Lever VC Insights

A Second Generation of Cultivated Meat Companies Breaks Through Projected Cost Barriers

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Background

When the world's first cultivated beef burger debuted in 2013 with an R&D price tag of €250,000 R&D, critics immediately questioned whether the technology could ever reach price points that would work. In the years that followed, and even after cultivated meat began to be sold commercially in several countries, such questions remained.

The skepticism of some toward cultivated meat mirrored similar criticism leveled in years and decades past at transformative new technologies in other sectors, such as solar panels and electric vehicles. Sectors such as these faced similar doubts about cost feasibility, complexity, infrastructure requirements, and consumer acceptance. Yet through persistent innovation and significant government support these industries proved doubters wrong. Technologies once deemed impossibly expensive have become mainstream solutions, fundamentally reshaping their sectors and continually setting new standards for cost-effectiveness and sustainability.

In the case of cultivated meat, the most comprehensive research to date doubting the economic viability of cultivated meat came from researcher David Humbird, a private engineering process consultant. With funding from the non-profit Open Philanthropy Project, in 2021 Humbird published a roughly one hundred-page projected techno-economic analysis of large-scale cultivated meat production. Humbird's key conclusion: it was essentially impossible for cultivated meat media costs (the key cost driver in cultivated meat production) to get below $1 per liter, and therefore essentially impossible for total costs of production to go below $16 per kilogram. The Humbird TEA suggests that at scale media costs would likely be around $6.50 per liter, and in the most optimistic scenario $2.50 per liter, with cultivated meat cost of production at least $21 per kilogram.

Shortly after Humbird's lengthy analysis was published, independent news outlet The Counter (now owned by Grist) ran a long-form piece echoing the assumptions and conclusions of Humbird's TEA. In the years that followed, these pieces helped foment an increasing level of skepticism, with the key conclusions reiterated and amplified in mainstream publications such as Bloomberg and the Wall Street Journal.

Multiple cultivated meat companies have blown past the Humbird TEA's projections

While it will be many years if not decades before we'll have a sense of how the cultivated meat sector as a whole will ultimately fare, in the past several years one thing has become clear: the skeptical predictions of Humbird and peers have been proven spectacularly wrong.

Media costs are already up to 10-30x cheaper than Humbird the TEA thought possible
Less than four years after the Humbird TEA (and media outlets citing the independent researcher's projections) estimated that media costs would be roughly $6.50 per liter, and certainly no cheaper than $2.50 per liter, and that there was no way for cultivated meat media costs to get under $1 per liter, today numerous cultivated meat companies are producing cultivated meat using media at costs of $1 per liter or less. Several are under (or well under) $0.50 per liter. In short, it took just four short years for at least some cultivated meat companies to reach media costs up to thirty times cheaper than Humbird's TEA predicted would ever be achieved.

Maximum cell densities are already up to 50% higher than the Humbird TEA thought possible
In addition, several leading cultivated meat companies have demonstrated cell densities between 60-90 g/L, easily surpassing Humbird's projections that the maximum cell density achievable in air-spared fed batch systems was 60 g/L.[1]

Total COGS are already up to 50% lower than Humbird TEA thought possible
The above achievements in reducing media cost and increasing cell density have translated to production COGS for cell mass as low as $10 to $15 per kilogram, with some leading-edge companies achieving costs below $10 per kilogram today. These current-day COGS, as well as media costs and cell densities achieved, have been vetted by Lever VC across numerous companies in the cultivated meat sector.

Easily breaking through the floor of what skeptics thought possible took multiple leading companies in the sector just several years and tens of millions of dollars in spend. This progress was also achieved without any meaningful government support (support that was critical for the cost reductions generated in technologies like solar, electric vehicles, and similar) and without any economies of scale.

Costs are on track to decrease further
While the industry has already achieved remarkable cost reduction milestones, further cost reductions are on the horizon. Companies are employing a range of innovative strategies to continue driving down costs, including:

- Hybrid Products: By blending cultivated meat with plant-based ingredients, companies can reduce the amount of cell mass required while maintaining the desired taste and texture
- Undifferentiated Cell Mass: Focusing on producing basic cell mass, rather than fully structured tissue, simplifies production and lowers costs.
- In-House Media Production: Cultivated meat companies are producing growth factors internally, eliminating third-party pharmaceutical markups and ensuring consistent quality.
- Efficient Bioreactors: Leveraging innovations such as continuous production models and perfusion reactors to increase yields while reducing overall capital expenditure.

A more detailed discussion of these and other strategies that leading cultivated meat companies are using to drive further cost reduction follows below.

[1] Assuming 15 million cells/mL with 20 micron diameter cells

Current OPEX reduction strategies

Second-generation cultivated meat companies are laser-focused on profitability, and consequently demonstrating much more pragmatic process development plans. These plans significantly dial back cultivated meat's original ambitions of making bioidentical meat products, and instead ask what is the minimum but still significantly noticeable value-add that can be generated at the lowest cost, complexity and risk. Additionally, technologies which have already been demonstrated in academia a decade ago have become much more accessible to startups, which are leveraging them for impressive cost reduction gains.

Low Inclusion Ratios

Low-cost cultivated meat products reaching the market first will undoubtedly be in a hybrid format (combining plant-based with cell-cultivated). Companies are using product-specific formulation optimization strategies designed to evaluate the minimum biological mimicry required to achieve the desired organoleptics. Second-generation cultivated meat companies have demonstrated large improvements in the mimicry of plant-based products with the inclusion of cell mass at low tens of percent (mass ratio). An adjacent strategy is to reduce the number of cell types (muscle, connective tissue, fat). Novel replacements for animal fat derived from precision fermentation or functionally modified plant oils can obviate the need for adipocytes, thereby reducing overall production cost/complexity.

Undifferentiated Cell Mass

Animal tissue structure and composition are incredibly complex as they serve to meet biological functions. However, cultivated meat doesn't require biological function; it only needs to deliver the organoleptic properties consumers expect. Interestingly, many of the most commercially viable companies are no longer focused on fully differentiated cell products, but instead on undifferentiated or minimally differentiated cell mass. Since undifferentiated cell mass lacks extracellular matrix, muscle fibers, and other organoleptically important attributes of mature tissue, it works well in hybrid products where the plant-based matrix can fulfill the role of those missing components. Consequently, the inclusion of cell mass contributes to flavor, and in some cases an improved mouthfeel and binding properties for improved texture. Eliminating the need for differentiation improves cultivated meat productivity, saves time, and reduces the overall complexity, risk, and cost. These shifts indicate that the cultivated meat industry is transitioning from early innovation to a more mature phase of growth, with a clearer focus on cost efficiency and scalability.

Directed Evolution

Despite direct genetic modification tools rapidly improving in efficiency and accessibility, a comprehensive framework for identifying and interpreting optimal target combinations remains limited and challenging to navigate. As high throughput screening technologies also become more efficient and accessible, directed evolution becomes an increasingly attractive tool for achieving target phenotypes, especially when genotype-to-phenotype relationships are unknown. Even with rudimentary screening technologies, cultivated meat companies today have managed to demonstrate "spontaneous" immortalization, suspension culture, and adaptation to low-cost growth media containing reduced growth factor varieties and concentrations. These attributes massively reduce OPEX and CAPEX in a variety of different ways. Weeks or months of adaptation may be sufficient for the achievement of a single improved attribute.

Protein Engineering

Protein engineering approaches applied to growth factors can significantly boost potency and stability, thereby requiring lower concentrations to maintain efficiency. Increasing potency is typically achieved by optimizing how well the growth factor's active domain physically fits the binding site of the specific cell receptor. Additional modifications can be made to increase thermal stability for the temperatures and durations of cultivated meat bioreactor runs, which also effectively increases potency over time. While protein engineering requires significant expertise, it can yield large reductions in growth factor requirements. Due to the non-linearity in electrostatic forces, small reductions in distance make large changes to the binding strength of growth factors[2].

Optimized Recombinant Growth Factor Production

Culturing microorganisms is incredibly cheap, as they can easily grow on a number of basic nutrient supplies and equipment. Simultaneously, growth factors are used in very small quantities, thereby alleviating the need for breakthrough productivity and titers as compared to precision fermentation of higher volume and lower value commodities. With the advent of synthetic biology, recombinant protein expression in microorganisms has become widely accessible, enabling companies to achieve fairly decent titers with relatively minimal effort. In-house production removes third-party margins, which can be quite high given the incumbent prices intended for the pharmaceutical industry. The most costly component is the purification system. However, growth factors for cultivated meat don't require pharma levels of purity, so lower grade and less effective purification components (e.g. chromatography columns) can be used or even re-used. This can enable the production of negligible-cost media while requiring minimal resources from cultivated meat companies.

Current CAPEX reduction strategies

With very low media costs now achieved for leading companies in the cultivated meat sector, and a pathway for low operating expenses having been secured, reducing CapEx is the primary challenge that remains for companies to economically scale the production of cultivated meat. While the amortized CapEx costs don't dominate unit economics, utilizing commercially existing pharmaceutical-grade bioreactors and ancillary equipment in a 10 kTA production plant would require hundreds of millions of dollars to build. [3,3] Reducing the CapEx required for large-scale production would dramatically increase the likelihood of such large-scale cultivated meat production being achieved in the nearer term.

Fortunately, leading companies in the cultivated meat sector are using a range of strategies to significantly lower CapEx requirements for commercial cultivated meat production.

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[2] El-Gewely, M. R. Biotechnology Annual Review. (Elsevier, 2003).

[3] CE Delft "TEA of cultivated meat. Future projections for different scenarios." https://cedelft.eu/publications/tea-of-cultivated-meat/

Continuous culture

Continuous modes of production are one strategy that can reduce CapEx by boosting the yield of meat from a reactor's volume basis, without necessitating an increase in cell density or dramatic change in equipment. By reducing the time spent in expanding seed trains across multiple orders of magnitude in cell density, continuous production maintains the reactor at the last order of magnitude in a steady state for the longest possible time by continuously harvesting and feeding cells. This can easily increase cell mass yield by 4-fold per reactor volume basis and in some cases up to 10-fold for high-performance setups with improved cell densities[4,5]. The disadvantage of continuous production is the high level of expertise required for execution and the increased risk of contamination.

The complexity of maintaining high-performance continuous production requires a higher level of in-line monitoring systems to optimize complex time-dependent bioprocess conditions, feeding regimes, and harvesting regimes. Fewer media replenishments over a long time create a better environment for opportunistic and unwanted microorganisms and increase the amount of product that may need to be discarded due to contamination. Today an increasing number of companies are opting for a fed-batch model, which is a good compromise between batch and continuous modes of production. Only a small handful of players are executing fully continuous production modes at the lab scale or working to demonstrate fully continuous production at the pilot scale.

Perfusion reactors

Another way to increase the yield of meat per unit volume without changing the production mode is by increasing cell density. While there are several proposed methods for increasing cell density, including unique media formulations and some lesser-known mechanical interventions, perfusion reactors are the most robust and promising in our opinion. Perfusion reactions require some form of cell retention such that media can be perfused/exchanged in a cell culture. The perfusion of media can dramatically increase dissolved oxygen and mass transport in general (e.g. nutrient delivery) while simultaneously enabling waste product removal. This facilitates a more attractive environment for cells to proliferate, allowing them to reach much higher cell densities.

In static cell cultures, cells can adhere to a matrix and each other, allowing tissue to mature. This process involves producing an extracellular matrix, cell swelling, and the fusion of muscle cells to form long muscle fibers. This can help significantly improve the overall biomass yield in a manner that is less dependent on cell proliferation. Cell densities in perfusion reactors can easily be 5-fold higher and in some cases 10-fold higher in high-performance reactor/bioprocess schemes with static cultures[6,7,8] [15–17]. If the perfusion reactor design enables a static cell culture regime, then the opportunity for creating a structured meat product is present. The disadvantage of perfusion culture is the lack of commercially existing hardware and practicality of

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[4] Pasitka, L. et al. Empirical economic analysis shows cost-effective continuous manufacturing of cultivated chicken using animal-free medium. Nat. Food 5, 693–702 (2024).

[5] SuperMeat's Cultivated Chicken Outperforms Most Efficient Farm Animal in Carbon Footprint Study - Cultivated X. https://cultivated-x.com/meat/supermeats-cultivated-chicken-outperforms-most-efficient-farm-animal-carbon-footprint-study/ (2024).

[6] Watson, E. Israeli startup Ever After Foods addresses 'critical scaling challenge' in cultivated meat: 'We have a huge cost advantage'. AgFunderNews https://agfundernews.com/ever-after-foods-addresses-critical-scaling-challenge-in-cultivated-meat (2023).

[7] Li, X. et al. A conceptual air-lift reactor design for large scale animal cell cultivation in the context of in vitro meat production. Chem. Eng. Sci. 211, 115269 (2020).

[8] Pajčin, I. et al. Bioengineering Outlook on Cultivated Meat Production. Micromachines 13, 402 (2022).

operation for scaled production. Using an external cell retention device is a low-risk option and can be done with some pharmaceutical-grade equipment, however, it has limitations in scale, is very expensive, and doesn't offer the benefits of static culture. A number of companies are now engineering their own reactors by modifying stirred tank reactors or starting from scratch with a complete redesign. The risk and scalability associated with this approach depends on the engineering design itself and execution at large.

Lower-grade manufacturing

Lastly, another viable method for decreasing CapEx is through the modification of existing pharma-grade reactor designs for food-grade needs, largely through the substitution of high-grade stainless steel with a lower-grade alloy or even non-metallic materials such as durable polymers. This requires an alternative solution for clean-in-place and sterilization-in-place to be practical in large-scale production. Additionally, it requires the establishment of a robust manufacturing pipeline for these reactors. There are a small handful of companies exploring this approach and working to demonstrate proof of concept at larger scales.

Additional work on reducing non-reactor CapEx will also be critical with this approach. While the cost of the reactor itself may be reduced by an order of magnitude, the reactor costs still only make up approximately ~30-40% of the total facility costs. Storage tanks, media tanks, and other equipment would need to be (and could be) be manufactured with less-expensive materials.

Conclusion

In just four years leading companies in the cultivated meat sector have driven key costs dramatically lower than the Humbird TEA (and its related media coverage) deemed possible. These key achievements include:

- **Media Costs:** Leading cultivated meat companies have reduced media costs to below or well below $1/L, translating to well under 8 USD/kg in contribution to cell mass, surpassing by an order of magnitude Humbird TEA's projections of what was possible in even the long run.

- **Cell Density:** Leading cultivated meat companies have been able to improve cell density significantly beyond the Humbird TEA projected max of 60 g/L[9], demonstrating 60-90 g/L densities, which increases product output yield proportionally.

- **CapEx:** Leading cultivated meat companies' expected CapEx numbers have been reduced by nearly an order of magnitude as companies get smarter about how and where to manufacture their bioreactors, including through avoiding off-the-shelf pharmaceutical-grade materials.

While there is major company-to-company variance in the cultivated meat space, leading companies are progressing quickly on cost reduction. This trajectory, and the speed at which leading companies have blown past the price floors predicted by skeptical TEA's such as the Humbird TEA, reaffirms the promise of cultivated

[9] 15 million cells/mL with 20 micron diameter cells in air sparged fed batch operations

meat as a transformative solution in food production with sustained efforts toward overcoming the remaining cost hurdles.