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Cellular Agriculture: An Outlook on Smart and Resilient Food Agriculture Manufacturing

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Abstract:

Over the centuries, the application of grassland and cutting of livestock are the primary foundations for the production of food agriculture manufacturing. Growing human population, accelerated human activities globally, staggering food inequity, changing climate, precise nutrition for extended life expectancy, and more demand for protein food call for a new outlook to smartness in food agriculture manufacturing for delivering nutritious food. Cellular agriculture, 3D printing of food, vertical urban farming, and digital agriculture alongside traditional means are envisioned to transform food agriculture and manufacturing systems for acceptability, availability, accessibility, affordability, and resiliency for meeting demands of food in this century for communities across the US and the world. This technical note illustrates the thought leadership for cellular agriculture as a part of the new food agriculture manufacturing revolution.

1. Drivers for food agriculture manufacturing revolution

It is estimated that the world population will reach 9.5 billion by 2050 [1]. The food supply for this growing population will be constrained due to limited resources, land, water, and the impacts of climate change. The issue is how to sustainably feed a growing population with minimal impact on the environment and resource consumption while ensuring dietary wellbeing. Approaches such as digital agriculture (use of Industry 4.0 principles in farming), vertical urban farming (for local and resource-constrained fresh produce) alongside alternative protein manufacturing are being explored to increase food production and meet consumer demands. For the majority of this world population, animal protein is a critical food nutrient source for a balanced diet and it is predicted that the global demand for this protein will double by 2050 [2–4]. In the US, it was reported that about 78% of consumers rely on meat as a source of protein [5]. USDA projects both meat production and demand to steadily increase over the coming years [6]. Over the years, cutting animals for meat has evolved from hunter-gatherers -to local butchers -to large-scale industrial slaughterhouses. Even though the efficiency and outputs of meat production have increased, the modus operandi has stayed the same - cutting animals raised through farms, ranches, and others. Over the last few decades, it has been recognized that this top-down manufacturing approach of cutting animals is resource-intensive in terms of land, water,

energy, and time. Additionally, the macro supply chains of meat processing, packaging, and transportation remain vulnerable to disruptions, a fact recently evidenced during the COVID-19 pandemic, worsening food insecurity and challenging the resilience of communities [7]. The above factors, in addition to, distribution inequity, growing concerns over the spread of zoonotic diseases [8], and reducing animal cruelty call for new disruptive thinking for the development of complementary sustainable and humane food production approaches (schematically represented in Figure 1) [9–11] as a part of the upcoming food agriculture manufacturing revolution delivered by the convergence of many disciplines.

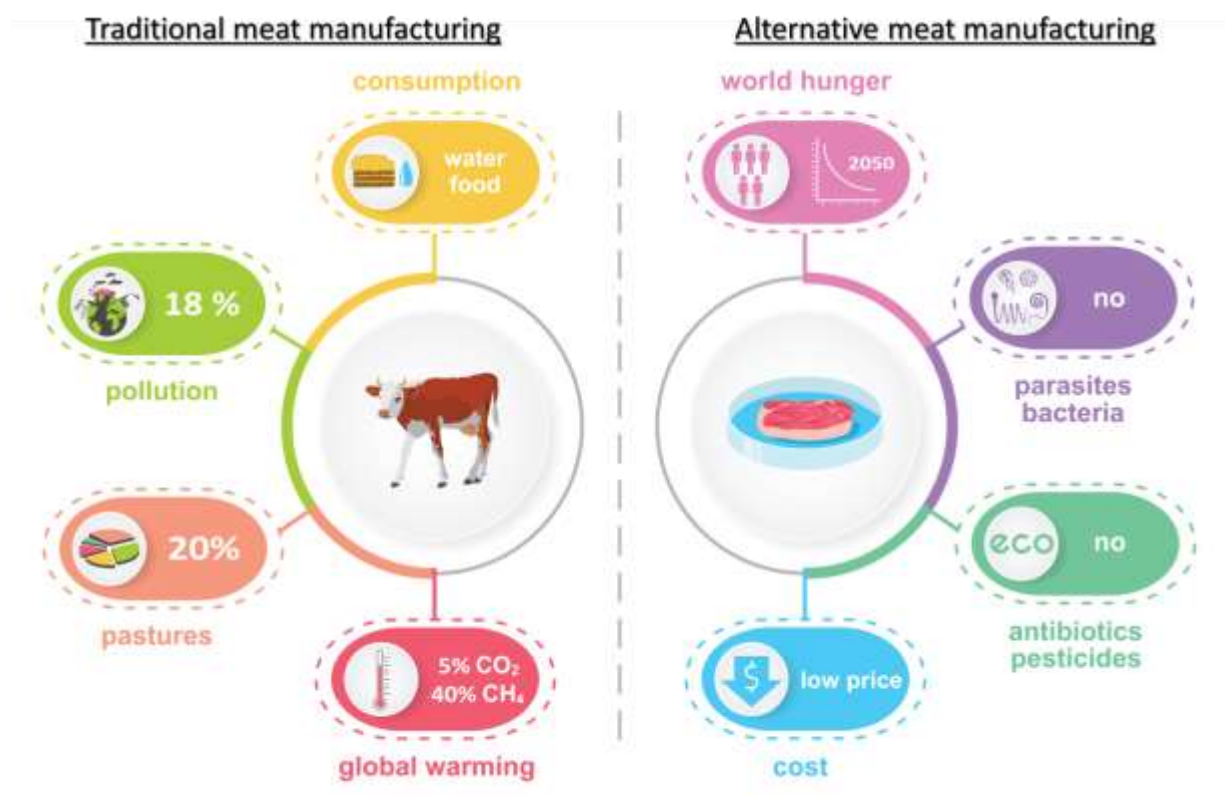


Figure 1: Potential benefits of alternative cell-based protein meat manufacturing

Complementary to today's livestock and poultry farming, two protein-rich food production approaches [12] to address these issues are plant-based meat and cell-based meat (*also called cultivated meat or in-vitro meat*). Plant-based meat alternatives have attracted significant attention over the last few years through the introduction of meat substitutes by Beyond Meat®, Impossible® Foods, and others into the market. However, it is noted that these plant-based protein sources, when compared to beef, have lower levels of some essential amino acids like lysine and methionine, vitamin B12, minerals, and some secondary nutrients [13]. Additionally, these products primarily [14] appeal to a limited population with vegetarian and vegan (a minority of the population) dietary interest. Their nutritional benefits as highly processed foods are still being debated and their advantage over eating established plant-based foods (vegetarianism as observed in older cultures like in India and other parts of the world) remains questionable. On the other hand, manufacturing of cell-based meat (CBM), which has an identical physicochemical composition to conventional meat products has the potential to have a significant impact on American (2018 Gallup poll, only 5% of U.S. adults consider themselves to be vegetarian [15])

and global nutrition, meat production, and distribution systems as a part of future food agriculture manufacturing. Since this field is still in infancy, this is an opportune time to map and incorporate CBM manufacturing into flexible, customizable supply chains [16], as a part of sustainable and smart manufacturing. This paper presents open challenges and opportunities for cellular agriculture as a part of sustainable food agriculture manufacturing.

2. Cellular Agriculture (Cell-Ag, CA): State-of-the-art, opportunities, and challenges

2.1 Overview of cellular agriculture process steps

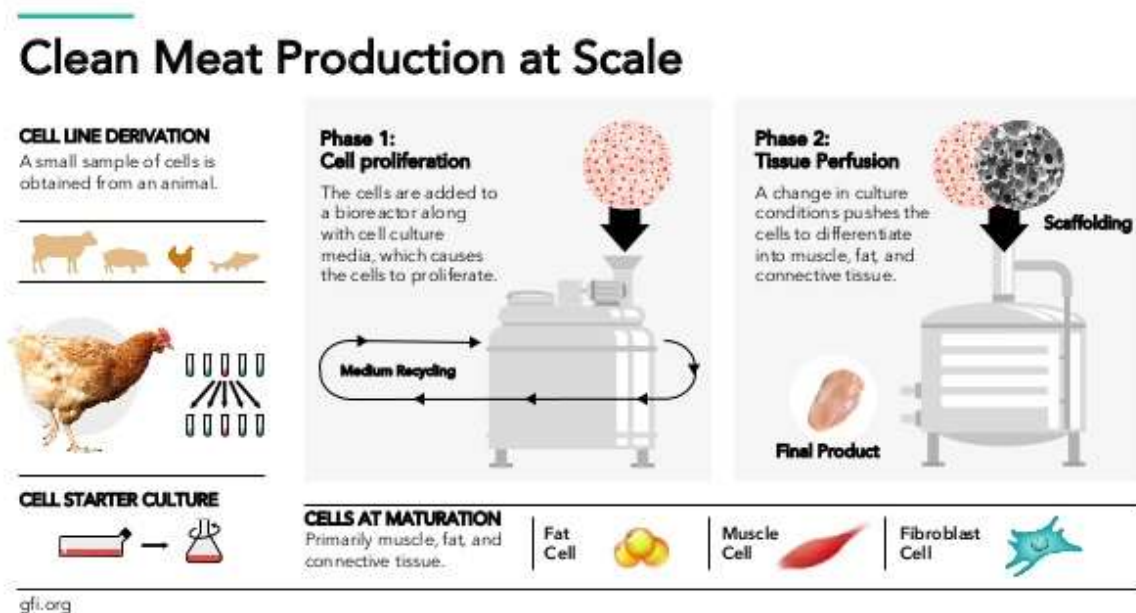


Figure 2: Process schematic for manufacturing cell-based meat [19]

Since the unveiling of the \$325,000 in-vitro burger by Dr. Mark Post in 2013 [17], the cellular agriculture industry has progressed in reducing the costs to a certain extent associated with cell-based meat (CBM) with cultured chicken nuggets now being served in Singapore [18]. This section will introduce cellular agriculture to the readers and give an overview of the current challenges and research innovation opportunities in CBM production.

For this manuscript, cellular agriculture is defined as the manufacturing of animal- or bio-inspired protein food derived from cell-cultures producing cell-based foods. Typically, CBM production involves extraction and isolation of stem cells from the animal, subsequent cell growth, proliferation, and differentiation in increasing sizes of bioreactors containing cell culture medium followed by meat harvesting as summarized in Figure 2 [19]. The individual processing steps shown in Figure 2 each have their own unique scientific and technological barriers for large-scale production and are discussed in the next subsection.

2.2 At-scale manufacturing challenges for cellular agriculture

Current steps as outlined above and state-of-the-art approaches in the industry are derived from tissue engineering and biomedical manufacturing methods. But for CBM, tissue production needs to be

inexpensive and manufactured at a much larger scale compared to the aforementioned approaches for its affordability as a consumer food product. For comparison, the cost of organs cultured with biomedical tissue engineering methods justifies the expensive cell lines and culture media but for CBM production, the cost needs to be comparable to conventional meat [20], and therefore, needs to be orders of magnitude lower. On the other hand, even large-scale tissue culturing methods for therapeutic purposes result in the final culture comprising of $\sim 10^6$ - 10^9 cells [21] contained in ~ 5 L bioreactor [22] for clinical scale but for CBM, the final culture needs to comprise of $\sim 10^{15}$ cells (with $\sim 10^{12}$ cells/kg) housed in a ~ 10000 -liter bioreactor [23]. In addition to that, the resulting CBM should be similar or superior to conventional meat in sensorial and nutritional aspects [24]. Therefore, the manufacturing of CBM needs to overcome numerous serious scientific and manufacturing challenges. These challenges can be broadly classified [25] into four categories (see Figure 3): (a) cell lines, (b) cell culturing, (c) bioreactor design, and (d) scaffold design.

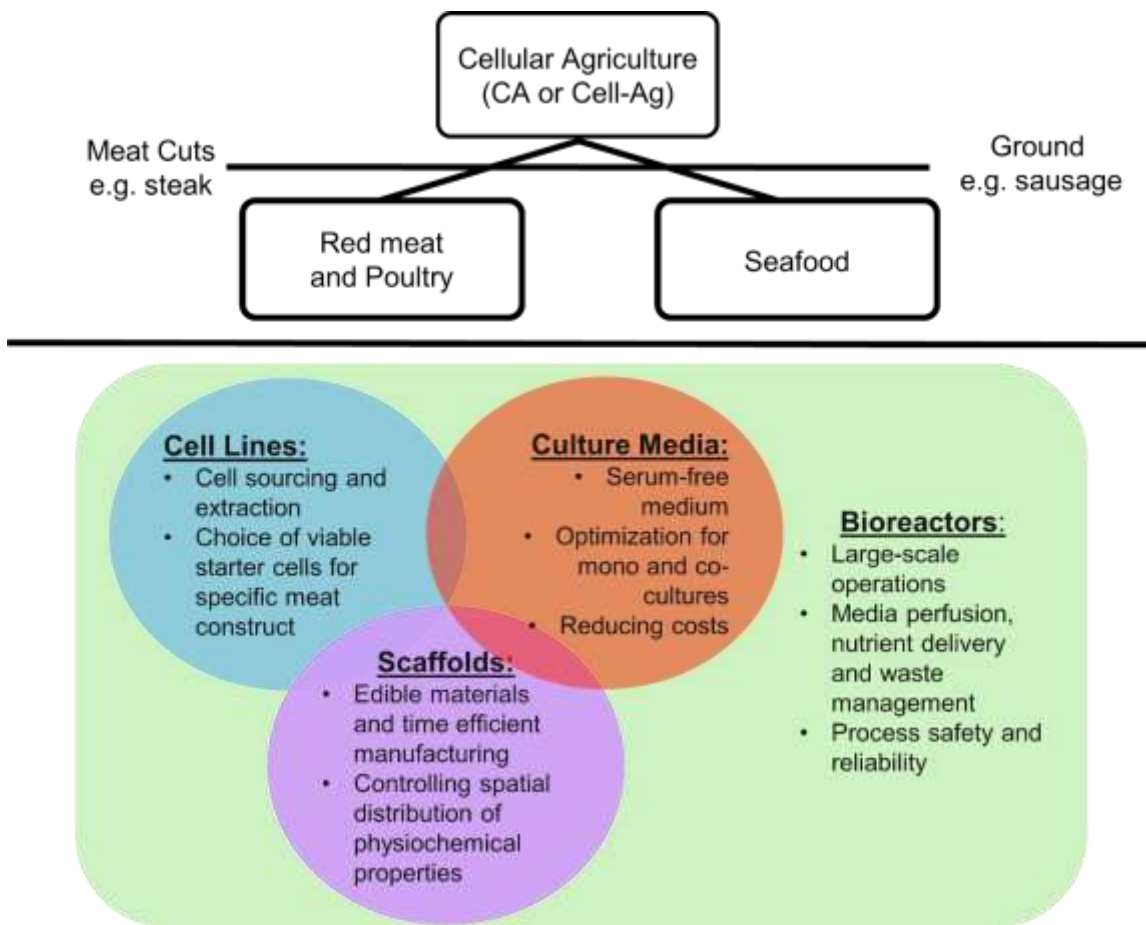


Figure 3: Challenges and opportunities for cellular agriculture meat manufacturing

- a. **Cell line:** The selection of appropriate cell lines from an appropriate species of interest is important for being able to manufacture the high number of cells in the final culture as well as controlling their differentiation into fat, muscle, and connective tissue at desired locations. On the later issue, choice of starter cell(s) will dictate the downstream optimization of cell-culture media, nutrient delivery, scaffold design, and bioreactor design to achieve location-specific expression of desired tissues.

- b. Culture Media: The growth and differentiation are also controlled by cell culture media used at various stages of manufacturing. The medium needs to be optimized with required nutrients and growth factors at each stage for the cell line used and its cost needs to be lowered with manufacturing processes for its components being suitably modified following economies of scale [26]. For this, and for reproducibility, the culture media also needs to be serum-free i.e., it should not contain Fetal Bovine Serum, Horse Serum, or any other living animal-derived component [27].
- c. Bioreactors: For bioreactors, two key challenges for research and innovation are addressing nutrient transport and mixing limitations and sterilization. Addressing the first challenge involves the design of bioreactors such that no significant gradients in nutrient and oxygen concentrations exist throughout the volume at each stage and this homogeneity needs to be achieved without increasing the shear rates for agitation which may cause cell death. For the second challenge, in addition to accommodating the sterilization constraints similar to industrial fermenters for bioreactors and supporting equipment design, it will be important to limit/eliminate the use of antibiotics (as is common in tissue culturing) in the culturing media.
- d. Scaffolds: Animal stem cells need to adhere to a surface for growth, division, and differentiation. For comminuted and non-structured CBMs, this function can be served by microcarrier bead suspensions. But for making cell-based food of whole meat cuts like T-bone, sirloin, or ribeye, the differentiation needs to be more targeted to mimic the physicochemical and sensorial properties of these cuts which can be enabled only through scaffolds. Despite recent developments in manufacturing processes of edible scaffolds involving food-safe materials like alginate and pectin and processes like electrospinning [27], large-scale manufacturing of edible and hierarchical scaffold structures, that allow cells to adhere and proliferate and ensure nutrients are accessible to the cell culture at all stages of maturation, is an open challenge that demands extensive research and a combination of bio-inspired, additive and hybrid manufacturing approaches.

Additionally, cellular agriculture processes and related hardware and software are expected to face other challenges including but not limited to high biological variability in raw materials, low-profit margins, compliance to current good manufacturing practice (cGMP) regulations and consumers, and producer's acceptance and concerns. Optimization in supply chain and distribution will be required to make CBM commercially acceptable, available, accessible, and affordable along with profitable in the current form of capitalism [28].

In conclusion, although the cellular agriculture industry has come a long way while lowering the cost of the quarter-million-dollar beef burger patty to making CBM a super-luxury dining menu option it is far from a solution to food inequity. Scaling of cellular agriculture processes for feasible CBM manufacturing of unstructured and more importantly structured meat is rife with opportunities from design, materials, and manufacturing perspectives and requires convergent and sustainable techno-socio-economic interventions to thrive alongside conventional meat manufacturing systems. Along these lines, a closer examination of the sustainability outlook is important and presented below.

3. Cellular agriculture: A perspective on sustainability

The life cycle stages of traditional meat production consume materials, chemicals, and energy resources, and produce a variety of waste streams. Figure 4 shows the life cycle stages of traditional meat and CBM production. For example, animal feed is an important input to animal agriculture that is the major cost for cultivating animals. Animal agriculture accounts for an estimated 15% of global greenhouse gas (GHG) emissions [29–31]. In addition to animal feeding, animal agriculture consumes a large amount of energy and water throughout the entire livestock production and meat processing chain. These energy and water investments are inculcated within the animals during their growth stage and required for other life cycle stages. Biswas and Naude [32] reported that beef has embodied energy of 29.6 MJ/kg, whereas chicken and soy protein have embodied energies of 22.2 MJ/kg and 9.17 MJ/kg. These values vary by geographical location (e.g., where the farm is located) and the conditions under which the animals are raised. Major energy demands for meat products are the pre-farm inputs, e.g., the energy needed for feed, pumping water, equipment, and chemicals. The cultivation of cows, pigs, and chickens consumes water directly and indirectly and could be assessed through embodied water associated with beef, pork, and chicken products [33]. According to Chen et al. [34], the entire meat production chain accounts for 20% of total global water consumption. These data illustrate that animal agriculture consumes significant energy, water, and land resources.

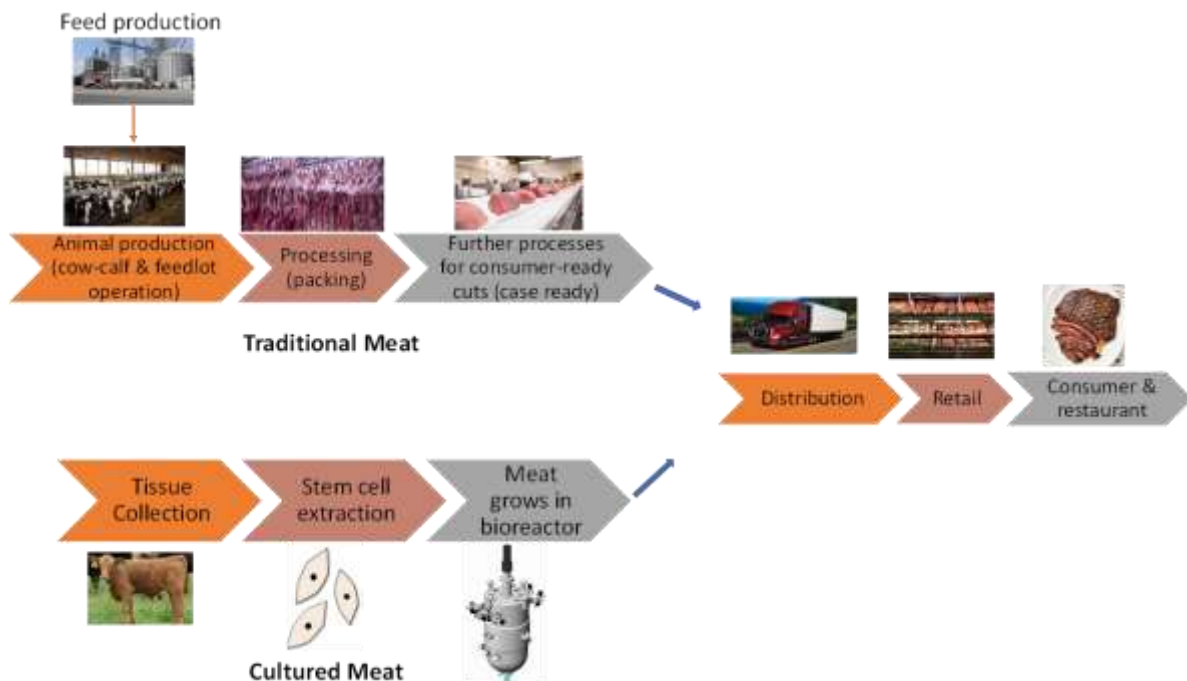


Figure 4: Life cycle stages of traditional and CBM production

Livestock influences the environment through feed production, animal husbandry, changes in land use, manure, transportation, etc. For example, pig farming creates numerous impacts on the environment where wastes and feces spread to surrounding areas and pollute water and air with toxic wastes. Chicken farming operations also have substantial negative environmental impacts, such as odors and emission of ammonia, hydrogen sulfide, and poultry dust. These waste streams also impact workers and neighbors in terms of breathing polluted air, ingesting polluted water, and polluting soil where crops may be grown. To illustrate the environmental impacts of livestock cultivation and processing, consider

the beef life cycle. Figure 5 shows the contribution of different life cycle stages of traditional beef production on common environmental indicators. It is seen that cattle feeding contributes about 90% of the total consumptive water usage, energy consumption, land use, ozone depletion potential, and human toxicity potential. Feed production requires pesticides and other chemicals and uses equipment that consumes fossil fuels to prepare fields and harvest crops [35]. These activities consume resources and produce wastes that increase the environmental burden. A cow-calf operation (i.e., the raising of calves from a permanent herd of cattle until they are sold to a processor) involves weaning calves grazing on a pasture that is irrigated with a foraging diet until they are 16 months of age (mass of about 581 kg) for harvest [35]. A cow-calf operation contributes to the highest acidification potential, global warming potential, solid waste, and abiotic depletion potential [35]. Moreover, it is estimated that about 5%-25% of animal feed goes to wastage that could dramatically increase the environmental burden [36,37].

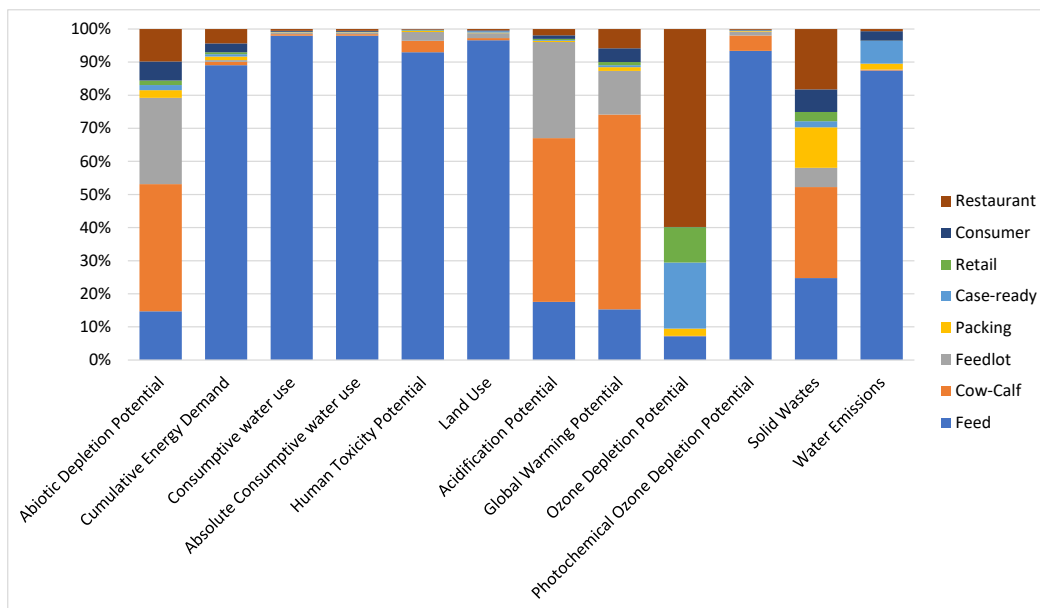


Figure 5: Percentage contribution of different traditional beef production life cycle stages to common environmental indicators [35]

While still an emerging technology, cellular agriculture methods seek to produce cell-based meat through the manufacturing sequence discussed above, rather than breeding and raising animals for their meat. Through the process logistics discussed in the previous section, a considerable amount of meat could be produced from only a few animals by extracting the necessary cells without breeding/raising them. It is predicted that land use, water use, and GHG emissions (mainly methane) could be reduced by two orders of magnitude with the implementation of CBM [38,39]. The comparison between traditional meat and CBM production in terms of energy consumption, GHG emission, land use, and eutrophication is shown in Figure 6 [40,41]. All the collected data for each environmental indicator were normalized where the environmental impact of beef is the benchmark. It is seen that beef has the highest environmental impact for all the indicators except energy consumption while CBM requires more intensive energy consumption than other meat types. This may result from more energy costs of the infrastructures required for cell culture. However, culture meat has potential environmental benefits in terms of GHG emission, land use, and eutrophication. Therefore, CBM shows promise as an alternative for animal protein production in terms of environmental impacts. Recent efforts [42] have looked into

the economics of cell-culture medium [26] and bioreactors as well as other sustainability [27] concerns for CBM. The major contributors to CBM's environmental impact are projected to be resources used to maintain temperature, sterility (which can draw energy from renewable energy sources for sustainability), and the water used for manufacturing serum-free media (which can be reduced through culture medium recycling). However, since the current research approaches for CBM span a variety of meat products, cell lines, scaffolding methods, and bioreactors, conducting a full cradle-to-grave life cycle on CBM is premature at this stage, largely because of the many unknowns related to production-scale manufacturing.

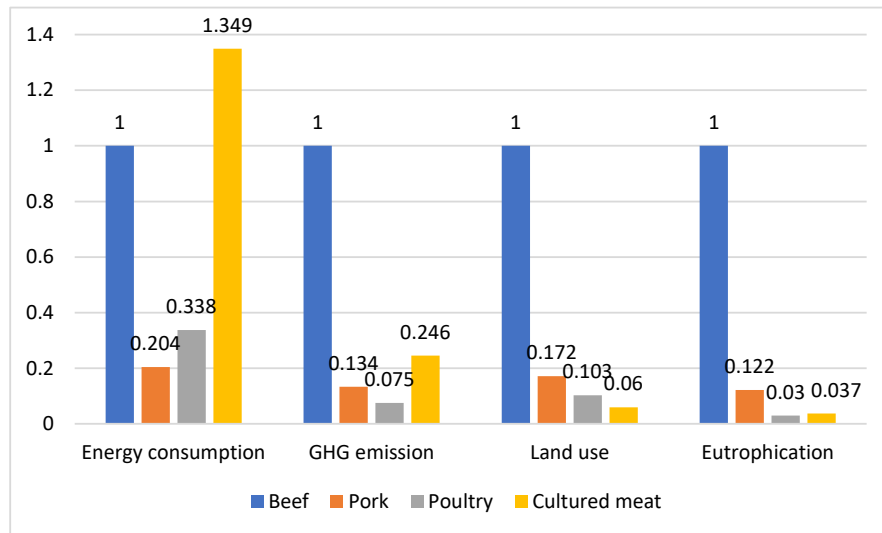


Figure 6: Comparison of relative environmental impacts of CBM with traditional meat products (adapted from [41]) – impacts shown relative to the beef impact which has been scaled to 1.0

While promising from an environmental standpoint, CBM manufacturing as new technology could face challenges in terms of technical, environmental, and social issues. Technical challenges include cell sources, culture media, and commercial-scale bioreactor as discussed in the previous section. Initial estimates suggest that CBM might offer energy savings; however, scaling up to an industrial scale may erode energy benefits and result in higher carbon emissions, and thus needs further research for advancements. A comprehensive analysis of the environmental impacts between traditional meat and CBM at the commercial scale needs to be conducted. For the social dimension, potential barriers must be identified, e.g., consumer acceptance, integration of ranchers/farmers in these manufacturing advancements, and regulations for the cellular agriculture industry.

4. Summary and future directions

Current food manufacturing methods are inequitable and unsustainable to support the needs of the growing population. Furthermore, complex techno-socio-economic dynamics and globalization are perpetuating issues for equity and access to basic human needs, including food [43]. The COVID-19 pandemic exemplified the vulnerabilities of mass-scale food manufacturing in large-scale factories and global distribution while putting issues such as increasing demands with increasing population, urbanization, constraining resources, and supply chains for distribution to the forefront. Convergent engineering and resilient manufacturing efforts are needed to solve the convergent social problems [44]. To address these challenges, traditional agriculture and meat manufacturing approaches must be

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supplemented with alternate food manufacturing methods including cellular agriculture, vertical and urban farming, 3D food printing, and others.

This paper specifically discussed one such convergent emerging food manufacturing approach in the form of cellular agriculture. CBM manufacturing would lessen the burden on land use and animal husbandry while also could be beneficial to reduce the environmental impact of traditional meat manufacturing. Additionally, the advantages include potential micro-micromanufacturing setup for close-to-consumer manufacturing, increased resilience, control over nutritional profiles for population-specific needs, and humane production of meat. While promising, there are several technological, social, economic, and sustainability challenges for CBM as discussed in this paper as opportunities for convergent research and innovations for addressing the challenges and meeting the future needs through smart and sustainable manufacturing.

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