Opportunities for applying biomedical production and manufacturing methods to the development of the clean meat industry

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A B S T R A C T

Clean meat (meat grown in cell culture rather than obtained from animal slaughter) is an emerging biotechnology industry that will ameliorate the serious environmental, sustainability, global public health, and animal welfare concerns of industrial animal agriculture. While many technologies and products developed for the cell therapy industry can already be applied to clean meat, significant opportunities exist to expand product lines to supply this emerging industry. Large-scale cell culture for clean meat production presents a number of unique requirements that are not currently met by existing products and processes from the biomedical industry – most notably related to cost constraints and scale requirements. Developing these tools for clean meat would simultaneously advance the technology and reduce costs for biomedical and therapeutic applications. We will discuss new applications of current biomedical products and manufacturing methods for clean meat, as well as opportunities for synergistic product development through partnerships between academic researchers, established industry players in cell-based therapeutics, and the emerging clean meat industry.

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1. Introduction: what is clean meat?

Clean meat entails producing the cell types present in meat – muscle cells, fat cells, connective tissue, etc. – through a cell culture platform, using cells derived from meat-relevant species including avian, mammalian, and piscine cell lines. While food applications of animal cell culture have appeared in the literature since the early 2000s [1], in recent years this field has experienced a surge of interest among academics [2–4] and the for-profit sector. In the past two years more than a half-dozen companies have formed to commercialize clean meat, moving this endeavor from the realm of academic inquiry into rapid industrial scale-up and manufacturing. Concerted efforts to achieve commercialization within the coming half-decade will require considerations for scale-up and large-scale manufacturing, even in strategic early-stage research and development decisions.

In a report released earlier this year, the National Academies of Science, Engineering, and Medicine (NASEM) identified clean meat as an emerging biotechnology area with high growth potential and commercial relevance within the next five to ten years [5]. The NASEM report, compiled and peer reviewed by more than two dozen esteemed scientists in biotechnology, is a reflection of the extent to which the underlying technologies that enable clean meat have advanced in recent years. It also signals that the clean meat industry is likely to transition from a pre-competitive space to a highly competitive field within a short timeframe and that the present moment represents a pivotal period for the emergence of this technology.

1.1. Motivation: comparison with industrial animal meat

Animal agriculture poses substantial threats to human health, the environment, and animal welfare. It is a leading cause of environmental destruction – including deforestation, ocean dead zones, and water and air pollution – and it contributes more greenhouse gas emissions than the entire global transportation sector [6]. Furthermore, rearing animals poses significant public health threats from antibiotic resistance [7,8] and zoonotic disease epidemics [9] as well as acute consumer risk in the form of foodborne illness from fecal contamination introduced during slaughter and rendering [10]. Finally, consumers are increasingly concerned about the treatment of farmed animals, as evidenced by a growing number of legal reforms and governmental mandates to improve conditions [11,12].

Producing meat via large-scale cell culture significantly alleviates all of these burdens. In the case of the public health and animal welfare concerns, these issues are virtually eliminated by clean meat as animal rearing, slaughter, and antibiotic use are absent from the process. The resource burden is also likely to be significantly reduced relative to industrial animal meat production. While
only a limited number of life cycle analyses have been performed to date – and these are highly speculative as they make myriad assumptions and projections about large-scale process attributes and material sourcing – the consensus at present is that land use, water use, and greenhouse gas emissions will be reduced by one to two orders of magnitude [13,14]. Removing animals from the process also eliminates fecal waste, a leading cause of environmental pollution of both air and water, and associated methane production, which is a significant contributor to animal agriculture’s climate impact.

1.2. Critical technology elements for the clean meat industry

Many of the critical technologies necessary to bring clean meat to fruition are the same as those that have been pioneered for other large-scale cell culture applications such as antibody protein therapeutics, cell-based therapies, and regenerative medicine. The industry mind map (Fig. 1) illustrates several critical technology elements of cell lines, culture media, scaffolding, and bioreactors that are necessary for the process, as well as considerations for supply chain and distribution as the clean meat industry will entail substantially greater input and product volumes relative to biomedical cell culture industries. Note that while this article covers the critical technologies necessary for the successful commercialization of clean meat, it is not an exhaustive list. A deeper dive into each of the technology areas will be required to address the details in each step of the production process.

1.3. The competitive landscape

Virtually all of the companies that have emerged to commercialize clean meat have arisen within the last two to three years, including several in the past year alone. There are nearly a dozen companies pursuing this technology at the time of publication and they encompass a wide variety of approaches, both in terms of production process and product focal area. These considerations determine the extent to which the companies require technology from each of the critical technology areas identified above. Some companies are exploring cultured animal cells as ingredients for incorporation into predominantly plant-based products, in which case they have little need for scaffolding. Others are focusing exclusively on ground meat products for their initial market entry, only requiring scaffolding sufficient for supporting the development of individual muscle fibers – perhaps microcarriers in suspension, for example.

Ultimately, however, the aim of this approach is to create products that are – for all intents and purposes – genuine cuts of meat exhibiting multiple cell types within thick, vascularized tissues. These are the types of meat products that are unlikely to be satisfactorily mimicked by plant-based meat analogues, and thus clean meat offers a more environmentally sound and humane production method for satisfying consumer demand for these products. Due to the pre-competitive nature of the field and these differences in technological focus, there is tremendous opportunity to foster collaboration among the clean meat companies themselves as well as with established companies in the biomedical and life sciences. These companies can serve as vendors, service providers, or contract researchers to address shared needs among the clean meat companies, as discussed in Section 3.

1.4. Regulatory and food safety considerations

Given that commercial interest in clean meat is still nascent, the regulatory framework for this industry has not been fully established but is expected to vary from country to country. Authorities responsible for food safety – rather than those with oversight of medical applications – will have the most appropriate expertise to oversee clean meat production. They should communicate clear
Table 1
Design requirements and parallels within the cell-based therapeutics industry for clean meat critical technology elements. QC: Quality Control.

<table>
<thead>
<tr>
<th>Critical Technology Element (CTE)</th>
<th>Design requirements for clean meat</th>
<th>Relevant technologies and advances within the cell-based therapeutics industry</th>
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</table>
| Cell line development            | • Derived from agriculturally-relevant species  
                                 | • Capable of differentiation into meat-relevant cell types  
                                 | • Genetically stable and immortalized  
                                 | • Optimized for large-scale growth (tolerate suspension, controlled differentiation, etc.)  
                                 | • Development of small molecule cocktails that can replace the need for genetic approaches to induce pluripotency  
                                 | • Footprint-free methods of cell line engineering using RNA or protein delivery or excisable transposons  
                                 | • Improved protocols for cell freezing to maintain viability and phenotypic fidelity  
                                 | • Biocompatible, non-animal-derived scaffolding materials pioneered in the regenerative medicine field  
                                 | • Use of tunable scaffold parameters (stiffness, etc.) to spatially direct differentiation  
                                 | • Degradeable materials that enable cell migration and vascularization after patient implantation  
                                 | • Bioreactors to integrate, closed systems with increasing automation to reduce errors and contamination risk associated with human handling  
                                 | • In-line monitoring of media components to adjust perfusion in real time  
                                 | • Novel technologies to improve efficiency of cell separation and harvesting |
| Cell culture media               | • Animal component-free, antibiotic-free, ideally chemically defined  
                                 | • Optimized for meat-relevant cell lines and co-culture of multiple cell types  
                                 | • Extremely low cost and high-volume production capacity  
                                 | • Engineered or synthetic growth factors  
                                 | • Development of methods for streamlining iterative optimization of animal component-free media formulations  
                                 | • Immobilizing growth factors on beads to prevent depletion in the media via perfusion  
                                 | • Bioreactors to integrate, closed systems with increasing automation to reduce errors and contamination risk associated with human handling  
                                 | • In-line monitoring of media components to adjust perfusion in real time  
                                 | • Novel technologies to improve efficiency of cell separation and harvesting  
                                 | |
| Scaffolding materials            | • Edible and/or biodegradable and food grade materials  
                                 | • Support cell adherence  
                                 | • Support vascularization and media perfusion  
                                 | • Biomechanical properties suitable for tissue maturation  
                                 | • Scalable production capacity  
                                 | • Biocompatible, non-animal-derived scaffolding materials pioneered in the regenerative medicine field  
                                 | • Use of tunable scaffold parameters (stiffness, etc.) to spatially direct differentiation  
                                 | • Degradeable materials that enable cell migration and vascularization after patient implantation  
                                 | • Bioreactors to integrate, closed systems with increasing automation to reduce errors and contamination risk associated with human handling  
                                 | • In-line monitoring of media components to adjust perfusion in real time  
                                 | • Novel technologies to improve efficiency of cell separation and harvesting  
                                 | |
| Large-scale bioreactors          | • Support cell proliferation as well as tissue maturation/perfusion  
                                 | • Large volume, low maintenance  
                                 | • High-yield cell harvesting  
                                 | • Real-time, in-line cell monitoring for QC  
                                 | • Integrated media filtration and recycling system  
                                 | • Highly automated; closed system  
                                 | • Bioreactors to integrate, closed systems with increasing automation to reduce errors and contamination risk associated with human handling  
                                 | • In-line monitoring of media components to adjust perfusion in real time  
                                 | • Novel technologies to improve efficiency of cell separation and harvesting  
                                 | |

2. Application of cell-based therapy technologies to clean meat

Aside from biologics production (vaccines, antibodies, etc.), cell-based therapy is the largest commercial application of animal cell culture. However, some components of clean meat, such as scaffolds and cell culture media, may require additional safety reviews if they are not otherwise used in the food supply.

While food safety will need to be demonstrated conclusively, the clean meat production process poses several notable advantages from the perspective of food safety. It is free of microbial contamination – which is omnipresent in industrial animal meat as a result of slaughter – and the cell cultures can be monitored continuously and immediately treated or aborted if contamination is detected. With the exception of the bacterial load and very low-abundance cell types like nerves and white blood cells, the cellular and molecular composition of the final product will mirror the composition of industrial animal meat, which already exhibits tremendous variability between various animals, cuts, and products. Thus, the nutritional value and the digestive response by the consumer are projected to be the same as for meat derived through animal slaughter. All of the media components can be sourced as food ingredients, and even recombinant growth factors would not pose a novel protein risk because they are identical to the proteins and hormones that are naturally found in meat from an animal.

Finally, clean meat exhibits no risk to the consumer regarding the meat cells taking residence in the consumer’s gut because all meat cells – whether derived from animal slaughter or a cultured production process – are non-viable by the time they are ingested. Animal cells of this nature do not survive longer than a few minutes or, at most, hours outside the context of an animal body or a bioreactor, so they are non-viable by the time they reach a consumer’s plate even if they are never cooked or frozen. Clean meat versions of steak tartar or tuna sashimi will be equally safe to consume raw or cooked because the only cells that currently survive in uncooked meat – microbial cells – will simply not be present in clean meat; the animal cells in these products are not alive at the point of consumption regardless of production method.

expectations about necessary regulatory submissions, with the goal of allowing clean meat to come to market quickly while ensuring safety and consumer confidence. Fundamentally, clean meat should be held to the same safety standard as industrial animal meat; however, some components of clean meat, such as scaffolds and cell culture media, may require additional safety reviews if they are not otherwise used in the food supply.

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(muscle and fat) are much larger than CHO cells, so two tons of wet cell weight is likely an underestimate of the comparable figure for clean meat cultivation. Also note that this production cycle length does not make any assumptions about maintaining the stability of the cell line longer than about 25 generations, though the overall production cycle length could be shortened significantly (and thus drastically increase yield per reactor per year) if the seed train can be maintained in a semi-continuous fashion.

2.1. Cell line development and banking

While cultivation of primary cells is possible for small-scale clean meat applications, ultimately the process is best suited for robust cell lines that exhibit consistent performance over many production cycles, rather than primary cell harvests, which introduce variability and increased risk of contamination from the isolation protocol. Long-term cultivation is critical for reducing costs for clean meat because it allows for continuous cultivation of the seed train with only the final scaling and maturation stages of the production process requiring batch processes. It is likely that clean meat cell lines will be utilized in a similar fashion to fermentation strains in brewing: cultures can be used continuously for some number of generations, but periodically they are re-started from frozen stocks to avoid genetic drift. One barrier to long-term culture of proliferative cells has been maintaining stem-ness in continuous culture, but recent work has shed light on a number of strategies for maintaining stem-ness including subjecting cells to hypoxic conditions [18] and modulating parameters like scaffold stiffness [19].

While cell line immortalization is not common in cell-based therapies, there exists a wealth of experience in developing genetically stable, immortalized cell lines for the biologics industry. However, the cell-based therapy industry, with an eye towards personalized medicine and gene therapy, has been the impetus behind much of the research on induction of stable pluripotent stem cell (iPSC) lines from an individual patient including footprint-free methods rather than classical transgenesis [20]. Epigenetic memory, which influences the efficiency with which iPSCs differentiate into various lineages [21], should be considered when selecting donor cells from which to derive iPSC lines for clean meat. Epigenetic influences have also been harnessed to differentiate human cells directly from embryonic stem cell lines to skeletal muscle without intermediate transitions [22], suggesting that similar approaches could be used to substantially increase both the efficiency and the speed of skeletal muscle derivation for clean meat.

Cell line development may encompass a number of additional approaches to increase the robustness of clean meat cells for large-scale cultivation, improve their metabolic efficiency, and reduce the cost or design requirements of other critical technology elements. For example, one strategy for reducing the cost of growth factors in the media (see Section 2.2) is to adapt or engineer cell lines such that they require lower levels of exogenous growth factor signals to proliferate and/or differentiate in vitro [23]. Gene editing techniques like CRISPR have already been used to accelerate cellular adaptation to conditions such as suspension growth [24], and it is likely that additional signaling pathway editing can increase tolerance to other stressful conditions of large-scale growth. Microfluidic screening techniques to select for metabolic efficiency or robust activity of various metabolic pathways have largely been applied to microbe selection for industrial biotechnology applications [25], but these methods can also be applied to clean meat cell lines to select for high performers.

Once cell lines for clean meat have been established, cell banking best practices derived from the use of sensitive stem cell lines in biomedicine [26,27] can be applied to clean meat cell stocks to enhance their stability, reproducibility, and long-term maintenance.

2.2. Animal component-free cell culture media

Animal component-free media has advanced considerably in the past ten years due in large part to the needs of the cell-based therapy industry, for which media containing animal components is problematic from a reproducibility, contamination, and regulatory perspective. Currently hundreds of formulations of commercially available animal-free media exist [28], resulting from a push within the cell culture community to designate serum-free, chemically defined media as an integral part of good cell culture practice (GCP) [29]. The demonstration that serum-free and animal-origin-free media can support cell survival, proliferation, and differentiation is perhaps the single most significant advancement that has allowed clean meat progress to proceed, as a serum
requirement for this process would render it completely infeasible at scale.

A number of studies have outlined best practices for developing new animal-origin-free media formulations, serving as roadmaps for expanding formulations to meat-relevant cell lines and species [30]. Recent advances in multiwell microfluidics devices for animal cell culture can drastically accelerate the media screening process by parallelizing hundreds or thousands of conditions and facilitating screening for sophisticated phenotypes through automated image analysis [31].

While in vitro skeletal muscle differentiation has historically struggled with low efficiency in the absence of transgenic lines, recent studies have tested serum-free media formulations, growth conditions, and supplements for their capacity to support myogenic differentiation, even from fully pluripotent stem cell lineages [32–35].

Special media considerations at scale include not only optimizing parameters like viscosity and pH in accordance with the fluid dynamics of large bioreactors, but also the addition of components to improve cell survival within the context of unique stressors within the large-scale growth environment. For example, ROCKI (Rho-associated kinase inhibitors) can increase cell viability in suspension growth during the proliferation phase [36], while perfusion within thick tissues may require an oxygen carrier to facilitate oxygen transfer [37,38].

To reach price parity with conventional meat, drastic cost reductions of both the basal media and the growth factors will be required. Demonstrations of growth factor engineering approaches for improved stability or potency have recently been extensively reviewed [39]. Alternatively, small molecule libraries can be screened to identify molecules that mimic the activity of growth factors, eliminating the need to produce them recombinantly [40,41]. Transcriptome [42] and proteome [43] analyses can be used to identify which media components are limiting cellular growth, as well as to optimize the basal media formulation to compensate for various cell stresses.

### 2.3. Tissue engineering scaffolds from regenerative medicine

Scaffolding is paramount for clean meat, as it provides the basis for structured, thick-tissue products that are more complex than simple ground meat mimics or cells used as ingredients. Scaffolds need to support co-cultures of multiple cell types, perfusion of media through the material directly or via a pore or vascular network [44], and ideally help guide differentiation to allow spatial heterogeneity in the final product that will resemble the natural structure and marbling of meat. Scaffolding can guide cell differentiation either through its biomechanical properties or by physically anchoring specific signaling moieties or growth factors, or a combination of these approaches [45]. The elasticity of the scaffold plays a well-documented role in skeletal muscle renewal and maturation in particular [46].

Scaffolds for tissue engineering have historically been derived from animal sources, but recently significant activity has focused on developing alternative materials ranging from synthetic hydrogels to decellularized vascular plant scaffolds [47]. 3D printed and electrospun materials have also been used for tissue engineering and can even harbor nanocarriers for controlled growth factor release [48], but these scaffold fabrication methods may be less amenable to the scaling required for clean meat applications.

Hydrogel scaffolds show perhaps the most promise both for low-cost, large-scale production and for precise fine-tuning of the biomechanical properties to suit the various needs of co-cultured cells for clean meat. These parameters can be modulated with 3D spatial specificity using light [49], and this modulation can be reversible [50], meaning that the scaffold may be dynamically regulated throughout the clean meat production process to facilitate unique cellular demands as cells transition from proliferation to differentiation to maturation. Nano-scale incorporation of additional materials within hydrogel scaffolds can enhance the scaffolds’ ability to induce directed differentiation in the absence of exogenous growth factors [51], or the growth factors can be physically integrated and immobilized within the scaffold to assist in differentiation with high spatial resolution [52]. Scaffolds could also be used as carriers for molecules that contribute to the flavor or nutritional value of the product.

The use of edible or biodegradable scaffolds will be required for clean meat applications. Significant work has already been done to develop tunable scaffolds made of food-safe, plant-derived polymers like gellan gum [53], alginate [54,55], pectin, and modified cellulose [56], which may be ideal for clean meat applications.

Ideally, fabrication of these hydrogel scaffolds can be directly integrated into the closed-system process design to reduce the risk of contamination from introducing a prefabricated scaffold – which can be difficult to sterilize by traditional methods without damaging the material – in the middle of the process. This will require concerted engineering efforts and considerable collaboration with bioreactor developers.

### 2.4. Large-scale bioreactors

Bioreactor technology has benefitted from advances in biologics and vaccine production using animal cell lines as well as in the cell-based therapy industry. A wealth of published literature in this area, including systematic comparisons among various bioreactor types and process design considerations [57,58], facilitates decision-making for new large-scale cell culture applications like clean meat. Large-scale growth of CHO cells is routine, but recent work to improve perfusion systems – including tangential flow and alternating tangential flow filtration – has significantly increased maximum attainable cell densities (above $1 \times 10^8$ cells/ml) and cell performance [59,60]. Similar systems will likely be applied to clean meat production at scale.

The filtration criteria (membrane size, flow rates, etc.) may be more sophisticated for clean meat applications as the parameters may change depending on the stage of the process – for example, different factors will need to be removed and added in the proliferation versus the differentiation phase. Systems to monitor not only the concentration of media components but also the cell density should be incorporated in the bioreactor design at this stage, which may entail including parameters like impedance for inferring cell density within solid tissues where turbidity cannot be measured.

The cell-based therapy industry has pioneered several aspects of automation of the cell manufacturing process, both as a result of the necessity of closed systems to reduce contamination risk under antibiotic-free conditions and to reduce variability from human handling. Functionally closed systems have been described for a number of cell types and applications, including adipose-derived cells [61], bone marrow-derived cells [62], and T-cells [63]. A suite of technologies for in-line, real-time monitoring of system performance, media conditions, and cell viability has been developed [64], including sophisticated Raman-based methods for in situ monitoring [65]. These controls and monitoring platforms will be critical for clean meat production to enable real-time system modulation to address production variability.

The choice of cell type during both the proliferation and maturation phase, in addition to the level of sophistication of the target product, will dictate the optimal bioreactor system. For proliferating cells with minimal structure, suspension cells or adherent cells that can be cultured in aggregates or with biodegradable microcarriers are suitable for systems such as stirred-tank or air-lifted bioreactors currently used in other large-scale cell culture indus-
tries. For maturing cells into more complex three-dimensional tissues, perfusion bioreactors that facilitate even nutrient flow through a porous scaffold will be required. For both of these types of reactors, fluid dynamics will be taken into account to ensure that the desired cell types can tolerate the hydrodynamic forces to which they are exposed in these systems. In fact, computational modeling of fluid dynamics [66] may allow these parameters to be leveraged to support directed cellular differentiation [67,68].

For intact tissue perfusion platforms, there is considerable need to engineer systems for automated harvesting of large-scale intact tissues. Automated large-scale harvesting of single cells or aggregates has been pioneered for cell therapy applications [73], but tissues for regenerative medicine are currently produced at volumes no larger than what is needed for a single patient. Thus, automating the harvesting and downstream processing of intact tissue for clean meat applications will be a novel area of development within bioreactor design and process engineering.

3. Opportunities for accelerating the path to commercialization

The nascency of the clean meat field represents an opportunity to develop strategic partnerships and collaboratively navigate the pathway to commercialization. This includes strategic plans for conducting basic research, bolstering supply chains to proactively address material bottlenecks, developing a robust talent pipeline for future industry growth, and achieving regulatory approval.

As all of the companies that have emerged in recent years to commercialize clean meat are still relatively small and early-stage, there is considerable advantage to leveraging expertise through contracted research – especially with companies that have provided contract work, including contract development and manufacturing, for the cell-based therapy industry. There is also ample opportunity to involve academic collaborators at this early stage, as a plethora of basic research questions with significant downstream importance are not urgent priorities for the clean meat companies, which have limited time and resources.

In order to leverage funding most effectively across the entire technology readiness level (TRL) development of this industry, a concerted effort to bridge the gap between academia and industry is needed (Fig. 3). Developing academic/industry collaborative consortia is one approach to ensure that early-stage research is performed with large-scale manufacturing considerations at top of mind, thus positioning industry partners at the receiving end of successful research outcomes. Facilitating robust dialogue among all the stakeholders, including contracted researchers, vendors in life sciences, and the clean meat companies themselves can de-risk investments in this space by reducing duplicative effort and maximizing the licensable opportunities for intellectual property (IP) that is developed by each clean meat company. Models for pooling IP or establishing patent pledges that reduce the risk of litigation have proven successful for fostering open collaboration in other fast-moving, disruptive technology sectors [69–71].

Taking a TRL-guided, systems-level perspective of industry growth not only allows for strategic coordination among all parties but also enables forecasting of long-term hurdles. While many parallels exist between the needs of the clean meat industry and those of the cell-based therapy industry, it is important to acknowledge where entirely new developments are needed. Development of supply chains specific for the clean meat industry is one such area, as both the scale and the regulatory specifications of the media components for clean meat will be unique. For instance, food-grade components may be acceptable for clean meat applications, whereas current cell culture media suppliers are only working with more expensive pharma-grade or research-grade materials.

4. Conclusion and future directions

Clean meat is rapidly emerging as an area of tremendous commercial interest and growth, presenting significant opportunities for both academic researchers and industry partners to utilize their large-scale cell culture and tissue engineering expertise to advance a novel field. Likewise, many research advances made in pursuit of commercializing clean meat will exhibit significant cross-applicability to other industries that utilize large-scale cell culture, including biologics, cell-based therapy, and regenerative medicine. The number of prototypes, demonstrations, and tastings in the last two years indicate that there are no fundamental technological flaws that are prohibitive to the feasibility of the endeavor. As clean meat comes to fruition, the main challenges will reside in scale-up and cost reduction, with an abundance of opportunities within each critical technology element to increase the efficiency of the process and continuously decrease the cost.

The growing clean meat field is fertile ground for developing collaborative partnerships, exploring licensing opportunities, and pioneering paradigm-shifting technologies that catapult cell culture from the exclusive realm of the bench and the bedside to the scale of industrial agriculture.

Competing interests statement

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