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Scientific, sustainability and regulatory challenges of cultured meat

Mark J. Post[1,2]✉, Shulamit Levenberg[3,4], David L. Kaplan[5], Nicholas Genovese[6], Jianan Fu[7], Christopher J. Bryant[8], Nicole Negowetti[9], Karin Verzijden[10] and Panagiota Moutsatsou[2]

Cellular agriculture is an emerging branch of biotechnology that aims to address issues associated with the environmental impact, animal welfare and sustainability challenges of conventional animal farming for meat production. Cultured meat can be produced by applying current cell culture practices and biomanufacturing methods and utilizing mammalian cell lines and cell and gene therapy products to generate tissue or nutritional proteins for human consumption. However, significant improvements and modifications are needed for the process to be cost efficient and robust enough to be brought to production at scale for food supply. Here, we review the scientific and social challenges in transforming cultured meat into a viable commercial option, covering aspects from cell selection and medium optimization to biomaterials, tissue engineering, regulation and consumer acceptance.

Cultured meat aims to resolve problems related to industrial livestock farming by circumventing some of its undesirable consequences[1]. The Intergovernmental Panel on Climate Change stated the need to substantially reduce our consumption of conventional animal products to avoid the worst effects of climate change, yet most consumers are not willing to do so[2]. Harnessing the potential of stem cells to multiply and form skeletal muscle and fat tissue could lead to a vast reduction in the amount of livestock needed to produce meat. Advantages of cultured meat broadly fall into three categories: sustainability, animal welfare and public health.

In terms of greenhouse gas emissions, water consumption and land use, cultured meat is anticipated to be far more efficient than conventional meat[3–5]. However, cultured meat production might be more energy intensive[3,4], and so some environmental benefits are dependent on a transition to clean energy sources[6]. Cultured meat presents advantages in terms of animal welfare[7] — the Sentience Institute estimates that 99% of animals used for food are factory farmed and considered to be industrial products rather than sentient beings[8]. There are substantial public health benefits from cultured meat production. Conventional meat is the most common food source of potentially fatal infections, such as *Salmonella* and *Listeria*[9]. The production process for cultured meat guarantees the absence of contaminants and antibiotic use during cultivation. Antibiotic abuse in agriculture is a large problem that is contributing to antimicrobial resistance in human pathogens[10,11]. Livestock meat production requires an estimated 70% of arable land to be used for growing livestock feed[12]. With an anticipated 70% increase in global meat demand, we will have insufficient planetary resources to provide meat to the world population by 2050.

What is cultured meat?

Cultured meat aims to replicate conventionally produced meat through (stem) cell and tissue culture. This idea is not new, and was first referenced in utopian literature from the nineteenth century[13]. Originally coined as 'in-vitro meat', as the cells and tissue are cultured in vitro, the nomenclature of cultured meat is still a subject of debate. Up to now, 'cultivated meat', 'cultured meat', 'cell-based meat' and 'clean meat' are the most prevalent names among proponents of the technology. Although some institutions represented by the authors favour a different name, for the purpose of this Review Article we use 'cultured meat'. We use 'cell-based meat' only when describing the US regulatory landscape as it is the US legal text preference. Culturing meat is part of a novel industry referred to as 'cellular agriculture', that is, using cell-based biotechnology to replace traditional animal-derived products such as meat, seafood, leather and milk.

The discovery of stem cells enabled in-vitro cell production and opened up the possibility of cultured meat. Stem cells can be isolated from a biopsy from a living animal[14] and expanded in vitro to generate a large number of cells. Subsequently, the cells can be stimulated to differentiate into muscle or fat cells, depending on the isolated stem cell type. Tissue-engineering techniques, typically involving a biomaterial scaffold that gives temporary or permanent support and three-dimensional organization of the cells, lead to the assembly of a tissue that is anticipated to resemble meat in its sensory and nutritional qualities as closely as possible. In theory, one can approach mimicry of meat in different ways, ranging from single protein production of individual muscle proteins to fully fledged tissue engineering of a complex muscle tissue containing muscle, fat, blood vessels, nerves, fibrous tissue and perhaps resident immune cells, in a meat-like architecture (Fig. 1). The generation and assembly of multicellular muscle fibres and fat organoids into a minced meat product lies in between these extremes. This Review Article focuses mostly on tissue-engineered meat as this method is most commonly employed by investigators and startup companies, it is the most scientifically comprehensive process and it enables the production of a meat copy, resulting in a final product that contains mature muscle fibres.

[1]Department of Physiology, Maastricht University, CARIM, Maastricht, the Netherlands. [2]Mosa Meat B.V., Maastricht, the Netherlands. [3]Department of Biomedical Engineering, Technion, Israel Institute of Technology, Haifa, Israel. [4]Aleph Farms Ltd, Ashdod, Israel. [5]Department of Biomedical Engineering, Tufts University, Boston, MA, USA. [6]Memphis Meat, Berkeley, CA, USA. [7]PAN-Biotech Ltd, Aidenbach, Germany. [8]University of Bath, Bath, UK. [9]Harvard Law School, Cambridge, MA, USA. [10]Axon Lawyers, Amsterdam, the Netherlands. ✉e-mail: m.post@maastrichtuniversity.nl

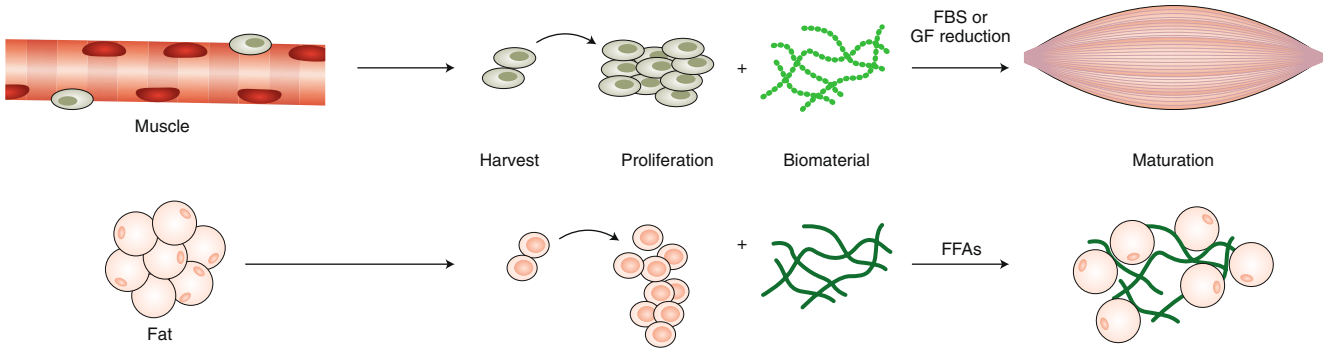

Fig. 1 | The concept of cultured meat. Stem cells are harvested from mature muscle tissue and adipose tissue precursors and expanded. Mature muscle fibres and pieces of adipose tissue are formed and matured using a gel biomaterial and a specific differentiation protocol. Muscle maturation occurs in the presence of medium with reducing concentrations of fetal bovine serum (FBS; from 20% to 2%) or equivalent serum-free differentiation medium with reducing concentrations of serum-supplementing growth factor (GF) mix (tenfold reduction). Adipose-tissue-derived stem cells mature in the presence of free fatty acids (FFAs).

Cell selection

The biomanufacturing process begins with one or more starting cell populations. The starting cell population may be homogeneous or exhibit heterogeneity. Although meat is a complex tissue, current thinking is that skeletal muscle cells and adipocytes are the minimal necessary components of cultured meat. The suitability of the starting cells is based on their capacity for self-renewal and differentiation in an environment where other animal components, such as serum, are minimized or eliminated.

Self-renewal is defined by a cell's ongoing ability to replicate and proliferate while retaining its potential to differentiate in one or more tissue lineages. Embryonic stem cells (ESCs), also known as pluripotent stem cells, are one type of stem cell that can differentiate into any tissue[15]. During embryonic development, ESCs give rise to progeny that lose pluripotency. For instance, so called mesenchymal stem cells (MSCs) have limited differentiation capacity but can still form bone, cartilage and adipose tissue. The progeny cells can remain quiescent in tissues as an adult stem cell, or can contribute to a developing or regenerating tissue as a transit amplifying cell[16] in a process called asymmetric division. Prior to terminal differentiation, amplifying cells proliferate quickly and extensively into post-mitotic cells that form most of the mature functional tissues with limited replicative capacity. The use of cells from various stages of stem cell development has been proposed for cultured meat manufacturing[17,18]. Here, the suitability of a given stem cell type for meat production will be evaluated with respect to its capacity to expand and differentiate into skeletal muscle, the predominant constituent of most meats. Similar considerations also apply to the adipocyte lineage.

Satellite cells, the adult stem cells of skeletal muscle, constitute the most accessible myogenic progenitor in skeletal muscle tissues and require little input to differentiate into skeletal myotubes. The amplifying progeny of satellite cells, called myoblasts, were used to create the first cultured meat hamburger prototype[14]. Myoblasts propagate rapidly and exit the cell cycle as spindle-shaped myocytes, which fuse with multinucleated myofibres during tissue repair and development[19]. Satellite cell culture protocols — especially myoblasts — require substantial optimization to increase their proliferative capacity for adaptation to industrial-scale cultured meat manufacturing applications[20].

Satellite cells inherit their tendency to mature as type-specific skeletal muscle fibres from their originating tissue[21]. Broadly speaking, red meats constitute oxidative slow-twitch skeletal muscle fibres and white meats are composed of glycolytic fast-twitch fibres — so the muscle of origin is an important consideration. Starting cell purification can be aided by relatively simple differential adhesion protocols or by fluorescence-activated cell sorting (FACS) on the basis of biomarker characteristics[22–25]. Industrial manufacturing of cultured meat at a scale sufficient to satisfy commercial demand heavily relies on cell propagation, starting in small planar culture system, followed by volumetric expansion in a seed train and finally product maturation in large bioreactors[26,27]. As transient amplifying cells, myoblasts can only undergo a finite number of doublings and gradually lose their differentiation capacity. Therefore, efficient biomanufacturing could benefit from retaining satellite cells in their stem cell stage, with an indefinite replicative capacity, until these calls are required to differentiate into muscle fibres. This renewal potential can be extended in vitro by inhibiting the cell signalling pathway p38-MAPK (ref. [22]), theoretically enabling mass expansion of satellite cell populations. On withdrawal of p38-MAPK inhibition, the native differentiation capacity of the satellite cells is restored. Similar interventions might lead to a more efficient use of satellite cells taken from a single biopsy. In our hands, a 0.5 g biopsy results in a yield of 10,000 cells. Calculations show that 30–40 doublings are required to get a meaningful multiplication factor for scale up. This is well below the empirical Hayflick limit of 50 doublings for diploid cells[28].

Functional immortalization may provide another approach to extend the replicative capacity of skeletal muscle cells for industrial-scale expansion. For over four decades, differentiation-competent immortalized skeletal muscle cell lines have served as model systems in skeletal-muscle-biology research. Isolated from rat[29] or mouse[30] model organisms and spontaneously derived through consecutive passaging, these cell lines lack a species identity that is culturally acceptable for producing meat for human consumption[7]. Although a myogenic quail cell line exists, the ability of this cell line to form mature myofibres is severely impaired[31]. Targeted genetic approaches developed for functional immortalization of human skeletal muscle cells[32] adapted to cells from traditional livestock species may provide an alternative source for industrial biomanufacturing of cultured meat[33]. Unlike satellite cells, ESCs and induced pluripotent stem cells (iPSCs) have an indefinite renewal capacity as their early commitment to specific tissue lineages is inhibited. iPSCs are derived by reprogramming cells isolated from somatic tissues to the pluripotent state through directed expression of a combination of transcription factors, often including POU5F1, SOX2, KLF4 and MYC (ref. [34]). Human and mouse models have constituted most of the research and development reported on pluripotent stem cells to date. These findings therefore still require translation to livestock species[7]. ESCs and iPSCs from agriculturally relevant ungulate species, such as pigs and cows, have recently been successfully derived and characterized[35–38], while the

derivation of bona fide ESCs or iPSCs from avian species, namely chicken, remains elusive. Established culture conditions can support stable long-term culture of pluripotent cells derived from the avian blastoderm, and attempts to derive avian iPSCs have resulted in partially reprogrammed cell lines[39].

Protocols for differentiating pluripotent stem cells to skeletal muscle have taken numerous approaches with varied results. One approach relies on culture regimens of growth factors and small-molecule inhibitors to direct cells from the pluripotent state toward the myogenic lineage[40]. An alternate approach employs conditional activation of ectopically expressed transcription factors to program cells to a myogenic lineage from a progenitor state. The latter approach is reported to derive myogenic cells and direct their differentiation in a more efficient manner[41] — a variation of this programming approach was demonstrated to result in contractile myotubes in a porcine iPSC model[42]. There is a strong precedent for the derivation and maintenance of pluripotent stem cells in serum-free[43,44] and animal-component-free cell culture medium[45], as well as cultivation of these cells in a carrier-free suspension environment[46,47] — features that would greatly facilitate industrial-scale production. However, societal and regulatory concerns around the combination of genetic modification and cultured meat should be addressed (see European Union (EU) regulation below).

These advances open up distinct and promising avenues for the manufacture of cultured meat. With technologies for cultured meat production rapidly evolving, it is likely that multiple stem cell paradigms will find applications in industrial manufacturing based on the advantages inherent to their respective biology.

Cell culture medium

The predicted scale of cultured meat production requires resource efficiency (feedstock, water and power usage), scalability and cost considerations. The cost of cell culture medium has been identified as one of the major cost drivers during upscaling of stem cell production[48].

Substrate availability and concentration are key parameters[49] in the optimization of the overall yield of the metabolic reaction network towards a more efficient biomass production. Mammalian cells can show inefficient consumption of carbon, nitrogen and energy sources and overproduction of metabolic byproducts, such as lactate and ammonium[50]. To mitigate this, fed-batch or perfusion processes can be used, which can increase cell density 3.4-fold (ref. [51]) and result in a more effective metabolism, perhaps due to lower concentration fluctuations of substrate or metabolites. Alternatively, media composition can be optimized to drive metabolic pathways, which has been used to successfully optimize medium for cell lines to produce pharmaceutical products[52–54].

Besides productivity, media composition will define the final characteristics of the cultured meat product. In the livestock industry, factors such as climate, nutrition and stress define the final meat product. For example, it has been suggested that acidosis caused by rapid glycolysis leads to degenerative changes in muscles, which are solitary and rich in type II fibres[55–57]. Affected muscles show undesired characteristics, such as being pale, soft and exudative[58]. In cell culture, highly proliferating cells can metabolize more than 70% of the glucose to lactate — with associated acidosis — leaving only 20%–30% of the glucose available for tricarboxylic acid (TCA) cycle[59]. Nutritional deficiencies, such as lack of vitamins, cause degenerative changes in muscle, as indicated in the case of vitamin D[60], vitamin E and selenium[58].

The medium for proliferating cells needs to be different to that used for differentiating cells as primary metabolic activity changes from energy and general nutrient usage to highly specialized protein production. With more complex tissues, that are composed of muscle and fat tissue for instance, different media compositions will again be required.

Cell culture media present a challenge for sustainability. Animal-derived components, including fetal bovine serum (FBS), introduce contamination risks and undefined substances and violate the ethical principle of using fewer animals — and they are unsustainable. FBS is a universal supplement, containing 200–400 different proteins and thousands of small-molecule metabolites in undefined concentrations, so full replacement with defined components can only be achieved at high cost. Most commercially available products show either lower performance or are suitable for a limited number of cell lines. Developing cell-specific media may be more cost effective as the only components included in the formulation will be those necessary for that specific cell line, and FBS can be replaced by chemically defined components, such as proteins, growth factors, sugars and fatty acids, according to established strategies[61]. Growth factors are essential — they regulate cellular activities, including stimulation of proliferation and differentiation, by activating signalling pathways. The most commonly used growth factors for adult stem cells are bone morphogenetic proteins (BMPs), epithelial growth factor (EGF), fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), while insulin-like growth factor (IGF) and platelet-derived growth factor (PDGF) are also required for primary cells. For muscle tissue, hepatocyte growth factor (HGF), IGF, PDGF and FGF are considered relevant[62]. The disadvantages of growth factors, such as high cost and instability, can also be compensated or reduced by using small molecules (<1,000 Da). However, there remains a lack of knowledge around muscle-specific signalling pathways and safety for use in food production, and the optimal dosage data for in-vitro myocyte cultivation still needs to be established[62]. Commercially available growth factors are mainly produced with research grade or cGMP standards for applications in drug discovery and production of bioactive or therapeutic products. Matching the standard of quality to the food industry — combined with more effective expression platforms and cell culture media — will be the most important strategies to reduce growth factor production costs.

Components that need to be present in high concentrations, such as glucose and amino acids, will have a strong impact on the environmental footprint of the process. Amino acids are most effectively produced through fermentation[63], mainly using glucose as substrate. The industrial production of glucose is well established, with little waste production and a high level of integration: 57% of the electricity and 59% of the heat input are produced by a combined heat and power system[64]. This is based on hydrolysis of a raw material such as starch, which is naturally produced by plants through photosynthesis and therefore requires the use of land and water. To achieve media with the lowest environmental footprint, ingredients need to be sourced and dosed cautiously. Alternative sources of amino acids and peptides, such as biomass from algae and certain bacterial cultures, could provide cheap sources of enriched amino acids, fats, vitamins and minerals, and also offer opportunities to couple cultured meat production with other sustainable processes such as waste treatment or CO_2 capture[5,65–69]. Furthermore, culture media recycling has been increasingly investigated for cell culture processes, and a strategy has been successfully demonstrated in bacterial and algae cultures with promising results respective to cost reduction and extended batch duration[70–72]. In combination with perfusion, this approach could significantly minimize the use of sterile purified water, which is an energy-intensive resource. However, medium recycling has not yet been applied to mammalian cell cultures.

Metabolic engineering will increasingly rely on constraint-based modelling and flux balance analyses that have been widely applied to predict and quantify the metabolic state of cells[73,74]. Multi-omic flux balance analysis can help to predict flux distributions in a more reliable way based on limited experimental data due to comprehensive crosslink of multiple omics[75]. Metabolic modelling will be

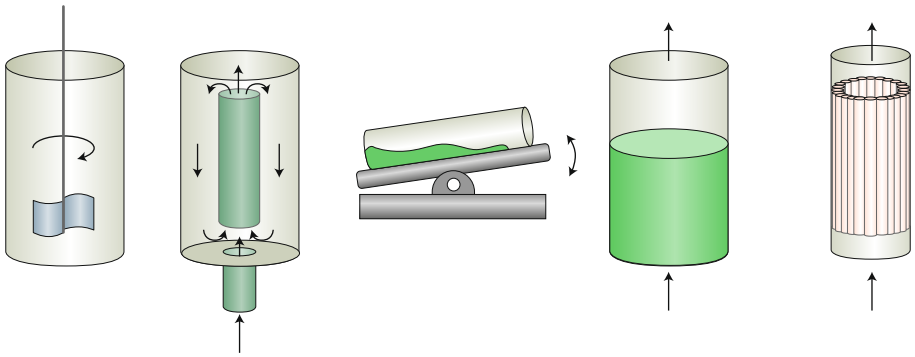

Fig. 2 | Most common bioreactor designs for mammalian cell culture. Left to right: stirred tank, airlift, rocking/wave, fluidized bed or fixed/packed bed, and hollow fibre.

a powerful tool to predict not only the functional state of cells, but also optimal nutrient formulations for cell growth in vitro. In the future, interactions between genome and metabolites using association mappings[76] will probably improve objective and comprehensive function (not only growth maximization) for modelling[77–81]. However, to effectively validate and employ these methods, quantitative information on metabolic pathways and deep knowledge of the effect of a huge number of medium components and their synergies are required. To add complexity, this input will probably be species- and cell-type specific. In such a multivariable field of research, large amounts of data are required to support the optimization of experimental and manufacturing processes.

Scaling up, bioreactors and automation

For cultured meat to become a viable alternative to traditional meat, production has to be scalable and economical. The specifics of scaling depend on the final intended product and the number of doublings the stem cell can sustain. For a minced product, the scaling is different than for a full-thickness meat product. This is especially true for the final stage of the organoid or tissue production.

Cell production will probably be similar as long as the cell and tissue production phases are separated — a seed train, within a series of bioreactors of increasing volume, enable cell upkeep in a proliferative state. This generates the required number of cells for manufacturing while minimizing the required feedstock, materials and culture manipulations. The seed train is used to expand from the initial harvest number, which is typically in the order of 10^4 cells to the desired batch amount, in the range of 10^{13} cells, to create 1 ton of cultured (muscle) meat. Seed train optimization aims to maintain the cells in an exponential growth state while preventing them from precocious differentiation, and is highly dependent on cell type[82,83]. Therefore, the initial culture is performed in regular culture dishes or flasks, and as cell number grows, the culture is gradually moved to bioreactors with controlled conditions such as temperature, pH and dissolved oxygen and carbon dioxide.

Bioreactors. Bioreactors offer scalability, controllability and higher achievable cell densities than planar systems[84,85]. The most commonly used bioreactors are stirred tanks and rocking bioreactors (also known as wave bioreactors). Alternate bioreactor configurations include perfused fixed- and packed-bed reactors and hollow fibre, air-lift, vertical-wheel and fluidized-bed bioreactors, but also novel operation modes of the stirred-tank and rocking bioreactors[26,86].

The industry standard for mammalian cell bioreactors are stirred tanks where cells are either in suspension or attached to microcarriers suspended in the agitated medium[87]. Most mammalian cells are anchorage dependent, so microcarriers provide a suspension surface for the cells to grow. Cell suspensions are beneficial because of higher achievable cell densities and ease of harvesting. Similar to MSCs, bovine myoblasts can be expanded on microcarriers in suspension[88]. Recent developments show some success in modifying iPSCs so that they can grow in aggregates[46,89], similar to earlier achievements in ESCs from mice[90] and humans[91,92]. More committed stem cells, such as MSCs, can form aggregates and grow but the aggregate size is hard to control[93], leading to unpredictable cell yield. No large-scale cell culture data using aggregates are available. Cells from the C2C12 myoblast line can also be cultured in aggregates but these cells express markers of quiescent satellite cells, which does not fill the requirement for cell expansion[94]. Experience with large-scale cell culture of anchorage-dependent mammalian cells is being developed mostly for the MSC cell therapy field[95].

There are advantages and disadvantages with each type of bioreactor (Fig. 2). For example, the stirred-tank reactor is commonly used for mammalian cell culture and is beneficial for scalability, but is associated with high shear stresses on the cells due to the mechanical agitation needed to provide sufficient mixing. In contrast, hollow fibre reactors allow cell growth on the outer surface of microfibres or are suspended in the space between them, while nutrients diffuse to the cells from the fibre lumen, which reduces shear stresses[96–98]. However, hollow fibres are single use and lead to high operational costs. Although high cell densities can be achieved, scalability is limited when close to in-vivo conditions due to the high nutrient, waste, pH and dissolved oxygen gradients created in the bioreactor. Packed/fixed-bed bioreactors present mass-transport limitations that result in the production of cells of differing viability and quality throughout the reactor[99]. In fluidized-bed reactors, cell carriers can be cultured at high densities because mixing is achieved through fluidization with medium circulation and no mechanical mixing is required. However, these systems have only been scaled to 100 l and it is yet unknown if this productivity would be applicable to larger-scale vessels.

The ultimate goal of bioreactor development is to increase the percentage of nutrients in the medium that is converted to edible animal tissue, known as the medium conversion ratio, equivalent to the feed conversion in traditional livestock meat production. Cell density (cell number per ml medium) and medium use can be optimized using recycling techniques. A second and equally important goal is to scale up cell production to achieve cost effectiveness. In addition to the production of cells, tissues need to be formed by the cells. In the absence of a fully integrated system where cells can not only divide but also mature as a tissue after (self) assembly, the tissue formation stage occurs in a different bioreactor that is optimally suited to condition the forming tissue. Here, the diversity in reactor designs will be even bigger depending on the type of tissue to be formed and its specific conditioning needs. The labour-intensive parts of the process will need to be automated to reduce cost and the risk of microbial contamination.

Table 1 | Polymer options for scaffolds for cellular agriculture via non-animal sourcing

Biopolymer class	Specific type	Source and features
Polysaccharides	Cellulose and cellulose derivatives (CMC, HPMC, MC)	Plants, bacteria
	Starch (amylose, amylopectin)	Plants
	Chitin/chitosan	Crustaceans, insects, fungi, yeasts
	Hyaluronic acid, methacrylate derivatives	Heterologous expression
	Alginate	Plants
	Agarose	Plants
Proteins	Collagen/gelatin, zein, methacrylate derivatives	Heterologous expression
	Silk	Silkworms, spiders, heterologous expression
	Elastin	Heterologous expression
	Keratin	Heterologous expression
	Laminin	Heterologous expression
Polyesters	Polyhydroxyalkanoates (and variants of homopolymers, copolymers)	Heterologous expression
Synthetics	Polylactic/polyglycol acids	Chemical synthesis
	Polycaprolactone	Chemical synthesis
	Polyethylene glycol	Chemical synthesis
	Polyvinylalcohol	Chemical synthesis
Complex natural composites	Mycelia	Fungi
	Lignin	Plants
	Decellularized tissues	Plants
	Soy hydrolysate	Plants

There is insufficient data to date to assess suitability of these scaffold polymers for specific food tissue-engineering applications. CMC, carboxymethyl cellulose; HPMC, hydroxypropyl methylcellulose; MC, methylcellulose.

Bioprocess development and optimization are also key to bring down production costs. In-silico modelling of cell behaviour will play a pivotal role in the next few years, as to realize consistent production at scale — especially when the source material is primary cells — significant efforts are needed to shift away from the current semi-scaled up systems and the 'trial and error' upscaling approaches that currently dominate the field of cell and gene therapy[100,101].

Finally, the manufacturing process does not only include cell and tissue production, but also harvesting and purification of cells after production; cell storage, banking and transport; standardization and traceability of tissue harvest from animal donors; quality control of the produced tissues; and regular food technology to process those into meat products.

Biomaterials

Scaffold biomaterials are a key component to cellular agriculture, serving as an integrated support network onto and into which cells expand and differentiate in an anchorage-dependent manner. This porous network allows oxygen and nutrient flow and waste product removal to maintain cell metabolic functions and avoid necrotic core formation. A balance between morphology, structure and chemistry is required. Historically, scaffolding was developed for medically relevant outcomes in tissue engineering and regenerative medicine[102–106]. However, cellular agriculture for food requires a different set of criteria (Table 1). Scaffolding is usually degradable, but if it is not it must be palatable and safe to eat, cooked and uncooked. Specific texture, taste, cooking and nutritional qualities are required for consumption, as is thermal stability. Importantly, scaffolding must be safe, economic and readily available for large-scale production.

Scaffold options. Biomaterial scaffolds being pursued for cellular agriculture are derived from biological sources but processed for desired structure and morphology, while retaining native chemistry (Table 1). To reduce cost, manipulation of the biologically sourced material should be kept at a minimum. Products derived from traditional livestock animals, such as collagen, should be avoided as they are non-replicative and would still require a substantial production of livestock for production. Thus, more promising materials are polysaccharides such as cellulose, starch (amylose/amylopectin), chitin/chitosan, pullulan, alginates, hyaluronic acid and others[107,108]. If sourced through recombinant technology, protein-based systems can include fibrin, collagen/gelatine, keratin or silk. Other materials of interest include the family of polyesters, polyhydroxyalkanoates, expressed in bacteria and other systems[109]. Finally, complex composite matrices generated from plants and microorganisms are also actively pursued, including lignins, plant matrices (for example, decellularized leaves), fungal mycelia and others[110]. Aside from biopolymers, there are a number of synthetic polymers that can be considered, including a range of polyesters. Generally, these systems are safe in the human body and can have a tailored degradation rate via chemical hydrolysis[111]. Benefits of synthetic polymer systems are consistent quality and supply, but cost and requirement for surface functionalization may be limiting. For bioprinting, biomaterials must have additional requirements to allow them to be used as bioinks.

Testing and methodology considerations. Scaffolds for cellular agriculture require particular aspects of texture, digestion, cooking loss, water-binding capacity and taste that are less commonly considered in medically related scaffold designs. Each feature must be assessed with appropriate methods (Table 2) to ensure compatibility for human consumption as part of food. For example, nutritional analyses, including extraction and chromatographic quantitation of key nutrients, mechanical testing to assess texture (for example, Warner–Bratzler shear force, water-holding capacity and cooking

Table 2 | Physical, chemical and biological considerations for biomaterials in cellular agriculture applications

Property	Features to consider	Analyses
Physical		
Processability, structure, thermal stability (cooking)	Rheology, flow behaviour, thermal stability, changes in structure with temperature	Viscometer, rheometry, dynamic mechanical analysis, differential calorimetry, thermal gravimetric analysis
Architecture, texture	Crystallinity, porosity, content	Instron compression testing, XRD, FTIR, Warner–Bratzler shear force
Surface features	Chemistry, functionalization	Immunohistochemistry, NMR
Morphology	Fibre size, surface topography, porosity, alignment, manufacturing approaches	SEM, mercury porosimetry, histology; fibres (extrusion, electrospinning), films (casting, rolling), sponges (porogens, gas evolution, freeze fronts for alignment), hydrogels (self-assembly, covalent crosslinks, selective chemistry), 3D printing
Chemical		
Edible/digestibility/stability	Polymer chemistry, enzymes, chemical hydrolysis	In-vitro mimetic solutions (enzymes: proteases, oxidases, hydrolases; chemical composition, gut/saliva simulants, pH, bile, and so on), macrophage screens, LPS assays, endotoxin screens, chemical screens for residuals (antibiotics, endocrine mimics, and so on)
Biological		
Safe for human consumption	GRAS, nontoxic	Various assays: bacterial toxicology assays, 3D tissue in-vitro screening
Source/sourcing	Consistent source, scalable	Composition analysis Viscometer, rheometry, dynamic mechanical analysis, differential calorimetry, thermal gravimetric analysis
Taste	Palatability, flavour and aromatic compounds (or as byproducts of cooking), Maillard reaction products (for sugar-based scaffolds), oxidation, stability	Tasting panels, chromatography, GC–MS, TBARS assay
Nutrition	Metabolites, metals, sugars, amino acids, vitamins	Digestion, analysis via HPLC–MS, metal analysis
Cell and tissue compatibility	Surface chemistry, metabolites, physical structure, morphology	FTIR, NMR, SIMs, tissue mimics in vitro (oral cavity, stomach, intestine)
Environmental		
Sustainability	Water, land, energy footprint, greenhouse gas emissions related to production, synthesis, processing	Life-cycle assessment

XRD, X-ray powder diffraction; FTIR, Fourier-transform infrared spectroscopy; NMR, nuclear magnetic resonance; SEM, scanning electron microscopy; LPS, lipopolysaccharide; GRAS, generally recognized as safe; GC–MS, gas chromatography–mass spectrometry; TBARS, thiobarbituric acid reactive substances; HPLC–MS, high-performance liquid chromatography–mass spectrometry; FTIR, Fourier-transform infrared spectroscopy; SIMs, secondary-ion mass spectrometry.

loss from the meat industry) and nutritional safety need to be considered. Three-dimensional printing can allow defined morphology, including defined fibre size, surface topology, porosity and alignment.

Additional considerations. Cultured meat applications need product stability and digestibility. These are preferably determined with in-vitro screening simulating gastrointestinal conditions (pH, mechanics and digestive enzymes). Such screens would be performed on both pre- and post-thermally modified 'cooked' versions of the scaffolds to compare outcomes, similar to the testing of other novel food ingredients[112].

Scaffolding cost is a key issue to consider — scaffolds should be a minor portion of the total cost so that production quality and cost remains consistent. Many of the polymers in Table 1 are already being produced at scale.

Complex tissues

Meat from livestock is not only muscle, but a tissue composed of muscle, fat and connective tissue[113]. Currently, most cultured meat tissues consist solely of muscle tissue[17]. Minced cultured meat composed of muscle and fat are made by separately growing muscle fibres and adipose organoids, which are later combined to form the final cultured meat product. To capture the entire scope of livestock meat production, whole-thickness tissues (that is, steaks) need to be engineered, and so a more advanced tissue-engineering approach is needed[108,114–116] (Fig. 3).

Endothelial cells secrete growth factors and cytokines that promote proliferation and differentiation of muscle progenitors into fibres[117] and adipogenesis[118]. Extracellular matrix components secreted by microvascular endothelial cells and fibroblasts stimulate preadipocyte differentiation and muscle maturation, which provide texture to meat[119–122]. Currently adopted protocols to stimulate adipogenesis in human and murine cells are not suitable for generating edible tissue as they typically include adipogenic stimuli that are toxic, such as 3-isobutyl-1-methylxanthine[113]. Thus, food-compatible adipose tissue differentiation from livestock animals should be established before addressing the challenge of combining fat cells with muscle cells. Co-culturing different cells requires an elaborate optimization of growth medium and differentiation protocols[123]. The formation of a complex muscle tissue is dictated by the properties of the scaffold biomaterial, which — to be suitable for muscle and adipose tissue formation — should be formulated to yield appropriate stiffness[124] for both tissues[125,126].

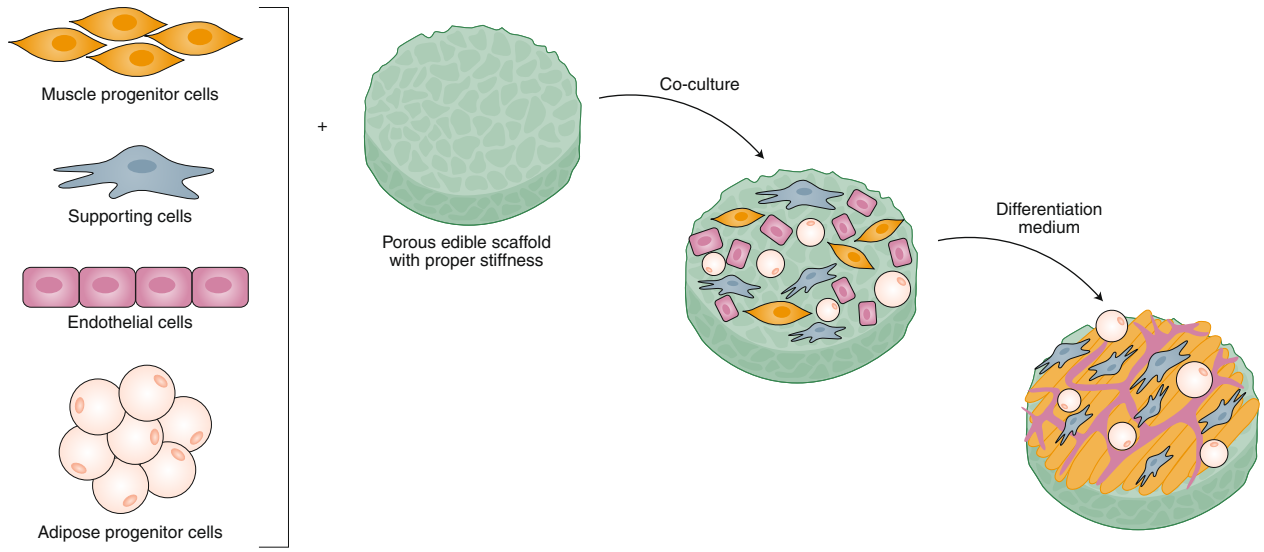

Fig. 3 | Production of complex meat products from muscle, fat, connective tissue and vascular cells using a scaffold method. The advantage of culturing complex tissue is not only that the composition of the produced tissue will a better approximate of livestock meat, but also that mutual beneficial interactions between different cell types can be leveraged. The minimum requirement is the presence of muscle fibres, adipose tissue and fibrous and vascular cells. This can be achieved by combining the respective progenitor cells and triggering differentiation to the final functional phenotype.

However, adipose tissue requires low stiffness, whereas muscle tissue requires a higher stiffness; a suitable combination might therefore be challenging. Muscle fibres and muscle contractility can be promoted via mechanical and/or electric stimulation that is applied on the complex tissue construct[127,128]. Achieving muscle contractility presents an added value for cultured meat, as it stimulates muscle cell production of proteins such as myoglobin, which is responsible for the red colour of meat and is an important source of iron[129].

To create attractive meat analogues, a thickness of 1 cm or more is preferred — this scale is far beyond the diffusion limits of oxygen and nutrients. To prevent tissue from dying, a perfusion system that allows even and sufficient delivery of oxygen and nutrients and adequate effusion of metabolic waste is required[130,131]. This system can be derived from spontaneously assembling endothelial cells into a network of blood vessels or from a printed hierarchical vascular tree, as has been recently demonstrated at small scale[132]. The functionality of such a manufactured blood vessel perfusion system may affect muscle maturation through paracrine interaction or may be a conduit system, and is unlikely to appreciably contribute to the taste and texture of the cultured meat product. Although technologies and principles to create full-thickness meat cuts have been established for medical tissue-engineering applications, and recent advances have been made towards creating these cuts, large-scale commercial production still needs to overcome considerable hurdles. Therefore, the introduction of whole cuts will probably follow after the introduction of minced-meat products.

Regulation

Regulatory frameworks differ across countries and continents. The following review focuses on US and European regulatory frameworks that are being discussed and analysed in detail.

United States. Federal responsibility for food safety rests primarily with the Food and Drug Administration (FDA) and the US Department of Agriculture Food Safety and Inspection Service (USDA–FSIS). The FDA has the authority to regulate production of all food — except meat and poultry — in the United States to ensure that food products are safe, nutritious, wholesome and accurately labelled. USDA–FSIS, however, has jurisdiction over meat and poultry products under the Federal Meat Inspection Act (FMIA).

In recognition of the US jurisdictional complexity, USDA–FSIS and the FDA formally agreed to jointly regulate cell-based meat and poultry (excluding seafood), setting forth some details of a regulatory framework (available at ref. [133]). Although the formal agreement does not create enforceable obligations against individual agencies, it represents the agencies' intention to collaborate and share jurisdiction. First, the agencies agreed that cell-based meat and poultry products are 'meat' and 'poultry products' within the definitions set forth in the FMIA and Poultry Product Inspection Act (PPIA). USDA–FSIS and the FDA also affirmed that existing statutory authority under FMIA, PPIA and Federal Food, Drug and Cosmetics Act (FDCA) is sufficient to regulate cell-based meat and poultry products through the agreed-on framework, indicating that no new statutory authority is required (as detailed in the statement from USDA Secretary Perdue and FDA Commissioner Gottlieb available at ref. [134] and statement available at ref. [133]).

Under the formal agreement, the FDA will leverage its expertise in biomedical technology to oversee the initial phases of cell-based meat development that cover cell collection, development, proliferation and differentiation processes. When the cells or tissues are ready for 'harvest', jurisdiction will shift from the FDA to USDA–FSIS, which will regulate the production and labelling of cell-based meats. Both the FDA and USDA–FSIS will inspect cell-based meat and production facilities, but USDA–FSIS will be solely responsible for inspecting the final stages of production. The formal agreement states that cell-based meat must bear the USDA mark of inspection and the FSIS must pre-approve all labels on slaughter-based meat packaging. Although not in the formal agreement, FSIS officials have publicly announced that the agency has initiated the process of drafting regulations for the labelling of cell-based meat and establishing a standard identity (see ref. [135]). The regulations could specify the qualifying language, such as 'cell-based', 'cultivated', 'cell-cultured', to be used in labelling of the meat and poultry, or could set forth requirements regarding composition or ingredients to be used in such products in order to fall under the existing 'meat' and 'poultry product' definitions.

The FDCA grants the FDA the authority to regulate food production in the United States to ensure that all domestic and imported food products — except for most meats and poultry — are safe, nutritious, wholesome and accurately labelled. The FMIA allows

Table 3 | Comparison of US and EU cultured meat regulatory systems

	US FDA (pre-harvest)	EU
1	Pre-market consultation to evaluate production materials and processes.	No formal pre-market consultation procedure in EU novel foods framework, except the optional consultation at member state level in the case of doubt whether the product qualifies as a novel food (which is clear in the case of cultured meat). Changes to be implemented as of 26 March 2021.
2	Oversee cell collection and quality of cell banks.	Oversight of preparatory production steps, as well as registration of a company as an FBO, will be done at member state level. In the Netherlands, FBOs working with products from animal origin require a so-called recognition (erkenning). This is a more detailed procedure (average term of 8 weeks) than FBO registration (average term of a few days).
3	Oversee production process until harvest.	
4	Ensure companies comply with FDA requirements: facility registration, cGMP and other applicable food legislation.	
5	Where needed — issuing regulations or guidance or additional requirements regarding sections 2 and 3 to ensure that biological materials exiting the culturing process are safe (FFDCA).	EU hygiene rules for food of animal origin[164] to apply, and potential national legislation. In the Netherlands, the Commodities Act decrees on hygiene[165] and the preparation and packaging of foodstuffs[166] are applicable. Additional requirements (conditions of use) may also be included in individual novel food authorizations.
6	Inspections and enforcement directed at safety of cell banks and culturing facilities.	Inspections and enforcement are done at member state level. In the Netherlands, the responsible entity is the Dutch Food Safety Authority.
	USDA (post-harvest)	**EU**
7	Determine whether harvested cells are eligible to be processed in meat or poultry products.	The novel food framework requires FBOs to specify the source of the product, its production process and typical compositional features in their market authorization applicaiton[141]. No additional eligibility test is required for cell harvest prior to production of food products.
8	Require each cultured meat company to obtain a so-called grant of inspection.	Not required under EU legal framework. Registration (or recognition) with the competent food safety authority provides the authority with the legal basis for inspection. A novel food authorization must be obtained before placing the product on the market.
9	Conduct inspections in establishments where cells cultured from livestock and poultry are harvested, processed, packaged or labelled to ensure that the resulting products are safe, unadulterated, wholesome and properly labelled.	Inspections will be executed at a member state level based on the Official Controls Regulation 2017/625 (ref. [167]), which targets products of animal origin for human consumption inter alia.
10	Pre-approval of labeling of cultured meat products and inspection thereof.	No pre-approval of product labels under EU novel food framework. It is the responsibility of the FBO to comply with applicable labeling legislation, such as the Food Information to Consumers Regulation 1169/2011 (ref. [136]).
11	Where needed — develop additional requirements to ensure the safety and accurate labeling of cultured meat products.	Safety and labelling provisions are already in place at EU level. These are embodied in the General Food Law Regulation 178/2002 (ref. [168]) and the Food Information to Consumers Regulation 1169/2011, respectively. Specific labelling requirements may be included in novel food authorizations. Post-market monitoring requirements may be imposed. In any event, FBOs should inform the European Commission of any new information that arises regarding the safety of the novel food placed on the market.
12	Enforcement actions regarding adulterated or misbranded food products.	See section 6. Competitors, consumers and watchdog organizations may also bring cases regarding misleading food information before self-regulatory bodies. For example, unpermitted references to 'meat' could be a topic of such cases.

FBO, food business operator.

USDA–FSIS jurisdiction over most meat and poultry products. The FDA and USDA share jurisdiction over food additives in meat and poultry.

As of January 2020, 12 states have passed laws that restrict the use of certain terms, such as 'meat', on cultured meat products. However, both the FMIA and PPIA prevent states "from imposing any marking, labeling, packaging, or ingredient requirements on federally inspected meat and poultry products that are in addition to, or different than, those imposed under the FMIA or the PPIA. (70 Fed. Reg. 29214. See also 21 U.S.C. § 678 (meat); 21 U.S.C. § 467(e) (poultry))". Thus, a clear labelling scheme disseminated by the FSIS will pre-empt state laws restricting 'meat' terms on cultured meat and poultry. USDA–FSIS and the FDA have created inter-agency working groups to address any remaining questions regarding the regulatory framework for cell-based meat. These include how the FDA and FSIS will initiate and transition regulatory oversight, how the agencies will allocate jurisdiction over cell-based food products blended with conventional meat or plant-based ingredients, pre-market approval process requirements, timelines for agency review, production facility inspection processes, the regulatory framework for cell-based seafood (traditionally regulated by the FDA except for catfish, which is regulated by the FSIS) and legislation or new regulations that will be required to address these and other related regulatory issues.

European Union. Contrary to the United States, the regulatory framework for cultured meat in the EU has been in place since 1997, and was updated in 2018. Depending on the starting cell types used, either the EU Novel Foods Regulation[136] or the genetically modified organism (GMO) legislation (embodied by the GMO Directive[137] and GMO Regulation[138]) will be applicable. The EU Novel Food Regulation excludes genetically modified foods and therefore the use of iPSCs for cultured meat production will most likely be covered by the EU GMO legislation[18].

Table 4 | Summary of key outcomes from consumer surveys on cultured meat

Survey source	Year	Sample size and demographics	Question	Would eat	Do not know	Would not eat
YouGov[169]	2013	1,729 adults (18+ years) in the UK	Imagine artificial meat was available commercially, do you think you would eat it?	19%	19%	62%
Pew Research[147]	2014	1,001 adults (18+ years) in the US	Would you…eat meat that was grown in a lab?	20%	2%	78%
Flycatcher[145]	2013	1,296 adults (18+ years) in the Netherlands	Suppose that cultured meat is available at the supermarket. Would you buy cultured meat in order to try it?	52%	23%	25%
The Grocer[148]	2017	2,082 adults (16+ years) in the UK	Would you ever buy 'cultured meat' grown in a laboratory?	16%	33%	50%
Wilks and Phillips[146]	2017	673 adults adults (18+ years) in the US	Would you be willing to try in vitro meat?	65%	12%	21%
Surveygoo[162]	2018	1,000 adults (18+ years) in the UK and US	Would you be willing to eat cultured meat?	29%	38%	33%
Bryant et al.[152]	2019	3,030 adults in the US (18+ years), India and China (18+ years)	How likely are you to try clean meat?	52%	34%	13%

Analogies between the European Union and United States. Both regulatory systems aim to assure that cultured meat products entering the market are "safe, wholesome and unadulterated" (see point 4 B (3) of ref. [133]). The EU Novel Foods Regulation[136] aims to ensure "the effective functioning of the internal market while providing a high level of protection of human health and consumers' interests". To achieve this, both regulatory systems require prior market authorization, but the authorization procedure is quite different. The procedure described below provides an overview with a focus on novel foods and not on GMO legislation.

Differences between the European Union and United States. Table 3 outlines regulatory differences. On the left side, the authority of the FDA and the USDA under the 7 March 2019 agreement has been summarized. On the right side, it has been outlined how legal authority is attributed in the EU and in its member states under the Novel Foods Regulation. As a reference member state, the Netherlands has been retained, as this is one of the EU countries where cultured meat activities are prominent.

European Union market entry of novel foods. Under the EU Novel Foods Regulation, an application for an authorization of a cultured meat should be made via the e-submission system operated by the European Commission, who will subsequently distribute the application to all EU member states. Minimum requirements for the application consist of information on the identity of the product, its production process, compositional data and specifications, proposed uses, use level and anticipated intake of the product. Other safety information relates to the source of the product; absorption, distribution, metabolism and excretion (ADME); nutritional and toxicological information; and allergenicity. Applications are evaluated on a case-by-case basis.

On receipt of the novel food application, the European Commission will usually request a safety opinion from the European Food Standards Authority (EFSA), who will evaluate if the novel food is of comparable safety to food from a similar category already on the EU market. EFSA's evaluation should not exceed a nine-month term. Within seven months of receipt of a positive safety opinion, the European Commission should publish its implementing act, resulting in the inclusion of the approved novel food in the Union List[139]. Two open ends in this procedure include: (1) the term for response for the member states (this was 60 days under the previous Novel Foods Regulation prior to 1 January 2018, but this term is not mentioned in the current Novel Foods Regulation); (2) the questions that EFSA can ask the applicant, resulting each time in a so-called stop-the-clock moratorium.

Pre-market consultations and Union Register of commissioned studies. Unlike the US regulations, the EU Novel Foods procedure requires no formal pre-market consultation procedure to evaluate production materials and processes. However, from 26 March 2021, the new Transparency Regulation 2019/1381 (ref. [140]) will give applicants the right to request advice on the pre-submission phase from EFSA. This procedure is a response to industry demand, especially from small–medium enterprises, for further support in the preparation of applications. However, the advice will be provided without input from EFSA's Scientific Panels and shall not cover the specific design of a study. Applicants will have to notify EFSA of any study they commissioned to support a future authorization application, which will become part of the Union Register of commissioned studies. The majority of cultured meat applications will probably be made once this new regulatory regime is applicable, requiring applicants to thoroughly design their strategy to secure safety evidence.

Written EFSA guidance. The 2016 EFSA Scientific Opinion[141] provides detailed guidance on data required for the novel food application. The cells used to culture the meat product and the cell substrate used during the cultivation process should be described in detail. The 2018 EFSA Technical Report[142] provides applicants with a completeness checklist and provides a helpful overview table of study reports contained in the technical dossier.

Enforcement. In the United States, the organizations who define the regulatory framework also enforce them. In contrast, individual EU member states enforce novel food regulations and measures may vary between states. For example, the Dutch Food Safety Authority's enforcement policy is on public record — marketing cultured meat without a proper novel food authorization results in a penalty and prohibition of further marketing. In other member states, the penalties or potential imposed measures, such as a warning or injunction for further marketing, may differ from the Dutch measures. Thus, marketing cultured meat in Europe requires knowledge of the EU framework and local regulations.

Terminology. Much like in the United States, cultured meat will be impacted by ongoing debates regarding meat names for meat alternatives. The Committee on Agriculture and Rural Development (AGRI Committee), under the former EU Parliament (in place until May 2019), formulated a proposal prohibiting use of the terms steak, sausage, escalope, burger and hamburger for non-conventional meat products. After the election of the current EU Parliament (in place since July 2019), this proposal was still pending. However, certain meat products have protected legal names under national

legislation, such as 'tartar', being minced meat from beef with a fat percentage >10%.

Consumer acceptance

Cultured meat raises several social questions and challenges, including how the technology should be regulated, the implications of shifting power in the food system and the economic impact on communities that are dependent on animal farming[18]. One major question is whether consumers will buy cultured meat. Indeed, consumer acceptance is a necessary component for commercial success of cultured meat in the short term, and for its ability to bring about societal benefits in the long term.

Survey data on this question are inconsistent and dependent on a number of factors, including the phrasing of the question and the nationality of the sample[143,144]. Table 4 shows a summary of the results of nationally representative survey questions about cultured meat to date.

Different samples and question wording affect survey responses. However, the main differences appear to be based on the amount of information given to participants. The three most optimistic survey results come from longer cultured-meat-focused surveys that gave participants plenty of positive information[144–146]. The most negative findings result from surveys where participants are given very little information about cultured meat, often as part of a longer omnibus survey[147,148] — this explanation fits with the finding that positive (and negative) information about cultured meat influences attitudes in the direction of the information[149]. Various experimental studies have demonstrated a number of ways in which acceptance of cultured meat can be increased. When cultured meat is primarily framed as a technological innovation, it is significantly less appealing than when the focus is on its societal benefits or its similarity to conventional meat[144]. Similarly, overly technical descriptions are less appealing than more straightforward descriptions[150], and names such as 'lab-grown meat' that invoke science and unnaturalness are significantly less appealing than names such as 'clean meat' that highlight the benefits relative to conventional meat[143]. Consumers are also more likely to choose cultured meat when the price is lower, and when the perceived popularity amongst others is higher[151].

Familiarity with the technology is a major predictor of acceptance, and food neophobia is a major predictor of rejection[152,153] — most Americans (57.3%) are 'not at all familiar' with cultured meat[152]. In focus groups, initially negative attitudes towards cultured meat often become less negative after further consideration of the concept[154,155]. Therefore, despite a lack of meaningful longitudinal data, it is possible that attitudes and intentions towards cultured meat will become more positive. Given that attitudes are influenced by positive and negative information[149], consumer acceptance could depend on the information people are exposed to — media coverage of cultured meat thus far has been largely positive[156].

Various studies have found higher acceptance of cultured meat amongst men compared to women, amongst younger people compared to older people, and amongst omnivores compared to vegetarians[145,146,148,151,152,154]. The gender disparity may relate to women having more cautious stances towards foods in general[143], while the age trend is likely due to higher openness to new experiences amongst younger people[157]. Cultured meat circumvents the primary ethical and environmental motivations for vegetarianism[158]. However, it is common for vegetarians to acquire an emotional disgust reaction to meat in general, which may supersede rational reasons for avoiding meat[159,160]. This should not be a major concern for producers or advocates: those who avoid meat are a small fraction of the market, and are not contributing to the problems of conventional meat production. Moreover, if cultured meat is to displace demand for conventional meat in the long-term, it is important that it is not viewed as a product that is 'for vegetarians', as this might limit its appeal to non-vegetarians and therefore its ability to displace demand for animals.

Cultured meat is likely to be more appealing to consumers in America and Asia than to those in Europe[3]. Whilst the British were amongst the most accepting of cultured meat in Europe in a 2005 survey[161], they are substantially less accepting than Americans[162]. Americans are less willing to eat cultured meat than consumers in China and India[152]. Such differences may be related to the different roles that animal agriculture plays in these societies and cultures.

A major limitation of all research on consumer acceptance is its hypothetical nature. As there are no cultured meat products currently available commercially, researchers have been unable to observe consumer preferences in practice or explore specific aspects of the product which are appealing. Others, however, have observed that consumer perceptions of cultured meat are similar to perceptions of genetically modified food in terms of demographic trends[143]. Some consumers view these technologies as conceptually similar[163], and attitudes are often underpinned by similar sets of concerns.

Conclusion

Cultured meat arose from growing concerns around the ethics and sustainability of livestock meat production. The technologies to culture meat are derived from tissue and bioprocess engineering, and include isolating and propagating stem cells, identification and modification of suitable biomaterials, and designing co-culture systems with various cell types such as muscle and fat cells. Informed choices must be made to achieve scalability and reduce cost, and to avoid regulatory hurdles. High-volume cell production in industrial bioreactors using a serum-free medium is a prerequisite for commercial cultured meat manufacturing. Technological advances and investment in cultured meat research suggests that cultured meat will become a food commodity in the near future. We see a trend towards increased public acceptance of the concept of cultured meat in surveys covering different geographical areas. Future social analyses should consider a broader set of issues, including power in the food industry and the impact on rural economies. Regulatory pathways and conditions are being established simultaneously in the United States and Europe. Although research and development continue primarily in private companies, the many scientific and technical challenges in creating a full spectrum of cultured meat concepts warrants the nurture of a robust scientific and academic discipline of cellular agriculture in the coming decades.

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Competing interests

M.J.P. is chief scientific officer, co-founder and shareholder of Mosa Meat B.V.; P.M. is lead bioprocess engineer at Mosa Meat B.V.; S.L. is chief scientific officer, co-founder and shareholder of Aleph Farms; N.G. is chief scientific officer, co-founder and shareholder of Memphis Meats; J.F. is chief scientific officer and employee of PAN-Biotech GmbH; K.V. is lawyer and partner at AXON lawyers, a law firm that is active in the cellular agriculture space.

Additional information

Correspondence should be addressed to M.J.P.