Anticipated growth factor and recombinant protein costs and volumes necessary for cost-competitive cultivated meat

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Executive summary

Numerous studies have described the high costs associated with growth factors and other recombinant proteins used in cell culture media for cultivated meat. However, there remains a gap in the understanding of the future demand, production cost profiles, and regulatory requirements for these proteins that would be expected in a more mature cultivated meat industry. This report provides guidance for navigating these knowledge gaps by modeling the quantities of specific growth factors and recombinant proteins that will be needed to support the cultivated meat industry as it scales. Additionally, the report estimates the cost profiles for growth factors and recombinant proteins that would make them suitable for a cost-competitive cultivated meat market and, lastly, provides details on safety and regulatory considerations for their use in cultivated meat manufacturing.

Data and scenarios from previously published studies were used to estimate a range of anticipated production volumes in 2030 for six growth factors (FGF2, IGF1, NRG1, PDGFB, EGF, and TGFβ) and three other recombinant proteins (albumin, transferrin, and insulin) that are expected to be most commonly used throughout the cultivated meat industry.

The analysis found that 96.6% of production volume is expected to be attributable to albumin, 2.42% to transferrin, 0.97% to insulin, and only 0.02% to all other growth factors. Based on these numbers, capturing just a fraction of 1% of the global meat market with cultivated meat could require a corresponding volume of recombinant albumin protein to be produced in the millions of kilograms, far exceeding the current production volumes of many industrial enzymes.

In a scenario examining future cost-competitive cultivated meat, growth factors and recombinant proteins were modeled to make up 10% of production costs, equivalent to $1/kg of cultivated meat. To satisfy this ambitious cost projection, albumin would need to be produced at $10/kg, insulin and transferrin at $1,000/kg, and growth factors at $100,000/kg. Furthermore, cell culture media would need to be used efficiently, defined as 8 to 13 liters of media per kilogram of cultivated meat. Producing albumin, transferrin, and insulin at such low costs poses a significant challenge to achieving cost-competitive cultivated meat in a timely manner, as new infrastructure for scaled production will be needed.

Capturing just a fraction of 1% of the global meat market with cultivated meat could require a corresponding volume of recombinant albumin protein to be produced in the millions of kilograms, far exceeding the current production volumes of many industrial enzymes.

However, growth factors are not expected to be as limiting, as they are used in substantially lower quantities and can thus tolerate a higher, more easily achievable cost of production that would satisfy cost-competitive cultivated meat.

This report examines three recombinant protein manufacturing platforms spanning precision fermentation, plant molecular farming, and cell-free protein synthesis to provide greater insight into the challenges and innovative approaches to cost reduction. In addition to scaling production and optimizing production efficiency, the cultivated meat industry should seek ways to reduce the cumulative amounts of recombinant proteins and growth factors that will be required, especially for albumin, transferrin, and insulin. Opportunities to achieve this goal are highlighted, including media recycling technologies, replacement strategies, protein engineering, encapsulation or other slow-release systems, the discovery of plant-derived homologs or orthologs, and other novel approaches.

In the absence of further innovation, manufacturing the necessary volumes of specific recombinant proteins will require a sizable infrastructure buildout that may quickly become bottlenecked without sufficient planning. The environmental impact of this supply chain expansion must also be factored in.

This report adds important nuance to understanding the role of growth factors and recombinant proteins in achieving cost-competitive cultivated meat. While the exact numbers, cost profiles, and market sizes in this report may ultimately evolve, the directionality and magnitude of desired production volumes and cost reductions are anticipated to be consistent as the industry scales. Accordingly, investors, researchers, and businesses with an interest in developing growth factors and recombinant proteins for the cultivated meat industry can use this analysis to ascertain potential market sizes and proactively address future cost, scale-up, and regulatory challenges.

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Introduction

Cultivating animal cells outside of the body requires a suitable cell culture medium that contains the oxygen, nutrients, and other factors needed for cell growth. The makeup of the cell culture medium can be split into two groups of components, where the amount of each component in a group is typically tailored to the metabolic requirements of a given cell type and species. The first group of components is commonly referred to as the basal medium, which generally contains a buffered solution of glucose, amino acids, inorganic salts, and water-soluble vitamins critical for cell survival. The second group of components contains specific added factors such as recombinant proteins, growth factors or hormones, lipids, and antioxidants that permit the long-term maintenance, proliferation, and differentiation of cells (Swartz 2021; O'Neill et al. 2020).

Cell culture media is currently the largest cost and environmental-impact driver for cultivated meat production. The vast majority of current media costs and a sizable fraction of environmental impacts are incurred by the second group of added media components: growth factors and recombinant proteins (Vergeer, Sinke, and Odegard 2021; Sinke, Vergeer, and Odegard 2021; Specht 2018). These added components serve a variety of critical functions in metabolism, transport and delivery of nutrients and other macromolecules, and control of cellular activities (Box 1), making them difficult to replace in the serum-free media formulations expected to be used in the cultivated meat industry. Thus, efforts to lower the costs and environmental impacts of the production of growth factors and other recombinant proteins are needed.

Box 1. Nomenclature

The growth factors and recombinant proteins analyzed in this report include fibroblast growth factor 2 (FGF2 or basic FGF), epidermal growth factor (EGF), insulin-like growth factor 1 (IGF1), neuregulin 1 (NRG1), transforming growth factor beta (TGFβ1 or β3), platelet-derived growth factor subunit B (PDGFB), albumin, insulin, and transferrin. Albumin and transferrin are blood plasma proteins that play important roles in the transport and delivery of nutrients and other macromolecules, and insulin is a protein hormone that plays an important role in cellular metabolism and shuttling glucose into the cell. The other proteins listed are canonical growth factors that play a broad role in the control of cellular functions via signal transduction pathways. ***For the purposes of this report, albumin, transferrin, and insulin are referred to as recombinant proteins, while FGF2, EGF, IGF1, NRG1, TGFβ, and PDGFB are collectively referred to as growth factors.***

Previous analyses (Specht 2018; Vergeer, Sinke, and Odegard 2021; Humbird 2021) modeled the potential magnitude of growth factor cost decreases by benchmarking to existing recombinant protein production in other industries. However, a crucial piece of missing information for stakeholders along the value chain is understanding how relevant this benchmarking will be to the cultivated meat industry. To determine this, a greater understanding is needed of the growth factor and recombinant protein quantities anticipated to support the cultivated meat industry as it scales, how growth factor and recombinant protein costs could be reduced to fit the needs of the industry, the timescale over which cost reduction is expected to occur, and how these components will be regulated. Furthermore, in regions such as Europe and Japan, it may also be important for consumer acceptance that cultivated meat is free of components from genetically modified (GM) organisms (Bryant, van Nek, and Rolland 2020), which may impose an additional regulatory burden (Derbes 2021). Meeting these requirements will influence the technical challenges and costs of suitable growth factors and recombinant proteins for culture media in different regions.

To answer the questions outlined above, we began with a survey of the cultivated meat industry that previously identified a set of six growth factors and three recombinant proteins that are expected to be most frequently used by cultivated meat manufacturers ("Cultivated Meat Media and Growth Factor Trends" 2021). We then used prior cultivated meat market size estimations by 2030 [small market size = 0.4 million metric tons, large market size = 2.1 million metric tons; (Brennan et al. 2021)] along with media use efficiency estimations [low media use = 8 L/kg, medium media use = 13 L/kg, high media use = 42 L/kg; (Sinke, Vergeer, and Odegard 2021)] to arrive at scenario-based estimations for the anticipated production volume requirements of the six growth factors and three recombinant proteins by the year 2030. We describe some of the approaches being pursued for growth factor and recombinant protein production and discuss cost reductions toward ambitious benchmarks for using growth factors and recombinant proteins in a cost-competitive cultivated meat industry. Together, these data provide a more comprehensive summary of the expected use of growth factors and recombinant proteins and cost reduction targets that the cultivated meat industry needs to achieve as it scales.

Anticipated production volumes of the most commonly used growth factors and recombinant proteins by 2030

Many of the growth factors and recombinant proteins anticipated to be used in cultivated meat production are already commonly used in biomedical research and the pharmaceutical industry. However, the rapidly increasing scale of the cultivated meat industry will demand growth factors and recombinant proteins to be produced in significantly higher quantities, cost significantly less, and have other attributes that make them more fit-for-purpose for consumer acceptance (e.g., non-GMO) or use in the cultivated meat industry (e.g., food-grade, species-specific) (Venkatesan et al. 2022). Projections for the anticipated volume of growth factors and recombinant proteins required for cultivated meat production as the industry scales are needed to inform suppliers' business strategy and their understanding of when and how to scale up manufacturing capacity.

To calculate the anticipated production volumes of growth factors and recombinant proteins, we selected six representative growth factors and three recombinant proteins for analysis, based on GFI's 2020 industry survey that asked which proteins would be most commonly used by cultivated meat manufacturers ("Cultivated Meat Media and Growth Factor Trends" 2021).

Note that these are not the only proteins that may be used in cell culture media. Other serum proteins (e.g., fetuin, catalase) may be included, as well as oxygen-carrying proteins (e.g., heme or myoglobin), proteins that influence differentiation and maturation (e.g., interleukin-6, myostatin), scaffolding proteins or peptides (e.g., collagen, fibronectin, RGD), or proteins that affect other aspects of the process or end product. For example, a recent study by scientists at the cultivated meat company Mosa Meat detailed a total of 10 proteins in a serum-free media for bovine myoblast proliferation (Kolkmann et al. 2022). Accordingly, the cumulative sum of all recombinant proteins and growth factor production volumes will be influenced by the possible inclusion of additional inputs in some media or end-product formulations.

We first conducted a literature review to estimate the average concentration for each growth factor and recombinant protein (g/L) typically used to grow various cell types relevant to cultivated meat, such as pluripotent stem cells, mesenchymal stem cells, fibroblasts, and myosatellite cells (see supplementary data in Tab 1 (Swartz et al. 2021).[1] The average concentration of the growth factor or recombinant protein was then multiplied by values derived from scenarios for the media volume required to produce one kilogram of cultivated meat (8 L/kg, 13 L/kg, and 42 L/kg; Table 16 from Sinke, Vergeer, and Odegard (2021)) and different cultivated meat production volumes (0.4 and 2.1 million metric tons[2]) anticipated by 2030 under certain market growth scenarios (Brennan et al. 2021). This resulted in six production volume estimation scenarios for growth factors and recombinant proteins based on media use efficiency and market size projections by 2030 (Box 2; Figures 1-3).

Box 2. Parameters for the six scenarios used to derive production volume estimates.

	Media use efficiency[3]	Market size
Scenario A	Low: 8 liters / kg	Low: 0.4 million metric tons
Scenario B	Medium: 13 liters / kg	Low: 0.4 million metric tons
Scenario C	High: 42 liters / kg	Low: 0.4 million metric tons
Scenario D	Low: 8 liters / kg	High: 2.1 million metric tons
Scenario E	Medium: 13 liters / kg	High: 2.1 million metric tons
Scenario F	High: 42 liters / kg	High: 2.1 million metric tons

[1] Note that the concentrations sourced from the literature for this analysis were for pharmaceutical-grade growth factors, which may have higher potencies than food-grade proteins. The standard deviation for sourced values is high, owing to the intentional range of species and cell types sourced from representative publications.
[2] This is equivalent to 0.1% and 0.56%, respectively, of global meat production volume in the year 2030. This assumes that the 2030 global meat production volume is 375 million metric tons, not including seafood.
[3] Media ingredients can be used more or less efficiently depending on cell metabolism, waste management, and other variables, resulting in different volume estimations. More data will be needed to refine these numbers as the industry matures. See Sinke, Vergeer, and Odegard (2021) for more details.

Figure 1. Production volume estimates for recombinant albumin protein in 2030.

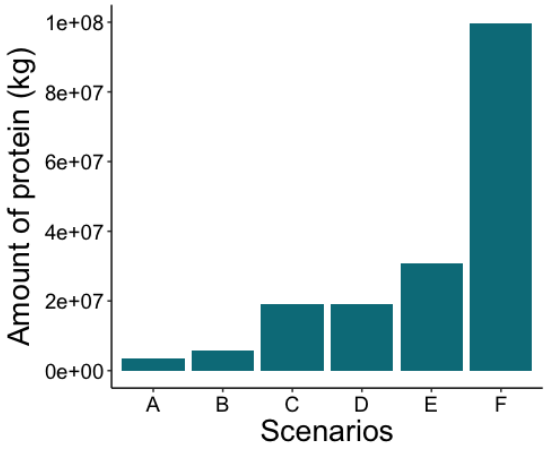


Figure 2. Production volume estimates for recombinant transferrin and insulin proteins in 2030.

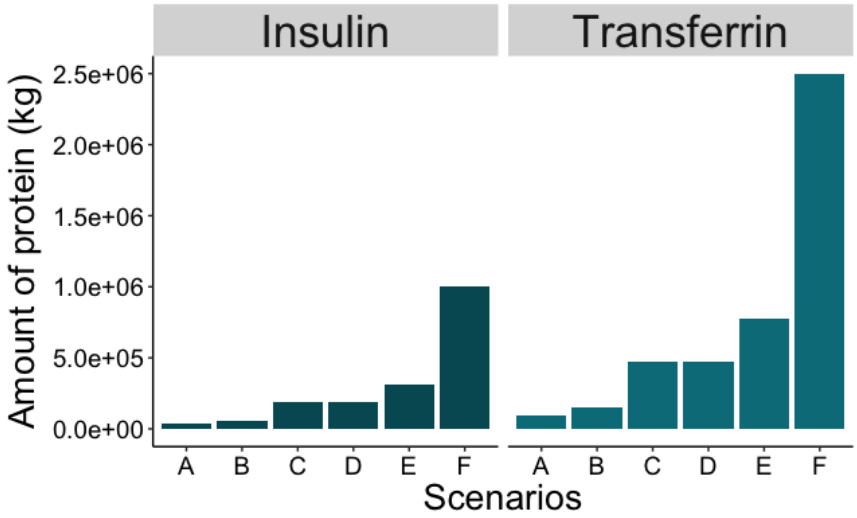
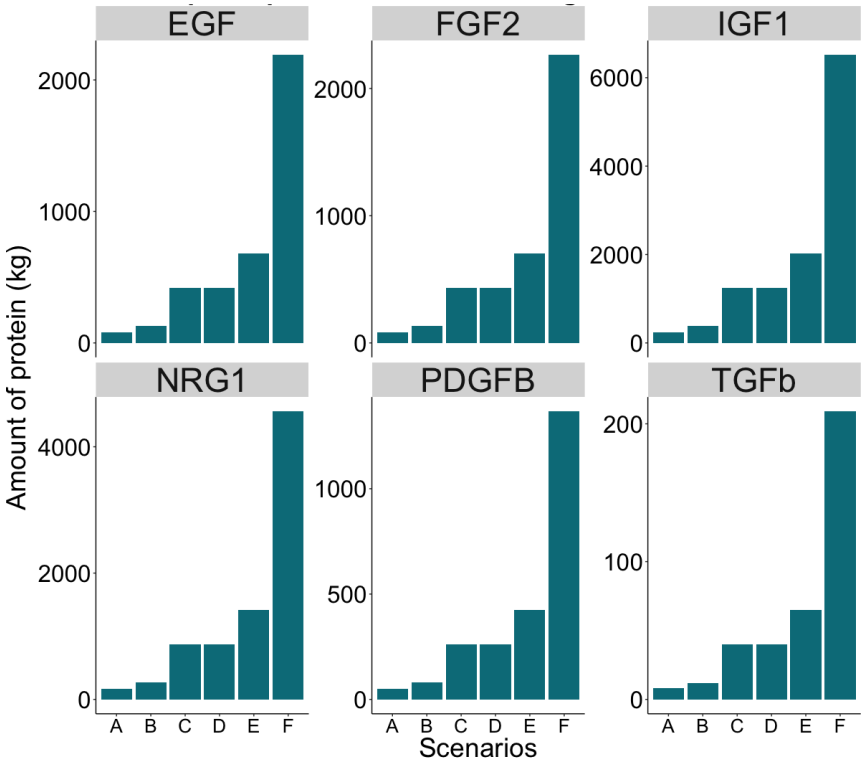


Figure 3. Production volume estimates for growth factors FGF2, EGF, IGF1, NRG1, PDGFB, and TGFβ in 2030.



The figures highlight the dramatically different production volume requirements expected between growth factors and recombinant proteins and between recombinant proteins. For instance, albumin is anticipated to make up approximately 96.6% of production volume, with transferrin making up 2.42%, insulin making up 0.97%, and all other growth factors making up just 0.02% of volume (numbers are rounded; Figure 4). These percentages apply to all scenarios in the report, as the average concentration for each growth factor and recombinant protein is fixed for each scenario.

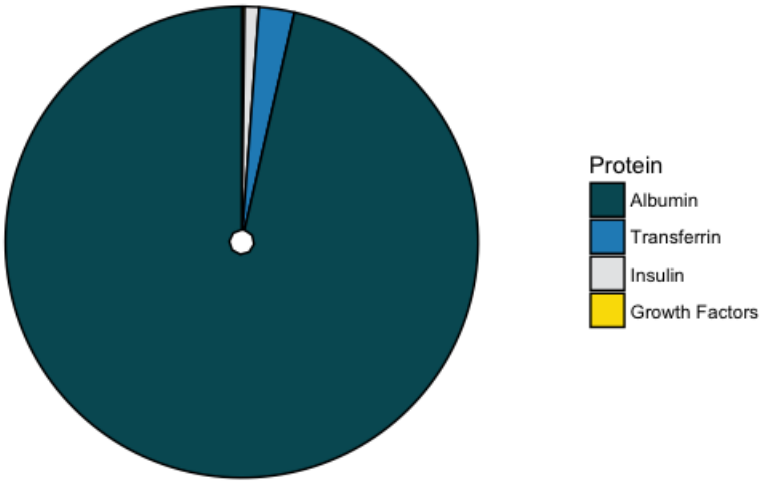


Figure 4. Percentage of anticipated production volumes of growth factors and recombinant proteins for the cultivated meat industry in 2030. Albumin is anticipated to make up approximately 96.6% of production volume, with transferrin making up 2.42%, insulin making up 0.97%, and all other growth factors making up just 0.02% of volume. Numbers are rounded.

For albumin, estimations fall between approximately 3,600 and 100,000 metric tons per year to meet demand, which could make its production volume requirements by the end of the decade significantly larger than the current production of some of the most heavily used industrial enzymes such as amylase (Humbird 2021). For insulin and transferrin, the anticipated production volumes fall within a range of dozens to hundreds of metric tons per year to meet demand, while growth factors would require significantly lower volumes of dozens to hundreds of kilograms per year to meet demand. For perspective, it is estimated that the current global production volume of transferrin is only 0.2 to 0.3 metric tons annually (Negulescu et al. 2022).

These calculations collectively show that the manufacturing capacity for growth factors and recombinant proteins would need to scale rapidly alongside the cultivated meat industry to realize the market growth scenarios used in this analysis, which comprise just 0.1 to 0.56% of projected global meat demand expected in 2030.

Determination of a cost-reduction target for growth factors and recombinant proteins for use in the cultivated meat industry

To understand the gap between the costs of current growth factor and recombinant protein production and the costs that may be demanded by the future cultivated meat industry, we used previously derived estimates for the percentage of cultivated meat's costs attributable to growth factors (Humbird 2021). This analysis estimated that if cultivated meat production were scaled to 100 kilotons annually, the costs for cultivated meat under favorable scenarios would be $37/kg. In addition, in that analysis, growth factors and recombinant proteins would account for $3/kg to $4/kg or approximately 10% of the total costs, which we set as the target for growth factor and recombinant protein cost contributions.[4]

Setting a hypothetical and ambitious future benchmark production cost for cultivated meat at $10/kg, we calculated the total budget allowable for growth factors and recombinant proteins at a 10% cost contribution, equivalent to a total cost contribution of $1/kg of cultivated meat.

In this scenario, the budget for growth factors and recombinant proteins at 10% of total costs becomes $400M in the low market growth scenario and $2.1B in the high market growth scenario (Supplementary Data (Tab 3)).

We first calculated the average cost needed to stay within the 10% cost contribution under three medium-use efficiency scenarios using the cumulative growth factor and recombinant protein production volume estimates previously calculated (Figure 5).[5] This results in very low average costs below $107/kg of growth factor and recombinant protein, which we deem to be excessively challenging to expect for all growth factors and recombinant proteins used in the industry.

We next assume that the vast production volume discrepancies between growth factors and recombinant proteins would incentivize the market to reduce or eliminate the use of certain

[4] The previous analysis also shows that the percent cost contribution of growth factors and recombinant proteins decreases as the overall cultivated meat market size increases due to the inverse price to volume relationship for growth factor and recombinant protein production. Thus, at market sizes of 0.4 to 2.1 million metric tons modeled in this report, the expected percent contribution for growth factors and recombinant proteins may actually be less than 10%. However, the medium formulation in the Humbird analysis includes insulin (0.0194 g/L), transferrin (0.0107 g/L), FGF ($1x10^{-4}$ g/L), and TGFβ ($2x10^{-6}$ g/L), but lacks albumin, which as a result would increase the cost contribution. Taken together, we estimate 10% of costs as an ambitious but reasonable cost contribution target for this analysis.

[5] While the majority of media formulations used by cultivated meat manufacturers are unlikely to contain six or more of the growth factors examined, many media formulations may contain the three recombinant albumin, insulin, and transferrin proteins. Because the overall production volume for growth factors is only 0.2% of the total, we include all of it in the first calculation to obtain an estimated average total cost requirement.

recombinant proteins to save on costs. Research in the cultivated meat sector has already described replacing albumin proteins with homologs found in chickpea protein (Watson 2021; Nahmias, Cohen, and Caspi 2021) and rapeseed protein isolate (Stout et al. 2022), while certain cell types—such as pluripotent cells—can be readily grown in albumin-free media (Kuo et al. 2020).

For these reasons, we recalculated the average cost of growth factors and recombinant proteins needed to stay within the 10% cost contribution assuming that recombinant albumin could be eliminated from some media formulations used in the cultivated meat industry (Figure 5). With low to medium media use, average costs rise to a range of $1,929/kg to $3,135/kg, which we deem to be a reasonable ambitious target range for most growth factors and recombinant proteins produced at large scales.

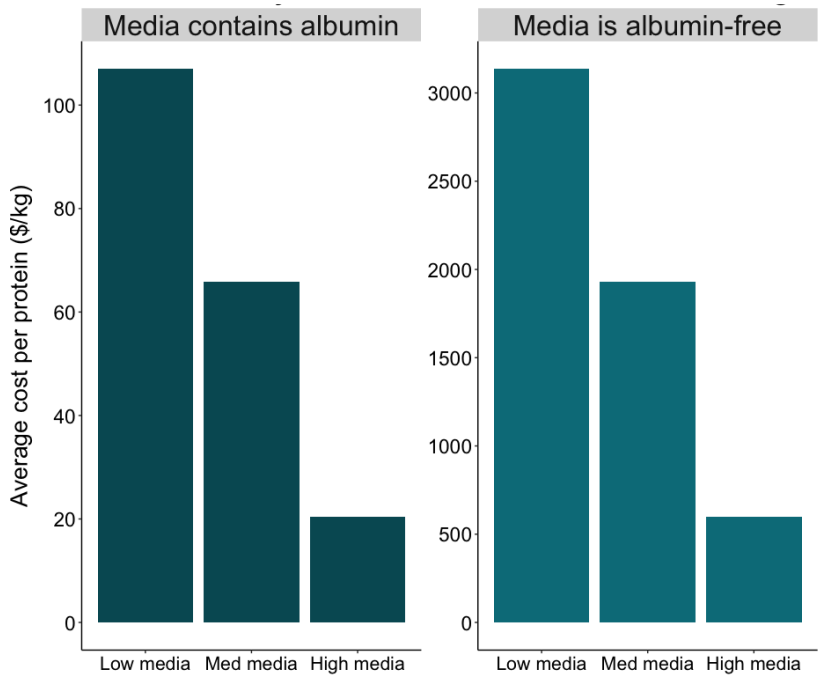


Figure 5. (left) The average cost of growth factors and recombinant proteins needed to stay within a 10% cost threshold for cultivated meat produced at $10/kg meat, equivalent to $1/kg proteins. **(right)** The average cost of growth factors and recombinant proteins, minus recombinant albumin, needed to stay within a 10% cost threshold for cultivated meat produced at $10/kg meat, equivalent to $1/kg proteins.

Average cost expectations are illustrative but are not indicative of reality because the costs of growth factor and recombinant protein production are dependent on their expected demand and, in turn, the scale at which they are produced. The smaller production volumes anticipated for growth factors compared to recombinant proteins mean that they are likely to have dramatically different corresponding expectations for production cost.

To stay within the 10% cost contribution, we created three tiers of hypothetical production costs based on their anticipated scale of production, which were cross-referenced to fall within the range of previously derived price-to-volume relationships for recombinant protein production (Humbird 2021; Table 1). We set the lowest cost tier for albumin at $10/kg protein, as there is evidence that these costs may be achievable for proteins manufactured at that anticipated production volume.[6,7,8] We then scaled the production costs for tiers 2 and 3 based on the order of magnitude difference in their anticipated production volumes compared to albumin. These cost tiers can be used as guidance for producers of growth factors and recombinant proteins that aim to supply the future cultivated meat industry.

At these production costs, the cost burden for growth factors and recombinant proteins stays within the 10% cost contribution threshold in low and medium media use scenarios, but costs are above this threshold if media is not used efficiently. This remains true at these production costs regardless of whether albumin is in the media or not, as the costs for transferrin alone are higher than the 10% of the total production costs for cultivated meat in the high media use scenario (Figure 6).

		Protein production cost assumed in this study	Extrapolated prices from Humbird based on estimated production volume scenarios in this study	
			Average	Scenario A to Scenario F range
Tier 1: Albumin		$10/kg	$26.94/kg	$68.68/kg to $3.95/kg
Tier 2:	**Insulin**	$1,000/kg	$1415.22/kg	$3,607.98/kg to $207.56/kg
	Transferrin		$642.98/kg	$1,639.22/kg to $94.30/kg
Tier 3: Growth factors		$100,000/kg	$549,820.21/kg[9]	$5,320,271/kg to $15,822/kg

Table 1. Hypothetical future production cost tiers for growth factors and recombinant proteins. Costs are assumed to be dependent on the scale at which they are produced. Costs were cross-referenced to price-to-volume relationships for recombinant proteins previously derived by Humbird. Calculations available in the supplementary spreadsheet.

[6] Lowest price found for a recombinant protein—cellulase (Puetz and Wurm 2019).
[7] ReThinkX estimates that production of recombinant proteins via precision fermentation could fall to $10/kg by 2025 (Tubb and Seba 2019).
[8] Bulk ordering of common food enzymes at 200-1000kg scales were quoted from Novozymes at costs between $12-25/kg.
[9] The average of all growth factor scenario values. Refer to supplementary data (Tab 2) to see the full set of calculations.

Cost of growth factors and recombinant proteins to stay within a 10% cost threshold

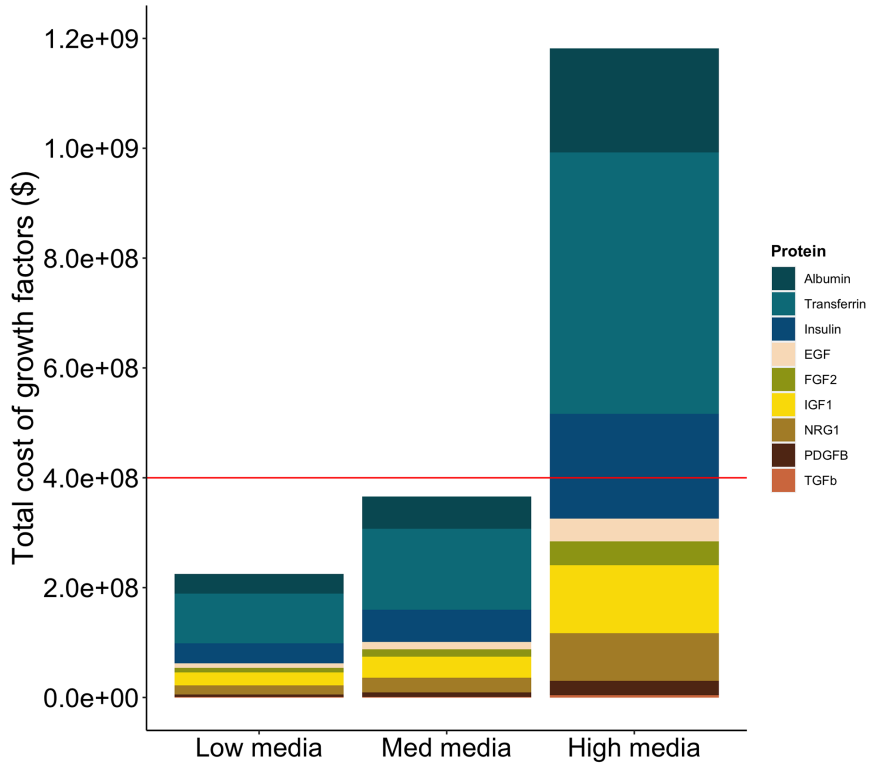


Figure 6. The cumulative cost of growth factors falls below the 10% cost threshold (red line represents the budget of $400M) under low and medium media use scenarios when albumin is produced at $10/kg, insulin and transferrin are produced at $1000/kg, and growth factors are produced at $100,000/kg. The data shown are for the low market growth scenario of 400,000 metric tons of cultivated meat by 2030. Data for the high market growth scenario are included in the supplementary spreadsheet.

These data collectively illustrate that achieving cost-competitive cultivated meat will require growth factors and recombinant proteins to be produced at significantly larger scales and lower costs than their current production formats and scales in the biopharmaceutical sector. This is especially true for recombinant proteins. Additionally, media must be used efficiently such that growth factors and recombinant proteins do not go to waste. As discussed later, innovations that enable fewer growth factors and recombinant proteins to be used are expected to play an important role in achieving cost-competitive cultivated meat.

Platform technologies for growth factor and recombinant protein production

Recombinant DNA technology involves combining genetic material from multiple sources. A common example of an application of this technology is the production of human insulin protein, whereby the DNA sequence for insulin is inserted into a production host such as E. coli, the insulin protein is produced by the host, and the protein is harvested and purified. This strategy has since been used to manufacture a variety of proteins in the biopharmaceutical and food sectors.

The majority of growth factors (excluding steroidal hormones) are proteins or peptides that can be produced using recombinant DNA technology. The recent discovery of more robust tools for recombining DNA and manufacturing proteins has led to an expansion in the library of growth factor and recombinant protein production hosts and manufacturing strategies: precision fermentation in filamentous fungi or microbes such as bacteria and yeast, molecular farming in plants, cell-free production, production in insects, and production in plant or animal cell cultures.

Below, we highlight three different growth factor and recombinant protein production platforms (Figure 7), using contributed perspectives from exemplar companies in each category, to describe some of the challenges and cost reduction opportunities for each approach as they apply to the cultivated meat industry (Figures 8-10). The figures illustrate that how cost reduction is achieved depends on the production platform, but each production platform will need to optimize multiple aspects of the production process to realize costs suitable for cultivated meat. The numbers in these figures and the percentage of cost reduction indicated for each parameter are best interpreted as estimates based on individual company calculations. Full techno-economic models will be needed to elucidate the cost drivers and cost reduction expectations for each platform at scale.

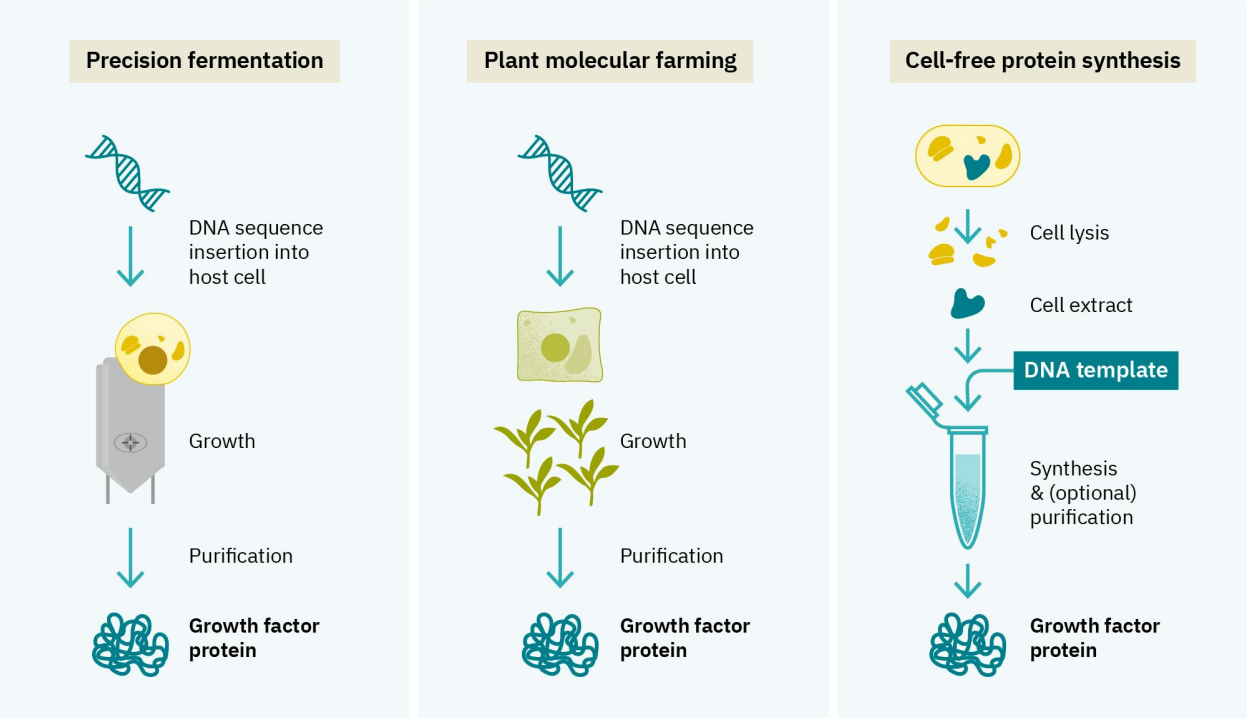


Figure 7. Exemplar platform technologies for protein production. Precision fermentation and plant molecular farming rely on a similar approach of using microorganisms or plants as factories for proteins. Cell-free protein synthesis does not use an entire organism as the factory but rather takes the necessary cellular components and machinery for protein synthesis to produce proteins *in vitro*.

Precision fermentation (Contributing coauthor: Laurus Bio)

Precision fermentation involves the engineering of microbes such as bacteria, yeast, and fungi as "cell factories" that can be used to manufacture animal growth factors and recombinant proteins without the animal (Waschulin and Specht 2018). In this process, a target gene is inserted into a microbial host, and the microbe is trained to selectively manufacture the protein of interest encoded by the target gene (Figure 7). This animal-free mode of protein production has several advantages compared to conventional animal agriculture: it is free from viruses and other pathogens that may otherwise reside in an animal host, it has a long history of safe use in the biopharmaceutical and food industries, and recent studies indicate that it can significantly reduce greenhouse gas emissions and other environmental impacts (Järviö et al. 2021; "Comparative Life Cycle Assessment of Perfect Day Whey Protein Production to Dairy Protein" 2021).

Laurus Bio has produced growth factors and other recombinant proteins for use in the biopharmaceutical sector for 15 years, and we are now leveraging our expertise in recombinant protein production to meet the needs of the cultivated meat industry. There are several differences in the needs and requirements for growth factor and recombinant protein production in the biopharmaceutical versus cultivated meat sectors, with the most important difference being in cost tolerance.

There are several ways to reduce production costs using precision fermentation (Figure 8). The first is in economies of scale, where the overall costs of building and operating a larger fermentor diminish in relation to their increased production capacity. It is also important to realize these economies of scale by building out manufacturing capacity ahead of demand. For example, to meet the anticipated demand and cost profiles of the cultivated meat industry, we are scaling our installed manufacturing capacities from 200,000 L to 2,000,000 L within the next 12-18 months. We anticipate having the capability to manufacture recombinant proteins and growth factors in very large-scale fermenters of up to 500,000 L, which is over 10 times larger than what we currently use. We estimate that the cost of manufacturing recombinant proteins and growth factors can be reduced by ~35 to 40% from its current baseline as a result of this scaled production.

Other cost reduction levers available for precision fermentation are yield enhancement and product innovation. For example, higher-yielding variants can be obtained by targeted engineering, resulting in enhanced gene expression, protein folding, post-translational modification, secretion, reduction of proteolysis, and other desirable changes. Additionally, developing improved growth factors and recombinant proteins can be achieved through structure-based and random mutagenesis combined with screening for improvements in attributes such as potency or thermal stability. These can be performed

for species-specific versions of growth factors and recombinant proteins, as we expect to be demanded by the industry ("Cultivated Meat Media and Growth Factor Trends" 2021). Collectively, we estimate that improvements in yield enhancement and product innovation can reduce the cost of manufacturing by ~30 to 35% from its current baseline.

The third major cost reduction lever is in process and downstream protein purification innovation. To meet the needs of the cultivated meat industry, our growth factors and recombinant proteins are produced in a food-certified precision fermentation facility rather than a more tightly controlled pharmaceutical facility that meets the requirements for drug manufacturing. This provides an immediate cost reduction while not compromising on safety or efficacy.

Currently, it is common to use traditional, well-known carbon and nitrogen feedstocks for fermentation processes, however, the use of alternate, lower-cost carbon and nitrogen sources is possible. These sources can be associated with lower costs in different geographies depending on their accessibility and abundance. Furthermore, ease of processing can also influence the cost and selection of carbon and nitrogen sources.

Finally, it is possible to eliminate or optimize downstream purification steps that are typical to meet pharmaceutical specifications but are not required for food applications such as cultivated meat. Specifications such as purity level, amount of impurities, formulation, and physical form can be altered to obtain a growth factor or recombinant protein product that performs well in cell culture and is suitable for food. Altogether, process improvements such as feedstock optimization and downstream process innovations can reduce costs by ~25 to 35% from their current baseline.

These estimates provide insight into the different cost levers available for precision fermentation of recombinant proteins, all of which can be tackled simultaneously and applied additively. Achieving substantial cost reductions of up to 99% is not possible by optimizing a singular aspect of production but rather by simultaneously improving the entire production pipeline. This provides companies and researchers with many innovation opportunities to target from R&D to manufacturing.

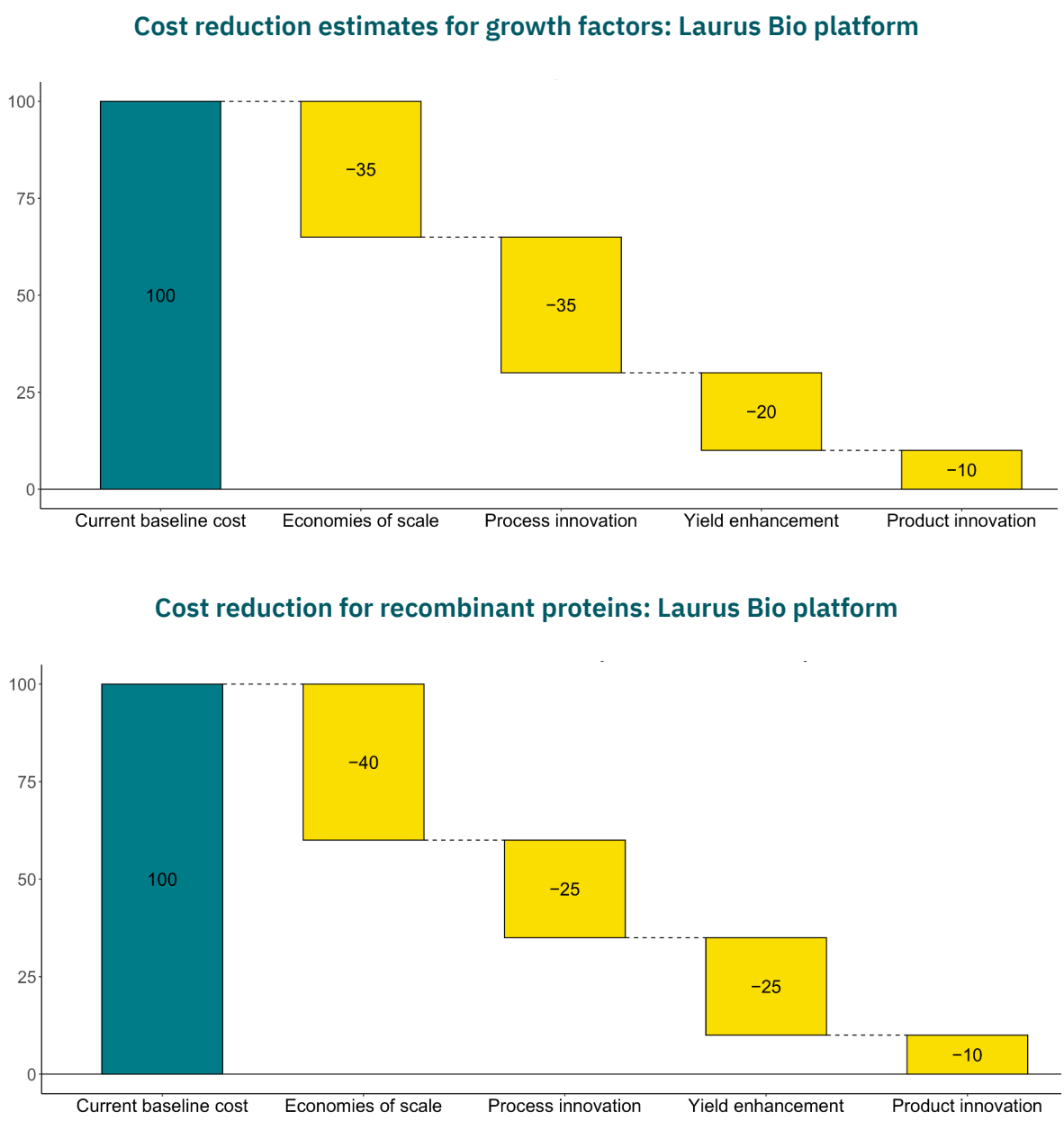


Figure 8. Cost reduction opportunity estimates in precision fermentation as a percentage of current baseline cost. Variance in the reduction for some parameters is expected to be present due to sensitivity to the scale of production between growth factors **(top)** and recombinant proteins **(bottom)**. Numbers are rounded to the nearest whole number.

Molecular farming in plants (Contributing coauthor: Core Biogenesis)

Molecular farming involves the use of plants as an expression host for the production of growth factors and recombinant proteins (Shanmugaraj, Bulaon, and Phoolcharoen 2020). Recombinant expression of the growth factor or protein can take place throughout the entire plant or be restricted to a specific portion such as the leaves or seeds. As in other recombinant expression systems, DNA is inserted into the plant providing the code for the plant to synthesize the corresponding growth factor or protein. The accumulated protein of interest is then extracted and purified into a final product (Figure 7). To meet the production volumes and price targets needed for the cultivated meat industry, plant molecular farming must leverage its inherent advantages in scalability while solving challenges related to yield, extraction, and purification (Figure 9).

At Core Biogenesis, we use the oilseed plant *Camelina sativa* as the host for the stable expression and production of growth factors and recombinant proteins. We target our growth factors and other recombinant proteins to the seed compartment of the plant, which captures the benefits of the exponential scalability of agriculture where, once a stable plant line is obtained, each plant yields thousands of seeds that each give birth to a new plant, and so forth, without the need for any further transformation of the plant between the succeeding generations. This enables a streamlined scale-up process where we employ agricultural practices and principles that have been in use for millennia by cultivating *Camelina* in open fields. For example, we plan to scale our open field cultivation area to dozens of hectares in the coming years, which will enable us to produce 10 kg of growth factors per hectare and per harvest (two harvests per year), allowing us to produce hundreds of kilograms per year.

From an environmental perspective, relying on sunlight as the primary energy input is expected to have a low environmental impact profile, similar to other oilseed crops such as soy, in addition to saving on utility costs (Ritchie and Roser 2020). Open field scale-up is also fundamental in our cost reduction strategy as it forgoes the use of fermentation tanks, vertical farms, and other CAPEX-heavy infrastructure.

Challenges in plant molecular farming relate to yield and the extraction and purification of the target protein. Downstream purification costs can be expensive due to the substantial biomass of plants relative to the mass of the protein of interest. Targeting protein expression in the seeds of the *Camelina* plant minimizes this issue and allows for the development of scalable, phase-specific downstream process developments. By leveraging plant biotechnology methods like the oleosin fusion extraction method, our downstream process is primarily based on mechanical processes derived from the agri-food industry, allowing for the industrial-scale

production of growth factors and other recombinant proteins (Ling 2007). Collectively, we estimate that scaling plant production in open fields and optimizing downstream purification can reduce costs by approximately 75% from the current baseline.

Our downstream process allows for two distinct versions of our recombinant proteins: a final product free of impurities, or a cruder protein product that contains the recombinant growth factors of interest and some well-characterized, edible, and GRAS (generally recognized as safe) plant proteins and lipids. This second option brings specific advantages to the cultivated meat industry in terms of cost reduction. Lastly, to enhance the achievable yield, we have identified various combinations of genes that are involved in plant defense mechanisms and can be leveraged to increase the expression yield by orders of magnitude. We estimate that this yield-boosting technology can reduce costs by approximately 25% from the current baseline.

Achieving substantial cost reduction estimates of 98% or greater will require leveraging the inherent advantages of plant molecular farming while tackling its challenges, mostly centered on increasing yields and purification efficiencies. Understanding these advantages and limitations of the technology will enable companies and researchers to be best positioned to scale up rapidly and reduce costs.

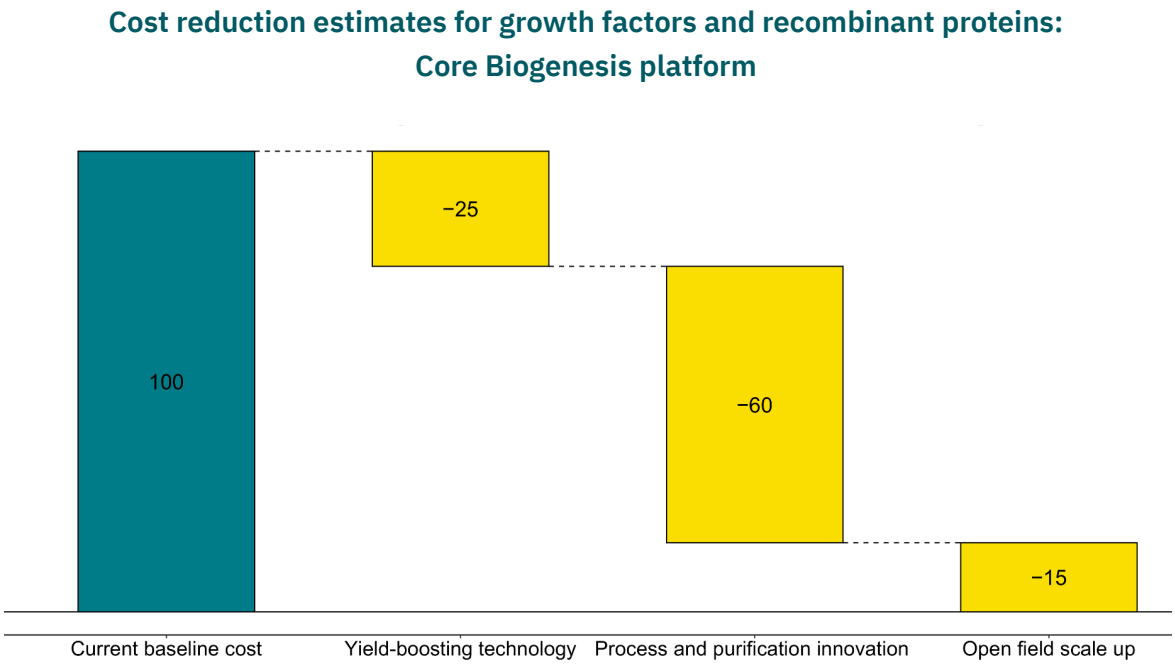


Figure 9: Cost reduction opportunity estimates in plant molecular farming as a percentage of current baseline cost. Numbers are rounded to the nearest whole number.

Cell-free protein expression systems (Contributing coauthor: LenioBio)

Cell-free protein expression (CFPE) produces proteins using the lysates of cells, which are obtained after the mechanical disruption of the cell membrane or cell wall. The cell lysate is then collected into an appropriate vessel and genetic material is added to initiate the expression of a corresponding protein of interest (Figure 7; Silverman, Karim, and Jewett [2020]). Thus, CFPE systems rely on recombinant or synthetic DNA sequences but lack an intact, recombinant host organism.

CFPE systems have several advantages related to their ease of use. First, the same lysate can be used for a wide range (i.e., thousands) of proteins. Secondly, protein expression completes within 24-48 hours following the addition of the genetic material, whereas expression in living cells can take days or weeks. Third, because CFPE is performed in an open environment, different expression conditions such as pH, redox potentials, temperatures, and the presence of chaperones can be optimized using high-throughput techniques for each specific protein of interest. Importantly, in the context of scaling, those conditions are the same for gram, kilogram, or metric-ton scale. This allows CFPE to be used for the rapid iteration or production of new growth factors and recombinant proteins on accelerated timelines, especially when new needs arise, such as species-specific growth factors that are not currently widely produced or entirely redesigned growth factors.

Although not new, CFPE technology was not previously considered for large-scale production due to challenges associated with low yields. To address this issue, LenioBio leverages a new plant-based CFPE system called ALiCE®, which enables high yields of up to 3 g/L of even the most difficult-to-express growth factors and recombinant proteins. Notably, the mitochondria in the lysate are active, allowing for much more affordable expression than previous CFPE platforms. As of writing, we have scaled reaction volumes to 10 L, producing highly potent growth factors with the potential for more affordable production at larger scales. We were also recently awarded a grant from EIT Food and GFI-Europe to further optimize the system for cultivated meat applications.

ALiCE® has several attributes that contribute to affordable production. First, the lysate production is generic, meaning one cell line and a generic process can produce the lysate to be used for any protein, regardless of the protein's complexity or the species it originates from. This is in contrast to recombinant production in animal, plant, or microbial cells, which can require costly tailored cell line or strain development for specific growth factors. Second, expression conditions are similar across scales such that it is relatively straightforward and affordable to scale production from micrograms to kilograms and beyond. Third, the generic processes allow for streamlined scaling with demand, reduced risks, lower

capital costs, and reduced stockpiling. Collectively, we expect economies of scale and unique capabilities of ALiCE® in this context to contribute 50% of the needed price reduction from current baseline costs (Figure 10).

A second important cost reduction factor is the optimization of yield and potency. Because ALiCE® is an open system that produces proteins rapidly, improving yield and potency can be done by tweaking reaction conditions in a high-throughput manner. The open system also enables more control over factors that improve potency such as optimal and homogeneous folding and dimerization. We estimate that potency and yield optimization can together contribute 40% of the needed cost reduction.

A third factor is that purification costs can potentially be avoided by using CFPE systems like ALiCE® because the protein of interest and lysate remnants can be used together in a final product. Lysate remnants for ALiCE® are awaiting safety and regulatory approval, which we expect to receive in 2023 through the GRAS process. Mitigating the need for purification will further increase yield and potency and can contribute another 10% of the needed cost reduction.

Other cost effects occur at the operational level because the lysate does not require expensive growth media to maintain energy homeostasis like a cell culture, and optimization can be performed in a high-throughput manner, potentially cutting operational costs in half. Additionally, when it comes to innovation (e.g., exploring novel or improved growth factors or designing entirely new ones), the costs of discovery-development-scaling iteration cycles can be greatly reduced. Finally, the environmental impact of CFPE systems may be lower than recombinant production in cellular systems, although life cycle assessments are needed to verify this.

The ALiCE® system also has several advantages specific for application in the food industry, including the use of lysates derived from plant cells, which means that growth factors and recombinant proteins are both animal-free and endotoxin-free. The system performs post-translational modifications such as disulfide bonding and glycosylation, which is vital for proteins' correct folding and functionality but cannot be performed equally in all recombinant production systems. Lastly, the lysates are derived from non-GMO plant cells such that the resulting growth factors and recombinant proteins are also non-GMO, which is expected to be important for consumer acceptance and regulatory considerations in certain geographic areas. In summary, cell-free protein expression has the potential to be pivotal in the success of cultivated meat.

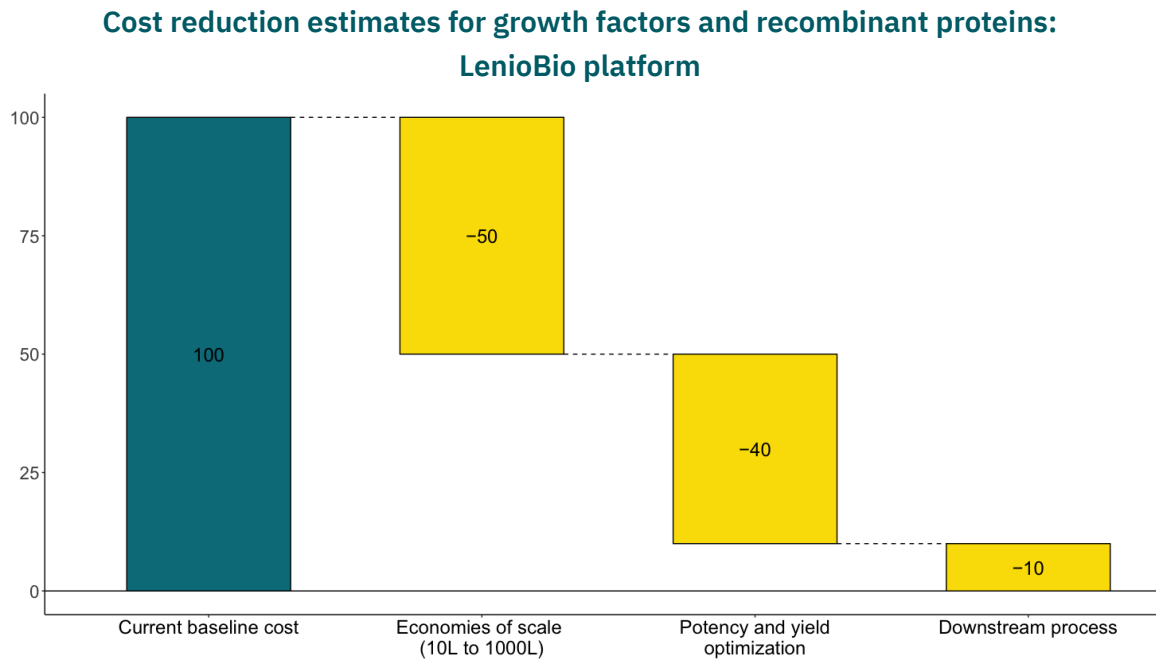


Figure 10. Cost reduction opportunity estimates in cell-free protein expression systems as a percentage of current baseline cost. Numbers are rounded to the nearest whole number.

Summary of platform technologies for growth factor and recombinant protein production

While the three platforms above were selected to illustrate the different levers for cost reduction across different production modalities, it is important to note that the production of growth factors and recombinant proteins is not limited to precision fermentation, plant molecular farming, or cell-free protein synthesis. Other companies and researchers are using insects, insect cell lines, or mammalian cell lines as expression hosts (Tripathi and Shrivastava 2019). All of these systems are also being used to cultivate animal proteins for use in other alternative protein products, food applications, or next-generation materials.

As cited previously, existing technologies permit the production of certain proteins at costs as low as $10/kg. A new wave of companies is now using cutting-edge technologies to achieve similar levels of cost reduction for fit-for-purpose proteins in the cultivated meat industry. Different production platforms have certain advantages, disadvantages, and challenges

to overcome. Some of these tradeoffs may be platform- or protein-specific, while others may influence parameters such as environmental impact, CAPEX, or R&D iteration speed. Ultimately, future analyses that more rigorously assess the techno-economics and environmental impact of scaled protein production will need to be performed. However, given the size of the future demand for growth factors and recombinant proteins in the cultivated meat industry, there is a large opportunity for many players to exist simultaneously to fill the supply gap and prevent future bottlenecks.

To learn more about the companies using recombinant protein technology in the alternative protein sector, visit GFI's company database.

Additional practices, technologies, and innovations for reducing the cost burden of growth factors and recombinant proteins

The calculations above demonstrate that growth factors and recombinant proteins will need to be produced at large scales and low costs for use in the cultivated meat industry. Moreover, this is just one part of the supply chain that will need to be scaled and optimized. Accordingly, cultivated meat manufacturers will be incentivized to find ways to reduce the use of costly growth factors and recombinant proteins, especially those with a higher overall cost burden such as albumin, transferrin, and insulin.

The scenarios used in this analysis intentionally result in a broad range of anticipated growth factor and recombinant protein production volumes to account for potential errors in assumptions at this early stage of industry development. It is possible that the actual production volumes could fall below this range if additional innovations to reduce their use are employed throughout the industry. Below, we discuss some of the ways the industry may pursue lowering the cost burden of growth factors and recombinant proteins.

1

Media recycling technologies.

Several studies have demonstrated proof of principle for the use of size-exclusion dialysis to capture and reuse growth factors and recombinant proteins in bioprocessing applications (Torizal et al. 2021; Nath et al. 2016). Similar strategies may be pursued by cultivated meat manufacturers to reduce the need to resupply growth factors and recombinant proteins during production.

2

Engineering of growth factors and recombinant proteins.

Growth factors and recombinant proteins can be engineered in various ways to enhance their stability, reduce protease activity, increase their potency, and serve other beneficial purposes for a given application. For example, the native FGF2 protein suffers from a short half-life within warmed cell culture media due to degradation and instability. In 2019, an engineered variant called FGF2-G3 was shown to have a dramatically increased half-life compared to the native protein, and FGF2-G3 is now manufactured by numerous global growth factor suppliers for use in cell culture media (Koledova et al. 2019).

Additionally, the concentrations sourced from the literature for this analysis were from pharmaceutical-grade growth factors, which may have higher potencies than food-grade proteins due to their higher purity. If potencies are not equivalent, food-grade proteins may need to be used at higher concentrations, demanding even higher quantities. Thus, engineering proteins to have increased potency could significantly impact the overall demand for these proteins. It is anticipated that a variety of engineered growth factors and recombinant proteins are likely to be used in the cultivated meat industry. Read more about GFI-funded growth factor engineering work (Venkatesan et al. 2022).

3

Encapsulation or slow-release systems.

Because growth factors can display short half-lives or variability in cell culture, a variety of systems have been developed to control how much, when, and where growth factors are released (Wang et al. 2017). These systems may be employed at multiple process stages, including the differentiation phase where growth factors may be immobilized within the biomaterials that make up the scaffolding structure (Bomkamp et al. 2021).

4

Use of conditioned media.

Conditioned media refers to the spent media containing metabolites and other secreted factors that accumulate during cellular growth. Cultivated meat company Integriculture is developing a platform called CulNet that aims to provide an artificial serum by growing liver, pancreatic, and other tissues in independent vessels and shuttling their secreted factors into separate bioreactors used to cultivate meat. Growing organ tissues that naturally produce many of the necessary growth factors for cultivating meat may more fully recapitulate the composition of serum and thus could offset some demand for the recombinant production of individual growth factors or serum proteins.

5

Self-sustaining cultures at high density.

Certain animal cells secrete growth factors and recombinant proteins that can be beneficial to sustaining their own growth or the growth of other cell types. At high densities anticipated to be typical in the cultivated meat industry, certain cell cultures can secrete growth factors in a self-sustaining manner (Torizal et al. 2021). This may reduce the need for or the amount of exogenously added growth factors and recombinant proteins beyond certain process steps. Co-culture of different cells may provide an additional way to capitalize on this opportunity.

6

Discovery of biofunctional equivalents that replace the need for recombinant protein production.

In a 2021 article, Dr. Yaakov Nahmias, the founder of Future Meat, stated that the company had identified a chickpea-based albumin protein homologue that could replace the need for recombinant animal albumin (Nahmias, Cohen, and Caspi 2021). Similarly, bulk protein extracts from rapeseed were shown to fully replace recombinant albumin in bovine myoblast cell cultures (Stout et al. 2022). These examples indicate that cultivated meat manufacturers and researchers are already clued in on the importance of reducing albumin use to save on costs. Similarly, the discovery of biofunctional equivalents of transferrin, insulin, or other proteins derived from plants, fungi, or other microorganisms will be important avenues to pursue. For some cell types, the growth factor IGF1 can functionally replace insulin in cell culture and can be used at substantially lower concentrations (Wamaitha et al. 2020). Thus, in some cases, recombinant proteins could be substituted by growth factors used in lower quantities.

7

Use of small molecule compounds.

In cell culture, small molecules can be used in a similar fashion as growth factors and recombinant proteins to activate or repress biochemical pathways to impart control over cell metabolism, behavior, and activities such as proliferation and differentiation (Liu et al. 2016). The synthesis of certain small molecules could be more cost-effective than the use of certain growth factors and recombinant proteins. Among other considerations, the safety profiles and history of use in human medicine of small molecule compounds may need to be assessed prior to their use in cultivated meat production processes.

8

Creation of protein-free media.

In the biopharmaceutical sector, chemically defined, protein-free media (e.g., PowerCHO, ESF 921, CD CHO) are commonly used to simplify the downstream purification of therapeutic proteins. Together with certain implementations of cell line engineering, the development of bioreactor systems with on-demand, component-specific feeds into the media may facilitate greater use of protein-free media, particularly to reduce the need for proteins like albumin that function as a source or sink for nonspecific binding of various macromolecules to modulate their availability to cells. While cell culture can be performed under protein-free conditions, more research is needed to determine whether this would provide the best performance for cultivated meat applications.

9

Novel innovations.

Other approaches should be explored to reduce the quantities of growth factors and recombinant proteins needed in the cultivated meat industry. For example, a new company called CellCrine claims that its enzyme media additive can reduce the need for growth factors and recombinant proteins by 90% or more, while the company Prolific Machines claims it can grow mammalian cells without the need for exogenous growth factors at all.

Safety and regulatory considerations for growth factors and recombinant proteins (Contributing coauthor: Future Ready Food Safety Hub, Nanyang Technological University)

Ensuring the safety of novel foods such as cultivated meat is paramount to their success in the marketplace. Suppliers of input materials such as growth factors and recombinant proteins must ensure that their product attributes are suitable for use in the cultivated meat industry. Below, we reference existing regulatory documents from the European Union (EU), the United States, and Singapore to help cultivated meat manufacturers and growth factor and recombinant protein suppliers navigate the evolving regulatory landscape.

Regulation of cultivated meat in the European Union

In the EU, cultivated meat is considered novel food and falls under the scope of Regulation (EU) No. 2015/2283 on novel foods, which require pre-market authorization. Where the technology used to produce the food falls under the scope of Regulation (EC) No. 1829/2003 on GM food and feed, the relevant regulation would apply. Cultivated meat as a food item is also subject to the general principles and requirements of the general food law Regulation (EC) No. 178/2002. Regulation (EU) No. 1169/2011 on the provision of food information to consumers also applies.

See guidance on the preparation and submission of an application for authorization of a novel food in the context of Regulation (EU) 2015/2283 (Revision 1) (2021) for more information.

Regulatory oversight of foods comprised of or containing cultivated animal cells in the United States

In 2019, the United States Food and Drug Administration (FDA) and the United States Department of Agriculture - Food Safety and Inspection Service (USDA-FSIS) agreed to establish a joint regulatory framework for foods meant for human consumption made from cultivated cells of livestock and poultry to ensure that products placed on the market are safe and appropriately labeled.

In regulating products derived from cultivated animal cells, FDA will require a pre-market consultation process and inspections of records and facilities. The pre-market consultation process will include the evaluation of the production process and produced biological material, including tissue collection, cell lines, cell banks, manufacturing controls, and all components and inputs.

The first pre-market consultation process was completed on November 16th, 2022, and contains valuable information related to the safety of growth factors in cultivated meat. More information can be found on FDA's website: Foods made with cultured animal cells.

General safety and regulatory considerations in Singapore

As of August 2022, Singapore is the only country where cultivated meat products have been approved for sale.[10] Cultivated meat is considered novel food in Singapore, and its manufacture, import, and sale require pre-market approval. This approval process falls under the purview of the Requirements for the Safety Assessment of Novel Foods and Novel Food Ingredients, published in November 2020 and updated on September 26, 2022 (Singapore Food Agency 2021).

It should be noted that under these requirements, safety is assessed for the final food item on a product-by-product basis. While there is no specific clause addressing growth factors and recombinant proteins used in cultivated meat production, a key requirement is characterizing the composition of the novel food and assuring the safety of all components comprising the food, including any additives or functional ingredients, as well as components used in the culture media and other aspects of production.

Therefore, growth factors and recombinant proteins used at any stage of cultivated meat production are required to be declared and their safety assured at anticipated levels of consumption. Any risk assessment of growth factors and recombinant proteins used in cultivated meat production should be based on appropriate safety data of the protein and estimated consumer exposure in the final product, following similar approaches used for food additives. Evaluation of the purity, sequence analogy to known proteins, toxicity, and allergenic potential are all factors that should be considered in assessing the safety of growth factors.

At this point in time, the requirements for growth factors and recombinant proteins as a component in novel food fall under the requirement for the pre-market approval of novel food. Under this requirement, the purity of the component is an important part of the approval process. However, there are no specified analytical approaches required. It is the responsibility of the notifying company to provide relevant purity data and validation of the analytical methodology.

Growth factors and recombinant protein manufacturers within the biopharmaceutical sector have established standardized Good Manufacturing Practices (GMPs). Growth factor and recombinant protein manufacturers may refer to them to establish their internal quality standards. However, there is currently no guideline, regulatory requirement, or standard for growth factors or recombinant proteins to be used in food production.

[10] Cultivated chicken nugget and chicken breast products manufactured by the company Eat JUST, Inc are currently the only cultivated meat products approved for sale in Singapore or anywhere in the world.

Singapore Food Agency (SFA) has suggested that similar approaches used by the Joint FAO/WHO Committee on Food Additives (JECFA) for ascertaining the identity and purity of enzymes and food additives may be used for growth factors and other media components.

Furthermore, the use of GM organisms to produce growth factors and recombinant proteins also needs to be considered. An individual assessment of the production organism may be required if it is not a commonly used organism with a safe history of use in food production. With respect to the novel food being approved, particular attention will be given to any residual levels of growth factors and recombinant proteins that are present in the final food product.

Use of genetically modified organisms in growth factor and recombinant protein production

In Singapore, the Singapore Genetic Modification Advisory Committee (GMAC) and SFA are responsible for assessing the safety of GM foods to be sold in Singapore. SFA takes reference from the Codex Alimentarius guidelines on conducting food safety assessments of foods produced using recombinant DNA microorganisms (CAC/GL 46-2003). If the GM organism is present in the finished food product, the food would be subject to review by GMAC, and companies may consult SFA to determine if a review is required.

Manufacturers will therefore need to demonstrate there is no GM organism present in the final cultivated meat product if they wish to avoid this review. When

Documentation should be submitted for a safety assessment if GM organisms are used for novel food production. Documentation can include but is not limited to a detailed procedure of the genetic modification process, the genetic stability of the production strain, safety information of the host or recipient strain such as whole genome sequencing and proteomics data, and documentation on the absence of potential hazards to human health. Additional details can be found in the current SFA requirements (Singapore Food Agency 2021).

In the EU, the European Food Safety Authority's (EFSA) guidance on the risk assessment of genetically modified microorganisms (GMM) and their products intended for food and feed use categorizes GMM-derived products into four categories. For products where GMMs that are capable of multiplying or transferring genes are not present (categories 1-3), it is necessary to demonstrate the processes by which the GMM has been removed or inactivated in the product.[11] It should also be confirmed that the product does not contain viable but non-cultivable (VBNC) cells or spores. For categories 1 and 2, it should be demonstrated that no recombinant genes remain in the product.

The marketing of products derived from GMMs is regulated by different legislative instruments within the EU depending on

[11] Growth factors used in food production are not applicable to category 4.

whether they are intended for use in food or feed, and a risk assessment is required prior to the authorization of such a product. Additional details can be found in the EFSA guidance (EFSA Panel on Genetically Modified Organisms (GMO) 2011).

Allergenicity of novel proteins

Because all proteins have the potential to induce sensitization following consumption, assessment of allergenic potential is a key consideration for the safety of new and novel proteins. In the case of proteins that are demonstrated to be the "same as" or "substantially equivalent" to known proteins, regulatory authorities will usually accept equivalence and will treat consumption of the protein in the same manner as the known protein with respect to safety. Determination of equivalence is based on the bioinformatic assessment of sequence analogy and demonstration of conserved function. This is important for growth factors and recombinant proteins since these are typically representative of the endogenous proteins present in farmed animals.

Nonetheless, the company registering a new protein has the responsibility to provide sufficient evidence that demonstrates a lack of allergenic potential. While any protein could be an allergen, research over the past decade has demonstrated that food allergens belong to a rather limited number of protein families and are characterized by a number of similar biochemical and physicochemical properties. Hence, attention should first be given to bioinformatic approaches to compare the amino acid sequence of the growth factor against known allergens for sequence homology and structural similarities.

A number of rules have been developed to determine acceptable limit values for sequence similarity (Ladics and Selgrade 2009). For example, a protein with more than 35% sequence identity spanning a window of 80 amino acids or the presence of an identical hexamer (peptide of six amino acids) compared to at least one known allergen is to be regarded as a potential allergen. Over 2,000 proteins are currently registered with the WHO/IUSI Allergen Database and various other allergen databases, including FARRP, COMPARE, and ALLERGOME. *In vitro* digestion and stability studies may also be requested to determine whether the growth factor or recombinant protein is readily degraded or denatured by digestive enzymes, pH, or temperature and thus unlikely to present a risk of toxicity or allergenicity. In situations where the outcome of bioinformatic analysis suggests the potential for cross-reactivity to a major allergen, additional testing may be requested on a case-by-case basis such as *in vitro* assays with serum or blood cells from sensitized individuals, or in some cases, *in vivo* studies in animals or allergic humans.

The SFA currently requires information on allergenicity or allergen profiling using bioinformatic approaches to be submitted as part of the pre-market regulatory approval for novel foods, including cultivated meat.

Further details can be found in the updated requirements (Singapore Food Agency 2021).

Further information on allergenicity determination can be found in the following documents:

1. EFSA Scientific Opinion on the evaluation of allergenic foods and food ingredients for labeling purposes (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) 2014).
2. Foods derived from modern biotechnology (Joint FAO/WHO Codex Alimentarius Commission 2009).

Discussion

Growth factors and recombinant proteins are components of serum-free cell culture media widely used to support animal cell growth in the cultivated meat industry. However, as illustrated in this report, their use in significantly different quantities corresponds to dramatically different anticipated production volumes and price profiles that will be necessary to support the scale-up of a future cost-competitive cultivated meat industry.

Although cultivated meat manufacturers have made substantial progress in reducing overall media costs (Swartz et al. 2021), much of this cost reduction comes from simply replacing pharmaceutical-grade growth factors and recombinant proteins with food-grade versions. As demonstrated in this report, further cost reductions must be achieved by scaling new production platforms and optimizing yields, downstream processes, and aspects of the product itself.

Across all of the production platforms featured in this report, economies of scale are perhaps the most important lever for cost reduction, but a key variable for reaching scaled production of low-cost growth factors and recombinant proteins will be their demand. In the short term, pooled procurement may be desirable for buyers and suppliers of growth factors and recombinant proteins to aggregate low levels of demand for individual proteins. On longer timescales as demand rises, it may still be difficult to finance facilities that output hundreds of tons of proteins annually many years before the industry will need them.

Accordingly, ambitious cost profiles of $10/kg for albumin, $1000/kg for transferrin and insulin, and $100,000/kg for growth factors will not be achieved overnight. As shown in this analysis, the cultivated meat

industry will need to grow to a certain size,[12] likely in the millions of metric tons, before some of the modeled cost profiles for growth factors and recombinant proteins may be achieved. The market size of cultivated meat will also be dependent on the successful cost reduction and optimizations for other components along the value chain (e.g., bioreactors, amino acids, and other media ingredients). Thus, the scalability of supply chains for input materials and their corresponding cost profiles will be largely dependent on the overall success of the cultivated meat industry in scaling its production and reducing costs more broadly.

Innovations that lead to an overall reduction in the need for growth factors and recombinant proteins will be equally as important to achieving the lower cultivated meat costs that will further drive its adoption. Media recycling systems, protein engineering, encapsulation and slow-release systems, the use of conditioned media, non-recombinant replacements, small molecules, and other novel approaches all offer complementary paths forward. However, many of these ideas remain underexplored and more attention should be given to these whitespace opportunities in the future.

Reducing the overall need for growth factors and recombinant proteins will also affect how new capacity is distributed. Time and cost considerations should be given to the strategic installation of new greenfield infrastructure that will be required to produce the quantities of certain growth factors and recombinant proteins needed for the cultivated meat industry. For example, the production volume range of transferrin detailed in this analysis is estimated to be 300 to 8200 times larger than its current estimated global production capacity (Negulescu et al. 2022). Clearly, new capacity buildout—especially capacity that requires large capital expenditure—will need to be carefully planned. Future studies may aim to analyze the amount, cost, and environmental footprint of the new infrastructure and capacity that will be needed to support cultivated meat industry growth.

The list of innovation opportunities above could not only reduce cultivated meat costs on faster timescales but also enable new recombinant protein manufacturing capacity to be dedicated to other high-value proteins or flavoring molecules for cultivated meat. Given that this capacity will also be in competition with other fast-growing industries that leverage synthetic biology, it will be crucial to plan ahead to lower the risk of future capacity bottlenecks.

Although most safety considerations for novel proteins are well defined based on their prior use in foods, how each growth factor, recombinant protein, or production platform in cultivated meat will be regulated is still under development in many parts of the world. Certain considerations such as how GM organisms are viewed may vary

[12] Some growth factor and recombinant protein suppliers may also dedicate production capacity to the biopharmaceutical, food, and materials industries, where different protein products and downstream purification are tailored to the needs of each given industry.

significantly between regions.

Manufacturers of cultivated meat or suppliers of growth factors and recombinant proteins are encouraged to open dialogue with regulatory agencies in specific markets early in the process to understand region-specific complexities or nuances. Increased international regulatory harmonization and standards for the cultivated meat industry will be an important area of focus in the coming years.

In summary, this analysis serves as a starting guide for researchers and businesses with an interest in developing growth factors and recombinant proteins for the cultivated meat industry. As more information becomes available, this model can be adjusted and refined to more accurately predict the production volumes, costs, expected timelines, and market sizes for the production of these important inputs.

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Partners

The Good Food Institute (GFI) is a 501(c)(3) nonprofit working internationally to make plant-based and cultivated meat delicious, affordable, and accessible. GFI advances open-access research, mobilizes resources and talent, and empowers partners across the food system to create a sustainable, secure, and just protein supply.

Laurus Bio (formerly Richcore Lifesciences) is an integrated research-driven biomanufacturing organization with over 15 years of experience in precision fermentation and recombinant DNA technology. We engineer microbes as factories to manufacture novel and sustainable animal-free proteins for applications in healthcare, food, nutrition, personal care, and bio-based materials markets.

Core Biogenesis is developing the world's most scalable bioproduction platform for the production of recombinant proteins. Its plant-based production technology allows for the mass production of recombinant growth factors for the cellular agriculture industry, at costs reduced by multiple orders of magnitude.

LenioBio is developing the first scalable eukaryotic cell-free expression platform (ALiCE®). ALiCE® provides access to life-changing proteins wherever, whenever. It stands out through its ability to express even the most complex proteins, at any scale and within 24-48 hours.

Future Ready Food Safety Hub (FRESH) The Future Ready Food Safety Hub (FRESH) is a national research & support platform under the Singapore Food Story R&D Programme. Jointly established by Singapore's Agency for Science Technology & Research (A*STAR), the Singapore Food Agency (SFA) and Nanyang Technological University (NTU), the platform aims to build local food safety science and R&D capabilities to support Singapore's goals of reaching 30% nutritional security locally by 2030.