Stirring the pot: Bioreactor breakthroughs

Central to the realm of cell-based meat are bioreactors – engineered systems that are pivotal in scaling up cellular agriculture processes from laboratory to commercial production. These fermentation tanks provide a controlled environment where cells derived from animal sources can proliferate and differentiate into muscle, fat and other tissue types. In this feature, *The Cell Base* unpacks the latest innovations in bioreactor technology that are poised to stir up the sector.

Bioreactors play a crucial role in mimicking the natural conditions essential for cell growth, regulating factors like temperature, pH levels, oxygenation and nutrient supply. In the cultivated meat sector, bioreactors are a relatively new technology. Originally adapted from pharmaceutical and biotech industries, early bioreactors were small-scale and designed for controlled laboratory environments, not large-scale cultured meat production.

"Though widely used, [bioreactors] fall short in terms of scalability and efficiency for cell-based meat production," Illtud Dunsford, CEO of cell-based meat start-up Cellular Agriculture, explained. "They often result in higher costs and slower production cycles, which don't align with the industry's growth trajectory or sustainability goals."

As the sector has evolved and scaled up to meet commercial demands, there has been a shift towards developing bioreactors that are specifically tailored for cultivating meat. Bioreactor manufacturers and companies in the cell-ag sector are now focusing on designing larger-scale bioreactors that address the unique challenges of producing meat from cultured cells more efficiently and sustainably.

On the next page, we highlight some of the key players introducing innovative bioreactor technologies to the cell-based space.

Modern bioreactors are now engineered with features that optimise cell growth:

- New bioreactors are larger and capable of accommodating greater volumes of cell cultures compared to their predecessors. Sizes have evolved from tens of litres to bioreactors exceeding 250,000 litres available today.
- Bioreactors are now designed with features that cater specifically to the needs of cultivated meat cells, including systems for precise control of temperature, pH, oxygen levels and nutrient delivery.
- Advances in automation technology have been integrated into bioreactors, allowing for more efficient operation and reducing the need for constant manual oversight. This automation helps in maintaining consistent conditions throughout the cell culture process, enhancing overall productivity and reducing labour costs.
- Bioreactors used in cultivated meat production are designed to meet stringent hygiene and sterility standards to prevent contamination and ensure the safety and quality of the final product.
- Manufacturers now offer bioreactors that can be customised to meet the specific requirements of different types of cultivated meat cells, allowing companies to optimise their processes for different product formulations and market demands.

The Cultivated B

The Cultivated B (TCB), a subsidiary of Infamily Food, Germany's second-largest animal-based sausage manufacturer, was founded after analyses of upstream processes and bottlenecks in cultivated meat production revealed that key tech was missing.

"Bioreactors were predominantly designed for pharmaceutical use and capacity demand massively exceeded available supply, contributing to long delivery times and increased costs," CEO Hamid Noori explained. "We focus on fit-for-purpose machines that are affordable, easy to operate and designed with an emphasis on rapid delivery."

In July last year, the company signalled that its Auxo V industrial-grade bioreactors were ready to start rapid-delivery manufacturing at its plant in Burlington, Ontario, Canada. TCB said that while bioreactor delivery times from other vendors can be as much as two years, its delivery times were only a few weeks. Months later, in November, TCB introduced its new bioreactor monitoring and control software, set to 'revolutionise' bioprocessing with user-friendly, remote capabilities.

"The software delivers cutting-edge remote and direct monitoring control for any bioprocess and is engineered for precision, efficiency and scalability – allowing for robust data and parameter

management," Noori continued. "Pre-programmed recipes for all sorts of hosts further enhance automation of the process and usability by anyone."

The software enables the bioreactors to be customised by the user. "In the case of cultivated meat, you can for example choose between recipes for cow, chicken and fish cells," Noori added. "We have assessed and pre-installed all relevant parameters for the selected cell cultivation. As a result, the person who operates the bioreactor does not require a scientific background, allowing the food industry to access this technology more easily."

FermenteQ

Canada-based specialist manufacturer of custom bioreactors and fermenters, FermenteQ, has made significant strides in enhancing the control systems within its bioreactors. The firm integrates advanced sensors and automation features that allow for precise manipulation of the bioreactor environment.

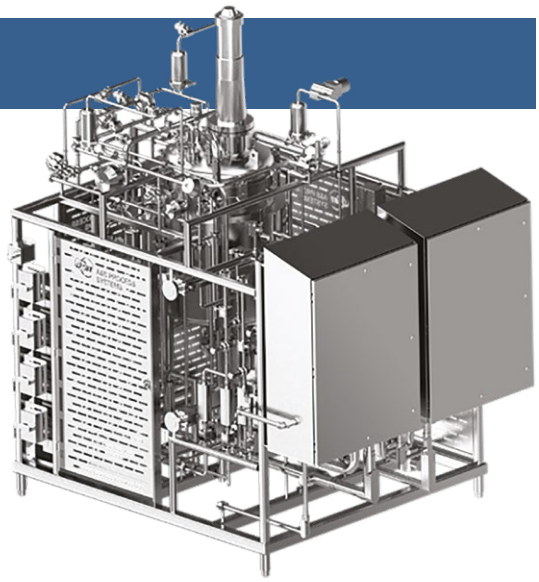
These advancements help maintain optimal growth conditions, thereby increasing yield and reducing production costs. The company's focus has also been on improving energy efficiency and system modularity to support scalable operations from lab to industrial scale.

"What sets our bioreactors apart is the integration of our software system, which brings high levels of automation and precision monitoring to the bioprocesses," Srinivas Reddy, president and CEO of FermenteQ Innovations, pointed out. "Our software is tailored to meet our clients' specific needs, offering features

that are fully automated along with thorough validation capabilities."

"This software ensures precise monitoring of all bioprocess parameters and integrates AI technology to dynamically adapt to changes, guaranteeing consistent quality and efficiency. This level of customisation and technological integration, along with cybersecurity features, provides our clients with a competitive edge in the rapidly evolving field of cell-based manufacturing." ►

A&B Process Systems



JBT-owned A&B Process Systems designs, builds, automates and installs stainless steel process systems for various industries. The company can adapt these process systems for bioreactor technology in the cultivated meat industry.

A&B's bioreactor designs are robust and adaptable, specifically engineered to optimise production efficiency and maintain product integrity. They integrate advanced control systems and scalable configurations, tailored to meet the precise needs of large-scale cultivated meat production.

"Designed to reduce the historically high cost of capital expense associated with cell culture bioreactors, our ReadyGo bioreactor meets the necessary needs of the cell-based meat market without unnecessary added expenses," Dave Mitchell, JBT's product line director of pharma and life sciences, told *The Cell Base*. "We designed this platform specifically to allow customisation and tailoring of the features based on a client's specific requirements for cultivated meat products."

A&B manufactures its own vessels, performs its own process piping and develops and integrates its own controls. "As a result, we are constantly honing our skills in all areas of our operations and maintaining our certifications and compliance with global standards organisations, including the American Society of Mechanical Engineers, the US Department of Agriculture and the US Food and Drug Association," Mitchell said.

Cellular Agriculture

Cellular Agriculture, founded in 2016 as the 'UK's first' cell-based meat start-up, designs capital-efficient bioreactors and bioprocess technologies. The company's approach utilises hollow fibre membrane technology and is specifically designed to address the gaps in the market.

Hollow fibre membranes consist of small, tubular structures with porous walls that allow for the exchange of gases, nutrients and waste products between the culture medium and the cells. This design mimics the natural extracellular matrix found in tissues, providing a conducive environment for cell attachment and growth.

"By applying principles of tissue engineering, our bioreactors are designed to efficiently replicate the body's vascular system, creating an environment that nurtures cell growth more naturally and effectively," Dunsford highlighted. "Our bioreactors are engineered to significantly lower both capital and operational expenditures, enabling our clients to scale production effectively and bring products to market more quickly."

As well as performance, Cellular Agriculture's focus is on designing equipment for user-friendly operations that is as universal as possible with respect to cell types, from species to phenotype.

User-friendliness requires focus on the design of hardware, the software and particularly how these aspects interface with the user. "We have made large strides in testing our systems with non-expert users," Dunsford added. "A combination of robust, simple operating protocols and automation are helping us deliver this."

Another design aspect Cellular Agriculture is working on is how it can support retrofitting into existing bioprocesses. "Many of our customers are struggling with yield and quality in stirred tank systems, but often have already made sizeable investments in vessels and ancillary equipment. Our aim is to be able to fit our system into their facility with as much common ground as possible, being complimentary to their existing ways of working whilst minimising costs of overhauling their process."

Pluri

Israeli biotech firm Pluri identified a critical gap in scalable adherent cell production technologies. This drove the development of its advanced bioreactor systems, specifically designed with scaffold and packed bed configurations. These innovations create a conducive 3D environment for cell growth, enhancing productivity and quality across various cell types.

In the context of bioreactors for cultivated meat production, a packed bed typically consists of scaffold materials that provide a substrate for cell attachment and growth. These scaffolds are arranged densely within the bioreactor, allowing for efficient use of space and optimal interaction between cells and the growth medium. The packed bed configuration helps to maximise surface area for cell adhesion and nutrient exchange.

Pluri's proprietary bioreactor system provides a 3D micro-environment for cells that can mimic various cell growth environments using scaffolds in a packed bed bioreactor. When the cells adhere to the scaffolds, they extract extracellular matrix components and expand rapidly, transforming into products and solutions.

"Since the cells are attached to scaffolds, we created a design of packet bed flow chambers connected to a feeding bioreactor," a spokesperson for Pluri told *The Cell Base*. "The flow to each chamber is controlled in order to maintain low shear and laminar flow allowing us to preserve the cells' quality."

"In this design, we can scale the feeding bioreactor to any size, apply the needed forces for mixing and homogenisation, and connect it to several flow chambers. This design leads to the ability to scale the system to different industries, including the cultivated meat sector." ▶

Ever After Foods

Ever After Foods, a subsidiary of Pluri, has emerged as a trailblazer in the cultivated meat industry, leveraging Pluri's bioreactor technologies for scalable and efficient production. Founded as a strategic partnership between Pluri and Israel's largest food producer Tnuva Group, Ever After Foods has developed a bioreactor system tailored for natural cells.

The start-up uses edible plant-based scaffolds within its bioreactors, maximising cell attachment and proliferation and achieving 'unparalleled' efficiencies in meat production.

"The scaffolds are packed in columns and can be sterilised and seeded inside the bioreactor in a scalable way," CEO Eyal Rosenthal pointed out. "As these scaffolds are very porous with a high surface-to-volume ratio, we've been able to create an ideal environment for efficient cell attachment and proliferation."

He continued: "By ensuring natural biological conditions for natural cells, we can advance tissue formation and cell differentiation to yield more nutritional- and flavour-value from cells. In fact, we can get 6x more protein and 25x more collagen from a cell before differentiation. Upon cell differentiation, we can get 80x more muscle-related proteins and 700x more lipids."

Ever After Foods' edible-packed bed bioreactor is said to facilitate the production of cell-based meat at an extremely high scale. "While the cultivated-product-to-bioreactor-working-volume ratio for stirred-tank is limited to only 2-5%, our system can produce inefficiencies of 40-50%," Rosenthal highlighted.

This is because cultivated meat is solid and sensitive to shear stress. When increasing the solid phase in stirred-tank bioreactors, the stirring mechanics are no longer effective and can damage the cultivated product.

"In our system, the cultivated meat products are fixed and decoupled from the media, thus protecting them from mechanical stresses generated by any agitation," Rosenthal added. "With such efficiencies, our current pilot system produces more than 10kg of cultivated meat from only 25 litres of edible-packed beds."

GEA

GEA, one of the world's largest tech suppliers for food processing, has made its foray into the realm of cell cultivation. "The move is a strategic extension of GEA's core competencies," Frederieke Reiners, the company's VP of new food, told *The Cell Base*. "The initiative harnesses our comprehensive in-house technology portfolio and extensive experience in processing food and beverages at the highest levels of food safety and efficiency."

This allows GEA to offer manufacturing customers essential support in product development and scaling up to industrial levels. GEA's bioreactor designs are distinguished by their focus on regulatory compliance, scalability and operational efficiency.

Tatjana Krampitz, GEA's head of technology management for new food, discussed the challenges faced when designing bioreactors for cell-based applications. "These particularly arise due to the shear sensitivity of cells and the critical need for maintaining uniform conditions throughout the culture environment," she explained. "At GEA, we address these complexities through our 'GEA Virtual Bioreactor Testing' using advanced computational fluid dynamics modelling in a digital twin, combined with decades of experience in designing bioreactors for mammalian cell applications from the pharma business."

"Our highly specific and accurate process control systems play pivotal roles in managing and preventing gradients of concentration, pH, dissolved oxygen and temperature," Krampitz continued.

GEA opened its New Food Application and Technology Center of Expertise in Hildesheim, Germany, last year. The centre has space for customers to conduct proof-of-concept tests before investing in industrial systems. This facility supports the transition from lab to pilot plant and is designed to optimise process conditions through virtual bioreactor testing.

GEA also employs software mitigation strategies that ensure continuous operation, preventing the loss of entire batches if a component fails. Its fully automated bioreactor systems minimise manual supervision, reduce production costs and enhance response times through remote monitoring and alerts sent directly to the mobile devices of controlling personnel.

Krones

Germany-based firm Krones designs, develops, manufactures and installs machines and lines for the food processing, filling and packaging industries. Leveraging its technical knowledge in fermentation, the firm has developed various specialised bioreactors.

Krones uses a circulation system instead of a traditional agitator in its bioreactors. This system is designed to maintain a sterile environment while minimising shear forces, crucial for cell culture survival. The circulation system, equipped with aseptic valve technology and low-shear pumps, ensures that cells are evenly distributed and adequately supplied with nutrients, enhancing cell vitality and proliferation.

The company's holistic approach to plant engineering includes considerations for downstream processes, such as cell harvesting and purification. By integrating these processes seamlessly, Krones ensures that the entire production line operates efficiently, reducing downtime and production costs.

The evolution of bioreactor technology from small, generic designs to larger, specialised systems tailored for cultivated meat reflects the industry's maturation and marks a pivotal advancement in the scalability and efficiency of cell-based meat production. From tailored designs that mimic natural cell environments to advanced automation and control systems, start-ups and legacy companies alike are pushing the boundaries of what is possible in bioprocessing.