcolemma and beneath the basal lamina become activated. The cells then express myogenic regulatory factors, proliferate, and form myoblasts that can fuse together or with existing fibers.[23] Satellite cells undergo a hierarchical lineage progression from the satellite stem cell to the satellite committed progenitors genotype and phenotype.[24] As few as seven satellite cells associated with one transplanted myofiber can generate over 100 new myofibers containing thousands of myonuclei.[25] As a result, satellite stem cells present both opportunities and challenges for cell-cultured meats. First, it is a challenge to reproduce an animal's exercise routine at a cellular scale, as muscle development throughout an animal's life will impact muscle composition and therefore texture. However, stem cells also present opportunities for researchers, as they can potentially be used to build tissues from the ground up, following similar pathways to those used inside the animal.

4.1.2.5 Fat Adipocytes and Stem Cells
Fat contains specialized cell types called adipocytes which hold lipid storage droplets that contribute to the taste, texture, and nutrition of meats. As with muscle fibers, adipocyte properties like size and nutrient composition depend on species and tissue location.[26] Cows differing in lactation performance have been compared in terms of fat cell size,[9] and fat nutrients can be enhanced using innovations in beef production systems.[27] For example, the effects of feeding regimens (such as grain feeding that stimulates adipogenesis in beef cattle compared with pasture feeding that depresses

the development of adipose tissues) may be at least partially recapitulated with supplements like vitamin C or zinc.[28] Fat tissues can also be recreated using stem cells. Adipocytes are derived from mesenchymal stem cells through a process termed adipogenesis, which has been studied in animal models including cow.[29] Culture conditions can be used to select growth of bovine subcutaneous or intramuscular preadipocyte differentiation[30] and to achieve differentiation of these cells in serum-free medium.[31,32] To produce meat products from the ground up, both muscle and fat need to be taken into account, with fat providing a number of distinct factors depending on the location in the body. It also means that fat, like muscle, can be recreated to a limited extent using stem cells.

4.2 History of Cell Culture and Tissue Engineering

The earliest use of cell cultures for food production dates to the beginning of agriculture with the use of yeasts for fermentation.[33] With the invention of the microscope, scientists could directly observe these life forms and by the late 1800s microbiology emerged as a science.[34-36] Animal cells and tissues were more difficult to culture than yeast because the conditions found inside the body are difficult to recreate in the laboratory. In the body, the immune system protects from infection and the circulatory system regulates temperature, oxygen, and nutrient exchange. Protocols for the growth of animal cells and tissues were first developed about 100 years ago and have advanced rapidly since then.[37-39] In the 1950s, cells originating from certain types of tumors were found to be immortal, with the ability to replicate *in vitro*. These cells were then used as miniature vaccine factories, and several large biotechnology firms got their start selling HeLa cells in industrial quantities[40]. In the 1960s, stem cells were identified,[41] demonstrating that some healthy cell types retained the ability to proliferate, with proliferation or quiescence being tightly regulated in the body. Later research showed that a wide variety of stem cells exist in the body with tissue-specific attributes and varying degrees of plasticity, which is the ability to differentiate into multiple cell types with lineage specification controlled by microenvironmental cues.[25,42,43] Recently, methods have been introduced to induce stemness in previously committed cells, giving rise to the induced pluripotent stem cell (iPSC).[44-46] Standard protocols and textbooks now describe how to culture animal cells,[47,48] stem cells,[49] and how to design bioreactors suitable for cell and tissue engineering.[50,51]

4.2.1 History of Animal Cell Culture: Focus on Agricultural Species

Animal cell culture became a routine practice in the early 20th century, following the development of sterile culture techniques and cell culture media that could substitute for blood.[38,48] Cells in culture require a pH-balanced, water-based (aqueous) environment with nutrient supply and exchange. These roles, which are fulfilled by blood circulation *in vivo*, were first recapitulated in culture media by including animal blood and blood components. Blood and serum containing media formulations continue to be in widespread use, but research over the last few decades has delineated specific molecular components of cell culture media that not only keep animal cell cultures alive long-term but also direct cell phenotypes and tissue organization.[52-55] These discoveries included the identification of specific growth factors, cytokines, and other molecules.

Such molecules can be used to culture proliferative stem cells, or to induce differentiation of skeletal muscle and fat.[52,56-59] It is common to classify synthetic culture media into groups based on the type of supplements added. These include serum-containing media, serum-free media, protein-free media, or chemically defined media.[60] Livestock species that are routinely cultured *in vitro* include cow,[55,61-63] pig,[64-66] chicken,[67] turkey,[52,58,59] and others discussed in more detail below the second case study.

4.2.2 History of Cell Culture Scale-up: Bioreactors and Process Control

Humanity's earliest written records of food production describe the use of cells like yeasts for fermentation.[33] Although fermentation techniques were valued and refined over many centuries, it was not until the advent of the microscope and the emergence of biotechnology in the 19th century that cell-cultured manufacturing became industrial.[34-36] The economic success of biotechnology received a boost during World War II, with the development of large-scale sterile fermentation technology to produce penicillin, and the subsequent development of genetic engineering widened commercial targets from biofuels to personalized medicines.[68] Pharmaceutical bioprocessing with suspension cultured mammalian cells such as Chinese hamster ovary cells (CHO) became widespread following efforts in the mid-1980s to adapt them for growth in suspension.[69] Recent work suggests that altering adhesion-related gene expression can increase the yield of suspension-cultured pluripotent stem cells.[70] The manufacturing scales for yeast, suspension cultured mammalian cells like CHO cells, and stem cells, are approximately 30-80, 25, and <1, in cubic meters respectively.[68] These culture systems are described in more detail in the case studies. The ability to culture cells at this scale leads researchers to focus on tissue engineering, where the scale and organization of cells is controlled to recreate functional tissue units in a laboratory setting.

4.2.3 History of Tissue Engineering: Form and Function

Tissue engineering refers to the assembly of cells into larger multi-cellular structures with defined functional attributes. More than 100 years ago it was recognized that cells isolated from living animals could survive for some time in the laboratory and responded to structural cues provided by the substrates they were cultured on. For example, cells were observed to attach, elongate, and spread across spider web fibers[39]. This is important for cell-cultured meat because muscle and fat tissues have specific structures, metabolisms, and protein content that depend on location and level of maturity. The majority of recent tissue engineering research has focused on medicinal goals that include *in vitro* disease modeling and regenerative medicine research.[71-73] These engineered tissues are normally small, with thickness limited to ~0.2 mm due to oxygen and nutrient diffusion limits and ongoing challenges associated with engineering functional vasculature needed to support thick tissues.[74,75] Recent years have, however, seen progress in stem cell-cultured muscle production,[76,77] muscle tissue engineering,[78-80] and vascularization.[81-85]

4.3 Designing Cultivated Meats

Cell-cultured meats should begin with design criteria that account for the structure and composition of the final product while addressing cell line development, cell culture media, scaffolding materials, bioreactors, and other critical technology elements. Key properties of cells that are common to most cell-cultured meat strategies are the ability of the cells to proliferate to large numbers (scale-up) and, in some cases, the ability to then differentiate into muscle, fat, and other specific tissues.

4.3.1 Cell Line Development

Specht et al identified the following key design requirements for cell-cultured meat cell line development: cells should be i) derived from agriculturally relevant species, ii) capable of differentiation into meat-relevant cell types (muscle, fat, connective tissue, etc.), iii) genetically stable and immortalized, and iv) optimized for large-scale growth (tolerate suspension, controlled differentiation, etc.).[86] The authors also cite there is a need for technological advancements within the cell-cultured therapeutics industry:
Development of small molecule cocktails that can replace the need for genetic approaches to induce pluripotency and to facilitate maintenance of pluripotency, footprint-free methods of cell line engineering using RNA or protein delivery or excisable transposons, and improved protocols for cell freezing to maintain viability and phenotypic fidelity. [86]
Lessons learned from the cell-cultured therapeutics industries will partially translate to cell-cultured meats in efforts to scale the production of agricultural cell types.

4.3.2 Culture Conditions

Culture conditions are specific to each cell type, and cell manufacturers often supply media formulated for specific cell lines and culture protocols. Interspecies differences are notable, and optimal culture conditions such as temperature and pH may depend on the species of origin. For example, while most mammalian cells are cultured at 37 °C, cell lines originating from fish are often cultured at lower temperatures. In all cases, environmental factors that must be regulated include culture media pH, osmolality, and temperature. This culture media must be supplemented with the growth factors and cytokines required to sustain cell proliferation and differentiation. Introductory level descriptions of cell culture methods and culture media composition is provided online by several suppliers, including the American Tissue Culture Collection (ATCC), and by many reference textbooks.

4.3.3 Texture

The rich textures of natural meat cuts, together with the relative abundance of muscle or fat tissues, influence cooking conditions and contribute significantly to the consumer's dining experience. Ultimately, the texture and nutritional output of cell-cultured meat analogues should be compared with natural meats[5]. Texture includes a variety of characteristics such as hardness (some authors call it toughness), springiness, and chewiness, with hardness being the most important to the consumer[87]. Texture can be imparted to cell-cultured meats either by culturing cells in fibrillar scaffolds or by post-processing methods such as extrusion and printing. The texture of these final products can be compared to meats using industry standard tests such as texture profile analysis[87-89] and Warner–Bratzler shear tests[89,90]. These methods have been shown to be good predictors of meat sensory texture[87,89] and are familiar to materials scientists that may develop scaffold materials[91].

4.3.4 Nutrition

Replicating the unique nutrients stored in meat myofibrillar proteins[92] and peptides[93] will likely require tissue culture specific muscle and fat cells. Producing these cell types in culture requires conditions that replicate the natural tissue environments[43,78,94-99]: This includes accounting for substrate stiffness[43] and biochemistry[95], muscle alignment[94,99], and chemical factors secreted by supporting cell types[78]. The final step in the large effort required to recapitulate protein signatures of whole meats requires that future work include studies of gut microbiota in the context of meat analog digestion and nutrition. Specifically, cell-cultured meat nutrient release needs to match that of traditional meat in the many stages of digestion.

4.4 Building Cell-cultured Meats: Cell Culture and Tissue Engineering

4.4.1 Culture Media and Growth Factors

Culture media is required to nourish cells during culture and to direct their lineages. Depending on the nutritional composition of the media, it can direct certain cell types to either proliferate (growth phase) or differentiate into specific tissue lineages such as skeletal muscle or fat that are found in meats (maturation or aging phase). Culture media can be classified based on the type of supplements added (for example, serum-containing, serum-free, protein-free, or chemically defined).[60] Growth factors added to serum-free media often include fibroblast growth factors (FGFs) and insulin-like growth factor (IGF).[58,63] Currently, producing sufficient supplements or growth factors in a scalable way is one of the main economic factors limiting the expansion of cell-cultured meats.

4.4.2 Growth Factors Produced in Cell Suspensions

Yeast cultures[100-102] and selected mammalian cells such as the Chinese hamster ovary (CHO)[103-105] lines are routinely used for biopharmaceutical production. They are relevant to cell-cultured meats because expensive molecules included in cell culture media may be produced at lower costs using methods similar to biopharmaceutical production. These cells have proven scale-up in industry and can be used as cell factories (expression systems), notably to produce cell culture media components such as growth factors,[106-108] hormones,[109] or antimicrobial agents[110] that may otherwise be too expensive for cell-cultured meats. Yeasts can also be used to produce recombinant extra-cellular matrix components,[111,112] suggesting a path to scalable animal-free production of non-cellular tissue components. This is described further in ‘Case Study I’.

4.4.3 Bioreactors and Bioprocesses

Bioreactors provide a closed sterile environment with regulated conditions that permit biological cells to grow in culture. Based on the history of fermentation technology,[113]

sophisticated process design, monitoring, and control,[114] the basic principles of suspension culture in bioreactors are summarized by Meyer et al.[68]:
While the basic principles of suspension culture in bioreactors and the very basic design of these bioreactors remain the same for all applications, they need to be adapted and modified in response to the particular requirements of the cultivated cell type and the target product with regard to parameters such as follows: oxygen demand, heat transfer requirement, sensitivity to shear, sensitivity to process and culture variations, sensitivity to local variations within the bioreactor, current good manufacturing practice (cGMP) requirements, biosafety requirements (containment levels are normally BLS1 and BLS2), specific safety requirements for highly potent active pharmaceutical ingredients (HPAPI).

Volumetric adherent cell culture bioreactors are available in a variety of formats, which include stacked or rolled sheets, gas-permeable bags, spinner flasks, and bioreactors similar in principle to fermentation reactors.[115] Likewise, several of these culture strategies can be applied to suspension culture (for example to immobilize yeast for continuous fermentation). [116,117] High-yield suspension cultures of adherent cells[70,118-120] include scalable systems with serum-free defined media for embryonic stem cell expansion in aggregate,[118] pluripotent stem cell expansion in spinner flasks,[119] suspension culture of chicken stem cells,[120] as well as strategies that increase adherent single-cell survival efficiency, growth rates, and yield.[70]

Most animal cells used for cell-cultured meat applications are anchorage-dependent adherent cell types. Because of this, their culture in bioreactors requires special attention to microcarrier materials that provide cells with an attachment surface when cultured in suspension. Microcarriers have been reviewed in terms of anchorage dependence,[115] as well as attachment and detachment strategies.[121] Edible materials used to build microcarriers include corn zein,[122] cellulose,[123] chitosan,[124] gelatin,[62] and combinations thereof.[125] Microcarriers are used for stem cell expansion in serum-free conditions,[126] but serum-free media formulations are cell line-specific.[127] Microcarriers are most often spherical but can also be formulated in different shapes such as fiber-shaped microcarrier aggregates.[62,128]

4.4.4 Post-Processing and Alternative Meat Architecture
Following large-scale production of cells for cell-cultured meats, it will often be necessary to further process these cells into meat products with texture and taste that are similar to existing meat products. By varying the concentrations of muscle and fat, for example, meat marbling may be controlled to impart specific cooking properties and mouthfeel. Existing extruder systems and emerging 3D printing methods may be used to control tissue architecture. Prior work building model muscle tissues for medical research showed that recapitulating natural muscle phenotypes in culture required biomimetic culture conditions[43,78,94-99] that account for substrate stiffness,[43] biochemistry, [95] anisotropic muscle alignment,[94,99] and chemical factors secreted by supporting cell types.[78] We also note that natural tissues contain extra-cellular matrix (ECM) proteins that direct tissue assembly,[129] with collagen being the most abundant ECM protein in skeletal muscle and accounting for ~1-10% of the muscle mass.[130]

Collagen and collagen-derived gelatins are used in food and pharmaceutical industries due to their biocompatibility, biodegradability, and weak antigenicity.[131,132] Alternative forms of gelatin or peptides produced synthetically in microorganisms may provide a fully animal-free source for these materials.

4.4.5 Increasing Complexity of the Technology

Meat analogs based on plant proteins may increasingly mimic natural meats, but the nutrients found in meat include myofibrillar proteins[92] and bioactive peptides[93] produced by specialized muscle and fat cells that cannot be recapitulated using plants. For this reason, the continued development of agricultural cell lines is expected to be an active field for many years to come. Cell line development will continue, with new types optimized for high proliferation rates, potentially immortalized, and banked.[133] Stem cells will be improved to increase proliferation and reliable lineage specification. Quality metrics will also be developed to provide unbiased comparison between cultured or animal derived meats.

To produce tissues with structural and functional maturity to recapitulate natural tissues, progress in tissue engineering will be required. Medical applications of tissue engineering have shown that small tissues can be engineered to resemble a wide variety of natural tissues, including muscle, fat, lung, heart, liver, brain, and others.[73] However, we do not suggest that principles applied to tissue engineering for regenerative medicine necessarily apply to cell-cultured meats. For example, cell-cultured meat may not require tissue vascularization if cells are grown in sufficiently porous scaffolds which permit nutrient exchange and that can subsequently be pressed or otherwise processed following cell culture. Scaffolds composed of plant proteins or other biomolecules (not animal-derived) may provide a suitably nutritious backbone for products that contain relatively small numbers of cultured cells. This concept of cells as an additive is not common in regenerative medicine but may provide cell-cultured meat production with a path to scalability.

Producing larger tissues at lower costs will be a significant challenge for cell-cultured meats. However, the potential to produce animal-free meat by design with well-defined textures and mouthfeel is a worthwhile goal. For example, exotic meat cuts like shark fin or foie gras could be designed and produced. To analyze the molecular composition of tissues, the emerging field of foodomics, which profiles whole food products on a molecular level, may be used to associate genetic markers and protein expression with meat performance traits.[134] Detailed analysis of meat composition can then be applied to models of digestion, including activity of bioactive peptides found in meats.[93,135]

For suspension cells like yeast, there is broad potential to expand their use for the production of growth factors,[106-108] hormones,[109] or antimicrobial agents[110] that constitute essential components of cell culture media and represent most of the cost for cell-based meat scale-up. Use of yeast for extracellular matrix production further suggests their potential for animal-free scaffold production.[111,112]

4.5 Converging Technologies with Relevance to Cell-cultured Meats

4.5.1 Background: Cell Culture Needs to Grow Up

All cell-cultured meat products will, by definition, contain a certain percentage of cells in their composition. Some products may be mostly plant protein-based and contain small amounts of cell additives, while others may contain mostly cells. For this reason, cells have been considered as a defining component of cell-cultured meats. In addition, many cell types beyond just animal cells will play increasingly important roles in cell-cultured meat production as expression systems for key growth factors. For this reason, presented here are three case studies that follow the progression from suspension cells to animal muscle and fat cell cultures to tissue engineering. These case studies aim to introduce the reader to multiple aspects of cells' broad applicability to cell-cultured meats. In all cases, scaling up production and lowering costs sufficiently for competition within the food industry will be challenging. Here, the temptation to use genetic engineering tools to improve cell expression systems, animal cell proliferation, and rapid tissue maturation must be tempered to meet safety and regulatory concerns.

4.5.2 Case Study of Technology I: Synthetic Biology and Suspension Cultures

Synthetic biology is the use of biological cells and organisms to produce molecules that are difficult or impossible to synthesize by other methods. By programming cells via methods such as genetic engineering, the cell's own internal machinery can be used to assemble the molecules coded in the programming. Genetically modified yeasts are often used this way as expression systems. They also have the advantages of scalability, as they grow easily to large numbers, and there is already technology built to accommodate for their large-scale production due to their established presence in the industry.[136] Current efforts aim to improve industrial yeast strains,[137] expand our yeast product repertoire,[138] and improve yeast culture properties.[139] These systems can provide key growth factors and cytokines used to grow stem cells, as well as fat and muscle cells in culture. Producing these factors in yeasts could drastically lower the cost of cell culture media, the largest expense in cell-cultured meats today. Important regulators of muscle and fat cell proliferation and differentiation produced in yeast (specifically, the yeast species *Pichia pastoris*) include basic fibroblast growth factor FGF-2,[106] insulin-like growth factors (IGF-1 and IGF-2),[107,108] epidermal growth factor (EGF),[140] vascular endothelial growth factor (VEGF),[141] as well as insulin precursors and albumin,[109] interferons,[142] and ECM proteins.[111,112] Yeast also show antimicrobial activity and probiotic properties, which could be leveraged to improve cell-cultured meat bioprocess. [143-145,110]

Mammalian suspension cells also have roles to play, especially in post-translational modifications that cannot be achieved by yeast. Post-translational modification of proteins refers to the chemical changes that proteins may undergo after translation, such as glycosylation (enzymatic conjugation with carbohydrates). Monoclonal antibody production in Chinese Hamster Ovary (CHO) cells constituted most of the ~8.5 metric ton pharmaceutical production in 2010.[146] Pharmaceutical bioprocessing with CHO cells became widespread following efforts in the mid-1980s to adapt them for growth in suspension,[69] and recent work suggests that altering adhesion-related gene expression can increase the yield of suspension-cultured pluripotent stem cells.[70] Many varieties of CHO cells have been evolved either naturally or by genetic engineering and have been selected for specific growth properties or expression systems.[147]

Additional suspension cell lines such as MDCK, BHK-21, EB66®, and AGE1.CR.pIX® are used to produce influenza, yellow fever, Zika, and Modified Vaccinia Ankara (MVA) virus.[148] The EB66® duck embryonic stem cell-derived line is used for the industrial production of therapeutic monoclonal antibodies and can be cultured in suspension at high densities (e.g., 1.6×10^8 cells/mL).[149,150] It is also noteworthy that, like with CHO cells, other formerly adherent cell types can be adapted to grow in suspension, including L-929 fibroblasts (ATCC® CCL-1™), HeLa (ATCC® CCL-2™), and BHK-21 (ATCC® CCL-10™). This suggests that adherent stem cells, myoblasts, or pre-adipocytes, can be adapted either by selection or genetic engineering to grow in suspension cultures. Bovine myoblasts can be cultured in microcarriers-based systems, suggesting that production can be scaled.[151]
Taken together, suspension cells—whether mammalian or not—will play important roles in cell-cultured meat bioprocessing. Their use is expected to focus first on the production of expensive growth factors for culture media additives, but further engineering will enable the production of other proteins, such as contractile proteins found in muscle or nutrients found in fat. The main advantage of using suspension cells for these objectives is their scalability because they can be cultured in large volumes using existing bioprocesses. A similar process is used in the brewing industry, in which yeast are cultured to produce alcoholic beverages at commercial scales. As a result, as synthetic biology improves, the expectation is that these techniques will be able to scale to industrial levels to accommodate the needs of cellular agriculture processes.

4.5.3 Case Study of Technology II: Animal Cell Culture

Animal cell culture is a well-established research topic and numerous cell types from a variety of species and tissue sources are routinely cultured *in vitro*. This case study focuses on muscle and fat cells isolated from agricultural animals. Summarized previously were the physical characteristics of beef muscle fibers (Table 2) and beef fat (Table 3), pig muscle fibers (Table 4), poultry muscle fibers (Table 5), and fish muscle fibers (Table 6). The following is a summary of the efforts to culture these cells *in vitro*, including cow muscle (Table 7) and cow fat (Table 8), pig muscle (Table 9) and pig fat (Table 10), chicken muscle (Table 11) and chicken fat (Table 12).

To culture skeletal muscle from cow, it is important to account for the effects that cytokines, small proteins secreted by the immune system, have on myogenesis in bovine myoblast cultures. Acidic fibroblast growth factor-1 (FGF-1) and interleukin-1 (IL-1) stimulate cell proliferation of bovine myoblasts, and insulin-like growth factor-1 (IGF-1) stimulates further cell maturation. This is marked by the formation of multinucleated myotubes, with bovine myoblasts expressing beta slow-type MyHC (MyHC-slow), fast-type MyHC (MyHC-fast), and developmental-type MyHC (MyHC-dev) isoforms.[55] Other factors such as lnc9141-a and lnc9141-b can also play important (and potentially competitive) roles in bovine myoblast proliferation, apoptosis, and differentiation,[152] proving that careful optimization of culture conditions are required for each cell type. Similar considerations apply to adipocyte culture,[153,154] porcine skeletal muscle-derived multipotent interstitial cells,[65] and multipotent porcine skeletal muscle satellite cells.[155,66]. Porcine stem cells have also been cultured in stirred suspension bioreactors and culture media factors have been developed to improve pluripotency of porcine pluripotent stem cells.[156,157]

The *in vitro* characteristics of chicken muscle cells have been extensively studied including myogenic satellite cells derived from the pectoralis major and biceps femoris.[158] The characteristics studied include temporal expression of growth factor genes and satellite cell proliferation and differentiation *in vitro*.[159,160] The effects of growth factors on muscle morphology during chicken embryonic and post-hatch growth and development have been studied in detail.[161-164] Other studied aspects include how temperature affects proliferation and differentiation of chicken skeletal muscle satellite cells isolated from different muscle types.[165] These characteristics have also been compared in layer or broiler chickens.[67] Muscle and fat cells can be derived from chicken germ cells or stem cells including primordial germ cells isolated from embryonic blood that retain their proliferative potential following cryopreservation.[166,167] Chicken muscle and fat co-cultures have been described,[168] and a detailed understanding of chicken skeletal muscle development[76] can inform culture protocol design to recapitulate muscle development *in vitro*.

Stem cells are of particular interest for cell-cultured meats because they retain the ability to both proliferate and differentiate into muscle, fat, or other tissues. These changes depend on culture conditions. Protocols now exist to produce induced pluripotent stem cells (iPSC) from skin or blood samples and to differentiate these cells into skeletal muscle,[77] white and brown fat,[169] and endothelial cells.[170] These methods have been applied to livestock iPSC such as chicken[45] and pig,[171] suggesting that iPSC culture protocols are at least partially translatable between species. This may open a path to minimally invasive cell sources.

4.5.4 Case Study of Technology III: Tissue Engineering

Tissue engineering is used to assemble cells into multicellular structures that resemble natural tissues or organs found in the body. Tissues are generally composite, consisting of one or more cell type populations embedded in an extra-cellular matrix (ECM) of proteins and associated molecules. Natural ECM materials include collagen, fibronectin, laminin, and proteins that support cell attachment and influence cell shape and assembly.[129] These proteins are also used for muscle tissue engineering,[62] to improve cell adhesion to microcarriers in suspension,[172] and in food and drug industries for their biocompatibility, biodegradability, and weak antigenicity.[131,132]

Soon after the discovery of reliable tissue engineering methods, the use of these methods for food production was discussed in popular press and by science fiction writers.[173,174] This interest was revived more recently with the advent of modern stem cell and tissue engineering methods.[175-177] To recreate meat's organoleptic properties (mouthfeel) and nutritional content, tissue engineering will likely need to be used to direct cell assembly and maturation towards specific tissue types found in animals. The fibrous and hierarchical structure of muscle, the number and size of fat deposits, as well as the composition of these tissues result from years of maturation in animals. Nutrients found in meat, including myofibrillar proteins[92] and diverse bioactive peptides,[93] are produced by mature cells: technically speaking, this means the cells have functionally advanced lineage specification. Using natural tissues as design inspiration, tissue engineering with biomimetic materials can promote the maturation of cells.[43,78,94-99] These materials can promote cell adhesion, shape control, and alignment. [94,99] Cell maturation can be further defined by controlling tissue stiffness,[43] and by using biochemical factors[95] secreted by supporting cell types.[78]

Biomedical research in regenerative medicine and *in vitro* disease modeling includes a wide variety of example tissues,[71-73] such as muscle[76,77,78-80] and fat.[178,179] The principal challenge facing cell-cultured meat tissue production is scaling up methods to produce large amounts of tissue at low costs. Recent publications from academic laboratories addressed issues of quantity (scale-up) using microcarrier suspensions[180] and quality (texture) by culturing muscle cells in fibrous gelatin[62] or textured soy[181] scaffolds. Commercial cell-cultured meat products are increasingly showcased in company press releases and taste testing events.

4.5.5 From Lab Scale to Large Scale: Integration of Technology in Development and Manufacturing Processes

More than 300 million tons of meat is globally produced per year, and this figure is rising[182]. Cell-cultured meat production offers theoretically high resource efficiency,[183,184] but muscle cells and stem cells used for cell-cultured meats[61,86,183,185] are typically adherent and require culture substrates for attachment, survival, proliferation, and maturation.[115] Cell adhesion complicates bioprocessing applications,[115,172] especially for muscle maturation and muscle fiber alignment.[76,186,187] For this reason, cell-cultured meats designed to replicate whole cuts will likely use multiple manufacturing steps that include suspension-type cell proliferation for scale-up. These will be followed by post-processing steps to add texture and to further mature the cells towards muscle and fat phenotypes.

Integrating bioprocessing methods with adherent cell types used for cell-cultured meats can be achieved using a variety of volumetric culture systems that include bioreactors with stirred or circulating media, spinner flasks, gas-permeable bags, hollow tubes, as well as stacked or rolled sheets.[115] Adherent cells can also be modified by selection or genetic engineering to grow better in suspension. For example, CHO cells became widely used for pharmaceutical bioprocessing after their adaptation to suspension culture in the 1980s.[69] Altering adhesion-related genes can increase the yield of suspension-cultured pluripotent stem cells,[70] suggesting these methods may be applied to cell-cultured meat suspension cultures. Adherent cells can also be cultured in aggregates, where several cells stick to each other to form a live, floating microcarrier. Cell aggregates in high-yield suspension cultures[70,118-120] include scalable systems with serum-free defined media for embryonic stem cell expansion,[118] suspension culture of chicken stem cells,[120] and strategies to increase adherent single-cell survival efficiency, growth rates, and yield.[70] The ability to expand pluripotent stem cells in spinner flasks and to obtain differentiation to >90% cardiomyocyte purity suggests that similar strategies may be used to derive skeletal muscle or fat used for meats.[119]

A major discussion to have in cell-cultured meat manufacturing will be the use of genetic engineering and associated topics of selection and immortalization. These methods are used to increase doubling numbers and rates, accelerate differentiation, enable cell expansion in lower cost media, and infer antibiotic resistance among other features. These advantages must be weighed against potential health risks and public acceptance. Some examples of these methods include: bovine and porcine fibroblast immortalization by the expression of mutant cyclin dependent kinase 4, cyclin D, and telomerase;[188] a telomerase-immortalized porcine bronchial epithelial cell line;[189] and pig fibroblast cells immortalized by transposon-mediated ectopic expression of porcine telomerase reverse transcriptase.[190] Expression of cell cycle regulators was used to extend proliferation of chicken- and Okinawa rail-derived fibroblasts,[191] to regulate chicken myoblast proliferation,[192] and to regulate proliferation of immortalized chicken preadipocytes.[193] Chicken fat preadipocytes can be immortalized by retroviral transduction of chicken telomerase reverse transcriptase (TERT) and telomerase RNA (TR).[194] These cells can be regulated by factors such as transcription factor HBP1, a regulator of senescence and apoptosis of preadipocytes.[195] Their proliferation can be regulated by cell cycle regulators such as the retinoblastoma 1 gene (RB1).[196] These examples of detailed cell culture methods are provided to demonstrate that there is currently a sufficient understanding of cellular growth processes to regulate them.

4.6 Limitations, Regulations, Cost Considerations, and Consumer Acceptance

4.6.1 Limitations of Cell-cultured Meats

The main limitations of cell-cultured meats can be summarized broadly as issues of quantity, quality, and safety. Engineered tissues are normally quite small, with thickness limited to ~0.2 mm due to oxygen and nutrient diffusion limits and the challenges associated with engineering functional vasculature needed to support thick tissues.[74,75] Recent years have seen progress in vascularization but there is significant need to prove the scalability of animal cell expansion at low cost using methods that are acceptable to consumers.[81-85]

Cell-cultured meat quality will mostly be determined in comparison with the natural products they replace. Meat from animals contains cells that developed over the animal's lifetime into highly specialized functional cell types. Natural skeletal muscle contains hierarchical bundles of contractile tubular cells (myofibers), and fat contains hypertrophic adipocytes with rich contents. In the body, these tissues form as part of a larger system regulating their development through multiple chemical and non-chemical cues. This process cannot currently be recapitulated in the laboratory. If cells used for cell-cultured meats are proliferative immature cells such as stem cells, then they will not accurately recapitulate natural meat composition due to insufficient maturation of the cells. For example, skeletal muscle tissues grown from the immortal murine cell line C2C12 may express more mature muscle markers and appear more like natural meat than muscle grown from agricultural animal stem cells, where tissue maturation is currently more difficult. However, these murine cells are essentially cancerous muscle cells and therefore not attractive to consumers. Similarly, the production of hybrid cell types such as porcine adipose derived stem cells (having myogenic potential) fused with C2C12[197] raise new discussions about cell sources and phenotype, broadly defined. Quality metrics that are used in food science to establish meat source and product quality are recommended to be increasingly applied to cell-cultured meat products.

4.6.2 Safety and Regulation

Cell-cultured meats would benefit from a regulatory framework that includes broad representation from consumers, stakeholders, and experts across academia and industry. Collectively, this group can define safety requirements, pool existing knowledge, and stimulate new safety research where data gaps are identified. Sharing third-party data with regulators and stakeholders will help define safety research priorities, delineate the manufacturing process, and identify potential risks or hazards. One potential risk in cell-cultured meat is infection: cell cultures do not have immune systems and instead rely on bioprocessing conditions to maintain sterility and limit the growth of unwanted microorganisms in the cultures. While the fermentation industry has had millennia to optimize these conditions to limit the growth of unwanted organisms, safety and regulation standards will accelerate the implementation of the conditions required for this nascent industry. Towards this goal in the US, in 2019 the USDA and FDA announced a formal agreement to regulate cell-cultured food products from cell lines of livestock and poultry. Both agencies have unique expertise in how to avoid failure in meat production, food processing, and bioengineering practices. Adopting these regulations to the cell-cultured meat industry will protect the consumer and aid in the adoption of these products. The design of culture substrates for adherent cell scale-up in food production should account for emerging food bioprocessing regulatory standards.[198]

4.6.3 Scale and Cost

Cell-cultured meat requires significant production scale-up to be competitive in the established food industry. This will require highly proliferative cells that give rise to skeletal muscle, fat, and other tissue types. To culture large numbers of cells at low costs, future directions will include a strong focus on the replacement of expensive culture media growth factors with comparable factors derived from plants or synthetic biology. Several synthetic biology systems were described in Case Study #1, where yeasts and other cell types were modified to produce the growth factors that support stem cell expansion, as well as muscle and fat production. Increasing the quality of starter cells will also be a future focus that can reduce the cost of cell-cultured meats through the development and quality control of novel cell lines. It is expected that livestock stem cells, myoblasts, and preadipocytes will undergo scale-up using some of the methods outlined in Case Study #2. Here, genetic drift that occurs naturally during cell division may be used through selection of cell types with desired proliferative capacity and potential for muscle and fat differentiation. Rigorous quality control includes metrics for genomic, proteomic, metabolic, structural, and functional aspects of cell lines. Future work will include applying these standards to the development and banking of diverse cell lines.[46,199-201]

4.6.4 Consumer Acceptance

The adoption of a new cell-cultured meat market requires that technological advancements in cell and tissue culture, implementation of safety and regulatory guidelines, and reduction in cost be timed with consumer acceptance of a new method of meat production. For specific information on the safety and regulatory guidelines surrounding cell-cultured meat, please refer to Chapter 13, *Federal Regulation of Cell-cultured Meat, Poultry, and Seafood Products in the United States*. While consumers may see cell culture as a non-traditional method to grow meat, this is a traditional method of making foods. Fermentation utilizes bacteria and yeast to transform starter ingredients into yogurt, cheese, pickles, and alcoholic beverages. To avoid spoilage in these products, producers control substrate, temperature, and environmental conditions. Cell-cultured meat requires the same strategy to develop more complex products: muscle and fat. If consumer adoption is to occur, it needs to be rooted in linking the abstract with the familiar. The explosion in consumer adoption of plant-based meat occurred when plant-based Impossible Foods and Beyond Meat products replicated the buying and cooking experience of ground beef. There are many additional challenges in the realm of market adoption, which are explained in more detail in Chapter 11, *Consumer Acceptance of Cell-cultured Meat*. To aid in encouraging adoption, the cultivated meat industry needs to advocate for its products' many benefits over conventional products of the traditional meat industry. These issues are discussed in more detail in recent reviews.[202]

4.7 Conclusion

Alternatives to meat have always been available but purely vegan diets remain rare. As the taste and texture of plant-based alternatives has improved in recent years, so has consumer acceptance and market share. Although plant-based meat alternatives can be formulated to contain all recommended dietary amino acids, the complex bioactive peptides, fats, and muscle proteins found in animal meats are missing from plant-based products. These proteins and molecules can have important sensory properties, like aromas and flavors, that influence the dining experience. These proteins and molecules can also influence digestion, including interactions with the gut microbiome with potential impacts on health and mood that require further study. There are thousands of molecules that are specific to meats and cannot be affordably synthesized. The most feasible way to reproduce protein families that are specific to meat, without using the animal, are the culture and expansion of animal cells to include in alternative meat products. The high cost and complexity of cell culture at industrial scales will likely dictate a path to scale-up where small amounts of cells are added to scaffolds to enrich their taste, aroma, and nutrition. Hybrid products, containing both plant proteins and animal proteins derived from cell cultures, will provide opportunity for cell culture facilities to test best practices and scale their technology platforms.

Fundamental Questions – Answered

1) What is the definition of a cell, and how is this relevant for the development of cultured meats?
Biological cells are the smallest unit of life and the building block of all known organisms. Single-celled microorganisms such as yeasts, or multicellular organisms such as plants and animals, are all built from cells that share fundamental traits. They contain code (DNA), the machinery to translate this code into molecules, and the means to use this machinery to make copies of themselves. Cells can multiply (proliferate) and alter their characteristics (phenotype) to meet specific functional needs. In multicellular organisms such as meat-producing animals, cells assemble into specialized tissues like skeletal muscle, fat, and connective tissues. These are the main components of meat.

Cells form a large taxonomy; this chapter will focus on a few examples that are most relevant to cell-cultured cultured meat production. Specifically, this chapter focuses on distinguishing between cells that are grown in suspension and cells that are adherent and require attachment to substrates for growth. At times there is some cross-over between these cell types as adherent cells may be selected or engineered to grow in suspension. Suspended cells like yeasts are relevant to cultured meat because of their widespread use in food and beverage industries, their ability to proliferate in large numbers, and because they are increasingly used to produce valuable biomolecules that help meat cells grow.

Culturing meat cells, namely skeletal muscle and fat cells from animals or animal stem cells, requires sterile conditions that protect growing cells from pathogens. It also requires recreating several conditions naturally found inside the animal. These include pH-balanced culture media containing nutrients, methods to exchange nutrients and waste, and consistent natural body temperature. These methods have already been used to create proof-of-concept cultivated meats and first-generation commercial products. The main objectives of such research now focus on higher production, lower costs, and better product quality. Cells are at the center of these challenges because production is limited by cell proliferation, high price of nutrients such as growth factors in cell culture media, and cell-cultured meat's ability to safely replicate the types of cells present in natural meats.

2) What type of materials can be used for the development of cells for cultured meat?

The main groups of materials used to produce cell-cultured cultured meat include: i) the cells themselves; ii) pH-balanced cell culture media that contains nutrients selected for each cell type and culture protocol; iii) substrates for adherent cell attachment such as microcarriers or scaffolds, including scaffolds that provide texture and structure to cultured meat products; and iv) bioreactors, media perfusion systems, and related process controls used to exchange nutrients and regulate cell metabolism throughout growth and maturation.

3) What type of cells and tissue architectures can be produced with the state-of-the-art technology?

A wide variety of cell types and tissue architectures relevant to cell-cultured meat can be cultured and structured to resemble small pieces of meat. Small samples of cell-cultured cultured beef, pork, chicken, turkey, fish, shrimp, and others have been reported in scientific journals and in the press, but few of these reports compare specific tissue architectures or protein compositions to animal-based meat products. Cell-cultured meat quality, as defined by its similarity to natural meats, will need continued improvement in architecture and composition. Methods now exist to produce animal stem cells and to initiate early-stage lineage specification towards skeletal muscle or fat phenotypes, but protocols to produce mature phenotypes found in natural muscle tissues are incomplete. It is not yet possible to grow skeletal muscle cells that have mature phenotypes matching those in natural meat cells, and the degree to which cultured cells match the protein expression of natural meats is still largely unexplored. Natural muscle tissues contain closely packed, metabolically active contractile muscle cells that are kept alive in dense tissues by a vascular system. Growing thick vascularized tissues at low costs is not currently possible.

4) How scalable is the preparation of cells, and are they cost-effective?

The cost of preparing cells for cell-cultured meat cannot yet compete with farm-raised meat production. To impact meat markets, cultured cells need to be produced at larger numbers and lower costs. However, strategies aiming to increase cell growth rates through selection or genetic engineering should result in new regulatory guidelines and public awareness. For more information on how price will specifically affect market adoption, please refer to the Chapter 11, Consumer Acceptance of Cultivated Meat.

5) How can cells be integrated into a cell-cultured meat production process?
Cells are expected to play several key roles in the cell-cultured meat production process. Skeletal muscle myoblasts and fat adipocytes form the principal components of meat, and, therefore, of most proposed cell-cultured meat products. Thus, cell-cultured meat requires significant scale-up of proliferative cells that give rise to skeletal muscle and fat. To culture these cells at low costs, the price of culture media growth factors needs to be reduced. Yeasts and other cells already grown at large scales will likely be modified to produce the growth factors that support stem cell expansion, as well as muscle and fat production.

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Tables

Table 1. Description and classification of key muscle fiber types

Fiber Type	Description	Classification
Type I or β-Red or SO	Slow oxidative (SO)	Dark Red
Type IIA or α-Red or FOG	Fast oxidative glycolytic (FO)	Intermediate or Red
Type IIB or α-White or FG	fast twitch glycolytic (FG)	White

Table 2. Physical characteristics of beef muscle fibers

Breeds	Tissue (cut, location)	Cells ● Relative abundance (Area %) ● Structure (cell diameter) ● Fat (%)				Other	Reference
		Type I (BR) (Area%)	Type IIa (AR) (Area%)	Type IIb (aW) (Area%)	Intramuscular Fat (%)		
Mertolenga young bulls	Longissimus dorsi	20.64	36.06	43.30			[203]
Mertolenga young bulls	Supra spinatus	36.06	33.33	31.11			
Mertolenga young bulls	Semitendinosus	43.30	44.00	56.32			
Angus × Gelbvieh steers at 13.5 months of age (High IM)	Longissimus thoracis muscle (LM)				6	0.65 Type 1/Type 2	[204]
Angus Steer	Longissimus muscle	19.52		80.48	2.85	5.31 mg of collagen/g	[205]
Angus Bull	Longissimus muscle	21.65		78.35	1.95	6.36 mg of collagen/g	
Angus	Longissimus dorsi				2.67	5.73 mg of collagen/g	
Angus	Psoas major				3.43	3.18 mg of collagen/g	
Angus	Semitendinosus				2.27	7.53 mg of collagen/g	
Angus	Semimembranosus				1.36	5.05 mg of collagen/g	
Angus	Biceps fermoris				2.17	7.43 mg of collagen/g	
Various Breeds		22.9	30.8	45.1		2.9 mg of collagen/g	[206]
English breeds, Steers					2.85	Sarcomere Length (1.78 µm); 5.41 mg of collagen/g	[207]
English breeds, Bulls					1.94	Sarcomere Length (1.79 µm); 6.49 mg of collagen/g	
English breeds	Longissimus dorsi				2.67	Sarcomere Length (1.65 µm); 5.87 mg of collagen/g	
English breeds	Psoas major				3.43	Sarcomere Length (1.75 µm); 5.3.45 mg of collagen/g	
English breeds	Semitendinosus				2.27	Sarcomere Length (1.99 µm); 7.69 mg of collagen/g	
English breeds	Semimembranosus				1.36	Sarcomere Length (1.77 µm); 5.49 mg of collagen/g	
English breeds	Biceps femoris				2.17	Sarcomere Length (1.77 µm); 7.64 mg of collagen/g	
Limousin	Longissimus dorsi (12-13 rib)	29.46 [35.99 µm]	26.54 [41.49 µm]	44.00 [49.47 µm]			[208]
Simmental	Longissimus dorsi (12-13 rib)	15.24 [36.55 µm]	28.58 [39.22 µm]	56.16 [49.46 µm]			
Luxi	Longissimus dorsi (12-13 rib)	32.73 [38.98 µm]	24.02 [41.42 µm]	29.17 [59.27 µm]			

Qinchuan	Longissimus dorsi (12-13 rib)	16.91 [60.00 μm]	29.17 [61.10 μm]	53.90 [67.80 μm]			
Jinnan	Longissimus dorsi (12-13 rib)	20.62 [37.58 μm]	23.23 [42.19 μm]	56.14 [47.94 μm]			
Crossbred steers	Longissimus	22.8	27.6	49.6	2.75		[209]
Crossbred steers+ Synovex-S®	Longissimus	22.6	26.1	51.3	2.08		
Crossbred steers+ Somavubove®	Longissimus	23.6	27.9	48.5	2.53		
crossbred steers+ Synovex-S®+ Somavubove®	Longissimus	22.4	30.2	47.4	1.85		
A-maturity, Select-grade	Longissimus dorsi	22.3 [41.9 μm]	22.9 [54.8 μm]	54.8 [60.7 μm]		Thirty-eight muscles of the beef characterized	[210]
German Angus (0 month)	Semitendinosus	15	45	40	0.43	Mean fiber area 618 μm^2	[211]
German Angus (12 month)	Semitendinosus	20	20	60	1.1	Mean fiber area 3,636 μm^2	
German Angus (24 month)	Semitendinosus	20	20	60	2.4	Mean fiber area 6,631 μm^2	
Crossbreed	Longissimus dorsi (13 rib)	19.36 (1895 μm^2)	18.50 (2120 μm^2)	62.43 3595 μm^2	3.89	1.73 μm sarcomere length; 5.83 mg collagen/g	[212]

Table 3. Composition of beef fat

Species	Tissue (cut, location)	Cells • Composition (key proteins, fats, nutrients)						Reference
		Intramuscular total lipids (ITL, g/100 g)	neutral lipids (NL, g/100 g)	phospholipids (PL, g/100 g))	α-tocopherol (mg/100 g)	cholesterol (mg/g)	heme iron (mg/100 g)	
Mertolenga young bulls	Longissimus dorsi	1.43	0.87	0.57	0.17	0.41	1.98	[203]
Mertolenga young bulls	Supra spinatus	2.25	1.65	0.68	0.25	0.53	2.18	
Mertolenga young bulls	Semitendinosus	1.53	0.89	0.62	0.19	0.42	1.74	
		saturated	monounsaturated	polyunsaturated				[213]
Belgian Blue	Longissimuslumborum	338 mg/100g	323 mg/100g	195 mg/100g				
Belgian Blue	Semimembranosus	173 mg/100g	172 mg/100g	386 mg/100g				
		Fat Content	Moisture Content					
Canada AA beef		20 – 160 mg/g	640 – 770 mg/g					[214]

Table 4. Physical characteristics of pig muscle fibers

Breed	Tissue (cut, location)	Cells • Relative abundance (%) • Structure (cell diameter)				Other e.g. Composition (key proteins, fats, nutrients)	Reference
		Type I (BR) (Area%)	Type IIa (AR) (Area%)	Type IIb/x (aW) (Area%)	Intramuscular Fat		
Landrace x Yorkshire x Duroc	Longissimus dorsi (8-9 rib)	4.10-8.47	3.43-7.42	92.47-84.992			[215]
Wild Boar	Longissimus dorsi	13.0	17.3	69.7		Cross sectional fiber area 3.49 10^3 μm^2	[216]
Wild boar	Semimembranosus	16.6	16.1	67.3		Cross sectional fiber area 3.64 10^3 μm^2	
Wild boar	Gluteus superficialis	17.9	16.4	65.8		Cross sectional fiber area 4.31 10^3 μm^2	
Wild boar	Infra spinam	55.3	33.5	11.3		Cross sectional fiber area 4.46 10^3 μm^2	
Wild boar	Masseter	68.0	28.7	3.3		Cross sectional fiber area 3.05 10^3 μm^2	
Domestic pig	Longissimus dorsi	6.5	3.2	90.3		Cross sectional fiber area 5.25 10^3 μm^2	
Domestic pig	Semimembranosus	6.6	3.6	89.8		Cross sectional fiber area 5.65 10^3 μm^2	
Domestic pig	Gluteus superficialis	6.8	4.0	89.3		Cross sectional fiber area 5.33 μm^2	
Domestic pig	Infra spinam	53.0	19.7	27.3		Cross sectional fiber area 5.14 10^3 μm^2	
Domestic pig	Masseter	22.5	79.8	6.7		Cross sectional fiber area 2.75 10^3 μm^2	
Large White Gilt	Longissimus (last rib)	6.5 (CSA 2,415 μm^2)	3.5 (CSA 1,868 μm^2)	90 (CSA 3.782 μm^2)			[217]
Large White Barrow	Longissimus (last rib)	6.8 (CSA 2,736 μm^2)	3.3 (CSA 1,571 μm^2)	89.9 (CSA 3,525 μm^2)			
Crossbred barrows (0.90 m2 /pig space allowance)	Longissimus (10-11th rib)	19.7	16.4	63.9			[218]
Crossbred barrows (0.90 m2 /pig space allowance)	Semimembranosus	24.3	18.6	57.1			
Crossbred barrows (9.45 m2 /pig space allowance)	Longissimus (10-11th rib)	18.4	16.6	65.0			
Crossbred barrows (9.45 m2 /pig space allowance)	Semimembranosus	21.6	18.4	60.0			
Swedish Yorkshire pigs (high protein diet)	Longlssimus dorsi	7.4	7.3	84.6	1.5	17.3 (mmol/kg dry wt)	[219]

Swedish Yorkshire pigs (low protein diet)	Longlssimus dorsi	7.9	8.4	83.3	2.5	Triglycerldes 29.1 (mmol/kg dry wt)	
Swedish Yorkshire pigs (high protein diet)	Biceps femoris	21.9	8.5	70.9	1.3	Triglycerldes 16.4 (mmol/kg dry wt)	
Swedish Yorkshire pigs (low protein diet)	Biceps femoris	21.5	11.6	66.7	2.0	Triglycerldes 18.7 (mmol/kg dry wt)	

Table 5. Physical characteristics of poultry muscle fibers

Species	Tissue (cut, location)	Cells ● Relative abundance (%) ● Structure (diameter, length)				Other	References
		Type I	Type IIa	Type IIb	Fat		
Chicken	Pectoralis			100 (3,346 μm^2)		1.63% lipid	220
Duck	Pectoralis		84.33 (301 μm^2)	15.7 (1,809 μm^2)		2.34% lipid	
Turkey				(99-112 µm)	0.81-1.05		221
Chicken, Gallus Domesticus (16 wk)	Pectoralis				0.37	5.09 mg collagen/g	222
Chicken, Gallus Domesticus (16 wk)	Biceps femoris				0.58	12.85 mg collagen/g	
Choicken, Commercial Broiler CP707 (38 days)	Pectoralis				0.68	3.86 mg collagen/g	
Choicken, Commercial Broiler CP707 (38 days)	Biceps femoris				0.81	8.70 mg collagen/g	
Chicken, Breast muscle					0.22-2.88%	7.15 – 28.3 mg collagen/g	223
Chicken, Thigh muscle					0.48-6.29%	10.33 – 42.2 mg collagen/g	
Goose	Pectoralis major	52 [27 µm]		48 [51 µm]			224
Quail	Pectoralis major	51 [23 µm]	11 [23.7 µm]	38 [47 µm]			
Pheasant	Pectoralis major	17 [47.5 µm]		83 [72.7 µm]			
Guiena-hen	Pectoralis major	11 [51 µm]		89 [83.6 µm]			
Chicken (broiler)	Pectoralis major	2 [48.1 µm]		96 [68.2 µm]			
Laying Hen	Pectoralis major	1 [36 µm]		99 [60 µm]			
New Hampshire chickens (1 week)	Pectoralis			100 [10.1 µm]			225
New Hampshire chickens (15 week)	Pectoralis			100 [38.3 µm]			
New Hampshire chickens (35 week)	Pectoralis			100 [62.1 µm]			
New Hampshire chickens (1 week)	Iliotibialis lateralis		21.5 [9.4 µm]	78.6 [9.3 µm]			
New Hampshire	Iliotibialis lateralis		39.1 [31.5 µm]	60.9 [40.1 µm]			

chickens (15 week)							
New Hampshire chickens (35 week)	Iliotibialis lateralis		53.9 [61.8 µm]	46.1 [70.5 µm]			

Table 6. Physical characteristics of fish muscle fibers

Species	Tissue (cut, location)	Cell diameter		References
		Type I	Type IIb	
Pacific bluefin tuna	dorsal ordinary		57-87 µm	[226]
Pacific bluefin tuna	lateral ordinary		59-90 µm	
Pacific bluefin tuna	Dark	30-43 µm		
Bluntnose minnow			20-90 µm	[227]
Rainbow trout			53-90 µm	
Muskellunge			20-60 µm	

Table 7. Properties of cultured cow muscle cells

Species	Type	Doubling rate	Doubling number	Largest scale	Notes	References
Cow	Primary myoblasts	~24hrs	Up to P8 tested	Micro-carriers 10^7	Isolated from fresh beef	[61]
Cow (Angus)	Primary myoblasts	30.3 hrs	Up to P2 (cultured for 2 days)	Culture plates	Markers for diff. capacity shown	[228]
Cow (Charolaise x Simmental)	Satellite cells	36.5 hrs	NA	Mm sizes (fibrin gels)	With myoglobin	[229]
Cow (Charolaise x Simmental)	Satellite cells	41.5 hrs	NA	Mm sizes (fibrin gels)	Differentiation shown	
Calves (Holstein Friesian) Cow (Holstein Friesian)	Satellite cells	<48 hrs (calves) >48 hrs (cows)	Up to P4-5 tested	Culture plates	Heterogeneous population identification Faster proliferation in young vs old cows	[230]
Cow (Longissimus thoracis)	Primary myoblasts	52.8 days	Up to P2-3 tested	Culture plates	Surface coatings (GAG and proteins) improve proliferation and differentiation	[231]
Cow	Satellite cells	~55 hrs	P10	10^{13} cells cultured (in culture plates)	p38 inhibition maintains stemness and differentiation capacity	[232]
Cow (Holstein Friesian)	Satellite cell	NA	Up to P2-4 (cultured for 21 days)	10^6 (at seeding) mm-sized soy scaffold	Co-cultures (ECs, SCs, SMCs) improved myogenesis	[233]
Cow fetus	MSC from bone marrow	NA	Up to P4-5 (cultured for 21 days)	Culture plates	Skeletal phenotype confirmed but not strong	[234]
Cow fetus (Western Shandong Yellow)	iPSC from fibroblasts	NA	P16 (self-renewal potential)	Culture plates /teratomas	Smooth muscle	[235]
Cow (ovaries)	Embryonic stem cells (blastocyte)	30-40 hrs	P50 (self-renewal potential)	Culture plates/teratomas	The first stable culture of bovine embryonic stem cells (ESC)	[236]

Cow	MSC (Wharton's jelly)	NA	P60	Culture plates	Serum-free culture Adipogenic, no skeletal diff. shown	237

Table 8. Properties of cultured cow fat cells

Species	Type	Doubling rate	Doubling number	Largest scale	Notes	References
Cow (Angus)	Stromal-vascular cells (subcutaneous and intramuscular adipose tissues)	NA	P9	Culture plates	Preadipocytes are capable of differentiation	30
Cow (Angus heifer)	Stromal-vascular cells	NA	Immortalized cells (pCI neo-hEST2)	Culture plates	Good differentiation Zfp423 is a critical regulator of adipogenesis in stromal vascular cells of bovine muscle	238
Cow	Stromal-vascular cells (subcutaneous fat tissue)	NA	Cultured for 14 days	2d and 3d (alginate scaffold)	Food compatible adipogenic differentiation	29
Cow (Angus)	Mature perimuscular fat	NA	Cultured for 16 days	Culture plates	Good re-differentiation	239
Cow (Wagyu)	Subcutaneous fat	NA	Cultured for 21 days	Culture plates	DFAT Differentiation efficiency still needs improvement	240

Table 9. Properties of cultured pig muscle cells

Species	Type	Doubling rate	Doubling number	Largest scale	Notes	References
Piglet	Primary myocytes	24 hrs	P2-3 (cultured for 20 days)	Culture plates	Derived from satellite cells	241
Piglet and Pig (Duroc × Yorkshire × Landrace)	Satellite cells	18.6 hrs (newborn) 23.2 hrs (adult)	NA	Culture plates /Matrigel	Red (RST) portions of the semitendinosus muscle of neonatal and adult pigs	242
Piglet (Large White)	Satellite cells	19 hrs	P10	Culture plates	Shows loss in myogenic potential with passages	243
Piglet (Landrace)	Satellite cells & muscle precursor cells	20 hrs	NA	Culture plates	Differentiation shown	244
Pig (Lantang and Landrace)	Satellite cells	32 hrs	NA	Culture plates	Markers for diff. capacity shown	245
Pig	Satellite cells	30-50 hrs	P12	Culture plates	Doubling time increases with passages	66
Piglet (Duroc × Yorkshire × Landrace)	Satellite cells	48 hrs	NA	Culture plates		155

Pig (Large White)	Satellite cells (myoblasts)	NA	P7 (cultured for 70 days)	Culture plates /Maxgel	Good differentiation	[246]
Pig	Interstitial progenitor cells	21.6 hrs	P40	Culture plates	Smooth and skeletal, but limited differentiation	[65]
Pig	iPSC	NA	Self-renewing claimed	Culture plates	Good differentiation	[247]
Pig	iPSC	~24 hrs	>P45 (self-renewing potential)	Culture plates, teratomas	Limited differentiation (no myogenic markers shown)	[248]
Pig (Hampshire)	iPSC	20 hrs	P8 (self-renewing potential)	Stirred bioreactor	No differentiation into muscle shown	[156]
Pig	iPSC	NA	P60 (self-renewing)	mm-sized PGA scaffold	Smooth muscle	[249]
Pig	iPSC	17 hrs	>220 doubling	Culture plates, teratomas	Differentiates in all germ layers in tumors	[250]
Pig	iPSC				Smooth muscle	[251]

Table 10. Properties of cultured pig fat cells

Species	Type	Doubling rate	Doubling number	Largest scale	Notes	References
Piglet (Landrace)	Subcutaneous adipose tissue	20-22 hrs	P60	Culture plates	DFAT Differentiation shown	[252]
Pig	Adipose-derived stem cells (visceral fat)	32 hrs	P27	Culture plates	Differentiation shown	[253]
Pig	MSC (various sources)	48-60 hrs	P6 (cultured for >30 days)	Culture plates	Some differentiation shown	[254]
Pig	MSC (subcutaneous and bone marrow tissue)	NA	P20	Culture plates	Proliferative potential decreases with passage	[255]

Table 11. Properties of cultured chicken muscle cells

Species	Type	Doubling rate	Doubling number	Largest scale	Notes	References
Chicken embryo (UK Chunky)	Primary myoblasts	21 hrs	NA	Culture plates		[67]
Chicken embryos (White Leghorn)	Primary myoblasts	25 hrs	NA	Culture plates		
Chicken broiler	Satellite cells	24 hrs	P3	Culture plates	Cell doubling was not sustained beyond day 8	[256]
Chickens broiler (ROSS 308 strain)	Satellite cells	NA	P2	Culture plates	Simple protocol – good differentiation	[257]
Chicken (Beijing Fatty)	Satellite cells	NA	P15	Culture plates	Differentiation limited – detach beyond P15	[258]

Chicken (Red junglefowl)	Primordial germ cells	13 hrs	P80	3d culture in polysaccharides	No muscle differentiation shown	[259]
Chicken (Donglan)	Primordial germ cells	44.4 hrs	2 months in culture	Culture plates with feeder cells	No muscle differentiation shown	[260]
Chicken (White Leghorn)	Primordial germ cells	45.6 hrs	20 months in culture	Culture plates with feeder cells	No muscle differentiation shown	[167]
Chicken broiler newborn	MSC (bone)	66-74 hrs	P8	Culture plates	Adipogenic diff. Myogenic markers shown	[261]

Table 12. Properties of cultured chicken fat cells.

Species	Type	Doubling rate	Doubling number	Largest scale	Notes	References
Arbor Acres broiler chickens	Preadipocyte cell line	NA	P100	Culture plates	Differentiation capacity Retroviral transduction of chTERT and chTR	[262]
White Leghorn	Fibroblast cell line	NA	P10	Culture plates	No differentiation shown	[191]
Chicken broiler embryo (Gallus gallus)	Adipose-derived stem cells	39-45 hrs	P37	Culture plates	Proliferation decreases with passages	[263]
Chicken embryo	MSCs	NA	P15	Culture plates	Differentiation	[264]

Media

Overview of Cell Culture Media for Cultivated Meat

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Chapter Abstract

Cell culture media is a nutritional solution composed of sugar, amino acids, vitamins, inorganic salts, and various endocrine factors. Media provides cells and tissues with the necessary components to survive and grow *in vitro*, and its composition is usually tailored to the needs of specific cell lines and their applications. Cell culture media is estimated to account for ~55-95% of the marginal cost contributions of cell-cultured meat, a burgeoning industry in cellular agriculture. The mass production of cell-cultured meat hinges on the development of novel, inexpensive and scalable media formulations. To that end, this chapter discusses the roles of key components in media, challenges with existing solutions, and strategies for producing new serum-free media formulations. It will then dive into considerations for making food-grade media, in particular safety, regional, and religious requirements. Next, the chapter discusses the sourcing and waste management constraints in scaling a food-grade media formulation. It ends with a summary of future directions for impactful research in this space.

Keywords

Cell culture media
Media
Serum
Fetal Bovine Serum (FBS)
Serum-free Media
Yamanaka Factors

List of Figures

Figure 1: Bicarbonate Buffer System
Figure 2: Media Pyramid: A Modular Approach for the Development of Serum-free Media
Figure 3: DOE Process Diagram

List of Tables

Table 1: Categories of Cell Culture Media
Table 2: The Main Components of Serum and Their Mean Concentration
Table 3: Features of Lipid Supplemental Approaches
Table 4: Serum-free Culture Media for Chinese Hamster Ovary cells
Table 5: Serum-free Culture Media for Embryonic Stem/ Induced Pluripotent Stem Cells
Table 6: Sequential Adaptation

Chapter Outline

5.1 Introduction
- 5.1.1 What is Cell Culture Media?
- 5.1.2 Why is Cell Culture Media Important?

5.2 History of Cell Culture Media
- 5.2.1 1880-1940: The Origins of Cell Culture
- 5.2.2 1940-1960 Part 1: First Successes of the Reductionist Approach
  - 6.2.2.1: The Discovery of FBS
- 5.2.3 1940-1960 Part 2: Synthetic Approach
- 5.2.4 1970s-Present

5.3 Key Components in Media
- 5.3.1 Background
- 5.3.2 Basal Media
  - 5.3.2.1 Amino acids
  - 5.3.2.2 Carbohydrates
  - 5.3.2.3 Vitamins
  - 5.3.2.4 Inorganic Salts and Osmolality
- 5.3.3 Monitoring pH and Buffering Systems
  - 5.3.3.1 Phenol Red
  - 5.3.3.2 CO_2-Bicarbonate System
  - 5.3.3.3 HEPES

5.4 Supplements
- 5.4.1. Serum
  - 5.4.1.1 FBS
- 5.4.2 Serum Components
  - 5.4.2.1 Growth Factors
  - 5.4.2.2 Hormones
  - 5.4.2.3 Carrier Proteins
  - 5.4.2.4 Lipids
  - 5.4.2.5 Trace Elements and Minerals
  - 5.4.2.6 Adhesion Factors
- 5.4.3 Antibiotics and Other Components to Consider
- 5.4.4 Current Serum Replacements
  - 5.4.4.1 Platelet Lysate
  - 5.4.4.2 Conditioned Media

5.5 Serum-free Media Formulations
- 5.5.1 Standard Method for Making Serum-free Media Formulations
- 5.5.2 Design of Experiments
- 5.5.3 Adaptation
  - 5.5.3.1 Considerations for Adaptation

5.6 Considerations for Proliferation and Differentiation

5.7 Cell Culture Media for Cellular Agriculture Applications

5.7.1 Food-grade Culture Media
5.7.2 Religious and Vegan Requirements
5.8 From Lab Scale to Large Scale
5.8.1 Economics of Food-grade Media
5.8.2 Ingredient Sourcing
5.8.3 Waste Management
5.9 Further Directions
5.9.1 Inexpensive, Stable Recombinant Growth Factors
5.9.2 Growth Factor Replacements
5.9.2.1 Sericin and Protein Hydrolysates
5.9.3 Heat Stable Ingredients
5.9.4 Media Optimization
5.9.4.1 Modeling Metabolism
5.9.4.2 Efficient Media Formulation Methods
5.9.5 Media Recycling
5.9.6 Sensory Effects
5.10 Conclusion

5.1 Introduction

The first attempts to grow cells outside of the body were more than a century ago. Since then, scientists have continuously strived to determine the exact mixture of nutrients to properly culture cells *in vitro*. The field now has a good understanding of not only which components are needed to support cell growth, but also why these components are essential and in what quantities. This has allowed for the development of media formulations that support cells of various types, encourage their proliferation, and even dictate the timing and degree of differentiation. Media can now be purchased from reagent manufacturers for many common cell lines. Although readily available, many media formulations come at a considerable cost, require animal-based components, and do not support most of the cell lines needed for cell-cultured meat. Thus, significant work is required to develop inexpensive, efficacious animal-free media at scale for cellular agriculture applications.

5.1.1 What is Cell Culture Media?

Cell culture media (or media) is a mixture of water, salts, a carbon-based energy source, amino acids, vitamins, and other factors needed to support cell survival *ex vivo*.[53] Media is one of the most important factors in cell culture technology, and its quality is a key determinant in research results and bioproduction yields. Scientists must diligently select or develop media formulations that are appropriate for their specific aims to ensure good performance.[54]

To that end, media formulations support a variety of dedicated functions including cell growth, proliferation, differentiation, or retention of multipotency. This variety of capabilities arise from the differences in formulations, especially growth factors, hormones, and micronutrients. Additionally, formulations tend to be tailored to specific cell lines; by considering the unique metabolism and stage of growth of different cells, media can be adjusted to best meet specific functions.

5.1.2 Why is Cell Culture Media Important?

Cell culture media is of particular importance to cellular agriculture researchers because (1) it is a key cost driver in cell-cultured meat production and (2) a vital factor in creating and scaling these products.

Recent techno-economic analysis of cell culture media estimated that 55-95% of the cost of cell-cultured meat will come from media.[55] Current projections suggest that media formulations will need to drop to below US $1 per liter to ever be economically viable at industrial scale.[56] Although many recent commercial advancements in optimizing serum-free

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formulations have reduced the cost of media, the industry is still far from reaching price parity with traditional meats. Therefore, cell culture media presents a significant economic risk to cell-cultured meat and addressing this is a priority.

Cell culture media is essential to maintaining cell growth and survival *ex vivo*. Thus, to create and scale cell-cultured meat, it is necessary to develop media formulations that allow relevant animal cell lines to grow *ex vivo*, specifically in large scale bioreactors. Although straightforward in theory, this is challenging in practice, because of the high number of cell lines, limited prior work on these cell lines, and a large range of possible formulations to explore. To meet the requirements of scale and remove ethical issues, such as the use of animal-based ingredients, it is also necessary to find a suitable replacement for components such as fetal bovine serum (FBS). Therefore, cell culture media also presents an important technical risk to the future of cell-cultured meat and is arguably the most important challenge to solve in this field.

5.2 History of Cell Culture Media

This section will describe the origins of cell culture and technological advancements over time. This knowledge is important because the main cost driver of cell-cultured meat today is the media formulation. Furthermore, current challenges, such as the dependence on FBS and the fact that serum is not chemically defined, highlight the need for innovation.

5.2.1 1880-1940: The Origins of Cell Culture

In 1882, Sydney Ringer created an eponymous solution containing sodium chloride, potassium chloride, calcium chloride, and sodium bicarbonate in physiological concentrations. This solution keeps frog hearts beating after dissection and removal from the body and is the first known *ex vivo* cultivation of animal tissue. Since then, scientists iterated on Ringer's solution and judged new variants by their ability to support animal tissue growth outside of the body. Not long after, Margaret Adaline Reed Lewis and Warren Harmon Lewis created the Locke-Lewis solution, which mimicked blood plasma. It served as the media for what is considered to be the first *in vitro* mammalian cell culture and was used for culturing explanted guinea pig bone marrow cells. The guiding philosophy of these early days involved biomimicry combined with a reductionist approach to identify core components of the solutions. Several papers written during this period helped to shed light on the important components of a solution able to sustain cells outside of their bodily environment.[57]

5.2.2 1940-1960 Part 1: First Successes of the Reductionist Approach

A key tipping point in cell culture history happened in the 1950s. Until then, most cell lines eventually stopped undergoing mitosis after a certain number of generations, known as the Hayflick limit. This changed in 1951, when a biopsy was taken from a 31-year-old woman, Henrietta Lacks, who died of cancer shortly after. Using her cells, scientists were able to create

[57] Yao, Tatsuma, and Yuta Asayama. "Animal-cell culture media: History, characteristics, and current issues." Reproductive medicine and biology 15.2 (2017): 99-117.

the first human immortalized cell lines, HeLa.[58] Although the emergence of these established cell lines enabled more growth in cell culture research and subsequent scientific advancements, the lack of consent in obtaining these cells stains this achievement and underscores how scientific progress is often intertwined with the surrounding socioeconomic context.

In 1955, Harry Eagle studied the minimum necessary amounts of low-molecular-weight components that are required by mouse L fibroblast cells and HeLa cells by using a balanced salt solution with the addition of dialyzed serum. This formulation is known as Eagle's Minimum Essential Medium (MEM). It contained inorganic salts, supplemented with 13 essential amino acids and eight vitamins. Further improvements were made to MEM and led to Dulbecco's Modified Eagle Medium (DMEM) in 1959.[59]

5.2.2.1 The Discovery of FBS

An important chapter in cell culture media history is the first use of FBS as a media supplement. A paper co-authored by Theodore Puck in 1958 is the earliest to mention the use of fetal calf serum as a supplement to a synthetic nutrient solution to support the growth of human and animal cells. The paper reported the use of fetal calf serum at 15% concentration in addition to a synthetic nutrient solution. The author reported long-term cultivation of a diversity of cell lines from different organs and organisms without their compromise. This paper was foundational for current cell culture techniques; more than 60 years later, in 2021, FBS is still used in conjunction with DMEM in concentrations from 5-20%. Hypotheses for its effectiveness as a supplement revolve around its high concentration of growth factors and nutrients along with other ingredients essential to cell growth and proliferation. FBS and the issues surrounding its use in cell culture are discussed later in the chapter.

5.2.3 1940-1960 Part 2: Synthetic Approach

While some researchers took a reductionist approach based on iterating the components found in working solutions, others focused on a synthetic approach to create chemically defined media. Medium 199, CMRL1066, NCTC109, Ham's F-12, are examples of synthetic media developed in the 1940s and 1950s. Researchers tailored these formulations to the available immortalized cell lines (typically mouse L cells). These compositions usually involve between 40 and 60 ingredients. This complexity and specificity made them less adopted than their counterparts which seemed to have more universal cell proliferation abilities.

The key successes of this 80-year journey came from biomimicry of known bodily fluids (a strong starting point given their ability to support cell proliferation), standardization of cell lines, and the development of statistical approaches to identify essential components able to support proliferation. While the reductive approach initially took the lead, the emerging synthetic approach offered a complementary paradigm.

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[58] Butanis, Benjamin. "The Legacy of Henrietta Lacks." Johns Hopkins Medicine, Based in Baltimore, Maryland, 9 Mar. 2020, www.hopkinsmedicine.org/henriettalacks/.

[59] Yao, Tatsuma, and Yuta Asayama. "Animal-cell culture media: History, characteristics, and current issues." Reproductive medicine and biology 16.2 (2017): 99-117.

5.2.4 1970s-Present

As of the early 2020s, most biology laboratories engaged in cell culture use DMEM + 10% FBS. Those core formulations were finalized in the late 1950s and have become the foundation of modern cell culture. A few improvements were made in the decades after and include the discovery of the value of adding growth factors in addition to those found in FBS. Recent developments that spurred the development of new, chemically defined media formulations were the discovery of embryonic stem cells (ESC) in 1981 and the ability to create induced pluripotent stem cells (iPSC) in 2007. These cells are used for regenerative medicine, disease modeling, and cultivated meat production and it is important to culture these cells in an affordable and safe way. An example of chemically defined media formulation for human iPSCs is Essential 8™ (Thermo Fisher, Waltham, Massachusetts).

While this situation leaves room for improvement, it is neither a significant pain point nor a bottleneck for most cell culture use cases since not much media is used and media formulation is rarely the most expensive component of cell culture. However, this is not the case for cell culture where new approaches are needed as media is the most expensive component.

5.3 Key Components in Media

5.3.1 Background

This section will focus on understanding what are the key components that make up cell culture media, what role they each play, and considerations in making custom formulations.

Different types of cell culture media formulations are distinguished by where the components are sourced from. The two overarching categories are natural media and synthetic media. Natural media is made mostly from extracts of natural biological material, often coagulants, tissue extract, and biological fluids (e.g., plasma, serum).[60] As the understanding of what components are necessary for cell culturing grew (especially in the late 1940s), newer synthetic media formulations were developed.

Synthetic media is composed of a basal media and mixture of supplements (e.g., serum, hormones, growth factors); the latter of which is a key differentiating factor for different synthetic media. There are five main types of synthetic media: serum-containing, serum-free, xeno-free, protein-free, and chemically defined media.[61] Serum-containing media is composed of basal media and supplemented serum; this formulation is one of the most used media in academic research. Serum-free media uses crude protein fractions (e.g., bovine serum albumin) instead of serum as a supplement (note that serum-free does not mean animal-free). Xeno-free media uses human derived components as supplements. Protein-free media uses peptide fractions or protein hydrolysates as supplements and is commonly animal-free. Chemically defined media

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[60] Arora, Meenakshi. "Cell culture media: a review." *Mater methods* 3.175 (2013): 24.
[61] Arora, Meenakshi. "Cell culture media: a review." *Mater methods* 3.175 (2013): 24.

has all known components and quantities, which often requires highly purified or recombinant components. The latter two synthetic media types are ideal for cellular agriculture applications.

Table 1: Categories of Cell Culture Media

TABLE 1 Categories of animal-cell culture media

Category	Definition	Type	Example
Natural media	Consisting of natural biological substances, such as plasma, serum, and embryo extract	Coagulant or clots	Plasma separated from heparinized blood, serum, and fibrinogen
		Tissue extracts	Extracts of chicken embryos, liver, and spleen and bone marrow extract
		Biological fluids	Plasma, serum, lymph, amniotic fluid, and pleural fluid
Synthetic media	Composed of a basal medium and supplements, such as serum, growth factors, and hormones	Serum-containing media	Human, bovine, equine, or other serum is used as a supplement
		Serum-free media	Crude protein fractions, such as bovine serum albumin or α- or β-globulin, are used as supplements
		Xeno-free media	Human-source components, such as human serum albumin, are used as supplements but animal components are not allowed as supplements
		Protein-free media	Undefined components, such as peptide fractions (protein hydrolysates) are used as supplements
		Chemically defined media	Undefined components, such as crude protein fractions, hydrolysates, and tissue extracts, are not appropriate as supplements, but highly purified components, such as recombinant proteins are appropriate supplements

The essential components of synthetic media include the basal media and a variety of supplements. Since media composition varies by factors such as cell type and stage, this chapter does not focus on the specific concentration of any components but instead lists the major components and what roles they play in cell culture.

5.3.2 Basal Media

Originally developed in the late 1940s and early 1950s, basal media was intended to be a chemically defined media formulation of just essential components. Both reductive and constructive formulation strategies were employed to make basal media resulting in a variety of effective formulations. Some of the common basal media formulations are Eagle; Connaught Medical Research Laboratories (CMRL); Tissue Culture Section of the National Cancer Institute (NCTC); Roswell Park Memorial Institute (RPMI); Hamm; and Molecular, Cellular, and Development Biology (MCDB) media. Ultimately, basal media is composed of the most basic components needed to support life: carbohydrate energy source, amino acids, inorganic salts, vitamins, and a buffering system. Understanding each component's role can provide a clearer understanding of what is in media and why.

5.3.2.1 Amino Acids

Amino acids are organic chemical compounds composed of a carboxyl group (-COOH), an animo group (-NH2) and a functional group that defines its functional properties. Since single amino acids are linked by peptide bonds through condensation reactions to form oligopeptides (<50 monomers), polypeptides and ultimately proteins, they serve as the primary building blocks in all biological systems.

Physiologically, amino acids can be classified as either essential or non-essential. Essential amino acids (EAA) cannot be synthesized by the cell and are necessary ingredients to include in the media. Conversely, cells have metabolic pathways for bio-synthesizing non-essential amino acids (NEAA). However, which amino acids are essential or non-essential is cell line- and species-specific and can also depend on the cell stage and environment. For instance, cell lines may not be co-cultured with other cell types that might require elevated levels of vital nutrients, causing NEAAs to become EAAs. Additionally, the solubility and stability of amino acids in media can change the necessary concentration of each. Supplementation of NEAAs to the basal media can enhance cell growth by reducing the metabolic energy otherwise required for their biosynthesis. Thus, richer basal media formulations often include high concentrations of all amino acids including several non-essential ones, resulting in stimulated growth to cells and longer viability *in vitro*.[62]

A subtype of essential amino acids are branched-chain amino acids (BCAA), which include valine, leucine, and isoleucine. BCAAs tend to be required in higher concentrations than other EAAs. However, L-glutamine is especially important and it is needed in ~3-40 times higher concentrations than others.[63] L-glutamine plays a vital role in providing nitrogen for nicotinamide adenine dinucleotide (NAD+/NADH), nicotinamide adenine dinucleotide phosphate (NADP+/NADPH), and nucleotide production and acts as a secondary energy source for cell metabolism. However, it is unstable on its own, and produces toxic ammonia when it breaks down. Over time, two additives were developed to address the need for a stable L-glutamine source: (1) alanyl-glutamine (GlutaMAX), an L-glutamine dipeptide additive which is enzymatically digested to attain desired concentrations; (2) glutamate, an L-glutamine isomer additive which is controllably converted to L-glutamine by glutamine synthetase.[64,65]

5.3.2.2 Carbohydrates

Carbohydrates act as the primary source of energy for cells in basal media. Glucose and galactose are primarily used, whereas maltose, fructose, and pyruvate are sometimes used as alternative or supplementary energy sources. The concentration of glucose is usually between 5.5 and 55 mM and varies between cell types and species.[66] Generally, high glucose concentrations are used for proliferative phases of most cell types, although excessive glucose levels have been shown to have an inhibitory impact on some proliferating cell types, such as skeletal muscle satellite cells.[67] Additionally, glucose metabolism produces acid byproducts

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[62] Yao, Tatsuma, and Yuta Asayama. "Animal-cell culture media: History, characteristics, and current issues." *Reproductive medicine and biology* 16.2 (2017): 99-117.
[63] Yao, Tatsuma, and Yuta Asayama. "Animal-cell culture media: History, characteristics, and current issues." *Reproductive medicine and biology* 16.2 (2017): 99-117.
[64] "GlutaMAX™ Supplement." Thermo Fisher Scientific - US, www.thermofisher.com/order/catalog/product/35050061#/35050061.
[65] Yao, Tatsuma, and Yuta Asayama. "Animal-cell culture media: History, characteristics, and current issues." *Reproductive medicine and biology* 16.2 (2017): 99-117.
[66] Arora, Meenakshi. "Cell culture media: a review." *Mater methods* 3.175 (2013): 24.
[67] Furuichi, Yasuro, et al. "Excess glucose impedes the proliferation of skeletal muscle satellite cells under adherent culture conditions." *Frontiers in cell and developmental biology* 9 (2021): 341.

such as lactic acid; when not removed, these waste products build up and lower the pH of the media, hindering cell growth and proliferation.[68]

5.3.2.3 Vitamins

Vitamins are organic micronutrients that are essential for cell function and important for cell growth and proliferation. Although only needed in small quantities, most cannot be synthesized by cells and need to be provided by the media. Vitamins serve a variety of functions such as biological antioxidants (e.g., vitamins C and E), enzyme cofactors (e.g., vitamin K and most B vitamins), and hormones (e.g., vitamins A and D)[69].

There are two categories of vitamins: fat-soluble (vitamins A, D, E, and K) and water-soluble (vitamins B and C). Concentrations of fat-soluble vitamins are generally lower or not included in basal media as they are only essential in certain cell types. Additionally, the concentration of vitamins is determined by the stability of the vitamin, other media components, and the culturing conditions. For instance, it has been shown that light, heat, oxygen, or reactive oxygen species (ROS) can cause vitamin degradation. Conversely, serum proteins such as albumin can stabilize vitamins.

5.3.2.4 Inorganic Salts and Osmolality

Since the first cell culture media formulations were developed, inorganic salts have been identified as important for maintaining osmotic balance and to act as cofactors for enzymes. Osmoregulation is achieved by controlling the membrane potential of various ions. For instance, DMEM contains calcium chloride, magnesium sulfate, ferric nitrate, potassium chloride, sodium bicarbonate, sodium chloride, and sodium phosphate monobasic. Several other inorganic salts are also used in other basal media such as copper and zinc. For mammalian cells, the acceptable osmolality range is approximately 260-320 mOsm/kg (milliosmoles per kg of solute) range varies for other cell types (e.g., ~300 mOsm/kg for fish cells and 340-390 mOsm/kg for insect cells).[70,71]

5.3.3 Monitoring pH and Buffering systems

5.3.3.1 Phenol Red

Although the acceptable pH of mammalian cell culture is 6.8-7.8, most protocols denote the optimal pH for cell growth to be between 7.2-7.4. The pH of media changes over time (see Section 5.3.3.2, *CO_2-Bicarbonate System*) and needs to be constantly monitored. One primary

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[68] Zagari, Francesca, et al. "Lactate metabolism shift in CHO cell culture: the role of mitochondrial oxidative activity." *New biotechnology* 30.2 (2013): 238-245.

[69] Schnellbaecher, Alisa, et al. "Vitamins in cell culture media: Stability and stabilization strategies." *Biotechnology and bioengineering* 116.6 (2019): 1537-1555.

[70] Rubio, Natalie R., et al. "Possibilities for engineered insect tissue as a food source." *Frontiers in Sustainable Food Systems* 3 (2019): 24.

[71] Kültz, Dietmar. "Physiological mechanisms used by fish to cope with salinity stress." *Journal of Experimental Biology* 218.12 (2015): 1907-1914.

method of pH monitoring is a colorimetric indicator, phenol red. At pH 7.4, phenol red is a bright red color that is characteristic of cell culture. When pH levels are high, phenol red turns the medium purple, while at lower pH levels, it turns the medium a yellowish color. However, this indicator is not ideal for all formulations or cell lines. For instance, phenol red has been shown to disrupt sodium-potassium homeostasis in serum-free media formulations. Additionally, phenol red can impact estrogen-sensitive cells like mammary tissue due to its ability to mimic estrogen and other steroid hormones.[72] Phenol red is an inexpensive, easy qualitative tool for monitoring pH, but at scale, more quantitative, robust, and automated methods such as pH meters built into bioreactors are needed.

5.3.3.2 CO_2-Bicarbonate System

As cells grow and respire, they actively produce carbon dioxide (CO_2). As equilibrium is reached, some portion of this CO_2 will remain in the air and some will dissolve into the media, combining with water to make carbonic acid (H_2CO_3) and reduce the pH. A buffering system known as the CO_2-bicarbonate system is used to maintain the pH at tolerable levels. Sodium bicarbonate ($NaHCO_3$) is added to the media and CO_2 is pumped into the cell culture container (e.g., incubator, bioreactor). The sodium bicarbonate dissociates in the media, and the bicarbonate ions can bind to hydrogen ions and increase the pH. The concentration of CO_2 in the gas phase can be adjusted to increase or decrease the concentration of dissolved CO_2 in the media, resulting in a decrease or increase in the pH respectively.[73] Gaseous CO_2 in cell incubators is typically held between 5-10% for cell lines using sodium bicarbonate media. The CO_2-bicarbonate buffering system is an inexpensive, non-toxic method for regulating the pH of media and is suitable for bioreactor scale-up.[74]

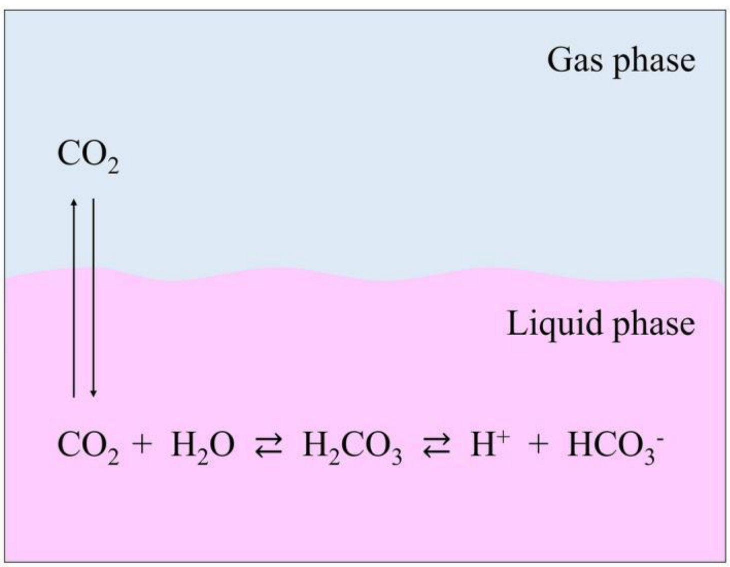

Figure 1: Bicarbonate Buffer System

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[72] Arora, Meenakshi. "Cell culture media: a review." *Mater methods* 3.175 (2013): 24.

[73] Yao, Tatsuma, and Yuta Asayama. "Animal-cell culture media: History, characteristics, and current issues." *Reproductive medicine and biology* 16.2 (2017): 99-117.

[74] Media and Supplements in Cell Culture, 2017, www.sigmaaldrich.com/US/en/technical-documents/technical-article/cell-culture-and-cell-culture-analysis/mammalian-cell-culture/the-cell-environment.

5.3.3.3 HEPES

Another commonly used buffer is 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, or HEPES. HEPES is a zwitterionic acidic buffering agent that works in the range of pH 6.8-8.2. It is a "Good's buffer," meaning it has been identified by researchers as a water-soluble, stable, and membrane impermeable compound well-suited for cell culture. In fact, HEPES is a more effective buffer than bicarbonate buffers at physiological pH 7.2-7.4. Additionally, because it does not require a controlled gaseous atmosphere, HEPES can also be better for high cell density settings where the buildup of waste metabolites can rapidly impact the pH.[75]

Although more effective, HEPES has some key limitations. For example, HEPES-containing media can be light-sensitive, potentially producing cytotoxic effects in the presence of light.[76] Some cell types are negatively impacted by HEPES, especially at high concentrations.[77] HEPES is also expensive, accounting for ~80% of the cost of serum-free media formulations such as Essential 8.[78] Thus, it should only be used when tight control of pH is needed.

5.4 Supplements

Basal media provides the essential components for sustaining cells *in vitro*; however, it is not sufficient for maintaining cell growth continuously for longer periods of time. To accomplish this, a variety of supplementary components are necessary. The selection of supplements and their requisite concentration is dependent on the cell types, cell stage, and a host of other environmental factors. Nevertheless, there are only a handful of supplement categories that serve specific roles.

5.4.1 Serum

One of the enduring supplements in cell culture media is animal-derived serum. Serum is an off-white colored, liquid fraction of plasma that does not contain fibrinogen or other clotting factors.[79] It is a complex mixture of proteins, fats, carbohydrates, growth factors, hormones, and minerals and is often considered the most important component of cell culture media. The most widely used serum is FBS. In serum-containing growth media formulation, FBS tends to account for 5-20% of the final solution.

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[75] Arora, Meenakshi. "Cell culture media: a review." *Mater methods* 3.175 (2013): 24.

[76] Zigler, J. S., et al. "Analysis of the cytotoxic effects of light-exposed HEPES-containing culture medium." *In Vitro Cellular & Developmental Biology* 21.5 (1985): 282-287.

[77] Furue, Miho K., et al. "Heparin promotes the growth of human embryonic stem cells in a defined serum-free medium." *Proceedings of the National Academy of Sciences* 105.36 (2008): 13409-13414.

[78] Specht, Liz. "An Analysis of Culture Medium Costs and Production Volumes for Cell-Based Meat." The Good Food Institute, 9 Feb. 2020, gfi.org/wp-content/uploads/2021/01/clean-meat-production-volume-and-medium-cost.pdf.

[79] "serum." Miller-Keane Encyclopedia and Dictionary of Medicine, Nursing, and Allied Health, Seventh Edition. 2003. Saunders, an imprint of Elsevier, Inc. https://medical-dictionary.thefreedictionary.com/serum

5.4.1.1 FBS

FBS is a near-universal media supplement, and there are several reasons why it is used. FBS contains high amounts of growth factors, which are helpful for promoting cell growth *in vitro*.[80] FBS also has a low level of immunoglobulins such as gamma-globulins, which can negatively affect cell proliferation.[81] Furthermore, it has good buffering capabilities and its viscosity helps protect cells from mechanical damage during the culturing process.[82] Thus, FBS is effective for a variety of applications and a number of cell types, but it has some major drawbacks which make it unfit for cellular agriculture applications.

First, FBS is expensive: approximately US $1200/L as of 2021.[83] When used at a 10% concentration, every 10 L of cell culture media costs at least this much to produce. For the cellular agriculture industry, which will need to scale to using thousands of liters of culture per week, this cost is prohibitive for progress. FBS is a byproduct of the beef industry and has a limited supply. It is estimated that about 8% of cows are pregnant at a given time, which is about two million fetuses, which produces about 800,000 L of FBS annually. Around 90% of this supply comes from just three countries: the US (~50%), Australia (~20%), and New Zealand (~20%). Researchers have even suggested that “peak serum” has already been reached and the supply will plateau at this level; however, the demand for serum will continue to increase as cell therapies are developed and approved.[84] Currently, serum consumption is estimated to be increasing by at least 10-15% annually and is soon expected to exceed peak supply.[85]

The second challenge with FBS is its heterogeneity. FBS is composed of hundreds of proteins and thousands of metabolites; its composition and concentration of components is not completely known. There are also some important components, such as extracellular vesicles, that have unclear mechanisms of action. This black-box nature is not optimal for producing food.

Third, FBS’ composition is quite variable. Since FBS is obtained from biological specimens, there is a considerable amount of variability from batch-to-batch. The composition and concentration of components in FBS is dependent on the season, geographical location, diet of the mother, administration of any antibiotics, and the age of the fetus.[86] It is a laborious process to control these factors and any other confounding environmental variables, which often

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80 Post, Mark J., et al. "Scientific, sustainability and regulatory challenges of cultured meat." *Nature Food* 1.7 (2020): 403-415.

81 Yao, Tatsuma, and Yuta Asayama. "Animal-cell culture media: History, characteristics, and current issues." *Reproductive medicine and biology* 16.2 (2017): 99-117.

82 Yang, Zhanqiu, and Hai-Rong Xiong. "Culture conditions and types of growth media for mammalian cells." *Biomedical Tissue Culture* 1 (2012): 3-18.

83 “Fetal Bovine Serum, Qualified, United States.” Thermo Fisher Scientific - US, www.thermofisher.com/order/catalog/product/26140079#/26140079.

84 Brindley, David A et al. “Peak serum: implications of serum supply for cell therapy manufacturing.” Regenerative medicine vol. 7,1 (2012): 7-13. doi:10.2217/rme.11.112

85 Karnieli, Ohad, et al. "A consensus introduction to serum replacements and serum-free media for cellular therapies." *Cytotherapy* 19.2 (2017): 155-169.

86 van der Valk, Jan, et al. "Fetal bovine serum (FBS): past–present–future." *Altex* 35.1 (2018): 1-20.

requires significant quantity testing and downstream processing. This variability hinders reliable reproduction of cell culture outcomes.

Fourth, FBS can be a key source of contamination. FBS has been known to carry endotoxins, mycoplasma, viral contaminants, and prion proteins. Several of these contaminants are damaging to cell growth in culture. For instance, mycoplasma are parasitic bacteria that are hard to detect if not explicitly screened for and can have significant cytopathic effects, depending on the cell type.[87] These contaminants are also potentially harmful to humans. For instance, FBS has been found to contain prion proteins that cause bovine spongiform encephalopathy (BSE) or mad cow disease.[88] Thus, the European Union Reference Laboratories (EURL), United States Food and Drug Administration (FDA), and other international regulatory bodies have guidelines on the testing, collection, and documentation for harvesting FBS to mitigate disease transmission; however, they recommend eliminating FBS when possible.[89] Since the major supplying countries are considered a low-risk source of these diseases, their FBS commands a higher price. Yet, the limited traceability and loose enforcement of regulation has resulted in some suppliers counterfeiting FBS, particularly in China. New screening methods are being developed to identify counterfeit FBS.[90]

The fifth challenge with FBS are the significant ethical and animal welfare issues. To maximize blood collection and reduce potential for contamination, FBS is extracted directly from the heart of a living fetus that is usually in its last trimester. At this stage of development, fetal calves may experience pain and discomfort from the FBS collection. Such practices can be seen as antithetical to the animal welfare goals that the cultured meat industry and cellular agriculture seeks to uphold. Therefore, a serum-free and chemically defined media formulation is an ideal substitute, and additionally much less expensive than FBS.

5.4.2 Serum Components

Since FBS and serum-containing media are not suitable for large-scale cultured meat production, it is necessary to develop serum-free, chemically defined media formulations. The following table is a summary of the main components in serum and their mean concentration. This section will discuss the most important components from this list that would play key roles in creating a serum substitute.

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[87] Drexler, Hans G., and Cord C. Uphoff. "Mycoplasma contamination of cell cultures: Incidence, sources, effects, detection, elimination, prevention." *Cytotechnology* 39.2 (2002): 75-90.

[88] European Commission. "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev. 3)." *Official Journal of the European Union;* (2011).

[89] van der Valk, Jan, et al. "Fetal bovine serum (FBS): past–present–future." *Altex* 35.1 (2018): 1-20.

[90] Baker, M. Reproducibility: Respect your cells!. Nature 537, 433–435 (2016). https://doi.org/10.1038/537433a

Table 2: The Main Components of Serum and Their Mean Concentration

Component	Mean concentration	Component	Mean concentration
Na^+	137mol/L	Alkaline phosphomonoesterase	225U/L
K^+	11 mol/L	Lactic dehydrogenase	860U/L
Cl^-	103 mol/L	Insulin	0.4μg/L
SeO_3^{2-}	26μg/L	Thyroid stimulator	1.2μg/L
Ca^{2+}	136mg/L	Folliclestimulating hormone	9.5μg/L
Fibonectin	35 mg/L	Bovine somatotropin	39μg/L
Urea acid	29 mg/L	Prolactin	17μg/L
Creatine	31mg/L	T_3	1.2μg/L
Hemoglobin	113 mg/L	Cholesterol	310μg/L
Bilirubin(total)	4 mg/L	Cortisone	0.5μg/L
Inorganic phosphorus	100mg/L	Testosterone	0.4μg/L
Glucose	1250mg/L	Progesterone	80μg/L
Urea	160mg/L	Prostaglandin E	6μg/L
Total protein	38g/L	Prostaglandin F	12μg/L
Albumin	23g/L	Vitamin A	90μg/L
α_2- macroglobulin	3g/L	Vitamin E	1 mg/L
Endotoxin	0.35μg/L	Fe^{2+},Zn^{2+}, Cu^{2+},Mn^{2+},Co^{2+}, Co^{3-},etc	μg/L to ng/L

5.4.2.1 Growth Factors

Growth factors (GFs) are secreted proteins or steroid hormones that are critical for an effective serum replacement. GFs have been found to induce proliferation and differentiation of cells as well as control cell migration and secretion. Only relatively small quantities of GFs are needed to perform these functions (i.e., ng/mL range). The major growth factors in FBS are insulin-like growth factor (IGF), transforming growth factor (TGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), platelet derived growth factor (PDGF), and nerve growth factor (NGF). In isolation, none of these growth factors is sufficient to replicate the effects of FBS, but certain combinations have been shown to elicit comparable levels of cell proliferation.

Although vital, GFs are by far the most expensive components in current formulations of serum-free cell culture media, accounting for upwards of 95% of the cost.[91] This is partly because GFs are inherently unstable molecules, as they are only intended to function as signaling molecules that exist in small quantities for short periods of time. But more importantly, GFs tend to be produced recombinantly by Chinese Hamster Ovary (CHO) cells, which are expensive chassis for production. Recent efforts to develop mutant variants of GFs that are amenable to production in less expensive production hosts such as bacteria and plants have experienced some success and is an active area of research.

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[91] Specht, Liz. "An analysis of culture medium costs and production volumes for cultivated meat." *The Good Food Institute: Washington, DC, USA* (2020).

5.4.2.2 Hormones

Hormones are secreted chemicals that mainly act as signaling molecules in multicellular organisms. Different hormones are responsible for regulating cell function and status (e.g., differentiation, proliferation), and they tend to be cell type specific. Some key hormones found in FBS are growth hormone, insulin, hydrocortisone, triiodothyronine, estrogen, androgens, progesterone, prolactin, follicle-stimulating hormone, and gastrin-releasing peptide.[92] One hormone that is particularly important is insulin. Insulin regulates glucose, fat, and amino acid metabolism by promoting the adsorption of glucose into cells. Generally, insulin is required in serum-free media formulations for maintaining cell survival.

5.4.2.3 Carrier Proteins

Carrier proteins (or binding proteins) are proteins that bind to low molecular weight material. The four main carrier proteins in FBS are albumin, transferrin, lactoferrin, and fetuin.

Albumin is the most abundant protein in FBS, accounting for ~50-60% of its total protein content. Albumin binds and carries a number of substances such as amino acids (e.g., cysteine and tryptophan), vitamins (e.g., B vitamins), lipids (e.g., cholesterol and fatty acids), trace elements (e.g., copper and nickel). This is especially useful for lipids, which cannot actively dissolve in media. Lipids can, however, effectively be transported into cells by forming complexes with albumin. Furthermore, albumin helps reduce shear-stress, neutralize toxins, and acts as an antioxidant. However, due to the large amount of albumin necessary for complete replacement of FBS in some cases, it must still be harvested from an animal source to be cost effective. Making vast quantities of animal-free serum albumin via recombinant protein expression and harvesting is currently not at the efficiency that is needed for industrial cell culture. Therefore, optimization of the recombinant albumin expression or increasing its function may be required. For certain molecules, inexpensive, generally recognized as safe (GRAS) synthetic carriers such as cyclodextrin could be considered.

Fetuin is another highly abundant carrier protein in FBS. It has been shown to carry calcium and phosphate ions as well as help facilitate cell attachment. However, fetuin is also known to inhibit TGF-beta signaling. Although not commonly present in serum-free media formulations, fetuin can potentially be a useful supplement for cultured meat applications.

Transferrin and lactoferrin are both glycoproteins and members of the transferrin protein family. They are carrier proteins that primarily shuttle iron throughout cell culture media and into cells.[93] Transgenic rice has been used to produce inexpensive, functional transferrin for serum-free media formulations. Although not the most expensive components, carrier proteins are not yet economical and developing scalable methods for producing them is important for cellular agriculture.

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[92] Yang, Zhanqiu, and Hai-Rong Xiong. "Culture conditions and types of growth media for mammalian cells." *Biomedical Tissue Culture* 1 (2012): 3-18.

[93] Hayashi, Izumi, and Gordon H. Sato. "Replacement of serum by hormones permits growth of cells in a defined medium." *Nature* 259.5539 (1976): 132-134.

5.4.2.4 Lipids

Lipids are versatile ingredients that build membranes, store and transport nutrients, and transduce signals. Some examples of such lipids are cholesterol, steroids, fatty acids (e.g., palmitate, stearate, oleate, linoleate), ethanolamine, choline, inositol, and others. Lipids vital for cell metabolism can be biosynthesized from acetyl coenzyme A in most established cell lines. The primary essential fatty acids for most animals are linoleic (omega-6) and alpha-linolenic (omega-3) fatty acids; however, there are some cancerous cell lines that do not require any exogenous lipids to survive. Cholesterol cannot be synthesized by all cell types. Thus, a source of sterols may need to be added to media when working with such cell lines. In general, the inclusion of lipids in cell culture media lessens the biosynthetic load that cells experience, regardless of whether the lipids are essential.[94] Ultimately, control over lipid profiles of cells can allow for reduction of undesirable fats (e.g., cholesterol) and increase in desirable ones (e.g., omega-3), improving organoleptic and health properties as well as cell growth and proliferation.

Lipid-containing media is practically challenging because lipids are not highly water soluble. FBS has high levels of a diversity of lipids including ~300 µg/mL cholesterol and ~30 µg/mL oleic acid, made soluble via carrier proteins such as albumin. Serum-free formulations rely on liposomes, emulsions, microemulsions, cyclodextrins, and low levels of polar organic solvents to deliver lipids. Not all of these are well suited for cultured meat media, especially organic solvents which can be toxic. Some key considerations for each lipid supplement are listed below.

Table 3: Features of Lipid Supplemental Approaches

	Physical stability	ADCF* potential	PF† potential	CD‡ potential	Active lipid capacity	Formulation adjustable
Serum	High	No	No	No	High	Minimally
Serum extracts	High	No	No	No	High	No
Solvents	High	Yes	Yes	Yes	Low	Yes
Albumins	High	rAlbumin	No	Nearly	Medium	Somewhat
Emulsions	Low	Yes	Yes	Yes	High	Significant
Micelles	High	Yes	Yes	Yes	Medium	Somewhat
Liposomes	Med	Yes	Yes	Yes	Medium	Somewhat
Cyclodextrin	High	Yes	Yes	Yes	High	Yes

* Animal-derived component-free
† Protein-free
‡ Chemically defined

94 Whitford, William, and John Manwaring. "Lipids in cell culture media." *Fish. Appl. Notes* (2004): 152-154.

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5.4.2.5 Trace Elements and Minerals

Trace elements are only needed in small amounts (< 0.1 vol.-%) by organisms to survive. The acceptable concentration range of each trace element required are cell type- and species-specific. Trace elements act as cofactors for enzymes and other physiologically active substances inside cells. Some examples of trace elements are iron, zinc, copper, selenium, chromium, iodine, cobalt, manganese, and molybdenum; the first four of which are generally added to serum-free media. Sufficient amounts of each trace element can be found in FBS, primarily complexed with a carrier protein or a compound.

One trace element that is needed in particularly high concentrations is selenium. Selenium is an important cofactor that helps form selenoproteins such as glutathione peroxidase and thioredoxin reductase. These enzymes act as antioxidants by reduction of hydrogen peroxide and thioredoxin compounds, reducing oxidative stress on cells. FBS contains a significant amount of selenium (~15-45 ug/L depending on supplier), mostly in the form of Selenoprotein P. [95] Selenium is often added to serum-free formulations in the form of sodium selenite.

5.4.2.6 Adhesion Factors

Many cell lines are anchorage-dependent, meaning they proliferate better *in vitro* when attached to a solid surface. Adhesion factors are proteins that promote attachment of anchorage-dependent cells to surfaces. Fibronectin, laminin, vitronectin, and collagen are adhesion factors that are commonly found in FBS. Supplementing serum-free formulation with these adhesion factors promotes cell growth and proliferation.

5.4.3 Antibiotics and Other Components to Consider

Although inclusion of antibiotic supplements such as penicillin and streptomycin (P/S) is a common practice in academic labs, antibiotics are not required to grow cells *in vitro*. The concept of culturing cells without antibiotics is not new, having been first published nearly a century ago. If a sterile environment is maintained and good manufacturing practices (GMP) are followed, there should not be any contamination. In fact, routine use of antibiotics can interfere with cell metabolism for certain cell types and potentially mask contamination by mycoplasma and resistant bacteria. Furthermore, for cultured meat-relevant cell lines such as bovine myoblasts, removing antibiotics has been shown to increase cell growth.[96] Thus, antibiotics are not necessarily required for serum-free media.

Protease inhibitors (e.g., soybean trypsin inhibitor), protective additives (e.g., Pluronic F-68), detergents, reducing agents (e.g., 2-mercaptoethanol), and polyamines (e.g., putrescine, spermidine) are all components that can also be found in serum-free media formulations to improve cell growth and proliferation under cell culture conditions. The reader is directed to published reviews which describe in detail the considerations for each of these components.

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[95] Karlenius, Therese C., et al. "[Letter to the editor] The selenium content of cell culture serum influences redox-regulated gene expression." *Biotechniques* 50.4 (2011): 295-301.

[96] Kolkmann, A. M., et al. "Serum-free media for the growth of primary bovine myoblasts." Cytotechnology 72.1 (2020): 111-120.

5.4.4 Current Serum Replacements

The problems with serum-containing media formulations are not new. Thus, various serum replacements have been developed to address different issues arising from using serum. Two frequently used serum replacements are platelet lysate and conditioned media.

5.4.4.1 Platelet Lysate

Platelets are a cellular fraction of blood which assists in clotting. Platelet lysate is the intracellular content of lysed platelets and is composed of growth factors, carrier proteins, adhesion proteins, coagulation factors, protease inhibitors, cytokines, and chemokines. Human derived platelet lysate used to supplement media has been shown to be at least as effective as FBS in promoting adhesion, survival, and proliferation of human mesenchymal stem cells.[97] However, there are still many questions that need to be addressed before platelet lysate could be used for cell-cultured meat, such as: (1) where to source large volumes of platelet lysate consistently; (2) how effective platelet lysate-containing media will be for cultured meat-relevant animal cell lines; and (3) how economical platelet lysate will be at scale. For now, platelet lysate-containing media will likely see more success in cell therapy applications than in cellular agriculture.

5.4.4.2 Conditioned Media

Conditioned media is a type of “spent” media obtained from the harvest of cultured cells following periods of cell growth. Thus, conditioned media contains all the components secreted from growing cells such as growth factors, waste metabolites, and extracellular vesicles and proteins. When supplemented with components that have been depleted, conditioned media can be used to culture a variety of cell types. The composition of conditioned media is variable and not defined. Nevertheless, conditioned media has been helpful in determining which growth factors are important for supporting stem cell growth and is an effective serum replacement in some contexts. Some cell lines require inexpensive media formulations containing only a few essential components and can thus be used to generate conditioned media for other cells. These are called feeder cells. As of 2021, a few companies (i.e., IntegriCulture and Fork & Goode) have developed new methods for using feeder cells to grow cultured meats. While it is unclear if such strategies will be feasible or economical, it remains an area of active research.

5.5 Serum-free Media Formulations

The development of serum-free media formulations, or more specifically ‘chemically defined media’, is vital to the success and scalability of cultured meat production and cellular agriculture. Many existing serum-free formulations have been developed for cell lines with therapeutic applications such as CHO (Table 4). These can serve as a starting point for the development of new formulations for embryonic and adult stem cells used for cultivated meat production (top-down approach), containing various components that were found to be vital to the growth of mammalian cells.

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[97] Guiotto, M., et al. "Human platelet lysate to substitute fetal bovine serum in hMSC expansion for translational applications: a systematic review." *Journal of Translational Medicine* 18.1 (2020): 1-14.

Table 4: Serum-free Culture Media for Chinese Hamster Ovary Cells

TABLE 4 Serum-free culture media for Chinese hamster ovary cells

Name (author[s], year)	Basal media	Supplements	Remarks
MCDB 301 (Hamilton and Ham 1977)	Ham's F-12	Trace elements (Al, Ag, Ba, Br, Cd, Co, Cr, F, Ge, I, Mn, Mo, Ni, Rb, Se, Si, Sn, Ti, V, and Zr)	A medium with 20 trace elements that are not present in Ham's F-12
GC_3 (Gasser et al. 1985)	Modified MEM/F-12	Insulin, transferrin, and selenite	Developed because Chinese hamster ovary cells could not be cultured in the MCDB301 medium
WCM5 (Keen and Rapson 1995)	IMDM	Amino acids, vitamins, transition metals (Cu and Zn), ferric citrate, insulin, ethanolamine, putrescine, Pluronic F-68, and soy peptone	Lacking high-molecular-weight proteins, it was developed for use with large-scale cultures (≥8000 L). Ferric citrate is used instead of transferrin
Name unspecified (Sung and Lee 2009)	IMDM	Amino acids, ascorbate, transition metals (Cu and Zn), ferric citrate, selenite, insulin, ethanolamine, phosphatidylcholine, hydrocortisone, putrescine, pyruvate, ascorbate, Pluronic F-68, dextran sulfate, and a hydrolysate mixture (yeast, soy, and wheat)	The combination and concentrations of the added hydrolysates were determined by using an experimental design method. It was developed to increase antibody productivity

Continued research with the focus on application in Cultivated Meat resulted in a number of chemically defined media that support both the growth and differentiation of embryonic/induced pluripotent stem cells (Table 5) and adult stem cells such as Satellite cells [98] [99] [100] [101] [102].

Table 5: Serum-free Culture Media for Embryonic Stem/Induced Pluripotent Stem Cells

TABLE 5 Serum-free culture media for embryonic stem/induced pluripotent stem cells

Name (author[s], year)	Basal media	Supplements	Remarks
Knockout DMEM (Amit et al. 2000)	DMEM	Amino acids, bFGF, 2-mercaptoethanol, and Knockout Serum Replacement (KSR)	A medium with lower osmotic pressure than DMEM and an added serum substitute containing animal-source components (KSR), it is for use with mouse embryonic stem cells. The cultures require feeder cells
TeSR (Ludwig et al. 2006)	DMEM/F-12	Vitamins, trace elements (V, Mn, Ni, Si, Sn, Mo, Cd, Cr, Ag, Al, Ba, Co, Ge, Br, I, F, Rb, Zr), selenite, LiCl, insulin, transferrin, human serum albumin (HSA), bFGF, transforming growth factor (TGF)-β1, γ-aminobutyric acid, pipecolic acid, glutathione, 2-mercaptoethanol, lipids (fatty acids, cholesterol), Pluronic F-68, and Tween 80	A xeno-free medium that does not require feeder cells
E8 (Chen et al. 2011)	DMEM/F-12	Ascorbate-2-phosphate, selenite, insulin, transferrin, bFGF, TGF-β1 or NODAL, and $NaHCO_3$	A TeSR-based medium. HSA (which results in large between-lot variation) and 2-mercaptoethanol (which negatively affects cells) were removed and supplements were refined down to the necessary minimum
(Name undefined) (Hasegawa et al. 2012)	DMEM/F-12	Amino acids, ascorbate, selenite, insulin, transferrin, Wnt3a, and indole derivative (ID)-8 (DYRK inhibitor)	The expensive bFGF and TGF-β are replaced with Wnt3a and the low-molecular-weight compound ID-8. Growth is slow, compared to conventional media
(Name undefined) (Hasegawa et al. 2015)	DMEM/F-12	Ascorbate, selenite, insulin, transferrin, ID-8, GSK3β inhibitor (eg, 1-azakenpaullone), and NFAT inhibitor (eg, tacrolimus)	Wnt is replaced with a GSK3β inhibitor and NFAT inhibitor (low-molecular-weight compounds), it can be manufactured cheaply, and quality management is simple

bFGF, basic fibroblast growth factor; DYRK, dual-specificity tyrosine-phosphorylation-regulated kinase; GSK, glycogen synthase kinase; NFAT, nuclear factor of activated T cells.

[98] Andrew J. Stout, Addison B. et al.; Simple and effective serum-free medium for sustained expansion of bovine satellite cells for cell cultured meat.
[99] Mcaleer, C. W., Rumsey, J. W., Stancescu, M. & Hickman, J. J. Functional myotube formation from adult rat satellite cells in a defined serum-free system. Biotechnol. Prog. 31, 997–1003 (2015).
[100] Kolkmann, A. M., Post, M. J., Rutjens, M. A. M., van Essen, A. L. M. & Moutsatsou, P. Serum-free media for the growth of primary bovine myoblasts. Cytotechnology 72, 111– 120 (2020)
[101] Eigler, T et al. ERK1/2 inhibition promotes robust myotube growth via CaMKII activation resulting in myoblast-to-myotube fusion. Dev. Cell 24, 3349-3363 (2021)
[102] Messmer, T. et al. A serum-free media formulation for cultured meat production supports bovine satellite cell differentiation in the absence of serum starvation. Nat Food 3, 74–85 (2022).

5.5.1 Standard Method for Making Serum-free Media Formulations

Serum-free media is composed of a basal media and a supplement. Attempts have been made to define standardized methods for the development of new serum-free media formulations that comply with GMP and good cell culture practice (GCCP). One notable method for serum-free media construction that takes a modular approach to formulation is the media pyramid.[103] The media pyramid starts with the basic, most essential components and works its way up to increasingly specific components (bottom up approach).

The media pyramid starts the construction process with a basal media, such as DMEM/Ham's F-12 (50:50, v/v), supplemented with insulin-transferrin-selenium (ITS). This provides necessary ingredients for cell survival *in vitro*. If adhesion cells are being grown, adhesion factors (e.g., collagen, fibronectin) are added or used to coat the surface of the growth vessel. Next, hormones and growth factors are added to the formulation. There are several such components that are used by most cell types (e.g., epidermal growth factor and glucocorticoids), while others are more cell type specific (e.g., nerve growth factor). Determining which cell type specific components are needed requires both a literature review of prior work and knowledge of cell signaling pathways as well as experimentation. Lastly, lipids, antioxidants and/or specific vitamins are added to the formulation. These components will likely be more specific to the cell line, the culturing conditions, and the desired application.[104] Once an initial working formulation is developed, additional media optimization steps can be performed to improve the quality, cost, and speed of production.

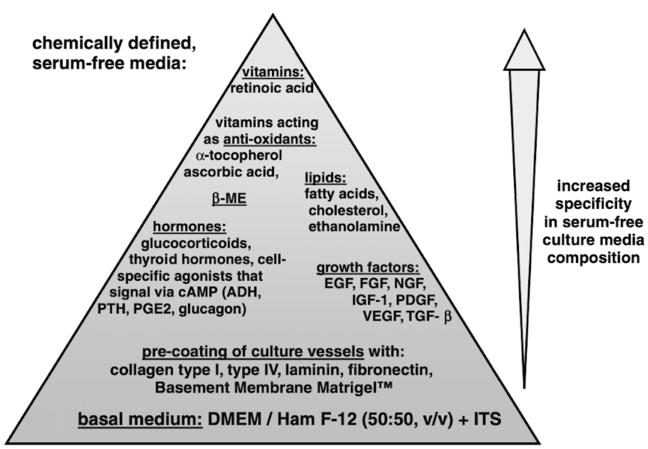

Fig. 1. Media pyramid: a modular approach for the development of serum-free media (for details see Section 2.3). Abbreviations: ADH, antidiuretic hormone; EGF, epidermal growth factor; FGF, fibroblast growth factor; IGF-1, insulin-like growth factor 1; ITS, insulin–transferrin–sodium selenite supplement; β-ME, β-mercaptoethanol; NGF, nerve growth factor; PDGF, platelet-derived growth factor; PGE2, prostaglandin E2; PTH, parathyroid hormone; TGF-β, transforming growth factor-β; and VEGF, vascular endothelial growth factor.

Figure 2: Media Pyramid: A Modular Approach for the Development of Serum-free Media

5.5.2 Design of Experiments

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[103] van der Valk, J et al. "Optimization of chemically defined cell culture media--replacing fetal bovine serum in mammalian in vitro methods." Toxicology in vitro : an international journal published in association with BIBRA vol. 24,4 (2010): 1053-63. doi:10.1016/j.tiv.2010.03.016

[104] van der Valk, J et al. "Optimization of chemically defined cell culture media--replacing fetal bovine serum in mammalian in vitro methods." Toxicology in vitro : an international journal published in association with BIBRA vol. 24,4 (2010): 1053-63. doi:10.1016/j.tiv.2010.03.016

One of the biggest challenges in designing an optimal media formulation is deciding which ingredients to include and at what level. This is a difficult task because formulations often involve 30-50 ingredients at different concentrations which can interact with each other. To illustrate the complexity involved, consider the development of a media formulation where there are 30 ingredients that can be at two levels (low, high). An exhaustive search would involve 2^{30} or around one billion different formulations. This is clearly out of reach and, as a result, there are techniques and frameworks that have been developed to navigate the design space with as few experiments as possible. This framework is referred to as statistical design of experiments (DOE).

This framework starts with listing the controllable factors (ingredients and levels) as well as uncontrollable variables and builds on models to map input to outputs. In the case of media formulation, the most important outputs are related to cell growth.

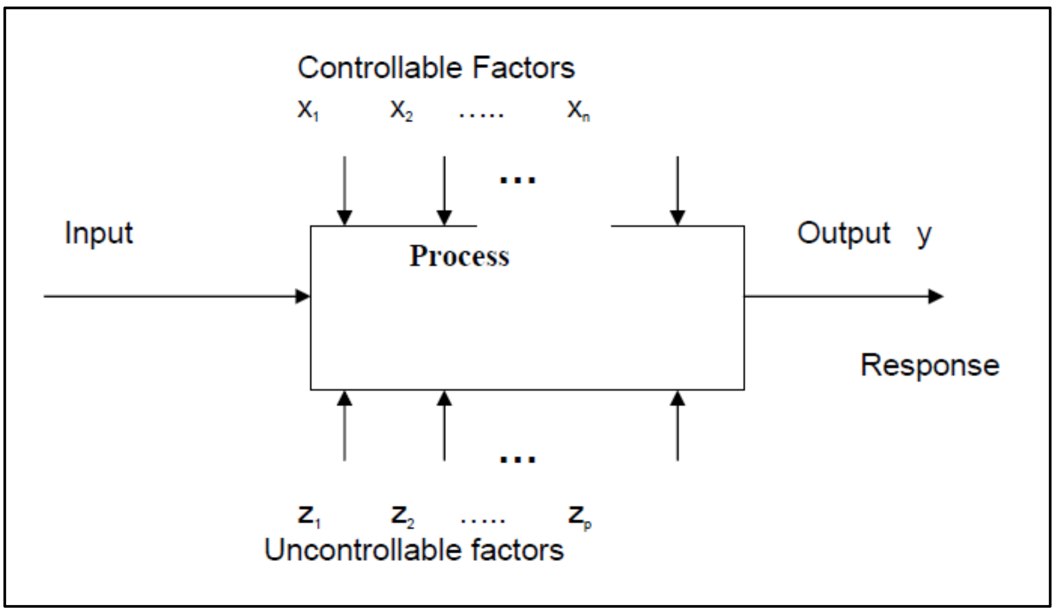

Figure 3: DOE process diagram

Given the number of inputs and the levels they can take, statistical methods can be used to learn the most from the least number of experiments. These strategies are one factor at a time (OFAT, variables affecting the activity of a system are sequentially altered while all other variables are held constant), Box–Behnken, and Plackett–Burman design.

Methods more complex than OFAT list the ingredients' names in columns and generate orthogonal row vectors such that there is no redundancy among the combinations tried. These processes will elucidate first-order effects by outlining a maximally informative number of variants of ingredients to be tested *in vitro*. First-order effects characterize the ingredients required or not required for cell growth. Further screening by varying the levels of required elements can help identify second-order effects.

In the DOE framework, it is assumed that data collection is expensive and difficult. As a result, the model capacity can often only account for first- and second-order effects.

In practice, biologists use DOE software that enables them to specify ingredients, levels, and optimization methods to design potential formulations for experimental testing. After inputting the responses and picking a model, the software enables them to fit the model to the data and identify the most promising ingredients.

5.5.3 Adaptation

Cells that are originally grown in serum-containing media will need to be adapted to use serum-free media. There are two main types of adaptation methods: direct and sequential. In direct adaptation, cells are switched from using serum-containing media to 100% serum-free media in one cell passage. Such a stark transition is challenging for cells to adapt to; generally, cell lines have more success making this transition when they are gradually weaned from nutrient-rich serum-containing media. Sequential adaptation is the process of progressively decreasing serum-containing media and increasing serum-free media content on each cell passage.[105]

Table 6. Sequential Adaptation[106]

5.5.3.1 Considerations for Adaptation

To maximize the number of cells that will survive the adaptation process, cells in the mid-logarithmic phase of growth with greater than 90% viability should be used. Additionally, cultures should be seeded at a higher than normal density (e.g. at 10.000 cells / cm^2 instead of 5.000 / cm^2) because a non-trivial percentage of cells will die during the adaptation.[107]

Antibiotics are not required for adaptation. As discussed, antibiotics should be avoided in cell culturing if possible.

Cell clumping tends to occur during the adaptation process. It is generally recommended that the clumps should gently be dispersed when passaging the cells. Additionally, there might be morphological changes to the cells as they get accustomed to the new serum-free media. If cells are viable and maintain their doubling times, then this should not be a cause for concern.[108]

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105 van der Valk, J et al. "Optimization of chemically defined cell culture media--replacing fetal bovine serum in mammalian in vitro methods." Toxicology in vitro : an international journal published in association with BIBRA vol. 24,4 (2010): 1053-63. doi:10.1016/j.tiv.2010.03.016

106 Adaptation of Cell Cultures to a Serum-Free Medium, Thermo Fisher Scientific - US, www.thermofisher.com/us/en/home/references/protocols/cell-culture/serum-protocol/adaptation-of-cell-cultures-to-a-serum-free-medium.html.

107 Adaptation of Cell Cultures to a Serum-Free Medium, Thermo Fisher Scientific - US, www.thermofisher.com/us/en/home/references/protocols/cell-culture/serum-protocol/adaptation-of-cell-cultures-to-a-serum-free-medium.html.

108 Yang, Zhanqiu, and Hai-Rong Xiong. "Culture conditions and types of growth media for mammalian cells." *Biomedical Tissue Culture* 1 (2012): 3-18.

5.6 Considerations for Proliferation and Differentiation

A prospective process of cell-cultured meat production can have two steps: cell proliferation followed by differentiation and tissue formation.[109] In this process, myoblast or myosatellite cells that are not fully differentiated are cultured in a proliferation bioreactor. The resulting slurry of cultured cells is transferred to a tissue formation bioreactor, where cells differentiate into multinucleated fibrous muscle cells.

Cell proliferation and tissue formation usually need different culture media with different sets of endocrine factors. For example, in a conventional cell culture of myoblasts, DMEM with 10% FBS is used for myoblast proliferation, but DMEM with 2% horse serum, or DMEM without serum, is used to trigger differentiation.

The goal of cell-cultured meat is complete tissue culture with vascularization, marbled fat tissues, and interwound muscle fibers, possibly by controlling both proliferation and differentiation in a single bioreactor. Such a system requires cell culture at a very high cell density (~1.0E9 cells per ml) and control over cell differentiation and organization. Correspondingly, the culture medium must deliver the required endocrine factors at the right time and conditions, but the exact conditions have not yet been determined as of 2021. In addition, the oxygen-carrying capacity of culture media may become an ultimate limiting factor (7 mg/L in DMEM vs. 250 mg/L in blood) in growing cell densities to those found in full tissues. In living organisms, blood and body fluids take this role, but a tissue culture medium that plays the same role as blood and body fluid is yet to be developed.

5.7 Cell Culture Media for Cellular Agriculture Applications

Most culture media formulations on the market are designed for pharmaceutical and biochemical research use. Pharma grade culture medium has detailed documentation of its high purity with significant effort spent to comply with GMP. However, pharma grade media comes with a high retail price not competitive for food production.

The cell culture medium for food production requires a different set of standards from pharma grade from both logistics and economics points of view. Such media formulations must first meet a food industry standard called hazard analysis and critical control point (HACCP). Depending on how a company wishes to label and market the final product, additional labeling standards such as organic, Halal, vegetarian, or vegan labels may apply.

5.7.1 Food-grade Culture Media

"Food-grade" is a generally used term for products that meet food safety rules and standards. For a certain food product to be marketable, the ingredients must use only approved food or food additives and a safety and quality control system must be in place for the entire production process.

[109] "What Is Cellular Agriculture?" *New Harvest*, 31 Dec. 2020, new-harvest.org/what-is-cellular-agriculture/.

Commonly used culture media such as DMEM contains components such as choline or choline chloride, iron nitrate, and phenol red that are not approved in certain countries as food or food additives. A food-grade media must be formulated using only approved ingredients to meet these standards.

Many countries have a list of approved food additives along with tolerance limits published by the regulating bodies. The list may vary between countries and in the case of the US, some substances are listed as GRAS, and they are exempt from tolerance requirements of the Federal Food, Drug, and Cosmetic Act (FFDCA).

Most of the basal medium components, namely sugar, vitamins and minerals are already approved or have equivalents in the GRAS category. However, very few endocrine factors and no antibiotics are currently approved as food additives. These ingredients would have to pass rigorous safety tests and have tolerance limits established if they are to be included in a food-grade media.

Production of food-grade media will require HACCP control, a systematic preventive approach, and management practice to ensure food safety. The critical points which determine the success or failure of the production process will depend on the method used. Likely critical points may include minimizing bacterial content of necessary sugar additives (it must be below the detection limit) and maintaining appropriate storage temperature (it should be sufficiently low, especially for long-term storage).

5.7.2 Religious and Vegan Requirements

In addition to adhering to food safety rules, some food products must meet additional standards to be labeled as Halal, Kosher, vegan, or vegetarian, to be marketed to specific consumer audiences.

The details of Halal requirements vary between different certifying bodies such as Islamic Society of the Washington Area (ISWA) certification and Halal Certification Authority (HCA), and some are mutually acknowledged. The Halal certificate by the Department of Islamic Advancement of Malaysia (JAKIM) is one of the most widely acknowledged standards. Common requirements found in most standards include the use of equipment dedicated for Halal products to avoid cross-contamination and non-usage of pork and other animal products that are prohibited in the Quran. Kosher certification similarly follows a certain set of rules but uses the Torah as the source text, and some certifying agencies include Orthodox Union (OU), OK, Kof-K and Star-K.

It is generally agreed that products without animal-sourced ingredients are vegan, and those without animal-sourced meat are vegetarian. However, there is currently no global consensus on what “animal cruelty free” entails, and thus the exact definition of “vegan” and specific requirements for this categorization differ between countries and certifying agencies. More discussions and developments around labeling are expected to occur in this space.

5.8 From Lab Scale to Large Scale

If cell-cultured meat products are to become commonplace foods, millions of liters of commoditized, inexpensive culture medium will be needed, the production scales for which are not available today. This will require sophisticated and strategic growth in the cell culture media market.

5.8.1 Economics of Food-grade Media

To make cell-based meat economically competitive with conventional meat, the price of medium must be below US$1 per liter.[110] Strategies to achieve this figure include food-grade ingredient sourcing at scale, the use of unrefined materials, and minimisation of additional cost factors such as transportation.

To date, a cost-of-goods analysis has been done for a chemically defined medium known as the Essential-8 (E8) medium. The E8 medium is a variant of a nonproprietary chemically defined TeSR medium and has an acceptable cell proliferation capability. The analysis concludes that the price of food grade E8 medium costs $376.80, out of which $362.30, or 99% is accounted for by the growth factors TGF-β, FGF2, transferrin, and insulin.[111] TGF-β and FGF2 take up 96.2% of the medium cost. Therefore, development of significantly cheaper or more efficient growth factors are needed to develop an economically competitive culture medium for cell-based meat production.

Unrefined materials may also be used in food-grade, cost competitive formulations. These may include fermentation waste products consisting of dead yeast and other components. Yeast extract can be metabolized by cells to produce a mixture of amino acids and endocrine factors.

In addition, since the main ingredient of culture media is water, its transportation cost can be considerably lowered by shipping the components in powder-form as opposed to pre-dissolved.

5.8.2 Ingredient Sourcing

Once cell-based meat is widely commercially available, the demand for food-grade media may exceed well over 100 million tons per year, reaching the "global commodity scale". Only sustainable and abundant sources can be used to supply media components at such scales. Currently, minerals and sugar are available at the global commodity scale, but amino acids need novel sources.

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[110] Specht, Liz. "An Analysis of Culture Medium Costs and Production Volumes for Cell-Based Meat." The Good Food Institute, 9 Feb. 2020, gfi.org/wp-content/uploads/2021/01/clean-meat-production-volume-and-medium-cost.pdf.

[111] Specht, Liz. "An Analysis of Culture Medium Costs and Production Volumes for Cell-Based Meat." The Good Food Institute, 9 Feb. 2020, gfi.org/wp-content/uploads/2021/01/clean-meat-production-volume-and-medium-cost.pdf.

As of 2021, six million tons of amino acids are produced per year, mostly by fermentation methods, for chemical reagents, food additives, and feed additives. In this process, the target amino acids such as glutamate and threonine are produced at high purity from input sugar and fertilizer in a fermenter that cultures genetically modified yeast. Other methods include chemical synthesis and extraction.

As the demand for amino acids rises to the global commodity scale, direct production of amino acid mixtures will be needed. In such a process, sugar and nitrogen-containing fertilizer are used to culture yeast or algae, and they are digested to produce a low-purity mixture of amino acids, dipeptides, tripeptides, and oligopeptides. Initially, the fermentation wastes from the beer industry may supply the raw material for digestion, but ultimately dedicated amino acid production facilities to produce at global commodity scale may be needed. Such a process would require large amounts of nitrogen-containing fertilizer produced via intensive nitrogen fixation, which may be constrained by energy availability.

5.8.3 Waste Management

Cells in culture generate potentially cytotoxic waste products such as ammonia and lactates that need to be constantly removed to ensure high cell growth and densities. A cell-cultured meat plant with multi-thousand-ton capabilities may generate thousands of tons of waste culture medium. Disposal of waste fluid at such volume would be very costly or impractical and therefore some medium recycling system is needed. Another case for medium recycling is the utilization of residual nutrients and various cellular metabolites including useful high-value growth factors.

The candidate methods of media recycling include dialysis and algae. Dialysis is an established and scalable technology used to remove substances dissolved in fluid. An algae-containing photobioreactor may remove ammonia and replenish sugar and dissolved oxygen to regenerate spent culture medium.[112] Food-grade media may have to be formulated with recyclability in mind to be truly economical.

5.9 Future Directions

Although several startups already claim to have developed inexpensive, serum-free media formulations suited for large scale cell-cultured meat production, their formulations are proprietary and heavily guarded trade secrets. Thus, based on publicly available knowledge as of 2021, there are still several key innovations needed to reach the ideal food grade media formulations.

5.9.1 Inexpensive, Stable Recombinant Growth Factors

Growth factors account for most of the current serum-free media cost. Thus, reducing the amount and cost of GFs needed for cell-cultured meat production is a high priority.

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[112] Y. Haraguchi, Y. Kagawa, K. Sakaguchi, K. Matsuura, T. Shimizu, T. Okano, Thicker three-dimensional tissue from a "symbiotic recycling system" combining mammalian cells and algae, Sci Rep. 7: 41594 (2017)

As mentioned in Section 5.4.2.1, *Growth Factors*, GFs are unstable by design. Since they are used as triggers for signaling pathways, GFs are not intended to remain active for long periods of time. However, they are required in cultures where cells are constantly growing and proliferating. Engineering more stable GFs should theoretically reduce their required concentrations. For instance, researchers used *in-silico*-driven methods to engineer a hyperstable version of fibroblast GF 2 (FGF2), which was confirmed by another group to reduce the amount needed in human iPSC culture medium.[113,114] In theory, similar methods can be used to engineer stable variants of other growth factors.

The cost of GFs is heavily dependent on the expression system used to produce them. For instance, GFs made by CHO cells are significantly more expensive than ones made in plants or microbes (e.g., *E. coli* or yeast). CHO cells are primarily used when the protein of interest requires complex post-translational modifications that cannot be adequately replicated by other hosts. While this is not the case for most GFs, CHO cells are still used to produce some of them. This is partly due to issues with protein aggregation in microbial hosts, though this could be addressed by protein engineering. Several GFs (i.e., IGF-1, IGF-2, FGF-2, EGF, VEGF) have already been shown to be expressible in yeast strains. [115,116,117,118] Furthermore, there are some commercial suppliers (e.g., Peprotech and Shenandoah Biotechnology) that already sell GFs made by *E. coli* at a fraction of the cost of their CHO-derived equivalents.[119]

An additional consideration when evaluating which GFs to use would be whether serum was used in the culture of the cells, such as CHO cells, that produce the GFs. To claim that a product is animal-free (other than the cells themselves), any ingredient that is used, including recombinant GFs, must not themselves use animal products. Fortunately, many CHO cells can be grown in serum-free conditions.

5.9.2 Growth Factor Replacements

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[116] Mu, X. P. et al. High-level expression, purification, and characterization of recombinant human basic fibroblast growth factor in Pichia pastoris. Protein Expres Purif 59, 282-288, doi:10.1016/j.pep.2008.02.009 (2008).

[117] Eissazadeh, S. et al. Production of recombinant human epidermal growth factor in Pichia pastoris. Braz J Microbiol 48, 286-293, doi:10.1016/j.bjm.2016.10.017 (2017).

[118] Arjmand, S., Tavasoli, Z., Siadat, S. O. R., Saeidi, B. & Tavana, H. Enhancing chimeric hydrophobin II-vascular endothelial growth factor A(165) expression in Pichia pastoris and its efficient purification using hydrophobin counterpart. International Journal of Biological Macromolecules 139, 1028-1034, doi:10.1016/j.ijbiomac.2019.08.080 (2019).

[119] Fonoudi, Hananeh et al. "Generating a Cost-Effective, Weekend-Free Chemically Defined Human Induced Pluripotent Stem Cell (hiPSC) Culture Medium." Current protocols in stem cell biology vol. 53,1 (2020): e110. doi:10.1002/cpsc.110

Small molecules are biologically active compounds of a molecular weight lower than 900 Da[120] that are being used in both pharmaceutical applications and cell culture as tools to modulate signaling pathways. Whether the purpose is to regulate cell biology, by inducing reprogramming, self-renewal, or differentiation, chemical treatment of cells is often more cost effective than using GFs. Small molecules can enter cells and modulate different signaling pathways by inhibiting or activating proteins, or by unknown mechanisms. There can be certain advantages to using chemicals over GFs. Small molecules can be cell-permeable, their effects can be reversible, and they are sometimes less expensive than GFs.

Small molecules have been shown to be capable of enhancing, partially replacing, or completely replacing the Yamanaka Factors when it comes to reprogramming somatic cells to become pluripotent stem cells.(1-5) Specific small molecule combinations have been developed to induce differentiation of human pluripotent stem cells (PSCs) into various neuronal subtypes such as dopaminergic neurons, GABAminergic neurons, motor neurons, retinal photoreceptor cells, and oligodendrocytes.(6-11) Efficient chemical differentiation of PSCs into cardiac, pancreas, liver, lung, gastrointestinal tract, and thymus cell types has also been successful (13, 14, 15). Many of these discoveries were based on existing known bioactive small molecules. One group determined that a single kinase inhibitor and an improved cocktail of kinase inhibitors can enhance differentiation of stem cells to chondrocytes and dopamine neurons.(12) This approach can be applied to identify chemicals that can steer iPSCs, isolated MSCs, or even other cell types towards target cell fates to improve differentiation into the muscle, fat, and connective tissue cell types found in meat.

Aside from using available inhibitors, it is likely that other small molecules that exist in nature can also act to replace signaling factors in many contexts. However, many of these remain to be tested for their utility in the cellular agriculture process. Phenotypic screening of thousands of naturally occurring compounds could lead to discoveries of compounds that affect growth and differentiation in a similar manner to GFs or transcription factors. The desired outputs (growth rate, cell density, muscle fiber length) would need to be looked for in high throughput. Phenotypic screening is used by cell biologists to identify small molecules that affect specific biological and measurable outcomes in the cell culture.(16) The major advantage of phenotypic screening is that it can select for any output (such as growth, differentiation, or ability to grow in suspension) in a specific biological context (such as a bioreactor or smaller culture condition), without knowing the proteins involved in controlling the desired phenotype. Target-based approaches to phenotypic screening are limited by the extent of human knowledge, while phenotypic screening explores all the possibilities contained within the biology of a cell or tissue.

One disadvantage of a small molecule approach for modulating cells is that if desirable small molecules are found and are added to the cell-cultured meat media, they

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[120] Macielag MJ (2012). "Chemical properties of antibacterials and their uniqueness". In Dougherty TJ, Pucci MJ (eds.). Antibiotic Discovery and Development. pp. 801–2

must be tested for their health effects in human consumption, or already be GRAS. The source and cultivation of the small molecules should also be sustainable, inexpensive, and aligned with minimizing environmental impact.

Another way to bypass the need for both expensive GFs and small molecules is by engineering cell lines through deletion, overexpression, or mutation of certain genes such that the cells' signaling networks promote the expression of selected desirable traits. Genetic phenotypic screening can be performed in a similar manner to chemical phenotypic screening with many of the same advantages. In fact, phenotypic screening was the primary method of drug discovery for decades before the development of genomics-enabled screening. In addition, a large body of knowledge already exists detailing which genetic changes produce the desired phenotypes such as immortalization or increases in cell cycle rate.

However, disadvantages of genetic engineering are regulatory and marketing hurdles. There is widespread lack of public understanding around GMOs, with many consumers considering them inherently bad for the environment or unsafe.(17) People could therefore reject the idea of eating GM cells without understanding that they are nutritionally equivalent and unlikely to have effects on human health when consumed. Genetic manipulation could be used as a simpler and more straightforward method to direct cells to perform in certain ways without having to constantly supply signals (GFs or chemicals) for growth in the media. It may be the next horizon in technology, but the success of GM foods relies on both consumer acceptance and global regulatory approval.

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Cell, Volume 163, Issue 7, 2015, Pages 1678-1691, ISSN 0092-8674, https://doi.org/10.1016/j.cell.2015.11.017.

6. Rapid induction and long-term self-renewal of primitive neural precursors from human embryonic stem cells by small molecule inhibitors

Wenlin Li, Woong Sun, Yu Zhang, Wanguo Wei, Rajesh Ambasudhan, Peng Xia, Maria Talantova, Tongxiang Lin, Janghwan Kim, Xiaolei Wang, Woon Ryoung Kim, Stuart A. Lipton, Kang Zhang, Sheng Ding

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5.9.2.1 Sericin and Protein Hydrolysates

Two of the core requirements for cellular agriculture success are to 1) create cells sustainably without animals and 2) use cost-effective media ingredients. Fortunately, these requirements are often aligned. In many cases, lower-than-pharmaceutical grade media components such as plant, yeast, insect, or algae hydrolysates, and byproducts of existing industries can achieve complete replacement of FBS, one of the most expensive ingredients in cell culture media. As discussed in Section 5.4.1.1, *FBS*, FBS is a complex, undefined media supplement that provides signaling factors and nutrients to cells.

Sericin, a protein found in silkworm cocoons, is one example of a byproduct from an existing industry that has potential as a FBS replacement. Silkworm cocoons are mainly composed of two proteins, fibroin and sericin.(1) The latter can be recovered from silk processing waste, which is often discharged, sometimes leading to environmental pollution. Several groups have found it to be a good replacement for FBS in multiple cell lines, and it even functions well as a cryoprotectant.(2-8)

Another way to replace FBS is to use animal, plant, or microorganism hydrolysates. (9). These hydrolysates have been enzymatically digested to form smaller peptides and amino acids and filtered to remove bulkier matter. In addition to amino acids, these hydrolysates can also contain other micronutrients that are not filtered out, such as trace metals.

One strategy for understanding how to formulate the media for a new species could be to add the remaining tissue material from the dissection as an animal hydrolysate, especially if FBS is not a favorable supplement for the health of the cells. This would be unsustainable and expensive, but the goal once cells are cultured would be to replace the use of FBS or animal hydrolysate with that of plants, insects, or microorganisms and create a serum-free formulation. This replacement would be necessary both due to cost and to provide an ethical, sustainable source of biological nutrients as an effective replacement for animal hydrolysates or FBS.

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5.9.3 Heat Stable Ingredients

Mammalian cells require a temperature of 37 °C (body temperature) to grow, so the development of a heat-stable media formulation is key for culture dependability. Moreover, most culture media has to be sterilized by filtration, whether serum-free or not. Unlike heat treatments, sterilization by membrane filtration cannot remove viral particles and mycoplasma, and it is expensive and challenging to maintain the quality of a cell culture medium on a large scale with filtration. Therefore, there are many advantages to developing a heat-stable culture media that can withstand autoclaving and long-term culture at higher temperatures.

Bovine serum albumin (BSA) and transferrin, which are required for the serum-free growth of many cell lines, are not very heat-stable at 37 °C. However, studies have shown that they can be replaced by cyclodextrin complexed with cholesterol and Fe-gluconate, respectively.(1) Similarly, L-glutamine is an essential amino acid but very heat-labile. Incorporating glutamine in a dipeptide form such as Gly-L-Gln or L-Ala-L-Gln can aid in the stability of this amino acid. The use of a more stable L-glutamine such as Glutamax has already been discussed in Section 5.3.2.1, *Amino Acids*. As new media additives are developed, it will be important to consider their stability, as the breakdown of any essential component of cell culture media could lead to a limitation in cell growth.

Minamoto, Y., Ogawa, K., Abe, H. *et al.* Development of a serum-free and heat-sterilizable medium and continuous high-density cell culture. *Cytotechnology* 5, 35–51 (1991). https://doi.org/10.1007/BF00573879

5.9.4 Media Optimization

Culturing differentiated cells requires both signaling factors to induce cell proliferation (such as GFs) as well as the nutrients required to build more proteins and membrane lipids for cell division. Media optimization is an important step in process development and should address both aspects: determining which components of the media the cells are responsive to, and what amounts and combinations are best for maximizing proliferation and yields.

In the cellular agriculture industry, especially at scale, it is necessary to determine what components of the media are being underutilized or completely used up. Providing more of the nutrients that are limiting cell growth can lead to a boost in proliferation. Conversely, if certain components are unused, then it makes economic sense to remove these from the media.

There are a few ways to optimize media. Spent media analysis, metabolic flux analysis (metabolomics), and expression analysis by RNA sequencing can provide a basis for rebalancing components on the next round, followed by more analysis. Alternatively, high-throughput automation of hundreds of media conditions combined with Design of Experiments (DoE) can be a powerful tool for media optimization based on maximizing an output.(1)

Minamoto, Y., Ogawa, K., Abe, H. *et al.* Development of a serum-free and heat-sterilizable medium and continuous high-density cell culture.

Cytotechnology 5, 35–51 (1991). https://doi.org/10.1007/BF00573879

5.9.4.1 Modeling Metabolism

5.9.4.2 Efficient Media Formulation Methods

The traditional strategy of testing one factor at a time while keeping all others constant is time-consuming and labor-intensive.(1) It also does not account for synergistic interactions of components.(1) DoE and statistical analyses enable less labor-intensive testing of several components at a time and identification of their interactions.

When beginning to work with a new cell line, a good approach is to start with existing basal media formulations and explore which media, or mixture of media, the cells grow best in.(1) Next, determine whether the cells require additional nutrients, or if they are missing GFs to prompt cell division. This analysis can be accomplished with spent media analysis or metabolic analysis of cell pellets via gas chromatography or mass spectroscopy.

Cells can adapt to the media conditions that they are given, resulting in further complications. Any media optimization experiment should run a long enough course such that cells are given time to adapt to the changes. Cell adaptation or clonal selection can be maximized by challenging cells in different media and selecting for the cheapest and best performers. One of the oldest cell lines used in bioprocess today are CHO cells, which were generated in 1956. Over the years, extensive clonal selection and mutagenesis have created several lineages of CHO cell lines. Modern CHO cells behave differently than they used to when it comes to growth rates and antibody titer.(2) They are also more adapted to growing in high densities in serum-free media due to modifications and accumulation of certain mutations. Similar approaches can be used in optimizing various animal cell lines to exhibit desired measurable outputs alongside the reduction in cost of the media formulations.

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5.9.5 Media Recycling

In the cell-cultured meat industry, seed trains such as those discussed in Chapter 7, *Bioprocess*, are often developed to culture cells for seeding larger and larger bioreactors. This is because, when seeded too sparsely, cells do not perform well and frequently fail to grow. From a process perspective, since it is difficult and labor-intensive to separate the media from the cells, it would be far more efficient if some of the spent media with cells could be transferred from one bioreactor to the next. This is called media recycling. The next bioreactor in the train would then start the run with a percentage of recycled media from the previous run. This can additionally lead to cost savings and benefits for subsequent cultures, since the spent media could also function as conditioned media as cells produce and secrete their own beneficial factors into the media (see Section 5.4.4.2, *Conditioned Media*). On the other hand, media that contains too much cellular waste can be less conducive to cell growth compared to fresh media.

5.9.6 Sensory Effects

An important question remains to be answered for the cell-cultured meat industry regarding the effects of media and cells on flavor, texture, and thermostability. Similarities can be drawn between the agriculture of whole animals as compared to cells. In some farming industries, a “finishing diet” is used to help the meat taste better.(1,2) For example, farmed fish are often fed with vegetable oils during most of their life and then given a more expensive omega-3 rich (fish oil) diet before they are slaughtered, to increase the omega-3 content and flavor of their tissues.(3, 4) A similar concept could be applied during the last stages of cell processing, where cells are fed certain flavors or fats, or are genetically induced to produce more flavorful compounds to contribute to the flavor complexity.

While fats are the main driver of flavor and can be influenced by feed, proteins are the main contributors to cell mass, texture, and thermostability. A terminally differentiated muscle fiber, made up of fused cells that are aligned and express large quantities of the muscle proteins actin and myosin, will have different physical properties than a mass of single cells that have been rapidly dividing in suspension culture. The closer the structure and composition of the cell-cultured product to actual animal tissue, the closer the flavor, texture, and physical properties of the final food product will be. As the field advances and knowledge is gained, it would be ideal to have a variety of cell types (fat and muscle) and extracellular matrix (connective tissue or animal-free, plant or synthetic replacements of these functions) that are combined.

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5.10 Conclusion

Cell culture media is a complex solution of nutritional ingredients designed to support and grow cells *in vitro*. As of 2021, cell culture media is the key cost driver of cell-cultured meat. Existing media formulations are not all suitable for the mass production of cell-culture meats because these formulations are not scalable or tailored for cell lines of interest, or require animal-based components. Thus, new inexpensive, scalable, and animal-free media formulations are needed.

Developing a suitable media formulation for cellular agriculture applications, such as cell-cultured meat, may not require any significant technical innovations given what is already known about cell culture. Most of the work required for successful cell-cultured meat production at scale will involve empirical research on different formulations using inexpensive ingredients. In fact, several companies already claim to have developed suitable formulations, but these are heavily guarded trade secrets.[121] Limited knowledge sharing by private companies and a dearth of public funding in this space has impeded progress. It is hoped that this chapter will serve as a resource to help others develop new media formulations suitable for cellular agriculture applications.

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Bioprocess

Overview of Bioprocess Engineering for Cultivated Meat

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Chapter Abstract

Bioprocess engineering is fundamental to the production of cell-cultured meat. The first section of this chapter covers the general function and steps of a bioprocess as well as its historical origins and key considerations. The second section covers the different steps a bioprocess may entail, along with the advantages, limitations, and functions of the various technologies that can be used in each step. The final section of this chapter covers the techniques, technologies, and approaches used for large-scale production of cellular agriculture products such as cultured meat. Continued advances in bioprocess engineering are necessary for the future production of cell-cultured meat at scales large enough to support the growing alternative protein industry.

Chapter Outline

6.1 Introduction
- 6.1.1 Definition
- 6.1.2 History
- 6.1.3 Typical Applications
- 6.1.4 Bioprocess Steps
- 6.1.5 Key Considerations Overall
- 6.1.6 Materials

6.2 Applications of Bioprocessing for Cell-cultured Meat Production
- 6.2.1 Relevancy of Bioprocessing for Cell-cultured Meat
- 6.2.2 Cell Line Development and Cell Banking
- 6.2.3 Expansion and Differentiation of Cell Cultures
- 6.2.4 Downstream Processing
- 6.2.5 Formulation

6.3 From Lab-Scale to Large Scale
- 6.3.1 Integration of Technology
- 6.3.2 Manufacturing Facility Design
- 6.3.3 Limitations
- 6.3.4 Future Directions

Fundamental Questions

1) What is a bioprocess and how is it relevant to cell-cultured meat?
2) What are the steps involved in a bioprocess?
3) What are the technologies that can be used for cell-cultured meat bioprocesses?
4) How scalable are bioprocesses for cell-cultured meat production?

6.1 Introduction

6.1.1 Definition

The Merriam Webster dictionary defines "bioprocess" as "a biological process that is used in the creation of a material or product."[1] Bioprocess engineering is the sub-discipline of biotechnology responsible for translating life science discoveries associated with or derived from living organisms or substances into practical products, services, or systems which can serve society.[2] Bioprocess engineering or bioprocessing plays a vital role in many food, chemical and pharmaceutical industries where new products are manufactured or harmful wastes are destroyed using animal, microbial or plant cells, or their components, such as enzymes.[3]

Advances in biochemistry, microbiology, immunology, and cell physiology have all contributed to this interdisciplinary field by rapidly expanding the tools of modern biotechnology, including recombinant DNA, cell fusion, and tissue culture.[3] While new products and processes can be conceived and partially developed in the laboratory, engineering skills and applied knowledge are key to reach industrial scales and commercialization.[3] Since biological systems obey the laws of chemistry and physics and are amenable to engineering analysis regardless of their complexity and controllability, significant engineering inputs are required for many aspects of bioprocessing, such as the design and operation of bioreactors, equipment for product recovery, and systems for process automation and control.[3] The advent of cutting-edge treatments like cell and gene therapies, cultured meat, laboratory-grown human organs for transplants, sustainable pesticides, synthetic biology products like spider silk, and pollution-degrading microbes produced using bioprocess engineering usher a revolution in the role of biology in industry.[3-5]

6.1.2 History

Although the field of bioprocessing has been rapidly advancing over the last 40 years, its origins are seen more than 7,000 years ago in traditional food and wine preparation as microorganisms were used to make foods like bread, potable alcohol, yogurt, vinegar, and cheese long before their existence was known.[6] Commercial bioproduction only took off in the mid-1800s after it was discovered that microorganisms were the causative agents facilitating bioprocesses.[6] As the understanding of bioprocessing grew during the late nineteenth century, microorganisms were employed to manufacture industrial products such as ethanol, acetate, lactate and glycerol.[6] However, environmental control or asepsis were not given much consideration as bioprocesses were limited to those that were self-sustaining.[6]

The two world wars drove the next advances in the engineering of large scale bioprocesses: stringent aseptic conditions and environmental control on an industrial scale.[6] The first bioprocess that was not self-sustaining was developed in 1915 for the production of the solvents acetone and butanol by *Clostridium acetobutylicum* to supply acetone for cordite and airplane dope (a plasticized lacquer that is meant to cover fabric-covered aircraft) for World War I.[6] To optimize the production of solvents, the process conditions had to be controlled and, together with rich nutrients, this created environments suitable for a variety of competing microorganisms. Therefore, sterile conditions had to be maintained to prevent contamination.[6] The development of equipment for the supply of considerable quantities of air to *Penicillium* mold for the large-scale aseptic production of penicillin was another pivotal breakthrough in bioprocessing, which happened during World War II. The second pivotal breakthrough during this period was the development of equipment dedicated to large-scale downstream purification processes which involved centrifugal extraction.[6]

The next 40 years saw great advances in bioprocess development leading to more complex engineering processes, such as the large-scale production of antibiotics, proteins, vitamins, and enzymes.[6] The use of isolated enzymes as biocatalysts in the late 1950s was followed by the development and optimization of large-scale continuous bioprocesses in the 1960s for the production of yeast, for instance.[6] The development of recombinant DNA technology in the late 1970s helped transcend many of the boundaries previously constraining bioprocess engineering, and allowed for the notable commercial manufacturing of insulin using genetically modified *Escherichia coli*.[6] Today, bioprocessing is favored over chemical routes for its moderate condition requirements, improved efficiency, and lower environmental impact.[6]

6.1.3 Typical Applications

Bioprocess-derived products are ubiquitous in many industries. Bioprocessing is used to create relatively cheap materials such as industrial alcohol and organic solvents like acetone and butanol. In addition, it is applied to make traditional foods and beverages, such as yogurt, bread, vinegar, soy sauce, beer, and wine. Bioprocessing is also employed in the creation of expensive specialized substances, including antibiotics like cephalosporins, therapeutic proteins like monoclonal antibodies to treat cancer, and most vaccines.[3,6]

Bioprocesses are used for wastewater treatment, microbial mineral recovery, and the manufacture of industrial enzymes, organic acids such as citric acid, pigments like β-carotene using *Blakeslea trispora*, nutritional supplements including amino acids such as L-arginine and vitamins like cyanocobalamin (B12), poly(β-hydroxyalkanoate) polyesters, and insecticides such as bacterial spores.[3] Furthermore, in contrast to biologics where cells are production hosts that are discarded at the end of the production run, cultured cells such as baker's and brewer's yeast as well as cell therapies, which include human chondrocytes, are also commercial products of bioprocessing.[3,7] In the future, bioprocessing will extend to new technologies, such as biological hydrogen production for fuel cells to generate power.[6] Bioprocess engineering is indispensable to humankind and the future of society.

6.1.4 Bioprocessing Steps

The steps required in a bioprocess vary greatly and depend on the product. Typically, a bioprocess has two main parts: upstream and downstream processing.[5] Upstream processing usually involves the use of a bioreactor to generate a controlled environment suitable for the *in vitro* management of cells. This could include two sequential cell culture phases of proliferation and differentiation.[5] All nutrients, including oxygen, must be provided to the cells to enable them to produce the desired product, whether it is a specific protein or biomass of the cells themselves. Waste products such as carbon dioxide, heat, and waste metabolites must be removed.[8] Following upstream production, downstream processing is a multi-stage operation concerned with the concentration and purification of a biotechnologically formed product to a state suitable for use.[8] Desired downstream processing outcomes such as cell harvesting and the removal of cell debris, spent media, contaminants, and waste by-products are achieved by initially separating the bioreactor output into a solid and a liquid phase, and using one or more membrane filtration, precipitation, (electro)dialysis, centrifugation, solvent extraction, and adsorption steps.[5,8] Thus, bioprocesses for cellular products include cell expansion in bioreactors, followed by the concentration and filtration of the cell suspensions to reach the required cell density and purity before they are formulated into the desired product.[9] Cultured meat formulation steps may include chopping, flavoring, drying, texturizing, packaging and labelling depending on the product of interest.[5]

6.1.5 Key Considerations Overall

Designing a bioprocess is an iterative task that requires the consideration of several factors for it to be successful and economically viable.[5] Upstream, the bioreactor must be designed to create an environment that promotes the growth of cells and in some cases, the formation of tissue that accurately resembles native tissue architecture.[10] To this end, various calculations of mass and energy balances are needed to determine output, input, and system requirements.[5] Of prime concern is the ability of a reactor system to provide optimal conditions for cells. The ability to maintain parameters such as energy dissipation rate, mass transfer coefficients, oxygen uptake rate, mixing time, and gas hold-up (the volume fraction of dispersed gas in liquid media) play an important role in the design and operation of the bioreactor. Dimensionless numbers such as the power number, a measure of the torque or resistance acting on the stirring impeller during production, are necessary parameters to calculate to scale-up these processes.[3] Downstream processing involves removing impurities, which may include microcarriers, and volume reduction to concentrate and wash the cells. Quality indicators which confirm low impurity levels, low process variability, and, if relevant, high cell viability must be considered for proper quality control. Indicators of efficiency and output including processing time, Cost of Goods (COG), and concentration factors are also important considerations for designing a bioprocess.[11]

Mass balances can be used to determine the rate at which different raw materials, such as cell growth nutrients in media, need to be supplied, and estimate output like the biomass of cells produced. They can also be used to help determine the mode of operation for bioreactors, which may be batch, fed-batch, or continuous depending on when media needs to be supplied and outputs have to be removed.[5] Such requirements are shaped by the type of cells used: dry cells have a chemical 'formula' of $CH_{\alpha}O_{\beta}N_{\delta}$, and can be represented by $CH_{1.8}O_{0.5}N_{0.2}$ – a general formula used when composition analysis is not available.[3] During cell growth there is, as a general approximation, a linear relationship between the amount of biomass produced and the amount of media substrate consumed. However, metabolic activities such as cell motility or maintenance of membrane potential and internal pH always consume a fraction of the media without necessarily producing cell biomass.[3]

Yield is the ratio of mass or moles of product formed to the mass or moles of reactant consumed.[3] It is a main indicator of the efficiency of a bioprocess step as it quantifies the output produced for a given level of input. The standard goal of bioprocessing is to maximize biomass or protein yields (e.g., biomass per gram of glucose) and minimize by-product yields.[5]

Cell concentration or density and throughput, otherwise known as the production rate over time, are key product requirements that influence numerous aspects of a bioprocess, such as the type, size, and number of bioreactors.[5] Seed trains or passaging, in the form of sequential transference of cells to reactors of increasing size, may be required to satisfy the minimum and maximum cell numbers or densities.[5] A comprehensive evaluation of the capabilities of various downstream processing systems to meet product requirements, including throughput and cell density, is vital to the creation of a successful bioprocess.[12]

Purity requirements depend on the type of product, and dictate downstream processing objectives and the technological systems, like centrifugation, used to fulfill them.[8,12] These usually include low levels of impurities, such as DNA, microbes (contaminants), and residual serum (high residual clearance).[12] In industries for which cells are the product, specific cell populations have to be isolated and enriched.[13]

Stability of product not only determines the suitability of extraction processes, but it is also an essential requirement for commercial distribution.[8] The stability requirements will depend on the end-product type and intended usage. Hence, the identity or phenotype of cells is critical in industries like cell therapy and cell-cultured meat.[14] Stability and purity are hallmarks of high-quality bioprocess products.[8]

Cost and scale-up are key bioprocess challenges.[7] Bioprocesses in the fields of regenerative medicine and cell therapies are expensive and heavily regulated.[15] Cell-cultured meat applies these processes and technologies to the food industry, which has one of the lowest profit margins, making expenditure reduction critical.[15] Biomaterials and their purity assurance, facilities, human resources, and measurement tools make up some of the main expenses for cell-cultured meat production.[15] Cost is a major factor to consider in selecting downstream processes, for which Costs of Goods become substantial.[8,11]

With cells as the end-product and a moderately large production scale, the burgeoning industry of allogeneic (off-the-shelf) cell therapies is the most pertinent to cell-cultured meat with respect to bioprocessing.[5] Cell-cultured meat products are most similar to cell therapy products in the sense that the cells themselves are part of the final product as opposed to secretion products, usually proteins, that need to be separated from the cells to generate the final products. This industry is experiencing a shift from manual, planar flask cultures to 35–50L automated bioreactors, and faces the same large scale production bottleneck as cell-cultured meat due to the difficulties associated with large-scale adherent cell culture.[5] The scale requirements for cultured meat make large-scale, fully automated bioprocesses, both upstream and downstream, even more imperative to meet production requirements and improve reproducibility.[5]

Scaffold design (if relevant) and materials are an intrinsic part of the bioprocess, which affect the size of the bioreactor(s) required, cell seeding requirements, downstream processing, mass transfer, and costs.[5]

Cells and media have decisive impacts on total protein yield, process robustness, and a plethora of other choices that shape a bioprocess.[5] While not the subjects of this chapter, bioprocess engineering cannot overlook the importance of cells, media and scaffolds, which are discussed in greater detail in other chapters of this textbook.

6.1.6 Materials

Although the materials used in cell culture media (feedstock), scaffolds, and for sourcing the cells themselves play an extremely important role in the bioprocess, these are outside of the scope of this chapter and are explored in greater detail in other chapters of this textbook. This chapter will focus on the materials used to make bioprocessing equipment including bioreactors, centrifuges, and ancillary units.

Stainless steel has been traditionally used in bioprocessing due to its corrosion resistance, biocompatibility, and excellent strength over a wide temperature range. In addition, it is non-reactive which enables its use in combination with relatively harsh chemicals, such as sodium hydroxide, for cleaning and relatively harsh temperatures of 130°C for sterilization between runs to prevent contaminations.[16,17] More recently, bioprocess industries have moved towards single-use (disposable) materials due to reduced cross contamination risks, capital costs, and cleaning and sterilization requirements leading to faster changeover between runs and lower water usage.[7,18] Moreover, the use of mobile disposable equipment offers greater flexibility and greater ease of relocation and duplication of manufacturing facilities because traditional stainless steel facilities use pre-installed hard piping to move material from preparation and filling locations to final places where the components are used within the facility.[18]

However, there are disadvantages of single-use equipment, which is usually plastic. These materials increase operating costs and the produce contaminated, non-recyclable, mixed plastic waste that will end up in landfills or the ocean.[5] Life Cycle Cost (LCC) analysis, which recognizes the total cost associated with a facility, including construction capital and operating costs for a facility, assuming 10–20 years of operation.[18] LCC can be used to decide between materials, and has favored stainless steel in some case studies.[18] While increased production rates (throughput) may offset the higher Cost of Goods for single-use systems, scalability remains a critical limitation.[5,18] Whereas stainless steel upstream processing facilities can be built to fit almost any size specification, single-use bioreactors have a maximum capacity of only 2

m^3 today, and 5 m^3 single-use bioreactors are still under development.[18] This size limit is mainly attributed to the achievable oxygen transfer; hence, using a perfusion process in which the cell culture media is constantly replaced with fresh media could surmount the scale limitations of upstream single-use systems.[18] Disposable downstream systems include centrifuges with disposable contact surfaces, such as the Ksep®6000S (Sartorius, Göttingen, Germany) can process input flow rates of up to 720 L/h, as well as Alternating Tangential-Flow (ATF) filtration technologies that can handle up to 1,000 L per day.[18] Thus, equipment and their materials must be carefully chosen depending on the volumes that need to be processed within a given timeframe.

6.2 Applications of Bioprocessing for Cell-cultured Meat Production

6.2.1 Relevancy of Bioprocessing for Cultured Meat

Cell-cultured meat, also known as clean meat, cultivated meat, *in vitro* meat, and cell-based meat, is a cellular agriculture product that utilizes the tissue engineering of muscle and fat cells to create meat without the need for living animals.[7] At laboratory scale, tissue engineering of muscle and fat, which is needed to produce cell-cultured meat, is relatively well-developed and understood. However, the only commercially available cell-cultured meat product as of 2021 is cell-cultured chicken in Singapore (GOOD Meat cultured chicken bites, Eat Just, San Francisco, California). To expand access and make the technology financially viable, a more automated and efficient process of production than lab-scale tissue culture is required – in the form of a bioprocess.[5]

Bioprocesses have typically been used in fermentation applications such as brewing or recombinant protein production in the pharmaceutical industry. These bioprocesses have many parallels with cell-cultured meat production. The more relevant cell therapy industry already has many technologies and products that can be directly applied to cell-cultured meat.[5,7]

Many of the advantages of cell-cultured meat over traditional meat from animal agriculture, which are also discussed in other chapters of this textbook, arise from its production via bioprocessing. Since cell-cultured meat production involves culturing only the muscle tissue that is needed for the final product, its production has reduced water, energy, and land requirements than traditional animal agriculture. In addition, scaling bioprocesses can be achieved by building vertically rather than by deforestation to create grazing pastures for animal herds.[10] Therefore, *in vitro* meat production systems could alleviate many of the environmental burdens of current animal farming practices.[10] In contrast to the months required for animals to reach average slaughter-ready age, production timescales for cell-cultured meat are estimated to be on the order of a few weeks.[10,19] Furthermore, the use of controlled, aseptic conditions ensures that the meat is free from contamination. This eliminates product losses from infected and diseased animals and prevents the spread of animal-borne diseases. In addition, cell-cultured meat production systems are expected to lower the incidences of zoonotic diseases due to the reduced amount of close quarter human–animal interaction.[10]

With industrial-scale cell-cultured meat bioprocesses still under development, this chapter aims to consolidate existing academic research and form the basis for future research and design of these systems in the field of cultured meat and cellular agriculture.[5] The following sub-sections: (i) break down the typical main steps of a cell-cultured meat bioprocess; (ii) highlight the advantages and limitations of the different technologies that can be used for bioprocesses; and (iii) provides pointers on how to choose the best options depending on the product.

6.2.2 Cell Line Development and Cell Banking

The establishment of large, cryopreserved stocks or “banks” of cell cultures has been key to the reliability and robustness of industrial bioprocesses. These cell banks remain available for decades because of standardization of cell freezing methods.[14] Cryopreservation is a process of preserving the biological function by freezing and storing material below −80 °C, typically in liquid nitrogen (−196 °C).[20] While primary cell cultures can be used for small-scale clean meat applications, they are subject to genetic variability and increased risk of contamination from the biopsy and cell isolation protocol.[7] As a result, robust, well-characterized cell lines that exhibit consistent performance over many production cycles are used to create the “master cell bank” or the seed stock which will be the source for all future work.[7,14] Cells from the same source are harvested, pooled, and cryopreserved to create a homogeneous master bank of cells, promoting vial-to-vial consistency.[14] Cultures for each production run or experiment are sourced from individual vials of large collections of “working” cell banks generated from individual vials of the master cell bank.[14] This master/working cell bank system is widely considered best practice and helps assure the long-term provision of high-quality cells.[14] Such a system can also lead to cost reduction, as long-term cultivation enables continuous culture of the seed train with only the final scaling and maturation stages of the production process requiring batch processes.[7] Similar to fermentation strains for brewing beer, cultures can be used continuously for some generations, and then periodically re-started from frozen stocks to avoid genetic drift.[7] While the ideal qualities of cell lines for cultured meat are discussed in detail in the ‘‘Cells’’ chapter of this textbook, some of the important attributes of cryopreserved cells in banks are listed below:[14]

- Viability
- Identity (the cells are what they are purported to be)
- Purity (freedom from microbiological contamination)
- Stability during growth or passage *in vitro*

Problems during cryopreservation can lead to failure to recover cells, altered cell cultures due to the presence of abnormal cells, and even the loss of cell lines.[14] Some of the bioprocessing techniques used to create, screen, and maintain cell lines with desired properties are discussed in the rest of this sub-section.

Although cell line immortalization is widely used in biologics manufacturing, the cell-based therapy industry has driven the development of stable induced pluripotent stem cell (iPSC) lines from patients, including “footprint-free” methods instead of viral transgenesis, which raises safety concerns due to genetic changes.[7,21] Such footprint-free methods should be employed to derive iPSC lines for cultured meat from donor cells that have favorable epigenetic memory. Epigenetic memory describes the non-sequence-related DNA signatures of different cell types, such as methylation patterns, that confer a preference for stem cells to differentiate along these lineages. These stable iPSC types can substantially increase both the efficiency and the speed of skeletal muscle derivation as previously demonstrated in human cells.[7]

Cell line development may include a number of different approaches to improve the robustness, efficiency, and cost of cultured meat cells for large-scale cultivation.[7] Cell lines may be adapted or engineered to require lower levels of growth factors to reduce the cost of the media, while gene editing techniques like CRISPR may be employed in the future to accelerate cellular adaptation to conditions such as suspension growth.[7] Microfluidic screening techniques have been widely used for biotechnology applications to select cell lines based on metabolic efficiency or robust activity of various metabolic pathways, and can also be applied to cultured meat cell lines to select for high performers.[7] Various strategies have been discovered for maintaining the ‘’stemness’’ of cells to ensure they can proliferate and differentiate as needed, such as modulating scaffold stiffness and subjecting cells to hypoxic conditions.[7]

Once cell lines for cell-cultured meat have been established, the stability, reproducibility, and long-term maintenance of cultured meat cell stocks can be enhanced by adopting cell banking best practices developed for sensitive stem cell lines in biomedicine.[7]

6.2.3 Expansion and Differentiation of Cell Cultures

Reviewing the production process from an industrial point of view, this chapter covers the crucial steps for selecting the right large-scale production platforms, essential for product development and for the product’s economic viability. The process of increasing the mass of cells and directing them to differentiate into specific cell types should be efficient and yield a high proportion of cells with the required phenotype of the specific cell type (such as myotubes, adipocytes and stromal cells). In some cases, this mass of cells will be grown further into tissue to form a structured meat product similar to the natural formation of the animal muscle tissue.

Diversity in cell sources (pluripotent stem cells, adult stem cells, progenitor cells and mature cells) and culturing methodologies has led to the development of many potential platforms and extensive research for the optimization of culturing conditions. The features that are common to all platforms should ensure scalable, reproducible, and consistent cell-cultured meat products, while minimizing time and costs. Nevertheless, factors such as the geometries of the bioreactor and the impeller are of great consequence, as they influence mixing time, oxygen uptake, substrate supply, and the timing of nutrient addition. Several large-scale production platforms for cell-cultured meat applications are discussed here with emphases on properties like those listed above.

Bioreactors for cultured meat production

The platforms to fit cell-based products must ensure that the release of the cells from any materials that support cellular production should be straightforward. If the removal is impossible or inefficient, these growth-supporting materials should be edible as they will become part of the final product. A second major consideration that is critical for cell-based products is avoiding high shear forces that can decrease the viability of the cells. Accordingly, mixing methods that create lower shear forces while maintaining the homogeneity of the culture are preferred. These two basic criteria for efficient manufacturing of cell-cultured meat products are met by several bioreactor systems, among them stirred tank bioreactors, WAVE Bioreactor™ systems, and Vertical-Wheel™ bioreactors.

Stirred tank bioreactor systems are the most frequently used as they are suitable for various expression systems. Stirred bioreactors are available as reusable systems made of steel and glass or as single-use systems in different sizes. The single-use systems, depending on their size, are either available as flexible bags or rigid vessels. These systems have become increasingly popular in recent years and are used in biopharmaceutical productions with volumes of up to 2,000 L.[22]

The WAVE Bioreactor™ system is comprised of a pre-sterilized, flexible, and disposable culture chamber (Cellbag™), CO_2- and/or O_2-air mix controllers, and a pneumatically controlled platform for rocking and heating the Cellbag™.[23] The rocking motion generated by this platform provides mixing and gas transfer in the Cellbag™. The system can be further equipped to provide online pH and dissolved oxygen (DO) monitoring and real-time feedback control.[24] The system produces a very low-shear environment while maintaining mixing and oxygenation.

Vertical-Wheel™ technology has a unique, vertically oriented impeller that differs from the horizontal style found in traditional stirred tanks. This results in fast, efficient mixing with uniform particle suspension and low shear stress.

Microcarriers

Eukaryotic cells usually exist as part of a cell layer, tissue, or organ, and as such, do not grow as single cells. Accordingly, in bioreactors the cells either grow adherent to matrix on microcarriers or adherent to each other as free-floating aggregates. The above bioreactor systems can use both methods of cell growth.

Microcarrier (MC)-based suspension culture: Some types of cells grow best when adhered to a matrix and are best suited for seeding and growth on MCs suspended in liquid culture. This technology has been well described for many cell types and different supporting matrices in the review by Chen and colleagues.[25] The shape, size, and surface properties of MCs have a significant effect on the proliferation and differentiation of cells.[26,27] For example, neutrally charged cylindrical and spherical MCs were found to support high cell yield and stable pluripotency of human mesenchymal stem cells, but on the other hand, positively charged microporous beads and spherical MCs did not.[27] Compared to 2D static systems, MC-based suspension systems have more advantages, resulting in a higher proliferation of human pluripotent cells by at least two-fold and with a total output on the order of 10^6 cells/mL.[28]

Cell-cultured meat production is possible using MC as the base material on which to grow and expand cells. MCs can become part of the final meat product if they are made of edible materials that contribute to the final nutritional value or consumer appeal of the meat product.[29] Products combining non-animal materials together with cultured animal cells are defined as “hybrid” meat products. In this scenario, the MCs must comply with regulations for use as a food ingredient or additive, and may affect sensory attributes of the meat product, such as color, texture, or taste.[29] Various types of edible polymers can be used as substrates including polysaccharides like starch and alginate, polypeptides such as collagen or gelatin (which can be derived from plants or fungi), mycelia matrices, composites/synthetics like polyethylene glycol (PEG), and lipids like paraffin, which can also introduce a fatty flavor.[29] These edible polymers have been widely used as emulsifiers, coatings, thickeners, and stabilizers in the food industry. The incorporation of novel cell attachment motif [arginyl-glycyl-aspartic acid (RGD)]-containing proteins into these substrates may further enhance attachment of cells, but any new materials will require regulatory approval for inclusion in food products.[29] Despite the available options, manufacturers may still prefer to separate cells from MCs to limit effects on the sensory profile of the meat. Less stringent separation methods, such as sedimentation or centrifugation, may be used for this purpose.[29]

If the MCs are not edible or animal-only cell mass is required, a protocol to remove the cells from the MC should be developed.[30] Adding this step to the production process should be considered for its implications on operational efficiency, yield, and total costs. The harvesting process might reduce the number and viability of the harvested cells. MCs should retain their physical properties (e.g., size, density, integrity, and shape) throughout the culture period because almost all cell recovery and purification techniques are based on separating by size, specific gravity, and/or shape.[29] As a result, the use of liquid/liquid systems or thermally-induced collapsing MCs simplifies and assists separation.[29] Even though MCs may be completely removed from the product, they will need to be inert so that they do not affect consumer health or food quality as food-contacting materials.[29]

Free floating aggregates suspension culture: Some types of eukaryotic cells can adhere to each other and form aggregates, while maintaining their proliferative capacity and phenotype over sequential passages in a matrix-free environment.[31,32] Optimized proliferation and differentiation protocols promote cell viability throughout the production process. The protocol should support a high yield of cells integrating into aggregates to sustain their viability through cell-cell interactions and maintain their proliferation potential.[33]

Optimization of Culturing Conditions

Some key considerations that are important for process development in bioreactors and optimizing the system for large-scale production are highlighted here.

Mixing is one of the most important operations in bioprocessing. In an optimal cell culture environment, the cells must have access to all substrates, including oxygen, in aerobic cultures. Any material added to the bioreactor, such as fresh medium to feed the cells or acid to control pH, must be rapidly and evenly distributed throughout the reactor to avoid the build-up of local concentrations to toxic levels.[3] Vessel geometry, liquid height, baffles, sparging, and impellers are all important factors that affect mixing.[3]

Impellers are rotors found in various shapes and sizes, but the most common types are marine and pitched impellers.[3] The number of blades and the angle in which they are positioned determines the distribution of the MCs or cell aggregates in the culture, their size, the expansion capacity, and the amount of shear forces that are applied on the cells.

Oxygen needs to be added to media to meet the high oxygen requirements of the aerobic cultures that produce cell-cultured meat.[5] Achieving high cell densities must be accompanied with adequate transfer of oxygen throughout the bioreactor.[34] For small volumes, gassing through the overhead space in a bioreactor is sufficient, but in larger vessels a gassing strategy is required, which might increase shear stress due to gas bubbles.[10] Oxygen in large scale bioreactors is traditionally supplied using bubble aeration, a process termed sparging. Alternative aeration methods include the use of media saturated with dissolved-oxygen upstream, gas permeable silicone tubing for feed piping, oxygen carriers to mimic hemoglobin-provided oxygen supply, or an external media aeration device.[5] Baffles may also be used to increase aeration and gas exchange. The need to provide and maintain oxygen levels will differ depending on the buffer used to maintain pH in the bioreactor.[5] Submerged gassing into protein-rich media is suspected to result in foaming that may cause damage to the cells when foam bubbles burst. The use of antifoaming agents such as Pluronic F68 or polyethylene glycol have been shown to reduce cell sensitivity to bubble damage and could be considered.[35,36] Antifoam agents could cause cell toxicity at certain concentrations and need to be evaluated before use.

Temperature control and maintenance through heat transfer is another important function of mixing, and bioreactors must be able to rapidly transfer heat to and from the broth of cells, media, and other components.[3] The main sources of heat are cell metabolic reactions and impeller shaft work. Cell metabolic reactions typically generate 5 to 60 kJ of heat per second per cubic meter. Impeller shaft work usually requires between 0.5 and 5 kJ s^{-1} m^{-3} in large vessels and 10 to 20 kJ s^{-1} m^{-3} in small vessels.[3] Cooling water pumped through an external water jacket is often used to remove excess heat; the rate of heat transfer depends on mixing conditions.[3]

Energy requirements for operating bioreactors are a major financial and sustainability consideration that must be minimized.[3] Electrical power is needed to drive impellers in stirred vessels, while the energy requirements of the bioreactor for either heating or cooling are defined by the heat released per mole of oxygen consumed and/or other measures of cell metabolic activity.[3,5]

pH levels have a major influence on eukaryotic cell proliferation and phenotype. The accumulation of compounds like ammonia and lactate and resulting changes in pH are harmful to cells and can decrease cell viability. In murine embryonic stem cells, it was shown that a below-neutral pH of 6.8 better preserved pluripotency, but significantly damaged cardiac differentiation as compared to a slightly higher pH of 7.2. Using the automated control system of the bioreactor, pH levels can be corrected in real time. The adjustment of pH can be achieved by gassing CO_2 into the media, titrating with a strong base (e.g., NaOH or bicarbonate), continuous perfusion which removes waste products from the culturing vessel and in turn adjusts the pH, or a combination of the above strategies.

Shear stress is a concern when culturing eukaryotic cells, especially stem cells, as the cells are very sensitive to hydrodynamic forces (shear and normal stresses). Shear stress can increase cell death, decrease the ability of cells to aggregate, and decrease the ability to direct the cells to a specific differentiation pathway instead of maintaining their phenotype. Moreover, cell-cultured meat requires myocyte precursors, which are anchorage-dependent and have lower shear limits.[5] Shear stress is influenced by: impeller design and diameter (shear stress increases with an increase in diameter); impeller heights inside the vessel; increased agitation speed; gas bubbles; and the presence of probes. The optimal hydrodynamic shear stress value can differ between cell types and should be calibrated according to the final product, taking fluid dynamics into account.[7] Since mixing is the major cause of shear stress, a balance must be found between sufficient mixing and optimal shear.

Diffusion capacity and homogeneity are critical to establish a robust industrial production system in bioreactors. Cell masses with radiuses of more than 150 μm will experience hypoxia and low nutrient concentrations in the core of the free-floating aggregate or the inner layer of cells on the MC. This will cause reduced viability and proliferative capacity of the cell masses.[37] Heterogeneous sizes of MCs with cells or cell aggregates might lead to differentiation between the cells due to concentration-dependent cues in different depths from the most outer cell layer. The diameter of the MCs with cells or cell aggregates can be monitored via offline sampling and microscope-based analysis. The size of the MCs with cells or cell aggregates is controlled by inoculum cell density and agitation speed. The homogeneity of MCs and aggregate size could also be controlled by impeller design.
All the parameters above should be optimized for the specific cell types and will likely require adjustments to fit the large-scale differentiation process to be followed. For example, an increase in oxygen concentration was found to be beneficial to the final maturation of beta-like insulin secreting cells, so changing the amount of oxygen introduced into the system in the last stages of differentiation may improve the functionality of the final meat product.[38]

Analytics

The tools that are used to ensure efficient growth in bioreactors include automatic online monitoring and control. The analytics system enables continuous tracking of culturing conditions and is essential for process optimization and scalability. Moreover, automated feedback looped systems reduce the heterogeneity that can arise from human errors in manual systems. To develop a fully automated, closed system that will deliver reproducible results in large scales, monitoring of key metabolites in real time is necessary. In-vessel measurements of glucose consumption and lactate production together with cell density, oxygen consumption, and glycolysis rate all help in maintaining culture stability in large-scale production and in reaching the goal of product release more quickly. Online monitoring of cell density and viability, for example, will be essential for the product approval by regulatory authorities as it prevents culture contamination and eliminates human variability resulting from the current need for manual sampling and aggregate dissociation off-line.[39] Some of these systems are discussed in detail in Chapter 8, *Automation and Artificial Intelligence*.

6.2.4 Downstream Processing

Downstream processing results in the recovery and purification of the desired products from the bioreactor broth including cells, media, and waste by-products. This typically incudes harvesting, concentrating, and washing cells after which they can be formulated into the final products, possibly frozen, packaged, and stored.[12] Harvesting is the process of removing cells from the culture vessel after upstream processes, and the protocol for this will be process-specific and require optimization in each instance.[40] In some cases, MCs may need to be removed from the product either through degradation or separation from the cells.[29] However, there is a lack of technologies developed specifically for separating cell/MC suspensions, despite the development of several cell/medium separation systems.[29] The high variability in the size and densities of commercial MCs that can lose their integrity during the bioprocess may render size exclusion methods unsuitable for separation.[29] Separation is followed by volume-reduction and wash steps which target a high concentration factor and a low system volume and impurity levels as key design requirements.[12] Commercial separation systems that achieve these targets are usually based on one of the following four principles: filtration, centrifugation, inertia, and magnetism.[29] While volumes under 10 L can be processed using bench-top systems, scalable technologies such as large-size continuous-flow centrifugation or automated Tangential-Flow Filtration (TFF) are needed to reduce volume and wash cultures over 20 L with greater than ca. 10 billion cells.[12] At present, the risk of foreign material remaining among retrieved cells and ending up in the food product needs to be minimized. In addition, the high cell loss percentages reported by the end of the process need to be minimize, and currently range from 15 to 25%.[29]

Dissociation from Microcarriers (MCs)

If the removal of MCs from the product is required, strategies based on chemical, mechanical, and thermal principles may be used to detach cells, ideally while maintaining their viability, proliferation, and differentiation capacities.[29] The chemical detachment of cells from scaffolds or MCs can be carried out using enzymatic or non-enzymatic dissociation of cells.[29] Enzymatic detachment uses proteases to break the bonds between amino acids involved in cell attachment, a commonly used dissociation process for planar cultures.[29] In contrast to animal-derived trypsin, which is widely used in laboratories despite batch-to-batch variation, there are non-animal derived enzymatic and chemical dissociation alternatives available for cellular agriculture. TrypLE is a recombinant version of trypsin that is derived from microbial sources. Versene (EDTA) is an enzyme-free cell dissociation buffer which promotes cell disaggregation.[5] Drawbacks of using chemical techniques for cell detachment include increased processing times and culture manipulation due to additional washing steps required before and after dissociation.[29] Harvesting a hollow fiber or packed-bed bioreactor culture may also require extended contact with the dissociation reagent, increased flow rates, and/or rotation of the culture vessel.[40]

Alternatively, the thermal responsivity of certain materials that undergo a morphological change and/or discontinuous phase transition in response to temperature variation can be exploited for cell detachment from MCs.[29] Cell detachment can be triggered by lowering temperatures below the lower critical solution temperature (LCST) of the material, at which point the MC material will become miscible with the liquid solution.[29] While various thermo-responsive materials, including methylcellulose, xyloglucan, and hydroxybutyl chitosan have been used in 2D cultures, the quick phase transition and LCST of around 32°C have made Poly(N-isopropylacrylamide) (PNIPAAm) a widely appealing candidate.[29] Reported advantages of thermal dissociation, such as enhanced cell viability, easier reattachment, and maintenance of secreted ECM proteins, must be weighed against reported disadvantages like lower speed and efficiency before implementation.[29]

In the future, smart MCs may be developed to harness the unique responses of materials to pH, light, or electric currents. However, research on these materials for use in cellular agriculture is still in early stages.[29] Other methods such as mechanical or shear-induced dissociation may also be adopted.[5] It is important to ensure that no additional debris or particulates are created, particularly while using mechanical forces to dissociate cells, to prevent the additional burden of the removal of such particulates on downstream operations.[40] The limitations of the various strategies mentioned above can potentially be overcome by utilizing a combination; for example, by combining thermal dissociation with mechanical forces.[29]

Degradation of Microcarriers (MCs)

MC degradation to obtain cell suspensions can be used as an alternative to a dissociation step.[29] Degradation generally affects MC chemical composition as well as physical parameters, such as chain conformation, molecular weight, chain flexibility and crosslinking of a polymer.[29] The MC degradation process can be classified into one of five categories: biological, chemical, thermal, mechanical, and photo degradation.[29] Diverse degradable materials including polystyrene, cellulose, collagen, gelatin, alginate, chitosan, poly (lactic-co-glycolic acid) (PLGA), polylactide (PLA), and poly(ε-caprolactone) (PCL), have been used for MC production.[29] Polymers used for degradable MCs can be either from natural or synthetic origin and degraded in several ways depending on their properties.[29] The biochemical and thermal degradation of polymers has been explored in tissue engineering, whereas mechanical or photo degradation compatible with cell culture is yet to be reported in literature.[29]

Stem cell cultures have been successfully cultured in various biodegradable hydrogels, including PEG, alginate, collagen, fibrin, and polyacrylamide. These studies targeted a degradation rate matching the tissue skeletal muscle regeneration rate (4–6 weeks).[29] As of 2021, there are four commercially available biodegradable MCs: CultiSpher®-G, CultiSpher®-GL, and Cultispher®-S (Cytiva, Marlborough, MA) are all composed of enzymatically degradable gelatin while Corning Dissolvable Microcarriers (Corning Life Sciences, Tewksbury, MA) are composed of EDTA-degradable polygalacturonic acid (PGA).[29] In the future, there may be more MCs which are compatible with accelerated degradation induced by enzymes, pH or temperature shifts, with or without concomitant application of mechanical forces.[29]

The stimuli needed for MC degradation should be compatible with cell culture requirements to retain cell function.[29] Dextran MCs are not usually degraded because commercially available dextranases are mostly active at higher temperatures (50°C) and acidic pH (5.0–6.0), conditions which are incompatible with cell culture.[29] Thermal and photodegradation are unlikely to be suitable degradation methods because high temperatures are typically required to thermally degrade polymers and the UV radiation needed for photodegradation causes protein and DNA denaturation and damage.[29] Therefore, the use of mechanical forces in combination with chemical degradation (enzymatic or non-enzymatic) to facilitate and/or accelerate the degradation process and reduce the concentration of enzymes may be ideal.[29]

Using degradable MCs eliminates the need for their separation as the cells can be washed and directly routed to downstream processing, which simplifies the process and results in increased cell recovery.[29] When using degradable MCs, cells are usually released as a sheet or clump which may need to be broken down further depending on the type of product and food processing requirements.[29]

<u>Filtration</u>

After the cells are harvested and MCs have been detached/degraded (if needed), the cells need to be separated from waste, washed, and concentrated.[40] This can be done by size-exclusion techniques, such as filtration and expanded-bed chromatography (EBC).[40] Dead-end or normal-flow filtration (NFF) systems, which involve the flow of liquid perpendicular to a filter membrane (porous material), typically involving disc- or cartridge-type filters alone or in series, have been widely used at small scale.[40] However, they are generally unsuitable for processing large volumes of liquid that contain large molecules and whole cells as filters will clog as the scale increases.[29,40] Tangential flow filtration (TFF) and continuous centrifugation are more suitable for larger-scales.[29] In TFF, fluid is pumped tangentially along the surface of a membrane while being driven through the membrane to the filtrate side by pressure across the filter, a phenomenon known as transmembrane pressure (TMP). Flat sheets and hollow fiber cartridges are typical filter formats. TFF is a generally affordable and more scalable option that can also be fully contained and automated.[40] It is also amenable to process development.[40] Furthermore, studies have shown shorter processing times with continuous filtration techniques as opposed to discontinuous operations.[40] Nevertheless, TFF is limited by filtration rate.[29] To reach an industrially relevant scale, engineers must rethink and redesign both key operating parameters and the systems themselves.[29]

Acoustic filtration is a promising new technique that uses standing waves to capture, separate, and concentrate particles in a fluid without having a physical barrier (membrane or filter).[40] This method allows for higher throughput and has fewer clogging issues than traditional systems, extending the lifetime of system disposables.[40]

Centrifugation

Centrifugation technologies have potential for use in cell separation, washing, and concentration in cell-cultured meat bioprocessing.[12] Centrifugation involves spinning molecules with different densities in solution around an axis (in a centrifuge rotor) at high speed to separate them.[41] Traditionally, open centrifugation systems (such as swing-bucket rotor centrifuges) have been used for cell washing and concentration.[12,40] To ensure the complete removal of any unwanted reagents and/or particles, multiple cycles consisting of the resuspension of cells in a suitable buffer after the disposal of the spent media or buffer may be required.[40] However, it may be difficult to achieve the required cell numbers and a high level of automation with such systems.[40] Conventional open-centrifugation systems are too time consuming and cost-prohibitive for processes involving >10 L of cells in suspension due to contamination risks and labor intensive designs, which may require several operators and cycles.[12]

While fluid flows opposite to the centrifugal force in counterflow centrifugation, it flows perpendicular to the centrifugal force in continuous orthogonal flow centrifugation.[12] Continuous orthogonal flow centrifuges can be single-chamber or disc-stack systems.[12] These can be fully-automated to process cell suspensions with high efficiency and low shear to prevent cell damage.[12] Disc-stack centrifuges without single-use technology can be used for larger scales, but they require routine cleaning and maintenance.[12] Moreover, cells are compacted in continuous orthogonal-flow centrifuge systems, diminishing washing efficiency.[12] Additional washing steps may be needed to remove any residual materials, which may reduce cell recovery by 10–30% and increase production time.[12]

Continuous counterflow centrifugation allow cells to remain in suspension while supernatant and residuals are cleared.[12] Such systems can be automated, single-use, and scalable from 0.1 L to >1,000 L enabling >80% cell recovery with >90% viability.[12,40] However, capital expenses for a Current Good Manufacturing Practice (cGMP) operation could range from US $200,000 to US $700,000, and the lack of scale-down models result in very high process development costs due to the large number of cells required for meaningful development runs.[12] Careful consideration is necessary during process development before using centrifugation because of the capital investment needed along with the cost of disposables.[40] Process development will be discussed in greater detail later in this chapter.

Flocculation

Flocculation is a promising technique for structuring cells into minced meat using enzymes, such as transglutaminase, which catalyze the *in vitro* crosslinking of plant and animal proteins.[42] Once a bioreactor is at the highest cell density, transglutaminase and binding protein are added whilst slowly stirring until aggregates form.[42] These settle at the bottom once the stirring stops, so the cell slurry from the bottom of the bioreactor can be pumped or drained out, and thus separated from the cleared supernatant at the top.[42] This process can be carried out under Good Manufacturing Practice (GMP) and aseptic conditions in the bioreactor. Flocculation is currently being considered for harvesting micro-algae at approximately the same size (∼10 μm) as animal cells.[42]

Miscellaneous

Multiple clinical blood processing technologies adapting centrifugation and filtration could be used for cell concentration, filtration, and wash steps.[12] These can provide increased control and reduce process risks like contamination through automation and the integration of single-use bag technology for both concentrating and washing cells.[12] All these systems already comply with the U.S. Food and Drug Administration's GMP regulations, and some of them, such as the CliniMACS Prodigy® system, also have integrated cell culture capabilities, which leaves only formulation and packaging for cell-cultured meat production.[9] The application of blood processing systems for cultured meat production is, however, limited because these systems usually process less than 1 L per cycle and the need for multiple, long cycles is incompatible with large-scale production.[12]

Cells can be separated from MCs using alternative devices based on various principles, such as inertia or magnetism.[29] MCs with magnetic particles (made from iron, cobalt, nickel or their alloys) in their core can be easily separated from cells by the introduction of a magnetic field after dissociation.[29] Although such microcarriers have only been used at small scales (50 mL cultures), they may be able to improve efficiency, yields and control over media exchanges.[29]

6.2.5 Formulation

After harvesting, concentrating, and washing, the mass of cells is further processed, likely outside of the sterile environment, to create the final food product by mixing with other ingredients and/or shaping it using methodologies like extrusion.[43]

Over 750 compounds contribute to the flavor of meat.[43] Meat from whole muscle has a mixture of muscle cells, fibroblasts, fat cells, fatty acids in both membranes and fat cells, protein collagen, and endothelial cells. Compounds such as heme-iron, creatine, carnitine and glutamate together with the above-mentioned components uniquely and collectively create the taste of meat.[43] As a result, cultured meat made of only muscle cells will have a different taste and texture compared to whole muscle products from animal farming.[43] To better simulate the texture of whole muscle, binders, flavors and other ingredients, such as collagen, xanthan gum, mannitol, or carrageenan, may be added, thereby classifying the product as a 'manufactured' meat, which contains ingredients added for texture, flavor, health, and functionality.[43]

The shape of meat is also a significant factor that can greatly affect consumer acceptance.[44] The initial cell-cultured meat product will be made of loose cells, which cannot simulate the feeling of chewing animal meat without further processing.[44] Once the cells are concentrated during downstream processing, they need to be structured into an appetizing end-product that has texture similar to traditional meat using affordable, scalable, and robust techniques.[42] The concentrated cell slurry could simply be pressed and divided into portions suitable for sale.[42] Alternatively, different cells (such as muscle and fat cells) can be placed onto a scaffold with attachment points to create multicellular, 3D structured tissue.[45] 3D printing has great potential for vividly re-creating the elastic and compact 3D structure of meat, controlling the toughness and graininess of meat, and even engineering blood vessels. However, to-date, the limited scalability of 3D bio-printing systems poses a prohibitive challenge.[44]

Volatiles in meat are critical to its flavor as they contribute to aroma (detected in the retro-nasal cavity) and taste (detected by receptors on the tongue).[43] The scent of meat, which can be appealing and promote nutrient absorption, is very important for consumer acceptance.[44] Hence, the addition of aromatic substances may be needed to make the scent attractive.[44] Fatty acids are also needed to mimic meat's unique flavor and can be synthesized separately and then added to the meat.[44] As cultured muscle, fat and fibroblast cells lack hemoglobin and myoglobin, the addition of stable hemoglobin may be required to replicate the color of conventional meat.[44]

The post-mortem aging or maturation process undergone by whole muscle from animals also significantly develops the tenderness and flavor of conventional meat, as proteases like calpains degrade microstructured proteins, particularly myofibrils.[43] For example, beef from cows, which is inherently tough, needs grinding/mincing in order to make burger patties.[43] Usually, meat is aged in an anaerobic environment for days or weeks, often in a vacuum-pack, and then stored at −1 to 1 °C.[43] Although cell-cultured meat products made of individual cells do not need to be aged for tenderness, whole muscle products of the future will likely require aging for optimal tenderness and flavor.[43]

The flavor of meat further develops during cooking, so ease of cooking and seasoning are also key to an appealing final meat product with desired organoleptic properties.[43] The entire production process must follow regulatory guidelines from the relevant authorities of the territory where the product will be distributed to consumers, and the final product must undergo safety testing to verify shelf life and to ensure there are no microbiological hazards.[43]

6.3 From Lab-Scale to Large Scale

Bioprocesses are usually developed at small laboratory scale. Established processes are then transferred stepwise to larger volumes until final industrial production scale is reached. This procedure is known as scale-up. A scalable system will support the transition from small lab scale to large scale without drastic changes, thus enabling its calibration in smaller, more cost-efficient volumes.

To date, extensive work has been done to convert protocols from lab-scale to industrial scale as scalability is the motivation for developing various types of bioreactors. System optimization is required for scale-up as mass transfer within a process is highly dependent on the scale. Bioprocess scale-up is, therefore, affected by several factors from bioreactor design to support cell culture homogeneity to perfusion systems for continuous media change and the integration of online monitoring sensors. Maintaining the height-to-diameter ratio for bioreactors is one critical factor for proper scale-up. These technologies are still under development to ease the transition to food-grade, large-scale, robust production.

6.3.1 Integration of Technology

Process Analytical Technology (PAT) is an initiative from the US Food and Drug Administration (FDA) that helps to ensure final product quality and to identify sources of variability and risk through in-process measurements of critical quality and performance attributes often using integrated analytics.[46] This leads to improved process understanding, and thereby continuous improvement.[46] Regulators are increasingly encouraging bioprocessing companies to introduce PAT in the early development phase, which leads to models based on multi-variate analysis (MVA), and ultimately an optimized manufacturing process.[47]

Quality by Design (QbD) is a complementary initiative to PAT which the FDA promotes to outline a complete cycle of process development. QbD emphasizes gaining a comprehensive scientific understanding of the bioprocess (including raw materials and controls), from early stages to help establish the process “design space” and identify the critical process attributes (CPAs) that will drive the process towards the desired outcomes rather than the present state.[46,47] Scalability and validation are integral parts of process development over the product's lifecycle in this framework which root it in sound experimental rationales and data through analytical measurements.[47] However, generating cell culture data that can reliably predict performance at large scales and fit QbD frameworks can be quite challenging.[47]

Design space is defined as “the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality”.[47] Ideally, factorial designs are used for experiments, where both main factors and their interactions are measured. Cultured meat, specifically, requires such an approach to optimize flavor (taste and aroma), texture, cost, nutritional value, and food safety.[15] A sample’s composition can be estimated with high accuracy using chromatographic separation followed by mass spectrometry to build molecular profiles and comparing these with compositions of known meat samples in reference databases.[15]

Computational modeling can be used for bioreactor design considerations and parameter optimization in general, including media, scaffold, and end products, as models can reproduce behaviors of a complex system and make predictions for new conditions.[48] This can result in immense cost and time savings because of a greater parameter search space and iteration speed compared to empirical experiments.[48] These approaches are explored in more detail in Chapter 8, *Automation and Artificial Intelligence*.

Small-Scale Models

Small-scale, high-throughput platforms are much-needed tools for expediting process development because running multiple small-scale experiments in parallel enables larger datasets to be collected and more conditions to be tested, while minimizing resource requirements.[49] This leads to greater efficiency, lower costs, and an accelerated path to market because of improved process understanding. In addition, small-scale models facilitate faster and easier implementation of changes in the future by referencing data from a wider range of conditions in the design space.[49] While scaling down a process effectively in a representative way is key, the compatibility and integration of QbD approaches, such as factorial design of experiments (DoE), and automation can further save time and resources.[49] Numerous ‘’scale-down’’, high-throughput systems, including microfluidic reactors, microtiter plates, and small-scale automated bioreactors have been developed to facilitate high-throughput screening of process parameters and culture conditions.[49] One such system, Ambr15, has successfully been used to improve cell yields at small-scale, and validation in larger vessels demonstrated equivalent cell growth, functionality, viability, etc.[49] Thus, high-throughput, miniature bioreactors can be used to model processes and optimize parameters to guide cell growth at larger scales without the larger capital expenses of scale-up.[50]

The development of miniature perfusion bioreactors has been slow and challenging as these systems are more difficult to accurately model and to do so may require microfluidics.[51] As a result, high-throughput models of perfusion systems require volumes as high as 250 mL.[51] In addition, the availability of scale-down models of other downstream processing steps is highly variable. While scale-down modeling of centrifugation has not been effectively achieved yet, leading to high development costs, the availability of a wide range of filter sizes for tangential flow filtration leads to low process development costs as fewer cells are required for each meaningful run, unlike centrifugation.[12] Ultra-scale down models of flocculation have successfully predicted outcomes at larger scales.[52]

Regardless of the operation unit, pilot-scale verification of scale-down predictions of any bioprocess is essential to validate design predictions before scaling up and manufacturing commercially.[52]

6.3.2 Manufacturing Facility Design

Good Manufacturing Practices (GMP) are guidelines for bioprocesses to meet safety and quality standards for preventing contamination and ensuring reproducibility set out by the FDA.[53]

Hazard Analysis and Critical Control Points (HACCP) is an internationally recognized system for ensuring the manufacture of safe food products that places more responsibility on food manufacturers than traditional inspection programs.[53]
From equipment selection and facility design to day-to-day operations, the HACCP guidelines cover almost every aspect of production.[46] Yet, the lack of specific ISO standards for cultured meat so far has led to the adoption of lab-scale techniques and Good Cell Culture Practice (GCCP) for the time being.[5]

Standard Operating Procedures (SOPs) detail stepwise breakdowns of each unit operation including containment, testing, instrumentation, cleaning, and sterilization.

Validation is defined as the process of "establishing documented evidence that a system will do what it purports to do," according to the FDA.[46] This is a crucial step for gaining regulatory approval before any manufacturing facility can operate commercially. Validation includes the inspection of applicable policies and SOPs, along with floor plans marked with raw material/product/waste areas, clean/used equipment designations, and personnel flow patterns.[46]

Cleaning and Waste Management

HACCP design and implementation requires the management of metabolic waste by disposal, recycling, or upgrading. Thus, to comply with regulations, cell-cultured meat factories must consider building on-site treatment or recycling systems, including steam-in-place (SIP), clean-in-place (CIP), sterilizing and/or decontamination autoclaves, and glasswashers.[43,46]
Important considerations for cleaning and waste management include cleaning and sterilization of water, steam, and air systems in product contact; containment in case of

contaminations or spills; aerosol control; appropriate handling of environmental discharges; waste water recycling; and overall life cycle analysis (LCA) to determine environmental impacts such as emissions.[43,46] Load patterns will dictate equipment requirements because the frequencies at which different cleaning systems are used vary greatly from daily for Water For Injection (WFI) systems to monthly in the case of clean steam.[46]

A comprehensive monitoring program should be in place for microbial contaminations, viable airborne particles, nonviable airborne particles, pressure differentials, airflow direction, temperature, and relative humidity. This is to minimize batch losses and ensure that a bioprocess continually meets quality standards and Health, Safety, and Environmental (HSE) regulations long after a facility or process is approved.[46] Water systems are the most scrutinized aspect during testing because it is used in most steps and in large volumes, which could lead to the build-up of impurities.[46]

Facility Layout

When it comes to the spatial arrangement of different areas and equipment in a bioprocessing facility, the principal considerations include HVAC classification of work areas, people and material flows, equipment arrangements, and the fit and finish of the different work areas.[46] Different operations must be segregated in different rooms by doors or through airlocks.[53] Media preparation, cell banking, the bioreactors, and product recovery and purification all require separate, designated areas to prevent contamination and to ensure optimal environments.[46] HVAC units ensure that each room has the appropriate air quality and controlled environment depending on the assigned cleanroom class, which must be reasonable and achievable during operation.[46,53] The flow of materials and personnel through the facility is particularly consequential to its layout because it needs to smoothly go through the various sequential steps of the bioprocess while ensuring that the path of raw materials does not cross areas where intermediate or finished products are handled or stored to prevent cross-contamination.[46] Furthermore, changing rooms may be needed for personnel working in certain areas of the plant where sterile operation and cleanliness are critical.[46]

Equipment

In addition to bioreactors, upstream processing requires ancillary equipment, such as media storage tanks and heat exchangers.[5] On the whole, in addition to all the bioprocessing equipment discussed in section ‘B. Applications of Bioprocessing for Cultivated Meat Production’, every bioprocessing facility must make room for a range of utilities, including cooling towers, air compressors to supply gases, chilled water systems, and steam boilers for sterilization. All these utilities play critical supporting roles in ensuring that the process runs smoothly under the required conditions.[46] Equipment selection must be given careful consideration, taking into account the sterility and inertness (stability) of materials, ease and efficiency of maintenance, repairs, cleaning and sterilization, and environmental impacts.[46]

Installation Qualification (IQ) precedes the commencement of operation and entails the documentation and review of a plethora of evidence to support that equipment selection, manufacturing, and installation were all done correctly according to design criteria and manufacturers' recommendations.[46] Manuals, purchase orders, passivation logs, pressure test data, spare parts lists, SOPs, calibrations/loop checks, hazard operability (HAZOP) results, and Piping and Instrument Diagrams (P&IDs) or isometric drawings are all carefully collected and examined at this stage after which the facility is ready for use.[46]

6.3.3 Limitations

As a cellular agriculture product, cell-cultured meat faces both cell culture and scale-up challenges. Efficient bioprocess design for scale-up is needed to make it financially viable.[5] Yet, as of 2021, full-scale cultured meat bioprocess at price-parity with animal farming still does not exist. In addition, technical demands of large-scale production are incomparable to the field of medical research, where tissue engineering has been applied and developed the most, so far.[5,10]
While larger bioreactors are used for microbial bioprocesses and 10-20 m^3 bioreactors can be custom built, commercially available bioreactors for mammalian cell cultures typically have working volumes of 1-2 m^3.[44] Unfortunately, for cell-cultured meat to be produced at mass scales comparable to traditional agriculture, it is likely that both the bioreactors and bioprocesses will need to be scaled-up by two orders of magnitude, which is a serious engineering challenge with no clear solution as of now.[44] The closest comparison to cell-cultured meat bioprocessing—allogeneic cell therapy production processes—result in final harvest volumes of only 0.02–0.035 m^3 at the moment and are being scaled up to 1 m^3, which will also present a major bottleneck for volume reduction using available equipment downstream.[12] The successful commercialization of cell-cultured meat requires critical technologies for enabling large-scale cell culture and bioprocessing while meeting cost constraints and tissue engineering requirements that have not been met by advances in the biomedical industry.[7]

6.3.4 Future Directions

Scale-Up vs. Scale-Out

Cell-cultured meat could be produced by small-scale factories capable of supplying their local areas to large-scale, industrial-sized, commercial production plants capable of exports.[5] The highly technological and capital-intensive nature of cell-cultured meat production means that it is likely going to be produced mostly by multinational corporations initially.[43] However, in a scenario where production occurs centrally and only in a few countries, the environmental benefits of cell-cultured meat will be negated by the environmental costs of transportation.[43] This leads to the emergence of distributive approaches where local regions have their own small-scale bioreactors.[43] Other benefits of using multiple smaller bioreactors include greater flexibility to adapt output to market fluctuations or to expand product portfolios and smaller losses due to contamination.[44] Conversely, the costs of labor, supporting equipment, and materials do not scale linearly and will be higher for the same quantity of output coming from multiple smaller bioreactors compared to one large bioreactor. Thus, a balance must be found.[54]

Structured Meats (Whole Muscle)

As of 2021, tissue engineering or *in vitro* generation of whole muscle, complete with muscle cells, fat cells, connective tissue, blood supply, and associated structure has not yet been achieved in any industry or setting.[43] The first generation of cell-cultured meat products following Eat Just's cell-cultured chicken bites will also be minced or processed meats, such as burgers and sausages, made of individual or aggregates of muscle and fat cells combined during downstream processing. This is because the accurate, cell-based production of whole muscle, including steak, still requires a range of technological breakthroughs as it is far more complex.[43]

There are two main technological factors for whole muscle production that have yet to be determined. First, researchers will need to define the set of biochemical, biophysical, and biomechanical cues needed for the simultaneous proliferation, differentiation, and maturation of numerous stem cells or other progenitors into functioning muscle, fat, and other cell types in the correct 3D structure. Second, the media and growth conditions for co-culturing these cell types and vasculature through the thick layers of muscle tissue also need to be developed.[43]

To promote tissue development and give it 3D structure, diverse cell types can be co-cultured in a 3D scaffold, which could be a hydrogel, a porous, sponge-like biomaterial, or a combination of the two.[15] Careful selection of the material for the scaffold to make it more representative and mimicking of the natural environment of meat cells is important.[15,43] This is discussed in great detail in the Chapter 9, *Scaffolding*.

Bioreactors

Novel, specialized bioreactors need to be developed and optimized for cell-cultured meat production to maintain low shear and concurrent uniform mixing for sufficient mass and heat transfer rates at large scales, improve the efficiency of media use, recycle media components, and enable the growth of tissue with native architecture for structured meats (whole muscle).[15,55] The most useful bioreactors will be flexible, and easily adjusted according to process requirements. For cell-cultured meat specifically, this determines whether both cell proliferation and differentiation can be carried out in the same bioreactor by changing parameters like mixing speed, gassing, and growth factor concentration in the same vessel. This removes the unnecessary step of transferring cells to a secondary bioreactor for differentiation, thereby reducing complications and capital expenses.[39]

Perfusion bioreactors, which flow media through a porous scaffold with gas exchange occurring in an external loop, are commercially available and could be suitable for scaffold-based cultures, and they come with several advantages and disadvantages.[55,56] A variety of different cell culturing systems including microfluidic devices and orbital shakers have been integrated with cell-seeded porous scaffolds to promote 3D tissue formation.[56] This also includes Rotating Wall Vessel (RWV) bioreactors that only achieve low cell densities due to repeated collisions with the bioreactor wall, and spinner flasks, which are limited by scale and culture duration due to the build-up of wastes over time.[56] It is, however, important to note that there are serious concerns about the suitability of 3D scaffolding in its current form for large-scale production due to its inherent limitations of mixing and mass transfer.[44] Consequently, there is an increasing focus on alternative approaches.[44]

Customized Nutrition

With the on-going improvements in public living standards and advances in nutritional sciences, there is increasing demand for meat products that are customized to different diets, taking into account each person's goals, genetics, tastes, microbiome, etc.[44] Techniques such as infrared spectroscopy and mass spectrometry can be leveraged to collect data on the physical composition and nutrient content of different cuts of meats from different animals. Swift and accurate analysis can be carried out with the help of Artificial Intelligence (AI) and other tools to build a database that lays the foundation for creating new meats with composition tailored to dietary needs.[44] While 3D bio-printing technology may not be scalable in its current state, its latest iterations enable the engineering of blood vessels and local control of the toughness, 3D structure, and texture of cell-cultured meat at scales that can match the needs for personalized nutrition.[44]

Fundamental Questions – Answered

1. **What is a bioprocess and how is it relevant to cultivated meat?**
A bioprocess is a process where we control a biological entity or organism to create or transform a nutrient source into a product which can be proteins, amino acids or nucleotides that has value to humans. It's relevant to cultivated meat as we're now taking a singular component from a farm animal and applying traditional bioprocessing to it but with a new outcome that has not been done before that has not been done before in human food production.

2. **What are the steps involved in cultivated meat bioprocess?**
First, create a sterile, closed environment. Secondly, isolate relevant organism/cell source. Develop a suitable media/environment for the cells to survive/thrive. Innoculate said cells in medium. Monitor and stabilize environment (pH, oxygen, temperature), optimal for cells so they can start intaking nutrients, necessary for cell division. Harvest cells for further processing. Processing can either directly thereafter, formulation into product, or differentiation into next phase of tissue formation.

3. **What are the technologies that can be used for cultivated meat bioprocesses?**
Stir tank bioreactor. Bubble column bioreactor. Microcarriers. Probes (for pH, oxygen, temperature). Harvesting devices. continuous flow centrifuge cell separation. Media filtration device. Standing acoustic wave cell separation. Sparger system. (Extra: several types of impellers, motors, pumps, heating system computer systems to monitor everything)

4. **How scalable are bioprocesses for cultivated meat production?**
Constraints will be on how well the cells perform in larger volumes of media, and withstands the shear stress of that environment; more R&D is needed and bioprocess capacity is likely to increase over the coming decades as funding fuels scaling/commercialization efforts.

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Automation

Overview of Automation for Cultivated Meat

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Chapter Abstract

Much research focusing on the science of cell-cultured meat underscores the challenges of making both the processes and products of cell-cultured meat cost-effective. This chapter discusses the use of automation and artificial intelligence to address the multidisciplinary challenges associated with making cell-cultured meat a commodity. This chapter begins with an overview of computational biology and automation, the relevant tools and methods, and then goes into its application in the research, development, and production of cell-cultured meat by providing example use cases. Finally, the main challenges that prevent the widespread adoption of these tools are discussed.

Keywords

Computer models reproduce some aspects of a complex system's real-world behavior, such as cell proliferation inside bioreactors. The models allow for exploration, quantification, and optimization for desired outcomes, such as product yield. Models are most useful when conducting physical experiments would be unfeasible, expensive, or time consuming.

Artificial intelligence (AI) is a tool of data science, where a computer effectively learns from experiences and can then make predictions or take steps towards achieving a certain goal. Combining robotic automation with AI is termed intelligent process automation (IPA). IPA can overcome some limitations of robotic automation, rendering it flexible and ultimately more powerful. **Machine learning** (ML) is a subset of artificial intelligence. It is based on the concept of computers learning functions/tasks without these functions/tasks being explicitly programmed. ML uses advanced statistical algorithms to uncover patterns and trends in large datasets.

Automation is the replacement of manual labor with mechanized labor. It generally involves increased speed of task completion, less human intervention, lower error rates, increased lab safety, and increased upfront costs. It can, however, save money in the long run through efficiency gains.[5,6] Automated data collection enables the generation of knowledge and insights from data, a field commonly termed **data science**. A typical automated workflow consists of iterative data collection and processing from various instruments. This is followed by exploration, which includes the use of AI methods, and ends with predictions. Inbuilt sensors in different machines, such as bioreactors, can automatically feed data to a cloud platform, a technology known as **the internet of things** (IoT). This real-time, automated collection and analysis allows faster data processing and more efficient process optimization. But automation can be taken one step further. It is expected to transfer back the generated *in silico* models, designs and/or simulations to the physical, also known as "wet-lab" experiments. For example, based on the results of already conducted experiments, algorithms can suggest which experiments to perform next to gather the most important data and/or optimize the target. In this way, IoT-enabled robots combined with AI can contribute to "smart" experimental design development, thereby "closing the loop" of laboratory process development, as shown in Figure 1. This **closed-loop feedback system**, connecting the physical and digital, is the primary vision for the role of automation in scientific research.

Chapter Outline

7.1 Introduction

7.1.1 History of Computational Biology

7.1.2 The Current Landscape

7.1.3 Automation and AI for Cell-cultured meat

7.2 Methodological and Technological Toolbox

7.2.1 Computational Modeling

7.2.2 Mechanistic Models

7.2.3 Data-driven Models

7.2.4 Machine Learning

7.3 Case Studies: Applications of Automation and AI in Cellular Agriculture

7.4 Challenges and Perspectives

7.4.1 Data Challenges

7.4.1.1 Data Generation

7.4.1.2 Data Quality and Storage

7.4.1.3 Data and Tool Standardization

7.4.2 Economic Challenges

7.4.3 Personnel Challenges

7.5 Conclusion

Fundamental Questions

1) What are the main challenges facing cell-cultured meat development and commercialization that automation and AI can help address?

2) What are the challenges facing the adoption of these technologies in the field? How can cell-cultured meat startups reap the benefits of these technologies?

3) What considerations need to be made when automating lab processes?

4) Define and give examples of why Design of Experiments or machine learning could address research problems in cell-cultured meat?

5) What are the most important traits for an AI/automation scientist in cellular agriculture?

6) Beyond production of cell-cultured meat, what is another challenge in cellular agriculture where automation and AI will be impactful?

7) Why is it most beneficial for companies to adopt automation and AI technologies early on in process development?

8) What are the different types of models? What type of model could be used to predict cell performance (biomass yield, titer and growth rate) under various bioprocessing conditions?

7.1 Introduction

Modern research and development labs demand precision, scalability, reproducibility, and traceability to be regulatory-compliant and offer commercially viable products. As a result, scientists are considering automation and AI to augment their research capabilities, while lowering costs and saving time.

The 21st century is the age of **computer-aided biology** (CAB), a framework and ecosystem of tools where machines can run experiments, analyze the data, and design the next experiments. This is made possible by the integration of computing and biological sciences. These two fields share numerous properties: both deal with data storing, integrating hardware with software, and they have grown extremely quickly in recent years. Interestingly, while biological evolution may find only adequate solutions to problems, computing is designed to find the optimal solutions.

Figure 1. Experimental data is fed into bio-design, experimental design, and simulation, thereby connecting the physical and digital realms.

7.1.1 History of Computational Biology

Life science disciplines have lagged behind most other industries in this fourth Industrial Revolution, or Industry 4.0, which refers to the digitization of technologies and methods. Industry 4.0 involves getting connected via the cloud, maximizing Big Data and Analytics, and establishing standards and best practices to move from automated (Industry 3.0) to autonomous, cyber physical systems. Cell culture, for example, has remained practically unchanged since the discovery of penicillin almost a century ago. But due to the growing importance of life sciences, there has been a great push for innovation, increasing speed to market, and cutting costs in the last 15 years. This push was bolstered by the US Food & Drug Administration's (FDA) introduction of a regulatory framework for the implementation of Process Analytical Technologies (PAT), encouraging continuous manufacturing.[2]

The food processing industry (relevant to cell-cultured meat production post-harvest from the bioreactor) leverages automation and AI across many categories, such as traceability, monitoring, food quality and safety control, and even predicting changing customer preferences, leading to more agile manufacturing, and therefore time and cost savings.[3] Moreover, in chemical engineering, AI is used to empower autonomous chemical plant operation in applications such as fault diagnosis, scheduling, and process control. The automation of data gathering and knowledge management systems is growing through technologies such as robotics, expert systems, and ontologies. In contrast, biological science's information infrastructure is in a nascent state. Domain specific technologies are needed for the utilization, manufacture, and deployment of biological systems, such as computer aided design (BioCAD), upon which computational frameworks for modeling, prediction, storage, and standardization of data are based.[24] These factors therefore constitute major bottlenecks for automation.

This contrast may seem surprising, as biologists have a long history of readily integrating tools from other disciplines to tackle their research questions.[13] The first computer, built in the 1950s, was rapidly adopted for crystallography. More recently, the Human Genome Project, another milestone in modern biology, relied on automation for DNA sequencing and computer science information technologies to store and share DNA.[15] Hence, the idea of looking at biology as a type of computation is far from new. One prominent area of computational biology is referred to as "Bioinformatics": the subfield that helps store, represent, and share biological information efficiently and precisely to uncover knowledge from the data.

An area of technology that has historically underserved the biological sciences is software programming, which includes the development of computational models. The first time an innovation in computational methods was awarded the Nobel Prize was as late as 1998.[14] But since then, increasingly more scientists have developed software programs that have led to remarkable discoveries. For instance, the 2013 Nobel Prize in Chemistry was awarded for the development of software programs that could elucidate the behavior of biomolecules. This led the Nobel's Academy of Sciences to recognize the use of computers as a fundamental tool, proclaiming in 2013, "today the computer is just as important a tool for chemists as the test tube."[16] Early computer programs in biology were used to study cell-cell interactions mechanics and led to large advances in the field.[13]

Artificial Intelligence (AI) is a nascent field in biology with enormous room for development. This contrasts with other fields where AI is more developed and widely used, such as in recommendation engines for companies like Google or for image/speech recognition.

Automation of single devices performing single tasks dates to the 1800s. This included polymerase chain reaction (PCR) machines adjusting temperatures automatically running on a computer program. The first robotic arm for the lab was built, followed by the fully automated lab by Sasaki in the 1980s.[17] The advance of high throughput screening for experimental parallelization was key to enable automation across entire experiments.[18] Since then, computer power, data availability, and hardware automation have propelled automation and AI in research and manufacturing. For example, the "Chemputer" allows the automation of complex reactions and purifications, which was used to produce pharmaceuticals and Eli Lilly has demonstrated scalable end-to-end automated manufacturing of different drugs.[19,20]

The 21st century has borne witness to promising advances in CAB in synthetic biology, which, among others, involves the engineering of organisms to address agricultural and manufacturing challenges. For example, EVA by the company LabGenius is an AI-driven discovery platform for protein therapeutics. The test cycle is fed back into AI models to generate an improved DNA library.[25] The company Ginkgo Bioworks uses automation in their biological labs, resulting in more efficient and faster product development.[9] AI, inline analysis, and genetic design software are also increasingly used in the development of cell therapies.[26] In 2009, a fully automated skin tissue factory, including cell extraction, producing a monthly throughput of a few grams, was created by the German Fraunhofer research organization.[4]

The development and history of automation and AI in biology emphasizes the importance of innovative scientific methods, standards, and best practices, in addition to efficient tools for the development of commercially viable products.

7.1.2 The Current Landscape

The main problem that the emerging CAB ecosystem intends to solve is the decline in productivity in the pharmaceutical industry, measured by the decrease in R&D's internal rate of return (IRR). This decline has been referred to as "Eroom's law", the inverse of Moore's law common to other fields characterized by decreased costs and increased digitization.[1]

The CAB ecosystem consists of academic and industrial research labs working on software and hardware, mostly clustered around technology hot spots like Silicon Valley. Figure 2 shows an overview of the CAB landscape with key players. The global market size of CAB is expected to expand at a compound annual growth rate (CAGR) of 21.3% to reach US $13.6 billion by 2026.[1] The most crowded space in the landscape consists of providers of data management tools (e.g., Tetrascience and Dassault Systems with their "Living Heart Project"), and models for design and simulation (e.g., Labgenius and Eagle Genomics). Fewer companies provide services to connect the digital to "wet-lab" experiments and address the lack of standardization between tools, a key barrier in the adoption of CAB technologies. Synthace and Riffyn are the major players in this niche.[2] Many of the largest biological and chemical companies and academic researchers in biological and chemical sectors, advanced therapies, and agrochemicals have their own in-house initiative to "close the loop." However, these closed loop systems have yet to be democratized for the benefit of the wider ecosystem.

Figure 2. Stakeholders in CAB.

7.1.3 Automation and AI for Cell-cultured meat

Automation and AI have been applied across industries to address or even solve challenges. To understand the scope of the application of automation and AI for cell-cultured meat, this section will first reiterate the current challenges in cellular agriculture research, development and manufacturing, and then in the subsequent sections dive deeper into how automation and AI could be leveraged to address those challenges.

Biotechnology R&D is notoriously risky and slow. Cell culture itself is costly and labor-intensive, with these challenges typically multiplying at an increasing scale. There is also a high risk of human error due to the work being difficult yet repetitive, as well as contamination risks.

One key challenge of cell-cultured meat production is the complexity of biological systems, which are very context dependent. Consequently, a deep understanding of the interactions between parameters is required. For example, biochemical kinetic reactions, while important, remain poorly understood. The large number and variety of variables and their interactions all pose further challenges to the development of a robust process model to represent a biological phenomenon.[21]

Bioprocesses, such as those used to produce cultured meat, are also time and scale dependent. Nutrients, for example, degrade and are metabolized over time, and factors change for each stage of scale up. This increases complexity and makes optimization more challenging. Hence, this is another area where automation and AI have potential to augment. Biological processes have many degrees of freedom—the number of values that cannot be fixed by the equations—arising from aspects such as cell line choice, medium choice, bioprocess parameters. Hence, finding the optimal combination for the desired performance requires an unrealistically high number of experiments. Refer to Chapter 5, *Cells*, and Chapter 7, *Bioprocess*, for a deeper understanding of the difficulties behind cell culture and bioprocess engineering respectively. Process characterization is necessary to ensure compliant and efficient designs, as it is used to determine acceptable operating conditions, and thus the design space can be better understood. A further challenge for cultivated meat process models is the large exploration space, which makes it likely that the optimization finishes at a local optimum (i.e., the optimum within a neighboring set of solutions only, not the global optimum for this problem) when using traditional DOE methods.

Manufacturing (i.e., scaling up or out to produce commercially viable cell-cultured meat) is another area which can benefit from automation and data science. As of 2021, it is a complex process that is far from optimized. The use of models helps address this by predicting the impacts of parameters on the system's behavior. This is important to prevent common and costly issues in the later stages of process development.

The main advantages of AI and automation for cell-cultured meat include improvements in time and cost savings, product quality, reliability and even discovery.

Industrial automation can lead to time savings, as experiments can be performed more rapidly with shorter data cycle times and result in quicker availability of information to guide the next production steps. For example, high throughput screening is one method that uses sensors, robots, and liquid handlers to dispense reagents, prepare assays and probe hundreds of experiments in parallel. Process characterization and optimization are also required for regulatory compliance.[5]

The main bottleneck for cell-cultured meat commercialization is cost. Cost savings are achieved in three main ways. First, high throughput robotic platforms can lead to efficiency savings. However, the cost of automated equipment may be prohibitive for startups. An alternative is to use cloud labs, which can save on capital expenditures and maintenance costs.[6] Second, using liquid handlers and other high-precision automated tools can save on expensive raw materials, such as growth factors for the culture media, as volumes can be more precisely measured to reduce waste. Third, laboratories can reduce costs associated with management through real time analytics for fault detection.[29]

Increased quality and yields of cell-cultured meat products can be achieved through improved testing and analysis. For example, a robust exploration of the search space would help find better product formulations, analysis of design parameters could limit batch-to-batch variabilities, and higher screening capacity would allow more data collection in the R&D phase. Ultimately, this can push the development of more complex products.

Cloud labs can elevate convenience and productivity through real-time remote access and control for scientists over their experiments. These technologies can also enable faster decision-making, especially in experiments that require real-time feedback. Furthermore, data analysis applied to laboratory results is facilitated by firmware that performs automatic data structuring and alignment.

Quality and safety are increased by reducing human errors, such as cell culture contamination, allowing better working conditions (as dangerous substances do not have to be handled), reducing operator variability, but also by increased process understanding leading to better decision making. Risk reduction in turn increases reliability for optimal production, and processes are made more robust. Lastly, closed loop automation helps tighten process controls, which are important for food safety assessments during the prototype stages of cell-cultured meat manufacturing.[20]

Discovery and innovation can also be enhanced by automation and AI as they enable researchers to solve more complex, interdisciplinary challenges thanks to real time data access as well as increased collaborations (as experiments can be conducted in the cloud remotely). These tools can also reduce time spent on training and conducting laborious experiments. AI can be used to gather insights from different data streams and publications, which can help uncover otherwise hidden knowledge. As the full experimental space is explored, a plethora of new products and materials may be discovered for sustainable manufacturing. In addition, increased efficiency from robots working continuously, controlled material usage, and better waste management in R&D and production can lead to improved sustainability.

Automation and AI are powerful tools with numerous potential applications in cellular agriculture. Even a 0.01% bioprocess improvement can lead to millions of dollars in untapped research value over the long run. The next section briefly outlines the business landscape before diving into the methodological and technological toolbox required for automation in cell-cultured meat. Subsequently, it will provide example applications of automation and data science in cell-cultured meat, before discussing the remaining challenges and offering future perspectives.

7.2 Methodological and Technological Toolbox

What could the “lab of the future” look like? While this term is widely used in scientific communication, the lab of the future or “cloud lab” is already here. Its important characteristics include the ability to control robotics using software and to automate repetitive or laborious experiments. The required technologies are accessible to both startups and academics and pave the way for a new era where “working in the lab” can happen from home.

Advances in biochemical sciences have been largely driven by toolkit additions (such as multinuclear nuclear magnetic resonance (NMR) to study cell machinery and transcriptional activity).[5] Hence, this section will first describe some key equipment. Additionally, ever more precise tools and high-throughput experiments generate larger amounts of data every day, driving the need for specialized hardware and software solutions.[6] As a result, novel methods are also being developed, which will be discussed next.

Robotic automation is particularly well suited for repetitive laboratory processes, such as heating, mixing, testing, and analysis. It can also be used to perform dangerous and/or difficult tasks. Robotic platforms are widely used in the bioengineering and pharmaceutical industries. They include robotic arms, computer vision for quality monitoring, as well as more complex robotic workflows automating the scientific process itself (e.g., "Robot Scientist"). As tissue culture requires high sterility, robotic systems can mimic the tissue culture hood by having features such as HEPA filtration, and laminar flow. A common lab robot is the liquid handler. Liquid handlers are used to automate workflows (Figure 3). They dispense precise volumes (ranging from 1-1000 µl) of liquids, such as reagents, using motorized pipettes. These robots are commonly used for PCR sample preparation, next-generation sequencing preparation, plate replication and serial dilution. The procedure and volumes are controlled through the associated software or programming interface. Liquid handlers increase quality consistency, minimize the use of reagents/sampling liquids, reduce risks (e.g., contamination) and generate structured and rich data as each action can be logged. Moreover, metadata (environmental conditions such as temperature) can be recorded. Liquid handlers can also increase throughput, as the robot can be equipped with one single-channel pipette for low throughput (<1000 samples/week) to hundreds of pipetting heads and channels for high throughput (>1000 samples/week). These instruments were originally developed to screen chemicals for drug discovery. Today, more advanced liquid handlers can be integrated into other laboratory devices, such as centrifuges, heaters, and PCR machines.

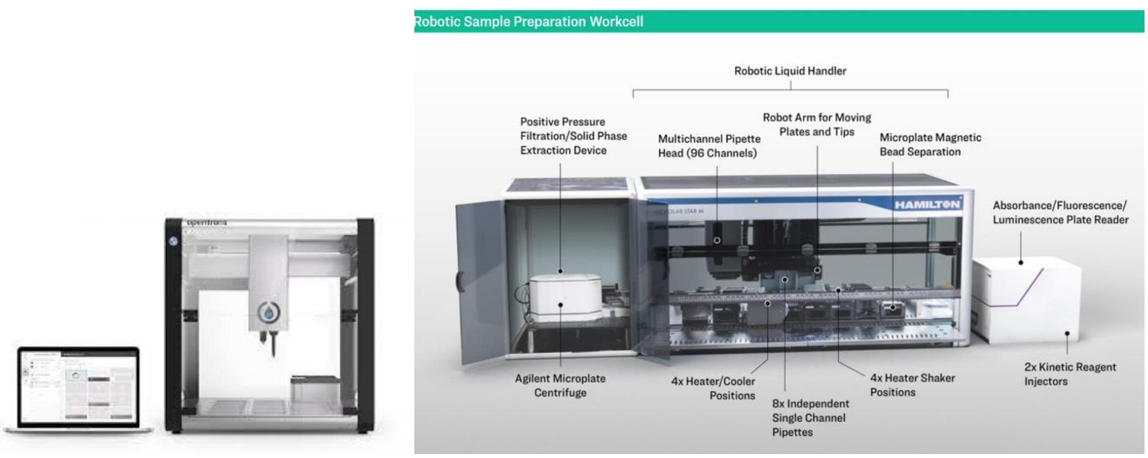


Figure 3. Liquid handler from OpenTrons (left) and the module layout of a standard robotic liquid handler (right).

An example of a physical automation system highly applicable to cell-cultured meat is the parallelization of arrays of bioreactors. This system uses liquid handlers for automated real-time control of the cultivation environment (e.g., pH, nutrients), as well as periodic sampling (for offline analysis).

Various automated cell culture systems are commercially available.[7] This includes an automated cell culture system for human induced pluripotent stem cells (iPSCs) with automated cell seeding, medium changing, cell imaging, and cell harvesting, shown in Figure 4.[8] Some systems are designed to overcome particular challenges of manual cell culture (e.g., cell density limitations), while others are not based on manual methods.

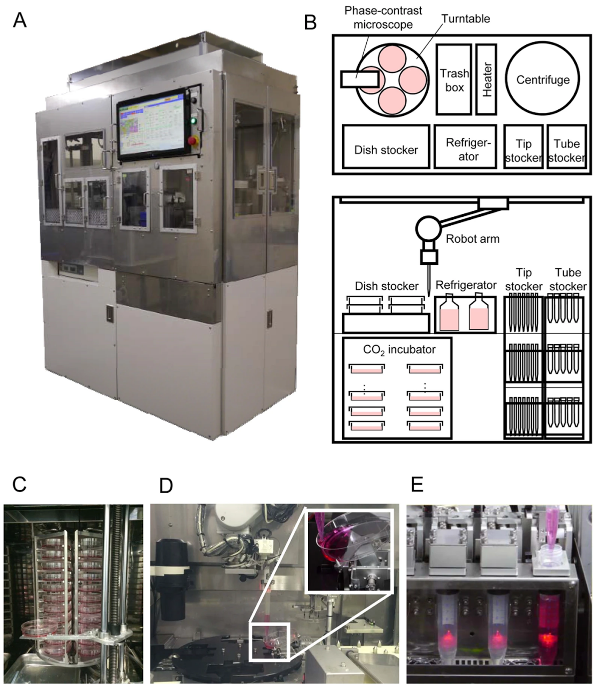


Figure 4. (A) Automated culture system of human iPSCs. (B) The system layout. (C-E) Cell culture modules, which include (C) an incubator, (D) turntable and robotic arm, and (E) heater.

With automation, there is often a choice between buying commercial hardware or building in-house. There are various commercial options with many pieces of equipment on the market. This equipment tends to be well-validated, with good technical support and software that can be easy to use, particularly for those without programming experience. However, commercial equipment can be expensive and cellular agriculture is a nascent field which can therefore find it unaffordable.[10] Additionally, some of the unique lab requirements (e.g., filtering steps and creating functional tissues) are not well served by commercially available products.

In-house automation equipment manufacturing is an alternative to the high price of commercial products, and was a solution long before the lab automation industry started. Whether it was building a two-photon microscope, flow cytometer, or simply rigging up a perfusion system with tubing and parts from a local hardware store, scientists and engineers have been building *ad hoc* automated systems for decades.[11–13] With the advent of affordable 3D printers that allow the creation of specialized parts, as well as open-source design sharing, this is an increasingly feasible option. In-house solutions can also rely on open-source programming languages like Python to control bespoke equipment and better integrate them into process control, data uploading, and analysis. Additionally, inexpensive open-source electronic platforms like Arduinos (US $10), and computers such as Raspberry Pi (US $35) offer many opportunities for lab automation engineers. They can be used to automate cell culture experiments, for example, and gather data continuously.

There are many resources available for in-house automation creation.[14] For example, a research team used Legos and other low-cost hardware to create modular systems of media exchange and microscopy.[15] An important advantage of this system is its modularity. Modularity refers to the ability to separate and change parts of a system, without having to change the entire system. A PCR thermocycler, for example, is not very modular, as only its heating block can be changed. Modular systems give many more options, as opposed to a one-size-fits-all approach that may not work when different conditions or samples need to be analyzed.[16] Examples of modular platforms include Ospin's bioreactor platform for cell-cultured meat, which comes with specific laboratory modules with distinct functions (e.g., for centrifugation, or analysis) and Sirius Automation's Minitasker, which can perform a range of common, important laboratory tasks (e.g., weigh, label, dilute, aliquot) enables reproducibility and traceability as the protocols are recorded and can be altered.[7] The downsides of in-house development include higher uncertainty that the product will work, the need for specialized personnel with programming knowledge to build, use, and maintain the equipment, and a longer time for development.[12]

The use of automated technologies allows for novel scientific methods that may be manually unfeasible. These methods can take advantage of the parallelization and throughput benefits of using high-density microplates in the context of liquid handling systems, for example. They also enable automatic workflows, which include the automation of protocol design and selection, thereby closing the loop to decide which experiment should be performed next. Cell culture automation solutions allow protocol sharing with precise instructions, giving more transparent and traceable results. These instruments also allow the culture to be kept sterile. Options for automated instrument choice include a semi-manual process automation system, a stand-alone unit with an operator interface, which has more flexibility, or fully automated systems, which are autonomous integrated unit operations, mostly used for high throughput.[1]

Historically, the one factor at a time (OFAT) scientific method is the most used to plan and perform experiments. This method involves changing only one factor per experiment, holding the other parameters constant. While this method is useful in a small search space or design space, it is prohibitive for finding global optima and factor interactions. It is also timely and cost intensive, as it requires more experiments to be run if the search space is complex. The DoE method provides an alternative. The components of DoE are an algorithm and the experimental data set. DoE is used for efficient statistical inference. It allows multiple parameters to be changed simultaneously to identify combinations of critical process parameters (CPP), areas that have the greatest impact on the objective (e.g., reducing greenhouse gas emissions), and multifactorial effects. DoE helps describe the design space, understand a system's properties and interactions between parameters, and find a global optimum, thereby making research more efficient. Commercial DoE software like MiniTab or Matlab are frequently used, or open-source tools such as Python.[21] Examples of typical culture conditions to be tested are gas concentrations, pH, agitation rate, feeding rate, seeding density, and temperature. A process characterization study involves testing a range of parameters fixed around a set point to define the required ranges for the desired productivity and product quality. In this way, acceptable operating conditions can be determined, and the design space can be approved by gaining greater process knowledge.

Another bioengineering principle for a smarter workflow is the Design-Build-Test-Learn cycle (DBTL), shown in Figure 5. It is based on measurements made in the previous prototype/experiment to improve the design of the next iteration. Protocol design may be automated using a data analysis pipeline.[12] The quality by design (QbD) paradigm is where the product quality is assured by the process itself, instead of subsequent testing.[11] The paradigm uses statistically designed experimental studies (described in the following paragraph) to identify CPP and the relationship between parameters.

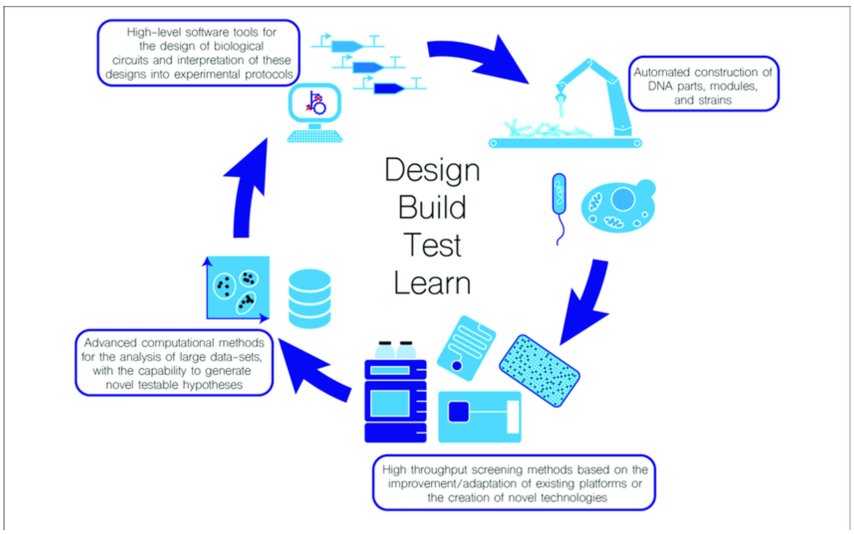


Figure 5. DBTL for automating cell culture.

High throughput screening is a method that automates experiments to generate high volumes of data. Typically, small scale batch reactions are run in parallel, allowing thousands of reactions to be conducted simultaneously. It plays a significant role in the discovery of medicinal compounds by efficiently screening hundreds of thousands of compounds. While high throughput revolutionizes laboratory research in terms of the scale of experiments possible, it may still only conduct low variation experiments, also known as "brute force" experimental research. Hence, software programs and ML tools should be leveraged in combination with high throughput screening for better exploration of experimental space. ML also allows more complex experiments to be conducted.[30]

Another important technique in cell-cultured meat manufacturing is PAT. It uses multivariate monitoring of the CPP to detect potential deviations in real time, for process control and root cause analysis.[9]

7.2.1 Computational Modeling

A model consists of rules or mathematical representations that map a set of inputs (e.g., temperature) to a set of outputs (e.g., yield). Process models can describe a single unit operation or provide a holistic representation of a full bioprocess. Models represent a system by embedding key properties, but not all of them. They are therefore an incomplete, abbreviated reality. Even a qualitative abstraction of a biological phenomenon is by definition a model. Modern modeling requires the characterization of a biological system or phenomena (e.g., cellular/molecular functions) through the identification of the important state variables, as well as the quantitative data related to the impact of changing these variables on the outputs.

Computational models have become a standard tool to investigate biological mechanisms.[13] They are used to help understand and identify CPP and enable process control, which will be discussed below. Computational models, based on simple concepts, have wide applicability–for example, nonlinear dynamics modeling has helped researchers understand the oscillatory behavior of systems like skeletal muscle.[36,10] A process life cycle consists of process development, scale up, and continuous optimization. Yield, safety, and efficiency are the most common targets of production processes. Process development and improvements require the characterization of the research/design space, as well as understanding the relationships between CPP and the required product attributes or process performance. These *in silico* models can help investigate initial conditions, such as the volume of the bioreactor, cell line, and culture type. Computational process models are mainly used for plant design, scale up and process control, as well as in digital twinning (virtual replicas of a real-world industrial object). In a dynamic manner, digital twinning technologies share data between the computational model and the physical object (e.g., the bioreactor).

Models can be used to make both qualitative and quantitative predictions and test those against real world conditions or hypotheses. The predicted variables may be hard to measure in the physical world. For example, useful and accurate predictions might be made from a simple model of cell aggregates, which have only a few assumptions and rules. Using the simulation as a tool, the researchers could identify which assumptions were invalid. In this manner, models can serve as tools to screen unpromising hypotheses and expand the range of meaningful questions that can be asked, thereby guiding experimental design. Models can also be used to store knowledge so it is more precisely and reliability transferred and leveraged than information from laboratory notebooks, for example.[10]

Figure 6 shows a general data analysis methodology for process development. Prior to data analysis, pre-processing techniques such as principal component analysis (PCA) may be used for dimensionality reduction (i.e., reducing the number of features in a dataset).[10] Data mining is used to uncover patterns and structure out of the data.[31] The most common programming languages used for data mining are R, mostly favored by biologists, and Python, which is more flexible due to its large offering of packages, and more widely used for biochemical and chemical engineering.

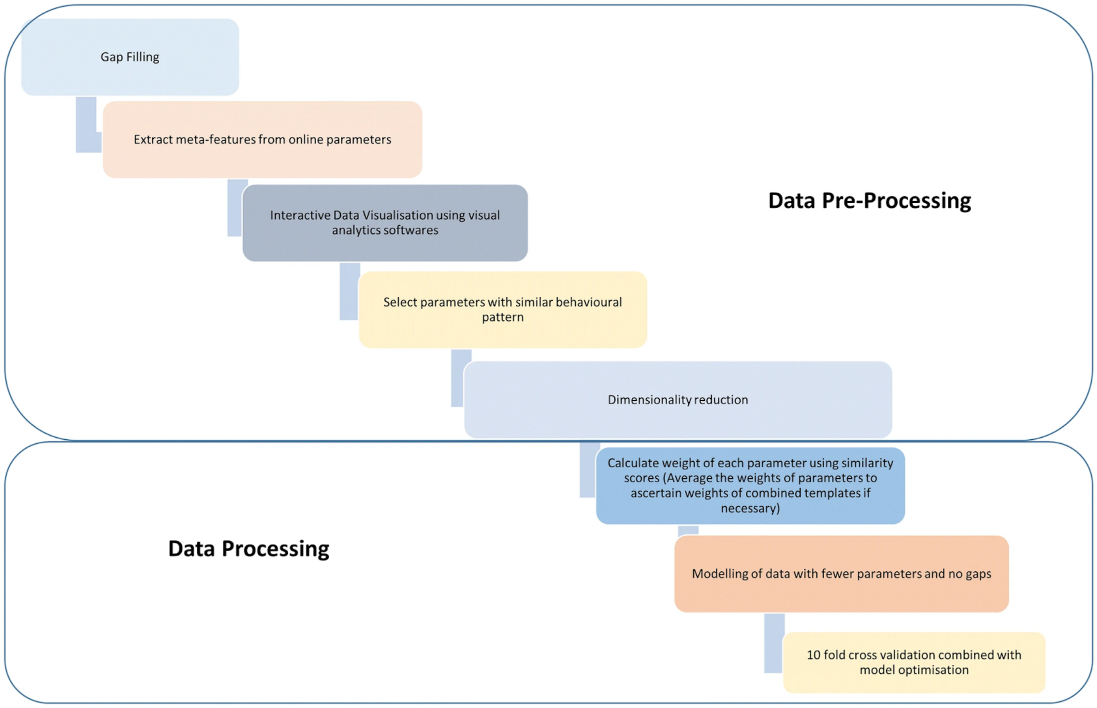


Figure 6. An example sequence of steps for data analysis, which can be divided into two main types.[11]

Heterogeneous data from different sources can be collected and maintained in an ontology, which is a knowledge base that allows for integration of domain-specific information in a structured and reusable manner.[69] An ontology for cell-cultured meat could enable better data handling and communication within an organization, in a computer-readable format that facilitates retrieval and utilization in models.

Models can be broadly classified into three types based on their different abilities: mechanistic models, data-driven, and hybrid models.

7.2.2 Mechanistic Models

Mechanistic (also known as white box) models start with prior knowledge, from empirical knowledge and first principles. These models should start simply, incorporating only the necessary detail for the desired performance (forming a zeroth order hypothesis using the limited knowledge available). The main limitations of this type of model are laborious development and poor prediction performance.[21] They are used when the dynamics of the system are understood. In this way, unexplored conditions may be tested to investigate their impact on the system. This approach is common in climate models, where physical processes such as fluid dynamics, evaporation, and condensation are used to derive the required mathematical relationships. The interaction between these different physical processes can then be modeled. Prior knowledge for physical/mechanistic models may be explicit equations like Newton's law, the relationship between input and output, or important features in the dataset (e.g., dominated by the first kinetic rule, or knowing that a particular concentration has the most impact on the final product).

Mechanistic models investigating cellular behavior can be further divided in various model forms, such as structured and unstructured, and segregated and unsegregated models.[34] Structured models treat the cell population as a multi-component system (having internal cell compartments). Segregated models add another level of detail, as the cell population is treated as heterogeneous, taking into account factors such as density, and cell cycle, unlike unsegregated models, where they are approximated as "average cells". Hence, unstructured, unsegregated models are simpler and more general. A well-known example of an unstructured, unsegregated model is Monod growth kinetics, which describes microbial growth.

The choice of the model necessarily depends on the objective. Structured models may be favored to build a detailed, realistic representation of a complex system, while unstructured models focus on process behavior (e.g., change in biomass, substrates) and not on intra-cellular processes.[35] Agent-based models are examples of structured models, and identify their constituent components as sub-parts or agents. These models are helpful when the system is divisible into agents, such as cells, that follow explicit behavioral rules. Since there can be many interactions between the cell agents, it is impossible to have mathematical equations to model the whole system. However, rules can govern the interactions between neighboring cells.

Many systems can be represented as network models, in which subjects (i.e., nodes in a graph), have interactions (i.e., the edges in a graph). The interactions may be described through prior knowledge or data. One example is biochemical reactions between molecules, where the molecules make up nodes of a graph, and the reactions between the molecules, the edges. There are multiple forms of representation and types of networks that can describe the biological system of interest. What these have in common is a systems' view of the problem and a simplification of larger range interactions. The relationships between concepts or entities can be maintained in ontologies.[35] Separate networks usually describe cellular processes with heterogeneous levels of detail, such as metabolic, protein–protein interaction, and transcription regulation networks. In the literature, these have been described as integrative frameworks utilizing rule-based modeling to unify the representation of cellular processes.[41]

7.2.3 Data-driven Models

In contrast, data-driven models (black-box) do not incorporate process knowledge to infer their structure. All possible information and data should be used to train and test the model, but only the simplest model that describes the data should be selected. Building a black-box model is an iterative process; it should be updated as new knowledge/data becomes available. Limitations of data-driven models are the poor extrapolation capability outside the characterized space, and as the latent space of the parameters normally does not have physical meaning, these models do not provide mechanistic insights.

Black-box predictive models include logistic regression, generalized linear models (GLM), random forests, and artificial neural networks (ANN). ANNs are the most commonly used type of black-box model. They can capture non-linear relationships in dynamic systems, as well as estimate parameters of other models. Data-driven models can infer prior knowledge using methods such as symbolic regression. Uncovering new phenomena or knowledge from data has the added benefit of being removed from potential assumptions and human bias. Search methods in symbolic regression are divided between heuristic search, like genetic programming, and deterministic search using numerical methods to the best model.[37]

The developed model should then be tested and validated, using experimental observations. To test the robustness of the model, extreme input values may be used. Sensitivity analyses should also be used to understand the impact of parameter variations on the model's outputs.[10] For a given set of training points, there are many functions that can fit the data. Gaussian processes can be used to select which function to use by assigning each a probability score.[39] For qualitative models, design approaches include Boolean or Bayesian Networks.[32] Tree models are commonly used for classification and root cause analysis in bioinformatics, such as for gene selection.[33] Active learning is a way to input and query data to feed to the black-box model, enabling an iterative workflow that optimizes the model.

Hybrid models combine both mechanistic and data-driven models in a particular structure (parallel or serial). Hence, they can overcome some of the individual model limitations. Hybrid modeling can incorporate the data in a digitized manner by creating neural networks of mathematical equations. In bioengineering, their use has led to more accurate predictions by using first principles of bioprocessing knowledge gathered over decades.[11] The need for data (which is generally expensive and proprietary in biological sciences) is reduced, and more complex problems can be tackled using hybrid models, as symbolic knowledge makes them more comprehensive. Furthermore, unlike data-driven models, hybrid models are easier to understand and provide explanations behind the model's decision.[11] However, creating hybrid models may be challenging, as fundamental relationships need to be translated mathematically and combined with empirical relationships.

7.2.4 Machine Learning

As machine learning (ML) algorithms rely on large datasets, their applications today are mostly deployed in advertising and manufacturing, where data is cheap (e.g., social media platforms segmenting users to make ads more targeted). In contrast, biochemical research data has traditionally been more expensive to generate and is generally kept proprietary. However, ML can benefit from systems biology and the use of more sophisticated equipment, which can generate greater volumes of data. The cost of DNA sequencing, for example, is rapidly falling, generating significantly larger volumes of freely accessible data. Moreover, data quality (i.e., the variety of the data which determines how much can be learned from it) is higher in R&D than in manufacturing.[21]

Predicting biological systems requires in-depth characterization of all components in the system from the biochemical, biophysical, and biomolecular and their interactions. This is challenging due to the limitation of the measuring tools, which can only capture a fraction of the important subprocess mechanisms. For example, the nonlinear behavior of metabolic networks limits the predictive power of the models. ML can help address some of these challenges.

ML falls into the following three categories:

1. Supervised learning is the most commonly used. This is where the ground truth of at least a part of the data is known, and algorithms can be trained to discover patterns or correlations from the labeled data.

2. Unsupervised learning is used to uncover hidden patterns and draw inference from unlabeled datasets.[21] It is used to cluster the data into distinct groups, without knowing the ground truth of the data.

3. Reinforcement learning relies on trial and error to achieve an objective. It was famously used to develop Google's AlphaGo program. It is particularly appropriate for describing real-world biological systems, where ongoing learning and flexibility are important. It has been used for bioprocess optimization, for example, to set up a control policy.[8] It allows simultaneous exploration and exploitation of the search space. Reinforcement learning can explore to gather new knowledge while maximizing its value by exploiting policies known to be useful.

Even though ML has only been recently introduced to biochemical research, it has already led to paradigm shifts across the life sciences. It is considered a fundamental tool in numerous fields like chemical discovery, process development, and optimization.[40] For example, the company Inscripta uses ML to synthesize novel enzymes with desired functionalities using a workflow similar to the one shown in Figure 7.[9]

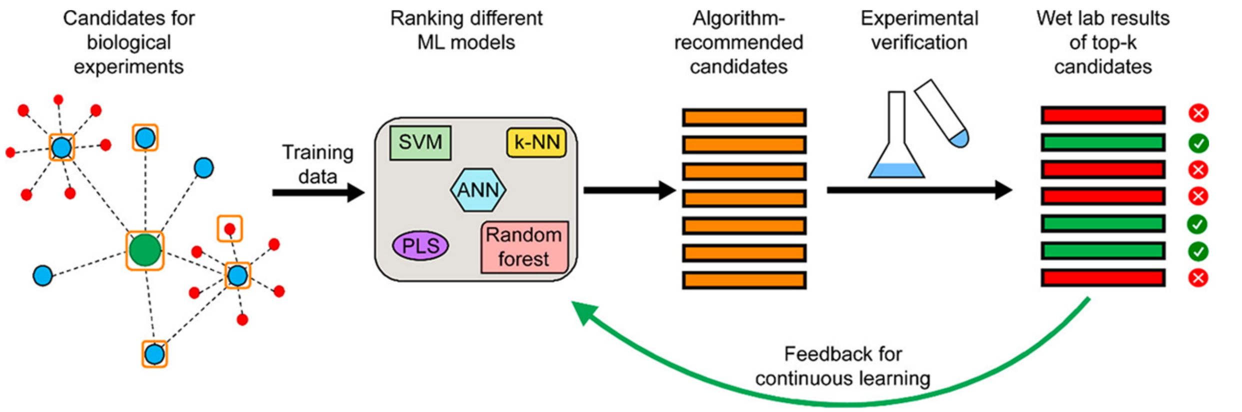
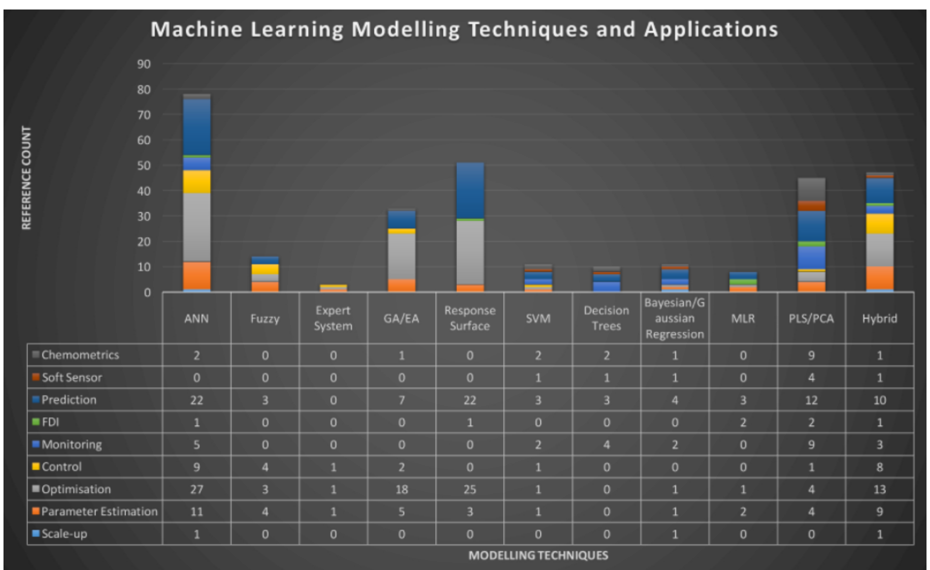


Figure 7. ML can help identify patterns in data and hasten the DBTL cycle for successful systems design. The models can predict how changes in a cell's DNA or biochemistry will affect its behavior, then make recommendations for the next engineering cycle. The newly generated data can be fed back into the model training stage, allowing continuous updates of the model's predictive capabilities, enabling a complete DBTL cycle. ML models can also be reverse-engineered to cast light on the underlying design principles of systems.

ML has far-ranging applications in cellular agriculture, which fall into four main categories: upstream bioprocess, process design, DoE, and control. Figure 8 shows the most common ML methods used for various applications in bioengineering.



	ANN	Fuzzy	Expert System	GA/EA	Response Surface	SVM	Decision Trees	Bayesian/Gaussian Regression	MLR	PLS/PCA	Hybrid
Chemometrics	2	0	0	1	0	2	2	1	0	9	1
Soft Sensor	0	0	0	0	0	1	1	1	0	4	1
Prediction	22	3	0	7	22	3	3	4	3	12	10
FDI	1	0	0	0	1	0	0	0	2	2	1
Monitoring	5	0	0	0	0	2	4	2	0	9	3
Control	9	4	1	2	0	1	0	0	0	1	8
Optimisation	27	3	1	18	25	1	0	1	1	4	13
Parameter Estimation	11	4	1	5	3	1	0	1	2	4	9
Scale-up	1	0	0	0	0	0	0	1	0	0	1

Figure 2: Distribution of different modelling techniques over the most common applications Google Scholar references in bioprocess operation/bioproduct manufacturing for the period [01/01/2017; 03/10/2017]. Modelling techniques and applications were assessed individually for both "bioprocess", "biopharmaceutics" and "monoclonal antibody" search terms.

Figure 8. Different modeling techniques and their applications in bioengineering[21]

Within upstream bioprocess optimization, the most common application is data-driven_biosystems design and less commonly cell line selection. ML for biosystems design can be used at four different levels of optimization: the nucleic acid, protein, metabolic pathway, and at the genome level.[12] The goal here is to design genetic circuits that enable spatial and temporal control of cell behavior by understanding the cells' regulatory mechanisms. ML has also helped find superior mutants in metabolic engineering when mechanistic models have fallen short, in part due to the steady-state assumption. Lastly, ML is useful to constrain genome-scale models and thus help predict systems-wide phenomena, such as cellular response based on the growth environment and genetics. ML algorithms are also beginning to be deployed to predict cell line performance (e.g., stability, growth rate) and assist cell line selection decisions to reduce the need for extensive experimental cycles.[12]

The second area in cellular agriculture for which ML can be used is bioprocess design. One of the biggest challenges in bioprocess engineering is scaling up to industrial scale. ML can help optimize culture conditions (e.g., shear stress, medium composition) by predicting cell performance from bioprocess data.[13]

A third area of application of ML in bioengineering is in the characterization and optimization of bioprocesses. This often involves DoE, used for example in strain improvement, where large libraries of pathway design from regulatory parts are statistically reduced to smaller representative libraries. ML has been successfully used to reduce the number of DoE combinations by changing the conditions during an experiment, so that fewer experiments need to be performed.[14]

Optimization refers to the task of maximizing or minimizing a desired objective such as yield or profit, given some constraints (physical, technical, or regulatory) and relevant variables. In general, an optimization problem requires specifying the problem space within which the optimal solution lies, where the space bounds are defined by the bounds of the variables, and the constraints give the space topography, which takes the form of mathematical equations.

There are different types of optimization problems, depending on the objectives, variables, and constraints present. First, scientists must consider the desired outcome of an optimal solution. This may be a single outcome, such as maximum yield, or a combination of outcomes, such as both highest yield and lowest process costs, leading to optimization problems with different numbers of objective functions. In addition, depending on the variables, the optimization problem may be continuous, discrete, or mixed. Optimizing, for example, a biochemical reaction system where both the temperature and the choice of medium are degrees of freedom, requires both continuous (temperature) and discrete (medium) decisions. Furthermore, mathematical equations usually define constraints and can be linear or nonlinear, convex or non-convex, requiring different search methods. Finding the most appropriate and efficient formulation of an optimization problem is thus not trivial, and should be performed with the consultation of experts, who will further recommend appropriate algorithms based on the nature of the problem.

Optimization needs to be carried out on different production scales, as the optimal solution at one scale is not necessarily the optimal solution at another. For example, a bioreactor optimized for profit maximization would choose to reduce expensive medium flow, which would lower the yield. When the unit is incorporated into the full process, however, the optimal point could shift to one with better yield, if downstream units could recover the medium and recycle it, thus mitigating the cost incurred by the loss of medium.

Optimization in cell-cultured meat processes is important in both computational and experimental approaches. Computational optimization based on numerical methods leverages mathematical models to solve problems by using gradients. More complex and non-convex problems cannot be solved using numerical methods and require non-gradient approaches like genetic algorithms. Systems that require detailed fluid modeling, such as those in biological systems, are typically computationally expensive and are treated as experimental optimization problems.

Experimental optimization problems arise due to the complexity or lack of rigorous models. In such problems, individual samples must be taken to find the optimal solution. If the procedure is costly, there is a great benefit in considering methods to improve sampling, such as closed-loop optimization approaches. Closed-loop experimentation is the grand vision for the integration of AI and automated robotic platforms in chemical and biological research. It involves 1) running experiments, 2) building models from the gathered data, and 3) leveraging the model to decide what points should be sampled next in order to explore the experimental space in the most time- and cost-efficient way. The goal is for these experiments to minimize the amount of data required. Figure 9 outlines the general pipeline and integration of the closed-loop optimization framework.

In an optimal system, experiments will be performed using lab robots, automated measurement techniques, and high-throughput screening methods. All data retrieved from one experiment will be collected through the experimental set-up itself. The data will then be further communicated and utilized to build models. The data collected will then be used to build models that can predict untested samples. Using ML algorithms is advantageous here to build complex models and correlate multiple parameters from a few points. If such a model is derived from experimental data, it falls into the category of data-driven models. The model can be queried to check the predicted quality of potential new samples, and only the most promising ones are chosen as the next samples. If the data-driven model was correct, the new sample becomes a new optimal point. Otherwise, the model is updated with the data point and queried again. This iterative approach leads to focusing the search only on the promising region of the space and reducing the number of required samples for the optimization problem.

There is a trade-off between exploration of the given space, aiming to find a global optimal solution, and exploitation of the most promising region given the initial data. In an ideal set-up, the algorithm communicates to the execution of experiments and hence closes the loop. As of 2021, although technically possible for simple systems, human intervention is often required in the loop, which does not hinder the benefit of such closed-loop formats.

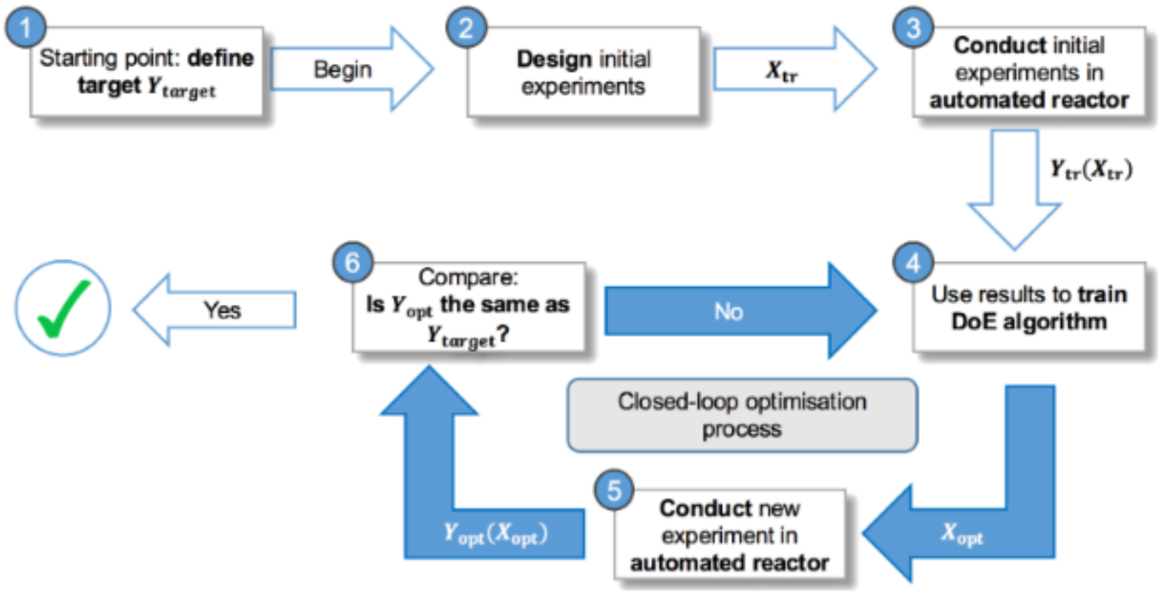


Figure 1: A framework of closed-loop or self-optimisation combining smart DoE algorithms, process analytics, chemoinformatics and automated reactor systems.

Figure 9. A potential pipeline for automation and data science to design, analyze, and iterate on experiments.

Bioprocesses are subject to disturbances such as human intervention or raw material variability which can affect the production quality or quantity. Therefore, they require monitoring or supervision of process parameters and variables for subsequent control. Monitoring also helps with the collection of measurements.[10] In addition, model-based monitoring methods can help estimate parameters that would be hard or even impossible to measure but are required for subsequent process control tasks. In an iterative fashion, automation is used to transfer the *in silico* models, designs and/or simulations, produced in part through monitoring, into physical systems and experiments (Figure 10).

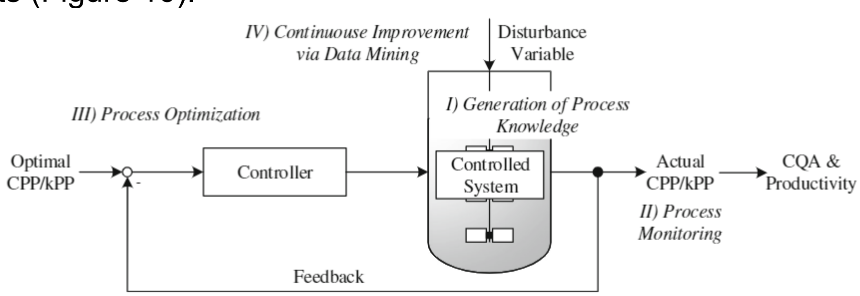


Fig. 1 A simple control loop with the related four challenges (I-IV) of process development and the process lifecycle. Challenge I is the generation and storage of knowledge within models. Challenge II is the process monitoring. Challenge III is the determination of optimal process conditions for different applications and IV the continuous improvement of a process by data mining tools.

Figure 10. Control loop involving knowledge generation, process monitoring and determination of optimal process conditions, and finally continuous improvement of a process using data mining.

Bioprocess control is another area where ML can be used. Control is important for fault detection and product monitoring. Upon disturbance, more advanced control strategies based on process models can recalculate new optimal set points. A predictive controller can even account for disturbances before they affect a process. Figure 11 shows a hybrid ML framework combining raw process measurements through soft online sensors with both kinetic and data-driven models.[15] It can help predict process behavior and identify optimal control actions. Reinforcement learning, where a policy gradient method is used to update a control policy parametrized by a recurrent neural network, is another popular approach for bioprocess control.[16]

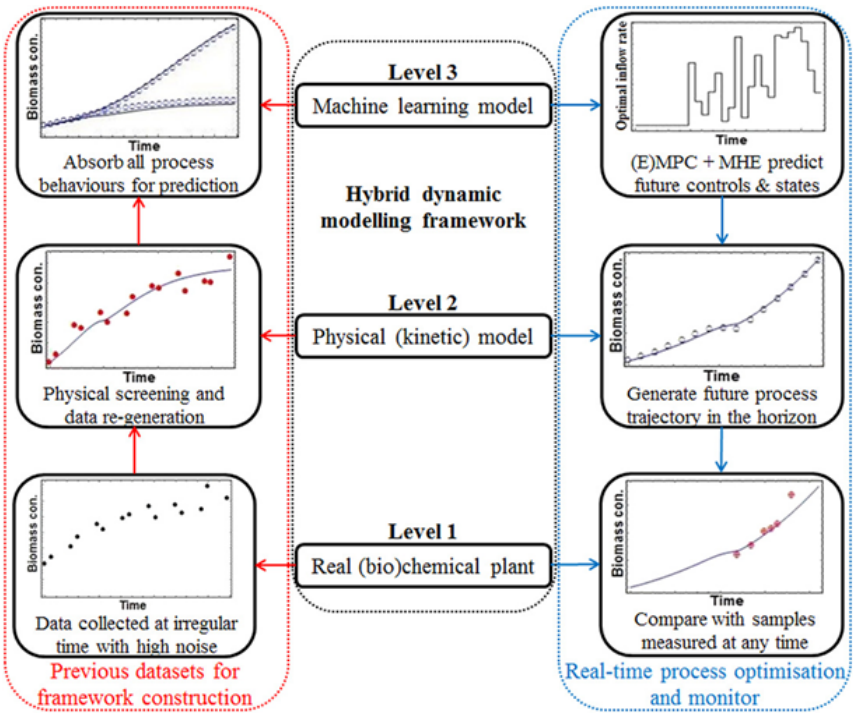


Figure 11. Monitoring of continuous bioreactors using hybrid modeling.

Network data has been used as knowledge representation and input for ML applications. For example, in graph neural networks, algorithms use the graph structure or the connections between pieces of information. In addition, networks can provide a range of new descriptors, where the neighbors of a node, the location of the node, and or the proximity to other parts of the network can be used. An example relating to the bioreactor, which is a complex dynamic system with many degrees of freedom and interactions, is shown in Figure 12.[17]

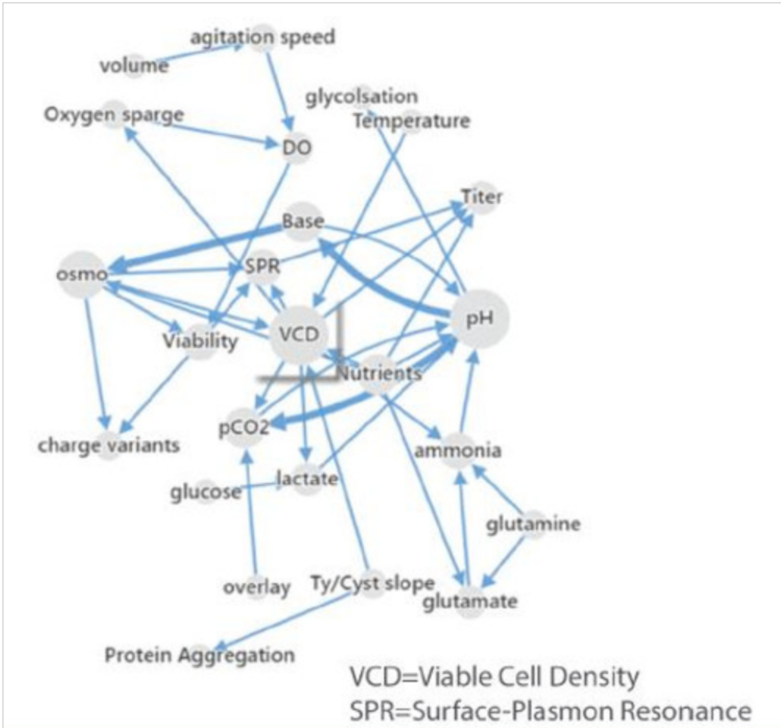


Figure 12. Network diagram of some of the relationships occurring in a bioreactor.

ML has also been used in image analytics to count the cells in different stages of differentiation, and hence the human error rate of counting. Finally, whole picture models (multifactorial network architectures of interacting parameters in systems biology) are required to understand complex biological systems.[9] However, they are limited in the number of parameters they can investigate due to limits on computational power or time requirements. This uncovers an additional area of ML application: parametrization.[21] It is used to link different levels of biological organization (such as intracellular interactions and cellular behavior) and determine which are the important parameters from small-scale models, so they can be integrated into the large scale, also known as meta, model. Effectively bridging this gap is a challenging but important endeavor.

7.3 Case Studies: Applications of Automation and AI in Cellular Agriculture

The illustrative problems selected in this section are some of the low-hanging fruit. More ambitious applications of automation and AI in cell-cultured meat are discussed in Section 8.4, *Data Challenges*.

Case study 1: Culture Conditions

One of the challenges of this field is growing up large quantities of cells before they are differentiated into fat and muscle. This case study assumes use of a defined mesenchymal stem cell (MSC) line that can become mature adipocytes upon differentiation. The goal is to create culture conditions that will best grow large numbers of healthy cells, knowing that cells that differentiate into fat are post-mitotic. The desired responses/outputs are defined as follows: high cell proliferation and viability, and low differentiation. The metrics for the outputs are attained by 1) counting cells to determine proliferation, 2) staining with trypan blue to determine viability, and 3) using an adipogenic differentiation marker, like adiponectin, that can be tied to a fluorescent reporter, indicating the cells are becoming mature adipocytes. The first step is to create conditions that optimize these outputs by looking at the inputs/factors that go into culturing cells.

There are three main challenges here. First, optimum culture conditions rely on many factors. The media alone can have upwards of 50 components in a serum-free formulation.[20] In addition, pH, temperature, dissolved oxygen, and cellular metabolic waste affect cell growth and viability. Considering all these media components and culture conditions results in 54 factors to optimize. Evaluating two settings for each of them (high and low), would require 2^{54} runs. Even if each run cost only US $0.01, the costs would be prohibitively high and require a lot of resources and time. A screening experiment to determine the important factors can help resolve this issue. Designing a good screening experiment requires consulting with domain experts to constrain the space to be explored. For example, it is unlikely that culture conditions outside of a limited pH range or temperature range will lead to viable cells.[21] In this case study, an automated system combined with a full factorial design was used to optimize the media concentrations for MSC growth. It found that two factors (the seeding density and the level of growth factors) had negative interactions, but a high level of either was conducive to cell expansion.[18] Another study used ML (a differential evolution based algorithm) and high throughput tools to navigate the high dimensional space of serum-free formulation (15 components at six different dose levels) and thus optimized the formulation.[19]

The second challenge in this case study is that metabolic models are needed to understand the functional state of cells, their uptake rates of different nutrients, and the buildup of toxic metabolic waste. Metabolic models use flux balance analyses and constraints. Metabolic engineering for cell-cultured meat production faces several technical challenges, mainly due to the lack of well-characterized metabolic pathways for the type of cells required in these applications. Metabolic models for Chinese hamster ovary (CHO) cells are common, but these cells are not used for cell-cultured meat production. There are also tools for the design of experiments, and biological data to constrain predictions. In addition, metabolic modeling of mixed communities of cells (e.g., fat and muscle) is in a primitive stage. As of 2021, the Good Food Institute (GFI) is inviting research proposals to map the secretome of stem cells from animals used for meat.[20] Kinetic models combined with large sampling-based methods have uncovered metabolic control circuits and allowed automated metabolic network reconstruction.[21] These can be used with dynamic regulatory controllers of metabolic pathways to determine, for example, the feeding strategies to optimize cell growth rate (Figure 13).

Lastly, components of the cell culture media need to be available, low cost, and sustainable. To provide an analogy from chemical engineering, scientists look at the sustainability of the feedstocks (e.g., if it is biobased or extracted from waste streams) and the sustainability of processing them (e.g., minimal use of toxic solvents). They may use AI to identify suitable molecules forming the backbones of the carbon supply chain by predicting their scalability and environmental impact to accelerate process development.[50]

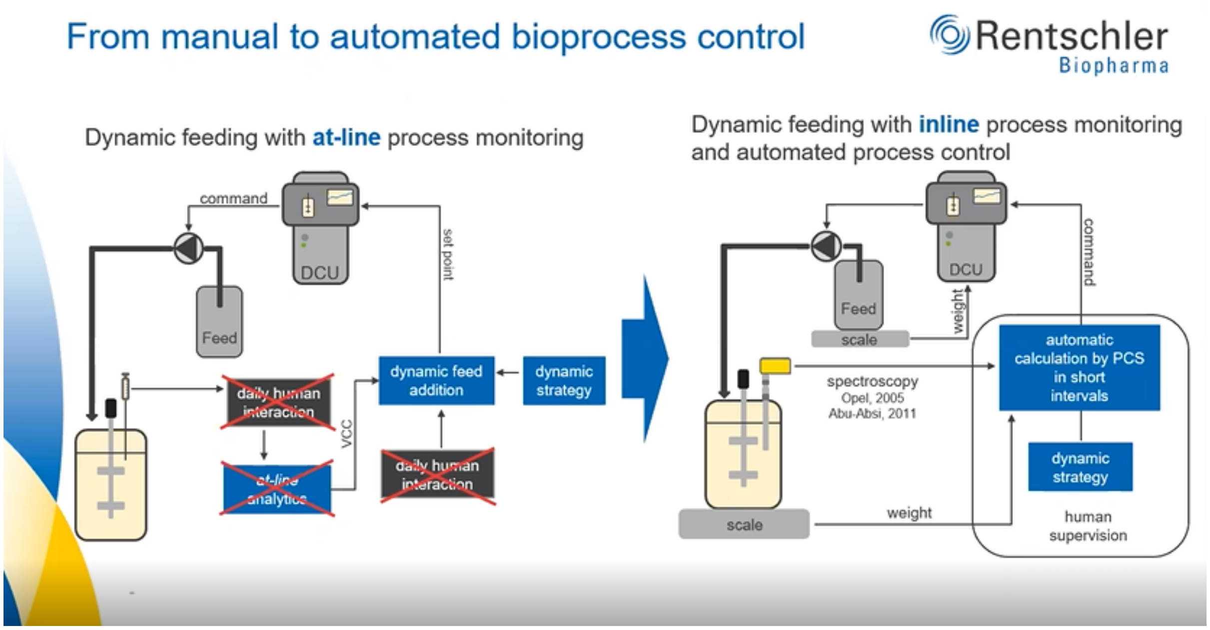


Figure 13. Dynamic feeding based on inline process monitoring and automated process control.

Case study 2: Bioreactor

Bioreactor design operating parameters (e.g., perfusion rate, liquid depth) determine numerous critical factors for successful cell cultivation: available growth area, nutrient requirements, shear stress, potential for scale up, contamination risk, batch variance and nutrient consumption. Novel bioreactors, as well as new design rules and standards, are needed to make efficient scaling up a reality.

Computational models are important to limit expensive and time-consuming physical testing.[49] GFI is supporting the development of a more holistic model-to-model cell expansion inside bioreactors, combining physio-mechanistic forces and computation fluid dynamics with cell behavior. This project will help evaluate different bioreactor configurations. Fluid flow processes impact cell behavior, such as attachment, migration and proliferation. Spatial gradients are inevitable in large bioreactors, so the model should also capture them.[28] Cell-cultured meat scientists are building a model of a stirred tank bioreactor that combines flux dynamics and agent-based modeling (cell aggregates). High-throughput screening platforms of robust scaled-down models of the bioreactor can be used to test these numerous parameters and understand their combined impact on success metrics ranging from yield to quality and cost. Microscale bioreactors like the Ambr→ 15, shown in Figure 14, can achieve the same or similar chemical and physical conditions that affect the cells' growth and differentiation as the production bioreactors. Smaller bioreactors are most often best for bioprocess development to reduce the time and costs of each experiment.

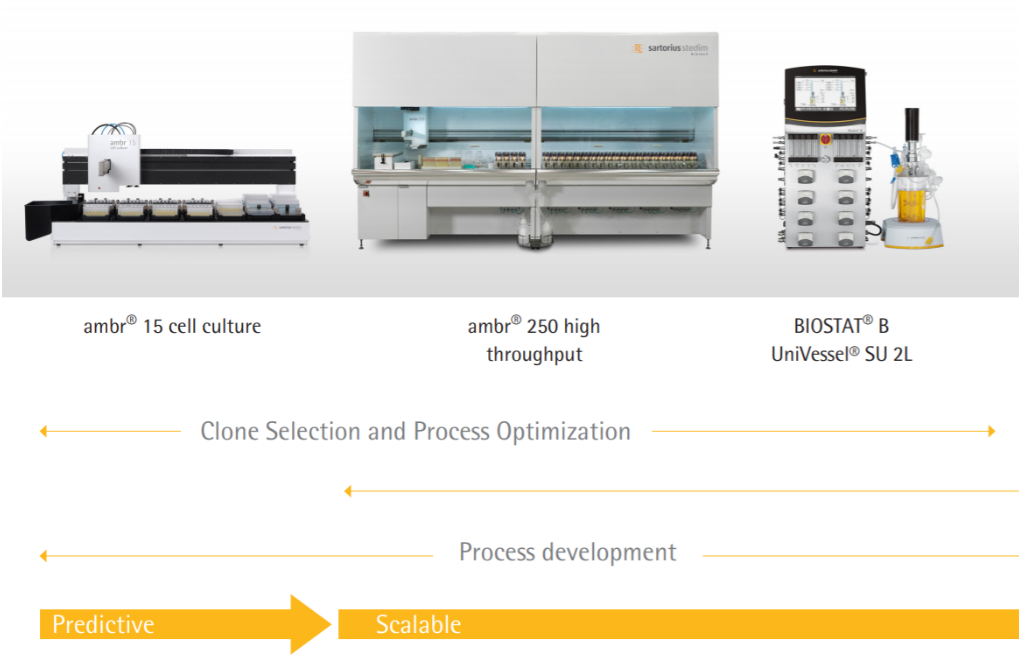


Figure 14. The Ambr→ 15 automated micro-bioreactor system for mammalian cell culture is mostly used for cell line screening and media/feed development.[22]

Case study 3: Cell Differentiation

Stem cells must be differentiated into muscle and fat cells for cell-cultured meat production (see Chapter 5, *Cells*). This complex process is currently inefficient, time consuming (~20 days are required for proliferation and maturation stages), laborious and incompatible with industrial large-scale production required to achieve economies of scale. However, biological systems can be programmed using big data and next generation sequencing to improve experimental outcomes for cell differentiation.[45]

Models and ML techniques can be used to identify the exact combination of small molecules required for directed stem cell differentiation, understand the underlying molecular mechanisms, and integrate with automated systems for efficient, reliable differentiation.[46] Networks have been used to help elucidate stem cell fate specification by enabling different types of data such as biochemical interactions and gene expression patterns to be combined into a single conceptual framework. For example, CellNet is a network biology platform that quantifies the similarity between the derived cells and the target *in vivo* cell type and generates hypotheses to improve the derived cell populations (Figure 15).[23]

Figure 15. CellNet queries gene expression profiles and classifies input samples by how closely they resemble the target cells and tissues. The platform also scores how likely different transcriptional regulators are to enhance cell engineering efforts.

Start-ups such as Mogrify and BitBio use computational frameworks to convert stem cells into functional skeletal muscle cells, for example. Scientists also programmed a culture robot to automate the “directed differentiation” protocol for large-scale production of cells from iPSCs, with the goal of producing larger cell banks.[47] The robot performed media changes and used the CompacT SelecT automation platform by Sartorius, which allows the expansion and differentiation of large batches of adherent cells. The live-cell imaging system controlled the cell culture environment (Figure 16).

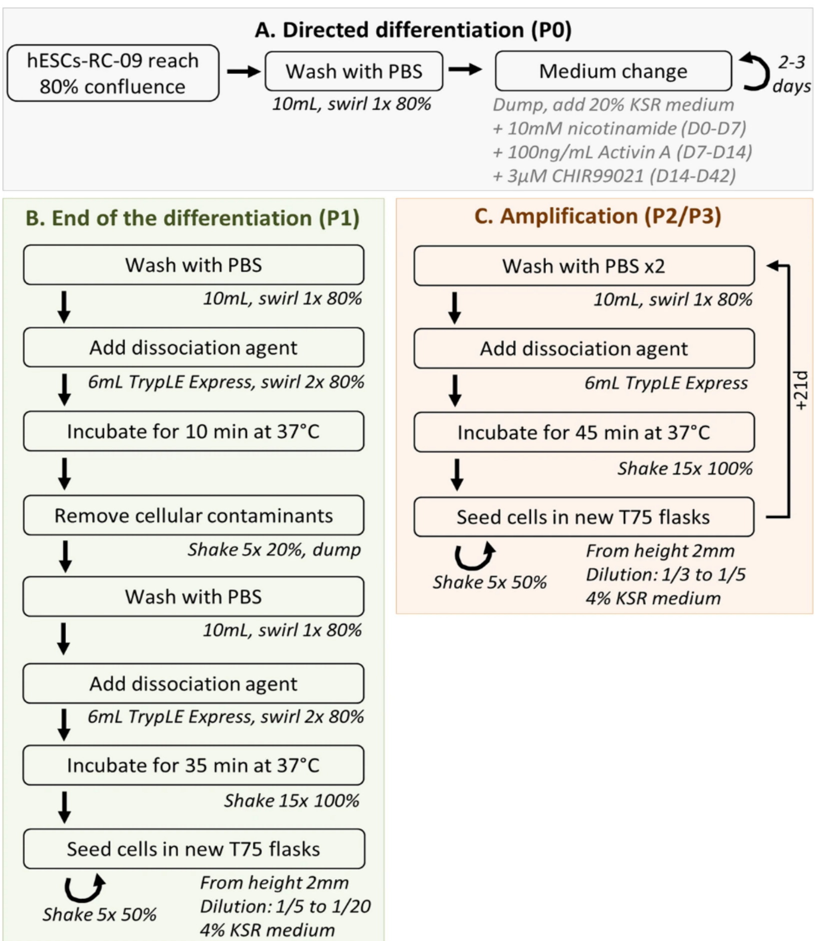


Figure 16. Automated cell culture protocol (including passaging and media change steps) using the Compact Select platform. The platform is composed of a robotic arm, an incubator, an automated live-cell imaging system (Incucyte) and connected pumps.[47]

Automating processes is also important to achieve controlled and standardized cell-cultured meat production, helping adhere to good manufacturing practice (GMP).

Case study 4: Proteins and Scaffolds Design

Bio design and simulation (bioCAD/CAE) computational techniques enable the design of completely novel proteins *in silico* that self-assemble into predicted shapes, so-called “programmable proteins”. These approaches open a wide range of opportunities for easier, cheaper, and faster bioproduct generation.[51] These can be used to, for example, catalyze growth factor production, establish host production platforms for culture feed, or produce small molecules or enzymes for degradation of scaffolding material.

Mammalian cells are adherent; hence, microcarriers or other scaffolding structures are required for their expansion and differentiation. Microcarrier size, density, and even shape can have different impacts on the viability and proliferation potential of the cells. Their porosity and cell-scaffold interactions can be evaluated using bioCAD models, for example by modeling mechano-sensing behavior in cell-matrix interactions. Computational models are necessary for the design, characterization, optimization, and scaling of scaffolding designs.[28] For example, computational flow dynamics (CFD) and finite element analysis (FEA) models have been used to predict flow regimes around and within the scaffolds, thereby optimizing the flow rates.

Case study 5: Sustainability

Life cycle assessment (LCA) framework and methodology can be used to assess the various environmental impacts of a product over its life cycle, from raw material extraction to disposal. It is a particularly useful tool in early product development, as it helps reduce uncertainty by predicting what the environmental impacts of the product will be on a large scale, thereby facilitating regulatory approval, investment, and marketing.[52,53] Other benefits of an LCA include identifying “hot spots” or CPPs. These can then be used in DoE and with ML algorithms for process development, optimization, and scaling. Modeling of large-scale production combined with scenario analyses can help avoid potential bottlenecks during scale up, as well as mitigate unintended consequences through prior identification of areas that require more concerted effort. LCAs are heavily dependent on process data from the energy requirement of the production facility, the mass of feedstocks used, and their provenance, as well as waste disposal. IoT-enabled machines can provide real-time data for analysis and incorporation into environmental assessment software, such as Gabi. In turn, these software allow for the breakdown of environmental impacts, as well as process and scenario comparison. LCAs are also frequently combined with techno-economic analyses (TEA) for multi-objective optimization. LCAs for comparison of cell-cultured meat production processes could compare different alternatives, such as fed batch versus perfusion, or assess the potential of single use versus stainless steel technologies.[54]

Case study 6: Monitoring and Control Strategies

The aim of cell-cultured meat production is to have reproducible culture conditions and control product quality in real time. Process characterization and validation under the QbD paradigm (described further in Chapter 7, *Bioprocess*) are required for regulatory approval. Factors that need to be controlled include growth and differentiation, nutrient consumption, and by-product accumulation.

Dynamic systems can solve biological control problems, converting environmental cues into programmable outputs. Key culture parameters should be continuously monitored, in real time, for adequate process control. This also means non-invasive methods for cell state analytics are required. To begin with process control, researchers must first assess which covariates need to be controlled by identifying the ones that have significant impacts on the output. Scientists can implement bioprocess control by using sensors for monitoring environmental conditions, such as culture pH, and biosensors, which can induce the gene expression of the cells.[24]

In recent years, the use of online PAT has become a high-profile endeavor in the biotechnology industry. The supply of nutrients and oxygen to replicating cells is a crucial part of bioreactor design and must be monitored and precisely controlled. The main species of interest in the off-gas are the respiratory gases and volatile organics, such as methanol, ethanol, and ethyl acetate. Their analysis can yield vital information. This requires precise off-gas analytical data through every stage of the scale up process, from laboratory to pilot plant to bulk production. In some cases, one mass spectrometer (MS) fitted with a suitable multi-stream inlet can monitor all the bioreactors. In other cases, separate MS analyzers must be used in the laboratory and on the plant.

Only an accurate comparison of sparge gas and effluent gas can provide accurate pre-screening for possible contamination of the cell culture and calculate real-time information regarding culture respiration and the availability of nutrients. Figure 17 shows the real-time comparison from a Prima BT monitoring 5 L bioreactors in which CHO cells were used to express monoclonal antibodies.

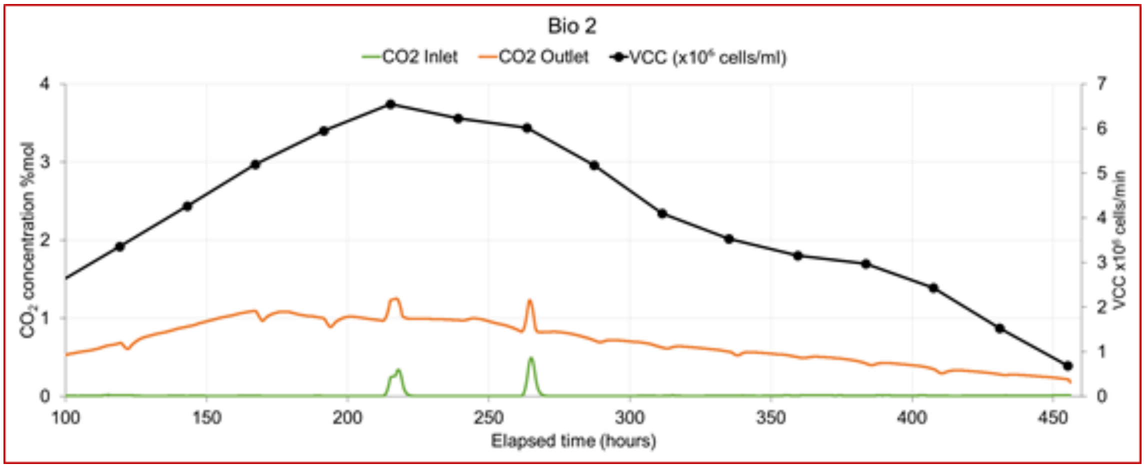


Figure 17. On-line CO_2 inlet and outlet data and off-line viable cell count (VCC) data from a mammalian cell culture bioreactor. During subsequent runs, the control strategy was modified, leading to further extensions in culture durations and increased VCC levels.[25]

Kinetic models can be used as soft sensors and combined with off-gas analysis to improve the reproducibility and robustness of a mammalian cell culture process.[10] Additionally, a multivariate analysis of cell culture bioprocess data can be used to provide new insights into factors affecting process performance, uncover hidden patterns behind large heterogeneity in time scale and data types, and provide a guide for QbD principles to enhance process robustness. Recognition of patterns is an important part of PAT. As an automation system improves, it can recognize changes in culture conditions and respond in an unsupervised manner (closed-loop system). For example, recognizing contamination at early time points will allow batches to be quickly discarded and reactors sanitized. Having sensors that calculate waste product accumulation, such as lactate and ammonia concentrations, can lead to new media being added at appropriate times to prevent cell death. Hybrid models have been successfully used in bioprocess engineering to predict cell biomass or cell behavior over time. For example, the hybrid modeling software developed by Novasign can understand what is causing deviation from the norm from online measurements. By knowing the relationship between the outputs and inputs, operators can change certain parameters to potentially recover a batch.[14]

7.4 Challenges and Perspectives

The main challenges facing the adoption of automation and AI in cell-cultured meat are addressed in this section (Figure 18). Unfortunately, neither the hardware nor the software solutions developed for the medical industry meet the different requirements of the cellular agriculture sector, and are also prohibitively expensive and inflexible.

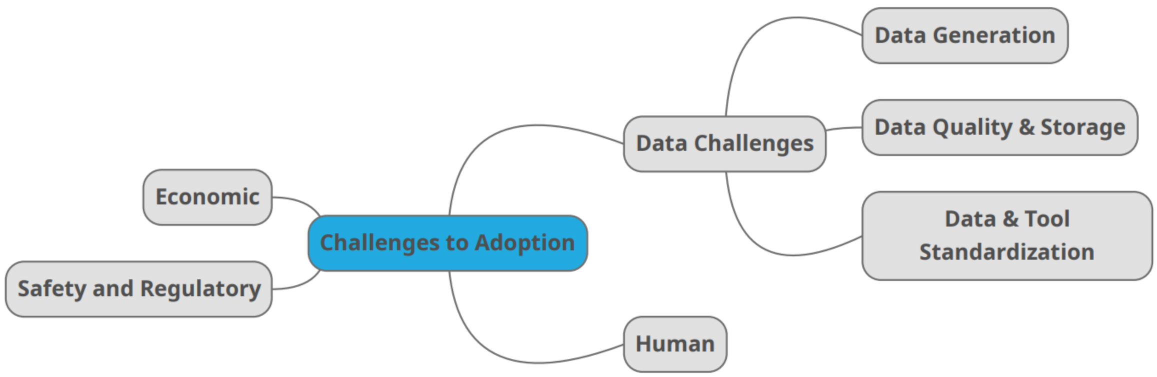


Figure 18. Main challenges preventing widespread adoption of automation and computational modelling in cellular agriculture.

7.4.1 Data Challenges

There are multiple challenges around data which include data generation, quality, storage, and standardization.

7.4.1.1 Data Generation

A preliminary, yet critical challenge in applying computational modeling techniques to any biological system is having access to sufficient data to construct the foundational models. Obtaining sufficient information on the biological systems (i.e., cellular functions, environmental factors) to constrain the models, high quality measurements for DoE, and having sufficient component characterization are prerequisites for ML.[43] Rich data describes when there is a large variety and volume of related data available. For instance, instead of building a sales model on previous sales data, it also considers other related data from finance or IT departments. Hence, the data is rich in information content. Structured data is data using a certain schema or predefined code of organization. The typical forms are tables, and the aim of structured data is to help the computer understand the organization and possible relationship of data. Representative data is a key issue in most AI domains. Data-driven models have a common drawback: they can be unreliable when it comes to extrapolation. This is because they do not operate on first principles but find approximations for a given data set. This means they can only supply relevant predictive models if the training data is representative of the actual testing data.

While in some areas of automation there is plenty of rich, structured, and representative data, that is rarely the case in biological systems. In such systems, data generation often requires experimental procedures or costly computer simulations. Hence, the first challenge is to collect enough data required for the task, which can be difficult in the early stages of research. However, this is arguably where data science and automation are most needed. Fortunately, there are a few ways to work around this issue. There are some helpful tools, such as WebPlotDigitizer which allow data extraction from literature figures. Moreover, hybrid models based on some first principles can leverage existing knowledge of natural laws and can advance the extrapolation capacity of systems. Bayesian approaches take into account the uncertainty of data and help navigate largely unknown data spaces based on relatively few data points.[26]

The second challenge in data collection is that biological and chemical systems are represented through a not yet completely understood space of heterogeneous data. Discrete data describes certain species and conditions, continuous data represents most environment conditions such as temperature, and string-based data contains additional information about the systems. Finding a structured way to take advantage of all the rich data in these systems poses a challenge, while finding representative data sets of unknown data spaces and limits is a major problem in large-scale explorative studies.

To obtain rich, structured, and representative datasets, the sample size must be sufficiently large and varied to refine the model. This requires adequate measurement methods and data capture systems to generate information during experiments. As measuring tools improve, more biology R&D data can be collected. Novel sensors relevant to cell-cultured meat include mass and Raman spectroscopes, used to measure substrate and metabolic by-product concentrations in bioreactors. Live cell imaging and fixed cell analysis are other examples of enabling technologies. In addition, soft sensors—pieces of software that combine measurements and mathematical models—may be used to process several in-line measurements simultaneously. The ability to sense growth factors, for example, would be beneficial for cell-cultured meat production. By acting as IoT hubs, metadata (e.g., environmental temperature) can also be measured by soft sensors. Lastly, these large volumes of data demand reliable storage solutions. There is commercial opportunity to provide an off-the-shelf solution with integrated software to manufacturers in this field.

Examples of public domain databases which can be mined for data include enzymatic or food databases, bio-based feedstocks, patents, and journals. The website WebPlotDigitizer can convert graphs from papers into quantitative data. Published microscope images also provide a rich source of information. For example, the open-source software CellProfiler can be used to identify cell phenotypes from microscopy images.[27] In the context of cell-cultured meat, applicable data systems must be developed first. Data repositories are well-established for common model research species, such as *Drosophila melanogaster* and *Xenopus laevis*. However, similar databases do not exist for the diversity of species of interest for cell-cultured meat. Information curation approaches should be applied to generate databases for those species, which are the focus of academic and industrial cell-cultured meat research. Here, modelers can work with stakeholders to create plans, protocols, and workflows to transition data into systems biology markup languages (SBML).

The increasing use of large-scale libraries, high-throughput screening, process monitoring, and real-time measurements helps to generate large data sets. To encourage companies to share their data and to promote industrial-academic collaborations, methods of anonymization encryption need to be developed in this field of scientific research.[12]

7.4.1.2 Data Quality and Storage

Data and protocols should follow the FAIR principles and be findable, accessible, interpretable, and reusable.[55] Both data and algorithms should also be free from biases. R&D data is particularly rich in information, as it can include metadata or contextualized data, and the context within which the data was collected should also be captured. Hence, the challenge is to first identify and store rich data. Ontological methods to build relevant schemes with information on the relationship of data need to be the focus of data storage. A mature computation infrastructure is required to fully exploit the DBTL cycle. It relies on the aggregation of biological information from diverse areas to provide a full picture of the system under study. These areas include the biological parts of the system, their environment, and the manufacturing processes.

However, the actual amount of data can also lead to challenges. There is a limitation in data storage capabilities, and supercomputers are expensive to buy and maintain. But there has been a significant increase in cloud-based systems, and computing powers are becoming more accessible.

7.4.1.3 Data and Tool Standardization

Data standardization facilitates sharing of scientific knowledge and the integration of different biological data for modeling. However, technological tools use different languages, which makes the adoption of a novel tool a prohibitive investment, while also making it difficult to integrate different tools and databases together. In addition, the wide variety of data types (e.g., genomics, geometric information for protein engineering, vector fields for CFD, spatial relationships between cells, metadata) pose a challenge to harness their power. The rapid adoption of robotic technologies, such as liquid handlers and medium/high throughput analytics, requires standardized protocols for reproducibility.

Standard parameters and units need to be agreed on, as well as standard schemes to report these. Standardization is a key stepping stone for field progression, especially for algorithmic discovery and data generation within newer fields like cellular agriculture. Data formats should be standardized for sharing and enabling automation. The use of ML appears promising to tackle this challenge.[12] The Antha software, for example, provides a universal language, and integrates with other software programs including design suites (e.g., JMP) and allows hardware interpretability.[57] Another example of common languages is extensible markup language (XML), a popular tool for metadata. However, it is not supported across all databases.[58] The cell-centered database (CCDB) allows sharing of microscopy data in the form of images.[59] Synthetic biology also has its own open language, “SBOL”, for information standardization and representing biochemical/genetic networks.[60] These tools must be interpretable by their users, which can be achieved by using their common language, the language of biology. There must also be vendor agnostic equipment and data integration tools (e.g., the Allotrope Framework).[61] To this end, a collaboration between start-ups for cell-cultured meat regulation has emerged, building upon the success of the Global Biofoundries Alliance for knowledge sharing, and open technology development, which offers scalability for progress in important but challenging areas. [6,65]

As of 2021, few techniques have been developed for automation in cell-cultured meat. Methods that are less sample dependent and therefore more suited to automation need to be explored, and unit operations should be uncoupled. It has also been argued that introducing error is beneficial to discovery, as multiple scientific discoveries have been due to human error, such as the discovery of penicillin. It is a challenge to amass and integrate first principles knowledge from process experts systematically to make the models required for automated discovery and production.[10] In addition, there are few experts and tools, as the integration of process engineering, computational models, and cellular agriculture is in its infancy. In the meantime, manually updating models with recent research is laborious and time-consuming. Hybrid models have the advantage of reducing the dependence on process experts by using experimental data to feed into the black-box model and provide estimates.[11]

Another limitation of predictive modeling is that, unlike humans, some models struggle with generalization. First principles are not always known for large biological spaces, and data-driven approaches bring challenges with extrapolation, as previously discussed. Moreover, algorithms are good at predicting correlations, but not for causal inference.[28] A model trained on one dataset may not be applicable to another dataset of another design (e.g., with a different bioreactor size). Grasping causality is crucial in scientific research and it will help with generalization of models. Standard ML cannot address counterfactual but transfer learning—training ML algorithms on one data set of a particular design (e.g., with a small-scale bioreactor) and then using it for initialization and further training it on the second design—can help. The drawback of the transfer learning approach is the need for large datasets. Hybrid models may be more practical for extrapolation, inference of knowledge, and prediction.

There are also ML-specific limitations. For example, supervised learning requires well-labeled data. However, the process of labeling is error prone, imprecise, and laborious. AI translational thinking is necessary to uncover new knowledge from past experiments and publications. Researchers have demonstrated that new knowledge can be discovered from disjointed articles, paving the way for the IBM supercomputer, Watson, which can process millions of articles, and datasets. to aid in medical research and diagnostics.[62]

Effective design across different scales of a model, such as across both genome and metabolic pathways, is lacking. Meta modeling is a novel field and there is limited literature on parametrization. Multiple optimization, or finding the optimal design vector, is also challenging due to being computationally demanding and hard to implement. Another drawback is that most data mining tools, including ML, suffer from poor interpretability due to the many variables and structures of the model. This is an important drawback because, in science, the reasons behind predictions are generally more important than the predictions themselves, as they can be applied in other contexts. To this end, better documentation of model development and the invention of novel ML tools that can handle complexity while being transparent are underway.[63]

Few tools are available for multiomics (which combines data sets of different -omes, such as genome and proteome), data analysis, mining, and ML. [42] In addition, even though the workflow leads to robust and reliable process models, the shortcomings of experimental efforts remain. Previous sections have highlighted the scientific and technical hurdles at the interface of computing and biology. However, there are also key infrastructure, human, and regulatory challenges to address in order to support research at this interface.

7.4.2 Economic Challenges

The biotechnology industry is already capital intensive due to the long R&D process, and also the expenses of manufacturing scale equipment. Hence, the high cost of commercial software packages, which may become obsolete over time, is prohibitive to their adoption. In addition, the upfront requirements of the software may be poorly defined, as the problem is not well understood.[64] Robotic platforms are also expensive, even though their costs are falling rapidly. For example, in 2021, a liquid handler costs upwards of US $5,500 and a cell culture work station is around US $12,600.[29,7] For some companies, the greatest cost may come from the need for large lab spaces to house robots, and size is another important consideration.

Each stage of digitization must deliver a strong return on investment (ROI) before proceeding to the next stage. But due to the high investment costs, the ROI timelines may be long, thereby affecting adoption rates. However, the ROI of intelligent process automation lies in the triple-digit percentages.[30]

7.4.3 Personnel Challenges

Scientists in industry have often required years of laboratory training to become proficient. However, due to the novelty and slow adoption of automation and AI technologies, especially in academia, companies must invest in further training for their employees on software, data science, and robotic equipment.[30] This can affect the successful implementation of these tools. Furthermore, start-ups may find it hard to hire talent to implement these solutions. On top of this, the right candidates should also have some domain knowledge so that they can work in interdisciplinary teams. Fortunately, universities are increasingly recognizing the need for more digital training. Additionally, new platforms such as AutoML include end-to-end automation and lower the barrier to adoption. They can prepare data, extract features, and deploy models in an automated manner, reducing the time taken for data cleaning and increasing agility.

For the transformation to Bioprocessing 4.0, transparent and easy to use solutions must be developed (including abstract user interfaces) and change must take place across organizational levels. Traditionally, data sharing and quality control have not been common practice in the life sciences. The benefits must be demonstrated, for example, by looking at how automation and AI have been used to tackle similar problems in parallel fields. Overall, the barriers to implementation are lowering, helped by the increasing adoption of ML tools by scientists in their daily lives (e.g., Alexa). The COVID-19 pandemic has also accelerated the adoption of flexible tools to assist work processes, such as Slack's messaging bot.[35] As of 2021, there is both a technology push and market pull for solutions that increase scientists' capabilities. However, both organizational and cultural changes are needed for wider adoption of CAB.[35] Digital security is another key consideration in an industry heavily dependent on IP and data. Clear guidelines, standards, certifications, and appropriate regulation must be developed, along with ongoing research development. These challenges reinforce the need for stepwise integration of automation and AI tools into cellular agriculture practices.

7.5 Conclusion

To succeed in transitioning from livestock to cellular agriculture, the industry needs to grow beyond the bench and bench scientists. Experiments must be done in high throughput, with the appropriate design and analyses. The production platform needs to be scaled to industry levels. This requires collaboration with fields such as mechatronics, data science, pharmaceuticals, and chemical engineering. Both the biological and information technology fields have recently experienced huge growth, and together the synergies they create are invaluable to the ambitious endeavor of cellular agriculture.[59] Data science and automation offer a roadmap towards efficient, sustainable discovery and scaling of cell-cultured meat. Therefore, focusing on the integration of unit operations, protocols, and computational elements into a standardized data computing environment should be a priority for this field.

Fundamental Questions – Answered

1. **What are the main challenges facing cell-cultured meat development and commercialization that automation and AI can help address?**
   Cell-cultured meat development requires intensive R&D efforts, where companies spend millions of dollars over multiple years to develop processes that are only reproducible at the bench scale. Automation and AI can improve complex system modeling and optimize processes, thereby reducing time and cost to create a viable product. In addition, manufacturing can be augmented via processes such as automation through virtual prototyping, process control, robotics, the internet of things.

2. **What are the challenges facing the adoption of these technologies in the field? How can cell-cultured meat startups reap the benefits of these technologies?**
   Cost, talent constraints, data availability, and data quality are the principal challenges to adoption. Organizations must be structured to reap the benefits of large datasets and consider the data's implications in the early stages. Startups and larger companies have different advantages and drawbacks to adopting computer-aided biology (CAB).

3. **What considerations need to be made when automating lab processes?**
   An important step in building automated lab processes is to identify key equipment and protocols based on the required functionality. Another important factor is the cost of process automation. A purchased system would require less expertise and maintenance at the expense modularity and flexibility compared to an automated process made in-house.

4. **Define and give examples of why Design of Experiments or machine learning could address research problems in cell-cultured meat?**
   Design of Experiments (DoE) involves changing multiple parameters simultaneously to better find a global optimum, not just a local optimum. It allows for a faster exploration of a large space, uses fewer resources, and allows the experimenter to determine interactions between parameters.

   Machine learning (ML) models utilize information from previous samples, and models can predict the quality of the next sample. Thus, ML-guided experimentation is an effective method to expedite the search for optimal operating conditions in complex processes like cell-cultured meat production.

5. **What are the most important traits for an AI/automation scientist in cellular agriculture?**
   In this novel sector, researchers cannot rely on past innovations, but must think creatively to solve the bottlenecks toward making cell-cultured meat a commodity. There are many possibilities, including data collection methods (analytical solutions), data types, analysis, modeling, decision-making tools, and multiple objectives (e.g., cost of goods, energy use).

   Cross-disciplinary thinking is also important, as the role of a data scientist will be pivotal in the research and manufacturing efforts of cell-cultured meat. In addition, understanding the bottlenecks faced by other team members (e.g., bioprocess scale up), collecting the right data, data mining, using the best models to guide the team to the next required physical experiments, and assisting to engineer solutions are all important skills.

6. **Beyond production of cell-cultured meat, what is another challenge in cellular agriculture where automation and AI will be impactful?**
   In the food science field, for example, ML has been used to uncover the governing laws behind flavor combinations and texture.[1] In the context of cell-cultured meat, specifically, the right cocktail of flavor molecules can be elucidated to replicate the sensory attributes of the aging process of animal carcasses.

7. **Why is it most beneficial for companies to adopt automation and AI technologies early on in process development?**
   The main benefits of automation and AI are achieved at an early stage of the R&D when many degrees of freedom remain. Modeling is especially useful to design experiments and virtual prototyping, saving time and costs.

   As many cell-cultured meat start-ups have not yet reached pilot plant development level, some would argue that modeling and AI are not as important for them at this stage. However, the Quality by Design (QbD) approach shows that it is important to start using AI and automation in the early development phase of a product. These tools should be implemented early because the cost of implementing those changes increases as the product development progresses.

8. **What are the different types of models? What type of model could be used to predict cell performance (biomass yield, titer and growth rate) under various bioprocessing conditions?**
   There are two main types of models: mechanistic and data-driven. Hybrid modeling is the combination of these two, where the key design features (i.e., the genetic modifications and bioprocess variables) are extracted from both data-driven bioprocess models from scientific literature and mechanistic models (e.g., genome-

scale metabolic modeling). Principal component analysis is a potential method to select influential factors on the performance of cell cultures.

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Scaffolding

Overview of Structuring for Cultivated Meat Products

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Chapter Abstract

Scaffolds are used in regenerative medicine as templates that provide the structure and three-dimensional cues for cells to grow and differentiate. This scaffolding allows the formation of physiologically relevant tissues and organs *in vitro,* such as bone, cartilage, and muscle. Scaffolding methodology also has tremendous potential for application in cell-cultured meats for the development of more structured meat products. Cell-cultured meats will benefit from the combination of animal cells with scaffolding elements that provide the architecture and consistency required to achieve a sensorial and organoleptic experience similar to the one attained with conventional meats. This chapter highlights the state-of-the-art of scaffold technology and depicts the roadmap towards its application in cell-cultured meats.

Keywords

Tissue Engineering
Scaffold Materials
Scaffold Architecture
Scaffold Processing Methods
Crosslinking
Scaffold Scalability
Extracellular Matrix

Chapter Outline

8.1 Introduction
8.1.1 Definition of a Scaffold
8.1.2 History of a Scaffold

8.2 Relevancy of Scaffolding for Cell-cultured Meat
8.2.1 Scaffolds as Templates for Cell Growth and Tissue Formation
8.2.2 Scaffoldings as Ingredients During Product Development
8.2.3 Scaffolds as Structures to Support Manufacturing of Animal Cells

8.3 Key Parameters to Consider When Using Scaffolds for Cell-cultured Meat Production
8.3.1 Biocompatibility
8.3.2 Biodegradability
8.3.3 Material Composition
8.3.4 Porosity
8.3.5 Mechanical Strength
8.3.6 Surface Chemistry

8.4 Methodologies for Production of Scaffolds
8.4.1 Cross-linking Methods for Scaffold Preparation

8.5 Increasing Complexity of Scaffold Decisions

8.6 Application of Scaffolds for cell-cultured Meat Approaches

8.7 Regulatory Considerations

8.8 Conclusion

Fundamental Questions

1) What is the definition of scaffold and is it relevant for the development of cell-cultured meats?

2) What type of materials can be used for the development of scaffolding structures?

3) What type of scaffold geometries and architectures can be produced with state-of-the-art technology?

4) How scalable is the preparation of scaffolds and is this a cost-effective approach?

5) How can scaffolds be integrated in a cell-cultured meat production process?

8.1 Introduction

The application of scaffolds for cell culture first became widespread in the field of tissue engineering. Tissue engineering is defined by the US National Institute of Biomedical Imaging and Bioengineering as "the practice of combining scaffolds, cells, and biologically active molecules into functional tissues" with the goal of restoring damaged tissues or organs [i]. Tissue engineering is considered a subfield within regenerative medicine, which also includes research into stimulating the body's own healing systems to rebuild damaged tissues, although the terms "tissue engineering" and "regenerative medicine" are often used interchangeably.

Cell-cultured meat takes many of the principles of tissue engineering and applies them to animal cells for the purposes of producing meat. As such, cell-cultured meat is a novel application of tissue engineering that lies outside the field of regenerative medicine. Given how recently the field of cell-cultured meat has developed, most of the relevant literature on scaffolding for cell-cultured meat is taken from tissue engineering in the regenerative medicine context. There are, however, key differences that must be considered in the case of scaffolding for cell-cultured meat, including, but not limited to: cost, scalability, edibility and organoleptic properties.

8.1.1 Definition of Scaffold

Scaffolds are 3D platforms that are typically made of polymeric materials, providing the structural support for cell attachment and subsequent tissue development [2]. Scaffolds, cells, and bioactive factors are generally referred to as the tissue engineering triad, and the success of tissue repair and regeneration relies on the application of one or multiple combinations of these three components [3]. Rather than simply introducing cells into a diseased site, cells are usually seeded in or onto biodegradable and porous biomaterials—scaffolds—before transplantation, to repopulate a defect and/or restore function [4]. In fact, even with cells of high proliferation and differentiation potential, such as stem cells, it is difficult to successfully regenerate tissue if they lack a solid platform on which to build the new tissue and unite the defect [5]. Scaffolds act as a local biochemical and mechanical niche, supporting cell attachment, proliferation, and differentiation and provide an appropriate template for neo-tissue genesis [6]. Ideally, as cells deposit their own matrix, the remaining scaffold degrades at a similar rate resulting in the formation of a biological tissue substitute, with no traces of the implanted biomaterial [7].

This description might suggest a rather straightforward path towards efficient tissue regeneration; however, reproducing *in vitro* the biological events occurring *in vivo* in a functional tissue is a complicated task. The use of one component alone or a simple combination of the elements of tissue engineering triad often fails to induce tissue regeneration [8].

This chapter covers the evolution of scaffold technology towards the increasing demands of tissue engineering, from early versions with simplified scaffold design and functionality to more intricate approaches mimicking the complexity of native tissues. Herein, we explore how to apply this technology to alternative targets other than biomedicine and pharmaceutical research, particularly the production of cell-cultured meat.

The development of an appropriate scaffold can be a key element for cell-cultured meat to mimic or even surpass the visual appearance, texture, and taste of conventional meat. Meat as we know it can be presented to the consumers as intact tissues (e.g., beef steak, chicken breast) or as minced or ground meats that can be processed into multiple formats (e.g., patties, nuggets, sausages). It is expected that different product formats will have distinct scaffold requirements to glue together the appropriate cellular composition and provide the mechanical stability, cooking experience, and sensory profile of meat. The application of scaffolds in cell-cultured meat production might also occur at different stages of production and might not necessarily involve steps of conventional tissue engineering approaches. Over the last decades there have been significant technological developments and an increasing demand for alternative and sustainable meat production systems. This chapter explores the potential role of scaffolds to produce real meat made from animal cells.

8.1.2 History of Scaffolds

The term "tissue engineering" was initially introduced by Professor Robert Nerem in 1988 at UCLA Symposia on Molecular and Cellular Biology [9]. The concept of tissue engineering relies on construct implantation via one of three approaches: 1) *in vitro* expansion of progenitor cells followed by seeding onto scaffolds and implantation *in vivo*; 2) delivery of cells without an *in vitro* expansion step via a scaffold; 3) acellular scaffold implantation that activates resident cells and associated endogenous healing cascades [2].

The design of scaffolds for regenerative medicine has seen significant evolution. Scaffolds can be classified in four generations according to their degree of complexity: i) scaffolds consisting of bioinert materials, mostly defect fillers, ii) scaffolds including bioactive or biodegradable composites, iii) scaffolds combining both resorbable and bioactive functionalities, designed to stimulate specific cellular responses at molecular level [5], and iv) fourth generation templates recapitulating the molecular architecture and biochemical niche of the implant site, designed to trigger specific cellular events to efficiently control the host microenvironment and recruit host stem or tissue-specific progenitor cells to the injured site [10].

This taxonomy represents an evolution in the design of tissue engineering strategies and the role attributed to the scaffold, from the simplistic approach of the first-generation structures to the complex micro- and nano-architectural features of fourth-generation designs. In general, the scaffold design should be inspired from the physicochemical nature of the ECM (extracellular matrix) and the biomechanical properties of the native tissue while simultaneously allowing mass transport and delivery of cells, proteins, factors (a substance that takes part in a biochemical reaction), and genes [11]. In addition to providing the adequate mechanical and structural support, scaffolds must actively guide and control cell attachment, migration, proliferation, and differentiation [12].

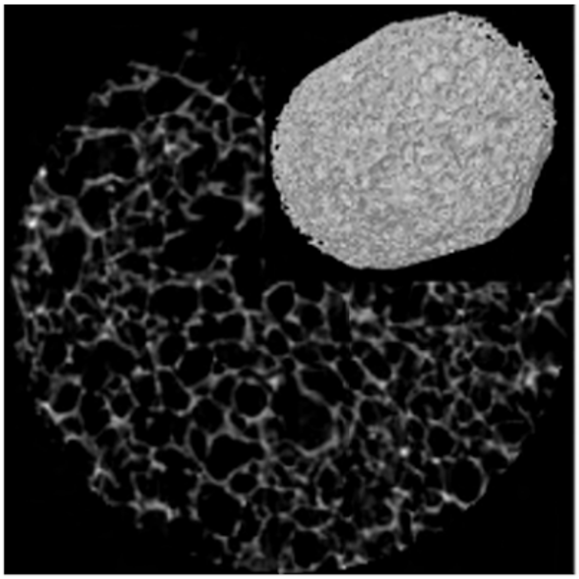

Figure 1. Representative micro-computed tomography images of the 2D surface and 3D structure of a polymer-based porous scaffold. Adapted from [13]. Copyright 2010, with permission from Elsevier.

The continuous crosstalk between cells and ECM is critical for tissue development, providing both structural and cell guidance at a sub-nanometric level [12]. A biomimetic material for tissue engineering can be any scaffolding material that replicates one or multiple features of native ECM. These functions include: i) providing structural support for cells to attach, grow, migrate and differentiate *in vivo*, ii) contributing to the mechanical properties of engineered tissues to fill the void space of the injured site/defect and to stimulate that of native tissue, iii) providing bioactive stimuli for cells to respond to their microenvironment by chemical or physical cues, iv) acting as reservoirs of bioactive molecules and serving as delivery vehicles to boost tissue formation, v) provide a void volume for vascularization and new tissue formation during remodeling as a response to tissue dynamic processes [3].

The resolution of scaffold architecture has increased significantly, and a wide variety of fabrication techniques has been investigated to mimic the microscale porosity and special organization of native tissues [14]. In addition, cells are inherently sensitive to local nanoscale, mesoscale, and microscale patterns of chemistry and topography, triggering distinct cell responses, from changes in cell adhesion, orientation, and motility to cytoskeletal condensation and modulation of intracellular signaling pathways that regulate transcriptional activity and gene expression [15]. Altogether, the positive impact of scaffolding improvements on tissue formation is expected because of the synergistic contribution of architectural cues from the artificial microenvironment and enhanced cellular performance.

Application of scaffolds in the biotechnology space has been demonstrated in multiple occasions, namely as drug delivery systems [16], for stem cell bioprocessing [17], or to simulate regeneration of bone [18], cartilage [19], neural tissue [20], muscle [21], skin [22], tendon [23], cardiac tissue [24], periodontal tissue [25], among others. There is a growing list of commercial products available, some of them included in Table 1.

Table 1. Commercially available scaffolds for tissue engineering applications. Adapted from [26].

Product	*Scaffold Composition*	*Application*
Integra™	Collagen/chondroitin-6-sulfate matrix overlaid with a thin silicone sheet	Artificial skin substitute
SQZ Gel™ Oral Controlled release system	Chitosan and polyethylene glycol	Hypertension
Myskin™	Cell-cultured autologous human keratinocytes on medical grade silicone polymer substrate	Epidermal skin substitute
TranCyte™	Polyglycolic acid/polylactic acid, extracellular matrix proteins derived from allogenic human fibroblasts and collagen	Human fibroblast derived skin substitute
Bioseed™	Fibrin sealant and cell-cultured autologous human keratinocytes	Epidermal skin substitute
Aquamere™	Interpolymers of Polyvinylpyrrolidone (PVP) and PVP grafted copolymers with urethane	Skin care, topical and oral drug delivery
Aquatrix™ II	Chitosan-PVP	Skin adhesive gels, wound and burn dressings, implants and drug delivery matrices
Apligraf™	Bovine type I collagen mixed with a suspension	Epidermal and dermal skin substitutes

Clinical application of scaffolds in tissue engineering has seen the most progress for planar tissues and organs that act in a barrier or transport role [27], such as skin [28], bladder [29], cornea [30], trachea [31], and blood vessels [32]. The engineering of connective tissues, such as bone [33] and cartilage [34], as well as nervous tissue [35], and muscle [36], has also been demonstrated in a variety of preclinical and clinical evaluations, and each has their own requirements for scaffold design [27].

Nevertheless, more complex and hierarchically organized tissues and organs, including multifunctional systems like liver, kidney, heart, and pancreas, still pose a significant challenge. Scaffolds and tissue engineered constructs for these organs have been evaluated clinically in the context of replacing specific organ functions, such as hydrogels that facilitate survival in transplantation of pancreatic islets [37] and extracorporeal hepatocyte constructs to support detoxification in patients with acute liver failure [38]. Despite the promise of scaffold technology in regenerative medicine, it is still clear that the translation of scaffolds to clinical applications represents a challenge [39]. Besides issues in mimicking structural and cellular functionality of the constructs, mass transport limitations, vascularization, and host tissue integration are important failures. As the tissue architecture to be replaced becomes more complex and hierarchical, scaffold design must also match this complexity to recapitulate a functioning tissue.

As clinical application of scaffolds and tissue engineering strategies is still somewhat limited by the high safety and functionality requirements of therapy, there has been an interesting diversification of scaffold applications in cell culture. *In vitro* disease modeling has taken significant contributions from tissue engineering laboratories as pre-clinical research has identified the need to improve the pathophysiological relevance of *in vitro* cell models used to screen new drugs [40]. These models should be able to recapitulate certain mechanisms of disease and mimic cell-ECM interactions found in those situations; however, because they will not be implanted, their quality attributes are certainly less restrictive than the ones required for therapeutic approaches.

8.2 Relevancy of Scaffolds for Cell-Cultured Meats

Cellular agriculture is an emerging field that supports the production of edible meat tissues such as conventional meat while obviating the need for raising and sacrificing a whole animal for consumption [41]. Proposed methods to produce cell-cultured meat include the attachment and growth of animal cells on a 3D structure (scaffold) and/or immersed in a solution containing a nutrient mix (culture media) for cell expansion and differentiation into the desired cell phenotypes typically found in muscle, fat, blood, and connective tissue. These constructs should be cultured in bioreactors or other tightly controlled culture devices that provide the appropriate physiological environment and the ability to scale-up production of tissues.

Besides the cellular composition of meat, structural elements also impact the nutritional value, product development and sensory perception of a finished meat product. The nutritional quality of conventional meat is essentially determined by the chemical composition of the tissue at slaughter, whereas product development and sensory experience result from intricate interactions between chemical composition and metabolic properties of muscle at slaughter and post-mortem biochemical changes [42]. Cell-cultured meat does not require slaughtering but will certainly present similar interactions between cells, ECM, and their dynamic evolution post-harvest and during processing of the final product.

For this reason, scaffolding can be an important element of a cell-cultured meat approach. Just as scaffolds provide the substrate for proper cell expansion and orientation of human cells towards the patterns and shapes found in native tissue for transplant in tissue engineering, the same is true of animal cells and cell-cultured meat. Ultimately, this is critical to enable the development of cell-cultured meat products with the desired shape and format typically recognized by consumers, ranging from a ground meat product to a thick cut of steak.

Interestingly, the scaffold support for tissue development during culture is not the only relevant application of scaffolds for cell-cultured meat production. Scaffold use can also expand to processes downstream of cellular production at the product development stage. Specifically, scaffolding materials can be blended with harvested cells or cells can be deposited into scaffolding structures only at the formulation step. By following these different approaches, scaffold requirements might differ substantially. Nevertheless, the critical parameters of scaffold design are still divided into similar categories. These categories are further explored in Section 8.3. In addition, scaffolds can also be used as temporary support structures to promote cell growth and/or differentiation during manufacturing of animal cells used for the formulation of cell-cultured meat products. These temporary scaffolds can be either composed of solid materials that require dissociation of the produced cells and the scaffolds during harvest, or alternatively be made of dissolvable materials that can be removed during the recovery of the animal cells at harvest.

8.2.1 Scaffolds as Templates for Cell Growth and Tissue Formation

The main application of scaffolds in the production of cell-cultured meat products is to recapitulate functions of native ECM. The main edible tissues to be produced are muscle as the muscle mass of the livestock and fish species used to produce human food represents 35-60% of their body weight [43]. Skeletal muscle predominantly consists of 90% muscle fibers and 10% connective and fat tissues [43]. Muscle fibers are elongated, multinucleated, and spindle-shaped cells of approximately 10 to 100 micrometers diameter and with a length that ranges from a few millimeters in fish to several centimeters in terrestrial animals. Muscle fibers are generally characterized by their contractile and metabolic properties. The connective tissue that surrounds muscle fibers and fiber bundles is a loose connective tissue. It consists of cells and an ECM that is primarily composed of a network of collagen fibers wrapped in a matrix of proteoglycans. Fat tissue can be found both around (intermuscular) and within (intramuscular) the muscle. Intramuscular fat tends to be more relevant for a cell-cultured meat process as intermuscular fat is trimmed during butchering, thus having a significantly reduced impact on meat quality. Intramuscular fat can be categorized as muscle adipocytes found between fibers and fiber bundles and a minor proportion is stored as lipid droplets within the myofibers in the cytoplasm.

When considering scaffolds as templates for muscle cell culture and tissue formation, their role is not only to provide the properties conventionally found in ECM of muscles but also to direct cells towards the desired phenotype which can then produce their own relevant ECM for the targeted application. Alternatively, the scaffold can be designed to compensate for aspects of *in vitro* tissue development that might fall short of native organogenesis, enabling cell-cultured meat products to achieve similar if not better sensory properties than conventional meat. Therefore, scaffold design for cell-cultured meat using this approach should focus on providing the appropriate cell culture template while bringing added value from a sensory perspective.

The main categories impacting sensory quality include color and appearance, tenderness, juiciness, and flavor [44]. Native ECM has a strong impact on tenderness of meat, and this is typically the most important sensory characteristic for consumers. The proportion, distribution, and nature of intramuscular connective tissue, together with its organization and crosslinking determine texture and tenderness properties of meat [45]. These can vary greatly among species, with beef consistently showing higher toughness than pork or poultry [46].

The different cell phenotypes present in meat and their respective ECM niches impart flavor and juiciness to the final product. Specifically, the marbling, or intramuscular fat, is critical for the quality of meat. Different scaffolding templates can be designed to engineer *in vitro* formation of muscle and adipose tissue separately, which can then be blended during product development. Alternatively, co-cultures of muscle and fat cells can be performed simultaneously using the same scaffold, benefiting from crosstalk between both cell types to recapitulate muscle tissue and intramuscular fat organization during tissue development.

Increased proportion of certain types of muscle fibers is also associated with improved meat juiciness and flavor [47, 48]. Moreover, the ratios of ECM proteins such as collagen, decorin, and tenascin as well as proteoglycans not only impact tenderness of meat but can also have a significant impact on flavor [49]. Composition of muscle fibers also influences meat color via the amount and chemical state of myoglobin. High myoglobin content of type I and type IIA fibers results in a positive relationship between the proportion of these fibers and red color intensity [43].

The appearance of meat is also associated with ECM structure and composition. The integrity of skeletal muscle is preserved by intramuscular connective tissue and during post-mortem aging, the collagen networks in connective tissue are degraded. The ECM not only contributes to the overall appearance of meat but also to the tenderness and overall mechanical strength [50].

8.2.2 Scaffolds as Ingredients During Product Development

Scaffolds are 3D templates that not only support cell growth but can also be applied for other functionalities. Scaffold structures can also be used later in production and product development as one partial bulk ingredient to provide texture and blend/encapsulate animal cells. In more processed meat products such as sausages, a blend of animal cells and filler material acting as a holder and structural element is already a common practice. In fact, plant-based proteins, starches, and fibers can provide desired properties for meat products, specifically expected bite and chew. The fiber component can not only provide additional nutritional value but can also improve texture and recapitulate the muscle fiber structure of whole muscle when processed using extrusion technology, commonly applied for plant-based meats [51].

By pursuing this approach, the focus would be on blending techniques to produce material at large scale that can recapitulate textural, mechanical, and even compositional features found in conventional meat products. Cells would be processed together with the scaffolding structures, blending the cell biomass with the structural component provided by the scaffold. Similar considerations for tenderness, juiciness, flavor, and appearance mentioned in the previous section (8.2.1) also apply here. This approach eliminates the need to account for the design parameters that are critical for an ideal cell culture process.

An alternative approach would be to deposit cells into prefabricated scaffolds during downstream manufacturing, without having to culture cells with the construct for an additional period. Fabrication of 3D scaffolds with tailored designs and high structural complexity has been facilitated with bioprinting approaches. Cell-laden 3D bioprinting has seen interesting developments and has been targeting organ transplantation. Compared with nonbiological 3D printing, cell-laden 3D bioprinting involves more complex factors, including the choice of printing materials, the strategy of gelling, cell viability, and other technical challenges. Although cell-populated 3D bioprinting has many complexities, it has proven to be a useful and exciting tool with wide potential applications in regenerative medicine to generate a variety of transplantable tissues [52]. Similar potential can also be expected for cell-cultured meat applications, offering a higher level of control over texture, architecture, and format of the final meat product, although there are challenges surrounding the scalability of this technology.

8.2.3 Scaffolds as Structures to Support Manufacturing of Animal Cells

An alternative application of scaffolds for cell-cultured meat production is their use as temporary templates during cell production to facilitate cell expansion and/or maturation into the desirable numbers of cells displaying the desired phenotype. These temporary scaffolds can be produced in different shapes and formats, with microcarrier type being one of the most common. Microcarriers were initially derived from spherical chromatography beads and were first used as substrates for attachment and growth of anchorage-dependent cells in suspension cultures [53]. Since then, these carriers have been used for several biotechnology applications due to their high surface area to volume ratio, reproducibility, potential for scale-up, and documented Good Manufacturing Practices (GMP). Multiple works have been reported on the application of microcarriers for scale-up of stem cell-derived products in large bioreactors as they can offer the appropriate template to modulate cell shape and organization [53, ii].

Numerous commercially available microcarrier types have been tested with stem cells in large scale cultures. These carriers differ in size (90-380 μm), core material (modified polystyrene, cellulose, dextran, gelatin) and surface coating (collagen, fibronectin, diethylaminoethyl, triethylammonium) [54]. Composition and coating of microcarriers affect cell growth and carrier settlement as well as required hydrodynamic conditions to assure a homogeneous suspension culture and an efficient mass transfer [54].

Most commercially available microcarriers are made of non-degradable and/or non-edible materials; therefore, a clearance step of separation between cells and microcarriers after scale-up must occur to assure complete removal of those components from the final product. If using edible carriers, the separation step is no longer necessary and those components can be considered as a part of the final construct and meat product, impacting the overall categories of quality of flavor, tenderness, appearance, and juiciness. Common coatings for microcarriers also include ECM proteins known to favor meat quality. Alternatively, dissolvable microcarriers have also been developed, which facilitates the cell harvesting step and reduces the carry-over of undesirable microcarriers into the final cell-cultured meat product [55].

Microcarriers are well established for expansion of cells in bioreactors; however, other scaffold formats can also be used as temporary templates. More complex temporary scaffold geometries also lead to more tedious and inefficient cell harvest protocols. These might also involve the design of alternative bioreactor systems amenable for growth of thicker tissues with an efficient mass transfer through all the sections of the 3D construct. Alternative bioreactor designs have been proposed for the culture of tissue engineered organs for maintenance and recapitulation of their native functionality. Large airway bioreactors with vertical orientation of tissue engineering constructs [56], whole lung bioreactors including ventilation and perfusion capacities [57], and devices for growth of cardiac constructs combining interstitial perfusion and electrical stimulation [58] have been proposed with demonstrated potential to induce the formation of physiologically relevant thick tissues. Nevertheless, scalability of these platforms still represents a challenge.

8.2 Key Parameters to Consider when using Scaffolds for Cell-Cultured Meat Production

Scaffolds can assume different shapes and formats, ranging from solid porous sponges, foams, and fiber meshes optimized for cell seeding and proliferation to microparticles designed to promote controlled release of bioactive molecules known to stimulate cellular performance. Other popular scaffold format includes aqueous crosslinked polymeric networks, known as hydrogels.

Engineering hard tissues like bone requires more distinct scaffolding properties than the regeneration of soft tissues, such as brain [59]. Thus, solid scaffolds with tougher mechanical properties are more suitable to engineering hard tissues whereas softer scaffolds such as hydrogels are leading candidates to promote formation of cartilage and other soft tissues. In fact, hydrogels strongly resemble the mild microenvironment found in native ECM for cell proliferation and survival, facilitating nutrient and metabolic exchange [60].

When considering the *in vitro* formation of tissues and organs, scaffold design should reflect chemical, mechanical, and physical parameters of targeted tissue microenvironment to maximize its potential to trigger formation of functional tissue. The critical parameters to be considered when designing a new scaffold can be divided in the following categories: i) biocompatibility, ii) biodegradability, iii) material composition, iv) porosity, v) mechanical strength, and vi) surface chemistry [61, 62].

The design of scaffolds for cell-cultured meat should follow many of the considerations described for scaffolds in therapeutic approaches, particularly if they are used during cell culture. Requirements for functionality, purity, and safety of the scaffold are not the same as these will not be implanted or injected into a patient. However, if scaffolds are a part of the final cell-cultured meat product, they will be ingested and digested through the human digestive tract and require the same scrutiny and regulation as all other food products.

8.3.1 Biocompatibility

Scaffolds for animal cell culture must be biocompatible and non-toxic [59]. Biocompatibility is a term that is used broadly within biomaterial science, but there is still a great deal of uncertainty about its meaning as well as about the mechanisms that collectively need to be inhibited to achieve biocompatibility [63]. Kohane and Langer (2010) [64] explained biocompatibility in a new context and redefined it as “an expression of the benignity of the relation between a material and its biological environment” [65].

The first criterion for any scaffold for tissue engineering is that it must be biocompatible and bioactive, allowing cells to migrate onto the surface and eventually through the scaffold [66]. The key aspect of biocompatibility is the understanding of which chemical, biochemical, physiological, or other mechanisms are activated by the contact of the scaffold with the cells and to understand the consequences of these interactions [67].

The selection of scaffold materials and processing technique are critical to ensure biocompatibility of the tissue engineering construct. It is common to find inaccurate statements claiming that certain polymers are biocompatible. Biocompatibility is related to the behavior of certain material in a determined context, and it is evaluated by the interactions between the implant and the cells or host tissue. Biocompatibility is a characteristic of a material and biological host system and not a property of a material per se [70]. One example of polymers that have a range of biocompatibilities in different context are carrageenan-based materials, used both in medical and food applications.

Carrageenans are commonly used hydrophilic polysaccharides. They are part of a family of linear and sulfated galactans used in several industrial, environmental, and commercial applications as gelling, thickening, emulsifying, and stabilizing agents [71]. Their reversible thermogelation properties together with their ionic crosslinking ability and mild conditions for cell encapsulation favor this family of polysaccharides to be used as potential bulk materials for scaffold and hydrogel development. Carrageenan hydrogels have been demonstrated to be applicable for entrapment and controlled release of growth factors for cell proliferation [75] and stem cell differentiation [76, 77]. Carrageenans are also widely used as thickening agents in dressings and desserts [78]. This diverse array of applications and distinct cell-material interactions highlights the specificity of biocompatibility results depending on the processing conditions of the material and the location of host tissue.

Overall, the effect of scaffold chemical and structural characteristics on cell behavior and host response such as adhesion, proliferation, migration, and differentiation are widely reported [62]. Scaffold properties including surface topographic features (roughness and hydrophilicity) and scaffold microstructures (pore size, porosity, pore interconnectivity, and pore and fiber architecture) are known to not only impact biocompatibility but also the success of tissue engineering approaches [62]. Biocompatibility of certain scaffolds allows for simultaneous formation of new tissue along with the degradation of the matrix [59].

Biocompatibility considerations for scaffold design aimed to be used in therapeutic targets or food applications are distinct. In cell-cultured meat approaches, if scaffolds are part of the final edible formulation, these are only exposed to the digestive tract system. Gastrointestinal transit is not linear; substances do not move uniformly through the digestive systems and edible materials do not leave segments of the digestive tube in the same order as they arrive. As food is initially ingested, the stomach typically takes up to 5 h to completely empty its content. Simultaneously, colonic filling starts approximately 200 minutes, or over 3 h, after ingestion. Complete transit through the colon takes 30 to 48 h [79]. Therefore, exposure of intact meat constructs to the digestive tract will be limited and biocompatibility of the scaffold can be evaluated by the products of enzymatic digestion. Scaffold biocompatibility will be tightly related to its edibility and digestibility. If the scaffold used for production consists of an edible material with a safe history of human consumption (i.e., with Generally Recognized as Safe, or GRAS status), it is expected that safety will be comparable.

8.3.2 Biodegradability

For most tissue engineering applications, scaffolds are not intended to be permanent constructs at the implant site [66]. After the host cells have populated the scaffold and started to produce their own ECM, the scaffold should degrade into biocompatible byproducts that can easily be excreted from the body [80]. The byproducts of degradation should be non-toxic, and the degradation process must not trigger a severe immune or inflammatory response from the body. The biodegradability considerations for cell-cultured meat scaffolds are more complex than for therapeutic uses, especially if used in the manufacturing stages and in the final product. During manufacture, the scaffold must provide the requisite structural support for cell growth, whilst in the final product any scaffolding material must be safely digestible.

Degradation of scaffolds takes place in biological environments where water and enzymes play an important role [81]. There are several factors that influence the degradation rate of polymers: functional groups, pH, copolymer composition, structure of materials, and water uptake [82, 83]. A straightforward measure of biomaterial degradation is overall mass loss in the degradative environment [81].

Material composition is the most important factor to determine the hydrophilicity and rate of degradation [81]. Crosslinking and polymer chemistry are known to modify the degradation kinetics [84]. Surface treatments indirectly influence degradation rates as they alter water intake and hydrophilicity of the surfaces, therefore influencing hydrolysis and enzymatic degradation process [85].

Scaffold shape, microstructure, and microporosity also influence degradation properties due to changes of the surface area and exposure to water and enzymes [86]. Enzymatic sensitivity of scaffolds can also be engineered by design of protease-sensitive crosslinked materials, mimicking natural ECM that degrades proteolytically through the action of matrix metalloproteinases [87]. Other parameters to consider when designing biodegradable scaffolds is the mechanical loading and pH that the structures will be exposed to, as well as the type, concentration, and activity of enzymes in contact with the biomaterial. When considering a generic biomaterial for implantation, these vary greatly depending on the target site.

For cell-cultured meat approaches, besides assessing the biodegradability of scaffolds, digestibility also must be considered. Exposure of ingested cell-cultured meat to enzymes will only occur through the digestive tract. Edible scaffolds will be degraded through the action of proteases, peptidases, lipases, amylases, and nucleases, depending on the composition of the scaffold [88]. These enzymes are either endogenous or produced by the host's microbial population in the gut. Cell-cultured meat products will be exposed to pH values ranging from 2 (stomach) to 8 (small intestine, colon) [89].

The design of biodegradable scaffolds for cell-cultured meat approaches should follow a distinct rationale, as these structures must be stable and provide appropriate mechanical strength and support during cell culture, with negligible material loss during the upstream stage of manufacturing. When cell-cultured meat is ingested, it should then be quickly degraded by the aggressive enzymatic and mechanical environment of the digestive tract.

Following the trend of designing “smarter” biomaterials, having further control of the degradation process in such a manner that it could respond differently to the environment provided by the host is a future direction of research [81]. Tailoring degradation kinetics to application could also be incorporated into the development of edible scaffolds for cell-cultured meat approaches, inhibiting degradation during physiological conditions of *in vitro* cell culture and manufacturing, and triggering fast degradation upon exposure to the acidic environments of the digestive tract.

8.3.3 Material Composition

Engineering artificial scaffolds for cell-cultured meat requires the analysis of the chemical diversity and composition of natural tissues. It is unlikely that scaffolds will be able to match the complex composition and organization of tissue macro- and micro-environments, as these involve a plethora of ECM components and bioactive molecules [59]. Nevertheless, tissue engineering approaches have evolved towards the recapitulation of key players in native ECM, including key biochemical components of the microenvironment.

ECM is composed of structural polymers, namely proteins, polysaccharides, glycoproteins, and proteoglycans [90]. Filamentous protein fibrils, including collagen, keratin, and elastin provide tissues with structure, guide cell morphology, and help to protect cells and tissues [91]. Cytoskeletal proteins, such as myosin and actin in muscle, provide tissue elasticity, enable contractility, and facilitate cell motility and mitosis. Within proteins, covalent crosslinks can occur through the side chains of amino acids that can increase the stability and durability of structural proteins [27].

The chemical composition in native tissue can vary dramatically depending on tissue type and tissue site; therefore, it is important to draw inspiration from nature when selecting materials for scaffold preparation [27]. Biomaterials used for building scaffolds can be divided into four major classes based on their composition: biopolymers, metals, ceramics (including carbons, glass-ceramics, and glasses), and composite materials that combine any two different classes of materials [81]. Biopolymers have two categories: natural and synthetic [92].

Natural polymers are derived from renewable resources, namely from plants, animals, and microorganisms, and they are widely distributed in nature [93]. Biodegradable scaffolds made from natural polymers were among the first to be used clinically, due to their better overall interactions with various cell types, and lack of an immune response. Natural polymers can be classified as proteins (silk, collagen, gelatin, fibrinogen, elastin, keratin, actin, and myosin), polysaccharides (cellulose, amylose, dextran, chitin, and glycosaminoglycans), or polynucleotides (DNA, RNA) [94].

Natural polymers have been extensively used for muscle and fat tissue engineering as they possess intrinsic bioactive signaling cues that promote optimal cellular performance [95, 96]. These polymers are commonly found in native tissues and organs, particularly meat products. Therefore, the selection of these materials for scaffold production of cell-cultured meat products is straightforward and should not represent a limiting safety hurdle if a natural polymer-based scaffold is a part of the final cell-cultured meat product.

Synthetic biomaterials are frequently made from polymers. Biopolymers are mostly used in tissue regeneration of soft tissues while harder materials such as metals and ceramics are mainly used for bone and cartilage [81]. Synthetic materials offer advantages over natural polymers for scaffold design, namely on their ability to have precisely tuned mechanical and structural properties that can be tailored to different applications [97]. These synthetic materials present a lower risk of pathogen transmission and lot-to-lot variability [98]. Synthetic polymers can be readily fabricated into a variety of geometries such as individual fibers or electrospun meshes with aligned or random nanofiber orientation [97]. However, a common criticism of synthetic materials is that their surfaces do not always readily support cell attachment [99]. Due to their inherent suboptimal bioactivity, many strategies exist to functionalize the surfaces of synthetic polymer scaffolds such as the addition of bioactive molecules and ECM proteins to modulate tissue responses [97]. Another important limitation of synthetic materials is that they typically stimulate a foreign body response as characterized by an increase in the number of foreign body giant cells upon implantation [97].

As natural polymers only offer limited mechanical stiffness and can be easily degraded, a variety of synthetic materials have been used for skeletal muscle regeneration such as PGA, PLA, and PLGA [95]. Myoblasts seeded onto electrospun meshes with aligned nanofiber orientation can fuse into highly aligned myotubes [100]. Furthermore, synthetic scaffolds can be easily engineered to facilitate the controlled release of growth factors for inducing muscle regeneration [97].

Bioactive composite materials have also been suggested to combine the advantages of two or more different materials (metallic, ceramic, and polymeric materials) [101]. Composite materials improve the scaffold properties and allow controlled degradation [102]. This fine control of scaffold degradation may be necessary when considering the different biodegradability and digestibility properties required at different stages in the cell-cultured meat production and consumption process as discussed in section 8.3.2.

The application of synthetic polymers for cell-cultured meat approaches is limited as these are essentially plastics and not suitable for human consumption. Their application is then limited to temporary scaffolding materials during upstream processes, either as porous materials for cell seeding or as spherical microcarriers. In both these cases, an additional step of cell dissociation from the scaffolds would be mandatory.

This chapter does not aim to provide an in-depth overview of the natural and synthetic polymers for scaffold production. Robust reviews have been published elsewhere [103] with core foci on the influence of scaffold materials on the performance of tissue engineering constructs. Table 2 lists some of the main polymers used for scaffold fabrication.

Table 2. Selection of polymers commonly used for production of scaffolds for cell culture.

	Polymer	Molecular formula	Observations	Refs
NATURAL POLYMERS	Collagen	$(C_{65}H_{102}N_{18}O_{21})_n$	Most abundant protein in mammalian ECM; derived from human, animal, and marine sources	[104]
	Gelatin	$(C_6H_{12}O_6)_n$	Denatured form of collagen	[105]
	Alginate	$(C_6H_8O_6)_n$	Derived from brown algae	[19]
	Hyaluronic Acid	$(C_{14}H_{21}NO_{11})_n$	Non-sulfated glycosaminoglycan component of ECM; found in almost all tissues in adult mammals	[106]
	Chitosan	$(C_6H_{11}NO_4)_n$	Obtained from deacetylation of chitin (from skeleton of crustaceans)	[107]
SYNTHETIC POLYMERS	Poly(lactic acid) - PLA	$(C_3H_4O_2)_n$	Group of thermoplastic aliphatic polyesters with proven satisfactory biocompatibility	[108]
	Poly(glycolic acid) - PGA	$(C_2H_2O_2)_n$	Group of thermoplastic aliphatic polyesters with proven satisfactory biocompatibility	[108]
	Poly(ethylene glycol) - PEG	$C_{2n}H_{4n+2}O_{n+1}$	Polyether that can be used as food additive	[109]
	Poly(caprolactone) - PCL	$(C_6H_{10}O_2)_n$	Biodegradable aliphatic polyester with a low melting temperature (60°C)	[110]
	Polystyrene	$(C_8H_8)_n$	Synthetic aromatic hydrocarbon polymer made from styrene	[54]

The origin of the materials used for scaffold fabrication might also be an interesting area of debate as the main motivations of cellular agriculture are associated with environmental awareness and animal welfare. Several scaffolds made from proteins such as collagen are obtained from parts of cows and pigs and the animal slaughtering or isolation processes of these polymers might still represent significant ethical challenges for the consumers. There are other means of producing these polymers of interest, particularly by fermentation processes or by isolation from residues and natural waste. Both approaches should be carefully considered as they might represent significant challenges for purification and create additional costs to the cell-cultured meat technology.

Production of scaffolds made from synthetic polymers for cell-cultured meat use would also face significant additional challenges. Since these materials are not edible and would only be used as temporary templates to support manufacturing, they would represent a significant added cost and additional plastic waste product. Due to their slow or non-degrading nature, this approach is also counterproductive to environmental issues that cellular agriculture aims to tackle.

8.3.4 Porosity

Pore structure is an essential parameter in the development of scaffolds for tissue engineering [62]. The porous structure of the scaffolds is necessary for both tissue regeneration and cell-cultured meat because it enables appropriate cellular performance, as well as diffusion of nutrients, oxygen, and waste [62]. Specifically, porous structure of scaffolds has been demonstrated to significantly influence cell migration, proliferation, and the build-up of a vascularization bed, which is one of the major shortcomings in the field of tissue engineering [62]. Various scaffold processing techniques have been used to design architectures with different pore sizes and overall porosity.

Pore architecture and pore interconnectivity of a scaffold should also be taken into consideration [111]. It has been established that large pores facilitate nutrient supply and waste removal, while small pores provide more surface area for cell adhesion [112]. It is also notable that the effect of pore architecture on cell behavior also depends on cell nature [3]. The effect of implant pore size on tissue regeneration is emphasized by experiments demonstrating the optimum pore size of 5 µm for neovascularization, 5–15 µm for fibroblast ingrowth, 20 µm for the ingrowth of hepatocytes, 20–125 µm for the regeneration of adult mammalian skin, 40–100 µm for osteoid ingrowth, and 100–350 µm for the regeneration of bone [113].

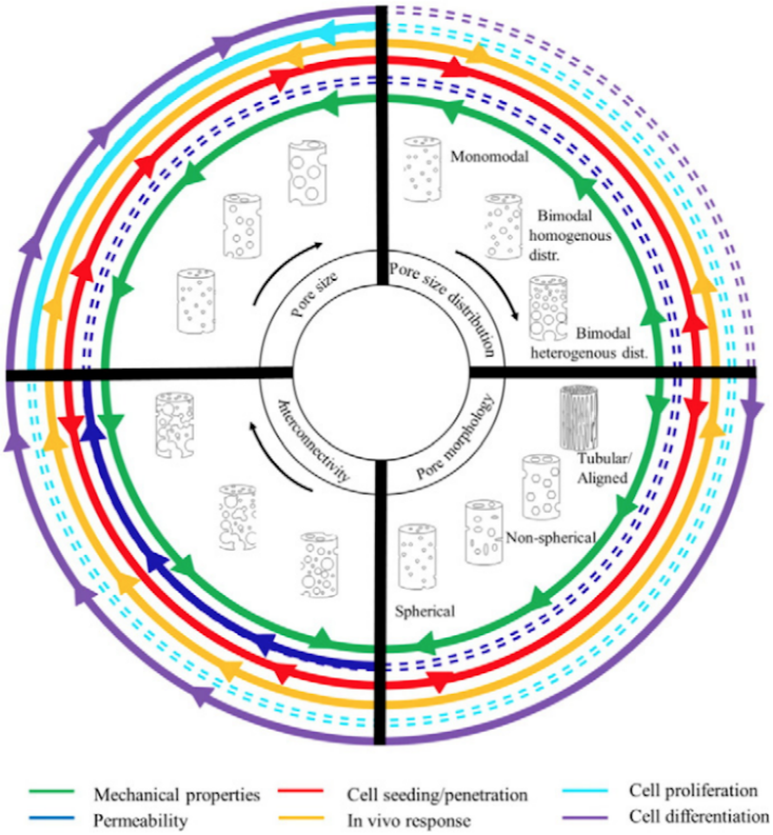

Figure 2. Schematic displaying how structural properties of the scaffold (interconnectivity, pore size, pore size distribution, and pore morphology) affect certain physicochemical and biological behaviors. The black internal arrows point out the increase of the structural property. The colored lines correlate the structural property of the scaffold to physicochemical or biological behaviors; whereas the arrows point out a trend and the dashed lines indicate controversy or a non-determined trend. Reprinted from [114], copyright 2016, with permission from Elsevier.

The first generation of scaffolds for muscle tissue engineering lacked precise control over porosity of the scaffolds [115]. However, tissue engineering scaffolds should ideally aim to exhibit similar structural complexity as the native tissue to satisfy the intended biological function [112]. Naturally porous materials, including tissues, typically have a gradient porous structure, in which porosity is not uniform [116]. Rather, it is distributed to maximize the overall performance of the structure [112]. There are now more complex methodologies that enable the preparation of scaffolds with defined porosity, narrowing the gap between natural ECMs and artificial scaffolds.

Moreover, most conventional methods used to fabricate porous scaffolds typically do not allow the porosity or pore size to be tuned once the scaffold is created [112]. A new generation of scaffolds with post-fabrication tunability and active adaptation to the dynamics of cellular performance could represent an important advance in the field of tissue engineering [6]. Porosity and architectural demands for proliferating and differentiating cells are likely to differ and the development of on-site tunable 3D templates could lead to significant improvements in the engineering of tissues *in vitro* and maximize expansion and differentiation capacity of animal cells used for production of cell-cultured meat.

8.3.5 Mechanical strength

Mechanical properties of scaffolds should match those of the tissues intended to be regenerated or replicated. Matrix stiffness varies with respect to different bodily organs. Brain is the softest tissue with an elasticity ranging between 0.2 to 1 kPa, while pre-calcified bone is the hardest tissue with an elasticity value of more than 30 kPa [117].

In addition to stiffness, there are a variety of mechanical properties that vary depending on the target tissue. Some of these include: i) elastic modulus, measured strain in response to a given tensile or compressive stress along the force; ii) flexural modulus, measured relationship between a bending stress and the resulting strain in response to a given tensile or compressive stress perpendicular under load; iii) tensile strength, maximum stress that the material can withstand before it breaks; and iv) maximum strain, ductility of a material or total strain exhibited prior to fracture [118].

Inherent properties of the selected material, together with geometry, porosity and processing techniques selected for the preparation of the scaffolds determine the strength, elasticity and absorption of the tissue engineered template. To ensure optimal performance, the scaffold used should be evaluated for its elastic modulus, tensile strength, compressive strength, and maximum strain [119].

These requirements were developed for the first generation of engineered tissues *in vitro*. Mechanical properties of the microenvironment at the implantation site are not meaningful for cell-cultured meat production. However, the relevance of mechanical stability of scaffolds goes beyond the structural support during tissue regeneration. Cells sense mechanical stresses through mechano-transduction pathways that relay these signals from cell membranes through the cytoskeleton to the nucleus and modulate gene regulation and cell differentiation [120]. Cells of different lineages survive in distinct natural environments, and they possess different stiffness, impacting differentiation of stem cells [117].

To maximize cellular performance, scaffold stiffness should match or target the original tissue being produced to expose cells to relevant mechanical forces, thereby directing cell fate towards the desired outcome [2]. For cell-cultured meat approaches, scaffolds should be designed to provide mechanical properties that support healthy cell proliferation or that promote efficient formation of skeletal muscle tissue. For instance, in muscle tissue engineering, a substrate substantially stiffer than native muscle ECM would alter the behavior and phenotype of myoblasts, ultimately preventing maturation and formation of striated myofibers. In fact, the impact of mechanical properties of materials on myogenic differentiation has been intensively studied. It has been shown that intermediate stiffness similar to that of muscle tissue (1-10 kPa) leads to myogenic differentiation in tissue engineering approaches [2]. Alternatively, there have been relatively few studies on the mechanical properties of fat tissue. Adipose tissue is normally considered to be a connective tissue of high expandability. Most of these have focused on its behavior in compression, which is relevant to its function as a shock absorber. Moreover, different locations in the body require types of fat with distinct composition and mechanical properties, depending on their function [121]. Adipose tissue can change its micro-structure such that at high strains or long times of harmonic excitation the material behavior changes drastically. This structural change is reversible after long periods of rest [122].

The new generation of tissue engineering approaches consider mechanical stimulation, not only as structural support for the cells, but also to directly activate or trigger certain biological events. For instance, in muscle, the impact of mechanical and electrical stimulation to enhance muscle repair is also now recognized to mimic the stretch and electrical coupling that naturally occurs in native muscle tissue [120]. There have been studies that utilize mechanical stimulation for tissue-engineered skeletal muscle structures demonstrating improvements in the differentiation, maturation, alignment, and contractility of the tissue-engineered muscle [123].

Nevertheless, not all studies employing mechanical and electrical stimulation led to improved cellular performance. Timing, frequency, and intensity of exposure cycles are critical for the success of the approach. Despite the potential of *in vitro / ex vivo* mechanical stimulation, tissue-engineered structures have not still been developed with contractility that matches the force generated by native muscle [120]. Moreover, these approaches still present significant shortcomings, namely the dependence on sophisticated equipment and culture devices for mechanical and electrical stimulation. These shortcomings are enhanced when considering scaling up the production of cells and tissues for human consumption. In addition, this approach reduces the panel of potential materials that are amenable to mechanical stretch or electrical conduction.

Besides the contribution to muscle tissue formation, mechanical properties of the selected scaffold ultimately impact the tenderness of cell-cultured meat [45]. Independent of the application of scaffolds during the cell culture process or only at the product development stage, if scaffolds are a component of the final product, their mechanical properties will greatly contribute to the sensory performance of the cell-cultured meat.

8.3.6 Surface Chemistry

The composition and architecture of scaffolds significantly impact cellular performance of seeded or encapsulated cells. However, the first level of interaction between cellular components or host tissue and the scaffold occurs at the surface of the template. Cell-material interactions consist of early events, such as cell adhesion and spreading, and late events, namely cell proliferation, differentiation, and functionality [99].

Scaffold surfaces can be modified by several approaches including surface etching, plasma treatment, and casting methods, depending on the scaffold material. By employing the appropriate treatment, scaffolds with surface properties less favorable for cell attachment can be significantly improved.

Hydrophilicity and water contact angle of scaffold surfaces are among the important features of polymers which can be altered by various chemical and topographical modifications. Decreasing surface roughness will reduce hydrophobicity and water contact angle. High hydrophobicity can inhibit culture media contact with scaffold surfaces and may negatively affect cell number for certain cell types [62]. While osteoblasts adhere well to rough surfaces, fibroblasts and endothelial cells tend to attach and proliferate more on scaffolds with a smooth surface [124].

Biochemical cues can be intrinsic to the scaffold bulk material as is the case for natural polymers that present functional surface groups. Alternatively, surface functionality can be tailored via physical or covalent adsorption of biological molecules such as heparin, fibronectin, or other ECM components. Surface functionality can also be altered through modifications to promote cell-surface interactions via integrins and subsequent induction of intracellular signaling pathways [62]. Functionalization is a common approach on synthetic polymer scaffolds that lack biological motifs to promote cell attachment and proliferation. Chemical functionalization also represents one of the main advantages of these synthetic designs. Tailored presentation of biological molecules with precise control over concentration and distribution of those agents is achieved, while natural polymers do not yet offer the same degree of control. Chemical functionality of natural polymers can be expanded, to a lesser extent, through non-canonical amino acid technology and enzymatic modification.

Incorporation of electrically conductive materials into aligned nanofibers is a proposed approach for muscle regeneration. It has been demonstrated that myogenesis could be improved by combining topographical cues with electrical cues [62]. In one study, blending conductive polymers such as polyanaline (PANi) into traditionally electrospun polymers improved levels of myogenesis on seeded cells [125].

For cell-cultured meat approaches, surface properties of scaffolds are critical for the success of cell expansion and differentiation if scaffolds are used in the upstream stage of manufacturing. For microcarriers, several commercially available carriers made of synthetic polymers coated with bioactive molecules promote cell attachment and spreading.

8.4 Methodologies for Production of Scaffolds

Various fabrication methods for constructing 3D scaffolds have been proposed for the production of cell-cultured meat. The de novo design and production of scaffolds using naturally derived, synthetic, or composite materials present the advantage of creating multiple configurations and geometries, such as meshes and foams [126]. Alternatively, the potential of decellularized scaffolds, derived from native tissues or organs in the form of scaffolds has been evolved as an alternative approach in tissue regenerative medicine for translating functional organ replacements.

Traditional tissue engineering strategies typically employ a “top-down” approach, in which cells are seeded onto a biodegradable polymeric scaffold and this has also been applied to cell-cultured meat [iii]. Methods for producing scaffolds following this strategy include electrospinning [127], phase-separation [128], freeze-drying [129], and others. There has been a growing ability to introduce structural complexity onto these scaffolds, narrowing the gap between artificial templates and the architecture of native ECM at the nanoscale level (hierarchical architecture formed with nanofibers and nanopores), which provides the initial space for regeneration of new tissue [130].

Traditional tissue engineering strategies employing top-down methods have difficulty recreating intricate but necessary microstructural features. The main limitations are associated with lack of vascularization and limited diffusion properties of these large biomimetic scaffolds. To address these shortcomings, tissue engineering approaches focused on building modular microtissues with repeated functional units facilitating a bottom-up approach were developed [131]. The assembly of building blocks into specific microarchitectures and larger tissue constructs can be done with control over features such as shape and composition of individual blocks. Fabrication of tissue building blocks can be achieved by multiple approaches, including self-assembly, rapid prototyping, generation of single or multi-stacked cell sheets, and direct printing of cells.

Table 3 summarizes methods for top-down and bottom-up methods to produce scaffolds for cell culture and Figure 3 shows some examples of scaffolds produced using these approaches.

Table 3. Scaffold top-down and bottom-up fabrication techniques and their applicability to cell-cultured meat manufacturing

	Method	Principle	Advantages	Disadvantages
TOP-DOWN	**Freeze-drying** [132]	● Based upon the principle of sublimation ● Polymer is first dissolved in a solvent to form a solution of desired concentration. The solution is frozen, and solvent is removed by lyophilization under high vacuum, resulting in a porous structure	● Scaffolds with high level of porosity and interconnectivity ● Common in the food industry as means of preserving nutrition, flavor, color, appearance, and texture	● Long processing time ● Small pore size ● Irregular porosity
	Solvent casting [133]	● Polymer is dissolved in an organic solvent ● Typically, this technique is coupled with particle leaching for generation of porosity ● The scaffold is created by evaporation of the solvent	● Simple, inexpensive, and widely used technique ● Uniform pore size	● Time-consuming ● Requires organic solvents
	Gas foaming [134, 135]	● Polymeric foams are made of a mixed solid and gas phase (such as high-pressure CO_2) ● The gas that is used in the foaming process is termed blowing agent and can be either chemical or physical ● Supercritical CO_2-water emulsion templating methods involving a co-solvent have been developed to improve CO_2 diffusion into a hydrophilic polymer	● Highly porous scaffolds with interconnected pores ● No organic solvents ● Processing of water-soluble polymers and edible materials ● Technique explored in the food industry	● Application of surfactants and highly viscous solutions with potential impact on biocompatibility ● Gas foaming technique using high pressure CO_2 is not efficient for the creation of porosity in crystalline and hydrophilic polymers ● Processing times can be long
	Phase separation [136, 137]	● Can be induced thermally or by a non-solvent and has been utilized to fabricate scaffolds by demixing a homogeneous polymeric solution ● A widely used method is the thermally induced phase separation (TIPS)	● Morphology of scaffolds can be adjusted by the polymer concentration, solvent type, and cooling rate ● Simple technique and it allows mass production	● Time-consuming ● It involves organic solvents, and it is not applicable for all polymers (e.g, thermoplastics) ● Provides a limited range of pore sizes
	Electrospinning [138]	● Electrostatic production of nanofibers, during which electric power is used to make polymer fibers with diameters ranging from 2 nm to several micrometers from polymer solutions or melts ● Used to fabricate fibrous scaffolds containing nano- to micron-sized fibers	● Architectural similarities to the ECM and high surface area-to-volume ratios ● Favors alignment of muscle cells and fibers	● Small pore size and high fiber packing densities lead to poor cell infiltration ● Limited scaffold thickness when not used in combination with other processing techniques ● High processing times ● Usage of organic solvents
BOTTOM-UP	**Self-assembly** [139]	● Autonomous organization of components into 3D structures ● Induced by noncovalent bonds or weak covalent interactions, including electrostatic, van der Waals, hydrophobic interactions, ionic, hydrogen, and coordination bonds ● Self-assembly of peptides represents the most comprehensively studied of	● Carried out in aqueous salt solutions or physiological medias ● Uses naturally occurring molecules such as peptides and proteins ● Low concentrations of materials are generally required to form biomaterials	● Scalability is yet to be determined ● Likely will require combination of self-assembly methods with other scaffold fabrication techniques

		the various classes of self-assembled biomaterials		
	Rapid prototyping [140], [141], [142], [143], [144], [145], [146], [147]	● Techniques used to generate intricate scaffold structures with precise architecture (size, shape, interconnectivity, branching, geometry, and orientation) directly from computer-aided design data inspired from imaging technologies such as computed tomography (CT) and magnetic resonance imaging (MRI) ● Includes techniques such as stereolithography, selective laser sintering, solvent-based extrusion free forming, 3D printing and fused deposition modelling that differ on the layering methods (liquid-based, solid-based, and power-based) ● Bioprinting processes are classified under three major modalities: extrusion-based bioprinting (EBB), droplet-based bioprinting (DBB), and laser-based bioprinting (LBB)	● 3D bioprinting produces scaffolds with well-defined architectures, with or without cells ● High speed of printing with the capability of supporting high cell viability ● Microextrusion bioprinters can successfully print high viscosity bioinks such as complex polymers, cells, and clay-based substrates ● Microextrusion enables to print very high cell densities for tissue formation ● Extrusion technology is currently used to produce fibrous plant-based meats at an industrial scale	● Limited printability of polymers for hydrogel formation ● Bioprinting of scale-up tissues at relevant dimensions is still a major roadblock ● Major limitation from microextrusion bioprinting is the distortion of cells and loss of cellular viability that results from the pressure used to expel the bioink
	Layer by Layer (LbL) [148]	● Sequential adsorption of complementary molecules on a substrate surface, driven by multiple interactions involving electrostatic and/or non-electrostatic interactions ● Deposition and wash steps are repeated to achieve the desired number and thickness of deposition layers ● Control of concentration, ionic strength and pH of the solutions enables adjustments on the composition, thickness, and topography of the multi-stacked layers ● Several deposition techniques have been proposed to develop LbL scaffolds, being divided in five categories: i) immersion; ii) spin; iii) spray; iv) electromagnetic driven; v) fluidic assembly	● Mild environments provided for cell interaction ● Hierarchical features such as cell gradients and layers of different cell types can be achieved by considering appropriate mixtures of cells and polymers ● Inexpensive method to improve surface functionality of scaffolds, enabling the entrapment of bioactive molecules supportive of cell culture	● Free-standing multilayered membranes lack the thickness and mechanical properties to be used as a scaffold for cell-cultured meat approaches ● Slow and long process to obtain thick scaffolds
	Cell Sheets [149]	● Temperature-responsive polymers are grafted onto the dishes, allowing cells to attach and proliferate typically at 37°C ● The cells spontaneously detach when the temperature is reduced without the needs for proteolytic enzymes. The confluent cells are harvested as single, contiguous cell sheets with	● Similar advantages as described for LbL approaches	● Difficulty in handling the sheets due to its fragile mechanical properties ● Effective methods for transfer and stacking of cell sheets are needed to move cell sheet technology into cell-cultured meat approaches ● Combinations of polymeric membranes with cell sheets can improve the robustness and thickness of final construct

		intact cell-cell junctions and deposited ECM ● The layer-by-layer stacking of detachable cell sheets generates thicker three-dimensional tissues		

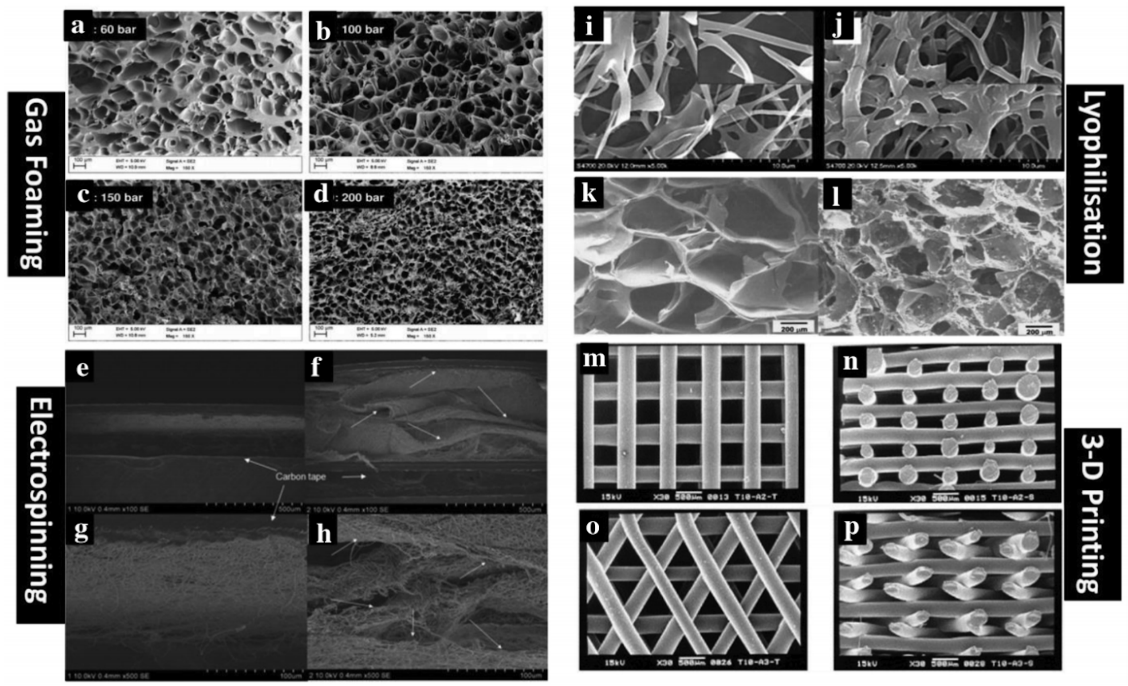

Figure 3. Fabrication methods of porous scaffolds by top-down and bottom-up approaches. Images (a-d) are Scanning Electron Microscopy (SEM) images of a scaffold fabricated with gas foaming technique. Images are taken along the foaming direction and foam specimens prepared at pressures: (a) 60; (b) 100; (c) 150; (d) 200 bar. Reproduced with permission [150]. All other conditions held constant T=40 °C, ST=30 min, and VT-12 min. Images (e) through (h) show SEM images of an electrospun mat. Images (e) and (g) show the polycaprolactone sheet, whereas (f) and (h) show a sodium borohydride treated polycaprolactone electrospun sheet to yield a 3D scaffold. Reproduced with permission [151]. Images (i) through (l) show Scanning Electron Microscopy images of scaffolds fabricated by freeze-drying (lyophilization). Hyaluronic acid (i) before and (j) after crosslinking. Reproduced with permission [152]. Gelatin scaffolds (l) with and (k) without hydroxyapatite nanoparticles [153]. Images of (m) and (p) show SEM images of 3D printed polycaprolactone scaffolds with different alignment. Images (m) and (o) are the top view of the scaffold and its respective side views are shown in (n) and (p). Reproduced with permission [154].

Conventional scaffold fabrication methods allow for some degree of control in scaffold geometry, pore size and interconnectivity [4]. Nevertheless, the ability to match the hierarchical organization and complexity of natural tissues remains a challenge. One alternative approach that narrows the gap between scaffolds and organs/tissues is the use of decellularized ECMs [126].

Decellularization removes cellular material from a tissue or organ leaving behind an acellular scaffold consisting of ECM and an intact vascular network which leads to an enhanced angiogenic capacity of the substrate. The composition of a decellularized matrix depends on the tissue from which it was derived and on the decellularization protocol [155]. This decellularization process involves physicochemical agents, enzymes, detergents, or combinations of these [156]. There are some commercialized decellularized scaffolds that have received FDA approval for use in humans, including: decellularized ECMs from porcine small intestine submucosa (SIS); human, porcine, and bovine dermis; porcine urinary bladder; and different species of pericardium and porcine heart valves [157]. ECM-derived materials have also been proposed for applications in bioprinting methods of scaffold production.

While ECM-derived scaffolds are thought to contain all the proteins and growth factors necessary to direct tissue regeneration, decellularization can significantly affect the protein and growth factor content within the scaffold [97]. Once decellularization is complete, these matrices can be perfused with the cells of interest, creating a construct for tissue engineering approaches [159]. Hydrogels derived from decellularized skeletal muscle matrix have been shown to enhance the proliferation of skeletal myoblasts when injected into an ischemic rat limb [160]. When compared to muscle-derived matrix, small intestinal submucosa-ECM can lead to contractile sheets of skeletal muscle with comparable contractile force [161]. For *in vitro* muscle tissue engineering, rat myoblasts have also been preconditioned on a porcine bladder acellular matrix in a bioreactor and then implanted in nude mice at a muscle defect to restore muscular tissue [162].

Decellularized ECMs from muscle or fat tissues offer, in theory, flavor, texture and tenderness features that are closer to the ones typically found in conventional meat. However, safety of these scaffolds would have to be closely inspected for any residual harsh decellularization agents which are harmful for human consumption. In addition, despite their tremendous potential, decellularized mammalian tissues are short in supply, expensive when available, and could represent a contradictory approach for producing cell-cultured meat. With the current technology, decellularized ECMs still require conventional mass animal slaughtering processes. Nevertheless, there is still potential for this method by exploiting cross-kingdom contributions. Specifically, plants and animals exploit fundamentally different approaches to transporting fluids, chemicals, and macromolecules, yet there are similarities in their vascular network structures [163].

Due to architectural similarities and availability, plant-based materials can then be used as templates for decellularization. Plant cell walls are composed of a variety of polysaccharides, namely cellulose, pectin, and hemicellulose. Cellulose has been studied for clinical applications, particularly wound healing with positive biocompatibility. For instance, cellulosic scaffolds derived from apple slices have shown ability to be seeded and colonized by mammalian cells [164, 165]. Other studies have also shown that human mesenchymal stem cells and human pluripotent stem cell-derived cardiomyocytes adhered to the outer surfaces of plant-based scaffolds, demonstrating functionality [163]. Challenges regarding the toxicity of decellularization agents will still apply but a plant-based approach expands the range of options for ECM sources.

8.4.1 Crosslinking Methods for Scaffold Preparation

Crosslinking is the creation of a bond that links one polymer chain to another. Crosslinking scaffolds has an impact on architecture, porosity, degradability, biocompatibility, and cellular performance. Thus, it is a critical parameter for the success of a tissue engineering approach [166].

The main risk in scaffold crosslinking is the reagent used; some of the chemical crosslinkers commonly used for implantable scaffolds might have established toxic limits for oral exposure. For instance, glutaraldehyde is a crosslinker for scaffold structures that is also allowed as a preservative in cosmetics in Europe at concentrations up to 0.1%. Glutaraldehyde is also commonly used in a 2% concentration for cold sterilization of surgical and dental equipment. It presents an oral lethal dose in humans of 0.5-5 g kg^{-1} [167]. Therefore, the selection of food-safe crosslinking mechanisms for scaffold production should be the main priority when designing new formulations.

Crosslinking techniques have been categorized into three groups: physical, enzymatic, and chemical methods. Physical crosslinking is typically accomplished by ionic, hydrophobic and hydrogen bonding interactions, stereo-complexation, self-assembly of amphiphilic peptides or polymers into micellar structures [168]. Ionic crosslinking involves the association of polymer chains by non-covalent interactions. Ions of opposite charges electrostatically attract each other to give rise to a crosslinked polymeric network. The network can also be disrupted by using specific chelators to remove the multivalent ions from the polymeric network to reverse the gelation process [169].

Chemically crosslinked hydrogels, characterized by covalent bonding between polymer chains, often provide better mechanical stability compared to physically crosslinked ones. Chemical crosslinking can involve exogenous crosslinking agents or formation of reactive species by photoirradiation [170]. Chemical crosslinkers include glutaraldehyde [171], carbodiimide agents [172], epoxy compounds [173], and other natural crosslinking molecules such as genipin [174] and citric acid [175]. Chemically crosslinked scaffolds are more robust and offer improved mechanical strength in comparison to physically crosslinked structures; however, the range of available non-toxic and edible compounds and their working concentrations is significantly restricted for cell-cultured meat applications.

Enzymatically activated or enzymatically crosslinked scaffolds can be both deliberately assembled or disassembled using enzymatic actions. This requires enzymatic engagement with materials bearing enzyme-specific substrates accessible to catalytic sites of enzymes. Enzymatically controlled materials can be designed to work with natural enzymes in tissue sites or exploited in situ in bioreactors [176]. In the field of tissue engineering, there has been a growing interest in polymers which can be effectively crosslinked without the use of any exogenous agents, thus minimizing the risk of chemical contamination or chemically induced toxicity. This is also relevant for cell-cultured meat approaches, especially if the scaffold is a part of the final product.

8.5 Increasing Complexity of Scaffold Designs

Scaffold preparation techniques have been under continuous development. More intricate designs reflecting the complexity of native ECM regarding architecture, topography, and biochemical composition are being considered due to the described impact on successful tissue regeneration approaches. Examples of topographic cues that influence cell morphology and organization include microscale topographical features presented by micropatterned substrates; aligned polymeric fibrous matrices mimicking native ECM proteins; and 3D scaffolds with anisotropic porosity [2]. For example, advances in electrospinning setups have expanded upon this initial potential to generate scaffolds with aligned fibers, patterned architecture, enhanced porosity, and gradients in composition or functional moieties [138].

The potential for the application of hierarchical designs in tissue development has been extensively demonstrated in muscle regeneration and myogenic differentiation studies. Muscle tissue engineering scaffolds require a unidirectional structure to pre-align muscle cells, guide cell fusion, and promote the formation of long and thick myotubes. Importantly, the design of anisotropic muscle tissue engineering scaffolds has been informed by research utilizing 2D micropatterned substrates that study the effects of topography and matrix elasticity on myoblast alignment and differentiation *in vitro* [2].

Scaffolds used to support skeletal muscle regeneration should accommodate and promote formation of densely packed, highly aligned myofibers throughout a large tissue volume [177]. Recent studies suggest that anisotropic materials may be preferred for developing muscle tissue engineering constructs as they present morphology and function more closely resembling the native tissue [178]. Aligned porous 3D scaffolds are popular constructs for muscle tissue engineering, where the anisotropic architectures promote myogenic differentiation, formation, and alignment of myotubes [179, 180].

Micropatterned substrates have been explored to examine the impact of topographical cues on muscle cellular performance. These microscale topographical cues include grooves/channels, ridges, holes, or posts that can influence myoblast adhesion, polarization, alignment, fusion and/or differentiation into myotubes [181]. Several of these studies sought to understand *in vitro* myogenesis. More recently, micropatterned substrates fabricated from biocompatible materials are utilized to build multi-layered cell-scaffold constructs. Although substantial research has been performed to characterize the response of skeletal myoblasts to engineered directionality, the mechanisms underlying cellular behavior in response to topographical cues remains to be clarified [182].

8.6 Application of Scaffolds for Cell-Cultured Meat Approaches

The cellular agriculture space has seen a significant boom in research and investment after Mark Post publicly unveiled the first cell-cultured beef burger in 2013 [183]. Until then, most of the efforts were scarce and came from a few individuals and research groups that had a vision of disrupting the food system. Despite the significant number of publications of scaffolds for biotechnology applications listed through this chapter, few of them describe their applicability as edible materials targeted for human consumption. It is likely that there will be a huge boost in this field as tissue engineers seek alternative applications for their technology and products. In its essence, this is good news as it opens the door to a quicker and more efficient transfer of technology to the cellular agriculture space. Simultaneously, this shift should be observed with some precaution as most tissue engineering research projects are not effectively directed towards commercial translation at industrial scale. Tissue engineers might be looking for a new "hot topic" for the application of their expertise, without grasping the whole concept of cellular agriculture, food science, sustainability, and safety for human consumption. For this reason, the development of multidisciplinary teams is critical to overcome these derivative challenges.

Scaffolding directs the differentiation of various cell types to encourage an organized pattern rather than randomly interspersed co-cultures of muscle, fat, and connective tissue cells. Several materials that are already used in food products are being explored as edible clean meat scaffolds, and some companies are exploring biotechnology tools to produce polysaccharides and proteins that could be used as bulk polymers for edible scaffold production. Different processing techniques and architectures might also provide added value to the quality of the final meat product. Cells are hierarchically distributed in ECMs, and that organization matters to provide a better sensory experience.

Developments are ongoing with decellularized plant-based scaffolds. Groups are investigating apple-derived cellulose scaffolds for mammalian cell culture [184] as well as leaves as backbone templates for cell culture [163]. Spinach presents a dense network of fine veins that resemble the vasculature found in animal tissues. Alternatively, other approaches using mycelium-based biomaterials at scale (MycoFlex™) are currently under development targeting not only cell-cultured meat approaches but also apparel and beauty. One of the main challenges of using plant-based decellularized scaffolds is encouraging animal cells to perfuse through the cellulose plant walls, leading to inefficient colonization of the scaffold. Another significant challenge is that, despite their natural origin and edibility, these scaffolds have been processed with non-food grade agents that could present for a safety risk for human consumption.

There are several mammalian-derived scaffolds that have been proposed for tissue engineering and regenerative medicine. Polymers such as gelatin, collagen, and hyaluronic acid are very promising and edible, but the origin of these materials will be under intense scrutiny and might not obviate animal slaughter, which is one of the main motivations of cellular agriculture [185]. Still, MacQueen et al (2019) [186] proposed a method of production of microfibrous gelatin scaffolds that support culture of adherent animal muscle cells. Gelatin microfibers were produced using immersion rotary jet spinning, a process that enables fiber formation at higher pace than conventional electrospinning systems and using a wider range of food-safe materials due to its dry-jet nature.

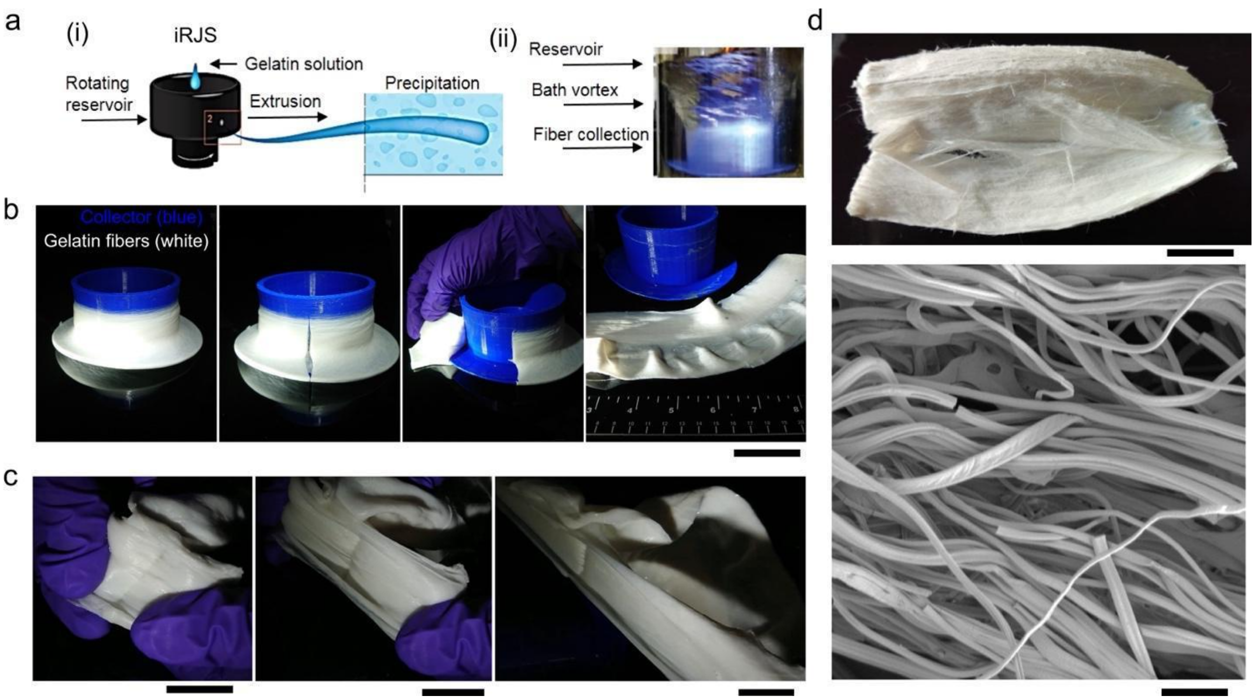

Figure 4. Fibrous gelatin production by immersion rotary jet spinning (iRJS). **a)** Schematic (i) and photo (ii) of iRJS fiber production. The schematic shows a precursor solution fed into an open-top rotating reservoir. The solution is extruded through small orifices in the reservoir wall into a precipitation bath where fibers are collected on a rotating cylindrical collector. **b)** Removal of gelatin fibers from the iRJS collector following a 10-min production run; Scale bar is 10 cm. **c)** Peeling fibrous gelatin; scale bar is 1 cm. **d)** Freeze-dried fibrous gelatin; scale bar is 1 cm, bottom panel shows scanning electron microscope image; scale bar is 50 µm. Reproduced with permission [186].

Non-mammalian polymers extracted from marine sources have been widely used for scaffold production; however, they typically demonstrate less than optimal cellular performance and require functionalization with certain bioactive molecules to stimulate cell attachment and proliferation.

In addition to the challenges for the selection of the bulk material, it is difficult to generate constructs that recapitulate the cellular density of edible tissues. Higher cell densities require more efficient mass transfer mechanisms and more complex culture devices that preserve cellular viability. As an example, in native tissue, cells exist no more than 150 μm away from a flowing blood supply [187]. Most of the large-scale bioreactors available for culture of biopharmaceuticals are optimal for the growth of single cells or small cell clusters and would not fit the hydrodynamic requirements for the growth of thick 3D edible constructs. These limitations open the opportunity for new bioreactor designs and modalities that are more oriented towards the growth of full thickness tissues and organs. Alternatively, companies in the space will have to decide whether that approach is feasible for scale-up or if scaffolds are more suited to be components of a downstream and product development process rather than a culture expansion to achieve the fold growth of cells needed to produce cell-cultured meat on a global scale.

The application of scaffolds either as components of cellular production or as an inclusive part of the final meat product is also a strategic decision by the players in the field. When considering culture systems like microcarriers for the expansion of stem cells in bioreactors, these pre-validated systems can find application in the cell-cultured meat space. They favor the scalability of anchorage-dependent cells, but they bring additional cost and complexity to the bioprocess as these would need to be cleared from the cell harvest if made of a synthetic material. Still, because they are only used as supports in a process, they offer more versatility of materials, functionalities, shapes, and applications, representing a wide potential avenue of exploration in the cellular agriculture space.

Time requirements to produce scaffolds and functional cell-material constructs are also an important factor. The time required to generate full-sized tissues depends on the production of both the scaffold material and the generation of sufficient quantities of cells, as well as the effort required to prepare a mature construct. This time frame must match a feasible timeline for consumption demands of cell-cultured meat. When compared to conventional meat production where animals take months (e.g., chickens) to years (e.g., cows) before slaughtering, cell growth and tissue development *in vitro* are still considerably more time efficient. Nevertheless, cost and production outputs should be comparable to the levels attained with conventional meat for this technology to offer a real alternative to current methods of meat production.

Overall, more time and complexity associated with producing a scaffold translates to higher cost of the product. Several advancements have been made in the areas of rapid or high-throughput manufacturing of therapeutic scaffolds, such as in-line production methods or automated printing. However, the pace of production for tissue-specific primary cells still presents itself as a limitation and should be an area of investment in the cellular agriculture space.

There will need to be an appropriate balance between building a network of materials and cells that provide a sensory experience that is close, if not better, than conventional meat, and the feasibility of producing a food product that is cost-effective. Scaffolds represent a promising element to bring cell-cultured meat to market and to meet the appearance, flavor, and texture expectation from consumers; however, the cell-cultured meat industry should fight the idea of creating a functional piece of flesh with all its intricate complexity that could delay its entry to market by decades, if not forever. The depth in scaffold design and production might be the key to bridge the more expensive cellular content produced in bulk to a cost-friendly thick cut of beef steak.

8.7 Regulatory Considerations

The regulatory considerations for cell-cultured meat are discussed in Chapter 13, including details of the joint agreement between the US Department of Agriculture (USDA) and Food and Drug Administration (FDA) to oversee regulation of cultivated meat and poultry in the United States [iv]. The FDA has overseen the regulatory approval of several scaffolds for human implantation. The same regulatory agency has also covered the manufacturing of human cells using similar technologies to the ones proposed for cell-cultured meat. Therefore, the FDA is well equipped to oversee the approval of scaffold products for application in cell-cultured meat, regardless of whether they are only in contact with cells during manufacturing or if they are a part of the final product.

Within the wider context of cell-cultured meat regulation, it is not anticipated that scaffolds specifically will pose significant regulatory hurdles, given they will likely be made from food-safe, edible or biodegradable materials [iii]. If, however, manufacturers choose to incorporate novel synthetic polymers this may lead to additional regulatory oversight. The stringency of these regulatory considerations will also depend on whether the scaffold is exclusively used in the production process or if it is present in the final product.

8.8 Conclusion

Scaffolds are a necessary component of cell-cultured meat approaches for these products to meet the expectations and demand from investors, regulators, and ultimately consumers. The expectations from scaffold contribution and their specific role are largely associated with the cell culture process, much like a conventional tissue engineering approach. However, this perspective may be skewed and ultimately set the cellular agriculture field up for major obstacles as it is very challenging to produce large quantities of cell-cultured meat products using current methods of scaffold fabrication to attain the functionality and complexity of conventional meat cuts.

It is critical that different approaches are taken for cell-cultured meat than those in the regenerative medicine field. Functionality and complexity are not necessarily synonyms of flavor and tenderness and one of the keys for success of scaffold design targeting cell-cultured meat production is to ask the right questions and formulate achievable hypotheses for the creation of food products.

Ultimately, the creation of structured cell-cultured meat requires the use of scaffolding materials capable of providing similar sensory profiles of tenderness and appearance to conventional meat, while the animal cells, and the ECM they produce, will fulfill the quest for flavor, richness, and juiciness of the final meat product.

Fundamental Questions – Answered

1) **What is the definition of scaffold and is it relevant for the development of cell-cultured meats?**
   Scaffolds for cell culture are supporting structures that provide the appropriate architecture, porosity, and surface chemistry for optimal cell attachment, proliferation, and differentiation. Scaffolds are commonly used as part of tissue engineering and regenerative medicine. They can also be a critical element for the development of cell-cultured meat products to assure the recapitulation of cell growth, extracellular matrix properties, functionality, and sensory experiences.

2) **What type of materials can be used for the development of scaffolding structures?**
   Scaffolds can be produced from a wide array of materials, from polymers to ceramics to composites. Considering cell-cultured meat approaches, if they are designed to be a part of the final product, they must be edible and safe for human consumption. Several studies have described the production of scaffolds for cell culture using naturally occurring and edible materials, such as collagen, hyaluronic acid, and more.

3) **What type of scaffold geometries and architectures can be produced with state-of-the-art technology?**
   Scaffolds can be produced in different shapes and formats, from porous foams and meshes to microparticles and hydrogels. Their design is dependent on the final application and on tissue requirements. Scaffold design can follow three distinct approaches: top-down, bottom-up and decellularization methods. These methodologies have been described for production of scaffolds with varying degrees of control over internal structure, geometry, and topography. More recent approaches have enabled precise control of architecture, enabling a hierarchical organization of materials that resemble natural extracellular matrix.

4) **How scalable is the preparation of scaffolds and is this a cost-effective approach?**
   Scalability is one of the main challenges of scaffold production. Advances in technology have led to production of templates with well-defined geometries that resemble natural extracellular matrices and offer ideal supports for cell culture. Nevertheless, most of these techniques are time-consuming, expensive, and not currently feasible to mass-produce cell-cultured meat. Research in the field must find the right compromise between tissue organization and functionality and feasibility of the process at scale.

5) How can scaffolds be integrated in a cell-cultured meat production process?

Scaffolds can be integrated into the cell-cultured meat production process in two different stages: i) upstream during cell expansion and/or cell differentiation; ii) downstream during product development. The requirements for the application of scaffolds in these two distinct stages are significantly different. If scaffolds are part of the cell expansion and differentiation process, they must ensure appropriate cellular performance and fit many clinical application requirements, despite their targeted food application. If they are only used in a product development stage, they do not necessarily involve a cell culture step and are formulated as an ingredient to provide texture and sensory experience. The cell-material interactions will significantly differ between the two approaches.

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IV

SOCIETY

SECTION 4

Consumers

Market Interest in Cultivated Meat

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Chapter Abstract

Consumer perceptions of cell-cultured meat are mixed. While there is excitement around the potential benefits associated with this technology, from health benefits to the reduction of animal suffering, consumers also raise concerns. This chapter addresses each of the key issues regarding potential consumer perceptions of cell-cultured meat and proposes marketing strategies to increase acceptance. Finally, it draws on macrotrends from similar technologies in other industries to examine how past consumer behavior may inform the future of consumer behavior towards the cell-cultured meat industry.

Keywords

Nudge
Framing
Food neophobia
Meat attachment
Absolute opposition
Appeal to nature fallacy
Social pressure
Market entry

Fundamental Questions

1. What are the most powerful barriers preventing potential consumer acceptance of cell-cultured meat, and why?

2. What marketing, branding, or other social strategies could increase acceptance of cell-cultured meat?

3. How does cultural background influence perceptions of cell-cultured meat?

4. What challenges have been encountered in promoting other technologies that could inform the progress of cell-cultured meat?

5. What, if anything, can surveys of consumer interest in cell-cultured meat reveal about how many people will purchase it once it becomes widely available?

6. Once there are affordable, widely available cell-cultured products that are identical to the animal-based counterparts in appearance, taste, and nutrition, how might that change consumer perceptions?

7. Could consumer acceptance barriers permanently prevent widespread adoption of cell-cultured meat, or just delay it by a few years?

8. Which demographics are most and least likely to quickly adopt cell-cultured products?

Chapter Outline

9.1 Introduction
9.1.1 Rates of Acceptance
9.1.2 Further Engagement

9.2 Differences in Consumer Perceptions
9.2.1 Cultural Differences
9.2.2 Demographic Differences
9.2.3 Psychological Differences

9.3 Key Consumer Perceptions
9.3.1 Environmental Impact
9.3.2 Animal Welfare
9.3.3 Ethical Concerns
9.3.4 Price
9.3.5 Taste
9.3.6 Health and Safety
9.3.7 Naturalness
9.3.8 Normalcy
9.3.9 Disgust responses
9.3.10 Concern for Farmers and Farmed Animals

9.4 Marketing strategies
9.4.1 Terminology
9.4.2 Market Entry

9.5 Lessons From Other Technologies
9.5.1 Profit Versus Ethical Motives
9.5.2 Hype
9.5.3 Positive Versus Negative Framings
9.5.4 Changes in Perception over Time

9.1 Introduction

This chapter explores what is currently known about consumer acceptance of cell-cultured meat. Understanding perceptions is critical to ensure successful market entry once the product has overcome the technological barriers to commercialization. Issues around consumer adoption of certain technologies, such as genetically modified food, demonstrate the importance of understanding acceptance and the potential repercussions if consumer concerns are not adequately addressed. An uprise in anti-science attitudes, such as anti-vaccination and climate change denial, highlights the need to be thoughtful in considering how the public engages with science and technology.

Understanding consumer acceptance will also involve fostering positive attitudes and encouraging adoption once it is available. By using evidence-based messaging and advertising, it may be possible to encourage positive perceptions of cell-cultured meat, increasing its success in the global marketplace.

A note on terminology.
This chapter, along with the rest of the textbook, employs the term “cell-cultured meat”. This chapter reports and discusses a range of experiments and surveys that have been conducted exploring consumer perceptions of cell-cultured meat. These researchers used a range of terms in their experiments, e.g., cultured meat, in vitro meat, clean meat. When referring to direct quotes or findings, this chapter will employ the terms used by the researchers (denoted with quotations), but all of these terms refer to the same type of product. This chapter also cautions readers to be mindful of methodological differences between studies: differences in the way that information is presented (e.g., terminology, amount of information supplied, positive or neutral frame, type of benefits) and the type of questions asked (e.g., engagement, attitudes) can be highly influential on people’s responses and make the direct comparison between studies problematic.

9.1.1 Rates of Acceptance

The first step in understanding consumer acceptance of cell-cultured meat is estimating the proportion of potential consumers who say they are willing to engage with cell-cultured meat. This information helps provide an understanding of the potential for cell-cultured meat to be a competitive product. As time goes on, carefully designed longitudinal studies will be able to track changes in attitudes—especially as cell-cultured meat enters the marketplace—and guide future consumer acceptance research.

As of 2020, at least 30 studies have directly surveyed participants about their willingness to try cell-cultured meat. Though findings are mixed, overall acceptance of cell-cultured meat is quite high, usually above 50%. Four of these simply explained the technology and potential benefits (Table 1).[1–4] Three studies took an initial measure of acceptance, then explored changes in perceptions once further, positively-framed, information was provided (Table 2).[5,6] + (Bekker, Fischer, Tobi & van Trijp, 2016) Two studies offered participants a range of food choice options and examined how many opted to select cell-cultured meat (Table 3).[7,8] Selecting from a range of food choices is a categorically different scenario than standard questions about willingness to try because presenting a range requires someone to choose cell-cultured meat instead of all other options. Finally, several research institutes have conducted surveys. Perceptions in these surveys are generally more negative. Two UK populations reported 18% and 19% of participants that may try cell-cultured meat, two US populations reported 20% and 39.8%, and a Chinese sample reported 26%. (Surveygoo, Yougov) (Pew, Surveygoo)

Other factors of these surveys must also be considered: characteristics of the samples and phrasing of the question. Additionally, survey responses are often very different from real-world behavior, especially with a product that is not yet commercially sold. Thus, these results should be interpreted with caution. For example, one of the studies used a convenience sample of educated consumers (scientists), which limits the generalizability of the results.[7] Nonetheless, considered together, the high numbers of people who say they are willing to at least try cell-cultured meat yields cautiously optimistic results.

Table 1. Studies testing initial acceptance of cell-cultured meat (willingness to try).

	Flycatcher (2013)	**Wilks & Phillips (2017)**	**Anderson & Bryant (2018)**	**Reese (2017)**	
Language used	*Cultured*	*In vitro*	*Clean*	*Unnamed (description only)*	
Definitely yes	23%	31.1%	33.8%	Strongly agree	11%
				Agree	16%
Probably yes	29%	34.2%	32.6%	Somewhat agree	20%
Unsure/indifferent	23%	11.7%	21.6%	No opinion	10%
Probably not	13%	12.6%	6.1%	Somewhat disagree	16%

Definitely no	12%	8.5%	6.0%	Disagree	15%
				Strongly disagree	13%

Table 2. Studies/samples tracking change in acceptance rates (willingness to try) pre- and post-exposure to positive information about the benefits of cell-cultured meat.

	Gasteratos & Sherman (2018)	**Gasteratos & Sherman (2018)**	**Gasteratos & Sherman (2018)**	**Verbeke, Sans & Van Loo (2015)**
Sample population type	**US Students**	**US Adults**	**Australian Adults**	**EU Adults**
Pre-attitude				
Definitely	21%	28%	20%	13.9
Probably	37%	33%	38%	
Unsure	23%	20%	18%	43.9%
Probably not	11%	10%	16%	
Definitely not	8%	8%	7%	42.2%
Post-attitude				
Definitely	39%	43%	25%	38.5%
Probably	34%	20%	36%	
Unsure	14%	13%	24%	27.9%
Probably not	7%	7%	7%	

Definitely not	6%	7%	8%	36.3%

Bekker at al., (2019) also tracked attitude change before and after information provision. However, the authors reported mean statistics, rather than percentage acceptance. As such, this data is not included in Table 2.

Table 3. Preferences for cell-cultured meat relative to other options.

	Hocquette et al. (2015)	**Hocequette et al. (2015)**	**Hocquette et al. (2015)**	**Slade (2018)**	
Sample type	International online convenience sample	French online convenience sample	French in-person convenience sample	Please add	
Eat no meat	8.9%	34.0%	1.4%	Beef burger	69%
Eat less meat	58.7%	41.3%	53.6%	Plant-based meat burger	27%
Eat in vitro meat	7.8%	5.3%	9.2%	Cultured meat burger	13%
Change nothing	24.7%	19.3%	35.8%	No burger	7%

9.1.2 Further Engagement

Willingness to try a novel food does not necessarily result in regular consumption. To better understand the degree of consumer interest in cell-cultured meat, some studies have directly explored further engagement—willingness to eat cell-cultured meat regularly, or as a replacement for conventional meat. Four studies have explicitly asked consumers about further engagement (Table 4).[1–3] +(Bryant, Szejda et al., 2019) Overall, the studies show that fewer people are interested in regular consumption or replacing conventional meat in their diet than in simply trying the product. This is not surprising: consumers might need the opportunity to engage with the product in a tangible way before they are willing to make a stronger commitment, such as willingness to purchase cell-cultured meat regularly. It should also be noted that some of these questions would have been asked of people who had already reported unwillingness to try, thus it is unsurprising that those same participants would be unwilling to engage further.

Two studies have also asked about willingness to engage with cell-cultured meat instead of soy substitutes (Table 5).[2,3] This measure provides an understanding of the potential for cell-cultured meat to act as a meat replacement. Willingness ranges from around 40-60 %, which is slightly lower than the overall general rates of general cell-cultured meat acceptance. This suggests that cell-cultured meat may be appealing for those who are already looking for alternatives to conventional meat.

Table 4. Further acceptance of cell-cultured meat.

	Flycatcher (2013) [Would you like to buy cultured meat more often?][i]	**Wilks & Phillips (2017)** [Would you be willing to eat in vitro meat regularly?]	**Wilks & Phillips (2017)** [Would you be willing to eat in vitro meat as a replacement for farmed meat?][ii][iii]	**Anderson & Bryant (2018)** [Would you be willing to eat clean meat regularly?]	**Anderson & Bryant (2018)** [Would you be willing to eat clean meat as a replacement for conventionally produced meat?]
	24%	6.4%	7.2%	17.5%	17.8%
Yes, probably	47%	26.2%	24.3%	28.4%	35.0%
Indifferent/unsure	25%	30.8%	26.3%	37.7%	30.4%
No, probably not	4%	18.9%	21.1%	8.9%	9.4%
No, definitely not	0%	7.5%	9.1%	7.5%	7.5%

[i] This question was premised with the statement ‘Imagine you have tried cultured meat and you find the flavor, texture and nutritional values the same as traditional meat. Would you like to buy cultured meat more often?

[ii] 1.9% of participants selected 'Not applicable (I do not eat farmed meat)'
[iii] Wilks and Phillips (2017) excluded participants who reported being 'definitely no' when asked if they were willing to try cultured meat (8.5% of participants, as noted in Table 1).

Bryant et al., 2019 also asked similar questions as in Table 4. They reported these statistics individually across the three cultures tested. For the sake of brevity, we did not include these statistics in Table 4.

Table 5. Willingness to eat cell-cultured meat as a replacement for soy substitutes.

How willing would you be to eat clean meat compared to plant-based/soy substitutes?	**Wilks & Phillips (2017)** **All participants**	**Anderson & Bryant (2017)[i]** **Current non-eaters of plant-based substitutes** **(N = 381)**	**Anderson & Bryant (2017)[i]** **Current eaters of plant-based substitutes** **(N = 804)**
Much more	19.3%	24.4%	28.2%
Somewhat more	28.4%	32.3%	34.5%
Neither more nor less	22.1%	28.9%	27.1%
Somewhat less	14.8%	8.4%	4.4%
Much less	5.3%	6.0%	5.8%

[i] 19 participants selected 'Not applicable (I do not eat conventionally produced meat).'

9.2 Differences in Perceptions

Looking closely at the acceptance rates in the previous section, there are some striking differences in rates of acceptance across different surveys (e.g., 23 % vs. 33.8 % of participants definitely willing to try cell-cultured meat, Table 1). This may be attributed to several factors: cultural differences, demographic differences, or psychological differences among participants or methodological differences between the surveys. This is an important topic to explore because it affects which groups will be most likely to try cell-cultured meat, which groups will be averse to cell-cultured meat, what market entry might look like for the cell-cultured meat industry, and how the industry might expand its market share once products are commercially viable.

9.2.1 Cultural Differences

Culture and country of origin are widely acknowledged as having major influences on diet.[9,10] This is particularly evident when we consider meat consumption in different cultures: while eating dog might seem taboo, or disgusting, to those from Western cultures, it is still an accepted practice in some Asian countries today.[11] Similarly, there is evidence of consumption of a range of animals in various cultures across history, such as elephants and flamingos.[12] There also appears to be cultural differences in the acceptance of food technology, as evidenced by research exploring perceptions of genetically modified food.[13]

Culture is likely to have a large impact on perceptions of cell-cultured meat. However, to date, only a small number of studies have directly explored differences in attitudes to cell-cultured meat across cultures.

The largest cross-cultural study found that participants in China and India reported significantly higher likelihood of purchasing cell-cultured meat compared to participants in the US.[14] Within each country, higher purchase intent was predicted by: higher income in India; politically left-wing orientation in the US and India; high meat attachment in China and India; and being female in China. But some factors were predictive of intent to purchase across all three countries: meat consumption (both being an omnivore and eating more meat); higher familiarity with cell-cultured meat; and lower food neophobia (fear of new food). Previous large-scale cell-cultured meat surveys primarily examined attitudes in the US and Europe, so this study provides initial insight into a broader potential cell-cultured meat market. However, the authors note that participants from China and India tended to be more urban, educated, and higher income than the general population. These same demographics have been shown to predict positive attitudes to cell-cultured meat in other studies, so one should be cautious when interpreting this finding.[2,15] The results of this study may reflect a sample bias rather than genuinely higher preference for cell-cultured meat in these countries. On the other hand, these urban, educated, high-income demographics might be the most useful population to survey because they will likely be the first consumers in India and China to have cell-cultured meat available.

Another large-scale survey included participants in an online survey from a range of geographies (North America; China, other Asian countries; and Africa) and compared these to French participants and a third French and English in-person survey.[7] The study found generally low acceptance and that many participants did not see cell-cultured meat as a viable alternative. However, because this survey employed a convenience sampling method and only recruited highly educated participants (students, meat industry workers, or scientists), it is difficult to extrapolate to any target population or to compare with other studies. Finally, as noted in Section 9.1.1, *Rates of*

Acceptance, several polls in China, the US and the UK have reported varying acceptance, ranging from 18-40 %. (Surveygoo, Yougov, Pew, Yougov China)

A small number of other studies have explored cultural differences but are limited from providing direct comparisons of acceptance across cultures. One study explored potential differences between Western and non-Western cultures, but it used qualitative methods such as free-association tasks with Dutch, Chinese, and Ethiopian graduate students and did not explicitly measure acceptance, thus their findings are not reported here.[16] Two qualitative studies have reported findings from European focus groups with participants from Belgium, Portugal, and the UK but do not report cultural differences.[17,18] Finally, one study collected data on cell-cultured meat attitudes between US adults and students and Australian adults. [5] Acceptance generally seemed to increase after further information, however the study did not report testing for statistical differences in acceptance rates between cultures.

Tentatively, it appears that non-Western cultures may be more open to cell-cultured meat than Western and that consumers from the US may be more accepting than European.

9.2.2 Demographic Differences

Like culture, demographic differences tend to be highly predictive of attitudes and behaviors. For example, political orientation is found to predict moral judgements and meat consumption habits.[19,20] In line with this, a number of studies have attempted to map demographic differences in attitudes towards cell-cultured meat. It is difficult to draw strong conclusions from such demographic data, as the methodologies and cultural samples vary widely between studies. Nonetheless, certain links appear somewhat consistent. In particular, several studies have found that liberals are more likely to support cell-cultured meat than conservatives and males are generally found to have more positive views than women, but this pattern was reversed in one Chinese sample.[2,14,15,21] People from urban/educated/higher income backgrounds also tend to be more supportive.[2,14,15] Finally, current meat consumption predicts cell-cultured meat attitudes, but it varies in whether it predicts positive or negative attitudes.[2,6,21]

9.2.3 Psychological Differences

Another recent avenue of research explores how particular psychological traits may relate to cell-cultured meat attitudes. As noted above, lower food neophobia and higher meat attachment have been linked to interest in buying cell-cultured meat.[14,21] One study found evidence that conspiratorial ideation and disgust sensitivity predict absolute opposition to cell-cultured meat (i.e., unconditional proscription or the notion that it should never be allowed under any circumstances).[21,22] Around 30-40% of the sample in this study report absolute opposition to cell-cultured meat. Similarly, one study has found that around 45% of participants who oppose genetically modified food were also absolutely opposed to it.[23] This might indicate similar psychological motivations between those consumers opposed to genetic modification of food and those opposed to culturing meat. However, much more work is needed to understand absolute opposition, such as establishing the defining cut-off for absolute opposition, and the permanence of such perspectives.

9.3 Key Consumer Perceptions

Beyond willingness to try, buy, or regularly consume cell-cultured meat, what do consumers think of it? Do they think it's environmentally friendly, good for animal welfare, healthy, safe, natural, normal, or even disgusting? Understanding these perceptions and their prevalence is an important component in understanding how consumers will react to cell-cultured meat. This section discusses ten key perceptions identified in the literature. Positive perceptions are that cell-cultured meat is environmental, good for animal welfare and ethical. These themes are distal to the consumer, providing benefit to the planet at large but not directly to the individual consumption cell-cultured meat. In contrast, other perceptions involve direct impacts on the consumer: price, taste, and health and safety. People also hold concerns that cell-cultured meat is unnatural, disgusting, not normal and potentially negative for farmers. The research on each perception is summarized at the beginning of each of the following sections.

Considering society's track record of unwillingness to embrace lifestyle changes to address other large-scale issues such as climate change, the proximal nature of the concerns remains a major issue for consumer acceptance of cell-cultured meat. It is critical to address these different types of concerns to encourage engagement and acceptance worldwide.

9.3.1 Environmental Impact

Products labeled "green," "environmentally friendly," or "sustainable" are a growing market. Across several labeling studies, environmental labels are shown to increase willingness to purchase products as long as consumers do not need to make big sacrifices of other elements of product choice, particularly price and taste.[24,25] This suggests that all else being equal, perceptions of a product as sustainable or environmentally friendly tend to be beneficial for consumer engagement. This has been one of the key discussion topics in the history of cell-cultured meat, especially after the 2011 life cycle analysis reported that this process would require 99% less land, 7-45% less energy, 82-96% less water, and produce 78-96% fewer greenhouse gas emissions.[26] These data may help to influence perceptions of cell-cultured meat as an environmental or "clean" meat product.

The perception that cell-cultured meat is “green” is reflected in research findings. In a convenience sample of educated consumers (e.g., other scientists easily accessible to the researchers), around one third believed that cell-cultured meat would significantly contribute to reduce the environmental impacts of livestock.[7] In one US-representative study participants rated cell-cultured meat as “somewhat more” environmentally friendly than conventional meat.[2] In another, participants rated cell-cultured meat 4.91 out of 7 where 7 represents “very ecological” and 5.12 where 7 represents “much more sustainable than traditional meat”.[6] Qualitative data from focus groups and online discussions mirrors this trend, with reducing ecological footprint identified as a key theme in perceptions of cell-cultured meat, as well as reducing waste and greenhouse gas emissions.[18,27] Analyses of media coverage of cell-cultured meat and reader comments on online news articles about the topic also suggest that cell-cultured meat is seen as environmentally friendly and, crucially, more environmentally friendly than conventional meat.[28,29]

Summary: Consumers see cell-cultured meat as good for the environment, but most consumers will likely be unwilling to buy an environmentally friendly food if it is much more expensive or lacks appealing taste.

9.3.2 Animal Welfare

Animal welfare has been a central theme in discussions of cell-cultured meat since early discussions of the idea. Farmed animal welfare has become an increasingly popular media and consumer discussion topic due to undercover investigations exposing animal cruelty in agriculture and activist campaigns for improved welfare standards (e.g., cage-free eggs). These views are also reflected in recent research that shows high levels of concern for farmed animal welfare and negative attitudes towards animal farming and slaughterhouses.[4] With the no-animal-slaughter production method employed in cell-cultured meat, this product has the potential to give consumers the products they want without the animal welfare concerns of conventional meat.

Several studies find evidence that people believe cell-cultured meat production would bring about positive changes for animal welfare. One study found that 45 % of educated consumers believe cell-cultured meat will significantly contribute to reducing the animal welfare problem in meat production.[7] Another found that participants agreed that cell-cultured meat would improve animal welfare conditions.[2] The same study also found that participants disagreed with the statement, “*in vitro* meat will reduce the number of happy animals on earth.” In line with this, two focus group studies identified an association with “reducing animal suffering”, while another found that the process negated animal welfare concerns, as animals are barely if at all involved in the process.[15,18,27] Analyses of media content and reader comments also suggest that people believe cell-cultured meat would improve animal welfare and help to address current industrial animal agriculture practices, which are seen as problematic.[28,29]

Summary: Consumers see cell-cultured meat as good for animal welfare.

9.3.3 Ethical Concerns

The term "ethical" often comes up in cell-cultured meat discussions. This is a vague term that can act as an umbrella for a range of relevant topics such as animal welfare, environment, antibiotic resistance, among others. Studies that ask about ethical concerns explicitly show much more mixed perceptions than on specific ethical topics, though this could depend heavily on the terminology and framing used in existing research. In one study that used the term "*in vitro* meat", participants reported that cell-cultured meat is "somewhat more" ethical than conventional meat and had average responses between "agree" and "neither agree nor disagree" with the statement, "*in vitro* meat is ethical".[2] Another study found that participants rated cultured meat as 4.73 where 7 represents "very ethical."[6] Finally, in a large-scale sample of the Dutch population, 16 % of participants reported being unwilling to purchase cell-cultured meat because they consider it unethical.[1]

Summary: Consumers have mixed views on whether cell-cultured meat is ethical, which makes sense given it is a very broad term that could reflect most of the subjective perceived upsides and downsides of cell-cultured meat.

9.3.4 Price

Several studies have shown that price is a barrier to meat consumption for both plant-based and conventional meat.[30] A recent nationally representative US sample reported that high meat prices were one reason listed by consumers as a motivation to reduce meat consumption.[31] As noted in Section 9.3.1, consumers tend to focus on price and taste over environmental and ethical labels.[24,25]

Most consumers appear unwilling to pay premiums for cell-cultured products, at least given the terminology and framing of existing studies. In one study 75% of participants rated the statement, "The price of cell-cultured meat is not higher than the price of traditional meat," as "important" or "very important."[1] In another, only 1% of participants who were willing to try cell-cultured meat were willing to pay much more, 14.8% somewhat more, and 33.6% neither more nor less.[2] In a third, after receiving basic information about cell-cultured meat, only 13.9% of participants reported being "surely" willing to pay more, with 43.9% reporting "maybe," and 42.2% reporting being "not" willing. After receiving additional information about the benefits of cell-cultured meat, participants were more open to an increased price: Participants selecting "surely" paying more increased to 38.5%, and those reporting "maybe" or "unwilling" to pay more decreased to 27.9% and 36.3% respectively.[6] These findings suggest a need for cell-cultured meat to be price competitive with other meat products available in the market. However, education around the benefits of cell-cultured meat and the transition of cell-cultured meat from a theoretical idea to a commercially available product may impact consumers' willingness to pay a premium.

Summary: Price is one of the most important determinants in everyday food purchases, and only a minority of consumers seem willing to pay more for cell-cultured meat, though consumer preferences have the potential to change once cell-cultured meat is commercially available.

9.3.5 Taste

Similar to price, taste is a top priority for consumers when making food purchasing decisions.[32] Moreover, there are a number of sensory characteristics that are specifically related to positive perceptions of meat: color, leanness, and juiciness.[33] For cell-cultured meat to be accepted by consumers, it might need to meet these characteristics. For now, the lack of commercial availability of cell-cultured meat makes this area particularly challenging to research. Any studies before cell-cultured meat is widely available will ask about anticipated taste perceptions and are limited in estimating how consumers will feel about cell-cultured meat once it is a tangible, testable product.

Unsurprisingly, consumers often express concerns about how cell-cultured meat will taste, and this could drive other concerns about the product that will be mitigated if the products are proven to taste the same as traditional meat. In one study, participants rated cell-cultured meat as somewhat less tasty and somewhat less appealing than conventional meat.[2] In another study, participants rated cell-cultured meat as 3.38 for tastiness, slightly below the midpoint of 4 on a 1 to 7 scale where 7 represents much tastier than conventional meat.[6] Finally, in the large-scale Dutch survey, 36% of participants were not willing to try cell-cultured meat because, "it does not seem tasty"[1].

Summary: Taste is one of the most important determinants in everyday food purchases, but it is very difficult to explore before these products are available in consumer research studies. However, much of the skepticism around cell-cultured meat could be due to preconceived concerns that it will taste worse or different than conventional meat.

9.3.6 Health and Safety

New technologies, and particularly new food technologies, often raise health and safety concerns for consumers. These concerns can escalate to a situation like the current strong opposition to genetically modified food, despite limited evidence of genuine health and safety concerns.[23,34,35,36] A number of studies have revealed consumer uncertainty around the health and safety of cell-cultured meat. In the large-scale Dutch survey, 41% reported that they would not buy cell-cultured meat because it "seems unhealthy."[1] In one online survey, participants rated cell-cultured meat, on average, as "neither more nor less healthy than conventional meat", and in another survey, the participants rated cell-cultured meat as 3.98 for healthy, where 7 is "very healthy" (i.e., around the midpoint of 4 on a 1-7 scale).[2,6]

Safety perceptions are also mixed. In one study, participants rated cell-cultured meat 4.67 for safety, where 7 represents “very safe”.[6] In another, participants reported that they thought cell-cultured meat would have somewhat less risk of zoonosis (transmitting diseases from animals to humans) than conventional meat.[2] Health and safety concerns remain a key barrier to consumer acceptance of cell-cultured meat. Long-term safety research, food safety approval, and clear communication of scientific opinion to consumers will be critical in ameliorating such concerns. In the meantime, education and transparency around the processing and production will likely assist in improving perceptions of the health and safety of cell-cultured meat.

Summary: Overall, health and safety perceptions are mixed. People hold concerns that cell-cultured meat may be unsafe or unhealthy. However, others note safety benefits, like a lower risk of zoonosis. It is not yet possible to understand the specific health and safety concerns (e.g., general healthfulness versus safety concerns about the product) as research is yet to distinguish these.

9.3.7 Naturalness

Naturalness has been referred to as one of the “4 N’s” of meat consumption, the four reasons people tend to give when asked why they eat meat: “natural”, “normal”, “necessary”, and “nice”. When consumers are asked to list three reasons why it is okay to eat meat, these categories cover 83–91% of responses.[37] The concerns of necessary (e.g., “humans need meat to survive”) and nice (e.g., “it tastes good”) are straightforward and less applicable to cell-cultured meat given that cell-cultured meat is molecularly identical to animal-based meat. The concerns of natural and normal, however, epitomize key potential roadblocks for consumer acceptance.

Concerns about naturalness are arguably the most frequently discussed concerns with cell-cultured meat. In one study, consumers reported somewhat agreeing that cell-cultured meat is unnatural, and that it is “much less natural than farmed meat.”[2] Similarly, in another study participants rated the statement, “growing meat in a lab is unnatural,” at 3.89 where 5 represents strongly agree.[6] These concerns also appear to carry over into consumer preferences: in an online survey, participants reported moderate agreement with the statement, “cultured meat is unnatural. I only want natural meat,” and 62% selected genetic engineering as one reason that they would not buy cell-cultured meat. Though for the latter statement, the framing of the question implies that cell-cultured meat is genetically engineered, which might have affected results.[1]

Across two experiments, perceived naturalness was found to account for negative perceptions of cultured lab meat.[38,39] In one study, health risks associated with cell-cultured meat were less acceptable than the same risks associated with conventional meat and this effect was fully accounted for by perceived naturalness of the two products.[38] Finally, a 2019 study found that a number of scales measuring general preferences for natural food were all predictive of negative attitudes to cell-cultured meat. (Michel & Siegrist, 2019) Free-text responses and focus groups also find naturalness themes, including “interfering with nature,” “chemical and therefore unhealthy,” “Frankenfoods”, and “playing God”.[15,17,18]

In addition, three recent experiments that have attempted to overcome naturalness concerns. The first explored how descriptions of either the production process or the product itself influences perceptions of cell-cultured meat. The authors found that highlighting the process increases acceptance of conventional meat. In a second experiment, the authors found that technical descriptions resulted in less positive perceptions of cell-cultured meat than non-technical descriptions.[39]

In the second study, participants were exposed to one of four messages: a control group with positive information about cell-cultured meat (without mention of naturalness); a message that argued “cell-cultured meat is natural”; a message that argued that “conventional meat is unnatural”; and a message that argued that “natural is not always good and unnatural is not always bad.”[3] Neither the “cell-cultured meat is natural” nor the “natural isn’t always good” appeals were effective, but the “conventional meat is unnatural” message appeared to have some influence on perceptions. Participants in this condition were willing to pay significantly more for cell-cultured fish, though not cell-cultured chicken or beef. They were also more likely to perceive cell-cultured meat as safe, healthy, environmentally friendly, and as similar in taste to conventional meat than participants in the “natural isn’t always good” condition, but not to the other two conditions. Finally, participants in the “conventional meat is unnatural” condition reported more positive attitudes to consuming cell-cultured meat than those in the “natural isn’t always good” or “cell-cultured meat is natural” conditions, but not compared to control.

In a third study, participants were exposed to one of four different messages: a control group with no reference to clean meat, a descriptive norm message that many consumers are excited and eager to try clean meat once it becomes available, a message that argued natural is not always good and unnatural is not always bad, and a message about how cell-cultured meat is similar to other unnatural foods that are already accepted (e.g. selectively bred fruits and vegetables, cultured dairy products). Half of the participants in all conditions also received anti-cell-cultured meat social information (quotes from previous survey respondents).[40] This study also included a survey 10 weeks after the treatment. Overall, all three treatments improved consumer perceptions immediately after the treatment, but only the “other foods are unnatural too” message was able to successfully offset the negative social information at 10 weeks.

Other research suggests naturalness concerns with cell-cultured meat might not be so important to consumers. In focus group research, some references were made to the unnaturalness of current farming methods and that some unnatural things are accepted.[17,18,29] In another survey, researchers found no relationship between an individual's general preference for natural things (not in the specific context of cell-cultured meat) and attitudes to cell-cultured meat.[21] As such, while perceptions of cell-cultured meat as unnatural are certainly a potentially major barrier to consumer acceptance of the product, a more nuanced exploration of how our preferences for natural things might influence our perceptions of cell-cultured meat is needed.

Summary: Consumers tend to believe cell-cultured meat is unnatural, and researchers have begun testing strategies to overcome this concern, with evidence that claims about the unnaturalness of other foods (and meat production) may be somewhat effective. There is also some evidence that naturalness concerns are less important than other factors in negative consumer reactions to cell-cultured meat.

9.3.8 Normalcy

Studies on a variety of behaviors and institutions have shown the influence of social norms on individual and group behavior. For example, an experiment on household electricity usage found that telling people how their usage compared to their neighbors (a happy face for below average and a sad face for above average households) significantly reduced usage.[41] If hotels want their guests to reuse their towels, telling them to, "join your fellow guests in helping to save the environment," had more of an effect than, "help save the environment," and the effect was largest when the researchers told guests that most guests in their own room (rather than the hotel as a whole) reuse their towels, which suggests people are more influenced by the behavior of people more similar to them.[42]

This could also apply to the consumer acceptance of cell-cultured meat. Until cell-cultured meat is commercially available and popularized, the normal option will be conventional meat. This could make initial adoption slow. However, there could be a tipping point when cell-cultured meat becomes the new normal, which could then speed up adoption. This dynamic would likely first occur in small scales, such as a local neighborhood where one maven—a resident known as a consumer expert or trendsetter—first adopts the product, then a few intrepid community members, and then a local tipping point is reached, and the rest of the neighborhood follows suit. This could be an especially common route among demographics that are particularly receptive to cell-cultured meat messaging, such as younger people and people who lean left-wing politically.

The importance of normalness could also make policy changes very impactful. Introducing policies that support cell-cultured meat could be a powerful method for fostering perceptions of normalness. For example, if the default option on a plane is a cell-cultured burger, consumers might be more likely to eat this rather than go through the hassle of switching to the alternative conventional meat burger. This is an example of a nudge, a small policy change that encourages positive behavior in any domain (e.g., environmentalism, health, food) without reducing consumer choice.

There is limited research on the effect of normalness on cell-cultured meat acceptance. One study varied the hypothetical market share of animal-based, plant-based, and cell-cultured burgers. The researchers found that the higher the market share, the greater consumer preference for that option. It is difficult to extract meaningful conclusions on perceptions of normalcy of cell-cultured meat as it is not commercially available yet, so manipulations that suggest it is commonplace are unlikely to be believed. However, as the industry grows, messaging around cell-cultured meat's normalcy could be one of the most important mechanisms for change.

Summary: Perceptions of normalness and social norms are arguably the most important determinant of individual decision-making. If cell-cultured meat successfully enters the marketplace and gains traction with consumers, perceptions of normalness could improve over time.

9.3.9 Disgust Responses

Disgust is a common response to unfamiliar foods, as noted earlier in the discussion of cultural norms around dog meat consumption. This is also found in response to cell-cultured meat. Two separate focus groups revealed initial reactions of disgust upon first exposure to the concept of cell-cultured meat, including comments that it is "creepy and unappealing" and that it is "unnatural."[15,18,27]

Quantitative studies also identify disgust sentiments. In one study, participants rated cell-cultured meat as closer to disgusting than tasty on a 5-point scale.[1] In another, participants considered cell-cultured meat as 3.71 where 5 is "much less appealing" than conventional meat.[2] In the experiment that explained the process and product of cell-cultured meat, willingness to eat was influenced by perceptions of unnaturalness, but disgust accounted for some of this influence.[38] Thus, disgust seems like an important reason why some consumers respond negatively to cell-cultured meat, even if these consumers explicitly state different reasons.

Further, as noted earlier, one study has linked high general disgust sensitivity—that is, how easily disgusted an individual tends to be—to absolute opposition to cell-cultured meat, suggesting that disgust-sensitive personalities might be predisposed to hold more opposition to cell-cultured meat.[21] Finally, perceptions of disgust are reflected in media coverage and online responses to cell-cultured meat.[28,29]

Summary: Disgust seems like an important driver of perceptions of cell-cultured meat, even when it is not explicitly mentioned by consumers. There is not yet research on how disgust reactions can be mitigated or overcome, though indirect means such as normalization and ethical arguments may be applicable options in reducing this sentiment.

9.3.10 Concern for Farmers and Farmed Animals

Cell-cultured meat will not be brought to market in a vacuum. The emergence of this new product will have a tangible impact on current food production practices, a fact that has not escaped the current meat industry.[43] A small number of studies have shown this as a concern about cell-cultured meat. In one survey, participants tended to somewhat agree with the statement, "the production of in vitro meat will have a negative impact on traditional farmers", and in another, participants tended to somewhat agree with the statement, "farming is an important activity for our society."[2] Finally, focus groups also raised concern for the fate of farmers and the farming industry in the wake of cell-cultured meat.[27] As such, concern for farmers may be a barrier to cell-cultured meat acceptance.

However, a recent US survey found that 42% of participants somewhat agreed, agreed, or strongly agreed with the statement, "I support a ban on slaughterhouses," while 29% somewhat agreed, agreed, or strongly agreed with the statement, "I support a ban on animal farming."[4] These new data suggest that attitudes toward animal farming may be changing, or, these attitudes may depend heavily on terminology and framing.

Finally, some focus group studies also had participants raise concerns about the lives of farmed animals when considering cell-cultured meat, with participants raising questions about what would happen to the animals currently in factory farms if farming practices were replaced by cell-cultured meat.[17] However, these comments are restricted to a small number of people in focus groups and are unlikely to be representative of concerns held by the wider community.

Summary: Consumers have concerns about the effects of cell-cultured meat on jobs in animal agriculture and where farmed animals will go if animal agriculture ends.

9.4 Marketing strategies

Based on these consumer perceptions and other evidence, we can discuss some of the possible marketing strategies for cell-cultured meat and their potential impacts on consumer acceptance. Although limited by (a lack of) commercial availability, some research has begun to directly test marketing strategies. This section discusses two important marketing topics: terminology and market entry.

9.4.1 Terminology

The terminology used to describe cell-cultured meat has been by far the most common topic in cell-cultured meat marketing generally, with a range of discussions and some research attempting to identify the best of many possible terms. Comparisons can be drawn to the plant-based meat industry, which is likely a few years ahead in discussion as plant-based products are already on the shelves. With increased consumer interest and a growing number of products available, vague legal definitions of terms like “milk” and “meat” have resulted in uncertainty among policymakers and food companies. There has been a particularly lively debate on whether nut- and plant-derived milks should be labeled milk, spearheaded by challenges from the dairy industry.[44] More recently, similar challenges have come from the meat industry toward plant- and cell-cultured meat products.[45]

Another question within the terminology (nomenclature) debate is which descriptors to use with such products when they need to be differentiated from the meat currently produced from animals (which is referred to as “conventional meat”). There have been mixed findings on appeal of different terms describing plant-based meat, with some research suggesting that “plant-based” was more appealing than “vegan,” while others find that “feel good” and “vegan” are more appealing than “plant-based.”[46–48] Overall, there tends to be research agreement that positive terms like “feel good” and “field grown” are more appealing to the average consumer than descriptive terms like “plant-based.”[49] However, descriptors do not just need to be appealing, but also informative, and it could mislead consumers to avoid informative terminology.

These concepts are potentially applicable to cell-cultured meat. A few studies have directly explored how different terms for cell-cultured meat may influence consumer perceptions. In one, participants were presented with information about cell-cultured meat described either as “clean,” “cultured,” “animal free,” or “lab grown.” Results showed that the terms “clean meat” and “animal free meat” were seen more positively than “lab grown meat” and for willingness to purchase “clean meat” was more positive than “lab grown meat.”[50]

In another survey, researchers labeled the product as “clean,” “safe,” “pure,” “cultured,” or “meat 2.0.” They found that the terms “clean meat” and “safe meat” were viewed most positively, followed by “pure,” “cultured,” and “meat 2.0” (in order).[51] Another study undertook a quasi-replication of this but focused only on the terms “clean” and “cultured,” finding that “clean” was generally preferred to “cultured.” Because a concern of cell-cultured meat proponents is that using the term “clean” might create backlash, such that it’s seen as putting an unfair positive spin on the product, the researchers in this quasi-replication also tested the resilience of the terms against negative information. The results showed that “clean” still led to more consumers saying they would purchase cell-cultured meat, even when consumers were shown a negative media article. The article for the “clean” group discussed whether “clean meat” was a misleading term while the negative “cultured” article instead had only standard critiques of cell-cultured meat, such as that it was unnatural and might be unhealthy.[52]

Finally, a 2018 study has taken a more systematic approach to naming research. The researchers first asked stakeholders for ideas to generate a large list of potential name options and subsequently narrowed that list down to five options: “clean meat,” “cell-cultured meat,” “craft meat,” “cultured meat” and “slaughter-free meat.” Overall, the terms “slaughter-free,” “craft,” and “clean” were considered the most appealing, in order, “slaughter-free” and “cell-cultured” were considered the most descriptive and “slaughter-free” and “craft” resulted in the highest likelihood of trying and purchasing the product. Notably, many appealing terms were considered non-descriptive and descriptive terms were unappealing, demonstrating the difficulty in striking a balance between informing consumers and retaining product appeal. Only, “slaughter-free” was rated reasonably highly on all measures.[53]

Overall, the evidence suggests that “clean meat” and “slaughter-free” are the most appealing terms commonly used to describe cell-cultured meat, as it highlights the potential benefits for the environment, animals, and human health. The terms “cell-cultured meat,” “cell-cultured meat,” and “cultured meat” seem less appealing but useful for contexts like this textbook when it is more important to focus on the process by which the product is made, rather than its ethical implications. “Cell-cultured meat” provides a convenient contrast with “plant-based meat” and “animal-based meat,” and it is favored by several leading companies in the field. The terms “in vitro,” “synthetic,” and “artificial” are accurate, but much less appealing. And finally, the term “lab-grown,” while popular among journalists because of its evocative nature, seems both negative and misleading because the commercially available products will not be grown in labs. As a point of comparison, Cheerios is not referred to as “lab-made cereal” just because food scientists originally developed the product in a food science laboratory.

9.4.2 Market Entry

The first commercial sales of cell-cultured meat will be a crucial fork in the road for the young industry. First impressions are powerful, and the location of market entry could lead to vastly different perceptions. For example, if people first encounter cell-cultured meat in the pet food aisle as a meat product that is not yet suitable for human consumption, this could cast a long shadow on cell-cultured meat in the public conscience for decades to come.

Contrast this with a market entry of foie gras, a luxury meat product made from the liver of ducks or geese. This is the meat product that has perhaps received the most negative media attention, given it is made by force-feeding the birds to develop fatty livers. Foie gras is typically served at high-end French restaurants. If this is the market entry for cell-cultured meat, the public narrative could be highly positive, given the product is exceptionally high-quality and expensive, something consumers might even see as unattainable for their social class. Also, having a replacement product for something seen as unethical could make it more appealing because of the consensus that it is beneficial to replace the original product. However, the general perception of foie gras depends largely on the culture and preferences of consumers (for more information, please see Part IV, *Cell-cultured Meat in Society*).

9.5 Lessons from Other Technologies

People do not make decisions in isolation. Consumer reactions to cell-cultured meat depend on a host of social forces that are not easily studied with polls or experiments. Sociology and history can yield some insights into these forces, but they come with their own qualifications. For example, smartphone ownership in the U.S. bounded from 35% in May 2011 to 77% in November 2016.[54] Does that mean that the same rapid spread of cell-cultured meat should be expected? Potentially, but there are a host of ways in which these technologies are not comparable.

First, the value proposition of smartphones is to benefit the end consumer. They can browse the web, take high-definition pictures and video, and play complex games all in the palm of their hand. While cell-cultured meat has potential direct benefits for the end user, such as food safety, the aspiration of the technology is mostly to benefit all of society. This might not lead to the same consumer avalanche that results in lines around the block to get the latest version of the iPhone.

Second, while both smartphones and cell-cultured meat require sophisticated technology, the logistics of cell-cultured meat production and distribution are far more daunting. Meat is far cheaper than consumer electronics, and it needs to be distributed to consumers in accessible locations like grocery stores and restaurants on a frequent, perhaps even daily, basis. In contrast, consumer electronics are purchased much less frequently, and once a production facility can make a hundred smartphones a day, it does not take that many more resources to produce thousands and eventually millions to meet demand.[55] In this way, the obstacles to widespread adoption of cell-cultured meat seem much more difficult to overcome.

While lessons from history can be extracted that transcend some of the limitations of polls and experiments, it is important to keep in mind the similarities and differences between technologies and take these research findings with the appropriately sized grains of salt.

9.5.1 Profit Versus Ethical Motives

Some would argue that the best technology to learn from is genetically modified (GM) food. In the 1970s and 1980s, scientists working on GM thought of it as a humanitarian technology that could solve some of the most pressing issues in the food system. The first companies to sell GM foods, Calgene and Zeneca, were “relatively transparent and socially conscious.”[56] Data from 2017 show that only twenty-four countries plant GM crops. The U.S. plants 40% of the world's GM crops, and 99% of the global GM crop consists of four vegetables: soy, corn, cotton, and canola.[57] In the eyes of many, this technology has failed. Why?

The main explanation is the activist backlash to GM foods, especially to large agri-tech corporations like Monsanto. Environmental and health activists framed these products as unnatural, dangerous, and being pushed on consumers to drive profits for those opaque corporations.[56]

This forebodes an existential risk for cell-cultured meat if the public perception drifts into a similar "activists versus corporations" narrative. This could be mitigated by cell-cultured meat scientists, advocates, and companies keeping ethics at the forefront of their discussions. As discussed in Chapters 2-4 of this textbook, there is compelling evidence that cell-cultured meat has the potential to benefit humanity, the environment, and animals. If these ethical motivations are left off the table in cell-cultured meat discussions, the industry could find itself locked in a dangerous public perception. If scientists and companies are not forthcoming and transparent about their motivation and goals, perceptions of the industry as profit-hungry and opaque may develop, with negative impacts on cell-cultured meat acceptance.

9.5.2 Hype

The development of a promising new technology like cell-cultured meat is often accompanied by media attention, hype among Silicon Valley investors, and a veritable gold rush of entrepreneurs and other professionals. This is especially true if the technology purports to solve important social issues, such as cell-cultured meat and biofuels.

Biofuels came with massive ethical potential: they could eliminate the need for fossil fuels, especially the much-discussed gasoline and diesel that powers automobiles. Yet despite raising hundreds of millions of dollars, biofuels have yet to make a dent in fossil fuel production, and funding and support for biofuels research has dropped significantly since 2013. What went wrong?

There are a few leading explanations, mostly related to research management and operations issues within the leading biofuels companies but there is also an issue of hype.[1] One of the companies, Amyris, set a timeline of producing 6-9 million liters of farnesene (a renewable hydrocarbon used in various industries) by 2011, and 40-50 million by 2012.[58] This timeline was known to be unrealistic at the time. It is just one instance where investors and supports to lose interest after ambitious promises were not kept.

Society might currently reside in a technological winter in the biofuels industry with too much disappointment due to the recent bubble that popped for the industry to gain momentum. It might be years or even decades before new biofuel research is able to gather steam. This is analogous to “AI winters,” periods when the field of artificial intelligence research lost momentum and slowed down for years at a time during the 20th century.[59]

Cell-cultured meat could face its own bubbles and winters due to hype. The field has already seen one company fail to deliver on a promise to have cell-cultured meat available to consumers by the end of 2018.[60] If entrepreneurs and advocates set unrealistic timelines, make unsubstantiated claims, or otherwise sensationalize the technology, it could result in decreased support for the technology down the road.

9.5.3 Positive versus Negative Framings

A third risk in the public narrative of cell-cultured meat is a transfixion on the potential downsides of the technology. Consider the example of nuclear power. What comes to mind when thinking of nuclear power plants? Two common associations are radioactive waste and nuclear disasters, such as the partial meltdown at the Three Mile Island nuclear power plant in 1979.

If this textbook were written in French, a reader might instead think of sustainability and energy independence, given that nuclear power is France’s largest source of electricity. Here, the reason for the success of nuclear power in France but not in other countries might have several causes. First, the French government began a push for nuclear power as a reaction to the 1973 oil crisis when oil prices jumped from US $2.90 per barrel to US $11.65 from October 1973 to January 1974. Second, the French government is known for its “centralization and technocracy,” allowing it to roll out a new technology more efficiently than other countries.[61]

Third, and perhaps most relevant for cell-cultured meat, French pro-nuclear advocates controlled the public narrative. Specifically, they focused conversations on the potential upsides of nuclear power like sustainability and energy independence, rather than rebutting the potential downsides like nuclear disasters and radioactive waste. Consider, for example, a report by the US Atomic Energy Commission that, in part, attempted to make the case for nuclear energy by showing that nuclear accidents were unlikely. The public discourse around this report centered on simply the fact that it acknowledged the possibility of nuclear accidents that could cause thousands of deaths, an effect opposite of what the authors intended.[61]

This has been an issue for GM foods as well. Proponents of GM foods spend substantial time explaining the scientific consensus that GM foods are safe for human consumption, yet experimental evidence suggests this approach fails to change minds.[62] This could be partly due to the fact that this narrative focuses the conversation on the negatives, which could increase the saliency and impact of those potential downsides due to something like the mere-exposure effect, the preference people have for things they have already encountered.[63]

By focusing only on potential health, safety, and feasibility problems of cell-cultured meat, the industry runs the risk of tarnishing consumer perception. Emphasizing the environmental, human health, and animal welfare benefits may protect against this.

9.5.4 Changes in Perception Over Time

The technologies examined so far in this chapter have spoken to the effects of different approaches to cell-cultured meat, primarily the strategies of proponents for the technology. But what does this evidence inform about how consumer acceptance of cell-cultured meat will change over time?

First, as discussed in the Section 9.3.8, *Normalcy*, consumer acceptance might increase over time due to people simply following the crowd. We see this with most historical technologies and consumer trends. For example, in fashion, after enough consumers make the switch, it becomes ‘uncool’ to remain with the status quo.

Second, there is much evidence of a somewhat inevitable march of technological progress. This chapter discussed a few technological failures, but they are the exception rather than the rule. Most technologies are more like smartphones, or distillation, fermentation, crop breeding, x-ray machines, canned food, refrigerators, automobiles, radios, pasteurization, microwave ovens, sliced bread, airplanes, credit cards, synthetic insulin, the internet, personal computers, video games, chicken nuggets, in vitro fertilization, video calling, social media, or any of the other widely adopted technologies in modern society. Moreover, consumers were cautious or opposed to many of these technologies in the early stages, yet they are now widely accepted and supported by society generally.[64]

It is important to be mindful of ways in which a new technology can fail to be accepted, but in most cases, failure seems to be a temporary impediment rather than a permanent rejection. If the benefits of cell-cultured meat outweigh the costs, then eventual widespread acceptance seems likely.

Fundamental Questions – Answered

1. **What are the most powerful barriers preventing potential consumer acceptance of cell-cultured meat?**
   The most powerful barriers are likely to be based on beliefs that cell-cultured meat is unnatural, disgusting, or abnormal. Because these beliefs are, to a degree, emotion-based, they will be difficult to address with information alone. This contrasts with health and safety concerns, which may be overcome with further research and consumer education, or price parity and taste, which will continue to improve as the field grows.

2. **What marketing, branding, or other social strategies could increase acceptance of cell-cultured meat?**
   Possible strategies, include:
   a. Terminology: Use terms that focus on the positive features of cell-cultured meat, such as "clean"
   b. Framing: Emphasize the potential benefits of cell-cultured meat, rather than focusing on the potential issues
   c. Nudges: Change the way choices are presented to consumers in the food service industry, such as making the default meal option cell-cultured meat instead of conventional meat
   d. Market entry: Make the first cell-cultured meat products high-quality, perhaps even experience-based rather than purchased, and limited in availability, so consumers see the products as desirable
   e. Public narrative: Focus on the celebrated public figures, scientists, and NGOs supporting cell-cultured meat for its ethical benefits, rather than on the profit-oriented companies
   f. Hype: Avoid a situation in which consumers and stakeholders expect cell-cultured meat to be commercialized or widely adopted unrealistically soon

3. **How does cultural background influence perceptions of cell-cultured meat?**
   While research is still limited, it appears that people from non-Western cultures, such as China and India may be more open to cell-cultured meat than those from Western backgrounds, such as the United States and Europe.

4. **What challenges have been encountered in promoting other technologies that could inform the progress of cell-cultured meat?**
   There have been examples of new technologies that attracted negative consumer perceptions by being overtly profit-driven and hyped, with a focus on defending the

downsides of the technology, rather than promoting the benefits to the consumer. This has resulted in a loss of stakeholder interest and subsequent reduced adoption by the consumer.

5. **What, if anything, can surveys of consumer interest in cell-cultured meat reveal about how many people will purchase it once it becomes available?**
   Consumer surveys of interest can act as an indication for cell-cultured meat acceptance and give a general understanding of how potential consumers perceive cell-cultured meat. However, when drawing these conclusions, it is necessary to be mindful of the discrepancy between people's intentions and future actions. This limits the capacity for such surveys to supply reliable data about future purchasing behavior.

6. **Once there are affordable, widely available cell-cultured products that are identical to the animal-based counterparts in appearance, taste, and nutrition, how might that change consumer perceptions?**
   Once cell-cultured meat is comparable in price and taste it is likely that consumers will be more open to trying it. Removing practical barriers will make it easier for consumers to view cell-cultured meat more positively.

7. **Could consumer acceptance barriers permanently prevent widespread adoption of cell-cultured meat, or just delay it by a few years?**
   If the technological promise of cell-cultured meat fulfils its aims—to be more efficient, sustainable, and ethical than conventional meat without sacrificing the culinary experience—then the human drive towards efficiency and the track record of humanity adopting new technologies are promising precedents, though market forces are also strong determinants of success. The pressing ethical issues surrounding our current food system suggest cell-cultured meat could eventually displace most (if not all) conventional meat production.

8. **Which demographics are most and least likely to quickly adopt cell-cultured products?**
   Current survey data suggests that young people, liberals, and those from educated/urban backgrounds are more likely to be early adopters of cell-cultured meat. Older people, conservatives and those from less educated or rural backgrounds are likely to be slower.

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Youth

The Upcoming Generation of Cultivated Meat Consumers

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Chapter Abstract

As scientific and political hurdles are overcome and cultivated meat becomes a reality, it is imperative to include youth in the conversation, both to ensure that there will be a future market for cultivated meat and to influence the social perception surrounding cellular agriculture. In the future, young people will likely have a variety of choices to make between different meat options and alternatives, cultivated meat included. Education about and introduction of cultivated meat to the younger generation of customers can therefore have a significant influence on product preferences and the success of the industry. It would be favorable to develop a strong customer base among younger demographics so that companies can expand their products to different markets, increase production, and feed a growing world population while safeguarding the environment.

As progress is made towards a world where meat is no longer solely sourced from the slaughter of animals, there should be considerations towards how the advertisement of cultivated meat products and understanding of the technology affects youth. While the science of producing cultivated meat on a large scale is still a work in progress, it is worthwhile to consider how youth will contribute to the field and how education can increase exposure to cultivated meat. This chapter aims to provide information to students looking for resources around entering the industry, educators seeking to teach youth about the importance of cultivated meat, and industry leaders looking for the best ways to market cultivated meat to young people.

A note on terminology
The term "youth" has been employed in this chapter to refer to individuals under the age of 19 years.

Keywords

Eating behaviors
Educational messaging
Peer influences
Social media
Conferences

Fundamental Questions

1. What changes are occurring in meat consumption, and how will cultivated meat figure in this?

2. How will family and social influences affect youths' consumption of cultivated meat?

3. What role does culture play in youths' diets, and how might cultivated meat become infused into different cultural groups?

4. How might youth play a role in cultivated meat becoming accepted into traditions that originally only considered animal-sourced meat?

5. How will youth adapt to cultivated meat?

6. How might youth perceive cultivated meat?

7. What role will food marketing, media, and advertising play in the consumption of cultivated meat by youth?

8. How will youth learn the science and benefits of cellular agriculture?

9. What should students who are interested in working in cellular agriculture consider studying?

Chapter Outline

10.1 Introduction

10.2 How Youth Learn to Consume Meat
- 10.2.1 Familial Influences
- 10.2.2 Peer and Social Influences
- 10.2.3 Cultural Influences

10.3 Educational Messaging
- 10.3.1 Food Marketing
- 10.3.2 Non-profit Organizations and Company Communication
- 10.3.3 Conferences
- 10.3.4 Role of Social Media

10.4 Adaptations to New Technology
- 10.4.1 Gen Z Advisory Board

10.5 College Majors to Consider
- 10.5.1 Science Majors
- 10.5.2 Business Majors
- 10.5.3 Policy Majors
- 10.5.4 University Programs Offering New Courses

10.6 Youth Involvement in the Industry
- 10.6.1 Problems to Solve
- 10.6.2 Automation and Simulation
- 10.6.3 Food Safety
- 10.6.4 Nutrition and Texture of Meat

10.7 Conclusion

10.1 Introduction

Youth will likely be the demographic that is most affected by the emerging technologies and innovations in cellular agriculture. In recent years, there has been an improved focus on ensuring that the educational materials produced in the field are more comprehensible and applicable to younger audiences. Online courses, social media accounts, and websites have made it increasingly easier for youth to get involved, especially if they are interested in the ethical and environmental implications of cultivated meat.[28]

On an international scale, having young changemakers involved in the discussions shaping the future of the industry could give a helpful perspective on the progress that needs to be made for cultivated meat to succeed with future consumers and younger audiences. In this chapter, there is an exploration of meat consumption, eating behavior, possible perceptions of cultivated meat, the importance of social media communication, and how youth all over the world can be the next influencers of cultivated meat.

Youth can be influenced by cultivated meat in a multitude of ways including changes in familial and social behaviors, education through different media, adaptations to new technology, and the pursuit of career opportunities in the field. Section 10.2 explores how youth learn to consume meat and what aspects of their lives can guide them to develop ingrained eating habits, including geographical, cultural, social, and familial pressures; the goal is to examine how youth may gain exposure to cultivated meat and what may influence their choices. Next, educational messaging and advertising's effect on youth is explored, including how companies can take advantage of media platforms to increase interest in cultivated meat products (Section 10.3). Sections 10.4, 10.5, and 10.6 describe advisory boards that have been created to include youth perspectives, post-secondary paths for youth to pursue a career in cultivated meat, and opportunities to solve problems in the industry.

10.2 How Youth Learn to Consume Meat

One of the most common practices around the world is eating meat. The consumption of it goes back to humans' earliest ancestors and it has become a fixed component in many diets. Most meat-eaters start consuming animal products when they are young. Family and social influences play a major role in developing the diets of the young, with eating behaviors originating at home and later being reinforced by peers.

The behavior of eating meat develops in childhood, usually around six to eight months.[12] At this age, and for most of young childhood, children are in a state of solipsism and without concern about where their food comes from. Reports show that young children are often highly unaware of where their food, including meat, originates.[7] This implies that children will often not have any preference towards whether their food is plant-based, traditional, or cultivated meat as long as they like the food. In the future, this could be an opportunity for parents to get young children acclimated to meat alternatives.

Once children get older and start questioning the origin of their food, it is not uncommon for them to express discomfort with meat after discovering it involves the slaughter of animals.[5] This could be a future opportunity for children to start preferring meat alternatives, including cultivated meat, over livestock meat on ethical grounds. Youth are emerging as an important demographic to consider as they will be a major part of driving the increased consumption of cultured meat in the future as massive consumer stakeholders in food and agriculture.

10.2.1 Familial Influences

From a young age, people's eating behaviors are influenced by the home environment, with the adoption of dietary habits in young children starting from parental guidance.[17,18] At young ages, children have limited autonomy and are more dependent on their parents to provide them with their meals, but this relationship changes over time.[19]

As children approach adolescence, they begin to develop newfound independence and can make their own food choices and preferences.[19] At this time, peers tend to exert a greater influence on eating habits and teenagers are more sensitive towards societal pressures to live a certain lifestyle, which could include switching to more sustainable sources of meat.[17] In this period, youth are most prone to extreme changes in their eating habits and the development of food practices that are significantly different from that which their parents introduced them to. This could mean that cultivated meat companies may have the largest chances at success among youth if they choose to market their products to environmentally conscious and animal-loving teenagers as they are more likely to make drastic lifestyle changes for the first time.

Parents and cultural groups can also have a huge influence on the practices that are adopted by youth, both detrimental and beneficial to an individual's health.[36] According to a 2021 study, a parent's attachment to meat and their associated habits play a crucial role in their meal choice and therefore the preferred meat choices of their child.[37]

Children and adolescents living in many western countries consume less plant-based food and more high-fat, animal-based foods such as meat and sausages.[37] For example, in 2006, the majority of German children aged 6 to 11 consumed more than double the amount of meat recommended by the German Nutrition Society. Additionally, 19% of boys aged 12 to 17 years consumed more than triple.[37] There is a clear preference for the consumption of meat in Western countries, which may explain the resistance in the majority of the population to adopting a plant-based lifestyle, despite the environmental and ethical benefits. For children and adolescents who choose to continue eating meat, cultivated meat may provide the option for people to eat the foods that they want more sustainably.

10.2.2 Peer and Social Influences

When young people spend time around their peers at school and in their free time, their diet and exercise behaviors have a big potential to change.[31] This is especially true during adolescence when eating behaviors are influenced by peer impacts and pressures are created from the desire to fit into social norms.[33, 34] Peer influences on food preferences can be demonstrated through face-to-face interactions,[35] and also through social media behavior.[32] Given this information, brands can encourage teenage consumers to purchase their products by using word-of-mouth marketing and also increasing their social media presence.

Furthermore, food preferences tend to form among peers through the process of role modeling, with individuals monitoring their consumption of food in front of others to make sure that it is consistent with the level of health and self-image that they want to portray.[38] This is especially true among individuals in the presence of a dominant role model who may influence what and how much they eat.[38] This modeling of socially acceptable and unacceptable food choices may encourage or discourage the perception of cultivated meat, and influence which brands youth prefer. There may be cases where certain brands of food may be considered socially acceptable because a large proportion of individuals enjoy eating it, while other food brands may be avoided if they are viewed as harmful to one's social position and appearance.[38]

In general, the academic field studying eating behaviors agrees with the notion that peer pressure may influence eating habits in the types, time, and places that youth and adolescents eat their food.[44, 45, 46] Focused marketing efforts for cultivated meat toward youth can ensure that cell-cultured met integration in adolescent diets can be smoother, and that cultivated meat brands may be preferred to traditional meat companies depending on the price, flavor, texture, and taste of the product.

Despite the necessity for effective marketing of cultured meat to youth, the concept of cellular agriculture as a sustainable and animal-friendly meat alternative may be attractive to young people regardless. A study from the Multidisciplinary Digital Publishing Institute that surveyed 812 young adults in the United States between ages 18 and 23 found that 93% of them would purchase sustainable food, citing environmental protection and health characteristics as major influences for doing so.[47] With the benefits of cellular agriculture already being of importance to young consumers, it is likely that with effective marketing and influence, cultured meat will quickly popularize among young individuals in the US and even globally.

10.2.3 Cultural Influences

Culture shapes values, behaviors, and beliefs across the globe. These internalized systems are learned in childhood and often guide the way individuals think, feel, and act throughout their lives.[8] This is especially true when it comes to food. Eating behavior is learned through enculturation, a process by which culture is transmitted from one generation to the next, and food is often an aspect of culture that is deeply rooted.[8]

Culture can influence youth eating behaviors directly and indirectly. Direct influences include family, care providers, or peers. Indirect influence occurs through marketing and the media (e.g., television, internet, movies, advertising).

As discussed in Chapter 11, *Consumer Acceptance*, culture is likely to have a large impact on perceptions of cultivated meat. However, to date, only a small number of studies have directly explored differences in attitudes to cultivated meat across cultures. The studies suggest that cultivated meat may be more easily integrated into some cultures than others. Young people of the world are likely to play a large role in its integration throughout cultures.
See Chapter 11 for further exploration on how specific cultures have responded to the concept of introducing cultivated meat into their diets.

Today more than ever, within almost all societies, intracultural variation and communication often exist. The current younger generations have grown up in a vastly different world than their elders, and they are much more connected at a global scale than any previous generation.[50] This connectivity has bridged cultural gaps not previously possible, and the closure of these gaps allows for the greater spread of new ideas and technologies.[50] Media exposure is increasing and large restaurant chains (e.g., Subway, McDonald's, Starbucks) are expanding worldwide.[51] Much more is shared across diverse cultures including the promotion of common food preferences. It could be implied that cultivated meat could become progressively popular within youth culture through increased exposure on global media platforms and at restaurants potentially featuring it as an option worldwide. In particular, fast-food chains like KFC have already partnered with cell-cultured meat company 3D Bioprinting Solutions, a subsidiary of Vivax Bio, to commit to producing the first 3D-printed chicken nugget, showing the potential for cell-cultured meat products to be featured and advertised by large restaurant chains in the future.[52]

10.3 Educational Messaging

Cultivated meat is just one of the various applications of cellular agriculture, a field of study that is relatively new and not yet incorporated into school systems worldwide. As novel information emerges on this topic and discoveries are made, the question arises: how will youth around the world learn about cultivated meat and the science behind it?

There is a vast difference in what youth are learning today in the classroom as opposed to in the outside world. While cellular agriculture may not yet be developed enough to be incorporated into school curricula, youth are exposed to globalization outside of schools. They are connected to the internet, and there are already many resources in which a young person could learn about cultivated meat.

For youth looking to learn more about the emerging industry, various educational resources are available. Because of increased global digitization, geographical barriers to learning are overcome and youth can be equipped with the knowledge necessary to be a leader in the cellular agriculture space even if they do not have access to the labs or physical innovation centers.[53] Numerous research papers on cellular agriculture exist as of 2021, which summarize the status quo of the cultivated meat industry and break down the complexities that challenge the increased commercialization of the product.[53] If interested, youth have these resources to learn the science behind cultivated meat and to understand the policy barriers that need to be overcome. However, since research papers often use complex academic language, it can take some time for youth to understand the content of the information presented, so there should be other resources available.

A potential comprehensive method of introducing cultivated meat could be the development of online courses. In 2019, an open-access online course by the GFI called “The science behind alternative proteins” was made available to the public and currently has over 9000 enrollments globally.[23] In the future, it is likely that more low-cost or open-access courses will become available not only to teachers but also to middle and high school students.

In the meantime, biology, earth science, and history courses can incorporate aspects of cultivated meat to increase advocacy of the technology and introduce the idea to young people.[18] It is crucial that the narratives surrounding cultivated meat focus not just on educating individuals on the science, but also place it in context and explain its importance to the sustainability of the food system.[54] There may also be the need to provide historical analogies of how certain technologies were once thought unsavory, but are now commonplace, such as the culinary integration of insects and intestines and other international foods that have arrived in the US over time.[55] Education should be focused on reducing the contention surrounding cultivated meat and introducing the benefits of the technology so that youth can be more informed when making choices in the future.[61] Engaging content mediums, such as social media, field trips to cellular agriculture facilities, and demonstrations are visual and comprehensive ways to teach youth about cell structure and growth of cultivated meat production.[61] The impacts of animal agriculture on the environment and the benefits of producing animal-derived products with cellular agriculture should also be emphasized.

School teachers who are willing to learn and teach about cellular agriculture could follow this textbook and contact companies in the field for further information. There have also been books published on the topic of cultivated meat, which could be helpful resources for youth, including Clean Meat by Paul Shapiro and Billion Dollar Burger by Chase Purdy.[24,25]

Regardless of how students learn about cultivated meat, there is immense value in investing in the education of the technology to spark interest and innovation in the field. Youth can add new ideas and perspectives that are important to a business or organization’s success.[56] Educational messaging has immense potential to encourage a new generation of changemakers to get involved in cultivated meat and to normalize consumer behavior of eating meat alternatives.[57]

10.3.1 Food Marketing

We live in a media-saturated environment and are exposed to an ever-increasing amount of advertising and marketing from a wide variety of sources. Food marketing, media, and advertising are forces that will likely impact the future consumption of cultivated meat. So, how might advertising be deployed to increase awareness and sales of cultivated meat with young audiences, and what demographics should be targeted?

Studies have shown that marketing companies target youth heavily. Children and adolescents are highly coveted by marketers, as they are not only potential future customers, but influence purchases made by their caregivers. Food products targeted towards young people often see a greater growth rate than those targeted at the general market.[15]

Food companies often have large marketing budgets, and their advertising impacts the eating behaviors of younger individuals.[62] As highlighted in Section 10.2.3, *Cultural Influences*, media, and advertising play a pivotal role in influencing consumer acceptance, indirectly creating new social norms for food preferences.[29] As cultivated meat becomes commercially viable, it is expected that this trend in marketing will continue, so that as children grow up, cultivated meat will already be a part of their lives through the advertising they experience. However, likely, the advertising tactics used for the first generation of cultivated meat consumers will be different from those used on future generations.[32]

Marketers use a range of strategies to build brand awareness and brand loyalty early in life that is intended to be sustained into adulthood.[9] Sources that potentially target youth include celebrity endorsements, licensing of popular fictional characters, food and beverage advertising, the internet, schools, video games, and books.

According to a study conducted on food marketing in primary and secondary schools in Canada, advertisements, food product displays, fundraising, exclusive marketing agreements, and incentive programs are present in a multitude of locations in schools, with 84% of schools reporting at least one type of food marketing.[29] This ever-present food marketing means youth will have the opportunity to learn about new technologies like cultivated meat through their everyday life encounters. However, owing to the lack of commercial availability, specific marketing strategies for cultivated meat effective at targeting youth are yet unknown. Nevertheless, research to test marketing strategies has started and is explored in Chapter 11, *Consumer Acceptance*.

Given the marketing methods already tested in the field, companies will be able to make more informed decisions when advertising their products to their target audiences. In the future, youth will gain more purchasing power as they grow older and become potential customers of cultivated meat.[60] When this happens, it is almost certain that youth will be targets of large-scale marketing promoting the consumption of cultivated meat.[60] The benefits of cultivated meat products need to be communicated in a way that appeals to all demographics, youth included.

10.3.2 Non-profit Organizations and Company Communication

Communication from non-profit organizations and companies is also an important aspect of how youth will perceive cultivated meat.[63] If there is an emphasis on the benefits of cultivated meat and transparency about limitations, youth will likely develop more trust for cultivated meat and be more likely to engage in the field as a consumer, future worker, or even industry leader.[62]

Companies and non-profits should find ways to communicate with youth in a way that is accessible, honest, and insightful. First impressions in an emerging industry like cellular agriculture are important, and the way that new products are marketed to youth will influence the future commercialization of cultivated meat.[63] Companies should therefore aim their marketing not only at adults but also at young people to ensure that they are also aware of the benefits of cultivated meat (which will influence their parents to also start paying attention to the technology).[9]

10.3.3 Conferences

When looking at the cellular agriculture space, there are many conferences geared towards adult and academic audiences. However, there are rarely any educational events taking place encouraging youth to get involved. This is a huge lost opportunity, as people aged 12-19 can start building interest in cultivated meat. Without this, they may fail to influence the space due to lack of exposure.

Companies and non-profits could run events that simplify concepts of cultivated meat in ways that are understandable to the average teenager. Studies have shown that the longer a person is exposed to a novel idea, the more accepting they are of the technology.[6] If conferences are held targeted at environmentally and ethically conscious youth to educate them on the benefits of cultivated meat, there is a greater chance that the technology will be accepted when it is time to market to them.

In other technologies, such as artificial intelligence (AI) and blockchain, conferences are held specifically geared towards youth. These include panels with experts in the field, which encourages young people to get a greater understanding of the frameworks driving innovation forward and to get involved in these industries. The same could happen with cultivated meat. When youth get older, some will be interested in attending adult-oriented conferences and in learning more about cultivated meat. The industry should prepare to host beneficial conversations with visualizations that appeal to younger demographics and get experts who can speak about the potential impact of cultivated meat on youth.

10.3.4 Role of Social Media

Social media is a popular mode of communication. Youth in the 21st century use social media networking in their day-to-day lives. It is estimated that ninety percent of teens ages 13-17 internationally have used social media at some point.[8] Seventy-five percent report having at least one active social media profile, and 51% visit a social media site at least daily.[8] Youth use social media websites to look up their friends online and communicate with them, chat, share information, videos and photos; they also seek to meet new people through social media, who share common interests and aspirations. Visiting a social networking site has become a habit for most youth.

If companies wish to communicate with youth and increase the visibility of their products, they must meet young people in places where they already are—online. Though the traditional modes of advertising and marketing such as television, print media, and outdoor media can still help spread information, companies may find that they need to use different strategies to reach younger target audiences.[59] As of 2021, using social media is a must if companies wish to promote their products to youth and increase the visibility of the technology.[59]

Certain sites seem to be more effective for reaching youth than others. During a fall 2020 survey, Snapchat was found to be the most important social network for 34 percent of US teens. TikTok was ranked second, with 29 percent of teenagers in the US stating it to be their favorite, ahead of Facebook and Twitter.[8]

Given the importance and prevalence of social media in our increasingly digitized world, companies should develop their social presence among youth. Industry leaders should understand which platforms are the most effective at delivering their message, craft campaigns that fit global trends and speak to global audiences online. Social media can be a great place for companies to interact with younger customers and get people excited about new products via word-of-mouth.[58] As an extension of everyday communication, social media can authentically generate excitement about the cultivated meat industry and increase the visibility of new brands on a global scale.[51]

10.4 Adaptations to New Technology and Customs

As cultured meat proliferates to youth demographics, it is increasingly important that youth are involved in the many aspects of the developing cultured meat market, especially policymaking and consumer acceptance. Generation Z (Gen Z), or individuals born between the years 1997 and 2012, make up around 25% of all foodservice traffic, which not only includes restaurant and grocery store visits, but fast food and deliveries as well. This figure will only grow with the Gen Z population, meaning that insight from Gen Z, the future majority consumers, will be necessary to ensure that cultured meat is integrated effectively, both from a technological and cultural lens.

10.4.1 The Importance of Youth in Categorizing Cultured Meat

Cultivated meat will likely impact halal and kosher designations, and youth may be part of the decisions that shape the future of religious and cultural food traditions. As a trend, many Western countries have increasingly larger markets for halal and kosher food products that comply with Islamic and Orthodox Jewish food laws respectively.[42, 43]

Youth has become more accustomed to religious traditions in these two groups and will be at the forefront of experiencing a shift in cultural acceptance of cultivated meat.

Currently, the debate about whether cultivated meat will be considered halal or kosher remains largely in the discretion of religious or ethnic groups (Islamic and Orthodox Jewish jurists), with factors including the source of original stem cells, the composition of growth media, and the process of cultivation. Cultivated meat products may be considered halal if the original stem cells are taken from an animal using a halal process and no blood such as fetal bovine serum (FBS) is used in the cultivation process.[40, 41] Similarly, cells secured from the ritualistic slaughter of a kosher species should be acceptable, but because specific manufacturing processes are highly proprietary, a decision regarding halal or kosher status will likely be delayed.[39] Since decisions about designations are yet to be taken, youths that choose to work in the cultivated meat industry may have opportunities to influence the outcome.

10.4.2 Gen Z Advisory Board

The passion of young generations for having an honest dialogue is believed to be derived from the situation they have grown up in. They have been exposed to huge amounts of information on the detrimental effects of historically poor decisions, absorbed the gravity of warnings, and became the defining face of #movements that urge for a positive change. Many have realized that they do not want to stand aside and let those warnings become realities. They show a keenness to engage with decision-makers and to take part in achieving solutions that are relevant to them.

Therefore, some cultivated meat companies have started introducing youth voices into their decision-making. In February 2021, Aleph Farms announced the establishment of a Gen Z advisory board, consisting entirely of young people who help shape their vision.[27] Perfect Day also announced their Sustainability Health and Advisory Council (SHAC) in April 2021, which included one high school student who later founded their Gen Z Board, which exclusively included high school teens. Shiok Meats also announced their first youth consultant through their inaugural “Meat the Young Voice” program advisor. By fostering a partnership based on trust and transparency, they focus on empowering these ambitious individuals, listening to their input, and allowing them to pilot decisions that affect their future.

10.5 College Majors to Consider

As with other technological industries, most of the jobs that are available in the development of cultivated meat require a college degree (either bachelor’s, master’s, or a doctorate). This section is a guide to the most useful college majors that youth can take to succeed in the cultivated meat industry.

Based on the current development of the field of cellular agriculture (i.e., mainly laboratory research, not yet product sales), there is a high demand for scientists and engineers. While biologists, chemists, and bioengineers might study how to improve the growth media or scaffolding structure for cells to attach to, mechanical and electrical engineers can design and build industrial-scale fermenters and bioreactors to produce cultivated meat for commercial sale.

Once current cellular agriculture companies start to sell and expand internationally, business and marketing experts will be able to lead this growth phase. Additionally, lawyers and policy specialists can aid firms when agreements are signed (non-disclosure agreements, collaboration, sales allowances) or when determining how these products will be labeled and what regulations will apply from the Food and Drug Administration (FDA) and US Department of Agriculture (USDA) as well as constitutional laws.

10.5.1 Science Majors

Ideally, high school students applying to college will already have some background knowledge about cellular agriculture and will therefore know what major they want to study, or at least the career direction they would like to take within the field. Nevertheless, a few majors are recommended here that are or will be, highly applicable to cellular agriculture, either at academic research institutions or cellular agriculture companies directly.

Chemical, bioengineering, and biochemistry students can take courses and conduct academic research to learn how to create better growth media, bioreactors, and scaffolds. Skills from chemical, civil, and mechanical engineers are needed for the scale-up and production process, which includes building the production plants and commercial-scale bioreactors and designing the control systems that will ensure the maintenance of the ideal conditions that cells need to thrive. Food engineers can also contribute by improving the texture, taste, and cooking instructions for cultivated meat.

The final product is not the only concern of scientists and engineers working with cultivated meat. For cultivated products to be fully sustainable, the whole supply chain must be examined. Thus, scientists and engineers could also consider, for example, if the factory can be run on renewable energy, whether the packaging of the products will be recyclable or biodegradable or needed at all, where the products will be shipped to, and how a cultivated company can reconcile the CO_2 emissions from transportation, for example. For youth to get the information they need to succeed in overcoming technological barriers, undergraduate majors and graduate studies in science—particularly biology and chemistry—can give aspiring engineers the frameworks and ground-based knowledge to guide the future of cultivated meat.

10.5.2 Business Majors

Once a product is created, there needs to be a focus on how to market it to consumers and build a brand that has the best interests of consumers in mind. When it comes to creating a company, it is necessary to motivate the teams of scientists, engineers, and other employees shaping the future of cultivated meat, to get investors to fund future projects, and to communicate the firm's vision with its customers. The cultivated space, therefore, needs business leaders, accountants, financial analysts, and investors to thrive.

By majoring in either business or marketing, students learn how to sell a product to a diverse range of customers. Market research, marketing tools, national and international sales strategies are all useful skills to have when part of the business, sales, or marketing team within a cellular agriculture company.

10.5.3 Policy Majors

When it comes to sales agreements that must be signed, safety approvals by the FDA and USDA, and even the controversial question of whether the term "meat" can be used for cultivated meat, policy experts and lawyers will be in demand.[16] Courses in food and agricultural policy and law might therefore be relevant to someone wanting to pursue work in cellular agriculture.

Statistics, climate science, political science, ecology, and economic majors can provide the knowledge necessary to advise on the laws regulating the distribution of cultivated meat. For example, climate scientists can use mathematical and biological models to understand the interactions involved within communities and ecosystems. Furthermore, ecologists can study the distribution and relationship between organisms and their environment to understand our natural ecosystems and the species they contain. They work in the field and the laboratory to provide advice on sustainability by balancing environmental needs and considering new ideas for land management. These perspectives are imperative in the development of the decisions made for the cultivated meat industry.

It is important to emphasize, however, that as of 2021 cellular agriculture companies are most in need of scientists and engineers, followed by business experts.[1,13] While law and policy specialists may be pivotal to ensuring that cultivated meat companies are allowed to go into large-scale production, many cellular agriculture companies will mainly consist of large R&D, sales, and marketing teams.[3,10] some companies may choose to employ lobbying and policy experts before growing a significant sales staff to ensure that the company's products will be sold in grocery stores and restaurants without many policy hurdles. There will always be opportunities available to people interested in developing the policy and regulation surrounding the cultivated meat space. Young people can therefore play a big role in the way future policies are shaped.

10.5.4 University Programs Offering New Courses

There are a variety of university programs that are available to educate youth about cellular agriculture in a structured academic environment. For example, Tufts University has created an entire course dedicated to cellular agriculture. Other institutions like Harvard, Bath University, Maastricht University, Seoul National University, Purdue, North Carolina State University, and the University of Melbourne are researching cellular agriculture and encouraging more academic research in space.

In the US, other future food activity is being taught at different universities with notable efforts that include UC Berkeley's Alt Meat Lab, and ReThink Meat courses at Stanford. Internationally, Singapore's Nanyang Technological University has created an alternative protein course called "Future Foods—Introduction to Advanced Meat Alternatives." In Israel, The Hebrew University of Jerusalem launched a pilot course titled "Cultivated Meat and Plant-Based Meat." An introduction to cell-based meat is now available for postgraduates at the Federal University of Paraná in Brazil.

Students themselves are perhaps the most powerful changemakers within academic ecosystems, and universities can make resources available to help student activities thrive. With assistance from the Good Food Institute's The Alt Protein Project, groups have been set up at Wageningen in the Netherlands, Stanford, and the University of North Carolina at Chapel Hill in the US, where students can become the largest leaders in the field by advocating for and successfully launching courses at universities around the world. Though universities have not yet launched formal courses, there have been several extracurricular courses that have been developed, such as the CellAg@MIT Course, inspired by Tufts' cellular agriculture course materials. To expand on their cellular agriculture curriculum advocacy efforts, Tufts plans to introduce a 4-course sequence to enable students to earn a formal graduate certificate in Cellular Agriculture in the coming years.

Certain organizations and venture capitalists are also funding the research and development of the scientific field within universities. In April 2021, the U.S. Department of Agriculture (USDA) awarded its first grant investment in cultivated meat, around $10 million USD.[48] Since then, other organizations, such as the National Science Foundation, have funded university-level cellular agriculture projects, many of which have come out of Tufts University.[49] Partnerships between undergraduate, Ph.D. students, postdoctoral researchers, and organizations can be formed to give scientists the funding that they need to afford the resources necessary to innovate.

10.6 Youth Involvement in the Industry

Young people tend to be more adaptable and accepting of new technologies and to be comfortable with change and innovation. They advocate for it and are often the ones that show older generations how to welcome new technologies into their lives. A key characteristic found globally in youth is curiosity; this is why young people are often the most willing to try new things, seek new adventures, and question old dogmas.[26] While older generations frequently benefit from experiential wisdom, this can be at the expense of inflexibility and ideological rigidity.[26]

An adaptation period will likely take place when cultivated meat becomes widely available, and it is expected that the older generations (who have only known and understood one source of obtaining meat) will be slower and less likely to adapt to it than younger generations who have already seen major changes in the types of food available, such as plant-based meat, and have incorporated them into their diets. Impossible Foods, maker of the well-known Impossible Burger, reported that "young people are far more likely to eat plant-based meat than older generations."[6]

During the mass introduction of cultivated meat, older generations may never choose to consume it. However, every generation born after will belong to a world where cultivated meat exists and the normalcy of it will eventually solidify if proven to be safe and sustainable. Youth will be the individuals who are likely to adapt most quickly and regard cultivated meat as a familiar technology.

10.6.1 Problems to Solve

There are a variety of issues that need to be resolved before cultivated meat becomes a reality. A useful tool to explain these, "Pathways into Cell Ag," has been made by Cellular Agriculture Australia.[16] Young people have an opportunity to look at the problems in the field and follow the college majors that will equip them to build solutions to existing technical challenges. Here are brief descriptions of some of the current topics and problems.[16]

Problems	Automation and Simulation	Food Safety	Nutrition and Texture of Meat
Descriptions	Automation at the lab stage with robotics, AI, and machine learning being applied to develop automated experimentation systems, including robotic lab equipment and data programs. These processes will support more robust cellular cultivation as well as create more efficient bioreactors at the larger scale production stage.[16]	New frameworks will have to be developed or existing frameworks modified to account for cellular agriculture products. Cellular agriculture researchers will have to continually engage with food safety regulators to ensure production processes maintain approval and youth can play a big role in the establishment of these new policies.[16]	Researchers need to thoroughly understand and control the elements that provide meat, eggs, and dairy products their desired flavors, aromas, mouthfeels, juiciness, and nutritional attributes.[16] There is a need to develop detailed meat assays covering major biochemical characteristics of meat and other tissue, such as fat.

10.7 Conclusion

Like in many professional settings or academic fields, the mindset of adultism, the mindset that adults are inherently and intellectually superior to adolescents simply because of age, is prevalent. This disbelief in youth, coupled with the fact that cellular agriculture is still an emerging field, is what often results in their lack of representation in the inner circles of cultivated meat development. However, there is a lot of value that can be extracted from engaging young people in upcoming conversations including ensuring that the products that companies create are things that young consumers want, that there will be a future market for cultivated meat, and how to best market to this demographic.

Once youth perspectives are incorporated into the cultivated meat industry, there will be more creativity, opinions, and insight to give policymakers and companies the information necessary to grow the industry. There should be considerations towards how the advertisement of cultivated meat products and education of the technology affects youth. It is also important to think about how youth will contribute to the field and how education can increase exposure to cultivated meat. Youth should be empowered with the resources they need to get involved in the conversation and development of cultivated meat and considered when business leaders and politicians are making decisions for the way cultivated meat is marketed.

Fundamental Questions – Answered

1. **What changes are occurring in meat consumption, and how will cultivated meat figure in this?**
   There is a growing trend in the consumption of free-range poultry, wild-caught fish, and grass-fed beef, especially in North America and Southeast Asia. While beef and poultry are more popular in developed nations. In addition, the popularity of the vegan diet and the consumption of plant-based meat are experiencing marginal increases that will grow over time. According to the Vegetarian Society, a non-profit in the United Kingdom advocating for vegetarianism, animal welfare is the primary concern for people considering eating less meat. Many vegetarians may be open to the idea of consuming cultivated meat, as minimal to no harm comes to any animals in its production. The field of plant-based meat production has rapidly expanded in recent years and cultivated meat could see a similar surge among those avoiding traditional meat.

2. **How will family and social influences affect youths' consumption of cultivated meat?**
   Family and social influences play a major role in developing the diets of young people. Youth eating behaviors originate in the home and are reinforced by their peers. The consumption of cultivated meat by youths may heavily depend on the acceptance of it by their family and social circles.

3. **What role does culture play in youths' diets, and how might cultivated meat become infused into different cultural groups?**
   Eating behavior is influenced by enculturation, a process by which culture is transmitted from one generation to the next. Today's youth however are connected on a global scale at unprecedented levels, and much is becoming shared across diverse cultures, including the promotion of food preferences. Cultivated meat may find its way into different cultural groups as it becomes increasingly popular within youth culture through intracultural variation and intercultural communication.

4. **How might youth play a role in cultivated meat becoming accepted into traditions that originally only considered animal-sourced meat?**
   Youth could act as a bridge between tradition and innovation. Young people have become accustomed to innovation, and their support of cultivated meat could allow for a balance between retaining the more traditional option of meat consumption and integrating technological and societal progress.

5. **How will youth adapt to cultivated meat?**
   Young people appear to be more adaptable to change and innovation than their older cohorts. They have already seen changes in the food available to them, such as with plant-based meat, and are likely to be the ones who support the normalization of cultivated meat should they be accepting of it.

6. **How might youth perceive cultivated meat?**
   Depending on the young person's age and the stage of development of cultivated meat, youths' perception of cultivated meat products could vary. People who grow up with cultivated meat will likely not perceive it much differently than other foods. Those who are growing up during the time that cultivated meat is beginning to be introduced to the market will likely perceive it differently than subsequent generations. Research shows that many children do not fully understand where their food comes from, and it is common for them to be upset when they discover that it comes from the slaughter of animals. Cultivated meat may be perceived more positively by youth who do not appreciate animal-sourced meat.

7. **What role will food marketing, media, and advertising play in the consumption of cultivated meat by youth?**
   Globally, youth are the future market and are likely to be explicitly targeted through food marketing, media, and advertising for the promotion of cultivated meat. Studies show that marketers frequently target youth specifically. While the specific tactics cannot yet be known, there are many ways in which marketing, advertising, and the media could influence cultivated meat consumption.

8. **How will youth learn the science and benefits of cellular agriculture?**
   As of today, there are various research papers published on cellular agriculture and open-access online courses available from organizations such as the Good Food Institute (GFI). Youth will likely learn of cellular agriculture through the media before it becomes incorporated into classroom curricula. In the future, as cellular agriculture is more extensively studied, it will likely enter certain school curricula. Future students may have the opportunity to visit a cultivated meat facility or attend a guest lecture on the subject.

9. **What should students who are interested in working in cellular agriculture consider studying?**
   High-school students considering the field of cellular agriculture have different choices depending on how they wish to be involved. Subjects such as science and engineering, business and marketing, and policy and law are all relevant.

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Regulation

Federal Regulation of Cultivated Meat, Poultry, and Seafood Products in the United States

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Chapter Abstract

This chapter examines the US regulatory prospects for the cultivated meat industry. Topics of discussion include i) the regulatory and legal history of cultivated meat; ii) how the cultivated meat industry fits into the broader food regulatory system; iii) how existing regulatory policies apply to cultivated meat; and iv) outstanding questions regarding cultivated meat regulation.

Keywords

Food and Drug Administration (FDA)
United States Department of Agriculture (USDA)
Regulation
Policy
Legal
Tradition
Innovation

Fundamental Questions

1. What are the major regulatory events that have occurred with respect to cultivated meat?

2. Which agencies will have jurisdiction over cultivated meat?

3. Going forward, what are the key uncertainties with respect to regulation of cultivated meat?

4. Does cultivated meat meet the legal definition for “meat”?

Chapter Outline

11.1 Introduction: From Innovation to Tradition

11.2 The Regulatory System for Food in the US
- 11.2.1 A Brief History of the Establishment of the US Federal Food Regulatory System
- 11.2.2 Foundational Concepts for Evaluating New Technologies in Food Production
  - 11.2.2.1 Risk-based Approach to Food Regulation
  - 11.2.2.2 Product-based Approach to New Technologies in Food Production
- 11.2.3 Regulation of Meat, Poultry, and Seafood in the US

11.3 Timeline of Major Regulatory Milestones for Cultivated Meat

11.4 Future Regulatory Considerations

11.5 Conclusion

11.1 Introduction: From Innovation to Tradition

Agriculture was a highly innovative food technology when it was invented across various civilizations roughly 10,000 years ago.[2] Since its early creation, agriculture has undergone numerous technological innovations, including developments that have optimized farming efficiency and significantly improved the overall quality of agricultural products. According to agricultural economist Jayson Lusk, in 2016:

We now get more than 500 percent more corn and 280 percent more wheat per acre of planted farmland than we did a century ago. Today, in the United States, we produce 156 percent more food than was the case in the late 1940s despite using 26 percent less farmland.[3]

Currently, innovation in food serves a wide range of purposes, including fortifying foods to have healthier nutrient profiles, reducing related environmental impacts, and increasing crop yields. The social impact of using technology in food is highly variable and depends entirely on the specific end that is being pursued. A technologically advanced food system could, in theory, both create and solve some of the major challenges facing our society. Many future innovations may be focused on enabling the food system to feed more people and to sustain a growing human population. Regulatory bodies around the world play a crucial role in this cycle. They provide the legal parameters within which food producers must operate and also set the standard for global acceptance of new food products and processes. This chapter focuses on the US federal regulatory agencies, as they have been at the forefront of helping determine whether and how products made using new and emerging technologies should be lawfully and safely commercialized.

While there are still some unresolved questions regarding the regulatory path to market, significant progress has been made. This chapter discusses key milestones and considerations regarding US regulatory oversight.

11.2 The Regulatory System for Food in the US

11.2.1 A Brief History of the Establishment of the US Federal Food Regulatory System

The US government's historical approach to regulating meat, poultry and seafood offers important context regarding how the government will consider future innovative food products and technologies from a regulatory perspective.

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[1] The authors would like to thank Deepti A. Kulkarni, J.D. and Sarah M. Goldstein, J.D. for their contributions to this chapter.

[2] Pinker, S. (2011). *The Better Angels of our Nature*. New York, NY: Viking.

[3] Lusk, J. (2016). *Unnaturally Delicious*. New York, NY: St. Martin's Press.

With the overarching goal of supporting the US agricultural industry, Congress established the USDA in 1862.[4] Within the USDA, the Division of Chemistry was established to conduct "practical and scientific experiments in agricultural chemistry".[5] After the creation of another USDA division, the Bureau of Animal Industry in 1884, regulatory responsibilities were divided between that bureau, which focused on the regulation of meat, and the Division of Chemistry, which was responsible for the remainder of the food supply.[6]

Throughout the 18th and 19th centuries, various states enacted food adulteration laws.[7] Annual reports issued in connection with early state laws reported adulteration in various types of products, including "formaldehyde and boric acid in milk; maple syrup adulterated with cane sugar; watering of milk; . . . addition of glucose to honey; and so forth".[8] Congress also passed legislation in the late 19th century to prohibit food adulteration with respect to certain products.[9] These efforts gained further traction at that time, when USDA scientists published reports on adulterated foods, and both scientists and legislators called for a law targeting adulteration and substitution.[10] In the following years, various congressional committees documented extensive food adulteration, and the USDA Division of Chemistry conducted significant investigations into adulteration of food and drugs.[11] It was also during this time that Dr. Harvey Wiley, USDA Chief Chemist from 1883 to 1912, assembled his "poison squad" of human subjects, who consumed foods containing substances such as boric acid and formaldehyde as part of an effort to evaluate the safety of various food preservatives.[12]

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[4] An Act to Establish a Department of Agriculture, 12 Stat. 387 (May 15, 1862) ("[T]here is hereby established at the seat of Government of the United States a Department of Agriculture, the general designs and duties of which shall be to acquire and to diffuse among the people of the United States useful information on subjects connected with agriculture in the most general and comprehensive sense of that word, and to procure, propagate, and distribute among the people new and valuable seeds and plants.").

[5] 12 Stat. 682, 691 (1863); *see also* Peter Barton Hutt and Peter Barton Hutt II, A History of Government Regulation of Adulteration and Misbranding of Food, 39 Food Drug Cosm. L.J. 2, 49 (1984) (citing 12 Stat. 682, 691 (1863).

[6] *See* 23 Stat. 31 (1884); *see also* Hutt at 53. The Division of Chemistry was later renamed the Bureau of Chemistry. Hutt at 49 n.386.

[7] *See* Digest of the Pure Food and Drug Laws of the United States and Foreign Countries, Together with Court Decisions Affecting Same, S. Rep. No. 3, 57th Cong., 1st Sess. (1901) (listing state food and drug laws).

[8] F. Leslie Hart, A History of the Adulteration of Food Before 1906, 7 Food Drug Cosm. L.J. 5, 21 (1952).

[9] Id. at 45-47 (discussing laws "to prevent the importation of adulterated and spurious tea" and "to control the manufacture of oleomargarine," as well as those "providing for inspection of meat intended for exportation and prohibiting the importation of any adulterated food," among others).

[10] *See, e.g.,* Annual Report of the Commissioner of Agriculture for the Year 1878, at 128-29 (1879) ("there was no doubt but that the so-called tea was a sophisticated product, intended and well calculated to deceive the ordinary purchaser"); *see also* Hutt at 50.

[11] *See, e.g.*, H.R. Rep. No. 3341, 50th Cong., 1st Sess. (1888); H.R. Rep. No. 970, 51st Cong., 1st Sess. (1890); H.R. Rep. No. 914, 52nd Cong., 1st Sess. (1892); s*ee* USDA, Div. of Chemistry, Foods & Food Adulterants, Parts 1-10, Bull. 13 (1887-1902).

[12] *See* H.W. Wiley, M.D., USDA, Bureau of Chemistry, Influence of Food Preservatives & Artificial Colors on Digestion and Health, Parts I-V, Bull. 84 (1904-1908).

There was widespread interest in the results of Wiley's experiments, which concluded that the proposed food preservatives could be harmful to human health.[13]

Wiley himself advocated for and was involved in drafting the Pure Food and Drugs Act (1906).[14] In fact it had taken more than 100 separate bills to be introduced in Congress starting in 1879 to address the rampant food adulteration during this era. The Pure Food and Drugs Act defined the essential elements of food adulteration and prohibited the manufacture or sale of adulterated or misbranded foods.[15]

Also in 1906, Upton Sinclair published *The Jungle*, a book which documented appallingly unsanitary conditions in the meatpacking industry in the early 20th century.[16] After representatives sent by President Theodore Roosevelt to inspect Chicago stockyards confirmed the "revolting" conditions in Sinclair's account, and President Roosevelt himself concluded that existing laws regarding meat inspection were inadequate, Congress passed a bill requiring federal inspection of slaughterhouse animals and meat in June 1906.[17] The law, later designated as the Federal Meat Inspection Act (FMIA), prohibited the distribution in interstate or foreign commerce of "meat and meat food products which are unsound, unhealthful, unwholesome, or otherwise unfit for human food." This legislation authorized the USDA to conduct ante-mortem and post-mortem examinations of meat, and to condemn adulterated products, in addition to prohibiting the misbranding of meat and other products.[18] In 1967, Congress passed the Wholesome Meat Act, which expanded and modernized the FMIA, but retained the food adulteration provisions as created in 1906.[19] In 1957, Congress passed the Poultry Products Inspection Act (PPIA), ensuring that poultry products were held to similar legal standards as meat, including being subject to continuous inspection and labeling.[20]

As part of a reorganization, the Bureau of Chemistry's regulatory functions were moved to the Food, Drug, and Insecticide Administration in 1927. In 1930, the name of that agency was shortened to the Food and Drug Administration (FDA).[21] In 1938, the Federal Food, Drug, and Cosmetic Act (FDCA) was passed into law.[22] To protect consumers from fraudulent practices in food marketing, the FDCA prohibited economic adulteration and false or misleading labeling. The law also required foods to be labeled with certain information including "a common or usual name" and a statement of

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[13] *See* Hutt at 51-52.

[14] Richard A. Merrill and Jeffrey K. Francer, Organizing Federal Food Safety Regulation, 21 Seton Hall L. Rev. 61, 79 (2000).

[15] Pure Food Act, 34 Stat. 768 (June 20, 1906); Hutt at 52-53.

[16] *See* Hutt at 53-54; U. Sinclair, The Jungle (1906).

[17] *See* H.R. Doc. No. 873, 59th Cong., 1st Sess. (1906); 34 Stat. 669, 674 (1906); 34 Stat. 1256, 1260 (1907).

[18] 34 Stat. at 1260-62.

[19] Poultry Products Inspection Act, Pub. L. 85-172, 71 Stat. 441 (1957).

[20] *See id.* at 62-63.

[21] 44 Stat. 976, 1003 (1927); *see* 44 Stat. 392, 422-23 (1930).

[22] Federal Food, Drug, and Cosmetic Act, 52 Stat. 1040 (1938).

ingredients. This mandate also authorized the FDA to establish standards of identity for foods.[23]

In 1940, the FDA was transferred from the USDA to the Federal Security Agency, which became the Department of Health, Education, and Welfare (HEW) in 1953. HEW was later re-designated as the Department of Health and Human Services (HHS) in 1979.[24] In 1988, the Food and Drug Administration Act officially established the FDA as an agency of the Department of Health and Human Services, where it remains today.[25]

As discussed further below, under the FDCA, FMIA, and PPIA, and certain other statutes, the USDA and FDA share primary responsibility over the regulation of food in the US at the federal level. The USDA's Food Safety and Inspection Service (FSIS) exercises authority over most meat, poultry, and egg products, and the FDA maintains jurisdiction over all other food products, including plant-based foods and seafood other than catfish (due to lobbying from the catfish industry asking for increased federal oversight to protect consumer health, particularly for imported fish).[26] In addition, the FDA regulates the safety of ingredients added to all foods, including plant-based foods, seafood, meat, and poultry.[27]

11.2.2 Foundational Concepts for Evaluating New Technologies in Food Production

11.2.2.1 Risk-Based Approach to Food Regulation

Overall, both the FDA and USDA have embraced a risk-based approach to regulating foods developed using new or emerging technologies. Bioethicist David Resnik defines a risk-based approach as one based on quantitative assessment and classification of risk in addition to estimates of the probability these risks will occur, based on empirical evidence.[28]

In practice, this generally means that there is no presumption that a particular technology, production method, or other food-related activity will cause food to be unsafe, but rather that the regulator and/or food producer will evaluate the hazards associated with the specific processes to assess the level of risk. A risk-based approach is flexible and focuses on identifying potential hazards and then preventing or mitigating them.[29]

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[23] *Id.*; at 1042, 1046-48.

[24] 54 Stat. 1234, 1237 (1940); 67 Stat. 631, 631-32 (1953); 93 Stat. 668, 695 (1979).

[25] Food and Drug Administration Act of 1988, Pub. L. 100-607 § 503, 102 Stat. 3120, 3121 (1988).

[26] See, e.g., 21 USC. §§ 392(b), 601(w)(2); FDA, Investigations Operations Manual 2017, Ex. 3-1.

[27] 21 USC. §§ 348, 601(m)(2)(C), 453(g)(2)(C).

[28] Resnik, David. "Is the precautionary principle unscientific?" Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences. Volume 34, Issue 2. 2003. https://www.sciencedirect.com/science/article/pii/S1369848602000742?via%3Dihub

[29] *See, e.g.*, FDA, Final Rule: Prior Notice of Imported Food Under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, 73 Fed. Reg. 66293, 66311, 66341 (Nov. 7, 2008) (explaining that FDA

For example, the USDA requires meat and poultry slaughter and processing operations that are subject to inspection to develop and implement Hazard Analysis and Critical Control Point (HACCP) plans, which are based on a determination of the food safety hazards likely to occur during the production process.[30] In addition, under the FDA Food Safety Modernization Act (FSMA), producers are required to adopt the Hazard Analysis and Risk-Based Preventive Controls (HARPC). These are similar to the HACCP approach and require facilities to assess hazards that may occur during food production and put in place plans to mitigate such occurrences.[31]

Outside of the US, the European Union (EU) uses the more stringent Precautionary Principle, under which new food products generally are not permitted to enter the market if there is a possibility that they might cause public harm.[32] In contrast, the risk-based approach in the US allows regulatory agencies to evaluate hazards and focus resources on known risks, while enabling innovation, particularly with respect to approving new technologies in emerging industries.

11.2.2.2 Product-Based Approach to New Technologies in Food Production

Generally, the US approach to evaluating new or emerging technologies in food production is based on the characteristics of the finished product, rather than the processes by which the product was produced. For example, the USDA's FSIS has historically evaluated products made using new technologies by comparing them to their conventional counterparts. Through this comparison, it has enacted different requirements such as new standards of food identity and labeling disclosures only when there is a “material difference” in the finished product.[33] A material difference means there is a discrepancy in the "basic nature of the food", the "consequences of use", the "nutritional properties" or presence of allergens that "consumers would not expect to be in food". Similarly, the FDA has also considered whether there is a material difference between a product made using a new technology and its traditional counterpart to

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uses a risk-based approach to assess foods at the border); FDA, Final Rule: Foreign Supplier Verification Programs for Importers of Food for Humans and Animals, 80 Fed. Reg. 74226, 74226 (Nov. 27, 2015) (putting in place a “flexible, risk-based approach” that “focuses on known or reasonably foreseeable food safety hazards, identified and considered through a hazard analysis and evaluation process, rather than all adulteration covered by the adulteration provisions in section 402 of the FD&C Act”); Remarks by Alfred V. Almanza, Deputy Under Secretary for Food Safety, USDA, International Association for Food Protection, St. Louis, Missouri, Aug. 1, 2016 (highlighting USDA’s “risk-based, data-driven approach to prevent foodborne illnesses”); Janell R. Kause, Daniel L. Gallagher, Daniel L. Engeljohn, FSIS, USDA, “Science to Support the Prevention of *Listeria monocytogenes* in Ready-to-Eat Foods,” International Association for Food Protection Conference, Tampa, Florida, July 10, 2017 (noting “[s]ystematic, sequential use of science and risk assessments to guide policies and inspection to prevent listeriosis”).

[30] *See* 9 C.F.R. part 417.

[31] *See* 21 USC. § 350g; 21 C.F.R. part 117.

[32] EUR-Lex. "Glossary of summaries." https://eur-lex.europa.eu/summary/glossary/precautionary_principle.html

[33] *See, e.g.*, 47 Fed. Reg. 28214, 28222-23 (June 29, 1982) (requiring a new standard of identity for mechanically separated meat based on, because of differences from hand-deboned product); 80 Fed. Reg. 28153 (May 18, 2015) (requiring a descriptive designation in labeling of raw or partially cooked mechanically-tenderized beef products, due to an increased pathogen hazard when compared with non-tenderized beef).

evaluate whether to require different labeling or other demands.[34] These regulations all have implications for labeling of cultivated meat.

11.2.3 Regulation of Meat, Poultry, and Seafood in the US

As noted above, the USDA and FDA share federal regulatory oversight for food through the FSIS, which regulates most meat, poultry, and egg products as part of the USDA, while the FDA regulates all other food products, including ingredients added to plant-based foods, meat, poultry, and seafood (other than catfish).

The FMIA and PPIA laws authorize the FSIS to establish and oversee inspection programs to ensure that meat products are not adulterated.[35] These inspections include pre- and post-slaughter examination of livestock animals as well as inspections of processing plant operations. The FSIS enforces a minimum standard for sanitation of slaughterhouses and meat processing plants.[36] The laws also authorize the FSIS to review labels for meats and poultry products prior to release to market and require certain product labeling.[37]

The FDA derives its jurisdiction over seafood products from the FDCA.[38] While seafood processing firms (including those that manufacture, pack, or label seafood products) hold primary responsibility for ensuring the safety of their products and identifying potential hazards, they must operate under a HACCP plan while implementing sanitation control procedures.[39] The FDA verifies compliance by inspecting processing facilities and regulating product labeling.[40]

11.3 Timeline of Major Regulatory Milestones for Cultivated Meat

During the first two years of the cultivated meat industry's existence, as dozens of companies were created across the globe, the USDA and FDA did not make any public statements regarding the new technology. During this time, cultivated meat companies faced significant uncertainty regarding which agency or agencies would oversee cultivated meat production and what a likely path to market would entail. As cultivated meat companies began to demonstrate their market potential, they raised capital from

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[34] *See, e.g.*, FDA, Draft Guidance, Voluntary Labeling Indicating Whether Food Has or Has Not Been Derived From Genetically Engineered Atlantic Salmon 7 (rev. Mar. 2019) (determining that food derived from AquAdvantage salmon, which is produced using genetic engineering, may be labeled as "Atlantic salmon" because its "composition and basic nature…does not significantly differ from its non-GE counterpart"); FDA, Guidance for Industry #179, Use of Animal Clones and Clone Progeny for Human Food and Animal Feed (Jan. 15, 2008) (requiring no additional controls for food derived from cloned animals compared with food derived from their conventionally bred counterparts).

[35] *Id.* 21 USC. §§ 606, 455; *see also* 9 C.F.R. §§ 302.1, 381.6.

[36] *Id.* 21 USC. §§ 603(a), 604, 608, 455(a)-(b), 456(a).

[37] 21 USC. §§ 601(n), 453(h); *see* 9 C.F.R. part 317, 9 C.F.R. part 381, subpart N.

[38] *See* 21 USC. § 321(f) (definition of "food").

[39] 21 C.F.R. part 123.

[40] *See* 21 USC. § 374(a).

established investors, including major meat companies such as Cargill, Tyson Foods, PHW-Gruppe and Bell Foods Group, as well as foreign governments. It quickly became clear that the sector was highly motivated to bring cultivated meat to market and that a regulatory pathway would be imperative to widely validate the safety of cultivated meat to consumers.

The catalyst for public conversations about the regulatory framework for cultivated meat came not from any cultivated meat company, but rather from a different stakeholder in the food industry: the US Cattlemen's Association (USCA), one of several trade associations representing US cattle ranchers. In February 2018, the USCA submitted a petition to the USDA arguing that food products should not be legally allowed to use the terms "meat" or "beef" unless they come from animals that "have been born, raised, and harvested in the traditional manner, rather than coming from alternative sources such as ... any product grown in labs from animal cells".[41] The petition mobilized responses from a variety of stakeholders across the cellular agriculture industry, including companies, advocacy groups, non-profits, and trade associations.

This issue of labeling also resulted in questions regarding whether the FDA or USDA, or both, should have jurisdiction over cultivated meat from livestock and poultry cells. For instance, in their respective comments to the USCA petition, the North American Meat Institute (NAMI) argued that cultivated meat should fall under the sole jurisdiction of the USDA, while the Good Food Institute (GFI) argued that the USDA should deny the petition and that the only action the USDA should take, if any, would be to coordinate with the FDA with respect to formalizing the use of cellular agriculture nomenclature.[42] The cultivated meat startup, UPSIDE Foods, urged the USDA and FDA to coordinate their policies toward cultivated meat.[43] Members of Congress also demonstrated interest in the topic, and some proposed progressing towards a possible legislative solution to the matter. In May 2018, several members of the House of Representatives' Agricultural Appropriations subcommittee introduced an amendment to an unrelated spending bill that would give the USDA sole jurisdiction over cultivated meat. This proposal ultimately did not pass Congress. The question of jurisdiction intensified in June 2018, when the FDA announced that it would hold a public meeting to discuss the safety and labeling of cultivated meat the following month, leading many to conclude that the agency was asserting its authority to regulate cultivated meat. In response to the FDA's press release, USDA spokespeople made public statements indicating that they believed the USDA should have jurisdiction over cultivated meat and poultry.

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[41] USCA, Petition for the Imposition of Beef and Meat Labeling Requirements: To Exclude Products Not Derived Directly From Animals Raised and Slaughtered from the Definition of "Beef" and "Meat" 2 (Feb. 9, 2018), Docket No. FSIS-2018-0016-0001 (https://www.regulations.gov).

[42] NAMI, Comment re: Petition 18-01 – United States Cattlemen's Association Petition for the Imposition of Beef and Meat Labeling Requirements: To Exclude Products Not Derived from Animals Not Raised and Slaughtered from the Definition of "Beef" and "Meat" (May 16, 2018), Docket No. FSIS-2018-0016-3976 (http://www.regulations.gov); GFI, Comment re: US Cattlemen's Association Petition to Restrict Beef and Meat Terms on Food Labels (Apr. 17, 2018), Docket No. FSIS-2018-0016-0002 (http://www.regulations.gov).

[43] Upside Foods, Comment re: Petition to Establish Beef and Meat Labeling Requirements: To Exclude Product Not Derived Directly from Animals Raised and Slaughtered from the Definition of "Beef" and "Meat" (May 2, 2018), Docket No. FSIS-2018-0016-0047 (http://www.regulations.gov).

Proponents of FDA-only jurisdiction argued that the FDA had the unique expertise to develop sensible regulations regarding cultivated meat production by virtue of its experience regulating food and drug production processes involving microbial fermentation and other cell- culture processes (e.g., beer and antibody production) that rely on technologies similar to cultivated meat production.[44] Proponents of USDA-only jurisdiction argued that the USDA's jurisdiction over meat and poultry products legally required the USDA to have jurisdiction over cultivated meat products.[45] Additionally, they argued that having the same agency regulate both conventionally produced and cultivated meat and poultry would ensure fairness.[46]

With both sides entrenched, two unlikely partners collaborated to propose a solution. In August 2018, UPSIDE Foods and NAMI co-signed a letter to the White House, urging the administration to clarify the regulatory framework for cultivated meat and poultry products. The letter argued that cultivated meat and poultry are real meat and poultry and that both the FDA and the USDA should play a role in regulating these products. They further suggested that the FDA should oversee pre-market safety evaluations and the USDA should be responsible for production and labeling requirements.[47]

Following this proposal, in September 2018, the USDA and FDA announced that they would hold a joint meeting on the regulation of cultivated meat and poultry, and that just prior to that meeting, the FDA would also convene an advisory committee meeting before its Science Board.[48] This was the first public indication that both agencies would share jurisdiction. Subsequently, in November 2018, the agencies released a joint statement announcing that they would share regulatory oversight for cultivated products.[49] And in March 2019, the agencies issued a formal agreement outlining their framework for joint oversight.[50]

In the formal agreement, the agencies clarified that the FDA would conduct pre-market safety evaluations, in consultation with the USDA's FSIS. It would oversee initial cell collection, development, and maintenance of qualified cell banks, plus the proliferation and differentiation of cells through the time of harvest. At harvest, regulatory oversight would be transferred from the FDA to the FSIS. The FSIS would then regulate the production and labeling of cultivated meat from livestock and poultry.[51] The joint

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[44] FDA, Statement from FDA Commissioner Scott Gottlieb, M.D. and FDA Deputy Commissioner Anna Abram On Emerging Food Innovation, "Cultured" Food Products (June 15, 2018).

[45] Helena Bottemiller Evich, "Welcome to the Turf Battle Over Lab-Grown Meat," Politico.com, June 15, 2018.

[46] National Cattlemen's Beef Association, "NCBA Lays Out Principles for Regulating Fake Meat," Apr. 10, 2018.

[47] *See* Letter from Uma Valeti, Co-Founder & CEO, Upside Foods, Inc., and Barry Carpenter, President & CEO, NAMI, to President Donald J. Trump, Aug. 23, 2018.

[48] 83 Fed. Reg. 46476 (Sept. 13, 2018).

[49] FDA, Statement from USDA Secretary Perdue and FDA Commissioner Gottlieb on the Regulation of cultivated Food Products from Cell Lines of Livestock and Poultry, Nov. 16, 2018.

[50] Formal Agreement Between the US Department of Health and Human Services Food and Drug Administration and US Department of Agriculture Office of Food Safety, Mar. 7, 2019.

[51] *Id.*

agreement did not directly address jurisdiction over cultivated seafood, but in early 2020, the FDA and USDA explicitly established that the FDA would have sole jurisdiction over cultivated fish (excluding catfish) and shellfish.[52] This had long been assumed to be the case, given that the FDA, rather than the USDA, oversees conventionally produced seafood as well as common additives.

In August 2019, five US cultivated meat companies announced the formation of the world's first formal industry coalition for cultivated meat and seafood products: The Association for Meat, Poultry and Seafood Innovation (AMPS Innovation). The Association's stated mission is to "work to educate the public about our industry and advocate for the policies and programs that will be needed to create a safe, fair and transparent pathway to market in the United States for our cultivated/cell-cultured meat products." In October 2020, AMPS Innovation co-signed a letter with NAMI to the FSIS supporting the mandatory labeling of cultivated meat and poultry and encouraging the FSIS to issue an Advance Notice of Proposed Rulemaking (ANPR) to solicit input on labeling for cultivated meat and poultry[53]. FSIS did exactly that in September 2021. This letter marked the first formal collaboration between AMPS Innovation and members of the conventional meat industry. Then, in March 2021, AMPS Innovation co-wrote a comment to the FDA with the National Fisheries Institute (NFI), one of the largest trade associations representing the conventional seafood industry. The comment was in response to the FDA's Request for Information (RFI) on the labeling of cultivated seafood, and it advocated for a safe, fair, and transparent labeling regime for cultivated seafood products.

On November 16th, 2022, the FDA concluded its first cultivated meat safety consultation and released its findings publicly, stating that it had "no questions at this time regarding UPSIDE's conclusion that foods comprised of or containing cultured chicken cell material…are as safe as comparable foods produced by other methods." . This conclusion was memorialized in a memorandum that detailed the way in which FDA conducted its analysis, its rationale for determining the safety of both the production process and the tissue material produced as a result, and a general audit of the data and information provided to FDA by UPSIDE Foods. FDA also indicated that it is in conversation with other cultivated meat companies, and that additional safety assessments may be underway.

11.4 Future Regulatory Considerations

With FDA's first safety consultation closed and public, the remaining outstanding questions regarding cultivated meat regulation hone on the specifics of safety that may be required writ-large as well as the labeling of cultivated meat products. Regarding

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[52] Michael, Matthew and Fasano, Jeremiah. "Animal Cell-Culture Food Technology: A New Regulatory Frontier." Food Safety Magazine. February/March 2020. https://www.foodsafetymagazine.com/magazine-archive1/februarymarch-2020/animal-cell-culture-food-technology-a-new-regulatory-frontier/

[53] *See* Letter from the Alliance for Meat, Poultry and Seafood Innovation and the North American Meat Institute, Oct. 19, 2020.

safety, FDA has publicly stated that they intend to release a draft Guidance for Industry (GFI) that would presumably contain the recommended data and information they believe is necessary to support an efficient and conclusive safety evaluation.

On labeling there is less clarity, but it is expected to resolve as companies secure pre-market labeling approvals for meat and poultry. , While USDA oversight of cultivated meat and poultry indicates that these products meet statutory definitions for "meat," "meat food product," and "poultry product," as well as related products, it is unclear whether the USDA would require these products to bear special labeling, such as a qualifier describing how the products were made, or even a separate standard of identity. Second, if the USDA were to require such labeling, as has been suggested by agency officials, what would be the agency's basis for mandating these disclosures and how would the USDA and FDA ensure consistency in their approach, as specified in the formal agreement? As explained above, the FDA's and USDA's product-based approach to new technologies in food production indicates that if cultivated meat products are not materially different from conventionally-produced meat products, there is no legal basis to require that cultivated products be labeled differently. Third, with the passage of several state laws and introduction of proposed state legislation that seeks to prohibit cultivated meat from using "meat" and "poultry" terms in product labeling or that would mandate additional qualifying language for cultivated meat, what will be the impact of federal regulation, which generally takes precedence over state laws?[54] In particular, would federal labeling requirements pre-empt such laws? In addition, would these laws withstand scrutiny under the First Amendment, which protects free speech, in addition to other legal challenges?

In addition, as of 2023, USDA has indicated they intend to seek public rulemaking to address how they intend to enforce labeling standards for cultivated meat. Indeed, such a process will necessarily tackle the need to address the multitude of terms used by industry and stakeholders as well as harmonize with FDA on cultivated seafood products, which are subject to distinct labeling requirements as compared to USDA for meat and poultry products.

There are also outstanding questions regarding the technical details of the FDA and USDA inspection regime. For example, while the formal agreement specifies that the transfer of authority from the FDA to the USDA would take place "at harvest," the exact point in the production process at which "harvest" likely will be evaluated on a case-by-case basis as different companies use differing methods to harvest cells and tissues.

Finally, these questions only address how the US government will oversee cultivated meat. Other jurisdictions outside the US will have to establish their own regulatory regimes. The first to do so was the Singapore Food Agency (SFA), which announced in December 2020 that it had approved the production and sale of a cultivated chicken product from GOOD Meat.[55] With that being said, due to resource and capacity sharing

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[54] *See, e.g.*, Ky. H.B. 311 (Mar. 21, 2019); Ark. H.B. 1407 (Mar. 18, 2019); S.D. S.B. 68 (Mar. 18, 2019); N.D. H.B. 1400 (Mar. 13, 2019); Miss. S.B. No. 2922 (Mar. 12, 2019); Mo. S.B. Nos. 627 & 925 (June 1, 2018).

[55] See "Singapore Approves a Lab-Grown Meat Product, a Global First," New York Times, Dec. 2, 2020.

that often occurs between the US and some foreign regulatory bodies, it is likely that some nations will adopt the US regulatory model when establishing their own regulatory pathways for cultivated meat.

11.5 Conclusion

While substantial progress has been made in clarifying the US regulatory framework for cultivated meat, there are still uncertainties that the USDA and FDA need to resolve. Specific pathways and details must be clarified to support innovation and establish a clear and predictable path to market.

Leaders in these food regulatory agencies have indicated a strong interest in ensuring appropriate regulation for cultivated meat. Indeed, in October 2018, former USDA Secretary Sonny Perdue noted, in reference to cultivated meat: “Shouldn’t we in the United States focus on how we can grow and feed people more efficiently and more effectively…these techniques need to be embraced, not kept out.” Similarly, at the October 2018 USDA-FDA joint public meeting on cultivated meat, former FDA Commissioner Scott Gottlieb embraced the FDA’s commitment “to enabling innovation and consumer choice while supporting public health and safety.”

Based on these statements, along with the history of the regulatory system in the US, the actions of the agencies to this point, and the substantial interest from US consumers in cultivated meat products, it is likely that the US will embrace this agricultural innovation and ensure appropriate regulation over such products. With the recent successful first-ever close of a cultivated meat safety consultation process, we are now closer than ever to not only seeing consumers purchase cultivated meat products, but also bearing witness to the continued modernization of the US food regulatory system as it adjusts to these new products. This is a promising situation, and likely one of the final steps in allowing a new, safe, and nutritious food to be enjoyed by US consumers.

Fundamental Questions – Answered

1. **What are the major regulatory events that have occurred with respect to cultivated meat?**
   One of the key events in the regulatory history of cultivated meat occurred in February 2018, when the US Cattlemen's Association petitioned the US Department of Agriculture (USDA) to establish its preference on the labeling of cultivated meat. This petition also accelerated a public conversation regarding which agency should oversee cultivated meat. Following a letter to the White House, co-signed by the cultivated meat start-up company Upside Foods and the North American Meat Institute (NAMI), the USDA and Food and Drug Administration (FDA) signaled their intent to jointly oversee cultivated meat and poultry. This was formalized in a joint agreement released in March 2019.[1]

2. **Which agencies will have jurisdiction over cultivated meat?**
   In March 2019, the FDA and USDA formally announced that they would share oversight for the regulation of cultivated meat and poultry. It was established that cultivated seafood will be overseen by the FDA alone (except for catfish), as it holds sole jurisdiction for most conventionally produced seafood products and their ingredients.

3. **Going forward, what are the key uncertainties with respect to regulation of cultivated meat?**
   Both agencies are working to resolve current uncertainties in the regulation of cultivated meat in the US. These uncertainties include elements of pre-market safety, labeling, and inspection practices for cultivated meat products and facilities. In addition to these, there is uncertainty surrounding how non-US regulatory regimes will oversee cultivated meat.

4. **Does cultivated meat meet the legal definition for "meat"?**
   Yes. There is broad consensus that cell-based meat does meet legal definitions for "meat," "meat food product," and "poultry product," among other terms. This is one of the reasons why cell-based meat and poultry are subject to oversight from the USDA.

Space

Cultivated Meat as a Food System for an Extraterrestrial Environment

Sangita Vasikaran
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Chapter Abstract

The mystery of space has long enraptured the curiosity of viewers from Earth. Many contend that space exploration could be the salvation for humankind, ensuring that humans always have a place to live. Food will be an integral part of extraterrestrial survival. In this chapter, the nutritional needs and practical challenges of producing food in space is discussed. These design considerations are then applied critically to how cell-cultured food systems can address these challenges, as well as what such a practice would mean for long-term life in space.

Keywords

Space food systems
Microgravity
Ionizing space radiation
Oxidative damage
Space Adaptation Syndrome (SAS)
Payload
Closed-loop system
In situ resource utilization

Fundamental Questions

1. Given the nutritional challenges for humans in space, how could cell-cultured meat serve as a potential solution? What are the major challenges?

2. Sociologically, what considerations should be made for the way cell-cultured food systems are introduced into a colony in space?

Chapter Outline

12.1 Introduction: Why Space?

12.2 Health Concerns with Long-term Life in Space and Nutritional Mitigation
- 12.2.1 Changes in Metabolism and Caloric Intake
- 12.2.2 Muscle Maintenance and Adequate Protein
- 12.2.3 Musculoskeletal Maintenance and Micronutrients
- 12.2.4 Regulation of the Immune System
- 12.2.5 Systemic Effects of Space Radiation
- 12.2.6 Sensory and Psychological Changes Towards Food
- 12.2.7 Evaluation of Cell-cultured Meat's Potential for Providing Nutritious Diets in Space
    - 12.2.7.1 Precise Composition Control
    - 12.2.7.2 Macro and Micronutrient Engineering
    - 12.2.7.3 Dynamic Flavors and Variety

12.3 Stability Requirements for Space Food
- 12.3.1 Long-term Storage in Radiation and Microgravity
- 12.3.2 Current Space Food Preservation Methods
- 12.3.3 Cell-Cultured Meat's Rapid Price Reduction Trend
- 12.3.4 Transport Considerations
- 12.3.5 Evaluation of Cell-cultured Meat's Potential for Maintaining Food Stability in Space
    - 12.3.5.1 Fresh, Familiar Food Production
    - 12.3.5.2 Adaptations to Cell Culture
    - 12.3.5.3 Automating Bioprocesses
    - 12.3.5.4 Considerations for Establishing Closed-loop Systems

12.4 Sociological Speculation for Colonies in Space
- 12.4.1 Space Program Origin
- 12.4.2 Labor Systems
- 12.4.3 New Cultural Practices

12.1 Introduction: Why Space?

Since the beginning of civilization, humans have been curious and, for many, space represents the greatest curiosity of all. In 1962, President John F. Kennedy championed the development of the Apollo program to the American people: “We choose to go to the Moon in this decade and do the other things, not because they are easy, but because they are hard.”[62] Stepping foot on the Moon in 1969 was a feat on its own, but the technology that came out of the Apollo 11 mission has since played into the development of many technologies, including alternative fuel sources, precise pacemakers, cordless power tools, and insulated clothing.[63] In essence, the challenges and transportable resource limitations of space catalyzed remarkable developments in technology, not only for use in space, but for practical improvements on Earth.

In 2019, the cellular agriculture startup Aleph Farms announced they had 3-D printed bovine cells into the first cell-cultured steak while in space. This was a moment some would consider analogous to “one small step for man and one giant leap for mankind’’ for this field.[64] By accomplishing precisely controlled production of cell-cultured meat with limited water in an extreme environment, this “small step for man” suggests that, in the future, humans will be able to make the “leap” and sustainably provide adequate nutrition to, in their CEO’s words, “anyone, anytime, anywhere”.[21] The less intensive resources needed for cell-cultured meat production on Earth may mean that fresh meat could be conveniently grown in places that are not traditionally able to do this, such as polar land or isolated communities.[49] Furthermore, and the focus of this chapter, knowing that humans could maintain a stable food supply in space opens doors to interplanetary expedition and colonization. These prospects have been thought by some to be valuable in ensuring human survival in the face of large disasters on Earth,[65] as well as for the increased access to resources a different location in the universe could provide, such as mining asteroid materials and solar energy.[66]

This chapter explores the unique nutritional and practical design challenges of supporting life in space. It will then evaluate cell-cultured meat production as an improvement to existing space nutrition systems, as well as speculate what the sociological implications of such an application might be.

12.2 Health Concerns with Long-term Life in Space and Nutritional Mitigation

The space environment, specifically its distinct features of microgravity and ionizing radiation, plus its general contrast with conditions on Earth have been shown to significantly impact human physiology and overall health.[1]

Microgravity, often tied to the term ‘zero-g force’ or the feeling of ‘weightlessness’, refers to there being little sensation of typical Earth gravity while in free-falling orbit, due to the lack of any opposing force from contact with the ground on Earth.[2]

Ionizing space radiation, sometimes referred to as simply space radiation, consists of highly energetic protons and heavy ions existing outside Earth’s protective atmosphere that can damage molecular and biological structures.[3]

The following section reviews concerns around the health of space travelers stemming from malnutrition, followed by an evaluation of cellular agriculture as a potential means of addressing these dietary challenges.

12.2.1 Changes in Metabolism and Caloric Intake

Consuming enough energy is perhaps the single most important aspect of nutrition for space travelers, according to the National Aeronautics and Space Administration (NASA).[1] A usable form of energy for the body is obtained by metabolizing carbohydrates, fats, and proteins (known as macronutrients); this convertible energy is quantified as calories. [4] Although there is evidence that individual energy requirements are similar before and during space travel, caloric intake by astronauts in space has been found, on average, to be lower than their estimated requirements. This gap between energy need and energy input can lead to, most immediately, loss of body mass and decreased physical capability.[1] Potential causes for this reduced caloric intake may include space adaptation syndrome or a decrease in perceived palatability of food (detailed in Section 12.2.6, *Sensory and Psychological Changes Towards Food*).

12.2.2 Muscle Maintenance and Adequate Protein

Exposure to microgravity reduces muscle mass through a process known as **atrophy** and results in a loss of muscle performance. It is therefore essential that space travelers compensate for the loss of muscle mass through consuming adequate calories and protein in their diet and by balancing with carefully planned exercise regimes.[1] Studies have shown that, during a brief space flight, protein turnover in the body increases, indicating that both protein production and protein breakdown increased, which is a common sign of physiological stress. In the NASA Twins Study,[7] the physiologies of astronaut twins Mark and Scott Kelly in space and on Earth respectively were compared over the course of a year. It concluded that decreased muscle mass was a direct result of space exposure. This is likely tied to reduced protein synthesis, a long-term effect of inadequate caloric intake.

12.2.3 Musculoskeletal Maintenance and Micronutrients

In space, increased bone breakdown or resorption occurs, hypothesized to be due to the lack of stress applied to the skeleton in microgravity.[1,8] This loss of bone density is accompanied by hormonal changes that decrease vitamin D use by the body, and subsequently, calcium absorption. Because altered metabolic pathways for these key vitamins and minerals (micronutrients) are the apparent cause of this phenomenon, rather than insufficient consumption, dietary supplementation has limited success in mitigating against bone loss. Potential complications, such as kidney stones, have also arisen in spacce.[9,10] However, intake of other nutrients, such as the polyunsaturated fats, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) found in fatty fish, show promising potential in counteracting bone and muscle loss.[1,10,11]

12.2.4 Regulation of the Immune System

The physiological stress of spaceflight, from microgravity, space radiation, and altered sleep cycles and circadian rhythms (bodily processes that normally occur on a 24-hour time scale) seem to affect the immune system at both innate and adaptive levels.[12] Spaceflight analog studies have found abnormal counts of “first-responder” innate immune cells such as neutrophils, macrophages, and monocytes. This was accompanied by lower production of “warning signals” such as interferons -γ, -α, -β, and interleukin-2 by lymphocytes. Taken together with the risk of infection from living in a closed, relatively crowded environment with limited disinfection, space travelers seem especially vulnerable to health concerns stemming from immunodeficiency. Preventing deficiencies in micronutrients such as iron and vitamin B12 may help regulate the immune response.[1] Further, supplements of specialized compounds such as dietary nucleotides[13] and active hexose-correlated compound (AHCC),[14] which can be sourced from yeast and mushrooms respectively, have been found to enhance immune activity in microgravity models.

12.2.5 Systemic Effects of Space Radiation

When outside of Earth’s protective atmosphere, space travelers are exposed to some degree of ionizing radiation. This will be higher if an astronaut is not protected by the spacecraft, for example when performing extra-vehicular maintenance. Ionizing space radiation can create unwanted reactive oxygen species (ROS) that can damage DNA and cellular regulation.[15] In space travelers, this oxidative damage can translate to increased risks of future issues such as cataracts, cancer, cognitive impairment, and musculoskeletal degeneration.[16] The body’s method of counteracting oxidative damage is with antioxidants, micronutrients that can inhibit the destabilizing effects of ROS; however, research suggests there is a downregulation of this defense mechanism in space.[1,4] As with other nutritional countermeasures discussed, simple supplementation of identified antioxidants, namely vitamins E, C, A, and selenium, does not seem to solve the complexity of oxidative stress in space and requires further research.

12.2.6 Sensory and Psychological Changes Towards Food

In the first few days after arrival in space, travelers often experience Space Adaptation Syndrome (SAS) which are issues with bodily acclimation to microgravity.[4] In SAS, the sensory vestibular system, which usually uses the pull of gravity to inform the brain about the orientation of the body, does not have perception of up and down.[17] This leads to dizziness, and often headaches, nausea, vertigo, or fatigue. Further, microgravity redistributes fluid in the body, pulling it upwards to swell the face, which can cause a similar feeling to congestion.[18] Therefore, microgravity may be one factor responsible for taste and smell being less acute in space.

Another factor mentioned previously in Section 12.2.4, *Regulation of the Immune System*, was the irregularity of circadian rhythms and sleep in spaceflight due to non-24 hour 'night and day', as well as various mental and physical stressors absent on Earth. Such biological shifts can have psychological implications on diet, as these cues can dysregulate hormones that control nutrient metabolism, thereby affecting appetite and satisfaction.[18] Although these changes are hard to quantify, steps can be taken to increase the appeal of food, thus potentially counteracting a decreased interest. In general, astronauts report increased positive appetite for food that is diverse,[19, 56] stimulates the senses (for example, spices),[20] or that is eaten socially, alongside crewmates. These three aspects have so far been identified as important tools to promote proper nutrition for astronauts during space missions.[78]

12.2.7 Evaluation of Cell-cultured Meat's Potential for Providing Nutritious Diets in Space

12.2.7.1 Precise Composition Control

A major advantage of cell-cultured food production is how it can enable precise control of composition of the final product.[21] By varying culture media composition (see Chapter 6, *Media*) or scaffold structure (see Chapter 9, *Scaffolding*), it is feasible to culture cells of certain phenotypic characteristics. In downstream processing (detailed in Chapters 8 and 10, *Automation and Artificial Intelligence* and *Generations of Cell-cultured Meat*), knowledge of the protein or micronutrient composition of certain cell culture products would allow for deliberate formulation of new and hybrid products, also with known composition. Such a controlled process can be compared to following a cooking recipe – for example, being able to choose how much flour, oil, and sugar to make eight slices of cake with the desired amount of sugar and fat for a particular dietary requirement. However, in traditional meat production, this is not as feasible to control, as the nutrient composition of meat selection is standardized, (e.g., "90% lean ground beef"). Cellular agriculture could make it possible to purchase and/ or order very specific cuts of meat, such as eight portions of bison T-bone steak with 15% turkey fat, 85% bison protein, and 10 mg of iron, in addition to other specifications. For further information on the customizability of cultured cell products, see Chapter 5, *Cells* for a detailed overview.

12.2.7.2 Macro and Micronutrient Engineering

In the dietary challenges of space travel discussed so far, the role of macro and micronutrients has been speculated to be important for specific physiological functions; however, more data from controlled trials is needed to support these findings. An example discussed in Section 12.2.3, *Musculoskeletal Maintenance and Micronutrients*, revealed that intake of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) through fatty fish was correlated to enhanced bone mass maintenance among astronauts. However, other studies found that direct supplementation of fatty acids through fish oil did not confer the same benefits to bone mass retention.[22] This finding supports the possibility that dietary pattern changes can, in certain cases, be more meaningful determinants of health than supplementation. As in this example, uptake of certain nutrients produced in the context of meat itself may lead to more favorable outcomes than the purified nutrient alone. Potential reasoning for this phenomenon can include **bioavailability**, which is how absorbable a nutrient is due to the characteristics of other nutrients consumed simultaneously. While this is not always the case, for other key nutrients discussed in Section 12.2.7, such as vitamin B12, heme iron, and fat-soluble vitamins K, E, and D, uptake in the form of meat could prove more efficient than in pure forms provided via supplementation.

The idea of augmenting nutrition via cell-cultured meat is an exciting one, as the biotechnology involved in cell-cultured meat production enables meat to be enhanced beyond its conventional definition and nutritional constraints. Stout *et al.* (2020) showed that bovine muscle cells could be engineered to produce antioxidant precursors of vitamin A. This demonstrates that micronutrients that mitigate harmful reactive oxygenation species (ROS) activity, such as vitamin A, could become associated with beef consumption. At the same time, these engineered cells could slow the meat's own oxidative spoilage.[23] Stout highlighted that a unique facet of the technology was how it could fit into and simultaneously solve a deficit in dietary pattern. It has the potential to target dietary intervention (ROS-fighting antioxidants) in susceptible people (those who consume red meat often) through a form with which they are comfortable engaging.

This seems imperative for the environment of space travelers, where there is already physiological stress from adapting to a different lifestyle.

If cell-cultured meat is "version 2.0" of meat, then nutritionally enhanced versions of cell-cultured meat are, in Stout's words, "version 2.1".[24] It should be considered how readily such a technology might be accepted, and whether the perception of these new production processes would make it too "unnatural" for ready adoption. Further, while cell-cultured meat could offer specialized products, it is not yet practical for space-scale yield. In 2002, a NASA-commissioned project by M. A. Benjaminson *et al.* (2002) reported results of growing goldfish muscle for the goal of being a food source for space travelers. This study found that edible protein yield was too low to be meaningful from a nutrition standpoint. [25] However, since then, much investment has gone into refining cell-cultured meat yield from a variety of perspectives (see Chapters 7 and 8, *Bioprocess Engineering for Producing Cell-cultured Meat* and *Automation and Artificial Intelligence*). One example of these refinements is the work of Dr. Ivana Gadjanski and Dr. Vasa Radonic, Good Food Institute research grant recipients. Their work entails producing bioreactor sensors which can monitor variables such as biomass and nutrient growth in real time.[26] In doing so, cell-cultured meat producers will not only be able to leverage better data but will also be able to extend protein yields beyond their historical limits. Moreover, this understanding, combined with the ability to specify many aspects of nutrient composition, could enable the controlled samples and trials needed to determine if certain nutrients in a diet are tied to health outcomes in space. Such research could clarify doses, interactions, and side effects to be considered in deploying nutritional countermeasures.[4]

12.2.7.3 Dynamic Flavors and Variety

As detailed in Section 12.2.6, *Sensory and Psychological Changes to Food*, space traveler well-being is benefitted by stimulating flavors and variety in diet. Cellular agriculture's control over product composition could also be applied towards these goals. For example, by modifying the culture media of cells, it is possible to enhance the amount of glutamate incorporated into cells.[21] Glutamate is a component of protein responsible for a hearty, "umami" taste that rounds out flavors, and are often a flavor note of good meat. This functionalization of cell-cultured meat systems could further be planned around the activities of the space travelers. For example, if a crew is scheduled to undertake a spacewalk, the appropriate antioxidant can be expressed at higher levels within the meat grown for those days giving enhanced protection against the extra radiation exposure. On other physically demanding days when more caloric density is needed, meats could be cultured with more fat, also making it more satisfying to the palate, while giving interesting variety to the senses. In theory, many opportunities are possible: engineering almost all variations of flavor and catering to nutritional needs on-demand could eventually be achieved with cellular agriculture. However, the timescale of developing larger scale, specific-use, cost-effective, and automated cellular agriculture processes is still a major challenge that requires further development.

By enabling the creation of a wide variety of customizable, appealing foods as they are needed, cell-cultured meat has the potential to nourish the dietary needs of space travelers. However, there are challenging practical issues for operating cell-based meat facilities in space that must be considered.

12.3 Stability Requirements for Space Food

The next section will explore the practical considerations of producing and storing food, followed by an evaluation of how cellular agriculture could address these stability challenges better than existing space food systems.

12.3.1 Long-term Storage in Radiation and Microgravity

Many packaged foods for eating on Earth are designed with a shelf life of up to two years; however, in deep-space missions, food is often shipped before the crew and thus may need to be shelf stable for at least five years.[27] In this time, foods can undergo chemical transformations such as degradation of vitamins and fats. These processes translate into unwanted changes to organoleptic, or sensory, properties, such as rancidity, off-flavors, discoloration, and loss of textural integrity.

Zwart *et al.* (2009) sent multiple food products aboard the International Space Station (ISS) and observed the sharpest decrease in vitamins A, C, K, folic acid, and thiamine after about 1.5 years.[28] Interestingly, the micronutrients in the products stored in space did not seem to degrade faster than control samples on Earth, suggesting neither radiation nor microgravity contributes to micronutrient degradation. However, this does not rule out the possibility of this environment affecting the nutrition of food in other ways, such as probiotic microorganisms or modifying biomolecules not tested for in this study.

12.3.2 Current Food Preservation Methods in Space

Currently, most food in space is pre-packaged; therefore, the nutritional requirements of the astronauts are all supplied by ground production and processing.[29] Refrigerators and freezers are used sparingly for food products on the ISS for a variety of reasons, including energy consumption and the fact that fresh food products are not restocked often enough on missions to warrant sufficient use. Common types of room temperature-stable food for storage in space, as well as their organoleptic impact, are detailed below. These methods aim to modify the food such that microbial growth is inhibited, either by killing bacteria or maintaining an extreme environment such that they cannot grow and spoil food.

- **Freeze-dried**: Virtually all water is removed from the food through freezing and vacuum evaporation.[30] Prior to consumption, space travelers rehydrate the product with hot water. Texture is often more amorphous in plant foods post-rehydration, due to, for example, the pressure changes damaging cell walls. Color and nutrients are typically retained.
- **Intermediate moisture:** Water is only partially removed from the food and often accompanied by altering the pH or salt content. An example is dried fruit, in which a chewy texture and slightly sour taste is present.[31] Color often changes, though nutrients are typically retained.
- **Thermo-stabilized**: Foods are heated to a temperature that can destroy microorganisms and functional enzymes, while staying sealed in packaging. This practice is also known as retorting. It is generally used only for liquid foods, as retorting can adversely affect the texture of solid foods. Because micronutrient content has been found to be close to depleted in storage periods beyond two years in space, alternatives that use slightly lower temperature are being explored: pressure-assisted thermal sterilization (PATS) and microwave-assisted thermal sterilization (MATS).[34]
- **Irradiated:** After cooking, foods are sterilized by a dose of ionizing radiation. The FDA has given a special dispensation to NASA to use this uncommon technique on only nine frozen, packaged meat products.[32] Irradiation does not alter the texture, color, or nutrient composition of foods, but may result in chemical changes such as protein aggregation, lipid oxidation, or vitamin degradation.[33]
- **Natural form and fresh foods:** Many packaged snacks such as nuts already have low water activity, thus giving a long shelf life in their "natural form". Sanitized fresh fruits and vegetables are provided occasionally to the ISS but must be consumed quickly before spoilage. They are more for the psychological satisfaction of familiarity for astronauts, rather than serving as a nutrition staple.
- **In situ plant growth system:** The ISS has also been exploring the possibility of growing vegetables in space. By generating fresh food during travel, space traveler diets would get a small portion of intact nutrients, variety, and familiar texture, flavors, and colors, which can boost psychological state and morale. One notable project is the Veggie Plant Growth System ("Veggie"). This has been developed by Orbital Technologies Corporation and is a system that grows plants from a portable clay and fertilizer base.[35] The ISS crew has already been able to grow batches of mixed greens, lentils, and zinnia flowers that are similar to precursors to fruit, and they are looking ahead to optimize this system's efficiency.

12.3.3 Cell-Cultured Meat's Rapid Price Reduction Trend

In addition to the challenges of maintaining food quality in space, early production costs for cell-cultured meat have been extremely high. Mark Post's burger, composed of thousands of thin strips of cultured bovine muscle tissue, was created for roughly US $325,000 in 2013.[57] However, companies have worked to drastically reduce costs, and today the price of both cultured beef and chicken is closer to US $35 per pound, and is projected to decrease by 10-fold in as few as five years.[58, 59] These jumps are a result of technological advances in the field, such as reducing culture media volume and reliance on animal-derived components, bioreactor scale-up, and expanded understanding of various cell lines.[61] The pace of development and cost reduction of cell-cultured meat technology has surpassed that of transistors in the well-known Moore's Law.[60] Computers and the internet have forever shifted paradigms and redefined how humans interact in the world. Cell-cultured meat and food production systems may soon follow a similar trend.

12.3.4 Transport Considerations

While the price reductions associated with producing cell-cultured meat are promising, the cost of transporting cargo into space is still high. Complex engineering of materials, structure, and fuel constrains the total mass of the rocket possible for successful deployment into and return from space.[37, 38] As a result, carrying cargo, also known as **payload**, is resource intensive and expensive. NASA space shuttles and ISS supply mission collaborations with private contractors SpaceX and Orbital ATK point to a current transport cost of roughly US $10,000 per pound of payload, though developments to reduce this are being pursued.[39, 40]

The recommended amount of drinking water per person per day–8 glasses or 2 L–weighs four pounds. Addressing the payload cost of transporting the drinking water needed for life in space, NASA deployed a remarkable recycling system on the ISS in 2009 that has been used to recover up to 90% of drinkable water intake from astronaut urine, drastically lowering the amount and resulting cost of water payload.[41] Such a system that can reuse its 'waste' output as new inputs to sustain itself is known as a **closed-loop system**. As closed-loop systems do not require new input of resources to function they are environmentally sustainable and energetically efficient. In space, this translates to lower-cost missions that do not require regular shipments from Earth, a factor that could enable long-term life in space.[42] While water has been adapted into a closed-loop system in space, completely closed-loop food systems with elements such as composting and waste diversion have not neared this standard.[42]

12.3.5 Evaluation of Cell-cultured Meat's Potential for Maintaining Food Stability in Space

12.3.5.1 Fresh and Familiar Food Production

As previously discussed, conventional food for space travel must be prepared in a way that accounts for long-term sterility, microgravity, and radiation. In situ production of cell-cultured meat might be able to bypass many of the negative aspects of this prepackaged pipeline. While micronutrients are prone to degradation in long-term packaged food storage, vitamins that are produced by genes in cell-cultured meats shortly before consumption (such as Stout's "meat version 2.1" mentioned in Section 12.2.7, *Evaluation of Cell-cultured meat's Potential for Providing Nutritious Diets in Space*) would not face this preservation issue. Similarly, if mimetic texture can be achieved in cell-cultured meat products, astronauts could enjoy the familiar mouthfeel of fresh meat when they harvest the tissue from the bioreactor, instead of the potentially compromised organoleptic experiences of preserved, rehydrated products. This is, however, dependent on the downstream cooking or preparation process, which may also differ in space. For example, a toaster oven was only used for the first time on the ISS in 2019, though other kitchen appliances are currently being developed for this use.[52, 53]

These cooking practices are opportunities to continue to build and pass down traditions and culture in an environment that may otherwise be entirely unfamiliar – a morale booster, similar to the proposed effects of taking care of a growing plant with the Veggie system outlined in Section 12.3.2, *Current Space Food Preservation Methods*.

Altogether, these prospects are exciting, as more sustainable, familiar food experiences pave the way for space traveler well-being, and eventually, long-term life in space. However, with introducing cell-cultured meat into space, the behavior of cell cultures in radiation and microgravity must also be considered. To this end there are cell cultures and bioreactors that are being tested for the ISS to understand mammalian tissue development,[43] as well as long-term growth in a closed-loop system at the microorganism level.[44]

12.3.5.2 Adaptations to Cell Culture

It is known that long-term radiation exposure in spaceflight can lead to changes in DNA integrity and/or expression within mammalian cells.[54, 55] Conflicting results exist, and more work is needed to assess whether these changes are a concern for the proliferation and other physiological functions of animal muscle and fat stem cells. Such findings could inform both the practicality of sufficient production and viability of genetically engineered micronutrients (like Stout's meat version 2.1) of cell-cultured meats in space.

Bioreactor studies have revealed that maintaining cells attached to a surface upon which they can grow and form a tissue in space is challenging, due to microgravity. On Earth, cells seeded on a 2D surface form a single layer at the bottom of the container; in space, cells do not anchor and instead move around when the culture media is changed. This movement can make the use of existing technologies to engineer complex tissues problematic – for example, **bioprinting**, in which a printhead nozzle extrudes cells in a scaffold matrix into precise, layer-by-layer 3D geometries.[46] However, recent findings indicate that there are certain facets of microgravity which might enhance 3D tissue development. First, it is hypothesized that microgravity may more closely mimic the embryonic tissue development environment than terrestrial experiments *in vitro.*[46] Further, the lack of gravitational forces better facilitates the modeling and use of alternative assembly forces to control the spatial distribution of cells. In a method named formative biomanufacturing, researchers used a low concentration of metal bead tags on cells and engineered magnetic fields to drive the assembly of cartilage cells into spheres in the ISS.[47] These techniques, while bypassing traditional tissue engineering components such as the scaffold, have their own limitations that require more research, such as how to address that metal tags are relatively cytotoxic.

Another difference that arises from engineering tissue under microgravity is maintaining the working vasculature, or circulation system, of the produced tissue. Vascularization provides vital nutrients and oxygen to the cells and discards waste. This vascular system must be composed of narrow micrometer-range capillaries to reach cellular bodies. On Earth, flow through some of these capillaries happens due to capillary action, the ability of a liquid to flow in narrow spaces due to surface tension overcoming external forces like gravity. In the microgravity of space, capillarity gives different motion to fluid droplets. This must be accounted for when designing cell culture platforms.[48] Whether this could make nutrient circulation for the purpose of cell-cultured meat more, or less, efficient is still underexplored. This property of circulation has important implications for designing a closed-loop system, as it is closely tied to how nutrient recycling could be accomplished. Maintaining essential nutrient circulation is one of the greatest challenges in establishing the feasibility of cellular agriculture in space.[21]

The vastness and variability of space should not be ignored. As discussed earlier, one cellular agriculture company (Aleph Farms) has been able to 3D print and culture bovine cells into a steak in space, growing their cells on the ISS, in low Earth orbit, about 248 miles away from ground. However, gravity and radiation depend on relative location to planetary and cosmic bodies.[67] Company researchers noted that it is difficult to predict how the cell culture process will be affected in deep space.[21]

12.3.5.3 Automating Bioprocesses

As discussed in Section 12.2.7, *Evaluation of Cell-cultured Meat's Potential for Providing Nutritious Diets in Space*, research has explored how the choice of scaffold, cell media, or even pH levels determine the properties of cultured meat. It has therefore been established that the necessary expertise exists to create controlled environments within a bioreactor to produce a specific product. To maintain these conditions, bioreactors require different components, such as a feeding/air pump to regulate nutrient and dissolved gas concentrations, a thermal jacket to regulate temperature, an outlet to discard waste materials, and internal sensors for feedback measurement. Chapter 7, *Bioprocess*, provides in-depth explanations on the engineering of the bioreactor and culture methods for cell-cultured meat. The argument can be made that cell-cultured meat production could be a continuously customizable, monitored, and stable process. Producing meat in a controlled-environment bioreactor allows for mechanical intervention against microbial contamination and other unwanted elements, in addition to potential mitigation of space radiation and/or microgravity in cell culture. However, the cost and technical feasibility of establishing such systems is still to be determined.

One of the main technical issues surrounding an automated food system is the possibility of bioreactor failure. Failsafe mechanisms are common for space technology, and this would likely require packing spare system parts and back-up food sources, developing a working knowledge for space travelers, plus engineering extensive reliability mechanisms. These are all necessary before such a system could be considered viable over the long-term.

12.3.5.4 Considerations for Establishing Closed-loop Systems

Based on current technology, it would take approximately three years for a human mission to reach Mars and return to Earth.[36] Such a mission could require up to 24,000 pounds of food for a crew of four people eating three meals a day. Given that such a quantity isn't practical for interplanetary travel, the development of closed-loop food systems that can efficiently and sustainably create food throughout the mission is required. While the focus of this chapter is cellular agriculture, many principles of bioreactor engineering and cell culture can also be applied to plant cell culture and microbial precision fermentation, both of which can create a wider variety of nutrient-rich foods. If a significant portion of the crew's food can be produced through cell-cultured methods onboard, combined with water recycling, the spacecraft could substantially decrease the initial payload weight as well as the necessity for restock missions for pre-packaged foods.[49] Further, the same could be applied to storage; with a continuous, sterile, and freshly produced supply in a bioreactor, less preserved stock of food would be needed; the cost and energy of freezing, canning, or drying prepackaged food could thereby be reduced[51]. However, to continuously produce cultured cells in situ, a source of nutrient media would be needed, as well as means to ensure the bioprocess is sterile. It is unclear whether the weight or volume of the reagents and equipment for cell culture would be less than that of prepackaged food for the same time frame in spaceflight.[21] Until these values can be computed, there is not yet quantitative evidence that cell-cultured systems of food production will cost less than our existing space food systems. Promisingly, bioregeneration of water in situ has been found to be economical for long-term travel;[50] culture media or feedstock recycling systems may one day be able to fulfill a similar role.

Although cellular agriculture could improve space traveler well-being and the sustainability of their food supply, there is a large gap in the quantitative comparisons that can currently be made. Future research should address the quantities of material and equipment needed to produce enough sterile, microgravity- and radiation-stable meat, as well as other food products, to feed a space crew over a specific timescale.

12.4 Sociological Speculation for Colonies in Space

If people are one day able to establish a longer-term colony in space, possibly on another planetary body, and they rely on food from cell-cultured systems, there are various aspects of society that could shift as a result.

12.4.1 Space Program Origin

The origin of the advancements needed to make a space colony a reality could shape the colony itself. At present, there exists both public governmental (e.g., NASA) and private commercial (e.g., SpaceX) space programs. The spaceflight of the first commercial crew by SpaceX in 2020 hallmarked the fact that private companies are now a very present player in the space ecosystem.[21,68] Both types of programs could differ in their resources and budgets, as well as their values. For example, would the focus of missions start by aiming to establish a colony on the Moon or Mars? What would be the most immediate goal of interplanetary colonization: permanent habitats for civilians or scientific study? It is likely that the legal framework laid down in the early days of such a colony would also be a direct result of the agency that establishes it. For public sector agencies, historically, cell-cultured meat systems have not been their focus. NASA, for example, is interested in new means of food production, as evidenced by their goldfish muscle production study in 2002 but has been more dedicated to rocket development/technology to date.

Further, as discussed in Chapters 11 and 13, *Consumer Acceptance* and *Regulation*, there might be more resistance in the US against cell-cultured meat from groups representing conventional food systems, such as the Cattlemen's Association. FDA legislation is comparatively more risk-averse than the commercial efforts in the private sector when it comes to bringing cell-cultured meat products to market. This caution is perhaps not surprising as the FDA, as a government body, must represent the interests of around 330 million people of all ages and backgrounds. For example, regulatory approval of fermentation-derived soy leghemoglobin from Impossible Foods and β-lactoglobulin (whey) from Perfect Day necessitated repeated dialogues with the FDA over extensive product analyses for low-dose usage in very specific cases.[75, 76] Moreover, soy leghemoglobin encountered substantial pushback from other non-governmental organizations such as the Center for Food Safety, and went through multiple rounds of review to finally be considered Generally Recognized As Safe ("GRAS") by the FDA.[77] If the FDA is the initial regulator for space food in the colony, such a public status could establish a cautious tone of regulation early on. For private sector agencies, because their background has been more intensively focused on the technology, a much stronger voice in support of cell-cultured food systems should be expected. One cellular agriculture company even considers the lack of existing regulation for cell-cultured meat in these new colonies to be opportunities for consumers to embrace the technology more quickly, without legal hurdles.[21] However, the success of private and public entities in establishing a cell-cultured food system in a space colony will depend on their deep expertise and knowledge in the technology that they develop.

12.4.2 Labor Systems

The types of labor that would be needed to sustain a cell-cultured food system in a colony would differ from that on Earth.[21] Ideally, full automation of bioreactors and control systems will be used to minimize the need for human labor. Even so, the roles of resource management and allocation, systems engineering, and system technical maintenance would be important in the early days. As this becomes closer, more training will be needed on Earth to prepare future workers for these capabilities may be expected. It could be possible that, as the development of cell-cultured systems for space colonies progresses, so too will its role on Earth. The degree of acceptance for consuming cell-cultured meat on a space colony and on Earth may become intertwined. For example, increased viability and adoption of cell-cultured meat systems on Earth may give public and private sectors the confidence that space colonies can be maintained with similar systems. Traditional roles of farming livestock for the global food system on Earth could also further decrease with increased consumer acceptance of cell-cultured meat across a space colony and a shift to training for these new workforce roles for maintaining such a system.

12.4.3 New Cultural Practices

As systems of cell-cultured meat production are refined to the point where they can feed a space colony, new kinds of cuisine and culinary practices could evolve. Initially, cell-cultured meat may focus on imitating familiar foods on Earth, but eventually, due to the distinct environment of a space colony, new textures and experiences that do not currently exist could be developed.[21] Change beyond the current realm of human imagination has historically always happened. For example, a century ago in the US, chicken was not available as the eight-ounce, purely white meat breast portions seen today in supermarkets.[71, 72] Rather, chickens were only around a third of the size, and more cuts were sold with dark meat. The need to meet an increasing demand for white meat has shaped our food production system towards new ideals and challenges that are very different from the past.

This same principle can be used to design cell-cultured food systems specifically for the new space-colony environment. They can be both sustainable and enjoyable, such as growing specific consumer-preferred cuts of meat without waste and minimizing the need for animal agriculture. It will be necessary to respect and account for traditional religious and cultural practices as they relate to adopting cell-cultured meat in a place different from Earth. Questions of culture and tradition as they relate to cell-cultured meat are discussed in depth in Part V, *Cell-cultured Meat Around the World*.

The paradigms of the world are continually shifting, and a world that is not Earth, in which humans are supplied with food that is beyond what is currently available will be vastly different. The idea of establishing a space colony and sustaining it with cell-cultured food systems might seem impossible, frightening, or too removed from immediately purposeful activities to some. These were also feelings common to the dawn of the space age itself.

On April 20th, 2021, the Perseverance Mars Rover produced oxygen from the Martian atmosphere for the first time in history.[73] This **in situ resource utilization**, using and regenerating the resources available, opens the door to the possibility that life in space is not as far away as it may seem, and it is one that can rely on sustainable, closed-loop systems.[74] Throughout its existence, the space program has proved to us that, like President Kennedy said, “We set sail on this new sea because there is new knowledge to be gained, and new rights to be won, and they must be won and used for the progress of all”.[67] Cell-cultured meat is a frontier in itself, with an uncertain outcome, but it could play a critical role in enabling the exploration and continuation of humanity.

Fundamental Questions – Answered

1. **Given the nutritional challenges for humans in space, how could cell-cultured meat serve as a potential solution? What are the major challenges?**
   Cell-cultured meat production has the potential to provide fresh, familiar foods to space travelers. This technology could enable precise control over composition of meat products, which could then allow appropriate introduction of vital macro/micronutrients and flavor profiles into the diets of space travelers. However, further work is needed to predict if it is feasible to engineer such precise control into the production system at scale, and to also consider the effort required by the crew.

2. **Sociologically, what considerations should be made for the way cell-cultured food systems are introduced into a colony in space?**
   The space programs that are building towards long-term life in space may pave the way for how cell-cultured meat is adopted and how a space colony's society grows. New skills, cultural customs, and values will evolve with the colony, and it is necessary to be considerate and inclusive of the environment in which these practices take place.

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V

WORLD

SECTION 5

North America

Cultivated Meat Around the World: Economics, Tradition, and Culture in North America

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Chapter Abstract

To date, North America, specifically the United States, has become a global hub of cellular agriculture development. This chapter explores how the US became a world leader in conventional meat production and is now at the forefront of researching, developing, and commercializing the cellular agriculture movement. It will discuss how various North American markets may affect the development of cellular agriculture and how cellular agriculture will alter them in return. It will look at how economists analyze conventional meat trends and forecast cellular agriculture meat trends. The final section of the chapter discusses how US cultures and traditions could both hinder and propel the advancement of cellular agriculture.

Keywords

Meat
Farming
Economics
Culture
Tradition

Fundamental Questions

1. How has the meat landscape in North America evolved?
2. Who are the major players in conventional animal agriculture and cellular agriculture?
3. What can armchair economics reveal about the future of cell-cultured meat in North America?
4. How will conventional meat and cell-cultured meat compete in North American marketplaces?
5. How can the public affect the advancement of cellular agriculture in North America?
6. Are various societies in North America ready for cell-cultured meat?

Chapter Outline

13.1 Introduction to Meat in North America

13.2 The Meat Landscape in North America
13.2.1 History of Industrialized Animal Agriculture
13.2.2 Current Leaders in Conventional Meat Production
13.2.3 The Meat Industry's Partnerships with Academia, NGOs, and Trade Associations
13.2.4 Current Leaders in Cell-cultured Meat Production
13.2.5 Conventional Meat Company Investment in Cellular Agriculture

13.3 The Economics of Cell-cultured Meat in North America
13.3.1 Demand
13.3.2 Supply
13.3.3 The Market

13.4 Influence of Tradition and Culture on Cell-cultured Meat Adoption
13.4.1 Evaluating North America's Readiness for Cell-cultured Meat Adoption
13.4.2 The Role of Media in the Cellular Agriculture Revolution

13.1 Introduction

Americans living in the US eat more meat per capita than any other nation, with Canada and Mexico in 9th and 19th place, respectively. Meat plays an integral role not only in the diets of Americans, but in the identity and psyche of the nation. In addition, researchers believe meat consumption positively correlates with economic well-being. , An economic theory called Bennett's law suggests as people become wealthier, they begin to eat a more diverse diet, including more vegetables, dairy, and meat, and fewer carbohydrates.

This chapter will provide a brief overview of industrialized animal agriculture in North America, with a focus on the US; the industry at large; and the emerging field of cellular agriculture.

13.2 The Meat Landscape in North America

13.2.1 History of Industrialized Animal Agriculture

In 1870, nearly half of the US workforce was directly employed in agriculture, both animal and crop. By the early 2020s, fewer than two percent work the land. According to the Johns Hopkins Center for a Livable Future, "Over the brief span of the 20th century, agriculture underwent greater change than it had since it was first adopted some 13,000 years ago."

Despite a shrinking workforce, the US agricultural sector doubled in productivity between 1948 and 2015 due to an increase in inputs, such as fertilizers and pesticides. Mechanization also had a major impact, as tractors began to replace mules and horses in the early 1900s and had fully replaced animal power by 1970.

As crop production industrialized, so did livestock production. In the early 1900s, farmers began to fortify chicken feed with vitamin D, which allowed them to raise chickens indoors year-round. At the same time, as the US population grew, farmers could not keep up with the demand for meat, resulting in high prices and protesting consumers. This desire for cheap, plentiful meat motivated researchers who, in the 1950s, discovered that adding antibiotics to feed made chickens, pigs, and cattle grow faster. Researchers later discovered that feeding otherwise healthy animals prophylactic (preventative) antibiotics also helped to prevent and control disease when farm animals were tightly confined together. Refer to Chapter 3, *Animals,* for more information on the conditions in which these animals are raised. In addition, the US animal agriculture industry purchase around two-thirds of medically-important antibiotics sold in the country. Increasingly, conventional meat producers are committing to phasing out the use of prophylactic antibiotics after facing public backlash and stricter FDA regulation over high antibiotic usage creating antibiotic-resistant "superbugs."

Through selective breeding, meat producers have also created breeds of animals who grow faster with less feed. For example, a 2014 analysis found that today's industrially raised chickens grow four times faster than chickens raised 50 years prior.

Lastly, vertical integration, pioneered by Tyson Foods, has led to higher scale production, lower prices, and market consolidation. Vertical integration is a business strategy where a company expands its operations to control multiple stages of production, distribution, and/or sales of a product or service. In the case of Tyson Foods, the company vertically integrated by acquiring and controlling various stages of the poultry production process, from breeding and raising chickens, to processing and packaging the poultry products, to distributing and selling them to retailers and consumers. This allows the company to have more control over the supply chain, reduce costs, and increase profits.

While animal agriculture has undoubtedly strengthened the US economy, some critics in academia, intergovernmental organizations, the media, and non-governmental organizations argue that large-scale animal agricultural operations' intense focus on growth, and lax federal and state regulation, has come at the expense of public health, the environment, and animal welfare. , , ,

13.2.2 Current Leaders in Conventional Meat Production

In the latter half of the 20th century, concentrated animal feeding operations (CAFOs) largely displaced smaller farms. Refer to Chapter 3, *Animals*, for more information from the Environmental Protection Agency (EPA) on CAFOs. From 1980 to 2008, the number of land animals raised and slaughtered for food approximately tripled from three billion to nine billion, while the number of beef cattle operations fell by 41%, hog farms declined by 90%, and dairy farms fell by 80%. , From 1950 to 2007, the number of poultry farms fell by 98 percent, though the number of chickens raised for meat grew by more than 1,400%.

Today, the top three US chicken producers control 50%+ of the market, the top four US pork packers control 71% of the market, the top four US beef packers control 85% of the market, and the top four milk processors control 50% of the market. , Three of the top five global meat packers are based in the US and the US produces more poultry and beef than any other nation . Some market leaders in the US and abroad are beginning to invest in cellular agriculture.

13.2.3 The Meat Industry's Partnerships with Academia, NGOs, and Trade Associations

Leaders in conventional meat production now fund a substantial amount of research through US academia. In 1862, the US federal government launched land-grant universities on public lands, in part to fund agricultural research in academia. However, by the 1990s, agriculture industry funding began to outpace federal government funding. Using USDA data, the nonprofit organization, Food & Water

Watch, calculated that in 2009, “corporations, trade associations and foundations invested $822 million in agricultural research at land-grant universities, compared to $645 million from the USDA (in inflation-adjusted 2010 dollars).”

Conventional meat producers also have partnerships with numerous nonprofits and trade associations. The largest nonprofit, the American Farm Bureau Federation, spent $33 million in 2016 on advocacy efforts. The organization focuses on various issues that affect farmers and ranchers, such as international trade, environmental deregulation, immigration reform, and disaster relief. The largest industry trade associations include the North American Meat Institute, National Pork Producers Council, National Chicken Council, United Egg Producers, National Cattlemen’s Association, National Cattlemen’s Beef Association, and the National Milk Producers Federation.

13.2.4 Current Leaders in Cell-cultured Meat Production

As of June 2019, the cellular agriculture field comprised 28 companies, 43% of which are based in the US. Two-thirds of these are based in the San Francisco Bay Area.

Known as a hub for technological innovation and a corporate culture that values “risk-taking, creativity, invention, and sharing,” it’s no surprise that nearly a third of all cellular agriculture companies in the world are based in the San Francisco Bay Area. From 2010 to 2014, 43 percent of all domestic venture capital funding went to businesses in Silicon Valley. The area is also known for its "accelerators” and “incubators”: programs that provide initial seed funding, mentorship, and access to second-round investors for fledgling startups. One accelerator, IndieBio, has launched several of the San Francisco Bay Area’s cell-cultured meat companies. , ,

13.2.5 Conventional Meat Company Investment in Cellular Agriculture

In August 2017, Cargill became the first conventional meat company to invest in a cell-cultured meat company (Upside Foods). In January 2018, Tyson Foods, the world’s second largest meat producer, responsible for producing one in every five pounds (2.2 kg) of meat consumed in the US, followed in Cargill’s footsteps and also invested in Upside Foods. , Commenting on the investment, then-CEO Tom Hayes said, "If we can grow the meat without the animal, why wouldn’t we?"

US companies have also formed partnerships abroad. For example, San Francisco-based Eat JUST partnered with Toriyama, a popular Japanese wagyu beef producer, to develop cell-cultured meat using wagyu bovine cells. Tyson Foods has also invested in Future Meat Technologies, an Israeli company developing bioreactors and other manufacturing technology to produce cell-cultured meat.

Cellular agriculture startups hope that market incumbents such as Tyson Foods and Cargill will help them get their cell-cultured meat on grocery store shelves and restaurant menus faster, as they have decades-long distribution partnerships and the infrastructure to produce cell-cultured meat at scale. However, some in the conventional meat sector are opposed to cellular agriculture and see it as a threat to the industry. In February 2018, the US Cattlemen's Association petitioned the US Department of Agriculture (USDA) to prohibit cellular agriculture companies from using the terms "meat" and "beef." Months later, then-Missouri Governor Eric Greitens signed a bill into law that "prohibits misrepresenting a product as meat that is not derived from harvested production livestock or poultry." According to non-profit the Good Food Institute, as of May 2019, 26 states have introduced plant-based/cell-cultured food label bills, nine of which have passed to become law.

Despite the uncertain future of state-level laws regulating the marketing of cell-cultured meat, in March 2019 the USDA and the Federal Drug Administration (FDA) announced a formal agreement to jointly regulate cell-cultured meat and other cellular-agriculture products. More can be read about the history, current state, and future projections for federal regulation surrounding cell-cultured meat in Chapter 13, *Regulation*.

13.3 The Economics of Cell-cultured Meat in North America

The conventional meat industry in the US is a multibillion-dollar industry; the USDA estimates that total American all farming generated $132.8 billion in revenue in 2017, and the United Nations estimates that livestock contributes about 40% of the value of global agriculture. , In 2016, meat consumption in the US was the highest per capita in the world. US citizens eat 108lbs of chicken (49 kg), 57lbs of beef (26 kg), 51lbs of pork (23 kg), and about 1lb of sheep (0.45 kg) per person per year. This high demand for meat leads to commensurate high demand on resources. Of the land in the contiguous US, 41% is devoted to livestock. Of all the mammals on Earth, 60% are livestock, 36% are humans, and 4% are wild, in terms of biomass. In contrast, cell-cultured meat is expected to be more efficient, as the resources necessary to keep an animal moving, breathing, and otherwise functioning, as well as the resources needed to grow organs, bones, hooves, beaks, feathers, and skin, will not be needed. Shifting consumption towards cell-cultured meat could have a significant economic and environmental impact.

Any research discussing the impact of future-facing technology, such as cell-cultured meat, is necessarily speculative. This section will apply basic economic principles with the intention to gain some insights about how the economics of cell-cultured meat in North America may operate.

13.3.1 Demand

As with any market, there is supply and demand. Demand is driven by the preferences of consumers. To determine demand, certain questions must be answered, such as “How much will people value cell-cultured meat?” and “Will people be willing to pay a premium for cell-cultured meat over conventional meat?” At present, researchers are trying to estimate demand using surveys. Researchers are also considering how to best market cell-cultured meat. Research of this kind may help to forecast future demand. However, it is hard to assign value to something that is abstract, and even more so when the effects of future marketing and peer-to-peer exposure cannot be considered. There could be a large gap between how people say they will behave in the future, and how they actually behave once commercial products become available.

Due to the lack of empirical evidence, the available data can only predict cell-cultured meat’s prospects. If cell-cultured meat gains widespread approval, consumers will likely have a wide range of attitudes as to how much they would be willing to pay; some may value cell-cultured meat less than conventional meat, while others may value it more. Having a sizable consumer base that values cell-cultured meat above the high marginal costs of production will be important for financing research and development of the technology.

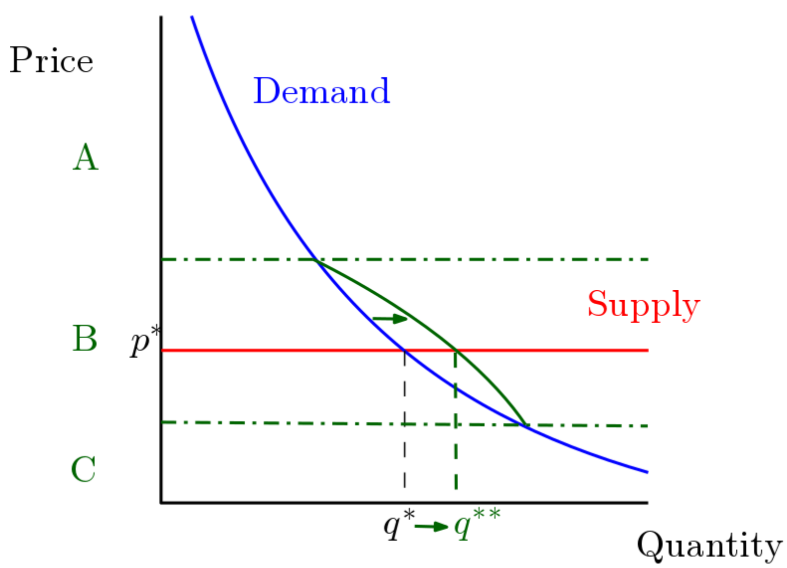

Figure 1. Advertisement targeting consumers in region B shifts out demand and increases equilibrium quantity from q to q**.*

Figure 1 illustrates this logic in a simple supply and demand chart. A constant marginal-cost supply curve and downward sloping demand curve intersect determining the equilibrium quantity, q, and equilibrium price, p*. Suppose advertising could be directed toward people in the three segments of the demand curve, A, B, and C, and the effect of advertising is to increase consumers’ valuation, thereby shifting out demand. Advertising should be focused on consumers at the margin in region B, who are consumers near the intersection point of the supply and demand curves, as only this* *would increase the quantity produced. Resources can also be focused on consumers in region A if there are ways to extract consumer surplus.*

Economists model advertising as an intervention that increases the value of a product. Advertising could be directed at either the high-demand early adopters or the marginal adopters. The former allows for the possibility of higher prices but with minimal increase in scale. The latter promotes more sales via the marginal adopters, but likely with less of an effect on price. Directing an advertising campaign instead toward those showing less interest in cell-cultured meat will likely be less effective: studies have shown that older women who currently eat more meat, are politically conservative, distrust science, or have food neophobia are less likely to be interested in trying cell-cultured meat.

Initial advertising could focus on early adopters and marginal adopters – that is people who are receptive to cell-cultured meat, but do not value it so much that they would buy it without the marketing. Marginal adopters may be individuals who like the taste of meat but are looking to cut back for environmental or animal welfare reasons. In April 2021, a survey of a large and diverse sample of the US population found that younger generations are more willing to try cell-cultured meat than older generations. In 2019, another survey found that, in the US, those who are more politically liberal, are more familiar with cell-cultured meat, and have less food neophobia report a higher intention to try cell-cultured meat. Other studies with US samples find a very high willingness to try cell-cultured meat, with 65% reporting definitely yes or probably yes, and nearly a third saying that they would definitely or probably eat cell-cultured meat as a replacement for farmed meat. In 2019, other research found very similar proportions with 65% probably or definitely willing to try, and 49% definitely or probably wanting to eat cell-cultured meat as a replacement. These figures present promising projections for the future consumer acceptance of cell-cultured meat, but there is still a significant gap between the common acceptance of conventional meat and this new product.

Whether consumers will view cell-cultured meat as a substitute for conventional meat is not yet clear. There are reasons to believe that the substitutability between cell-cultured meat and conventional meat will be less than perfect, especially in the early days. Companies will likely begin commercializing more simple meat products such as burgers and nuggets. For more information on the development timeline for cell-cultured meat products, please refer to Chapter 10, *Products Beyond the First Generation*. Minced chicken was the first commercially sold cell-cultured meat product due to its structural simplicity and small size, and additional minced meat products are likely to follow.[3,59] More research and development will be needed to produce cell-cultured meat with a complex 3D structure, such as a T-bone steak.

If cell-cultured minced meat or ground meat could be produced at a cost equal to or less than conventional minced or ground meat, there is strong reason to believe that conventional meat producers would not be able to compete in this product category. This could pressure farmers to cut the meat into steaks instead of mincing it. Ground beef is also made from lower-value parts of the carcass like chuck steak or round steak.

This means that asymmetric progress in the development of cell-cultured meat products could potentially lead to a *larger* supply of conventional meat products for which cell-cultured technology cannot currently produce an adequate substitute. However, the capacity to shift the output of conventional meat processes is limited, as there are still the byproduct cuts such as trimmings and other pieces of meat that are currently only commercially viable as ground meat.

It is possible that companies will eventually be able to manufacture a product that is near indistinguishable from conventional meat. As the substitutability of these products increases, large price differentials between the products may not be sustained. If a typical consumer does not perceive a difference between a conventional steak and a cell-cultured steak, they will lean toward the product that is priced lower. High substitutability could mean that products that have higher production costs will face strong pressure to exit the market. If cell-cultured meat is more costly to produce than conventional meat, and consumers do not place a large premium on cell-cultured meat, then cell-cultured meat will find trouble surviving in the marketplace. If cell-cultured meat is less costly to produce than conventional meat, then the pressure to exit will instead be placed on conventional animal farming.

Can demand support a price premium for cell-cultured meat in North America? Current consumption patterns are encouraging. The US and Canada have the 5th and 18th highest GDPs per capita in the world. Existing consumption patterns show robust demand for products based on production methods, such as organic and fair-trade. Organic food sales were around $50 billion in the US in 2019 with wide-ranging premiums up to 88%., As has been proved to be the case with plant-based products, it is likely that the US and Canada will develop an early and robust consumer base for cell-cultured meat products. Furthermore, in early 2021, researchers across several medical schools conducted a contingent-valuation study on a US sample to measure people's willingness to pay a premium for cell-cultured meat. The contingent valuation approach asks participants how much they would pay for a certain thing to happen. In this case they presented a hypothetical US $1 conventional hamburger and asked participants how much they would pay if the hamburger were instead cell-cultured. They found that participants were willing to pay a substantial premium in their two experimental conditions, with means of US $2.10 and US $2.66. Moreover, approximately 90% of consumers valued the cell-cultured hamburger more than the conventional hamburger. This result suggests that consumer demand may indeed support a price premium for cell-cultured meat.

In a future where cell-cultured meat can produce cost-competitive ground meat but not steaks, the profits of conventional animal agriculture are likely to decrease. An inexpensive cell-cultured ground meat could flood the market, providing cheap meat options for frugal consumers. Because there is some substitutability across meat products, these consumers may substitute ground meat even more frequently for steaks thereby decreasing the prices for all cuts. However, as long as some people highly value meat products that cell-cultured technologies cannot produce, conventional animal products will remain on the market, albeit at a decreased scale.

13.3.2 Supply

In producing conventional meat, the ratio of cuts is dictated by the fact that meat comes from the body parts of an animal with a fixed body plan. Since a chicken has two wings and two legs, the ratio of drumsticks to wings is 1:1. So, while conventional agriculture cannot produce just drumstick meat or just breast meat, this is theoretically not the case for cellular agriculture. In principle, any ratio of cuts could be produced assuming the technology to produce the cut exists. Moreover, with sufficiently advanced technology, entirely novel cuts could be made, potentially including novel varieties such as a chimera of beef tongue tissue and tenderloin tissue or a kangaroo and lamb steak.

As alluded to in the previous section, *Demand*, the flexibility of cell-cultured production technology may greatly change the pricing of different cuts. At present, pricing is based on demand (which cuts are valued by consumers) and supply, dictated by the fixed ratio inherent in the animal's body plan. In equilibrium, the price of a carcass should equal the marginal cost of producing a carcass; the price of a carcass is the mass of the carcass multiplied by the weighted average of the prices of all the different cuts, which can vary significantly. For example, with sufficiently advanced technology, a cellular agriculture manufacturing plant could produce only filet mignon from a specific breed of cow. This flexibility in production would result in very different pricing than the conventional meat equivalent. In equilibrium, the price of a pound of any given cut would equal the marginal cost of producing a pound of that cut, as opposed to the marginal cost per pound averaged over the whole carcass, as is the case with conventional agriculture. If the costs of production are the same for all cuts, then in a competitive market, all cuts would likely end up the same price.

The effect of scale is another important topic of production studied by economists. Usually, economists categorize the economies of scale into three categories. Decreasing returns to scale means that production becomes more costly per unit as the total output increases. Constant returns to scale means that the costs of production are independent of the scale, and increasing returns means that the costs decrease as the output increases. These properties of scale will have to be considered for large-scale cellular agriculture operations. First, consider the case of decreasing or constant returns to the scale of a manufacturing plant. Two plants, each of size X, would be as or more efficient than one large plant of size 2X. To defray shipping costs, it would be more profitable to have many plants across different regions. In this case, there would be many localized producers. In contrast, if there are increasing returns to scale the opposite effect would be expected: two plants, each of size X, would be less efficient than one large plant of size 2X. This would result in fewer but larger plants that would produce all the products and ship them around the world. Given that many of the cell-cultured meat companies are currently located in the US, Israel, and the Netherlands, it is possible that these regions would be the home to large production hubs. At some point, these companies and later entrants into the industry may choose to instead locate their production plants away from these areas. However, if cell-cultured meat is produced with increasing returns to scale, a few regions may become cell-cultured meat exporters while the rest of the world becomes cell-cultured meat importers.

The capacity for the products to be frozen could also have an important effect on the geographical distribution of production. It is likely that companies will initially aim for products that are freezable, as this would allow for later expiration times and therefore wider distribution and scale. However, some meats are best consumed fresh such as fish or shellfish. For example, in North America, major population centers are located thousands of miles away from each other across the continent (e.g., Los Angeles, Vancouver, Chicago, New York, Washington, DC, Mexico City). If importance is placed on freshness, plants may be located at regional hubs to distribute the freshest product possible.

Another force that would push towards regional concentration is what economists refer to as “agglomeration spillovers”, or the economic benefits that industries in a concentrated geographic area can gain from the proximity and interactions with other firms or industries in that area. Having a labor market filled with the right kind of specialized skills may be highly valuable to cell-cultured meat firms. This high value placed on a specialized labor pool is the accepted explanation for why technology hubs, such as Silicon Valley, exist. Technology hubs could grow and form around cell-cultured meat companies as well.

13.3.3 The Market

As the market for cell-cultured meat expands, market forces predict that costs will decrease, either because 1) manufacturing has increasing returns to scale and/or 2) more revenue will be available to fund research and development which will further decrease costs. As the costs come down, the total volume produced and consumed will increase. There are also some less obvious market implications. Generally, consumers prefer product diversity. With regards to aggregate consumer demand, a single model of car, for example, is unlikely to satisfy all consumers in the same way that a diverse product line-up would. With regards to individual consumer demand, a person doesn’t want to eat the same thing every day. But when markets are small, they cannot support product diversity as there are usually fixed costs associated with developing new products. As markets expand, the most successful markets offer a wide variety of products, including niche products that cater to the specific tastes of a diverse consumer base.

Initial products will aim to be generic and target large consumer bases. Later, with more advanced technology and a larger market, products may become specialized. North America contains the largest national economy, the US, the ninth largest national economy, Canada, and the 15th largest national economy, Mexico. This suggests that North American markets will likely sustain diverse cell-cultured products after the technology matures. Health-concerned parents may seek out omega-3 fortified chicken nuggets to feed their children; adventurous eaters may wish to experience a mastodon steak; consumers may even be able to request a specific formulation and cut of meat to make their favorite dish or try new cuisines. As there is potential to eventually produce any animal product from cells, cell-cultured meat may help conservation efforts to protect endangered species. Luxury food delicacies such as shark-fin soup, foie gras, and caviar, could become widely available at a much lower price, and then, lacking an air of specialness and exclusivity, potentially fall out of fashion. All of this is, of course, highly speculative and rests upon enormous progression from the current technological state.

13.4 Influence of Tradition and Culture on Cell-cultured Meat Adoption

Asked if they like animals, most US citizens will say that they do. But most will also say that they like eating meat. In one survey conducted at Oklahoma State University as many as 95 percent of people stated that the wellbeing of farm animals was important to them. At the same time, 92 percent of people in the US consume farm animals in the form of steaks, fish sticks, chicken tenders, or sausages. Researchers have dubbed concern for animal welfare while also enjoying eating meat the “meat paradox”. This, in turn, leads to cognitive dissonance, an uncomfortable feeling which arises whenever people hold dear two conflicting beliefs, for instance: “I love driving SUVs” and “I care about climate change.” Cellular agriculture can help resolve the meat paradox, allowing consumption of animal flesh without the potential for cognitive dissonance.

Similarly, some people’s desire for organic, antibiotic-free meat might prove problematic if people see cellular agriculture as artificial or synthetic. It would be important to stress in communications with consumers and the media that cell-cultured meat can be produced without antibiotics and with organic materials. On the plus side, the locavore movement (eating foods that have not traveled far) could play out positively for cellular agriculture, which can be developed in very close proximity to consumers. In the future, grocery or butcher stores could be equipped with small bioreactors to grow cell-cultured meat. Since such a village-scale approach might encourage contact with the donor animal and offer consumers a closer look at the technology involved, it could also help defuse worries of cell-cultured meat’s unnaturalness.

Yet meat-eating is about far more than consuming food. About 2.5 million years ago, human ancestors began eating scavenged animal flesh on the African savanna, and since then meat has been a central part of the human diet. Compared to other fare hominins relied on for nutrition, such as fruits, grasses or leaves, meat was loaded with calories and protein. It was highly valued, but on the other hand hard to obtain and spoiled fast. As such, it was a perfect food for sharing among the tribe. Men who brought a dead antelope or a zebra into the camp had power to decide who would get a chunk of the nutritious food and who would not, so that meat started to be linked with wealth and power. Throughout history, until very recently, meat was an expensive food, rarely eaten by the masses. In the US in 1909, the poorest consumed three times less chicken and 50 percent less beef than the rich. According to the scarcity principle formed by psychologist Robert Cialdini, such shortages of meat would have made it even more desirable. This symbolism behind meat, its connections with wealth and power, could potentially be made to work in favor of the public perception of cell-cultured meat.

13.4.1 Evaluating North America's Readiness for Cell-cultured Meat Adoption

Consumers are resistant to change their eating habits. When immigrants adapt their culture to that of their new country, traditional dishes from their homeland are among the last things to change. On the other hand, foods such as potatoes prove that products which may initially seem undesirable can find mainstream popularity after a relatively short time. Potatoes were considered pig food in 18th century France, until the royal court had a field of them planted and heavily guarded, as if they were treasure. Tomatoes were considered dangerous in 18th century England, and even pizza was not accepted at first, as it was seen as a communist food.

Openness to experience, which is a personality dimension, makes some people more likely to try new things, including foods. Such people could be targeted as early adopters of cell-cultured meats. Openness to experience tends to change after major life events; for example, it declines after marriage and increases after divorce. It also tends to decline with age. Evidence from countries as diverse as Germany, UK, Spain, and Czech Republic shows that openness to experience peaks somewhere between our 18th and 29th birthdays. Other surveys also suggest that Millennials (born between 1981 and 1996) like to experiment with novel products and flavors. Therefore, consumers in this age range would be prime adopters of cell-cultured meats.

Millennials may also adopt cell-cultured meats because of the potential healthiness of such products including lower saturated fat content and no hormones or antibiotics. A recent Nielsen Global Health & Wellness Survey showed that Millennials value food's health attributes more than any other generation. In addition, Generation Z (those born between 1997 and 2012), are the most willing to pay a premium for healthy foods.

Once cultivated meat takes hold in North America, it may spread quickly to other regions, particularly to Asia, like how Western meat-eating practices have spread to countries such as India or China in the past. In many Asian nations, meat-eating is seen as a sign of wealth, power, and freedom, as well as a symbol of Western culture and affluence, which many among the urban middle classes aspire to emulate. Even Gandhi, at some point in his life, believed that Hindus were weaker because they were vegetarian. He wrote in his autobiography: "It began to grow on me that meat eating was good… that, if the whole country took to meat-eating, the English could be overcome." In recent interviews young urban Indians talked about meat consumption as something that makes one modern and worldly. If Asia sees cell-cultured meat adopted readily in the West, it may follow suit. Cellular agriculture's spread to Asia is vital because of the rapid growth of demand for meat and seafood in this part of the world is projected to grow 78 percent from 2017 to 2050.

13.4.2 The Role of the Media in a Cellular Agriculture Revolution

The media's interest in cellular agriculture has potential pros and cons. For example, it could help popularize cell-cultured meat due to its novelty and coverage of mass venture investing, but it could also highlight potential problems with cell-cultured meat. According to some researchers, tasting events are a good way to focus the media's attention on the positive culinary values of cell-cultured meat, rather than a negative and inaccurate connotation with being "lab-grown" foods. Also, in certain outlets, the adoption of cellular agriculture is framed as being overly contingent upon vegetarian and vegan community adoption, while cellular agriculture will likely be adopted by a variety of different people and groups.

The language the media uses to describe cell-cultured meat is also extremely important. Just as calling horsemeat "cherry" helped 18th century Japanese people to stomach the food, a well-chosen nomenclature for cell-cultured meat may be critical for fostering consumer acceptance. However, despite the cell-cultured meat industry's efforts to encourage the use of phrases such as "clean meat", "cell-based meat", "cell-cultured meat" and similar terms, some major media outlets continue to reference "lab-grown meat" and "test-tube" steaks. The search for the perfect media-friendly name for cell-cultured meat continues, with some suggestions including "clean meat", "craft meat," "slaughter-free meat", and "cultivated meat." In one customer survey, these two last terms outperformed "cell-cultured meat" for appeal and likelihood to purchase.

Fundamental Questions – Answered

1. **How has the meat landscape in North America evolved?**
   Animal agriculture underwent greater change during the 20th century than it had since it was first adopted some 13,000 years ago. In 1870, nearly half of the US workforce was directly employed in animal agriculture, while by the early 2020s fewer than two percent work the land. To this end, animal agriculture processes have intensified greatly. For example, today's industrially raised chickens grow four times faster than chickens raised 50 years prior.

2. **Who are the major players in conventional animal agriculture and cellular agriculture?**
   In the latter half of the 20th century, industrialized factory farms largely displaced smaller farms. Three of the top five global meat companies are based in the US and the US produces more poultry and beef than any other nation. Similarly, the US is now the primary hub for cellular agriculture. Large conventional meat companies are enthusiastic about cellular agriculture, as former CEO of Tyson Foods Tom Hayes noted "If we can grow the meat without the animal, why wouldn't we?"

3. **What can armchair economics reveal about the future of cell-cultured meat in North America?**
   Basic economic principles can provide insight about the market repercussions of technological advances. The economic concepts of heterogeneous demand, value to the marginal consumer, substitutability, supply-and-demand curves, economies of scale, and preferences for diversity can help guide further inquiry.

4. **How will conventional meat and cell-cultured meat compete in North American marketplaces?**
   On the demand side, the degree of substitutability between cell-cultured and conventional meat will be a key determinant of the market outcome. On the supply side, not having animals' fixed body plans as a constraint could allow cellular agriculture to create new animal products much more efficiently.

5. **How can the public affect the advancement of cellular agriculture in North America?**
   The symbolism of meat consumption (of wealth and power) can be used to work in favor of cellular agriculture, while cognitive dissonance surrounding meat-eating can offer both challenges and opportunities: for some people cellular agriculture could help resolve the "meat paradox," while for others it can make the cognitive dissonance more pronounced.

6. **Are various societies in North America ready for cell-cultured meat?**
   Although food habits are hard to change, past sudden successes of potatoes, tomatoes and pizza suggest rapid societal acceptance is possible. Millennials and other demographic groups, who are generally more open to new experiences, and are more likely to be the early adopters.

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South America

Cultivated Meat Around the World: Economics, Tradition, and Culture in South America

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Chapter Abstract

This chapter exposes the history, current economic state, and culture and traditions surrounding meat production and consumption in Latin America to demonstrate the potential impact of cellular agriculture in the region. The heterogeneity of this territory has unique implications for developing the role of cellular agriculture in these diverse environments. At the same time, the adoption of cell-cultured meat will require recognizing the economic and political turmoil of the region and mitigating risks.

Keywords

Meat per Capita
Technology Transfer
Urbanization
Point of Diminishing Return
GDP
Capital
Free Trade Agreement
Gini Coefficient
Global Agriculture Trade
Scarcity of Natural Resources
Agricultural Commodities
Emerging Markets

Fundamental Questions

1. How can cellular agriculture alter the socioeconomic environment of Latin America?

2. How will the Latin American economy benefit from the adoption of cellular agriculture?

3. What elements make cellular agriculture attractive to compete with conventional meat practices in Latin America?

4. What economic and demographic elements can spark interest for cellular agriculture in the region?

5. How can cellular agriculture affect Latin America's farming sector?

6. How can Latin America's political environment promote or prevent the adoption of cellular agriculture?

Chapter Outline

14.1 Introduction

14.2 Conventional Meat in Latin America
14.2.1 History of Animal Agriculture in Latin America: From *Tierra del Fuego* to the Legacy of *La Conquista*
14.2.2 Conventional Meat Industry in Latin America
14.2.3 Cell-cultured Meat Prospects in Latin America and Intersections with Conventional Meat

14.3 Meat in Latin American Culture and Tradition
14.3.1 The Culture of Meat Consumption: Dishes, *ganaderia*, and *corrida de toros*
14.3.2 Other Latin American Meat Traditions
14.3.3 Historical Sentiment of Latin America Towards Western Technologies
14.3.4 Social Benefits of Developing Cellular Agriculture in Latin America
14.3.5 Cellular Agriculture Social Considerations in Latin America

14.4 Latin American Meat Industry Economy
14.4.1 The Current Economic State of Latin America and its Agriculture
14.4.2 Meat Consumption Trends
14.4.3 Potential Impact of Cell-cultured Meat in Latin America
14.4.4 Latin American Population Demographics
14.4.5 Income Levels in Latin American and Meat Consumption
14.4.6 Latin American Urbanization
14.4.7 Revenue Sources for Establishing Cellular Agriculture in Latin America
14.4.8 Latin American Technology Transfer in Worldwide Economies

14.5 Conclusion

14.1 Introduction

When correctly implemented, technological advancements can foster humanity's transcultural and societal advancement, thus fostering economic growth and global connectivity. Cellular agriculture is an innovative technology with the potential to improve the quality of life of Latin Americans. The uniqueness of the region can expose the complexity of transferring technologies into emerging economies. This chapter will examine the socioeconomic obstacles that cell-cultured meat products will face in Latin America, a territory where farming and livestock are essential elements for economic growth. Through this analysis, one can understand the factors driving the adoption of cellular agriculture and decipher its multifaceted benefits.

In Latin America, meat is ingrained into the culture to such a degree that it is intimately interwoven into the national identities of Latin Americans. Cellular agriculture can have a drastic impact in this territory, thereby also potentially shifting these cultures and identities. The early stage of the cell-cultured meat movement needs to recognize and address the barriers that can limit its adoption in Latin American territories.

Latin America has had periods of instabilities through dictatorships, corruption, and political scandals that interrupted the economic growth of many Latin American nations. If this technology is to become implemented throughout the region, the right partners must promote its integration into the region's meat culture. The perception of "Westernization" as a source of economic encroachment by highly developed nations could discourage the adoption of cellular agriculture. The cellular agriculture movement needs to become a pioneer, an altruistic conduit and mediator to fight economic inequality and poverty. Meat is a source of critical protein for the human body and a source of sustenance that can fight malnutrition. Therefore, whoever controls the products of this technology will likely transform the living quality of Latin Americans. Nations with the most highly developed cellular agriculture technology will decide how and to whom to distribute meat products in the future.

14.2 Conventional Meat in Latin America

For centuries, many rituals in Latin America used animal farming and hunting in their day-to-day activities. The evolution of tribes in the region depended on the consumption of animal meat and in improving agricultural techniques to feed the growing population. Presently, the consumption of meat has been normalized in the media and through its daily use in households and restaurants, and its production has become a lucrative part of the region's economy. All these factors have made eating meat an integral component of Latin American society.

To better understand the evolution of meat consumption in Latin America, this chapter will begin by evaluating how the region's history can be a symbol of cultural resilience. There is a lot to be learned from the anthropological origins of this region, which began with ancestors ancient tribes using tools to harvest their food. Moving forward into the present, humans have developed technological tools to suit society's feeding needs thus allowing us to better coexist with the natural environment.

14.2.1 History of Animal Agriculture in Latin America: From *Tierra del Fuego* to the Legacy of *La Conquista*

Agricultural practices in Latin America are unique because of their anthropological origin. In this regard, cellular agriculture does not have to reinvent the wheel. Instead, the meat industry can learn from Latin America's historical past to enhance the "future of meat." Practices from the Mesozoic era can teach us three main lessons about the evolution of food production. First, the environmental ecosystem can grow in peace with minimal intervention. Eating animal meat can hurt the environment through the processes in place that produce consumer meat products. Second, animals can be a source of inspiration to help build culture. Third, human technological advancements and ingenuity to look for multiple food sources can be the solution to living in harmony with the planet.

Scholars believe that mammals inhabited the territory that is now Latin America without human intrusion for more years than those who inhabited the African or European continents, which allowed for the ecosystems to grow with minimal anthropogenic intervention.[3] This may be one of the reasons why Latin America is presently so rich in its biodiversity and fauna. It is believed that the first placental mammals in the region originated during the Mesozoic era (251-66 million years ago), but it was not until many years later that scholars identified the first arrival of humans into the American continent.[4] The first evidence of human existence in the Americas dates to 11,000 years ago during the Paleolithic era, in *Tierra del Fuego*, what is now the area including and surrounding Chile.[4]

Upon the arrival of humans as a new species in Latin America, the region changed drastically. The entrance of humans to this new territory decimated the number of animals living in the area. There is archeological and paleontological evidence supporting the decline of large mammals as a result of human hunting.[5] The ecological changes combined with the appearance of human predators culminated in the extinction of animals and brought new challenges to the humans living in this land, with wave of extinction of two-thirds of the planet's megafauna during the Pleistocene era.[4] The American continent was one of the territories affected the most by this extinction:

> *Latin America suffered the most severe losses globally in absolute numbers: 52 genera or 83 percent of the total number of megafaunas. By the time the Holocene epoch began (11,700 BP–present), most of the megafauna of North and Latin America had disappeared forever.*[4]

Due to the extinction of large creatures, human tribes were forced to change their hunting habits and began domesticating more animals and working in the fields. This abrupt natural change enabled the shift of humans' relationship with the natural environment, one that would shape generations to come.[5]

Many indigenous communities of the pre-Columbian era developed their culture around inspiration from animals and nature. Latin America was one of the few places where animals lived among humans and were a source of companionship and ritualistic objects. For example, the pre-Columbian central Andean societies centered their economy and their social and ritual life around llamas and other mammals.[4] Andean communities built their civilization and rituals in the presence of animals as a source of inspiration to forge their culture. Similarly, other regions manifested the same patterns. Aztecs believed that the universe was connected by the same divine energy present in animals. For example, they would worship gods such as “el Xolote” (a sacred dog) and include animals in their sacred practices, commonly reptiles.[6] Animals were so ingrained in Latin America’s native culture that it became part of the status quo to protect their natural environment.

Indigenous Latin American tribes were one of the first people in the Western Hemisphere to use technological advancements to transform their environment and cultivate food. For example, the Incans carved terraces in the Andes and built irrigation channels to transport water into their cities.[7] This ingenuity enabled the Incas to cultivate crops that otherwise would not grow in their region. In the words of Samuel Beck, “The American Indian's greatest contribution to our civilization is, in the eyes of many experts, the patient cultivation from their original wild state… plants which are now more than half of our agricultural wealth.”[8] Table 1, below, details the origin of some goods that we consume globally in our modern diets. Foods such as avocado, tomato, and sweet potato originated in Latin America. Cellular agriculture is a similar technological advancement which mirrors those that generations before developed to improve their society, and, historically, Latin America is no stranger to embracing these changes.

Table 1.[9]

Common foods that Originated in the Americas.*

Name of food [Ref.]	Region of origin	How prepared	Major nutrients provided
Vegetables			
Casava [1]	Brazil	Cooked vegetable or bread	Carbohydrate
Chili & bell peppers	Central America	Cooked, raw, or seasoning	Vitamin C, flavonoids
Jerusalem Artichoke	North America	Raw or cooked	Probiotic fiber, minerals, B vitamins
Lima Beans	South America	Cooked	Protein, B vitamins, minerals
Pole Beans: black turtle, pinto, navy, kidney, & cranberry beans	Probably originated in South America but possibly North & South America	Cooked & used in breads	Protein, minerals, B vitamins, fiber
Potatoes [6]	Peru	Cooked & baked	Carbohydrate, potassium
Pumpkin	North America	Cooked	Vitamins A & C
Squash varieties	North America	Cooked	Variable
Sweet Potatoes [7]	South & Central America	Cooked	Vitamin A, folate, minerals
Tomatoes	South & Central America	Raw & cooked	Vitamins A, C, K, potassium, lycopene
Fruits			
Avocado [8]	Mexico	Raw & sauces	Essential fats, B vitamins & A, E, K, & potassium
Black raspberry	North America	Raw, cooked, juice	Vitamin C, anthocyanins, ellagic acid, manganese
Blueberry	North America	Raw, cooked	Vitamins C & K, manganese, anthocyanins
Cacao, chocolate	Central America & Mexico	Prepared as chocolate	B vitamins, minerals, polyphenols
Cranberry	Northern North America	Cooked, medicinal herb	Vitamins A, E, & K
Guava	Mexico to Northern South America	Raw, cooked, juice	Very high in Vitamin C, & lycopene
Papaya	Mexico to South America	Raw, cooked	Vitamins A, E, & K, potassium, lycopene
Pineapple	South America	Raw, cooked	Vitamin C, folate
Strawberry [9]	Eastern North America	Raw	Vitamin C, fiber, minerals
Grains			
Amaranth [10]	Mexico	Baked breads & cooked	B vitamins, protein, minerals
Corn [11]	Mexico, Central America	Cooked as vegetable & grain, baked & fried grain breads	Protein, B vitamins, fiber, magnesium, potassium
Quinoa	South America, Andes	Cooked cereal	Protein, B vitamins, fiber, minerals
Wild Rice [12]	North America	Cooked cereal	Protein, B vitamins, minerals
Nuts & seeds			
Black Walnut	Eastern North America	Raw, cooked, medicinal extracts	Protein, B vitamins, fiber, minerals, essential fatty acids [13]
Cashew	Brazil	Eaten semi-raw or cooked	Protein, minerals, B vitamins,
Peanut	Argentina	Raw, cooked, roasted	Protein, B vitamins, fatty acids, vitamin E, minerals
Pecan [14]	Southern USA, Mexico	Raw, cooked, baked	Protein, fatty acids, B & E vitamins, minerals
Sunflower	North (most species) & South America	Raw, cooked, roasted	Fatty acids, protein, B & E vitamins, minerals
Meats			
Bison (Buffalo)	North America	Cooked	Protein, B vitamins, iron
Turkey	North America	Cooked	Protein, B vitamins, minerals
Sugar & spices			
Allspice	Caribbean, Mexico, Central America	Seasoning	
Maple Syrup	Northeastern USA	Sweetener	Sugar, minerals
Vanilla	Mexico, Central America	Flavoring	

With the advent of colonization in Latin America, the natural ecosystem of the region shifted once again. The arrival of Europeans introduced new species such as horses as well as new farming technologies. The merging of "new and old worlds" culminated in many changes that affected the region. One of the Spaniard's legacies was pork diets and other greasy foods that continue to prevail in region today. This established diet suggests that cellular agriculture in the region should focus on producing pork products. At the same time, the encounter also brought new viruses and bacteria that decimated the populations. Scholars estimate that at one point, there were eighty million Mesoamericans living in Mexico, and by 1620 the population was reduced to one million.[6] Latin America would never be the same after *La Conquista*" (The Conquest).

When humans arrived in Latin American territory, it was a natural paradise with a seemingly unlimited supply of animals to hunt. This changed drastically due to temperature changes and extinction following unsustainable hunting. Due to this shift, native tribes had to adapt their practices and invent new technologies to survive and coexist with animals—a lesson that modern society can employ today to fight the current climate change battle. Perhaps the most important thing to be learned from Latin America's abrupt climate change and the legacy of *La Conquista* is that Latin American cultures are resilient and adaptive to a shifting environment and its associated challenges. This general sense of adaptability presents a strong case for why cellular agriculture should become an established practice in this region.

14.2.2 Conventional Meat Industry in Latin America

Globally, animal-based protein consumption is expected to increase up to 80% by 2050.[10] The perpetually increasing demand for additional protein in our diets pressures the farming industry to supply more meat. As a result of the rising demand for livestock, Latin America and the Caribbean regions have increased their production. Therefore, the meat sector contributes to 46% of the agricultural domestic product of Latin America, which is already 3.6 times higher than the worldwide average.[11] *The Food and Agriculture Organization of the United Nations* published that: "although Latin America and the Caribbean account for only 13.5% of the world's population, they produce a little over 23% of beef and buffalo meat and 21.4% of poultry at a global level."[11] These statistics are significant to the region and the globe because over one billion people in the world consume these products and 70% of the rural poor in Latin America depend on this industry to survive.[11] The same correlation is seen in the production of livestock, where Brazil is the world leader (see Figure 1).

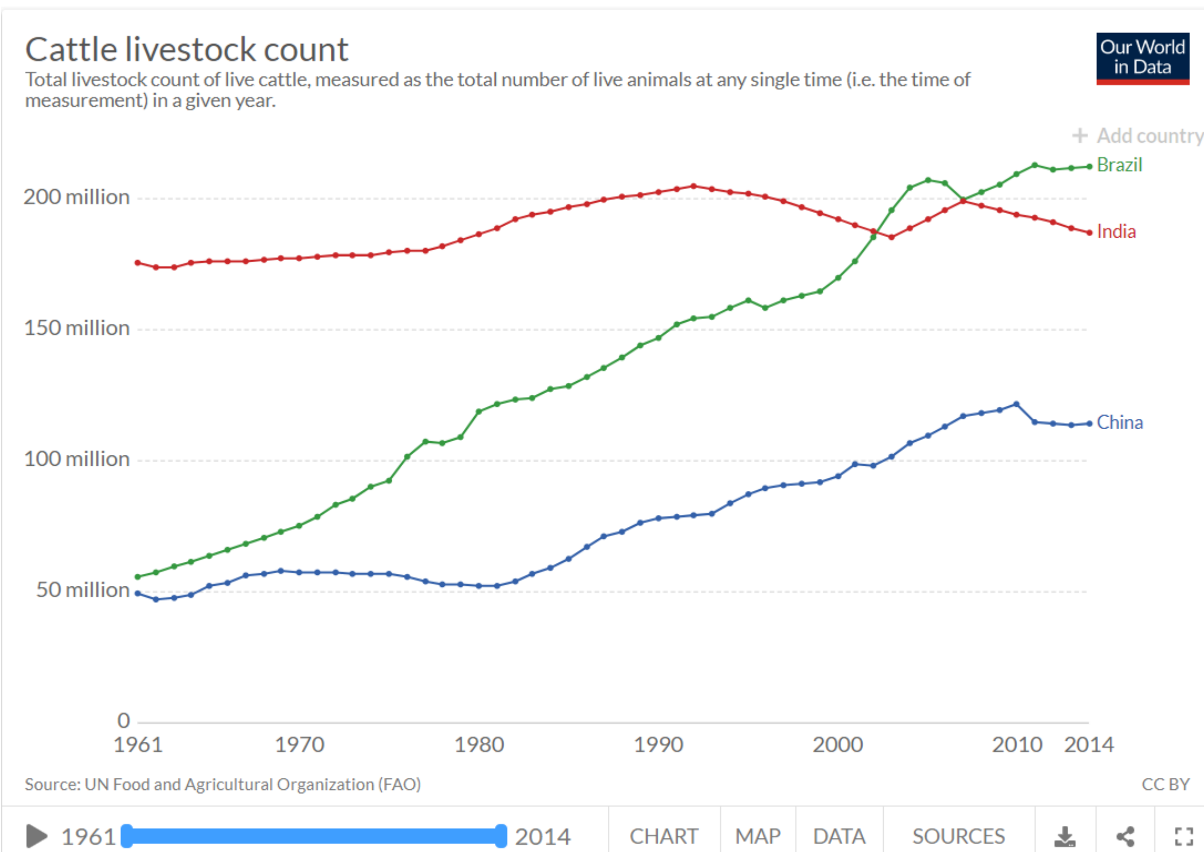

Figure 1.

Beef consumption in Latin America averages about 45 kg. This is approximately two and a half to three times the consumption levels compared to other global regions.[12] In 2010, XX stated:

> *With a modest $10,200 per capita gross domestic product (GDP), Brazil's population of nearly 200 million consumes much less beef on a per capita basis than Argentines (nearly 41 million consumers with a per capita GDP of $13,800) and Uruguayans (3.5 million consumers with a per capita GDP of $12,600).*[12]

Latin America is also the global leader in distributing meat to other countries, for example, to Asia and Russia.[12] *Our World In Data,* an online scientific publication based at Oxford University, discovered that: "Globally, cattle meat production has more than doubled since 1961 - increasing from 28 million tons per year to 68 million tons in 2014."[13] At this time, Latin America became a key player in the meat industry. Figure 2 displays the global production of meat in 2014 and the Latin American countries dominating the production of beef.

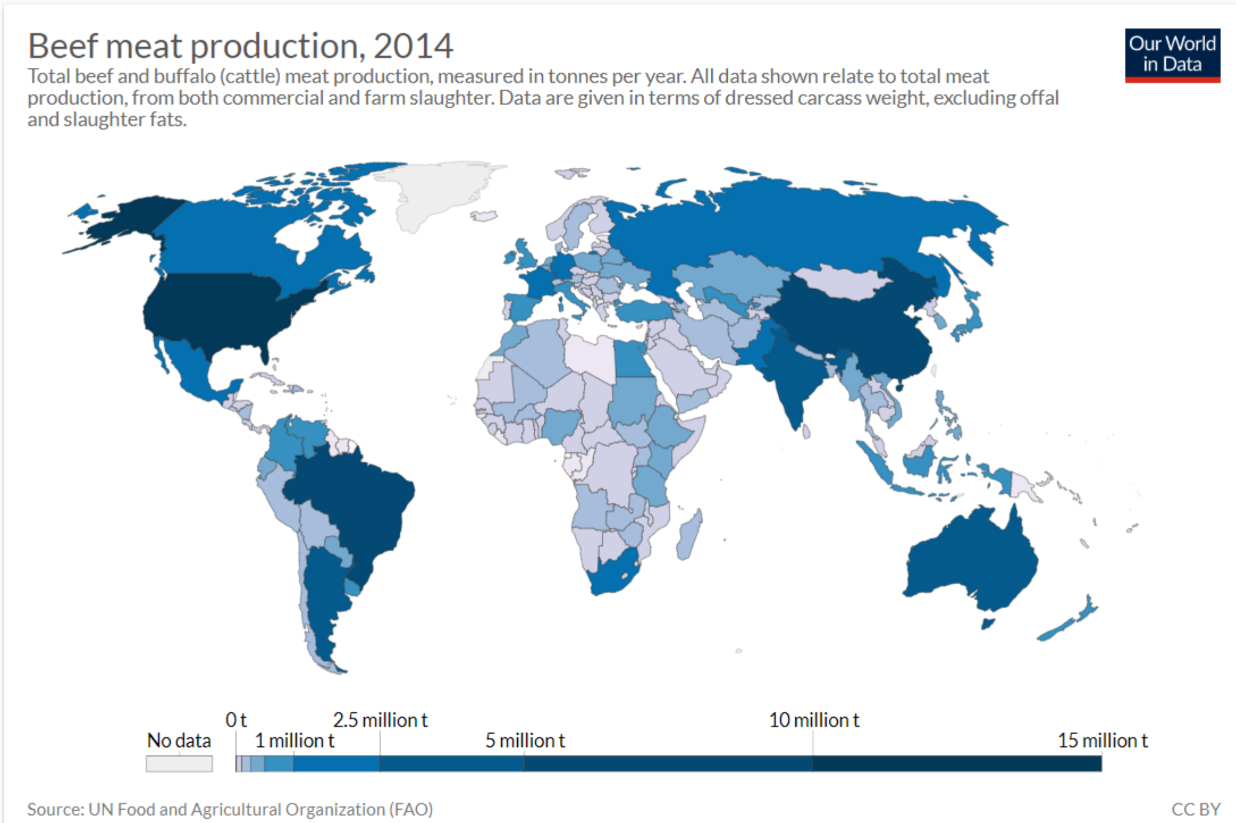

Figure 2.

While other countries such as the United States opted for factory farming to supply the enormous demand for meat, Latin America depends upon traditional, smallholder farms. To provide details, *The Food and Agriculture Organization of the United Nations* found that:[11]

- *In Bolivia, small producers own 43% of the national bovine population*
- *In Ecuador, 84% of rural households own livestock, with an average of 2.8 heads per household*
- *In Colombia, small producers represent 80.7% of the total of the properties nationwide*

However, the consumption of beef varies in each country and fish, and poultry are also very prevalent depending on the country. Table 2 below shows the overall production of meat in Latin America between 2013-2018. Overall, the total volume has consistently increased with Brazil as the country with the largest meat production in tonnage.

Table 2. Total Meat Volume (in tons) Produced in Latin American Nations Between 2013-2018[14]

Region	Product	2013	2014	2015	2016	2017	2018
Latin America	Meat	**34.109,30**	**34.641,70**	**34.743,10**	**34.888,10**	**35.246,00**	**35.094,30**
Argentina	Meat	3.324,60	3.460,70	3.394,20	3.414,70	3.381,00	3.337,40
Brazil	Meat	19.942,00	20.072,30	19.905,00	19.788,40	19.864,30	19.533,40
Chile	Meat	1.094,50	1.120,60	1.120,60	1.134,20	1.136,30	1.116,30
Colombia	Meat	1.650,00	1.680,90	1.710,20	1.730,20	1.773,10	1.817,00
Mexico	Meat	5.370,80	5.487,10	5.746,90	5.900,60	6.103,60	6.271,40
Peru	Meat	1.219,50	1.277,00	1.289,80	1.313,00	1.329,30	1.313,30
Venezuela	Meat	1.507,90	1.543,10	1.576,40	1.607,00	1.658,40	1.705,50

Poultry production across Latin America has also consistently increased between 2013 and 2018 (Figure 4). As was the case with beef, Brazil's production of poultry contributes to half of the total production in Latin America. Mexico and Peru follow as the next largest producers of poultry.

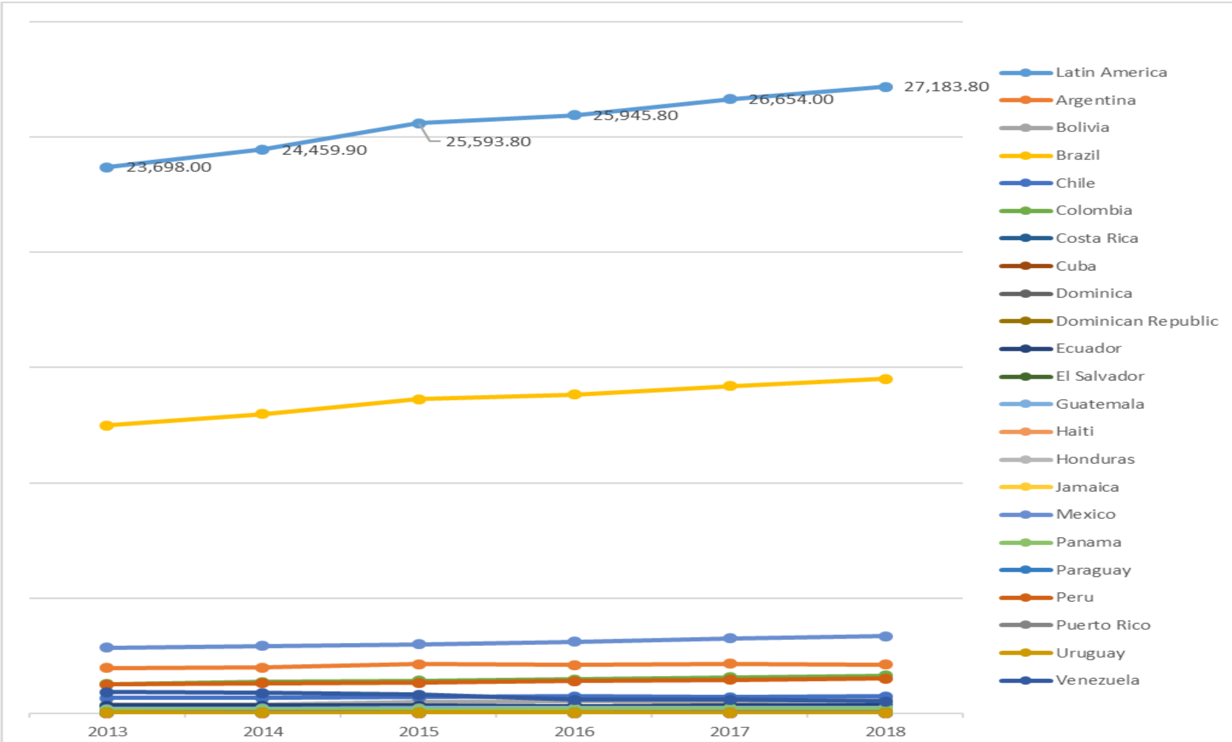

Figure 4. Poultry Market Size in Latin America between 2013-2018[14]

A similar pattern emerges across Latin America in terms of the market sizes of seafood (Figure 5). Between 2013-2018, the seafood industry in Latin America grew. As in the case of land-based meat production, Brazil's seafood production more than doubles that of other countries in the region, cementing it as the largest producer. Surprisingly, Peru´s seafood production ranks second in Latin America. This is largely because Peru's culinary culture is world-renowned for its unique seafood dishes.

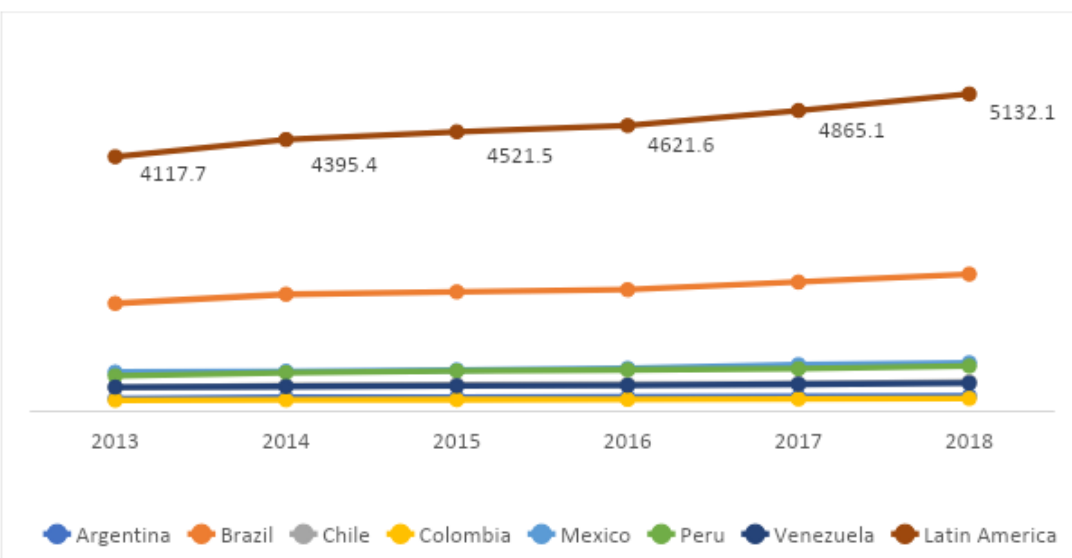

Figure 5. Seafood Market Size in Latin America 2013-2018[14]

Figure 6 shows the total market size of production in Latin America for beef, seafood, and poultry. As of 2018, the largest meat market segment corresponds to beef production with a total of >35 million tons, followed by poultry with >27 million tons, and >5 million tons of seafood. By aggregating this information together from these three sources of meat, Latin America emerges as a prime target region globally for replacing and/or supplementing conventional meat production and encouraging cellular agriculture to produce meat.

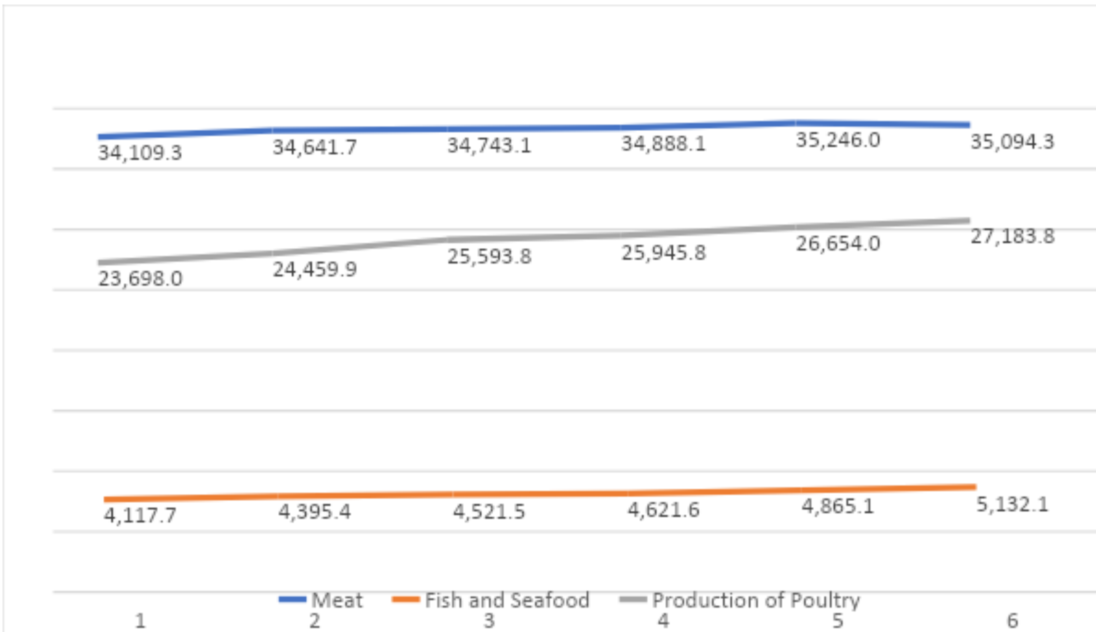

Figure 6. Market size comparisons of beef, poultry, and seafood in Latin America from 2013-2018.[14]

14.2.3 Cell-Cultured Meat Prospects in Latin America and Intersections with Conventional Meat

There is currently no formal body advancing the implementation of cell-cultured meat products in Latin America, and there are concerns about health problems as a result of high-meat diets. “The countries of Latin America and the Caribbean are in the middle of an obesity crisis. The UN’s Food and Agriculture Organization estimates that a majority of people are overweight in all but three countries of the region.”[15] There is a growing concern in how to shift the eating habits in the region to be healthier, but that may come at the expense of fighting traditional food habits. Poor health means an increase in government spending and taxes, which has prompted a dialogue around these issues, which culvitvated meat will need to address.

In the short term, it is highly unlikely that cell-cultured products can replace the consumption of regular meat in Latin America, mostly due to its current portrayal associated with a laboratory setting. If cell-cultured meat is to be successfully adopted in this territory, it needs to distance itself from its current association with laboratories. Latin Americans' idea of good meat depends on "*el corte de la carne*", which means the way the butcher cuts the meat. To do this, cellular agriculture companies will need to adjust how they present and display their meat products in the supermarkets to a way that is like how meat is currently marketed.

As of 2021, there are no Latin American meat corporations driving research and investments in cellular agriculture technologies. However, the potential for stem cell research in the region can change as the established industry becomes more accepting of this technology, along with the rest of the world. Over the past five years, major newspapers in Latin America have written about the evolution of cell-cultured products and their unique uses. There is minimal awareness of the technology, but this can change with strong partnerships. In Spanish, this technology has been described as "*carne artificial*" (artificial meat), "*carne de laboratorio*" (lab meat), and "*carne sintentica*" (synthetic meat).[17,18] An Argentinian startup called Granja Cellular partnered with the University of San Martin to do research.[19] However, one of the major concerns is how cultured meat companies will compete with their counterparts in other countries that have invested more time and money into cellular agriculture research.

Cell-cultured meat can use some existing infrastructure from the current conventional meat establishment including transportation, supply chains, supermarkets, cooling systems, and more. Adopting and adapting existing infrastructure will need to be done while being sure to distance cell-cultured meat products from an association with processed and artificial meat. As this shift occurs, cell-cultured meat will likely face resistance from the conventional meat industry that is entrenched in the region. To succeed, cellular agriculture companies can partner with the largest meat suppliers in Latin America and the vegan and vegetarian communities that exists in these countries.

The production of meat from traditional agriculture is detrimental to the natural environment. The Amazon is the largest tropical rainforest, often referred to as the lungs of the Earth. Animal pastures have been blamed for 90% of deforestation in the Brazilian Amazon.[15] Meat production in Latin America damages the natural environment and it is society's global responsibility to protect this natural resource.

Globally, the demand for meat "will put our agriculture at risk 3/4 of our agriculture land, and 2/3 of greenhouse gasses emissions will produce up to 37% of the protein consumed globally."[11] Latin America is home to numerous critical natural resources and the largest source of carbon capture in the world. It will be in the best interest of not only Latin American countries, but the entire world, to seek initiatives to protect their natural resources and investing in cellular agriculture to produce meat may be one of the best ways.

14.3 Meat in Latin American Culture and Traditions

Meat consumption in Latin America is deeply imbedded into its various cultural traditions. An increase or decrease in meat consumption affects Latin American people's sense of culture and national identity. Diego Vecino, an Argentinian writer, described the country's decline in meat consumption as the nation being "immersed in shame," since meat consumption has come to define Argentinian identity.[15] Latin America is widely known for its Brazilian and Argentinian *rodizios*, which are "all you can eat" restaurants that serve a variety of meat (Figure 7). *Rodizios* prepare their dishes to captivate even the most exquisite food connoisseur. They are a point of national pride, and thus spark rivalries that can equal those between national soccer teams. Therefore, cellular agriculture can prove to the world that this technology can re-create the best meat products to satisfy even the most demanding clients in Latin America and beyond.

Figure 7. Patrons at a *Rodizio*.[35]

14.3.1 The Culture of Meat Consumption: Dishes, *Ganaderia*, and *Corrida de Toros*

A great source of the region's employment, traditions, and even religious importance comes from cattle ranchers or *ganaderos*. Livestock is valuable in Latin America, and beef production or *ganaderia* is considered an important profession and economically valuable across the whole region. Some countries in Latin America, such as Uruguay and Argentina, have distinct names to refer to cattle ranchers as *gaucho*s or cowboys. This is a culture developed in the *Pampas*, the lowlands in Latin America. In the mid-18th century, *gauchos* hunted herds of wild horses and cattle that roamed freely on the extensive grasslands [36] Very much like American cowboy culture, *gauchos* have become an integral part of the local culture and representative of national pride.[37] To this day, many people in Argentina and Uruguay refer to themselves as *gauchos*.

14.3.2 Other Latin American Meat Traditions

Latin American countries celebrate several national holidays that use meat to gather the community. It is commonplace to see people gathering at parties and enjoying food prepared from a variety of traditional meat dishes such as *bandeja paisa*, *asado criollo*, *gallo pinto*, *chiles rellenos* use meat. In addition, another historical tradition that continues in some parts of Latin America, which involves meat, is *corrida de toros* pictured below when a bull fights for its life until it is killed. During this event, it is common for those watching to consume meat dishes. In addition, occasionally the next day after the event, people can buy meat derived from the killing of these animals. While there has been some opposition to this practice, some will argue that it is an integral part of Latin American history.

Figure 8. ***Corrida de toros***.[38]

14.3.3 Historical Sentiment of Latin America Towards Western Technologies

To study the influence of agricultural business in the region, one must examine the historical landscape and perception held by some that Western technologies are considered an "impending force that can hinder national development." The current negative sentiment towards these technologies has resulted from practices of exploitation from Western powers onto locals, such was the case of *las bananeras* or banana plantations. Historically, Western companies have underpaid their employees and shut down strikes that sought to denounce the poor working conditions of its workers. For example, in Colombia the US United Fruit company (now Chiquita Banana) was associated with a massacre that killed over 3,000 workers in 1928. Events such as these traumatized the region and have generated historical distrust of foreign companies. However, this exploitation is not limited to foreign companies. Often when new technologies are introduced into Latin America, a few wealthy individuals quickly build monopolized corporations that have a similarly harmful effect on the region. Cellular agriculture efforts need to avoid presenting themselves as a foreign effort detached from national interests. Rather, cellular agriculture initiatives in Latin America should be established as independent organizations. Furthermore, Latin America is unique in that historically, it has had militia groups that spread opposition of Western technologies. While these militia groups have been losing influence, cellular agriculture will need to recognize this challenge.

14.3.4 Social Benefits of Developing Cellular Agriculture in Latin America

Latin America is one of the most economically disparate regions in the world (Figure 8). Although income inequality has fallen in recent years, Latin America remains the most unequal region in the world. In 2014, it was cited in XX that "the richest 10% of people in Latin America had amassed 71% of the region's wealth."[36] To reduce this disparity, the region will need strong public policy. One point to consider in establishing policies which could address income disparities in the region is to encourage offering high protein and nutritious meat alternatives in places such as schools. If cellular agriculture technology manages to decrease the price of meat, the average household can potentially have access to cell-cultured meat.

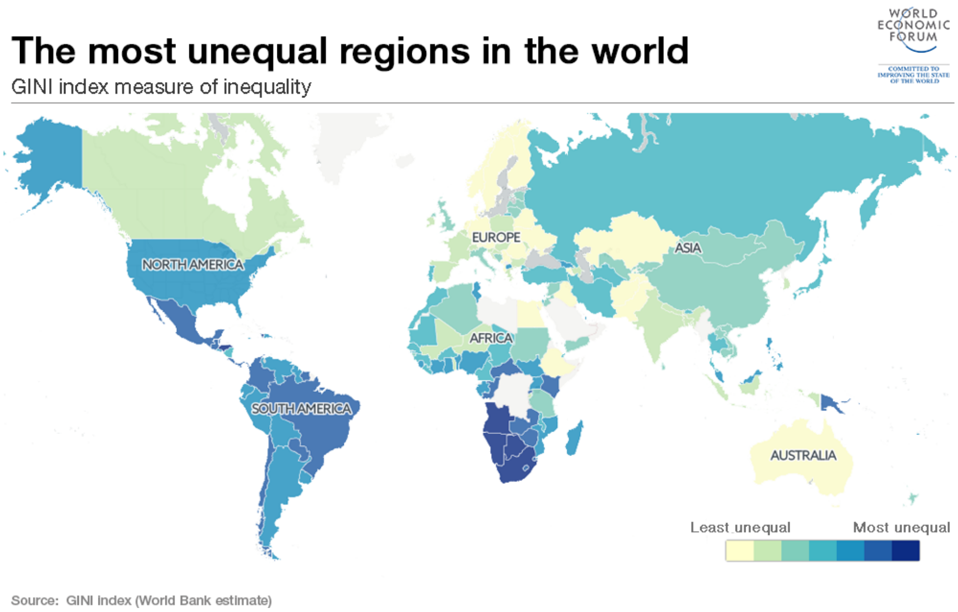

Figure 8. [35]

14.3.5 Cellular Agriculture Social Considerations in Latin America

There are a few important things considerations for introducing cellular agriculture to Latin America:

- Women are the primary decision-makers when buying food. In Latin America, gender relations mark the progress of technology, particularly in the food industry.
- Food regions and communities want to differentiate from one other by creating their own ethnic foods. Featuring cell-cultured meat in the local cuisine and ensure its presence in traditional dishes could address this potential challenge.
- As a result of rapid technological advancement worldwide following the COVID-19 pandemic, there is tremendous opportunity to disseminate information on cellular agriculture across a wide region such as Latin America.

14.4 Latin American Meat Industry Economics

14.4.1 The Current Economic State of Latin America and its Agriculture

When looking at global meat consumption, Latin America's meat appetite makes it a prime market opportunity to develop cell-cultured products. *The Organization for Economic Cooperation and Development* publishes a study of the yearly meat consumption per country. Their research revealed that in 2016, the United States was the largest meat consumer in the world with an average of 97 kg per capita per year.[20] Argentina and its neighboring country Uruguay followed with an average of 86 and 81 kg, respectively. Out of the ten countries that eat the most meat, four of them are in Latin America (Figure 9). To put this figure in context, if one were to add the average meat consumption per capita of Argentina, Uruguay, Brazil, and Chile, this would equate to 4.5 times more meat consumption than all 27 countries in European Union. Latin Americans love meat, and their high consumption rivals only that of a few others in the world.

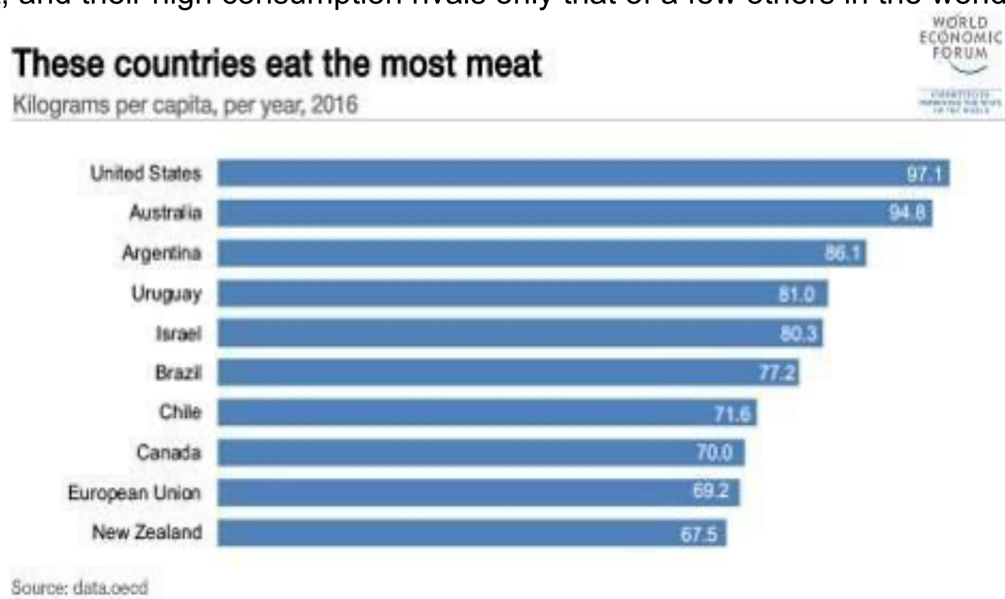

Figure 9. [20]

14.4.2 Meat Consumption Trends

Meat consumption has increased globally since 1961, with all types of per capita meat consumption having increased by approximately 20 kg per year.[21] The countries that have shown the largest increases of per capita meat consumption are China and Brazil, two countries which experienced major economic growth spurts throughout the last few decades. Per capita poultry consumption in Latin America from 1961 to 2013 increased 1,679%, and beef and buffalo consumption per capita increased 18% during the same period (Figure 10).[21]

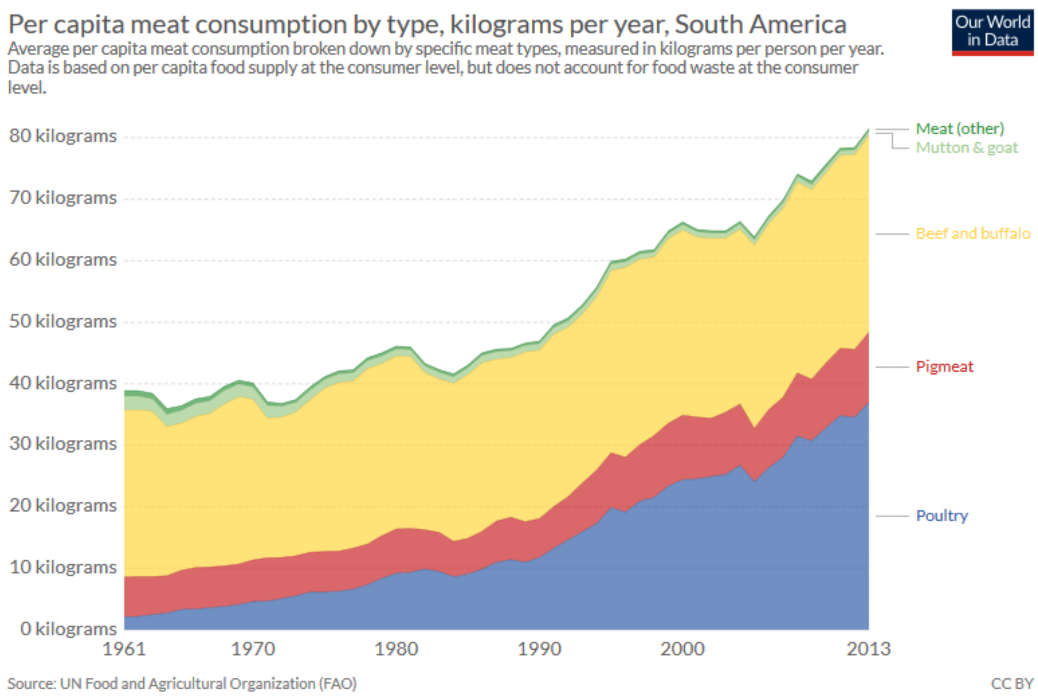

Figure 10. 21

14.4.3 Potential Impact of Cell-cultured Meat in Latin America

The World Health Organization cites three economic forces driving the demand for animal protein: 1) population demographics, 2) level of income, and 3) urbanization.[22] Latin America embraces these three elements, which makes it a salient target to study the adoption of cellular agriculture technologies.

14.4.4 Latin American Population Demographics

Latin America's population is younger than in most parts of the world.[23] According to the International Monetary Fund (IMF), Latin American women have, on average, a little more than two children, which is higher than in most developed countries.[23] In addition, the current technological improvements in healthcare can culminate in a good omen for the region.

Previously, many Latin Americans would abandon their countries to settle in other places such as the United States. However, the Pew Research Center, a non-partisan US fact tank, found that this migration trend is now the turning and there are now more people staying in Latin American countries than leaving.[24] This can be modeled by economists forecasting more accurate predictions for entrepreneurial opportunities which attracts private investments from other countries. However, emigration trends reversed in 2020 as a result of the COVID-19 pandemic. In addition, a series of natural disasters also impacted Central America.

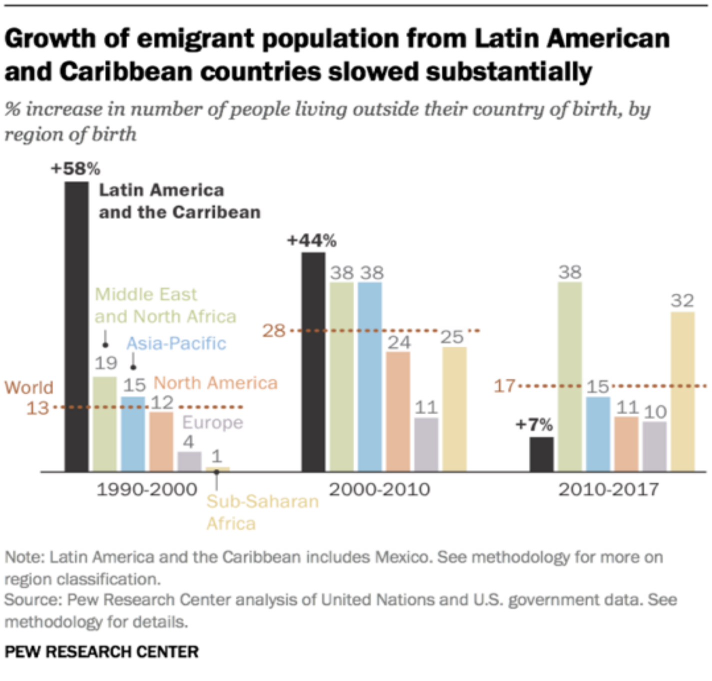

Figure 11.[24]

14.4.5 Income Levels in Latin America and Meat Consumption

Financial investing and spending theories argue that there is a positive relationship between an individual's rising income and their protein consumption. Paradoxically, as a country's GDP rises, there is a corresponding increase in meat consumption.[25] Although, this positive relationship has a point of diminishing returns in high-income brackets when they reach their maximum food spending. In simpler terms, just because people earn more money, it does not mean that they will spend all of it on food, since they can buy other assets to satisfy other non-essential needs. For the most part, a wealth increase in lower income brackets can augment protein consumption. To increase private investments and higher income in Latin America, the cellular agriculture industry could have a unique opportunity to monetize its investments because this territory has not reached its economic peak.

14.4.6 Latin American Urbanization

There is also a positive correlation between increasing urbanization and meat consumption. "Latin America is the planet's most urbanized region. In just over a generation - between 1950 and 2010, the proportion of people living in cities grew from 30% to more than 85%."[26] As more people move into cities, the population growth will likely drive demand for a variety of healthier food options. This could also potentially include cell-cultured meat products. Urbanization drives improvements in infrastructure such as roads, better cooling systems, and manufacturing. Altogether, urbanization advances the commercialization of perishable goods like meat. Latin America's population growth and worldwide technology advancements can also enable further urbanization in these territories.

14.4.7 Revenue Sources for Establishing Cellular Agriculture in Latin America

If Latin American meat production were to start supporting cellular agriculture, national economies would have to pivot to include revenue sources that can supplement the potential economic damage done to the conventional meat industry. Whereas global agricultural productivity is expected to increase by 10%, the Latin American region exhibits a more positive outlook. A report by the Organization for Economic Cooperation Development–Food and Agriculture Organization (OECD-FAO) of the United Nations Agricultural Outlook for 2018-2027 forecasted that the region's crop production would increase by 22% in this time frame. Similarly, livestock production would present an upward trend with a 16% increase that is considered a source of wealth in the region.[27] However, this increase was dependent on the export of beef and fish into other countries. The same report highlights that in the world economy, Latin America is responsible for 23% of fish production with an annual growth rate of 2.7%. With respect to meat, both organizations, the FAO and OECD, agree that meat consumption will decrease in the next ten years from 1.4% to 1.2%. Simply stated, they expect the consumption of chicken and fish to grow, whereas meat consumption will decrease in Latin America.[28]

The decrease in both meat consumption and production can hurt many Latin American economies.

Even countries such as Colombia that are famous for exporting non-meat products such as coffee and bananas still depend on meat production. Cattle production or *ganaderia* in Colombia represents more than twice the production of the poultry sector, three times that of coffee, and more than five times that of banana production.[29] (Figure 12). Yet, despite its overwhelming influence in the region's GDP, the meat industry is slowing down in terms of percentage of growth in the region over time.[29]

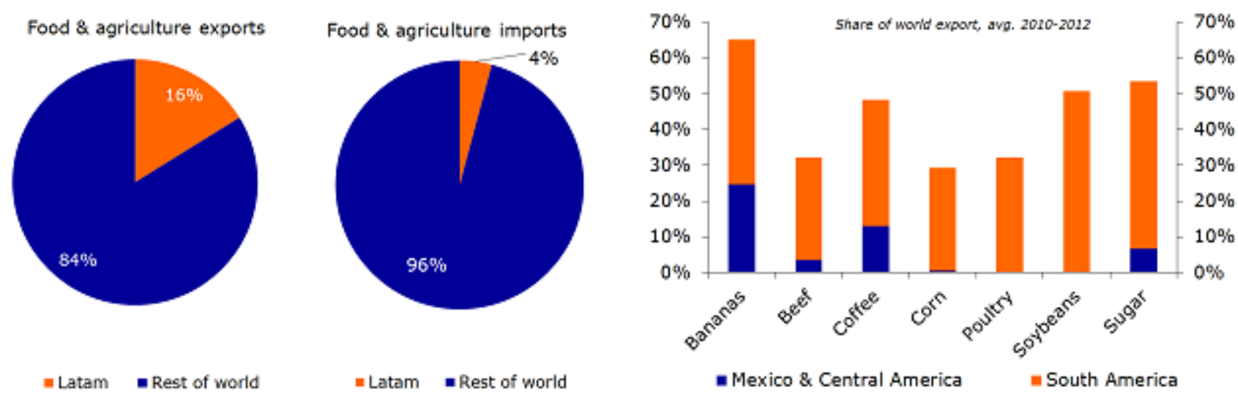

Figure 12. [30]

Latin America's agricultural economy depends largely on exports, rather than imports. Whereas most of these countries are large meat producers, as of 2021 there exist weak commercialization agreements between them. For example, the Southern Common Market or MERCOSUR, the official Latin American trade bloc, prioritizes meat exports to Asia and Europe. Many experts agree that since most of the countries in this organization harbor strong agriculture industries, there is very little need for them to buy from each other.[31] As a result, over the past years, the European Union and many Asian countries have been the main destinations and beneficiaries of exports resulting from MERCOSUR.[32] Figure 13 compares imports and exports per country and shows a large trend of exporting food and agriculture products.

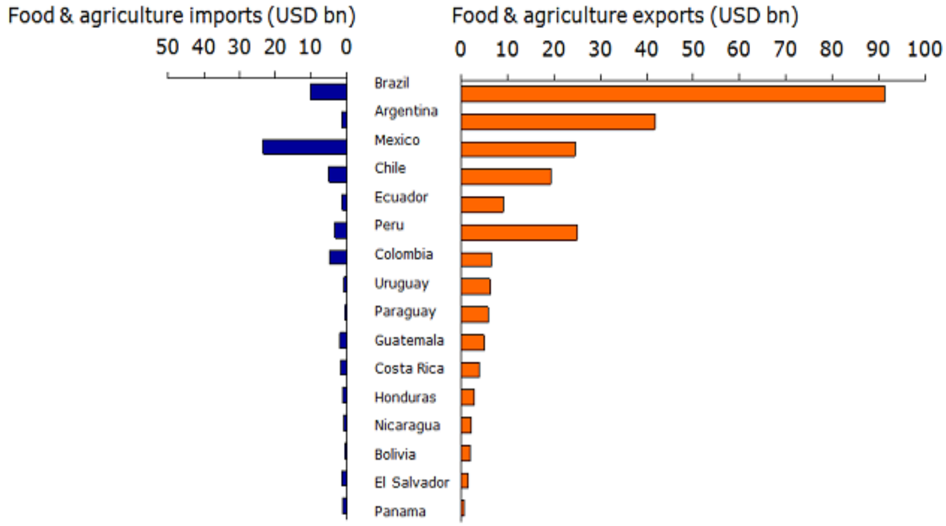

Figure 13. [30]

14.4.8 Latin American Technology Transfer in Worldwide Economies

Transfer of technology is defined as a transition of intellectual property from concept to consumer product. In other words, it is the act of applying the results of scientific research, while maintaining the originator's intellectual property. Cellular agriculture in Latin America will potentially be viewed as a case study for transfer of technology. In the process of technology transfer, an essential step is partnering with the public and private sector, usually represented by governments and corporations taking the products into the market. This will be an important step for cellular agriculture companies that aim to introduce a new food product to mass Latin American markets.

Cellular agriculture companies that are breaking into Latin American markets can examine the research, investment methodology, and path towards legislative approval of other organizations that have become established in the region. The successful adoption of technologies from country to country depends on properly understanding the cross-cultural barriers and a strong economic backing. In 2019, The World Bank Group assembled over US $14.4 billion in lending and guarantees to support programs focusing on sustainable development and poverty reduction in Latin America and the Caribbean.[33] This is good news because outside investment from a non-partisan organization could revitalize the region. Figure 14 shows the overall economic growth of Latin America from 2004 to 2019, which can attract investments in cellular agriculture.

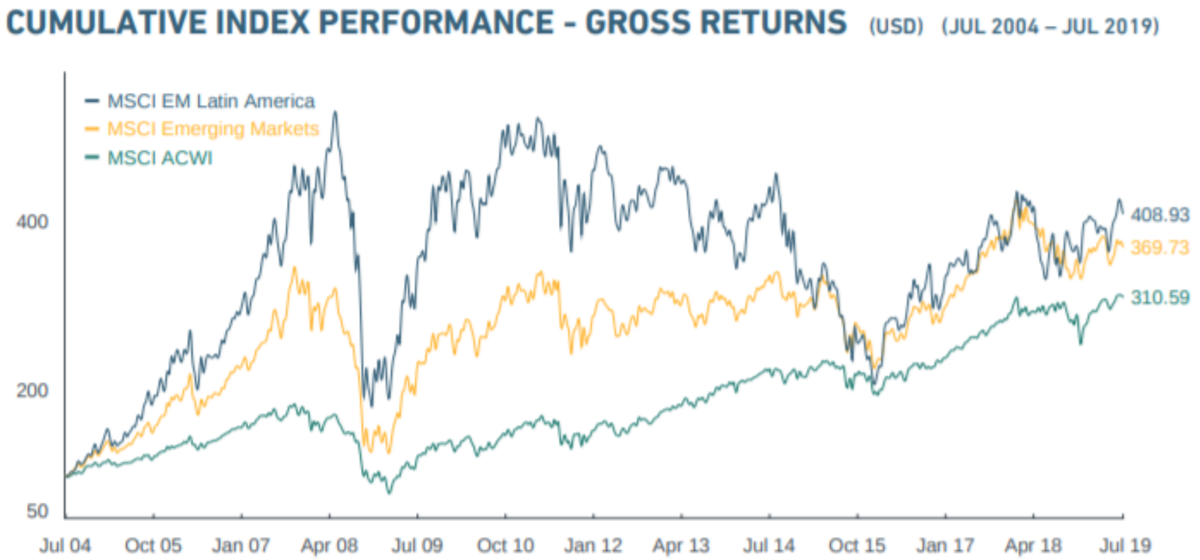

Figure 14. [34]

14.5 Conclusion

In the coming years, there will be a plethora of social factors that can propel the adoption of cellular agriculture technology throughout the world, and Latin America will prove to be a crucial and unique territory to advance this technology. Latin America's issues with economic inequality, corruption, and political turmoil will present a challenge for the growth of this new industry. Nevertheless, if cellular agriculture continues to progress towards creating a lower cost and higher quality meat product, then Latin America will be able to combine its unique position and culture surrounding meat with this technology to provide tremendous value across its region and the entire world.

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Europe

Cultivated Meat Around the World: Economics, Tradition, and Culture in Europe

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Chapter Abstract

Europe is the birthplace of cellular agriculture and is also a potential key market and producer. This chapter looks at the conventional meat market in Europe and its religious, cultural, and economic significance to European consumers within the region's varied political and social contexts. As one of few regions to have a joint governmental body, special attention is paid to the role of the EU in regulating cell-cultured meat. Also, the potential for the EU to be a source for funding innovation is considered, as cell-cultured meat could help further many of this region's goals related to health, the environment, animal rights and innovation. The potential role of national governments and the EU in supporting transitions to cell-cultured meat to reduce negative social implications for rural communities dependent on animal agriculture is considered. In the final section findings from the most recent studies on consumer attitudes toward cell-cultured meat are discussed.

Keywords

Consumer Acceptance
Culture
Lobbyists
Meat and Dairy Markets
Non-Governmental and Organizations (NGOs) and civil society
Regulation
Religion
Subsidies and Taxes
Tradition
Vegans and vegetarians

Fundamental Questions

1. What are the present and past trends of meat production and consumption in Europe?
2. What is the current landscape of the cell-cultured meat industry in Europe?
3. How are governments and intergovernmental organizations likely to respond to cell-cultured meat?
4. How are consumers likely to react to cell-cultured meat?
5. What are the likely impacts of cell-cultured produce on Europe's agricultural industry?

Chapter Outline

15.1 Introduction

15.2 Europe's Incumbent Meat Industry
15.2.1 History and Culture of Meat Consumption
15.2.2 Health, Environment and Animals
15.2.3 The Meat and Dairy Markets' Current Landscape

15.3 Overview of the Cell-Cultured Meat Industry in Europe
15.3.1 History of cell-cultured Meat
15.3.2 Major European Players in cell-cultured Meat
15.3.3 Relevant Non-Profit and Organizations

15.4 Predictions of Cell-Cultured Meat Industry in Europe
15.4.1 Europe and EU Regulation
15.4.2 Subsidies and Taxes
15.4.3 Social Implications of Cell-Cultured Meat
15.4.4 Increasing Consumer Acceptance

15.1 Introduction

Cell-cultured meat was born in Europe, with the first successful production of a cell-cultured hamburger in the Netherlands and the first tasting in London in 2013. While cellular agriculture has taken root across the world since then, the future acceptance of cell-cultured meat among European consumers is by no means guaranteed. For example, a 2018 survey of 1,000 consumers found that UK consumers were far less accepting of cell-cultured meat than consumers in the US, with only 18% saying they would be willing to eat it, as opposed to almost 40% in the US.[1] Two reasons have been suggested for this. First, Europeans tend to value natural food more and many European countries restrict use of genetically modified organisms (GMOs), whereas GMOs are permitted in the US and Americans accept more processed food. Second, Europeans may be more likely to see farms, farming, and the countryside as part of their identities and consider cellular agriculture as a threat to their traditions.

Europe is unique as a region in that its regulative decisions are led by one centralized body, the EU. EU policymakers' decisions and approach towards cell-cultured meat will directly impact its development and entry to markets. On the one hand, there are numerous areas to explore within cell-cultured meat innovation, and many of these will likely appeal to EU and national commitments and objectives concerning research, the environment and animal rights. Moreover, there are several substantial reserves of grant money for R&D projects, for which cell-cultured meat could be a good match. However, past regulation of plant-based meat products and ongoing financial and political support for traditional farmers may bode poorly for cellular agriculture. Policymakers and politicians are likely to be concerned about the effect of cellular agriculture on conventional agricultural industries, which represent significant cultural and economic value throughout Europe.

Nevertheless, if supporters of cell-cultured meat are successful in persuading the public and policymakers, Europe represents a major market for cell-cultured meat products. Meat consumption is considerable in Europe, with the average European consuming nearly 80 kilograms (176 lb) per year, the third-highest rate globally in 2019, trailing only Australia and North America.[2] The continent's higher-than-global-average income per capita could allow for a strong market for cell-cultured meat of early adopters who would be able to pay for the initially higher prices.

Multiple studies indicate that many Europeans would be willing to alter their diets for environmental reasons if they knew about these impacts. Many Europeans are concerned about climate change: a 2019 study found 93% of Europeans see climate change as a serious problem.[3] A recent open public consultation carried out by the

European Commission in member states showed that over 80% of respondents were willing to “consider the impact of their food purchases on greenhouse gas emissions.” Awareness of the climate-meat link has increased in recent years. A 2018 UK study indicated that people generally recognize that vegetarian diets are better for the environment, yet most consumers underestimate the extent of the differences and particularly tended to underestimate the climate impact of nationally produced meat products.[4,5]

15.2 Europe’s Incumbent Meat Industry

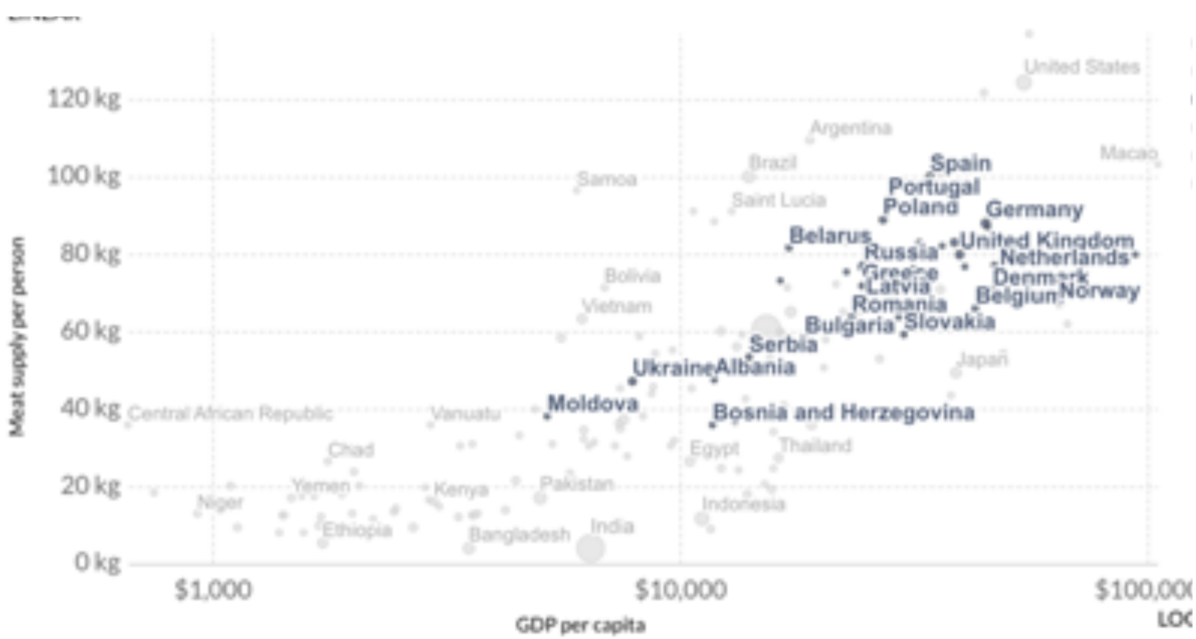
15.2.1 History and Culture of Meat Consumption

While cuisines across Europe vary, they generally are characterized by high meat and dairy consumption compared to other regions of the world, such as East Asia. Although there is much variation between European countries, meat and dairy agriculture tends to be associated with national identities. This link is evident in the form of staple dishes in European nations from Greek souvlaki (chunks of skewered pork) to German rouladen (roast beef) and numerous other favorites. The meat industry plays on association between patriotism and meat and dairy in marketing of these products alongside national flags and rustic countryside.[6] This contrasts with countries such as India where national dishes are largely vegetarian or vegan, or in many Southeast Asian nations, where consuming dairy produce has historically been uncommon.[7]

Meat has long held religious association in Europe, as sharing meat and animal products are a staple of many religious celebrations. However, there are interesting exceptions such as Romania, where meat consumption is low because many follow the Romanian Orthodox tradition, which requires devotees to maintain a diet without animal products during several fasting periods. This practice contributes to Romania’s overall lower than average meat consumption (see Figure 1). This is not limited to Romania, as according to the Eurobarometer survey in 2019, 10% of the EU consider themselves part of the Eastern Orthodoxy.[8] Yet sharing meat and animal products is part of most celebrations in the Roman Catholic Church, Protestant Church, Judaism, and Islam.[9] While religion seems to be diminishing throughout Europe, at least measured by the number of people attending regular religious ceremonies, and atheism is rising, it is not clear how this influences meat consumption associated with religion.[10] Many non-believers still celebrate religious festivities, which have grown to become a ubiquitous part of many European cultures independent of strict religious beliefs.

Meat consumption across European countries has been, and continues to be, culturally associated with high social status. Sharing meat has been instrumental to human bonding rituals, and the association of meat with social gatherings can be traced back to Roman or medieval feasts which were recorded as simply a list of meats: larks, boars, capons, and beef.[11] Going back even further, sharing meat was likely instrumental to the development of human cooperation in hunter-gatherer societies. Since game is large and perishable, it was in the hunters' best interests to share it to create ties of reciprocity.[12,13] The historical association of meat to high status is likely because meat was, and still is, relatively expensive, which makes consuming or sharing it as a staple in the diet a symbol of wealth. This association is still evident today between European nations, as there remains a significant positive correlation between national income levels and meat consumption. Those who can afford meat tend to consume more (see Figure 2). The association of meat with wealth likely explains the steady increase in meat consumption in growing post-Soviet economies.[14]

Figure 1 – Meat Consumption Compared to GDP Per Capita in 2017



Source: UN FAO; World Bank, World Development Indicators

Meat consumption within each European nation paints a more complex picture. Vegetarianism, veganism, and pescatarianism are increasingly seen as aspirational middle-class lifestyle choices. One study found that 41.5% of Brits considered vegetarianism "aspirational," meaning that within European countries, particularly in Western Europe, there is not such a straightforward wealth to meat-consumption correlation.[15] Most estimates put vegans in the UK at a little over 1% of the population, whereas vegetarians make up about 6%.[16,17] Globally, "meat-reducers" are growing rapidly with 400,000 people globally signing up for Veganuary in 2020, compared with

250,000 in 2019.[18] A survey in 2018 found that, of the selected countries, the two with the highest rates of vegetarianism were Italy and the UK, where 6% of respondents followed a vegetarian diet followed by France, the Netherlands, Germany and Spain with 5% and Sweden with 4%. Vegetarianism is also popular in Southern and Northern Europe. European Survey found that 6% of Italy's adult population, 5% of Spain and Netherland's populations, and 4% of Sweden's were following a meatless diet in 2018.[19]

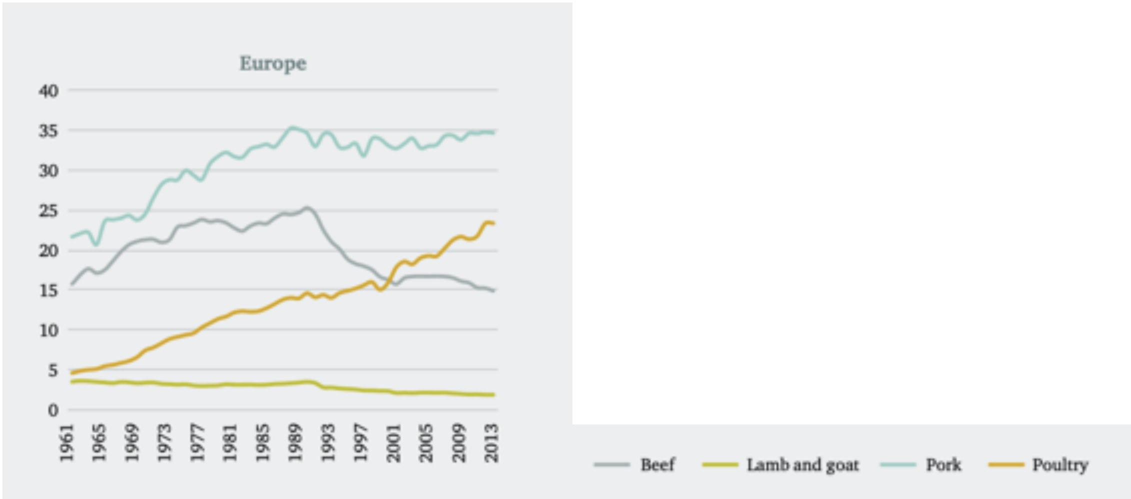
Within nations, there are generational differences in meat consumption. For example, a 2010 Food Frequency Questionnaire in the UK found that most vegans, pescatarians and vegetarians were either aged 15 to 25 and motivated by moral and environmental reasons, or between 45 and 65 and committed due to health reasons.[20] Similarly, surveys across Europe found that the proportion of vegans in age groups 18 to 24 and 25 to 34 was double that of age groups 35 to 44 and 45 to 54, individually.[21] Veganism and vegetarianism are growing in some parts of Eastern Europe. For example, in 2019 Warsaw was chosen as the sixth most vegan-friendly city in the world, and over 5% of the adult Polish population are full vegetarians, while almost half the population (43%) are "severely limiting their consumption" of meat.[22] Yet, this movement toward vegetarianism has met some adversity, voiced, for example, by the foreign minister of Poland, who warned of the need to combat the "leftist program" and specifically cited "vegetarianism" as part of this program. Also, there was backlash in 2019 when three vegan restaurants in Gdańsk were vandalized with neo-Nazi imagery and slogans. In addition, in other Eastern European countries such as the Czech Republic, reports suggest that there are few who identify as vegetarian.[23] Here, it appears that the low levels of meat consumption are more a product of lower incomes.

Variations in European meat consumption over the past several decades suggest that consumers have been reactive not only to price but also personal and health concerns. While survey data from Europe showed animal welfare as a more common concern for vegetarians, vegans, and pescatarians, this consideration is still a minority view, as vegan variations still make up a relatively small percentage of European populations. Health is the most common motivator for Europeans to reduce meat intake. One study found that, when asked about possible reasons for eating a more vegetarian diet, the most popular option chosen by omnivores and flexitarians was their health.[24] The environment and animal welfare were chosen by fewer participants, and for omnivores, these reasons ranked below 'to discover new tastes', 'to reduce weight', and 'no reason'.[25] These findings have been replicated elsewhere and imply that, for those not currently reducing their meat consumption, potential personal benefits are more important than environmental or ethical benefits.

Gross consumption levels, as shown in Figure 2, also suggest European trends in meat consumption are linked to multiple factors which may include health, financial, and environmental considerations. Europe has experienced a significant increase in poultry consumption from 2000 to 2013. This increase directly correlates with decreasing prices, which are largely a result of the widespread implementation of industrial or intensive farming practices over this time. By 2002 the UK's Environmental Agency had issued no permits for intensive farms, yet it grew exponentially and by July 2017, this number had leapt to nearly 1,700 permits for intensive poultry and pig farm licensing. This increase is also found in other nations throughout Europe and the rest of the globe, with concentrated animal feeding operations (CAFOs), accounting for 72% of poultry, 42% of egg, and 55% of pork production in 2017 according to the UN.[26] Some industrial farms contain more than one million chickens, 20,000 pigs, or 2,000 dairy cows and confine most animals indoors, allowing farmers to slash meat prices and provide these products to lower-income consumers. See Chapter 3, *Animals*, to read more about CAFOs according to the US Environmental Protection Agency (EPA).

Falling prices have not had a similarly bolstered effect on pork or beef consumption. As Figure 2 shows, Europe has witnessed a significant decline in beef consumption from 1990 to 2013, from an average of 25 g to 15 g of beef consumption per person. This is in part because of increased public awareness around the health risks with overconsumption of red and processed meat, such as mad cow disease (bovine spongiform encephalopathy, BSE), which has largely been displaced by white meat as shown in Figure 2.[27] The past thirty years of meat consumption suggests that Europeans make meat consumption choices based not just on cost but also changes in health and environmental awareness.

Figure 2 - Variation in European Meat Consumption Measured in Grams Per Capita 1961-2013



Source: FAO [28]

15.2.2 Health, Environment and Animals

As the Rural Investment for a Sustainable Europe, or RISE, Foundation's 2018 report states, Europe's livestock production and consumption are exceeding sustainable levels.[29] European farming tends to be less environmentally damaging than that which occurs, for example, in the US. This is partly because the majority of Europe has a wetter climate than America, so a higher proportion of the water input is "green" rather than "blue" water, meaning that it is supplied by natural rainfall rather than irrigation. The latter is more energy intensive and can create water stress on the resources from which it is abstracted. Also, deforestation related to animal agriculture is more of an issue for meat consumers in the US because American meat has been found to be more likely to be linked to harmful Amazon deforestation for grazing and animal feed.[30,31]

However, European meat consumption is still an issue as agricultural practices are polluting and energy-intensive, particularly due to reliance on imports. The high levels of imports both between European countries and from other nations, mean that meat consumed in Europe often has a high carbon footprint. The World Wildlife Foundation (WWF) found that British meals had the highest carbon footprint globally in 2018.[32] Europe is particularly reliant on imports from areas that are heavily forested, which means that Europe's meat consumption is indirectly responsible for extensive deforestation, as this land is converted to growing cattle feed or is made available for grazing livestock, destroying carbon sinks and biodiversity hotspots in these regions. For example, during 2019, Europe imported 317,200 tons of beef and veal, the majority from Brazil (52,957 tons), followed by Argentina (30,880) and Uruguay (21,864).[33]

Moreover, as the region with many of the world's most wealthy nations, research shows that a huge reduction in meat-eating here is essential to climate change mitigation. In 2019, it was reported that a global shift to a 'flexitarian' diet was needed to keep climate change below 2 °C, and that in particularly wealthy nations, such as the UK, citizens need to cut beef consumption by 90% and milk consumption by 60%.[34] The UN has called for a switch away from livestock farming, finding that methane from livestock accounts for 14.5% of greenhouse gas emissions—more than the direct emissions from transport.[35]

Meat-heavy diets also damage human health, and Europe's high consumption contributes to its high rates of disease and obesity.[36] Cell-based meat has the potential to be engineered to create a healthier product, altering the balance of harmful components, such as saturated fats, and replacing them with desirable components such as poly-unsaturated fatty acids.[37] While this technology has yet to be proven, it could help to reduce the risk of the numerous diseases associated with excessive meat consumption, including cardiovascular disease, type 2 diabetes, and certain cancers.[38] This is of particular concern for Europe, where these diseases are prevalent and, particularly in the case of cardiovascular disease, are major causes of death.[39] Being overweight and obese are also associated with excessive meat consumption, which is an important issue for Europe.[40] A 2014 study of adults from over 20 countries, using self-reported data from the European Social Survey, found that over half the population (53.1%) were either overweight or obese. Excessive weight is associated with numerous diseases including type 2 diabetes, coronary heart disease, breast cancer, bowel cancer and stroke. Additionally, it can also reduce quality of life and may lead to psychological problems such as low self-esteem and depression.[41]

Cell-cultured meat products could be made appealing to national and international governments as a means of helping them meet public-health commitments and reducing strain on health-care providers. The EU has multiple commitments to supporting healthy eating, including the Food and Nutrition Action Plan 2015-2020, which aims to create healthy food environments and tackle diet-related non-communicable diseases.[42] A 2019 study found that European governments could also save billions of euros every year in lower healthcare costs if they were to levy a tax on meat.[43] For example, this study found that if the impact on people's health was taken into account for processed meat, such as bacon and sausages, its price would need to double.

Since cell-cultured meats are produced in a sterile environment and do not require antibiotics, these products could help reduce the number of food safety scares that conventional meat products and agriculture repeatedly produced in Europe during the late 1990s and early 2000s. Of prominence was the outbreak of bovine spongiform encephalopathy (BSE), known colloquially as “mad cow disease.” It was first identified in cattle in the mid-1980s and had spread to humans by the mid-1990s, leading to bans on exported British beef. This outbreak resulted in 177 people contracting the disease, the slaughter of over four million cows, and severe economic losses. While BSE is controlled in the UK as of 2021, an ongoing health issue in meat agriculture continues to be the heavy use of antibiotics. Intensive farming allows meat to be cheaper, giving greater access to lower-income groups. However, keeping animals in confined, proximate conditions requires massive antibiotic use, with 73% of antimicrobials (predominantly antibiotics) being administered to farm animals, often prophylactically.[44] This practice risks increasing levels of antibiotic resistance and allows for the potential development of “superbugs”, which undermines the usefulness of antibiotics in human medicine.[45] While this phenomenon is not specific to Europe, the EU is in a strong position to become a “best practice region” in the fight against unsustainable antibiotic use.[46] Cell-cultured meat could be an important part of confronting issues related to antibiotics, while also offering a means of delivering a product that is healthier for Europe’s animals and people.[47] For more information on the use of antibiotics in animal agriculture, see Chapter 3, *Animals*.

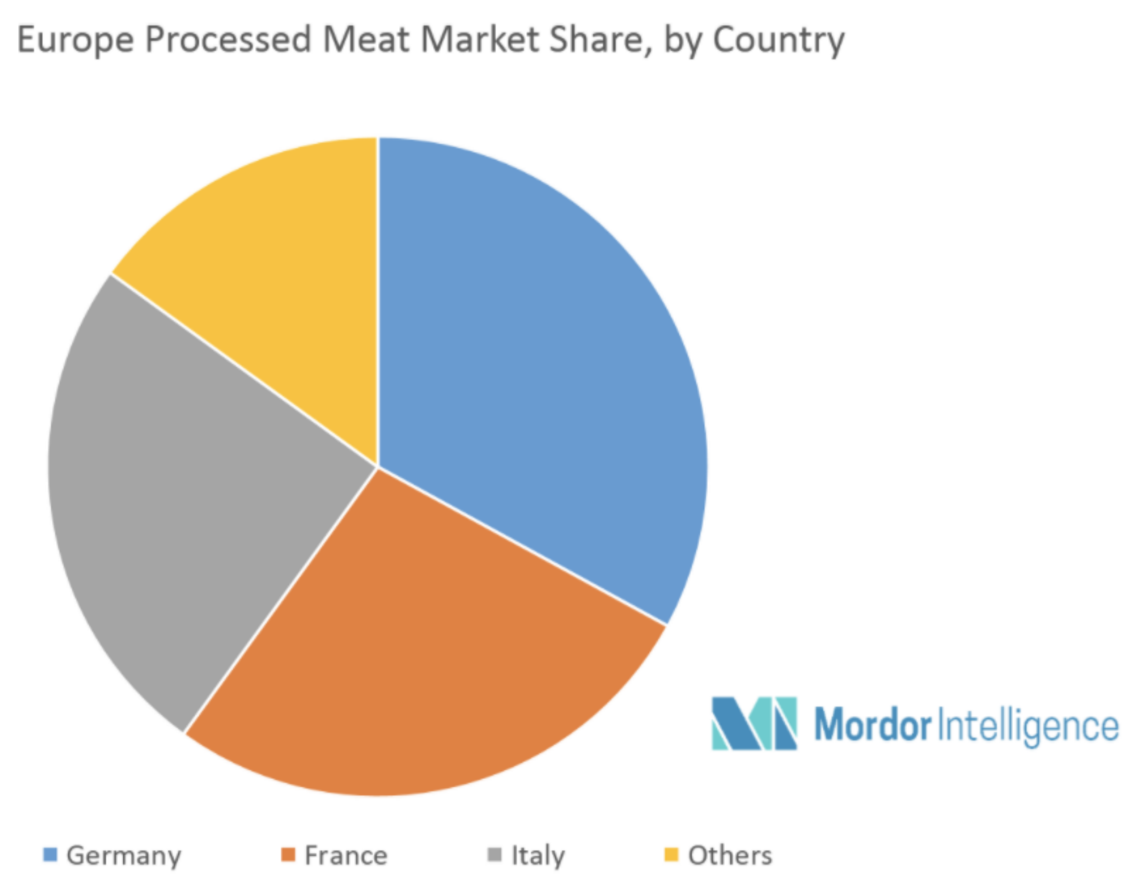
To sustain Europe’s high meat consumption, factory farming methods that may be considered cruel have become commonplace in factory farms. Tens of billions of animals reared in European factory farms live short lives, during which time they can be subjected to certain physical and psychological pains.[48] To save space, factory-farmed animals are often placed in pens and cages very close together, causing some of them to inflict injuries upon each other during stress reactions. To reduce injuries to the animals, some are subject to practices such as teeth clipping, tail docking, or beak trimming. The European Food Safety Authority (EFSA) found that more than 77% of Europe’s pigs are routinely tail-docked despite it being illegal to perform on a routine basis.[49] While the use of antibiotics purely to promote farm animal growth is outlawed under EU law, other methods of encouraging growth, such as selective breeding and concentrating feed, are common.[50] Such practices put certain animals at risk of developing physiological problems such as lameness, weakened or broken bones, infections, or lung failure.

The adoption of cell-cultured meat would be likely to reduce animal harvesting, as future cell-cultured meat factories may replace the need for conventional animal agriculture operations. Though early prototypes of cell-cultured meat products used animal inputs (notably fetal bovine serum), companies are developing alternatives with a goal of producing animal-free meat.[51] As of 2021, serum alternatives are expensive, but with economies of scale they could become viable alternatives to animal harvesting. For more information on cell media produced from fetal bovine serum see Chapter 5, *Media*.

15.2.3 The Meat and Dairy Markets' Current Landscape

Europe's meat processing industry is a significant part of its economy, generating roughly 21 billion euros in revenue during 2016 and accounting for 16% of worldwide meat production annually.[52] The economic importance of the processed meat industry varies significantly between European countries. As seen in Figure 3, Germany is Europe's largest market for processed meat with more than 30% market share, followed by France and Italy. Together, these three dominate Europe's processed meat market. Germany is also the market leader in pork production and exports, and second in beef production after France.

Figure 3 - Europe's Processed Meat Market Share by Country[53]

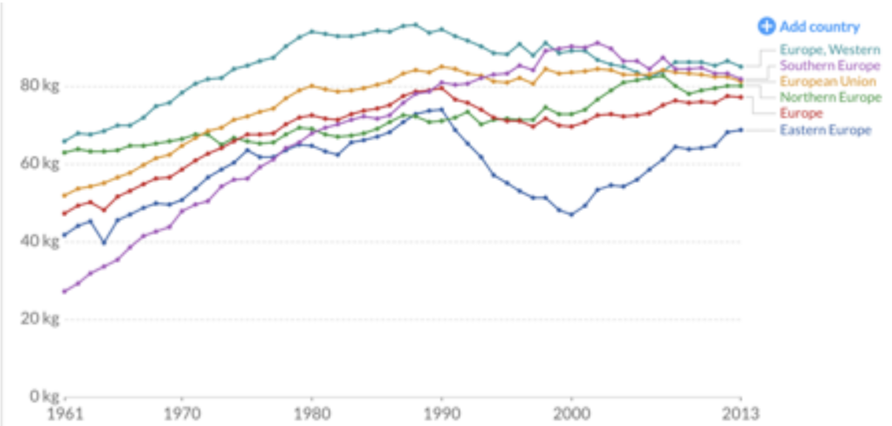


The dairy sector is also a large market throughout Europe, constituting the second biggest agricultural sector in the EU, and representing more than 12% of total agricultural output.[54] All 28 member states produce milk, but the main producers of cow milk are Germany, France, the UK, the Netherlands, Poland, Italy, and Ireland, which combined account for three-quarters of total EU production.[55]

Europe’s agri-food sector also encompasses a large part of Europe’s international trade with non-European countries, as they make up a significant part of an increasingly globalized food system. Excluding the UK, Brazil is consistently the largest source of beef and veal into Europe, followed by Uruguay, Argentina, and the US, which combined imported €223 billion worth of beef and veal in 2019.[56] Exports of beef and veal are sent to a mixed group of destinations, with Israel being the largest importer of European meat, followed by Hong Kong, Algeria, and Ghana.[57] Pork, on the other hand, predominantly exports to China, followed by Japan, Korea and Hong Kong, all of which are in the top five of the world’s largest importers of pork.[58] Exports from the EU have declined since 2017 and, as they are strongly influenced by the exchange rate, any growth in exports from the EU would likely be at a slower rate than those from North and South America.[59]

Looking at all of Europe, demand for meat grew significantly from 1960 to 1990 and has been relatively stable since, with some regional variations. Since the 1980s, demand in western Europe (represented in Figure 4 by meat supply per person) has declined, yet in 2013 western European consumption was still the highest of all European regions. Out of the five largest western European countries, France consumes the most meat per person. In contrast, meat consumption in eastern Europe fell sharply during the early 1990s, after the collapse of the Soviet Union, and has begun to increase since the turn of the century, likely a result in part of growing post-Soviet economies and westernization; however, output in these nations remains significantly lower than in other regions. Overall, Europe’s meat consumption is still high relative to the global average.[60]

Figure 4 - Meat Supply in European Regions 1961 to 2013 (meat per person measured in kilograms per year)



Source UN Food and Agriculture Organization (FAO)[61]

Overall, meat production in Europe is expected to grow marginally over the next five years. Europe's processed meat market is expected to register a compound annual growth rate (CAGR) of 3.2% from 2018 to 2023.[62] This is likely due in part to growing demand for convenience food, increasing disposable incomes, and rising demand for organic livestock products. A 2018 forecast predicted that in most developed countries over the medium term, per capita meat consumption will increase by 2.8 kg when compared to the period between 2015 and 2017.[63]

The current state of the European meat industry could provide an opportunity for the introduction of cell-cultured meat. This is because in Europe, as in the US, the meat market is dominated by a few large meat processing companies, but farmers are often technically independent. This could be promising for the cell-cultured meat industry if processors are persuaded to adopt cell-cultured meat, which they have shown signs of potentially doing. Below is a table showing a selection of the investments made into European cellular agriculture companies in 2021 and their investors.

European Cellular Agriculture Companies Receiving Investment in 2021

Name	Location	Total Funding	Stage	Funding raised	Investor(s)
Meatable	Netherlands	$62,900,000	Series A	$47,000,000	Dr. Rick Klausner, Section 32, Dr. Jeffrey Leiden, and DSM Venturing.
Gourmey	France	$10,200,000	Seed	$10,000,000	Air Street Capital, Point Nine
Multus Media	UK	$2,300,000	Seed	$2,200,000	SOSV, Zero Carbon Captial, Marinya Capital, Sake Bosch, Alvaro Martinez Barrio

	UK	$14,200,000	Convertible Note	$1,600,000	
Mosa Meat	Netherlands	$96,000,000	Venture - Series Unknown	Undisclosed	Leonardo DiCaprio
Formo	Germany	$54,200,000	Series A	$50,000,000	Led by Elevat3 Capital, EQT Ventures, Lowercarbon Capital and joined by Lionheart Ventures, Happiness Capital and Albert Wenger. Additionally, existing investors Agronomics, CPT Capital, Good Seed Ventures, Grazia Equity, and M Ventures
Roslin Technologies	UK	$15,500,000	Convertible Note	$1,300,000	UK Research and Innovation
Gelatex	Estonia	$1,200,000	Seed	$1,200,000	Change Ventures and Crosslight Partners

*Data sourced from crunchbase

15.3 Overview of the Cell-cultured Meat Industry in Europe

15.3.1 History of Cell-cultured Meat in Europe

Considering that cell-cultured meat is a relatively new technology, it has generated a significant amount of discussion and attention across Europe. Many startups have arisen following the initial 2013 launch, placing Europe as a hub of research and development in cell-cultured meat. Europe presents an attractive region for cellular agriculture startups, as it is home to some of the world's most prestigious research institutes, largest pools of R&D funding, and world-class scientists and researchers. In addition, once cell-cultured meat is approved, Europe represents a strong market. According to research published in March 2018, Europe presented the largest regional market for meat substitute products in 2017, with 39% of global market share.[64] There is opportunity for a variety of different startups within cellular agriculture to improve production techniques as well as to cater for different culturally specific dietary preferences. For example, Gourmey in France is developing cell-cultured foie gras, while Spanish company Biotech Foods is producing cell-cultured pork, poultry sausages, and ham. The diversity of meat-related practices across Europe will allow for differentiation across startups in the European market.

Cell-cultured meat requires considerable scaling up to become a viable consumer product, and there have been numerous investments across Europe to meet this need. For example, in the first quarter of 2020 Higher Steaks raised UK £200,000 (from an undisclosed US investor), while Meatable succeeded in raising US $3.5m from Future

Positive Capital, a London-Paris socially focused fund. Likewise, Mosa Meat announced partnerships with Lowercarbon Capital and Nutreco with the intention of bringing cell-cultured meat to market by 2022.[65] Higher Steaks (UK) and Meatable (The Netherlands) are banking on building new technologies off the back of exclusive academic partnerships.[66]

15.3.2 Major European Players in Cell-cultured Meat

Table 1: Major European Players in Cell-cultured Meat and their Investments and Specialties as of 2021

Name	Country	Founded	Funds Raised/ Investors	Description/Specialties
Mosa Meat	Netherlands	2013	EU €70 M+	Dutch start-up co-founded by Mark Post, the scientist who invented the first cell-cultured burger. At the end of 2021, they were scaling up production of cell-cultured beef with a view to submitting an imminent regulatory application to the European Food Safety Authority.[67]
Cellular Agriculture Limited	UK	2016	-	Bioreactors
BioTech Foods	Spain	2017	EU €5.1 M	Various cell-cultured meat products for sale to food processors, including sausages, burgers, nuggets, meatballs, and ham[68]
Higher Steaks	UK	2017	Undisclosed	Developing a production method that reduces the amount of media needed to produce cell-cultured meat; an intelligent in-process monitoring system to improve efficiency;

				and a biomaterial that allows the generation of more structurally complex meat products
Meatable	Netherlands	2018	US $172.8 M	Using a proprietary technique to produce cell-cultured meat from pluripotent stem cells
Cubiq Foods	Spain	2018	EU €16.5 M	Cell-cultured animal fat for cell-cultured meat
Gourmey	France	2019	EU €10.2M	Cell-cultured foie gras, a French delicacy
Mirai Foods	Switzerland	2019	US $4.5 M	Producing cell-cultured meat which is more efficient and can be cheaper at scale
Planetary Foods	Germany	2019	-	Cell-cultured seafood
Peace of Meat	Belgium	2019	EU €5.5 M	Cell-cultured meat, in particular foie gras and fat
Alife Foods	Germany	2019	-	Developing ‘consumer-first’ cell-cultured meat products.
CellulaREvolution	United Kingdom	2019	US $1.4 M	Specializing in self-assembling peptides for cultured meat
Ivy Farm	United Kingdom	2019	US $20 M	Initially focusing on cultured pork sausage products
Bluu Biosciences	Germany	2020	US $8.2 M	Cell-cultured seafood
Innocent Meat	Germany	2020	EU €600,000	Cell-cultured meat with a focus on efficiency
Hoxton Farms	United Kingdom	2020	US $3.8 M	Specializing in creating cultured fat for cultured meat products

15.3.3 Relevant Non-profits and Related Organizations

The potential for non-governmental organizations (NGOs), and civil society to shape public opinion, public policy, and regulatory responses on topics of agriculture and food should not be underestimated. Historically these groups have held significant sway, perhaps most evident in the civil society-led public discourse on genetically modified organisms (GMOs), contributing significantly to the low public acceptance and strict regulations of genetically modified (GM) technologies in the EU. Public attitudes to plant-based meat, and particularly to cell-cultured meat, will be shaped to a significant degree by civil society narratives.[69] Environmental groups have also played an important role in raising awareness among citizens about the climate-related impacts of meat-heavy diets, as they are considered trusted sources of information throughout most of Europe. Many of the larger environmental groups are actively promoting plant-based diets. Greenpeace, for example, has called for a 50% reduction in meat and dairy production and consumption.[70] The growing number of meat reduction campaigns, such as “Meat Free Monday” and “Veganuary” in the UK, Sweden, Germany and others[71], have also been influential in raising awareness of the benefits of eating less meat and fostering the consumption of more plant-based meat alternatives. Moreover, the influence of these campaigns shows signs of growth, with 400,000 people globally signing up for Veganuary in 2020, compared with 250,000 in 2019.[72]

Table 2: European Non-profits and Related Organizations in Cellular Agriculture as of 2021

Organization	Year Founded	Predominant Focus and Region(s)
New Harvest	2004	The technical science of cell-cultured meat production and other cellular agriculture. Makes grants to researchers and PhD students, including several in the UK.
ProVeg	2011	A wide range of issues relevant to reducing animal product consumption, including cell-cultured meat.
Cellular Agriculture Society	2017	Expanding the cellular agriculture community by connecting experts and people interested in the field. Present in the UK and Germany.
Cellular Agriculture UK	2018	Developing the cellular agriculture community in the UK by organizing events and compiling information.
The Good Food Institute Europe	2019	Developing the regulatory and market context, in addition to developing the industry for cell-cultured

		and plant-based meat. Present in the UK and Belgium.
50by40	2019	A wide range of strategies relevant to reducing animal product consumption, including cell-cultured meat.

Environmental and animal-related NGOs, such as People for the Ethical Treatment of Animals (PETA), Gaia, and Viva! appear to be welcoming of cellular agriculture's potential to be a less resource-intensive alternative to conventional meat. They are also supportive of the fact that cell-cultured meat could be produced with methods free from animal harm. However, there are some NGOs that do not support cellular agriculture, such as Friends of the Earth, preferring to support fully plant-based diets.[73] Many NGOs support may be conditional upon cellular agriculture processes being entirely free from animal harm, meaning they would strongly support an animal-serum-free media. Serum-free media is already in use or under development by several cell-cultured meat companies in Europe, such as Mosa Meat and Cellular Agriculture Ltd, and is expected to continue expanding.

15.4 Predictions for the Cell-cultured Meat Industry in Europe

15.4.1 European and EU Regulation

The EU is the major regulator in Europe. While only 28 of Europe's 45 states are EU members, and this section will touch on some non-EU states' policies, the EU makes up most of Europe's market. Also, the EU's regulation often has implications for states outside of the bloc. The decisions that the EU makes, for example, on the regulation, labeling, and marketing of meat replacements, is expected to have a significant influence on the cell-cultured meat industry's market direction and pace of growth, as most of the R&D hubs are located within EU boundaries. The EU's commitments to mitigate climate change, reduce environmental damage, and provide the best options for European consumers and producers may encourage them to support cell-cultured meat efforts.

EU regulation may support more facilitative policies for the development of cell-cultured meat and its introduction into the market if it can help meet increasingly ambitious greenhouse gas (GHG) emissions targets and other environmental goals. There are three major EU environmental commitments that concern livestock production and consumption. First, the EU aims to be climate-neutral by 2050 and some EU countries, such as Germany, are aiming for even sooner.[74] If the EU does not achieve the projected emissions reductions, other sectors such as transportation and heavy industry will need to reduce emissions to an even greater degree. This reduction would come at a considerable cost, particularly for hard to abate sub-sectors such as cement production and aviation.[75] Second, most nations within the EU have committed to reduce methane by 30% over 2020 levels by 2030.[76] Studies show that from 2000-2017, 25-30% of methane production came from livestock.[77] Third, as of January 2021, most EU nations have signed up to the UN Convention on Biological Diversity (CBD)'s proposal to protect 30% of land and seas by 2030 for biodiversity.[78] As part of this, the European Commission has set out a strategy to strictly protect carbon-rich ecosystems to benefit wildlife—which requires an overhaul to farming—with a budget of at least €20 billion a year.

There have already been some EU and nation-wide initiatives, campaigns, and regulations in the direction of reducing meat consumption and production. The EU's Farm to Fork (F2F) strategy, for example, encourages people to consume less red and processed meat and offers support for alternative proteins.[79] Ireland's government has been countering their farming lobby, particularly from their world-famous beef producers, to tackle climate change with the goal to add 8,000 hectares of forest a year.[80] Denmark's government has set a binding 2030 agriculture emissions goal and has committed $600 million to support farmers, particularly dairy and pork, to reduce their emissions by 55-65% by 2030 compared with 1990 levels.[81] The Netherlands government wants to buy out farmers to reduce levels of nitrogen pollution.[82] Forty-five governments have signed up to the UK-led "nature pledge" committing public investment totaling US $4 billion into agricultural innovation.[83]

The EU is likely to introduce regulations, as part of its responsibility to consumers and producers, that may also benefit future cell-cultured meat markets. First, policymakers are committed to ensuring consumers are sufficiently informed about products they buy.[84] This is enshrined in their Food Information to Consumers Regulation (FIC) (EU Regulation No. 1169/2011), which requires that clear, precise, and easily understandable food labeling be provided to enable consumers to make an informed choice, and to ensure the "safe use of food, with particular regard to health, economic, environmental, social and ethical considerations."[85] This could be beneficial in terms of consumer acceptance if it increases public trust that products are adequately regulated; however, such regulation could also deter consumers from accepting cell-cultured meat if it insists on restrictive or unappealing terminology and labeling. Second, policymakers could ease the transition for farmers who are currently dependent on livestock farming towards new forms of economic activity by diversifying their skills. Section 15.4.2, *Subsidies and Taxes*, discusses the benefits of this intervention in greater detail, drawing on lessons from historical examples of other major economic changes in the West.

While predictions of European consumer acceptance of cellular agriculture are not certainties, it is possible to make conjectures based on previous agricultural rulings and current legislation. Particularly relevant is legislation on (1) novel foods, (2) the naming of plant-based meat and dairy alternatives, and (3) GM crops.

First, cell-cultured meat will likely fall under the EU's "novel food regulation." In the EU, Article 3(2)(a)(vi) of Regulation (EU) No 2015/2283 on novel foods stipulates that any food consisting of, isolated from, or produced from cell culture or tissue culture from animals, plants, micro-organisms, fungi, or algae is considered a novel food. If cell-cultured meat is considered this way, it will require pre-market authorization which includes a safety assessment performed privately and submitted to the European Food Safety Authority (EFSA).[86] This would check that it is (1) safe for consumers; (2) properly labeled, so as not to mislead consumers; and (3) not nutritionally disadvantageous if it is intended to replace another food. In addition, the European Commission may, for safety reasons and to consider the opinion of EFSA, impose post-market monitoring requirements for novel foods. These pre- and mid-market regulations would likely not disqualify cell-cultured meat but could substantially increase the cost, reducing its potential to be an affordable, widespread, and viable product in the market.

Second, drawing on current commitments and previous legislation on plant-based meat alternatives, the EU's labeling requirements appear to be unfavorable for the widespread adoption of cell-cultured meat. This is important because, as discussed in Chapter 11, *Consumer Acceptance*, the nomenclature surrounding cell-cultured meat products will affect the degree to which European consumers accept these new products. For example, consumers are much more likely to prefer cell-cultured meat products with labels such as "slaughter-free," rather than "lab-grown."[87,88] Nonetheless, regulation which requires cell-cultured meat to use specific terminology could create more problems than it solves for consumers. For example, cell-cultured meat may not be able to include terms such as "meat" in their labeling. In 2018, the European Parliament Agriculture, or AGRI, Committee supported a prohibition on plant-based food products using denominations of meat or dairy products (Amendment Number 41). The European Parliament's AGRI Committee has reportedly begun to use the old proposal as a starting point for updated legislation.[89] Cell-cultured meat products could be prevented from being labeled as meat, as any cell-cultured products would not meet the current EU definition of meat as "skeletal muscles of mammalian and bird species recognized as fit for human consumption with naturally included or adherent tissues."[90] Furthermore, the European Parliament and of the Council's 2011 regulation on the provision of food information to consumers defines "skeletal muscle" as "muscles under the voluntary control of the somatic nervous system." Cell-cultured meat neither has a voluntary nervous system nor consists of "naturally included or adherent tissues."

Hence, if the EU's current legislation remains unchanged, cell-cultured meat's labeling will be prevented from using meat terms and will be obliged to highlight their bioprocessing origins.[56]

Regulatory decisions about cell-cultured meat are likely to be as much political as they are technical.[91] Agricultural lobbyists have a significant presence in many European countries. Over the past few decades, they have gained and maintained supportive policies and received subsidies on numerous occasions, demonstrating an ability to unite their interests.[92] This is in part due to agriculture's central importance to nations' economic and food security interests, as well as its cultural and heritage value. This power is evident in the significant percentage of the EU budget that is devoted to the Common Agriculture Policy (CAP) (see Figure 5), despite member states of the World Trade Organization pressuring the EU to reduce it in line with commitments to lowering international trade barriers.[93] There are many supporters of the traditional livestock industry, not only those with economic interests such as companies and trade unionists for farmers, but also rural-dwellers whose communities rely on the industry and many other citizens who value its importance to European cultural identity. It is also notable that Germany and France, the two largest meat producers in the EU and the two largest economies, are also the countries with the strictest national rules about meat labeling on plant-based products.[94]

Support for the meat and dairy industries is also evident throughout various international and national legislation that encourage animal product consumption in Europeans from a young age. For example, the EU's CAP funds a fruit, vegetable, and milk scheme, which includes EU €100 million per annum to support the distribution of milk to EU school children, with the aim of promoting healthy eating among children and "reconnecting them with farming."[95] However, national legislation paints a more mixed picture. Some governments require meat in school meals for nutritional value or rule against providing vegan options which may inconvenience schools. For example, in France, 20% of school lunches must comprise meat, 20% fish, and the remainder must contain egg, cheese, or offal (meat derived from organs).[96] In contrast, in some schools in Finland where veganism is popular at secondary school age, students are offered two options, a vegetarian and a non-vegetarian meal, on four school days a week, and one day a week, they have a choice between two vegetarian meals. However, in most other EU countries, there is minimal legislation on school meals, meaning there are no required meat minimums.[97]

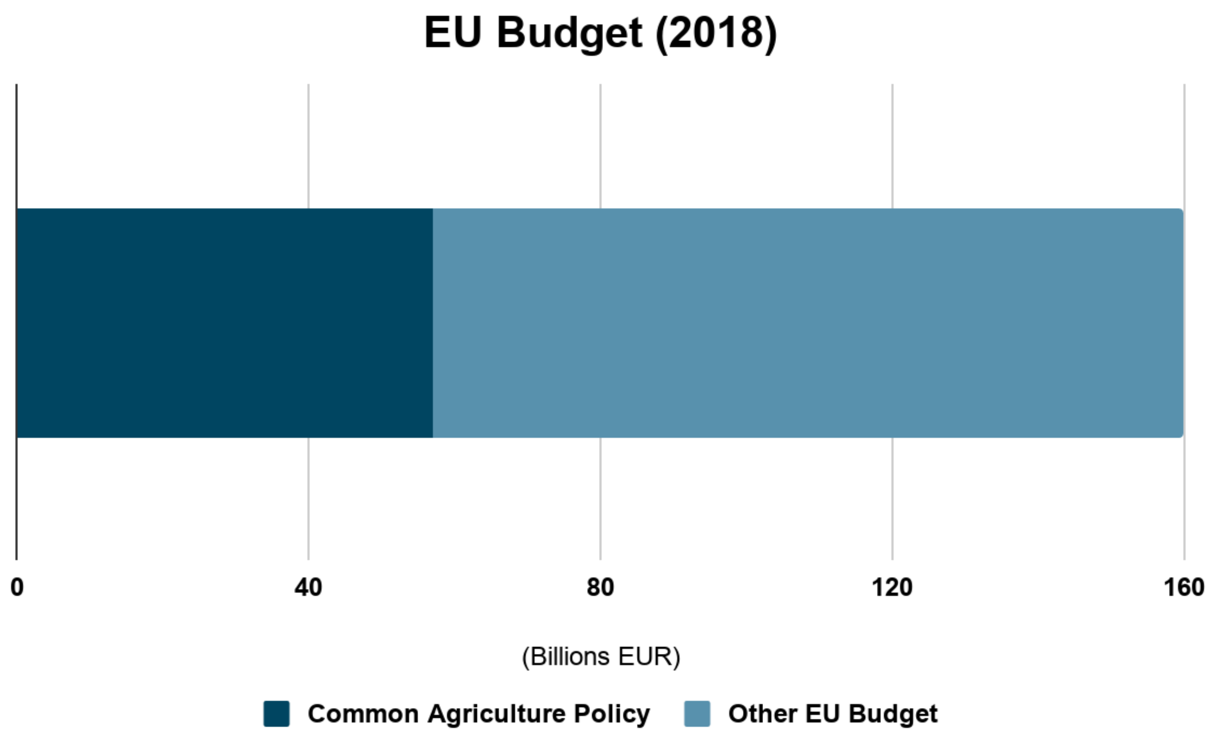
Another important consideration for acceptance of cell-cultured meat is GMO regulation for two reasons: first, cell-cultured meat may be produced using GM techniques, and second, it provides precedent for regulatory approaches to high-tech developments in food. Since its introduction to the agricultural landscape, the EU has had much stricter GMO regulation than the US. If cell-cultured meat contains GMOs or is produced from a GMO source material, it will be subject to separate approval under Regulation No. 1829/2003 on GM food and feed. It also requires a risk-based safety assessment through which member states consider economic and consumer acceptance factors before permitting it. Even if cell-cultured meat production avoids GMOs, the EU could pursue a similar regulatory approach towards cell-cultured meat. A significant reason for this regulation was the prevalent anti-GMO public attitude.[98] If negative attitudes toward cell-cultured meat prevail in Europe, the EU may similarly impose strict regulations towards these new products.

Since the UK's departure, there are now 18 non-EU countries within Europe, yet many follow similar regulations.[99] Norway, Liechtenstein, and Iceland are European Economic Area (EEA) members, meaning they are still part of the single market and thereby have much the same regulations on their products.[100]. Switzerland is neither an EU nor EEA member but is part of the European single market economy. Yet due to previous bilateral agreements allowing Switzerland to protect their domestic agricultural production at the expense of tariffs on meat and other processed agricultural products, Switzerland represents a minor agricultural producer.[101] The UK has the largest non-EU economy and is a major meat producer. While it has inherited EU rules by default upon leaving, it has the option to alter them in the future. Some believe that the UK will reduce regulations on conventional meat to be closer to US standards; however, the UK's Department of Environment, Food and Rural Affairs has vowed to resist any pressure to lower standards on animal welfare or the environment.[102] Nevertheless, new foods such as cell-cultured meat, which threaten neither animal welfare nor the environment, open up the possibility that the UK could take a less stringent regulatory approach than the EU.

15.4.2 Subsidies and Taxes

Under the EU's CAP, there are substantial farming subsidies in Europe, and it is possible to speculate how these may continue based on previous support for conventional meat. A CAP was one of the first focuses of the European Community (EC) as it was first developing in the 1950s and it was first launched in 1962.[103]. The CAP is a partnership between agriculture and society, and between Europe and its farmers, predominantly developed as a protective response to competition from low-income countries by raising agricultural subsidies. Contrary to the wishes of free trade intergovernmental organizations (IGOs), such as the World Trade Organization (WTO), the CAP has grown substantially since its introduction. In 2018, the CAP cost almost 60 billion euros, comprising nearly 40% of the overall EU budget, as shown in Figure 5.

Figure 5: Support for EU Farmers from Overall EU Budget 2018 (in Billions EUR) [104]



The EU also has other resources in place to support the dairy industry. This is relevant, not only because cellular agriculture will provide dairy replacements, but also because the dairy industry is inherently linked to the meat industry. The EC aims to support the dairy industry during periods when prices are low by purchasing dairy products at a set price.[105] With “private storage aid”, the EC grants private operators support for the storage of various dairy products (butter, skimmed milk powder, and cheeses), which Dairy Industry Ireland estimated to be worth approximately EU €30 million in 2020.[106] Furthermore, the international body enables “exceptional measures” during cases of severe market disturbance (as set out in Articles 219 to 222 of the Common Organization of Markets [CMO] Regulation). For example, the EU has committed to intervene if, over a representative period, the average market price of beef in an EU country, or region of an EU country, drops below EU €2,224 per ton.[107] This principle was seen in action during the 2014 to 2016 crisis, when raw milk prices dropped dramatically from around EU €0.40 to €0.26 per liter. The EC adopted two aid packages, including incentives for farmers to reduce production.[108]

However, despite its support for the meat and dairy industry, the EU may also be supportive of cellular agriculture, as, unlike overseas competition, cellular agriculture offers the potential for national food security, as well as environmental and economic benefits to Europe. There are two main methods through which the EU could seek to support this emerging industry: R&D investment and a meat tax. There are already various budgets set aside by the EU for international goals towards which cell-cultured meat could contribute. For example, the one billion euros Horizon 2020 Program, for which the EU has designated EU €32 million for innovation in "alternative proteins for food and feed."[109] A sizable chunk of this, 8.2 million euros, has been dedicated to the Smart Protein project, aimed at developing sustainable supplies of nutritious alternative proteins.[110] Another key project was LIKEMEAT, for which the EU provided over EU €1 billion for research into high-quality plant-based meat-like products between 2010 and 2013.[111] So far, most of this has concentrated on plant-based, fungi, or insect protein alternatives, and cell-cultured meat could be the next product to be included in this.[112]

Another way the EU can support the cell-cultured meat industry is a meat tax. Taxes on products or byproducts that are harmful to health and the environment, such as cigarettes, alcohol, sugar, and carbon emissions, are almost ubiquitous across Europe. While producing and eating meat does not result in many of the harmful effects of the aforementioned products, the first global analysis of meat taxes in 2016 by the Oxford Martin Programme on the Future of Food found levies of 40% on beef, 20% on dairy products, and 8.5% on chicken would save half a million human lives a year and slash climate warming emissions.[113] In February 2020, The Tapp Coalition recommended to the EU a "sustainability charge" on meat, which could raise billions to cover its environmental damage, and help farmers and consumers produce and eat better food.[114] This would have a large impact on highly environmentally damaging meats such as beef, which would increase by approximately EU €0.47 per 100 g, increasing the price of an average sized (227 g) supermarket steak by about 25%.

There is opposition to such a meat tax, as it would hurt many domestic farmers, yet with the pressing climate crisis and commitments of many EU countries to make a change, meat taxes are increasingly considered part of the political agenda. In 2017, meat taxes were predicted as "inevitable" by certain analysts for investors managing more than US $4 trillion of assets in the investor network Farm Animal Investment Risk and Return (FAIRR) Initiative.[115] Meat taxes have already been discussed in parliaments across Germany, Denmark, and Sweden. Officials in Denmark have suggested a tax of as much as US $2.70 per kilogram (2.2 lb) of meat.[116] In August 2019, politicians in Germany pushed for the 7% VAT on meat to be raised to 19% to help curb global warming and fund animal welfare improvements.[117] In November 2020, a coalition of UK health professionals called for a climate tax to be imposed on environmentally harmful food by 2025. Although so far unsuccessful, these initiatives demonstrate a growing political appetite for more severe measures on meat consumption. While it is not certain whether cell-cultured meat would be exempt from these taxes, it is likely that if the taxes were predominantly based on environmental concerns, or if the cell-cultured meat science developed healthier meat alternatives, then it would likely be subject to lower meat tax.

15.4.3 Social Implications of Cell-cultured Meat

While studies so far find lower levels of public acceptance in Europe than in the US (see Section 15.4.4, *Cell-cultured Meat and the European Consumer*), there are other signals suggesting that the market could be successful. As noted earlier, Europe was the largest regional market for meat substitute products in 2017, with 39% of global market share in alternative (usually plant-based) meats.[118] Also, some animal agriculture companies have indicated that they anticipate a decrease in demand in traditional meat by diversifying their investment portfolio to include cell-cultured products.[119] Therefore, while it is highly speculative, this section deals with the market implications on the assumption that the cell-cultured meat industry will become market-competitive with conventional meat producers at some point, which will face a diminishing market share over time.

Perhaps the largest issue resulting from the widespread implementation of cellular agriculture will be job losses. Europe has 12 million farmers operating in a diversity of contexts and farm sizes, and more than 47 million people are employed in some step of the food chain. Agriculture and food production make up only 4.4% of EU employment, yet those who work in this sector are mostly concentrated in rural areas that are often almost wholly dependent on agriculture. [120,121] Overall, it is likely that cellular agriculture will use fewer resources than conventional animal agriculture and will require fewer jobs. Moreover, the jobs created in the cell-cultured meat industry are likely to be largely technical jobs and not suitable for those displaced as animal farmers. However, it is likely that there will still be room for traditional livestock industries geared towards consumers who prefer traditional animal meat. There would also likely be room for traditional farms to diversify into other forms of plant-based agriculture, or inputs for cell-cultured meat processes, as well as more radical diversions into tourism, leisure activities, or non-food production.

However, most existing farmers who have historically relied on livestock farming would need to find new sources to maintain their current income. Farmers are vulnerable to this change for three main reasons: first, they are a larger share of the population in poorer countries, comprising approximately 2% of the population in the UK, versus approximately 30% in Romania.[122] Second, farmers tend to be less well educated than the population average, making finding new employment difficult.[123] Third, in many cases, the land they own is a farmer’s major asset, so the end of animal farming means not only the end of a job but a significant decline in the value of their assets overall. Moreover, there are rural areas that are highly dependent on animal agriculture, which would suffer drastic implications if it declined. It is also worth noting that a widespread cell-cultured meat industry in Europe would have impacts beyond Europe's borders, as Europe is a net importer of meat. The decrease in meat imports, as well as agricultural inputs, such as soy to feed the animals, would likely affect net suppliers such as Brazil, Uruguay, and Argentina.

Nevertheless, Europe has survived multiple large-scale industry changes in the past century, and there are lessons to learn from these on how best to manage disruption. The most effective strategies for intervention were deployed during the most recent major market change, the decline of manufacturing industries. Every industrialized nation in the world, including those that are committed to protecting their manufacturing bases, such as Japan, have experienced a decline in the relative share of manufacturing in their respective economies over the past few decades. Yet there are some stark differences between state approaches to this. Some countries, such as the US, and to a slightly lesser extent the UK, exposed workers to more technological and global competition to encourage the transition to a more service-based economy. These nations did not adequately re-train the manufacturers or invest in social programs designed to cushion their adjustment. These countries saw widening inequality and the near obliteration of their manufacturing industries.

More hope comes from countries such as Germany and, to a lesser extent, the Netherlands, which took more interventionist approaches. While not seeking to protect existing jobs (it is still easy for companies to lay off redundant workers), they invested heavily in labor-market interventions to improve working-class skills.[124] The effect of this on the average worker's income is stark. While Germany has experienced a significant increase in wages for the average worker, UK and US wages have stagnated since 1979, and the UK has witnessed historically unprecedented falls in real wages since the start of the Great Recession.[125,126] Counter to conventional economic wisdom, rising wages has not hindered economic growth, as both Germany and the Netherlands are growing at stable rates, while Germany has remained the third-largest exporter in the world.[127] Charges from a meat tax could help cover these costs. For example, the sustainability tax recommended by the Tapp Coalition would raise EU €32bn a year for EU member states, which, if half were shared with farmers to help transform their production, would increase individual farm incomes by thousands of euros per year.[128]

The idea of creative destruction—that allowing market change is necessary—has long been intertwined with the mainstream understanding of healthy capitalist economies. It is argued that maintaining surplus jobs in a certain industry will come at the cost of the consumer, or more likely, the taxpayer.[129] Capitalist systems consist of change and have natural cycles of "creative destruction" to which the world's historically unprecedentedly high standards of living and productivity are credited.[130] There are numerous examples of labor-saving technology throughout history, such as agritech and manufacturing automation, that are instrumental to our economy today, despite being responsible for job losses and market shifts at the time of their introduction. While the destruction can be cushioned with proactive political strategies, attempting to restrain them altogether for the potential mal effects on certain groups would be a public disservice, for it would cut-off entrepreneurship, innovation, and improvements in productivity, thereby impeding long-term progress.

15.4.4 Cell-cultured Meat and the European Consumer

Experts in the field have speculated that European consumers are likely to be more averse to cell-cultured meat than those in America or Asia, possibly due to stronger cultural affinity for rural life and natural farming.[131] Recent history of war in Europe has highlighted the importance of national food security, and many European nations have protectionist policies for farmers beyond those offered by the EU.[132,133] Indeed, survey data shows that while Asian consumers may be more accepting of cell-cultured meat than Americans, Americans are in turn more accepting than British, who may be more accepting than most Europeans.[134,135,136] Interestingly, more recent evidence suggests that South American consumers may be even more resistant to adopting cell-cultured meat than Europeans.[137]

There are also differing degrees of consumer acceptance between nations within Europe. One study of elderly adults found that Dutch and Finnish consumers exhibited a more positive opinion of cell-cultured meat than Polish consumers, with British and Spanish consumer's perspectives being between the two groups.[138] This could reflect how cell-cultured meat might be more readily accepted in more progressive cultures which tend to value environmental sustainability outcomes in their policies, while more conservative cultures are less likely to be open to the technology and new food products.[139]

Many studies of cell-cultured meat acceptance have used European samples: countries represented in these include the UK, Germany, France, Spain, Italy, the Netherlands, Portugal, Belgium, Ireland, Poland, Switzerland, and Finland.[140,141,142,143,144,145,146,147,148,120,149,150,119] However, relatively few surveys have been conducted across countries, so results across studies are not necessarily comparable since questions are framed differently in each. Early findings support the notion that more progressive nations, such as the Netherlands, Germany, and Finland, are likely to be early adopters of cell-cultured meat, while more conservative nations or those with stronger links to agriculture, such as Poland or France, will be more likely to resist the technology.

Compared to consumers of other nationalities, European consumers may be more discerning with respect to the naturalness of the meat products they are willing to eat. This is particularly true in nations which are more rural, agricultural, or conservative, while more pragmatic and progressive nations represent promising markets for cell-cultured meat. While Europeans value traditions and culture associated with meat consumption, they are also increasingly concerned with the environmental and ethical implications of industrial farming, and over time will be more likely to adopt alternatives including cell-cultured meat.

15.5 Conclusion

As this chapter explored, Europe represents a major potential market for cell-cultured meat products. Meat holds symbolic, religious, and historical significance for many European consumers, yet in many countries vegetarian diets are increasingly prevalent and seen as aspirational. Multiple studies suggest that Europeans are now willing to alter their diets for environmental and health reasons, which is relevant as cell-cultured meats have much lower carbon footprints and could be modified to be better for human health. Nonetheless, it is not yet clear consumers will be open to cell-cultured meats. Experts in the field have speculated that European consumers are likely to be more averse to cell-cultured meat than those in America or Asia and may be more discerning with respect to the naturalness of the meat products they are willing to eat. Some notable differences between countries within the EU may emerge, with more conservative nations or those with stronger links to agriculture likely to resist the technology, and more progressive nations likely to be some of the earliest adopters of cell-cultured meat.

Another important factor in consumer decisions is the EU's regulation on cell-cultured meat's labeling terminology and decisions on pre-market authorization processes, which may increase its price. The EU also represents vital funding opportunities for cell-cultured meat, as they have already allocated billions to innovation in alternative proteins. Historically, EU funding has propped up traditional meat and dairy agriculture through market intervention; this could bode well in the case for governmental support in the transition to alternative meats, which will be necessary if vegetarianism and cell-cultured meats are to develop further. The past five years have seen multiple suggestions and political attempts to raise an environmental tax on meat that could raise funds to support such a transition, thereby protecting the vulnerable farmers' rural communities that depend on animal agriculture.

As it stands, cellular agriculture's road through Europe is unclear. Europe's meat and dairy industries generate a significant part of its economy, and both directly and indirectly employ a sizable portion of its people. In disrupting this economy and requiring fewer (and mostly technical) jobs, cellular agriculture is likely to meet many opponents. The power of agricultural lobbies is already shown, as they have secured many subsidies and securities from the EU and national governments in contradiction to their external commitments to free trade. The industry will likely meet a second problem in consumer traction, as meat continues to represent a plethora of religious, cultural, and nationalist significance, with strong associations to nature and rural heritage. It is also unclear what proportion of NGOs and civil society, which have significant power to shape both public opinion, public policy, and regulatory responses, will support cell-cultured meat. The support of NGOs and civil society will have a large impact on consumer decisions, as they have historically held significant sway on discourse around modified agriculture products and alternative proteins. There is potential for animal rights, environmentalist, and health-concerned bodies both to promote it as an improvement on meat or reject it as a downgrade from plant-based options.

On the other hand, as the third-highest meat consumers in the world and with studies suggesting that most would be willing to alter their diets for environmental and health reasons, Europe represents a major potential market for cell-cultured meat products. Plant-based diets are growing in popularity and social status and studies suggest that cell-cultured meat might be more readily accepted in more progressive cultures which tend to value environmental sustainability outcomes in their policies. Likewise, both surveys and variations in levels of meat consumption over the last half a century suggest that European consumers are reactive to personal health issues and food safety scares, which cellular agriculture could help solve. National and international governing bodies have not been consistently pro-meat, with many politicians seriously considering meat taxes and the EU having recently made major investments into R&D for alternative proteins and meat-like products. Cellular agriculture's appeal to the EU's commitments to mitigate climate change, reduce environmental damage, ensure national food security, and provide the best options for European consumers and producers may encourage them to support cell-cultured meat efforts despite the lobbying of incumbent meat companies.

Fundamental Questions – Answered

1. **What are the present and past trends of meat production and consumption in Europe?**
   Europe has had relatively high meat consumption per capita for decades. While this is now decreasing in some regions, the trend is uneven across countries and generations. For example, in many growing post-Soviet economies meat consumption is increasing.

   Meat production in Europe is a significant part of its economy, though its economic importance differs significantly between European countries. For example, Germany, France, and Italy are leading meat-producing countries. Europe's meat production is an increasingly important part of the globalized food system indicated by their high levels of imports and exports, notably importing much beef and veal from Brazil, and exporting cows and beef to Israel. Overall, the meat production industry in Europe is expected to grow marginally over the next five years. In Europe, as in the US, the meat market is dominated by a few large meat processing companies, but farmers are often technically independent. This could be promising for the cell-cultured meat industry if processors are persuaded to adopt cell-cultured meat, of which there are some positive signs.

2. **What is the current landscape of the cell-cultured meat industry in Europe?**
   Europe, specifically the Netherlands, is the birthplace of cell-cultured meat, and remains one of the most important hubs for the industry. There are now several cell-cultured meat and cellular agriculture companies in the United Kingdom, Germany, France, Spain, Switzerland, and Turkey, including some with substantial funding and plans to bring products to market within a few years.

3. **How are governments and intergovernmental organizations likely to respond to cell-cultured meat?**
   The European Union (EU) has dedicated several million Euros in research funding in this area and has broad policy commitments towards climate change and specifically developing more sustainable food systems. However, the EU also heavily subsidizes animal agriculture and there are social, economic, and political barriers to changing this system. Several nonprofits which support cellular agriculture including the Cellular Agriculture Society and the Good Food Institute have a presence in Europe.

4. **How are consumers likely to react to cell-cultured meat?**
   Consumer surveys suggest a mixed reception, with some consumers having reservations based on perceived naturalness and safety concerns. However, there is also enthusiasm to try cell-cultured meat in many countries including Germany, France, Belgium, the Netherlands, and the UK. European consumers may be more conservative than elsewhere; consumer backlash ultimately led to the repression of genetically modified foods in the EU, and cell-cultured meat may be perceived similarly.

5. **What are the likely impacts of cell-cultured produce on Europe's agricultural industry?**
   If cell-cultured meat can be produced on a large scale and reach price parity with conventional meat, it may displace a substantial part of the demand for animal agriculture in Europe. Meanwhile, associated new industries, including culture media development, will create demand for more and different crops. Some visions of the cell-cultured meat industry seek to include animal farmers in the new meat production system.

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Africa

Cultivated Meat Around the World: Economics, Tradition, and Culture in Africa

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Chapter Abstract

Per capita meat consumption is relatively low across most African countries and production is dominated by small-scale non-industrial farming. While cultures are diverse and markets are regionally fragmented, meat is a symbol of wealth and associated with traditional and religious practices in most communities. As African economies and populations grow, meat consumption is projected to increase substantially. Cell-cultured meat could also meet high demand in the coming decades, although Africa has a long road ahead in creating strong markets and supply chains for these products. Currently, there are only a few companies and other stakeholders with active vested interests in the development of cell-cultured meat. However, there has been some progress among adjacent industries that may pave the way for cellular agriculture to successfully launch in Africa.

Keywords

Diversity
Tradition
Economic status

Fundamental Questions

1. What is Africa's historical relationship with meat and animal farming?

2. What is the forecast for meat consumption in Africa?

3. What are the key factors that will affect the success of cell-cultured meat in Africa?

4. What differentiates the African market from other international markets for cell-cultured meat?

Chapter Outline

16.1 Introduction

16.2 Conventional Meat

- 16.2.1 History and Culture of Meat
- 16.2.2 Trends in Consumption and Development
- 16.2.3 State of the Industry

16.3 Cell-cultured Meat

- 16.3.1 State of the Industry and Research
- 16.3.2 Demand
- 16.3.3 External Stakeholders

16.4 Conclusion

16.1 Introduction

In 2020, roughly 21 million tonnes of meat were produced across Africa, only around six percent of global meat production.[1] However, meat consumption in Africa is expected to increase by 30% until 2030 — the highest growth rate among world regions.[2] Cell-cultivated meat could find strong markets across Africa, as countries develop and their very young growing populations adopt new foods. [3] This chapter outlines in detail the current state of and projections for meat consumption and production in Africa. It then does the same for cell-cultured meat, highlighting existing players and potential future developments. In order to put all of this into context, the chapter starts by exploring the history and culture of meat in Africa.

16.2 Conventional Meat in Africa

16.2.1 History and Culture of Meat in Africa

History

The development of agriculture and livestock production across the African continent is vastly divergent. Geographic factors have been a dominant influence, resulting in a diversity of cultures surrounding meat across different regions. Additionally, the introduction of borders by the early Europeans in the late 19th and early 20th centuries, in the 'Scramble for Africa', has had a huge influence on the distribution of African people. However, the diversity in cultures surrounding meat extends beyond the post-colonial borders of many African countries, where meat consumption is often heavily dependent on ethnic, religious, environmental, and other factors.

While Africa is credited as the birthplace of modern humans, development of agriculture and livestock farming started much later here than in other parts of the world. Environmental factors, including an absence of fertile land, led Africa to become associated with the maxim of "cattle before crops", which is evidenced by the domestication of African cattle and plants that occurred around 8,000 and 2,000 BC, respectively.[3] As such, many parts of Africa developed pastoral forms of livestock farming, which became important for society and the economy.

Meat products in Africa cover a broad spectrum, from supermarket-stocked processed and chilled meat cuts to freshly slaughtered and consumed bushmeat. Between these two ends of the spectrum are other, somewhat commercialized but not yet regulated, products often produced locally and sold as region-specific, indigenous meat products. For example, Kenyans have developed various preservation techniques to increase the longevity of pastoral meat products, resulting in traditional dried offerings such as "koche".[4]

Bushmeat is the product of hunting wild animals through a variety of methods. This results in a more diverse repertoire of animal species prepared for consumption compared to the conventional farm animal products typically encountered in a supermarket.[5] Through local trade, bushmeat may provide a source of income as well as a nutritious addition to the diet. While some African nations have previously outlawed the bushmeat trade over various concerns, including the transfer of zoonotic diseases, its availability remains commonplace in many regions outside of more regulated urban areas.[6]

Meat consumption throughout much of Africa occurs primarily on a small or local level. This is necessitated by the high cost of transport combined with a lack of sufficiently industrialized processing facilities, in addition to limited access to cold supply chains. For these reasons, as well as more broad aspects related to general levels of economic development, industrialization of animal farming in Africa remains limited to affluent and highly populated areas in countries such as South Africa, Nigeria, and Egypt.

Culture

The symbolism of livestock ownership and meat consumption differs across cultures and regions within Africa. Meat is often regarded as considerably more important than simply a component of a balanced diet. For many nations, the value and symbolism of meat lies in its associations with wealth, whether that be in a physical sense, as a commodity for trade, leverage for loans, the bulk of customary bride prices or dowries (also known as ‘lobola’), or in a wider sense, as an indicator of social class.[7] As society develops, reliance on livestock as a financial asset diminishes, and is increasingly replaced by currency.[8] Despite that, for many smallholder livestock farmers in Africa, meat and livestock are seen primarily as a representation of wealth, with a level of cultural significance in certain populations.[9]

Religion is often a central component influencing meat consumption practices in many African countries. In a Western context, Islam and Judaism have established dietary restrictions, while some other religions, such as Ethiopian Orthodox Christianity, call for specific slaughter practices and restriction of meat consumption on certain fasting days, as well as abstinence from the consumption of certain animals.[10] Furthermore, many African countries have a Muslim majority, and abide by their own customary meat practices. It is also relevant to note that there are substantial Hindu and Seventh-day Adventist populations in some parts of Africa who observe vegetarian diets and contribute to reduced levels of meat consumption.[11]

For many ethnocultural groups within Africa, specific meat dishes have strong cultural associations. Such dishes may be accompanied by customs for when they should be eaten, and norms concerning who they should be prepared by and for whom.[12] The preparation and consumption of meat is also intertwined with norms around gender and the relationship between the sexes; preparation of meat dishes is often considered a key skill of an ideal wife.[13] These kinds of cultural demographic factors are important when assessing how meat fits into broader cultural paradigms.

16.2.2 Trends in Meat Consumption and Development in Africa

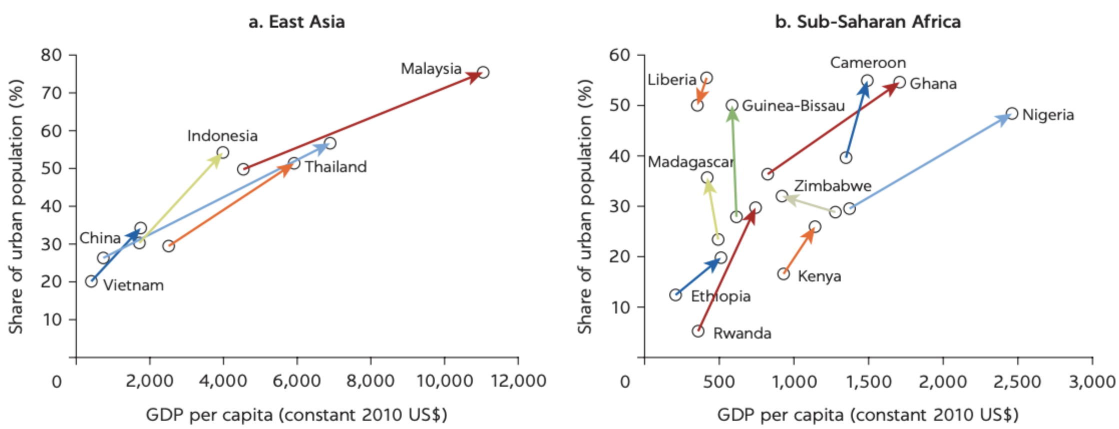
Economic trends

Evaluating economic and population trends is necessary to understand and predict changing patterns of meat consumption within a given region. Africa has the world’s highest birth rates, and it is also experiencing increasing life expectancy. Its population is projected to more than double by the mid-21st century, to 2.5 billion people. Moreover, Africa has the world’s highest proportion of young people; three-quarters of Africa's population is under 35 years old. This trend is not predicted to slow in the near future: in fact, the number of young people in Africa is expected to more than double by 2055.[14] By 2050, Africans under 35 will comprise about one-third of the global population.[15]

Overall, Africa's economy is growing at a rate above the global average, and it is projected to continue expanding.[16,17] Africa is the world's second fastest-growing region behind Asia. Of the world's ten fastest-growing economies, six are in Africa. According to the International Monetary Fund, Africa's largest economies are Nigeria, South Africa, and Egypt, in that order.

Africa is rapidly undergoing urbanization and, as of 2019, 40% of Africans lived in cities. Larger urban populations are associated with higher incomes, yet the World Bank found that Sub-Saharan Africa is urbanizing with lower per capita GDPs than other regions such as the Middle East and North Africa (Figure 1).[18] Despite this, poverty in African cities is declining at a faster rate than in rural areas.[19] To learn more about the long-term effects of urbanization relative to cell-cultured meat, please refer to Section 2.5, *Industry, Innovation, and Infrastructure*, in Chapter 2, *Humanity*.

Urbanization has been associated with uniform growth in East Asia, but the story is a mixed bag for Sub-Saharan Africa



Source: Calculations based on World Development Indicators.
Note: Data correspond to changes between 1990 and 2016.

Figure 1.

Meat consumption trends in Africa

Africa's economic trends indicate that meat consumption will increase, as research indicates that meat is symbolic of higher socioeconomic status.[20] Patterns of consumption in Africa may at least partially abide by Bennett's Law, which states that as income increases, people transition from eating mostly carbohydrates to a more diversified diet, specifically one higher in meat consumption.[21]

Africa, excluding South Africa, has the world's lowest per capita meat consumption. The Food and Agriculture Organization (FAO) of the United Nations (UN) found that between 2005 and 2007, per capita meat consumption in Africa was about 14 kg of meat and 30 L of milk annually. This figure is in stark contrast with that of developed economies, where the average person eats 87 kg of meat and 214 L of dairy in a year. More than one-third of African families reported consuming animal products less than once a week, but this varies significantly by country. For example, while the continental average was approximately one-third, 48% of families in Malawi reported low levels of regular animal product consumption.[22]

While annual meat consumption in Africa is relatively low, the FAO predicts that beef and pork consumption in Africa will double from 2015 to 2050 and poultry consumption will increase by 211%.[23] Milk is the most consumed animal product in Africa by volume, and beef and poultry are the most consumed meats.

16.2.3 State of the Meat Industry in Africa

Most meat in Africa does not come from industrial sources. Across the region, smallholder farmers are common, and many African farmers herd cattle traditionally. *Business and Livelihoods in African Livestock*, a 2014 report, found that only 5-20% of livestock farmers are "business-oriented" and seeking to increase production to supply rising regional meat demands. For example, in 2014, only about 5% of beef and milk production came from companies in Tanzania.[24] While a handful of efficiently run industrial-scale producers offer a vision for addressing future supply challenges, the majority of African livestock are raised in less-than-optimal conditions, often in inefficient smallholder environments isolated from slaughterhouses and markets by limited infrastructure.

It is commonplace, especially among rural households, to keep a small number of livestock. Almost two-thirds of rural households in Ghana, Madagascar, Malawi, Niger, Nigeria, Tanzania, and Uganda reported keeping livestock.[25] About half of rural families from this survey raise poultry, a quarter raise sheep or goats, and a fifth raise cattle.[26] As of 2019, 99% of cattle were still herded as per traditional practices in Nigeria.[27] In order to eat meat, rural families must raise livestock due to a lack of supply-chain infrastructure that would provide them with meat products from other regions.

As meat demand increases in Africa, industrial domestic production will struggle to match it, and the region could see a rise in meat imports. For example, beef demand in Nigeria is expected to surpass supply as early as 2023.[28] The FAO estimates that from 2007 to 2050, meat imports will increase more than five-fold, and milk imports will almost double (Figure 2).[29] By 2050, 14% of pork, 18% of poultry, and 13% of milk may be produced overseas.[30]

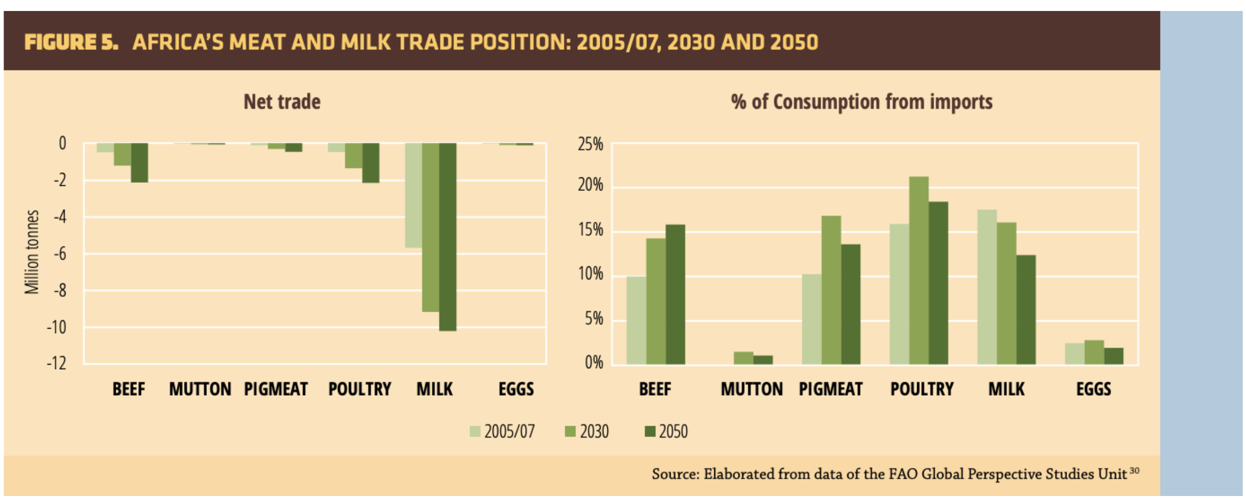


Figure 2.

Historically, Africa has produced only about 5% of the world's meat, but this figure is expected to increase.[31] South Africa leads the continent in meat production, followed by Egypt (Figure 3).[32] Karan Beef is Africa's largest cattle feedlot, located in South Africa.[33] Karan Beef exports throughout Southern Africa, North Africa, the Middle East, and Asia. Zimbabwe's beef industry is growing after recovering from a collapse in the 2000s. At its peak, Zimbabwe's commercial beef sales provided about 80% of income in provinces where the industry was well-established.[34] Notably, the majority of this beef was exported to the European market. In light of rising income and appetite for meat in Africa, there may be greater domestic demand and a stronger market to bolster the industry's rebound in the near future.

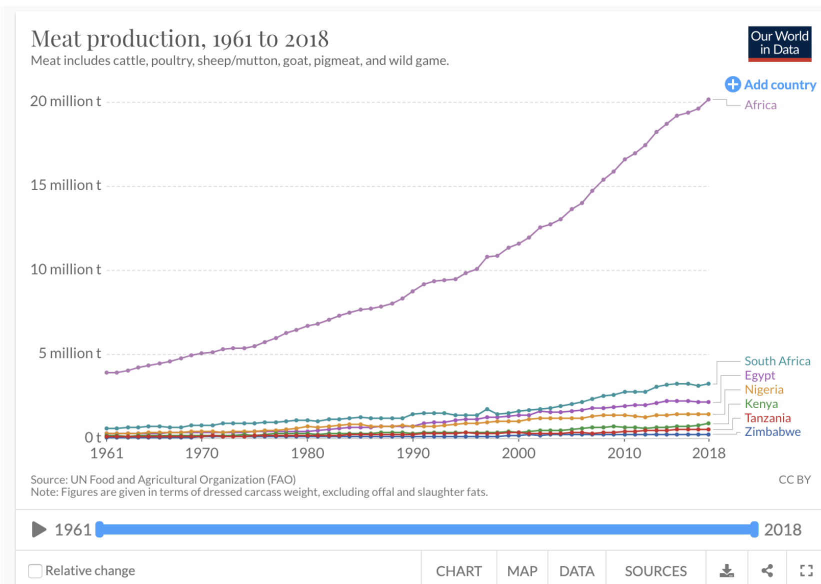


Figure 3

Large food retailers are spreading across Africa, giving industrial meat producers a more streamlined sales channel compared to small independent retailers and traditional wet markets.[35] The combined effect of increasing meat demand and large food retailers may further accelerate meat consumption.

16.3 Cell-cultured Meat in Africa

16.3.1 State of the Industry and Research

Due to ethical and environmental considerations, there is an urgent need for more sustainable meat-production strategies. As the movement to remove animals from the global supply chain strengthens, incumbent industries will likely resist this shift. If cellular agriculture is to grow to a scale comparable with existing animal agriculture corporations, the supply chain will have to be global and also at a scale consistent with current animal agriculture. As of 2019, the global meat industry was worth about US $1.7 trillion, and the alternative protein industry about US $2.2 billion.[36] Existing industries in Africa may be able to adapt to support cellular agriculture instead of foreign startups or companies introducing products into the African market. Globally sourced and processed products are already a norm, so the potential for African companies to supply ingredients for cellular agriculture could fit well into the existing context of exports from Africa.

In 2019, Mosa Meats, a Dutch cellular agriculture startup, known for developing the first cell-cultured burger in 2013, announced a partnership with Nutreco, a large livestock feed company. Mosa Meats explained that to scale cellular agriculture and achieve cost competitiveness, it required food-grade ingredients for its media rather than the much more expensive components used in medical-grade cell cultivation media that are not intended for the high production volumes of mass food production.[37] While not in Africa, this partnership demonstrates the potential for collaboration between cellular agriculture and existing industries.

Low-cost sources of plant-based protein are already produced in Africa. For example, pulses, such as various peas, beans, and lentils, are harvested throughout Africa.[38] These crops serve as an important resource that could potentially be directed into the cellular agriculture supply chain, both locally and internationally.

16.3.2 Demand for Cell-Cultured Meat

As of 2021, there are less than a dozen cell-cultured meat startups in Africa, including Mzansi Meat Co., Sea-Stematic, and Mogale Meat. However, there has been some progress among adjacent industries and interest groups that may pave the way for cellular agriculture to successfully launch in Africa.

The expansion of plant-based meat and dairy industries

The growing presence of plant-based meat in Africa may open the door for cell-cultured meat and eventual consumer acceptance. Infinite Foods, a South African company, has introduced plant-based meat and dairy products to several African countries. Infinite Foods offers turnkey solutions for non-African plant-based food companies that want to launch in Africa. Since its inception, Infinite has introduced major plant-based brands such as Beyond Meat, JUST, and Oatly into African markets.

High acceptance despite low familiarity

A 2021 study of South African consumers' perception of plant-based and cell-cultured meat showed very favorable results for both alternatives. Even though the broad population is not yet very familiar with such products, 53% of respondents in a representative sample indicated a high likelihood to purchase cell-cultured meat, once available. Given that prior familiarity was one of the most significant predictors for purchase intention, this share might even increase further, as cell-cultured meat becomes more widely known. However, these findings are based on only one study and further research is needed to confidently assert these claims and extrapolate them beyond the South African market.[39]

The expansion of a younger population

The above-described study and other research shows that young people are more open to trying new products, including food, than older generations.[40] Given that by 2050, under-35s in Africa will likely comprise about one-third of the global population, it may be easier for cell-cultured meats to gain acceptance in African markets than elsewhere in the world in the coming years.

Increasing awareness around animal welfare

The Guardian reports that since 2018, Happy Cow, an app that shares information on vegan restaurants, lists more than 900 restaurants offering vegan food in Africa. Happy Cow does not list restaurants with vegetarian options that are not vegan, so the plant-based food trend in Africa is likely larger than it appears. The majority of these listings are in South Africa, but many more restaurants in countries such as Kenya, Ghana, and Senegal also offer plant-based dishes.[41]

The African wildlife trade attracts animal welfare concerns, and several African countries now have laws in place seeking to protect animals.[42,43] It is likely that the animal welfare movement may strengthen as animal agriculture industrializes in Africa.[44] Animal welfare advocates frequently protest about the treatment of animals in industrial-scale operations and the practices of these large corporations. In contrast, the dominant model of smallholder animal production in Africa may not generate the same response and is significantly more challenging to confront given the wide distribution of stakeholders.

Increasing awareness around climate change

A 2019 survey of Africans on climate change awareness found that 58% of Africans have heard of climate change, and 52% of this group blame climate change on human activity. South Africa ranked among the lowest in climate change awareness with only 41% of residents reporting to have heard of climate change.[45] This is surprising as South Africa ranks above the continent's average for internet access and has a literacy rate of 95%, suggesting that data pertaining to climate change should be more accessible and intelligible than in other African countries. Moreover, South Africa has already experienced the effects of climate change, with inconsistent rainfall patterns and prolonged droughts.[46]

Leapfrog case study

If cell-cultured meat is made commercially available in Africa in the near future, it would be considered a leapfrog technology. Leapfrogging is when a radical technological innovation abruptly transforms a society, rather than gradually shifting through the longer timeline of incremental innovations. A well-known example of leapfrogging is cell phones: many Africans' first cell phones were smartphones, whereas people in countries where cellphones had been readily available often owned several versions of a cell phone before they purchased a smartphone. In regions where industrial meat production is not yet the primary supply of meat, there is opportunity for cellular agriculture, or other slaughter-free protein innovations, to leapfrog farmed meat.

However, the chance of cell-based meat leapfrogging farmed meat in Africa seems low. To do so, cell-based meat would need to be cheaper than farmed meat, become established through cold supply chains, and be readily available where meat is purchased. Plant-based meat is much better positioned for this scenario, particularly plant-based meats that are low cost and shelf-stable at room temperature; although such products also face similar challenges. However, it's possible that cellular agriculture could feasibly be introduced into luxury African markets before the general population has regular access to industrially produced meat.

16.3.3 External Stakeholders in Cell-Cultured Meat in Africa

Africa has a long road ahead when it comes to investments in cell-cultured meat. At present, there are few external stakeholders with active vested interests in the development of cell-cultured meat in Africa. African national governments have not spoken publicly about cell-cultured meat nor begun any processes to regulate such an industry. In contrast to many other highly developed economies where the conventional industrial meat industry is well-established and dominated by a few big players, Africa has yet to experience this level of market domination; therefore, it is difficult to identify any incumbent industry that may be open or resistant to potential disruption.

The Credence Institute, a South African advocacy organization founded in early 2020, is actively encouraging cell-cultured and plant-based meat alternatives in order to diminish animal suffering.[47] While still in its foundation stage, the Institute has stated that it aspires to advance the interests of animals through market-based solutions. Credence engages with the public, industry, and government to challenge attitudes and behaviors that are harmful to animals. ProVeg, an international organization campaigning to promote plant-based meat, also has a base in South Africa.[48] ProVeg advocates for the development of cell-cultured meat and has plans to pursue activities to promote product awareness. In the future, it is likely that the further emergence of cell-cultured meat stakeholders will be from urban and affluent regions in Africa, such as South Africa and Nigeria.

16.4 Conclusion

This chapter has shown that future meat consumption across Africa will be driven by economic development and population growth. As of 2022, per capita meat consumption is still relatively low, production is dominated by small-scale non-industrial farming, and conventional meat is associated with wealth as well as traditional and religious practices. The cell-cultured meat industry in Africa is in its nascent stages, with only few companies and other stakeholders actively involved. However, demand for cell-cultured meat in Africa could benefit from the ongoing expansion of plant-based meat and dairy industries, increasing concern around animal welfare and climate change, a generally higher acceptance among the vast cohorts of younger generations, as well as potential technological leapfrogging. While this shows that there is promise for cell-cultured meat in Africa, it remains to be seen whether strong markets and supply chains can be established in the coming decades.

Fundamental Questions – Answered

1. **What is Africa's historical relationship with meat and animal farming?**
   The African continent is host to a range of dynamic populations, comprising individuals with different cultural, religious, economic, and political backgrounds. The ownership of livestock and the consumption of meat are historically associated with wealth, which may challenge future alternative meat endeavors.

2. **What is the forecast for meat consumption in Africa?**
   The African population has the highest birth rate worldwide, and the consumption of meat and demand for protein-rich food sources are thus expected to rise accordingly.

3. **What are the key factors that will affect the success of cell-cultured meat in Africa?**
   The younger population is more receptive to meat alternatives and places less value on meat as a symbol of economic stability. Young people are often more educated than older generations due to increased resource availability and literacy, and express concerns for animal welfare and the environmental impact of livestock farming. A key determinant in the success of cell-cultured meat products in Africa depends on effective communication between product developers and the younger generation of consumers.

4. **What differentiates the African market from other international markets for cell-cultured meat?**
   Many groups of African people espouse traditional mindsets and may be resistant to change. In addition, cultures vary widely between countries. Effective marketing of cell-cultured meat is imperative to shifting conventional mindsets and established practices surrounding animal farming and the consumption of meat products.

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Asia

Cultivated Meat Around the World: Economics, Tradition, and Culture in Asia

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Chapter Abstract

Historically, many populations of Asia have not had a tradition of heavy meat consumption. In modern Asia, however, meat consumption is significant. In addition, some of the largest Asian countries such as China have directly contributed to the rapid increase in production of animal meat products. Meanwhile, others such as Israel and Singapore have strongly contributed to the advancement of the cellular agriculture and cell-cultured meat industries.

In this chapter, Asia is divided into 3 subregions—East Asia, South and Southwest Asia, and Central and West Asia—in order to better generalize meat consumption and production habits of different populations. This chapter analyzes the history, current state of industry, and future consumption and development of conventional meat, and the current state of industry and research, demand, and external stakeholders for cell-cultured meat for each of the subregions.

Keywords

Industrial farming
Religion
Diet
Tradition
Domestication
Government support
Small scale farms
Start-up

Fundamental Questions

1. What is Asia's historical relationship with meat and animal farming?
2. What is the forecast for meat consumption in Asia?
3. Who are the major players in conventional animal agriculture and cellular agriculture in Asia?
4. Who are the main actors that will affect the success of cell-cultured meat in Asia?
5. What differentiates the Asian market from other international markets for cell-cultured meat?

Chapter Outline

17.1 Introduction

17.2 East Asia
- 17.2.1 Conventional Meat
  - 17.2.1.1 History of Meat in the Region
  - 17.2.1.2 Current State of the Industry
  - 17.2.1.3 Future Trends in Consumption and Development
- 17.2.2 Cell-cultured Meat
  - 17.2.2.1 Current State of the Industry and Research
  - 17.2.2.2 Demand
  - 17.2.2.3 External Stakeholders

17.3 South and Southeast Asia
- 17.3.1 Conventional Meat
  - 17.3.1.1 History of Meat in the Region
  - 17.3.1.2 Current State of the Industry
  - 17.3.1.3 Future Trends in Consumption and Development
- 17.3.2 Cell-cultured Meat
  - 17.3.2.1 Current State of the Industry and Research
  - 17.3.2.2 Demand
  - 17.3.2.3 External Stakeholders

17.4 Central and Western Asia
- 17.4.1 Conventional Meat
  - 17.4.1.1 History of Meat in the Region
  - 17.4.1.2 Current State of the Industry
  - 17.4.1.3 Future Trends in Consumption and Development
- 17.4.2 Cell-cultured Meat
  - 17.4.2.1 Current State of the Industry and Research
  - 17.4.2.2 Demand
  - 17.4.2.3 External Stakeholders

17.5 Conclusion

17.1 Introduction

Meat consumption globally has increased by 40% since 2000 with half of that increase driven by Asian markets.[1] By 2030, seafood and meat consumption in Asia is predicted to increase by 33%, and by 2050, 78%. However, this massive increase in consumption, facilitated by the equally steep increase in production, is unsustainable for many reasons such as environmental pollution and proliferation of zoonoses. Alternatives such as the production of cell-cultured meat and seafood would be useful options to meet such large demands, especially in Asia. The vastly different geography and culture of Asian regions have historically influenced a variety of trends in meat production and consumption. For instance, people in East Asia have traditionally adhered to a more plant-based diet, occasionally supplemented by specific meats. The geographic terrain of South and Southeast Asia makes it a region prime for animal domestication, but one of the central religions in these regions, Buddhism, has historically limited the consumption of meat. West and Central Asia were previously home to many nomadic groups, and therefore the use of animal products and consumption of meat was common. However, the proliferation of religions such as Islam limited the consumption of specific meats such as pork. Therefore, analyzing the relationship people from different regions have with animal products and their attitudes towards cell-cultured alternatives becomes increasingly important.

17.2 East Asia

17.2.1 Conventional Meat in East Asia

Composed of China, Hong Kong, Macao, Mongolia, North Korea, South Korea, Japan, and Taiwan, East Asia makes up over 20% of the world's population and includes most high-income countries within Asia. For this section, the predominant focus has been placed on China, Hong Kong, and Japan, given their higher level of engagement with the cell-cultured meat industry. Meat consumption in East Asia, while dwarfed by Western consumption levels, far outweighs other regions within Asia. The region presents as a strong case study of Bennett's law: that rises in income correspond with rising consumption of protein, especially meat-based products.[2]

17.2.1.1 History of Meat in East Asia

East Asia is known for its development of grains and legumes that are now commonplace among diets internationally, such as rice and soybeans. The region also has a history of high meat consumption due to outliers like Mongolia, where nomadic lifestyles were dependent on domestication of livestock. Aside from this, diets in East Asia were largely plant-based and supplemented, rather than defined, by consumption of animal meat—predominantly pork—and seafood in some islands and coastal areas.[3]

Religion and spiritual systems originating and historically present in East Asia do not encourage heavy meat consumption. For example, Taoism preaches that food is a form of medicine composed of different properties. This was translated into an emphasis of consuming different food—classified in specific groups—to conserve a healthy balance in the human body. Confucianism connects animal slaughter and meat with immorality. Buddhism, in general, supports a diet of occasional animal-produce consumption, and therefore, strict schools of Buddhist doctrines call for vegetarianism. An example of a school of thought prohibiting meat consumption in a country is when Japan underwent a period where meat consumption was effectively prohibited (connected to Shinto and Buddhist doctrine). Although, the Japanese have historically had access to and consumed an abundance of seafood. (Krämer 2008). [4]

In the global timeline of animal domestication, China was responsible for the domestication of the wild boar into what is now known as the pig.[5] In the late 19870s, reforms in China loosened central control of agricultural production and distribution, which allowed more freedom to both farmers and consumers. Gradually, meat—especially pork—became a commodity accessible to the population, and today, China is the world's largest producer of pork. In the broader region, Japan and Korea also started to incorporate meat into their diets from the influence of external countries and now have built a strong tradition of pork consumption. The shift to large scale, centralized industrial animal farming—which utilizes concentrated animal feeding operations (CAFOs)—instigated in the US in the 1990s, and this system has spread globally in the last thirty years. For more information on CAFOs from the Environmental Protection Agency (EPA), refer to Section 3.2, *Life on Land,* in Chapter 3, *Animals*. Though China has been part of the worldwide shift to industrialize animal farming, small-scale animal rearing and farming still makes up a significant part of domestic industry: over 90% of farms in China are under 2.5 hectares.[6] Therefore, animal agriculture industrialization is still an ongoing process in China, encouraged by government policies that increase regulation for food safety.[7]

The environmental impact of industrial animal farming in China, especially regarding water pollution, is a critical issue for government, local communities, and public health. The density of China's population combined with poorly enforced regulations on occasion, make it a hotbed for the development of novel and deadly diseases developed from zoonoses.[8] This is evidenced by known human viruses from animal sources which were found to originate in China such as severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and SARS-CoV-2, which initiated the COVID-19 pandemic in late 2019.

All other East Asian countries are dwarfed in comparison to China's meat production levels and associated issues, as they have generally higher levels of regulation and enforcement. Despite this, negative externalities of animal agriculture remain, such as CAFO water pollution in Korea and the loss of biodiversity and degradation of the environment in Mongolia.[9] Prevailing examples such as these could very well threaten economies of many countries in the East Asian region.

17.2.1.2 Meat Industry in East Asia

Broadly speaking, civilization in East Asia developed out of the region now referred to as China. This often makes Chinese history a useful reference point when considering culture in other parts of East Asia. This includes important factors related to meat consumption, such as religion, food preparation and ingredients.[10]

East Asian diets remain relatively low in meat when compared to other high-income countries such as the US, Australia, and those in Europe. Although Bennett's Law states that high incomes correlate with high meat consumption, East Asia is an exception to this rule, and this can be tied back to culture. In China and other East Asian countries today, meat is often a small component of a dish, and sometimes simply a garnish or flavor addition, as opposed to being the center of focus. For this reason, an average meal may contain meat but not in great quantities. This reflects customary serving practices in many Asian food cultures of sharing multiple dishes amongst groups rather than each having individually plated meals. In this way, serving small bite-size pieces of meat from a large dish, instead of having discrete large portions, allows for enhanced group sharing and is suited for larger families.[11]

East Asia is a net importer of meat as a result of low production levels in Korea and Japan combined with high demand from these nations. This is compounded by further demand from China. Broadly speaking, China is the world's largest producer, consumer, and importer of meat in the world.[12]

As of 2020, China ranks as:

- The largest producer and consumer of pig meat (despite pig headcount falling by over 45% since African Swine Fever began in mid-2018)
- The largest producer of seafood
- The fourth largest producer of bovine meat
- The third largest producer and second largest consumer of chicken meat

Aside from this, China also has a strong domestic market in the production of other types of meat, chiefly duck, rabbit, and other animals that are rarely, if ever, consumed in Western nations. Unsurprisingly, China is also home to some of the largest meat companies in the world, including WH Group—the largest pig meat producer in the world, which also owns Smithfield—and New Hope Group, whose business includes both meat processing and animal feed.[13]

Japan and Korea also have strong meat production industries in seafood and pig meat, respectively. While Japan is home to three of the five largest seafood companies in the world, South Korea is the ninth largest producer of pork in the world.[14] [15] Mongolia does not make major contributions to world beef production, but headcount of cows per capita is one of the highest in the world, making cattle farming an important domestic industry.[16]

17.2.1.3 Future Trends in Meat Consumption and Development in East Asia

While Asia is touted to lead meat consumption globally in the coming decades, as stated before, most of such demand stems from China. More broadly in the general East Asian region, the overall increase includes an increased demand for seafood, except for demand in Japan where seafood consumption rates are decreasing.[17] As economic growth is predicted to continue in East Asia, meat consumption, supplied mainly from imported products, is projected to rise over the next decade.[18] This growth will occur across all types of animal meats, especially beef and sheep, and will be particularly fueled by a middle class with rising disposable income and a desire for a westernized diet.

Specifically, China and Mongolia will undoubtedly increase meat production levels in coming years. Both countries, particularly China, will continue to see a decrease in smallholder farms in preference for larger, commercial farming operations with higher productivity and efficiency. This transition will have a considerable impact on national production. It is also being encouraged by several factors including the establishment of domestic environmental regulations that smallholders will find increasingly hard to meet, crises such as African Swine Fever and Avian Flu (the devastating impact of which often cannot be borne by smallholders), and a growth in demand for industrially produced meat (for implied food safety reasons). While Chinese pig herds have been severely affected by the 2018 African Swine Fever, China is still expected to make up 50% of growth in pork production within ten years by applying increasingly industrialized operations.[19] Chinese beef production could also make significant traction from industrialization that is currently underway.[20]

17.2.2 Cell-Cultured Meat in East Asia

17.2.2.1 Current State of the Meat Industry and Research in East Asia

At an academic and conceptual level, cultivated meat has made a growing presence across mainland China, Japan, and Hong Kong. Cell-cultured meat companies have been publicly launched in both Japan and Hong Kong. Japan is home to Integriculture and Nissin. Integriculture is a cell-cultured meat start-up that grew out of the open-source community, Shojinmeat Project. Integriculture has been working on high-end products such as cell-cultured foie gras, and developing products to support do-it-yourself cellular agriculture, the cornerstone of the Shojinmeat Project.[21] Nissin, on the other hand, is a major global food company that is developing cell-cultured meat.[22] Hong Kong is home to Avant Meats, a start-up focusing on the Chinese market through the initial development of cultured fish meat products, specifically fish maw. Fish maw is a high-end seafood product with considerable demand in Hong Kong and Chinese markets. Both Integriculture and Avant Meats are working on products which command a higher price point than in their conventional form, which may make them more financially viable to produce through cellular agriculture.

While Integriculture has worked with researchers from Tokyo Women's Medical University, within East Asia, only China has dedicated public academics to work on cell-cultured meat at Nanjing Agricultural University. The first mainland-China based unveiling of cell-cultured meat was a 5-gram sample of pork during a forum on cell-cultured meat at Nanjing Agricultural University in November 2019.[23] Soon after, Joes Future Food (Nanjing Zhouzi Future Food Technology Co.), a company focusing on research and development of cell cultured meat, was developed out of the research team from the university. In late 2021, the company announced that it received 70 million RMB in a funding round. Moreover, the China Plant Based Foods Alliance (CPBFA) is a representative group for alternative proteins in China that also hosted a forum on cell-cultured meat, in September 2019.[24] Though, some contention has been raised over the validity of the unveiling and proliferation of companies such as Joes Future Food being the *first in China* given the existence of Avant Meats in Hong Kong.

17.2.2.2 Demand in East Asia

A comparative 2019 study between the US, China, and India focused on the acceptance of alternative protein (including cell-cultured meat) in these countries.[25] The results of the study illustrate that in the Chinese population, 35.5% felt familiar with cell-cultured meat, 31.9% moderately familiar, and 10.8% extremely familiar. Additionally, 6.7% said they are not likely to purchase cell-cultured meat, but 33.9% were moderately likely to, and 59.3% were extremely likely to. Cross country comparisons detail that the Chinese population is generally more accepting and familiar with cell-cultured meat than the US population, at a similar level with that of India. Evidently, there is a noticeable demand for cell-cultured meat in China.

17.2.2.3 External Stakeholders in East Asia

Governments across East Asia have not made explicit policies or public statements on cell-cultured meat as of 2021. However, the Japanese government has given tacit support for the technology through investing in Integriculture via its subsidiary body, A-FIVE (Agriculture, Forestry and Fisheries Fund Corporation for Innovation, Value-chain and Expansion Japan).[26] Within China, the CPBFA lobbies for the adoption of alternative protein and brings together industry and government to discuss the future in this area. Past CPBFA events have had representation from Avant Meats, Aleph Farms, and Bond Pet Foods. In addition, the Good Food Institute also has mission-aligned representation within China through the Good Food Institute Consultancy and The Good Food Institute Asia-Pacific (GFI-APAC).

The Shojinmeat Project in Japan is unique in bringing together a community, composed largely of the public, to create a shared vision of a future which incorporates the idea of giving individuals access to the technology of producing cell-cultured meat. Founded in 2014, its online platform (in both Japanese and English) shares do-it-yourself instructions on how to grow cultivated meat with basic equipment accessible to everyone.

While not as overt as in regions like the Americas, the influence of the meat industry in East Asia is significant. For instance, in Japan, big agricultural companies and the meat industry have political influence which gives them the power to impact the development of cell-cultured meat companies.[27]

17.3 South and Southeast Asia

17.3.1 Conventional Meat in Southern and Southeast Asia

Southern Asia includes Afghanistan, Bangladesh, Bhutan, India, Nepal, Pakistan, Sri Lanka, and the Maldives. Southeast Asia includes Brunei, Myanmar, Cambodia, Timor-Leste, Indonesia, Laos, Malaysia, the Philippines, Singapore, Thailand, and Vietnam. Rivaling parts of Africa in terms of its low levels of meat consumption, Southeast Asia has historically consumed little meat. This region has only recently experienced major increases in meat consumption. Nevertheless, consumption levels in Southern and Southeast Asia are approximately half of their East Asian counterparts.[28]

17.3.1.1 History of Meat in Southern and Southeast Asia

Southern and Southeast Asia's meat consumption historically differs from the rest of Asia, largely because of its economic, religious, and cultural demographics.

Southern and Southeast Asia have a long history of raising domesticated farm animals, especially cattle. Moreover, Southern and Southeast Asia's historical relationship with agriculture and livestock is distinct due to its environment, both in terms of weather and terrain. India and regions of Southeast Asia are commonly cited as origins of the domesticated chicken as the relatively low requirement of land area and feed required to maintain chickens reflects the nature of small farming in that region.[29] While the global sweep of industrialization across the Global South is transforming animal meat production across Southern and Southeast Asia, small scale farms with mixed crop and livestock have been the historical norm across the region.[30] Some countries with considerable coastline have diets historically high in seafood (e.g., Philippines, Thailand, Malaysia), while some countries have historically farmed less livestock due to lack of pastoral land (e.g., Singapore).

The impact of industrial animal farming in Southern and Southeast Asia is not as significant as other regions because of the predominance of smallholder farmers. These farms generally have less environmental impact because their mixed crop and animal farming system have many opportunities to recycle produced waste for other uses. However, some regions within Southern and Southeast Asia are inevitably transitioning to industrialized animal farming, and therefore problems associated with these practices are beginning to surface in extreme ways. Examples include the rise of antimicrobial resistance in India, the destruction of important mangrove habitat in Myanmar due to aquaculture, and human rights abuses in Thailand's seafood supply chains.[31,32] In addition, health-related harms of meat consumption are significant in Southeast Asia.

For instance, with the increase in Thailand's livestock farming sector from 1990 to 2010, the number of cases reported of foodborne illnesses—the majority stemming from ingestion of meats—had doubled. In addition, in 2017, approximately 70% of foodborne illnesses in India were caused by animal products, mainly meat.

17.3.1.2 Current State of the Industry in Southern and Southeast Asia

While India is home to the overwhelming majority of the world's vegetarians (up to 30% of the population are ethical vegetarians), Indonesia is projected to overtake India in meat consumption rates by 2036 with one fifth the population.[33] As such, Southern and Southeast Asia may be a difficult region of Asia to generalize in terms of their cultural relationship with meat.

Food habits in Singapore and other parts of Southeast Asia are characterized by regional historical migration, primarily from China, who has created Chinese diaspora communities. As such, many parts of Southeast Asia share similarities with the way the Chinese population approaches meat, especially regarding the diversity of animal meat eaten, as well as the relatively low consumption of certain cuts of meat.

Most protein consumed in Southern and Southeast Asia is in the form of fish and seafood, with Southeast Asian countries consuming the most seafood per capita in the world.[34] As of 2021, Vietnam is the world's sixth largest pork producer and Thailand is the world's fourth largest exporter of poultry. Furthermore, it is expected that there will be just under a 60% increase in Thailand's export of poultry between 2018 and 2028. The meat industry in these countries, as well as Malaysia, Indonesia, and the Philippines is expected to grow further, as are meat imports.[35]

17.3.1.3 Future Trends in Meat Consumption and Development in Southern and Southeast Asia

Southern and Southeast Asia are already home to some of the world's largest producers of poultry, such as Thailand, and pork, such as Vietnam but protein production is set to skyrocket in the coming decade. By 2022, Southeast Asia is projected to overtake the EU as the world's largest importer of soybean meal. Soybean meal is a key feedstuff for Southeast Asia's growing meat production.[36] Rising meat consumption in Southern and Southeast Asia is largely fueled by rapidly growing populations—Southeast Asian countries alone will reach 720 million by 2027—coupled with rising incomes.[37] Indonesia's total meat and seafood supply alone is projected to grow by nearly three times between 2018 and 2050.[38]

17.3.2 Cell-Cultured Meat in Southern and Southeast Asia

17.3.2.1 Current State of the Industry and Research in Southern and Southeast Asia

Singapore is often named as a hub for cellular agriculture. This is largely based on the Singaporean government's overt support for the development of the industry by being the first jurisdiction to publicly detail its plan for regulation of cell-cultured meat.[39] In December 2020, the Singapore Food Agency issued regulatory approval for the production and sales of Eat Just's cell-cultured chicken. Soon after, the first ever commercial sale of cell-cultured meat was made in Singapore by Eat Just, and the product was served by the renowned Singaporean restaurant, 1880, on December 19, 2020. The country is also home to the distinguished cell-cultivated meat and seafood company Shiok Meats, who is planning to commercialize in 2024.

The Singaporean government's Agency for Science, Technology and Research (A*STAR) has published several documents on its interest and research into cellular agriculture since early 2019. Additionally, Singapore is a proponent of research in the cellular agriculture space, attempting to attract international companies to its jurisdiction with favorable research and investment opportunities.[40]

17.3.2.2 Demand in Southern and Southeast Asia

Considering the projected growth rates for meat consumption across Southeast Asia, the region is expected to harbor considerable demand for cell-cultured meat once it is developed. Comparative research undertaken between the US, India, and China found Indian respondents were relatively open to cultured meat. More specifically, the results displayed that in the Indian population, 25.5% felt familiar with cultivated meat, 35.8% moderately familiar, and 38.7% extremely familiar. Additionally, 10.7% said they were not likely to purchase cultivated meat, 32.9% likely to, and 56.3% very or extremely likely to. Although, another important conclusion drawn from the study was that Indian's overall meat attachment (psychosocial bond with meat consumption) was significantly lower than the other countries, even after further studies excluding vegetarians was conducted.[41]

On the other hand, over 78% of Singapore consumers were willing to try cultivated seafood when presented with infographics on the concept of cultivated seafood production. Furthermore, the primary motivations stated in the study are sustainability, curiosity in the novel proteins and health and food safety concerns.

Singapore will likely experience the greatest initial surge in demand for cell-cultured meat, given that this is where cultivated meat was first sold, alongside strong government support.[42] Furthermore, a survey conducted for internal purposes by Shiok Meats in late 2020 details that more than 78% of the population is willing to try cell-based seafood products due to the ethical and environmental benefits of this alternative option.

For Indonesia and other countries with high Muslim populations, such as Malaysia, whether cell-cultured meat will meet halal food requirements will help determine demand. In Malaysia specifically, cultivated pig meat could also unintentionally resolve issues such as the political debates surrounding pig farming. (Neo and Emel 2017)

17.3.2.3 External Stakeholders in the Meat Industry in Southern and Southeast Asia

The Singaporean government is viewed as one of the most proactive governments internationally in supporting the development of cell-cultured meat. One reason for this has been the government's strong research support of A*STAR, which has been both developing cultured meat technologies and supporting the development of the industry.[43] The Singaporean government's long-standing interest in pursuing a policy of food sovereignty (30% by 2030) has been explicitly referenced in statements on cell-cultured meat development.[44]

The meat industry across Southern and Southeast Asia does not yet have the lobbying power of multinational agricultural companies in regions like the Americas. Despite this, it is still possible that the incumbent meat industry may try to jeopardize the development of cell-cultured meat in these regions, where established corporations currently supply. While research has indicated that cell-cultured meat may meet halal food requirements (if it is cultivated in a specific manner), this may be interpreted differently in different places and there is a possibility that this could be a barrier to cultivated meat's adoption in Indonesia and other countries with significant Muslim populations.[45]

17.4 Western and Central Asia

17.4.1 Conventional Meat in Western and Central Asia

17.4.1.1 History of Meat in Western and Central Asia

Western and Central Asia includes Afghanistan, Armenia, Azerbaijan, Bahrain, Cyprus, Georgia, Iran, Iraq, Israel, Jordan, Kuwait, Kyrgyz Republic, Lebanon, Oman, Palestine, Pakistan, Qatar, Saudi Arabia, Syria, Tajikistan, Turkey, Turkmenistan, United Arab Emirates, Uzbekistan, and Yemen. The Fertile Crescent (much of Western Asia) is considered the origin of the domestication of many modern farm animals. The more modern advent of religion over the past few millennia (largely in the form of Islam and Judaism) and resulting changes in lifestyle, excluded pig as a commonly farmed animal. Aside from this, farming animals and consuming meat has been historically central to life in the region. The most common animals eaten in these regions are sheep, goats, and chickens. (Redding 2015)

Central and Western Asia were historically home to many nomadic people, and animals were central to the region's diet as a convenient and reliable source of meat or milk for protein. Considerable expanses of arid and infertile land also lent the region to the raising of pastoral animals. As such, Central and Western Asian cuisine is often heavy in its use of meat products and includes the use of large and varied cuts, as well as the spit roasting of whole animal carcasses for special occasions. (Anderson, et al. 2018)

17.4.1.2 Current State of the Meat Industry in Central and Western Asia

In Central Asia, meat is an important reflection of wealth, and for many people, farm animals are still a substantial contributor to income and household wealth. Following the dissolution of the Soviet Union in 1991-1992, Central Asian countries largely went through an individualization of agriculture and fragmentation of large plots of land. This vastly increased the number of smallholder farmers in the region. (Lerman and Sedik 2018) As such, agriculture, including animal agriculture, is central to many people's cultural identity in these regions. Interestingly, Israel is home to the largest number of vegans per capita in the world as of 2017, but Israelis are also the third highest consumers of meat per capita globally, according to the Organization for Economic Co-operation and Development (OECD) figures.[46,47]

Central and Western Asian countries continue to import all forms of meat. Since the breakdown of the Soviet system, large scale production of meat has ceased to exist in these regions. In Israel, due to kosher slaughter practices and insufficient domestic production, live import is commonplace and reached record highs in 2019, though there is increasing pressure to end this practice.[48]

Future Trends in Meat Consumption and Development in Central and Western Asia

Central Asian countries demonstrate strong potential for the development of domestic meat production and export. Kazakhstan, for example, has the fourth largest area of arable land in the world. Kazakhstan has the support of international multilaterals in developing a livestock industry for export, including the World Bank.[49]

17.4.2 Cell-Cultured Meat in Central and Western Asia

17.4.2.1 Current State of the Industry and Research in Central and Western Asia

Israel is commonly identified as a hub for cell-cultured meat development. Most importantly, cell-cultured meat is socially affirmed in Israel as it is backed by Israeli regulatory policies, supportive government funding, along with private investment.[50] Moreover, in 2021, Israeli President Isaac Herzog became the first president to try cultivated meat, and in the previous year, Israeli Prime Minister Benjamin Netanyahu had publicly tasted cultivated meat as well. As of 2021, GFI Israel also has worked with the Israeli government to establish a National Policy Plan—a precise timeline set for the alternative protein industry to flourish in Israel in the coming years. With numerous academics contributing to the space, Israel is also home to a slew of companies pioneering new products, there are also numerous academics contributing to the space. Some companies founded in Israel are Aleph Farms and MeaTech 3D which culture steak using a variety of growing and scaffolding technologies; Future Meat which produces chicken, pork, and lamb in the world's first industrial cell-cultured meat facility, opened in 2021; and SuperMeat which is culturing chicken meat.[51],[52],[53]. These companies are just some examples of globally notable companies that are establishing

Israel as a leader in cell-cultured meat. Furthermore, in December of 2021, Future Meat raised $347M in order to build a production facility in the US, and in July 2021, Aleph Farms raised $105M for aiding the commercialization of their cell-cultured products. As of 2021, there is also one start-up based in Turkey, biftek.co, which specializes in developing animal-free cell culture media.

17.4.2.2 Demand in Western and Central Asia

Research on consumer acceptance of cultivated meat across Western and Central Asia has not yet been undertaken on a large scale. This is a prime area for future study, given that diets and cultural attitudes towards meat across this region are unique. Central and Western Asia are home to strong religious populations whose diet is influenced by their faith. While most of the region adheres to Islam and halal dietary restrictions, Israel has the second-largest Jewish population in the world, and observing a kosher diet is commonplace there.

Whether cultivated meat meets halal and kosher meat requirements has already been the subject of considerable debate.[54] Experts on halal and kosher diets have stated that cultivated meat can be consumed as part of the diet, although there still has not been statements on cell-cultured meat from official religious leaders.[177] Considering this, religious food preparation standards may still be a consideration for cell-based meat companies targeting consumers in these unique regions.

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17.4.2.3 External Stakeholders in the Meat Industries of Western and Central Asia

While there are no dedicated not-for-profit representative organizations or think tanks advocating for the adoption of cultivated meat in Western Asia, Israel is home to several of them. A branch of the Good Food Institute operates in Israel as well as an independent organization advocating for the alternative protein industry, including cultured meat, named the Modern Agriculture Foundation (MAF). MAF lobbies the government, promotes the field of alternative protein across a range of disciplines, and works directly with cultured meat companies to advance the replacement of traditional animal proteins.[178]

17.5 Conclusion

Regions of Asia have developed a strong tradition of meat consumption over the years, and are likely to be a key player in the future of the cell-cultured meat industry. Not only is China the world's largest consumer and producer of meat products, but two of the most notable "hubs" of cellular agriculture, Singapore and Israel, are part of Asia. Although specific statistics regarding the demand for cultivated meat in Asia is limited due to the emerging nature of the field, there is data that shows excitement and enthusiasm for these products—especially in China and India. Furthermore, significant government support of cellular agriculture has strengthened in parts of Asia, which will likely encourage the proliferation of companies and researchers within the field.

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Fundamental Questions – Answered

1. **What is Asia's historical relationship with meat and animal farming?**
   In East Asia, historically diets were largely plant-based and supplemented by animal meat and seafood—with exception of countries such as Mongolia with traditionally high meat consumption. However, China is responsible for the domestication of the modern pig and now is the world's largest producer of pork. With the industrialization of animal production in places such as China, meat consumption—predominantly pork—became more commonplace in East Asia, and consequently Japan and Korea have built a strong tradition of pork consumption.

   The South and Southeast Asian regions have a longstanding history of raising domesticated animals, especially cattle, owing to its ideal weather and terrain and is commonly cited as the origin of the domesticated chicken. Small-scale farms with mixed crops and livestock have been the norm across the region but industrialization is slowly transforming this standard today. Yet, some countries with a lack of pastoral land farm less livestock, and countries with considerable coastline have seafood rich diets.

   In Western and Central Asia, the fertile crescent is considered the origin of the domestication of many modern farm animals. Furthermore, as the region is historically home to many nomadic people, farming animals and consuming meat has been central to life. However, with the modern advent of religion—largely in the form of Islam and Judaism—changes in lifestyle excluded pig as a commonly farmed animal.

2. **What is the forecast for meat consumption in Asia?**
   Asia is touted to lead meat consumption globally in the coming decades, and most of such demand stems from China. This increase in demand will occur for all types of animal meats—especially beef and sheep.

3. **Who are the major players in conventional animal agriculture and cellular agriculture in Asia?**
   China is the largest producer and consumer of sheep meat and pig meat, largest producer of seafood, third largest producer of bovine meat, and fourth largest producer of chicken meat. Japan is home to three of the largest seafood companies in the world, and South Korea is the ninth largest producer of pork in the world. Vietnam is the sixth largest pork producer and Thailand is the fourth largest exporter of poultry.

   Singapore is widely considered a hub for cellular agriculture and the field is backed heavily by the Singaporean government. Furthermore, as of December 2020, it is legal to produce and sell cell-cultured meat in Singapore. Shiok Meats, a cell-cultured meat and seafood company aiming to commercialize in 2024, was founded in Singapore. Israel, another country identified as a hub, is home to a multitude of cellular agriculture companies such as Aleph Farms, MeaTech 3D, Future Meat, and SuperMeat. The field is also supported by private investment and funding and policies by the Israeli government. Turkey is home to one cell-cultured meat startup, biftek.co. China has dedicated public academics to work on cell-cultured meat at Nanjing Agricultural University. Cell-cultured meat companies have been publicly launched in Japan—Integriculture and Nissin—and Hong Kong—Avant Meats.

4. **Who are the main actors that will affect the success of cell-cultured meat in Asia?**
   Israel is home to several organizations advocating for the adoption of cell-cultured meat. A branch of the Good Food Institute (GFI) operates in Israel as well as the Modern Agriculture Foundation (MAF), an independent organization advocating for the alternative protein industry. MAF lobbies the government, promotes the field of alternative proteins across a range of disciplines, and works directly with cultured meat companies to advance the replacement of traditional animal proteins.

   Singapore has a highly proactive government supporting the development of cell-cultured meat. The government strongly supports A*STAR, a Singaporean agency both developing cultured meat technology and supporting the development of the industry.

5. **What differentiates the Asian market from other international markets for cell-cultured meat?**
   Parts of Asia (Central and Western Asia, Malaysia, Indonesia) are home to religious populations whose diet is influenced by their faith, and many adhere to halal or kosher dietary restrictions. Whether cell-cultured meat meets halal and kosher diet requirements is still highly debated, so it is unclear what the demand for cell cultured meat will be like in these areas of Asia.

   Singapore may experience the greatest initial surge in demand for cell-cultured meat—given that this was where cell-cultured meat was first sold and there is strong government support for the field. Furthermore, polls have shown that many Southeast Asian countries have populations willing to try cell-cultured meat.

   The meat industry across Southern and Southeast Asia does not yet have the lobbying power of multinational agricultural companies in regions such as the Americas, and it is possible that the incumbent meat industry may jeopardize the development of cell-cultured meat in these regions.

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Australia

Cultivated Meat Around the World: Economics, Tradition, and Culture in Australia and New Zealand

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Chapter Abstract

Part of the national identity of Australia consists of a deeply ingrained role as a global producer and exporter of meat. As of 2021, Australia has the third fastest growing vegan and vegetarian market on the planet. Australia appears promising as both a market for and a producer of cell-cultured meat due to its high average incomes, food purchasing power, and unique access to Asian markets. However, Australia’s strict biosecurity regulations, restrictive and costly import tariffs for meat products, and stringent agricultural lobby could present challenges to cellular agriculture industries. Will Australia rise from down under to be a global player in cellular agriculture?

Fundamental Questions

1. What is the current state of meat production in Australia?
2. What is the current state of cell-cultured meat industries in Australia?
3. How has meat consumption evolved in Australia?
4. Which factors will pose a challenge to the advancement of cell-cultured meat industries in Australia?
5. What factors suggest a positive outlook for cell-cultured meat industries in Australia?
6. What impacts could cell-cultured meats have on the conventional Australian agriculture industry?

Chapter Outline

18.1 Introduction

18.2 Conventional Meat in Australia
- 18.2.1 History of Animal Agriculture and Meat Production in Australia
- 18.2.2 Current State of Animal Meat Production in Australia
- 18.2.3 Current State of Cell-Cultured Meat in Australia
- 18.2.4 Meat's Role in Australia's Culture

18.3 Economics of the Meat Industry in Australia
- 18.3.1 Australian Meat Consumption Trends
- 18.3.2 Average Household Food Expenditure in Australia
- 18.3.3 Factors Challenging Cell-cultured Meat Industries in Australia
- 18.3.4 Australian Agricultural Subsidies
- 18.3.5 Existing Australian Animal Agriculture Industry
- 18.3.6 Australian Food Regulations and Labeling
- 18.3.7 Australian Biosecurity
- 18.3.8 Transitions for Australian Marginal Farmland after Cell-Cultured Meat

18.4 Factors Contributing to a Positive Outlook for Cellular Agriculture in Australia
- 18.4.1 Australian Global Trade Agreements
- 18.4.2 Geographic Location and Proximity to Asia
- 18.4.3 Australia's Evolving Infrastructure
- 18.4.4 Cell-cultured Meat's Potential Impact in Australia

18.1 Introduction

Meat and seafood consumption have been integral parts of the Australian and New Zealand culture for centuries. With vast coastlines and fertile lands, these countries have a long history of agricultural and fishing practices. However, as global meat consumption increases at an alarming rate, Australia and New Zealand are not immune to the environmental and health risks associated with unsustainable meat production. By 2050, the world's population is predicted to reach 9.7 billion, and with it, the demand for meat and seafood is expected to skyrocket. Cell-cultured meat and seafood production could be the answer to meet these demands while minimizing the impact on the environment and public health. The unique geography, culture, and religious beliefs of Australia and New Zealand have also shaped their relationship with animal products. Indigenous cultures have long relied on hunting and gathering practices, while European settlers introduced farming and husbandry practices. Today, vegetarianism and veganism are on the rise, and attitudes towards animal products are evolving. As the world faces the challenges of sustainable meat production, analyzing Australia and New Zealand's relationship with animal products and their attitudes towards alternative options becomes increasingly crucial.

18.2 Conventional Meat in Australia

18.2.1 History of Animal Agriculture and Meat Production in Australia

Australia has a rich agricultural history spanning thousands of years, with evidence of Indigenous Australian societies independently developing aquaculture systems and harvesting early forms of cereal.[10] Since European invasions of Australia in 1788, animal agriculture has become a major economic pillar for Australia, creating a national identity that is deeply rooted in animal agriculture.[2] For the first century of Australia's existence as a European colony, the wool industry granted Australia one of the highest living standards in the world. For this reason, Australia has been described as "built on the sheep's back."

Since these early days, the Australian livestock sector has become increasingly influential, with tens of thousands of farms across the country, primarily family-owned, rearing animals for meat production. Australia's red meat production mostly consists of farms implementing grass-fed systems with limited use of intensive feedlot production across the nation.

Today, livestock production remains Australia's largest single agricultural sub-sector, accounting for 1.4% of Australia's key industry GDP in 2018-19.[3] Australian red meat is predominantly exported, with approximately 70% of total red meat production destined for international markets. The largest importers for Australian meat are China, Japan, and the USA.[3]

Due to its heavy reliance on exportation, Australia's agricultural sector fiercely defends its perception as "clean and green", with strict biosecurity measures implemented by the Australian Border Force making the importation of animals and plants difficult, slow, and costly. This makes Australia somewhat isolated from global agricultural biotechnology innovations including new seed or plant breeds. Overall, Australia's heavy reliance on conventional meat production and exportation as well as an entrenched cultural reverence for animal industries could pose some challenges for the adoption of alternative protein products.

18.2.2 Current State of Animal Meat Production in Australia

Australia is a major meat exporter for the world, primarily of red meat, which includes beef, veal, lamb, and goat. These products are exported through two channels: Live export and value-added meat production. Live export is when live animals are exported by sea or air.[4] Value-added meat production is when animals are grown, slaughtered, and processed in Australia and shipped as processed meat. The live export part of meat production is rife with significant ethical concerns. The mortality rate for exported animals from Australia between 2006 to 2017 exceeded 2% for sheep and goats, 0.5% for cattle, and 1% for buffalo.

Australia's red meat sector consists mostly of free-range, grass-fed animals. Strict regulations exist for the use of both growth hormones and antibiotics in Australian agricultural systems. In Australia, conventional meat production is often separated between animal husbandry and meat processing, though vertically integrated companies are gaining strength, especially in poultry.[13, 14]

Table 1. Australia's Largest Meat Producers as of 2021

Meat Producer (Company Name)	Additional Company Information	Meat Product Type	Annual Turnover
Baiada Poultry	Headquarters: Pendle Hill, New South Wales	Poultry	No turnover numbers available
Huon Aquaculture Group Limited[12]	Headquarters: Dover, Tasmania Acquired by JBS in November 2021[15]	Salmon and ocean trout	Over $263M USD annual turnover in 2020
Inghams Enterprises	Headquarters: North Ryde, New South Wales Responsible for ~40% of Australian commercial poultry meat production[16]	Poultry	Poultry is highly consolidated and vertically integrated. These two companies sold approximately 432 million chickens in 2017-18.
JBS Australia	Headquarters: Brooklyn, Victoria Subsidiary of Brazilian-headquartered JBS	Red meat (beef, lamb)	No Australian-specific turnover numbers available
Tassal Group Limited[11]	Headquarters: Hobart, Tasmania	Salmon and prawns	Over $427M USD annual turnover in 2020
Teys Australia	Headquarters: Eight Mile Plains, Queensland A 50/50 partnership with US meat processor Cargill	Red meat (beef, lamb)	Approximately $2B USD annual turnover in 2018

18.2.3 Current State of Cell-Cultured Meat in Australia

Australia's cell-cultured meat industry is made up of five companies (two are B2C startups and three are B2B startups) and two NGOs operating publicly in the space as of March 2021. The Australian cell-cultured meat startups include Vow, Magic Valley, Heuros, Cass Materials, and Nourish Ingredients. Vow is a Sydney-based, vertically integrated startup focusing on food products drawn from a range of exotic and farmed species including kangaroo, alpaca, goat, pork, rabbit, and lamb. Magic Valley is a Melbourne-based startup focused on producing sheep meat using pluripotent stem cells. Heuros is a Brisbane-based company supplying high efficacy cell media and growth factors to the cellular agriculture industry. Cass Materials is a Perth-based startup producing plant-based scaffolds made from nata de coco. Nourish Ingredients is a Canberra-based startup producing animal fats and oils using yeast fermentation.

The Australian NGOs operating in the cell-cultured meat space include Cellular Agriculture Australia and Food Frontier. Cellular Agriculture Australia is a national charity dedicated to building the cellular agriculture research sector by developing talent pipelines into cellular agriculture, connecting research stakeholders, and promoting positive public awareness of cellular agriculture. Cellular Agriculture Australia is a member of the International Cellular Agriculture Nonprofit Consortium, a decentralised forum for nonprofits dedicated to promoting cellular agriculture to coordinate strategies, share resources, and find solutions to universal problems in the international cellular agriculture community. Food Frontier is a Melbourne-based philanthropically backed NGO focused on supporting alternative protein in Australia and New Zealand through advocacy, lobbying, and thought leadership. Food Frontier is active across both plant-based and cell-cultured industries.

18.2.4 Meat's Role in Australia's Culture

Australia has developed a culture around outdoor activities suited for its unique landscape and climate, with a culture of meat consumption to match this. One ubiquitous example of this is the outdoor barbecue, or "barbie," a favored option within Australian cuisine. The typical Australian "barbie" has traditionally consisted of lamb chops and beef steaks for adults and sausages, or "snags," as they are colloquially known, which are enjoyed by adults and children alike.

Barbecues are commonly held as fundraisers for schools, local communities, and other charity events, a communal activity known widely as a "sausage sizzle." Notable examples of this are the weekly serving of sausages outside the largest retail hardware franchise “Bunnings Warehouse” and the “Democracy Sausage” served to Australian citizens as they enroll to vote in local, state, and national elections.

Meat consumption overall in Australia has been stable since the 1960s[17], at around 110 kilograms per person per year[18]. Beef, mutton and lamb were once the most commonly consumed meats in Australia. Now, chicken is by far the most widely consumed meat, followed by pork[17].

On the other hand, the nation is experiencing increased interest in vegetarianism, veganism, and general meat reduction in diets, as it is the third fastest growing vegan and vegetarian market on the planet.[5] Fast food chains, supermarkets, and restaurants alike are increasing both the variety and visibility of their plant-based and meat-alternative products. The main motivation for this has been increasing public concern for animal welfare, personal health, and environmental protection. It is yet to be determined how much impact conscious consumption trends will have on overall meat consumption in Australia.

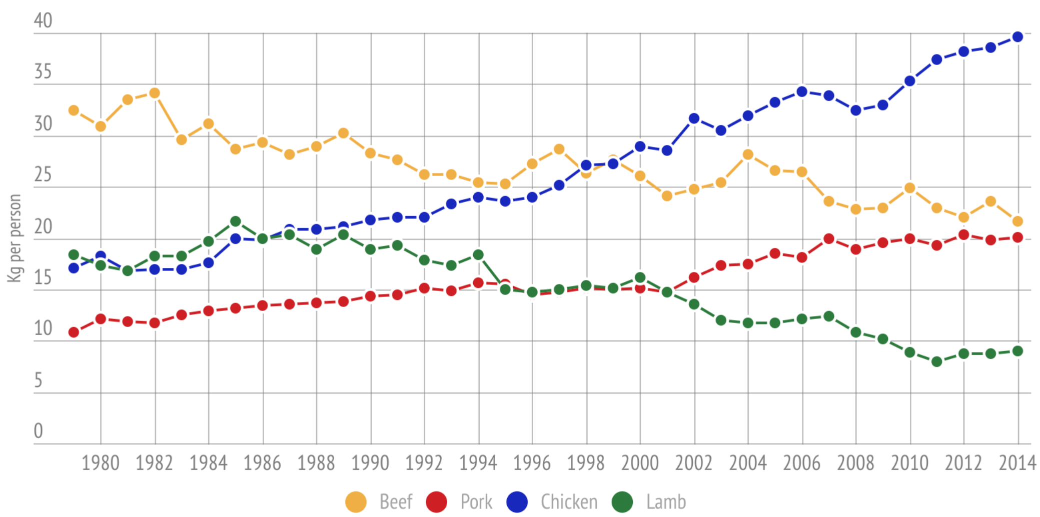
Meat and Livestock Australia (MLA), a private regulator of meat standards in Australia, funds the “We Love Our Lamb” campaign, an annual national-wide marketing campaign scheduled every Australia Day on January 26 (also known as Invasion Day) to drive the consumer demand and sales for Australian lamb. The campaign is a continuation strategy–a method of scheduling advertising at regular intervals–that established itself in 1999 to reinvent and reposition lamb as a modern meat for the Australia market. The campaign has proven to be the most successful campaign of its type, returning $3.99 of value for each $1 of advertisement investment.[6]

18.3 Economics of the Meat Industry in Australia

18.3.1 Australian Meat Consumption Trends

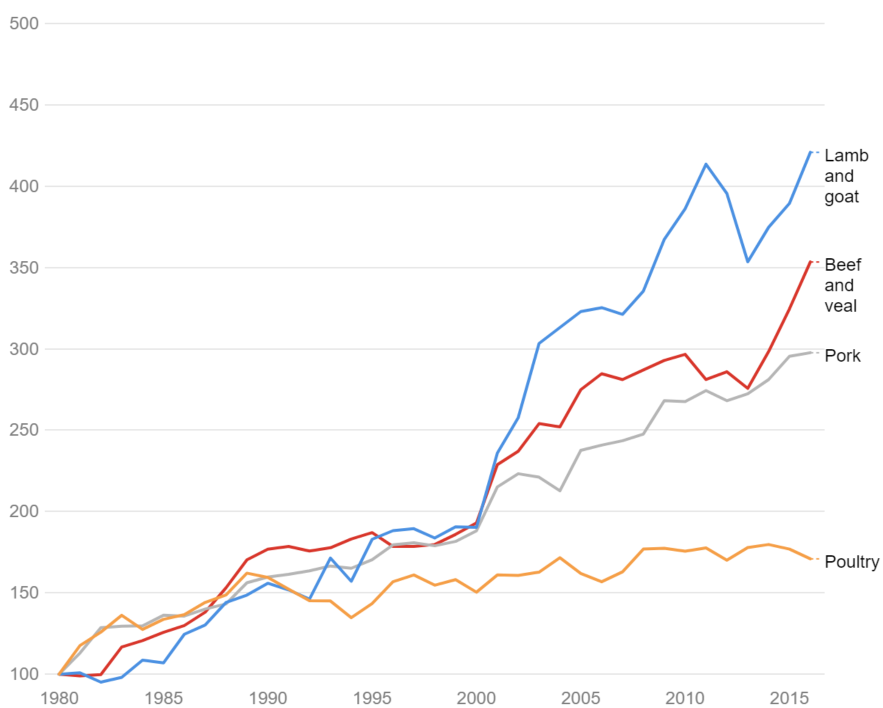
Australians are the third largest consumer of meat in the world (per capita).[1] Consumption of chicken and pork have increased, while red meat consumption has decreased over the past few years as Australians increasingly aim to adopt ethically and environmentally-conscious dietary habits (Marinova, D., Bogueva, D). This change is likely to be driven by two factors: 1) declining price of poultry and pork relative to other types of meat in Australia and 2) public health messaging from the 1960s onwards around the harms of red meat consumption.[7, 18]

Despite decreasing domestic red meat consumption, global red meat consumption has not decreased. As such, over 70% of Australian red meat is exported and the rates of demand for Australian meat in the United States, China, and Japan will be the deciding factors for the level of Australia's meat production moving forward.[8]



Beef and lamb were Australia's preferred meats in the early 1980s, but chicken is now the clear favourite.
Source: OECD-FAO 2015

Figure 1. Meat Consumption Trends in Australia from 1980-2014 in kg/per person[19]



Note: this is an index, not a depiction of actual prices. It shows how meat prices have changed over time relative to what they cost in the third quarter of 1980.

Source: [ABS CPI TABLE 9. CPI: Group, Sub-group and Expenditure Class, Index Numbers by Capital City Get the data]

Figure 2. Meat prices in Australia, indexed to Q3 1980 (1980 = 100).[1]

18.3.2 Average Australian Household Food Expenditure

On average, Australian households spend around AUD $235 (approximately US $170) on food and non-alcoholic beverages per week, comprising 17% of total weekly spending. Approximately $95 is spent weekly on takeaway and restaurant meals, and $140 per week is spent through the grocery and food retail channels. Between 55% and 60% of this expenditure passes through the Australian supermarket chain duopoly, Coles and Woolworths.

By comparison, in the United States, the average household spends approximately US $89 on food purchases at home per week.[9] As such, Australia's relatively high household food expenditure presents an opportunity for high-end cell-cultured meat products to take a position in the Australian market. At the same time, a lower-cost commercial product sold through this supermarket duopoly and/or through international establishments such as Aldi and Costco, could ensure more widespread adoption across a larger range of consumer budgets.

18.3.3 Factors Challenging Cell-cultured Meat Industries in Australia

Australia's large animal agriculture industry, reputation for strong food regulation, globally recognized biosecurity status, strong export focus, and research and development systems indicate that the nation is likely to be resistant to cell-cultured and plant-based meat alternatives.

18.3.4 Australian Agricultural Subsidies

Australian agriculture lacks the direct subsidies like those offered in the United States. Instead, the Australian Federal Government provides subsidies through research and development administered by the Rural Research and Development Corporations (Rural RDCs). These RDCs collect levies on every unit produced by Australian farmers. Overall, Australia invests over AUD $800 million annually in agricultural research and development through this system. This robust and well-funded agricultural research and development system is likely to allow Australian farmers to transition away from livestock towards alternative arid or semi-arid crops.

18.3.5 Existing Australian Animal Agriculture Industry

As previously mentioned in Section 18.2.1, *History of Animal Agriculture and Meat Production in Australia,* the Australian animal agriculture industry is a significant player in the Australian economy. For example, red meat and livestock production remains

Australia’s largest single agricultural sub-sector, accounting for 1.4% of Australia’s key industry GDP in 2018-19.[3] As such, the existing animal agriculture industry could potentially pose a challenge to the development of cell-cultured meat production, due to incentives for the industry to maintain the current system of animal agriculture.

18.3.6 Australian Food Regulations and Labeling

The Australian and New Zealand food safety regulator, Food Standards ANZ (FSANZ) has officially stated that cell-cultured meat will be labelled as a ‘novel food’ for the purposes of food safety regulation in Australia[20]. Conventionally, novel foods are regulated by FSANZ through a standardized novel foods process. Unless a food ingredient is listed as an approved ingredient by FSANZ, it cannot be sold as a food.

Typically, a company, NGO, or other industry body would approach the Advisory Committee on Novel Foods to compose a pre-market safety assessment, which would then be undertaken by the company as part of a formal submission to FSANZ. The process can take years and cost several hundreds of thousands of AUD per ingredient approval, posing significant barriers for cell-cultured meat companies looking to commercialize their product in the Australian market. Since 2019, the Australia and New Zealand Ministerial Forum on Food Regulation has endorsed an ambitious plan to reform the Bi-national Food Regulation System to ensure it is fit for purpose for the future. As part of that process, the effectiveness and operations of the Food Standards ANZ will be reviewed and reformed where necessary. As such, potential alternative regulatory frameworks may be preferable for cell-cultured meat companies in the upcoming years.

18.3.7 Australian Biosecurity

The Australian Border Force, the Department of Agriculture, Water and the Environment and the Department of Health are responsible for implementing and enforcing strict border security measures aimed to prevent the introduction and/or spread of harmful organisms to domestic animals and plants. Biosecurity plays a critical role in Australian agricultural competitiveness on a global scale. While strict biosecurity ensures a distinct absence of key diseases affecting comparable agricultural economies including bovine spongiform encephalopathy (Mad Cow Disease), foot-and-mouth disease, and rabies, it has also led to wariness towards meat imports worldwide. This has directly resulted in restrictive import policies for meat products and live animal imports, as well as thorough record maintenance on Australian products. As such, for the cell-cultured meats industry, importing of cell lines, products, and derivatives into Australia is likely to face considerable hurdles relative to exporting such products from Australia. Whilst the biosecurity import restrictions could in some ways be beneficial to the development of a domestic cell-cultured meat industry, the challenges in importing the relevant components for production of cell-cultured meat is also likely be a barrier for the domestic industry.

18.3.8 Transitions for Australian Marginal Farmland after Cell-Cultured Meat

Australia is the driest inhabited continent, with 70% of the landmass being arid or semi-arid. Australia has a significantly lower proportion of arable land in contrast to similar agriculture-driven economies. Unlike American cattle systems, Australian cattle and sheep are predominantly grass-fed, consuming native or planted pasture. In some cases, animals are grain finished, spending a few weeks consuming a grain diet prior to slaughter. The pastureland for Australian livestock is often in arid or semi-arid regions where conventional crop practices cannot presently occur. If cellular agriculture ultimately replaced conventional livestock farming, there is no crop for human consumption that is immediately suitable to be planted on this land to replace the currently planted grass feed[22]. Another option for transitioning Australian farmland in a post animal agriculture society would be to return it to the traditional custodians, the Aboriginal Australian peoples.

18.4 Factors Contributing to a Positive Outlook for Cellular Agriculture in Australia

18.4.1 Australian Global Trade Agreements

Australian trade agreements fiercely defend the reputation of Australia’s food export quality and these agreements function as a key factor for remaining in demand throughout high-value Asian markets. The Korea-Australia Free Trade Agreement (KAFTA) and the Japan-Australia Economic Partnership Agreement (JAEPA) have strengthened the food-trade relationship with two of Australia's most important food export markets. China is Australia’s largest trading partner, and with the bilateral China-Australia Free Trade Agreement (ChAFTA) enacted in 2015, Australia has established a powerful trifecta of Northern Asia free trade agreements.

18.4.2 Geographic Location and Proximity to Asia

The continent of Asia accounts for 60% of the global population, making it a massive market for cell-cultured meat products[21]. Australia’s close proximity to Asia gives it a unique opportunity to tap into this market. Australia already has very well-established trade agreements and trade policies in Asian countries built on strong agricultural exports, with 76% of Australia's agricultural exports going to Asian markets[22]. The high-quality standards attributed to Australian meat resonate with consumers in Asian markets. Currently, 60% of beef produced in Australia is designated for export, with Japan, the United States and the Republic of Korea being the top three export markets for Australian beef[14].

18.4.3 Australia's Evolving Infrastructure

The Western Sydney Aerotropolis is an infrastructure project centered around a new 24/7 curfew-free airport scheduled to open in 2026 after attracting over AUD $20 billion in public funding. A major focus of its development is to streamline the processes for high-value food and agribusiness exports, presenting a rich opportunity for Australian cell-cultured meat companies to take advantage of the resulting economic growth and increasingly strong export channels.

The Monash Technology Precinct is a research facility that will be developed at Monash University in Melbourne, Australia[23]. The Precinct will be a sustainability-focused center for advanced manufacturing in next-generation pharmaceuticals, biotech and medical therapeutics, data sciences, AI, and materials engineering. This facility will serve as a commercial hub for the research and development of new technologies in Australia such as cell-cultured meat. The Precinct has already established key partnerships with companies such as AstraZeneca and Johnson & Johnson, and have created spinouts such as Monash IVF and the Monash University Low FODMAP Diet™ app as of 2022.

18.4.4 Cell-cultured Meat's Potential Impact in Australia

The animal livestock industry is a significant part of the current Australian economy. In the 2019-2020 financial year, the gross value of livestock produced nationally was approximately $32 billion AUD[24].

Key results for 2019-2020 include:

- $14.6 billion for cattle and calves (up 14% from 2018-19)
- $4.8 billion for sheep and lambs (up 16%)
- $2.8 billion for poultry (up 2%)
- $1.5 billion for pigs (up 24%)
- $8.5 billion for livestock products such as wool, milk and eggs (down 12%)[24]

Livestock production remains Australia's largest single agricultural sub-sector, accounting for 1.4% of Australia's key industry GDP in 2018-19.[3]

Since the animal livestock industry plays such an economically significant role in Australia, the rise of cell-cultured meat (and the subsequent decline of the livestock industry) will have major economic consequences. In particular, the livelihoods of those who depend on the livestock industry, including farmers, exporters, and ancillary service providers, will be at risk if there is declining demand for livestock production. This impact will disproportionately affect rural communities, as the majority of those involved in livestock production are based on rural Australia and the loss of their livelihoods could have significant flow-on effects on the rest of the community.

As such, although the benefits of cell-cultured meat are obvious, the transition from industrial animal agriculture to cellular agriculture will have significant economic effects on Australia which will need to be mitigated. Those working in the animal agriculture industry will need to be supported in transitioning into new careers. They could potentially transition into other forms of agriculture or be re-trained to work in other industries. Rural communities most involved in the animal agriculture industry will also need significant support so that their economies are able to adjust to the changes.

Fundamental Questions – Answered

1. **What is the current state of meat production in Australia?**
   Australia is primarily a producer of red meat, which is predominantly derived from free-range, grass-fed animals. Australia's poultry production is primarily vertically integrated and split across a duopoly of companies. The majority of Australian red meat production is destined for export, through both live animal export and value-added processed meat production. Australia is the world's second largest exporter of beef behind Brazil, with the largest markets for import being Korea, Japan, and the US. Australia maintains strong regulatory frameworks and biosecurity laws around their meat production to maintain their high-quality meat standard and prevent food-borne illness.

2. **What is the current state of cell-cultured meat industries in Australia?**
   As of March 2021, there are currently seven for-profit companies and two non-profit organizations operating in the cell-cultured meat industry in Australia. Two for-profit companies, Vow and Magic Valley, are business-to-consumer (B2C) startups dedicated to developing cell-cultured meat products. Three for-profit companies are business-to-business (B2B) startups, Heuros, Cass Materials, and Nourish Ingredients, dedicated to producing serum-free growth media, plant-based scaffolds, and fats.

   Both non-profits are working together to ensure the commercial success of the cell-cultured meat industry. Cellular Agriculture Australia is building the cellular agriculture research sector by developing talent pipelines, connecting research stakeholders, and promoting positive public awareness of cellular agriculture. Food Frontier is providing support to the plant-based and cell-cultured industries through advocacy, lobbying, and thought leadership.

3. **How have meat consumption trends evolved in Australia?**
   Australians are the third largest consumer of meat in the world (per capita), though the breakdown of this has changed substantially.[1] Consumption of chicken and pork have increased, while red meat consumption has decreased since 1998, as as Australians increasingly aim to adopt ethically and environmentally-conscious dietary habits (Marinova, D., Bogueva, D. 2019).

4. **Which factors will pose a challenge to the advancement of cell-cultured meat industries in Australia?**
   Australia's reputation for strong food regulation through globally recognized biosecurity measures and a strong relationship with its farming heritage could pose challenges to the advancement of cell-cultured meat in Australia.

5. **What factors suggest a positive outlook for cell-cultured meat industries in Australia?**
   Australia's strength in international trade and existing trade agreements, its proximity to Asian markets, and its focus on infrastructure that supports high-quality export products make Australia a prime region for the evolution of cell-cultured meat products.
   Australia is also ranked fifth globally for biotechnology innovation, with internationally renowned expertise in plant biology, food science, stem cell and biomaterials research.

6. **What impacts could cell-cultured meats have on Australian agriculture?**
   Thought will need to be given to the use of land that is no longer required for the grazing of livestock. Similarly, there will need to be active engagement over time with traditional farming to ensure any displacement of animal-agriculture jobs are reinvented for the evolving industry.

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