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Cultured meat: every village its own factory?

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Rising global demand for meat will result in increased environmental pollution, energy consumption, and animal suffering. Cultured meat, produced in an animal-cell cultivation process, is a technically feasible alternative lacking these disadvantages, provided that an animal-component-free growth medium can be developed. Small-scale production looks particularly promising, not only technologically but also for societal acceptance. Economic feasibility, however, emerges as the real obstacle.

Prospect

Early in the 1930s, Winston Churchill first wrote about what today we call cultured meat or *in vitro* meat [1], and some decades later, Willem van Eelen came up with the same idea. Throughout the twentieth century the idea remained marginal, but growing problems associated with normal meat, especially unsustainability and animal welfare, have changed this. Although many vegetarian protein sources are available as alternatives, meat continues to be extremely attractive to most people. As large parts of the world become more prosperous, the global consumption of meat is expected to rise enormously in the coming decades. Cultured meat is therefore increasingly seen as a hopeful addition to the set of alternative protein sources [2–5]. A tentative life-cycle analysis estimated that if cultured meat can be grown on a medium of algae, energy use will not be reduced dramatically, but greenhouse-gas emissions, land use, and water use will: by more than 90% compared with European beef [3]. In August 2013, the Dutch researcher Mark Post presented a hamburger as a first 'proof of concept' in order to demonstrate that the idea could work and that it deserves research funding.

Although the potential advantages of cultured meat are clear, they do not guarantee that people will want to eat it. For example, a returning suggestion in societal debates is that cultured meat might deter people because it is 'unnatural' [4,5]. We argue that there is reason to think that a scenario that involves small-scale local factories is not only technologically feasible but may also meet with societal approval. Economic feasibility may turn out to be the greatest challenge for cultured meat.

Societal responses

Most people initially find the idea of cultured meat surprising; first (Dutch) responses vary from 'wow' (from the majority; mostly because of the prospects for animals) to 'yuck' (from a minority; prominent associations are genetic modification and hot dogs) [6]. After some thought, responses became more complex. Workshop discussions and media responses after Mark Post's hamburger presentation [6–8] suggest that many people regard cultured meat as a hopeful idea given their moral doubts about 'normal' meat. However, cultured meat comes with ambivalences of its own, such as worries that it might be 'uncannily unnatural' or 'technological', or that it will alienate us further from our food. Such questions are typically followed by the thought that the production of meat in factory-farming systems is not very natural either; the idea of cultured meat invariably inspires discussions on the drawbacks of factory-farmed meat. *The Times*' editorial comment on the *in vitro*-hamburger is illustrative: 'How absurd is it to imagine all our meat one day being produced by a similar process [tissue culturing]? Not much more absurd than it is to imagine all our meat continuing to be produced as it is now' [7].

Mode of production makes a difference for appreciation, just as it does for meat. A cultured meat scenario that generated not ambivalence but great enthusiasm among workshop participants was one in which pigs in backyards or on animal-friendly (urban) farms would serve as the living donors of muscle stem cells through biopsies. These pigs live happy lives as companion animals while their cells are cultured in local meat factories. Worries of cultured meat being unnatural, too technological, or alienating were absent here; the idea of local production and close contact with the animals seemed to dispel these concerns [6].

Manufacturing

Animal cells can currently be cultured in suspension in bioreactors up to a size of 20 m^3. In principle, it is possible to grow animal muscle or organ cells in suspension on that scale for meat production, provided that a robust continuous cell line is available, be it a bovine, chicken, fish, insect, or any other edible animal cell. An adult stem cell of the pertinent tissue is a logical choice. However, developing an appropriate robust continuous stem-cell line is still a real challenge. A cell that is relatively fast growing, with a doubling time on the order of days, and that is genetically stable for at least 50 divisions is desirable. If such a cell line is available, the next step is the design and development of a growth medium, allowing a US Food and Drug Administration (FDA)-approved commercial production process. An animal-component-free, full-defined medium that guarantees consistency of product quality is preferable. Growth medium is generally an important cost-determining factor. A price of €1 per liter for growth medium would bring the price of a minced-meat type of product within the price

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range of conventional minced meat, but this is when only the price of medium is considered (Box 1). This is already an ambitious goal, but not enough to make cultured meat competitive with conventional meat. For that, an order-of-magnitude increase in the price of the latter would be needed.

If a cell line and medium are available and the economics are good, the next step is to produce a sufficiently large

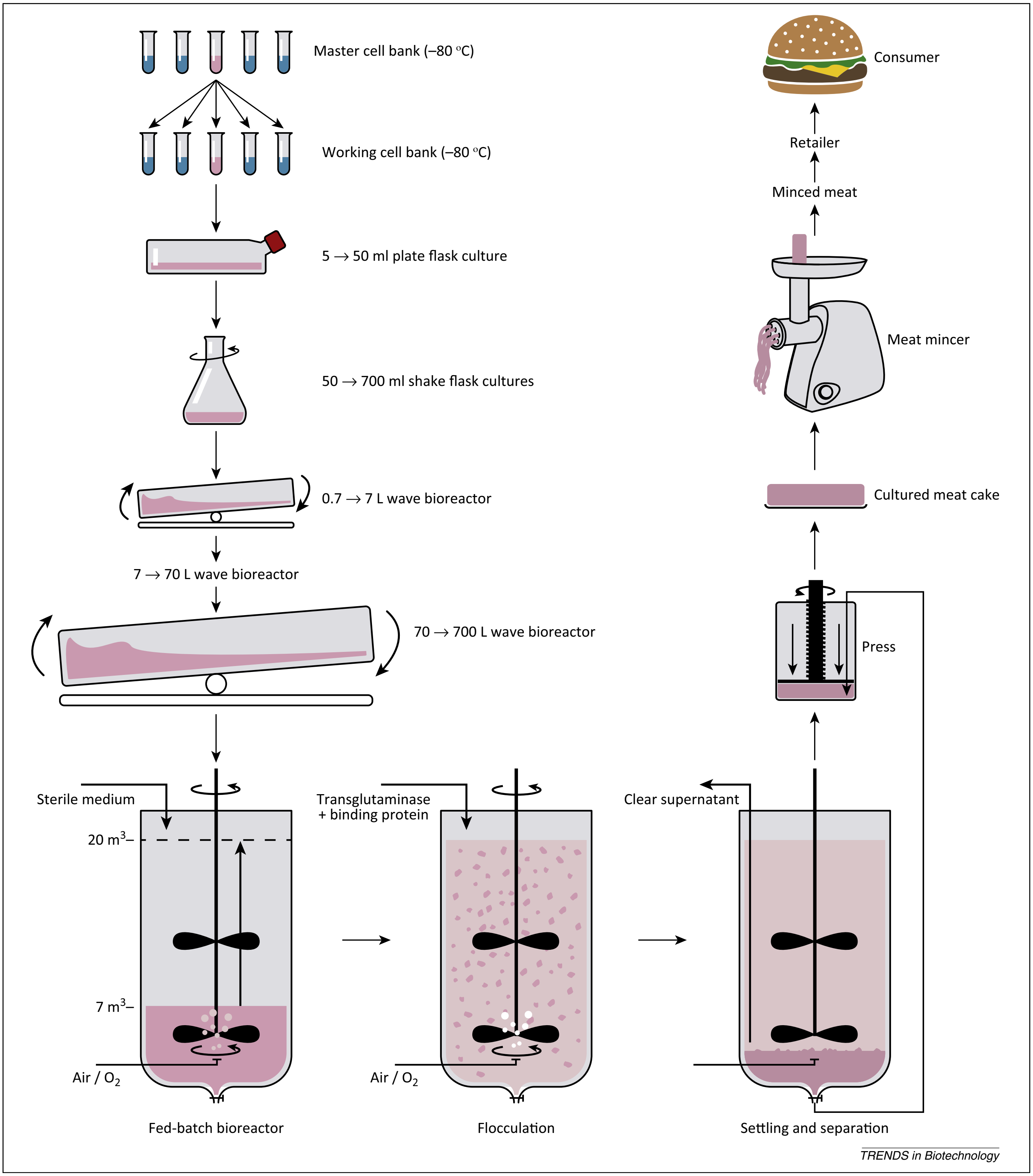

Figure 1. Flow sheet of a potential cultured-meat manufacturing process. The left column shows the stepwise increase in cell-culture volume, starting with a vial from the working cell bank (note that a new working cell bank is made from a vial from the master cell bank). Exponentially growing cells from each step serve, after growing to a certain cell density, as the inoculum of the next culture vessel, which is an order of magnitude larger. The final bioreactor starts only partially filled and is fed with sterile medium at such a rate that the cells grow further under optimal conditions. When the bioreactor is full and the desired cell density is reached, the protein-crosslinking enzyme transglutaminase and binding protein are added to induce the formation of easily settling aggregates of cells, which quickly settle when stirring is stopped (bottom right). The harvested cells are pressed and the cake is extruded into retailer- and/or consumer-size portions of minced meat (right column).

Box 1. Technical and economic aspects of cultured-meat production

The diameter of animal cells is generally between 10 and 20 μm. This means that the volume of one cell is on the order of 10^{-15} m^3, corresponding roughly to 10^{-12} kg/cell. If we assume that everybody in the world will eat 25–30 grams of cultured meat per person per day (10 kg/year), and if we further assume that in 2050 there will be 10 billion people, 10^{11} kg of cultured meat would be needed per year. In other words, we need to produce 10^{23} cells per year. The doubling time of animal cells is generally on the order of 2–3 days (one day is fast for an animal cell), which means that it takes minimally 2–3 weeks to grow cells from the lowest inoculum density of about 5×10^{11} cells/m^3 to the still challengingly high density [15] of about 128×10^{12} cells/m^3 in eight doublings. One run in a 20 m^3 bioreactor, the largest size used for animal-cell cultivation today, will therefore take about 1 month, including all steps (cleaning, filling, sterilization, and so on). To be on the safe side, we assume that 10 runs per year would be executed with this bioreactor, yielding 2.56×10^{16} cells in total per year, which corresponds to 25,600 kg cultured meat per year per bioreactor, assuming no losses. Given these assumptions, a bioreactor of 20 m^3 can thus supply the meat demand (10 kg per person per year) of 2,560 people, a small village.

One should realize that this can only be done in an ultramodern factory under Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP), or International Organization for Standardization (ISO) norms conditions, needing at least three to four highly educated and well-trained technical employees. In the Netherlands, the price of minced meat is not much more than €5 per kg; in other words, 25,600 kg of meat would only earn €128,000 per year, hardly enough to pay the salary of one 'butcher' and his/her assistant. Growth medium is also a cost-determining factor, certainly for growing stem cells. A price of €50,000 for 1 m^3 of defined medium is not extreme. Per run, at least 20 m^3 of medium is needed, corresponding to €1 million. This equates to a cost of €391 per kg of cultured meat. A price of €1,000 per m^3 is considered to be the absolute minimum for growth medium. In that case, the medium costs for 1 kg of cultured meat would be €8; and this price accounts for only the growth medium.

master cell bank, an essential feature for commercial production. Batch and fed-batch bioreactors are proven industrial systems in the fermentation world, and they can also be used for animal-cell cultivation [9]. The advantage of a fed batch is that the minimum inoculum size is reduced significantly. Furthermore, feeding the medium at such a rate that all nutrients are constantly available in excess assures optimal growth conditions until the reactor is full and the maximum cell concentration has been reached.

Further processing becomes more speculative, but not impossible. The cells have to be concentrated to minced-meat density and structured into a texture that is appetizing and with a good mouth feel after being prepared for eating. This requires cheap and reliable methods. Flocculation is promising and is currently being considered for the harvesting of micro-algae of approximately the same size ($\sim$10 μm) as animal cells [10]. A method for structuring conventional-meat residues into an appetizing piece of minced meat makes use of the enzyme transglutaminase [11–14], which catalyzes *in vitro* crosslinking of plant and animal proteins.

The aseptic conditions in the bioreactor can be used for flocculation and texturizing (Figure 1). When the vessel is full and the highest cell density has been reached, transglutaminase and binding protein (e.g., soya proteins) are added and the stirring is slowly continued until aggregates are formed that easily settle. Stopping the stirring allows the aggregates to settle. The cleared supernatant can be pumped or drained from the top of the bioreactor and the cell slurry from the bottom. After drainage, the cultured-meat slurry can be pressed and divided into portions with a solid mass content and weight of retail or consumer size. All of these handlings can easily be done under Good Manufacturing Practice (GMP) conditions. Producing cultured meat of the minced-meat type would thus be technically feasible. Developing an appropriate, robust, continuous stem cell line and substantially lowering the price of the growth medium are the major challenges.

Concluding remarks and future perspectives

Cultured meat has great moral promise. Worries about its unnaturalness might be met through small-scale production methods that allow close contact with cell-donor animals and thereby reverse feelings of alienation. From a technological perspective, 'village-scale' production is also a promising option. From an economic point of view, however, competition with 'normal' meat is a big challenge; production cost emerges as the real problem. For cultured meat to become competitive, the price of conventional meat must increase greatly.

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References

1 Churchill, W. (1932) Fifty years hence. In *Thoughts and Adventures*. pp. 24–27, Thornton Butterworth
2 Hopkins, P.D. and Dacey, A. (2008) Vegetarian meat: could technology save animals and satisfy meat eaters? *J. Agric. Environ. Ethics* 21, 579–596
3 Tuomisto, H.L. and Teixeira de Mattos, M.J. (2011) Environmental impacts of cultured meat production. *Environ. Sci. Technol.* 45, 6117–6123
4 Specter, M. (2011) Test-tube burgers. In *The New Yorker*. 32–38 23 May
5 Bartholet, J. (2011) Inside the meat lab. *Sci. Am.* 304, 64–69
6 Van der Weele, C. and Driessen, C. (2013) Emerging profiles for cultured meat; ethics through and as design. *Animals* 3, 647–662
7 Meat the future. *The Times* 6 August (2013), p. 24
8 Chivers, T. (2013) Why I've a healthy appetite for stem-cell meat. In *The Daily Telegraph*. 17 6 August
9 Chu, L. and Robinson, D.K. (2001) Industrial choices for production by large-scale cell culture. *Curr. Opin. Biotechnol.* 12, 180–187
10 Vandamme, D. *et al.* (2013) Flocculation as a low-cost method for harvesting microalgae for bulk biomass production. *Trends Biotechnol.* 31, 233–239
11 Griffin, M. *et al.* (2002) Transglutaminases: nature's biological glues. *Biochem. J.* 368, 377–396
12 Motoki, M. and Seguro, K. (1998) Transglutaminase and its use for food processing. *Trends Food Sci. Technol.* 9, 204–210
13 Zhu, Y. *et al.* (1995) Microbial transglutaminase – a review of its production and application in food processing. *Appl. Microbiol. Biotechnol.* 44, 277–282
14 Zhu, Y. and Tramper, J. (2008) Novel applications for microbial transglutaminase beyond food processing. *Trends Biotechnol.* 26, 559–565
15 Clincke, M-F. *et al.* (2013) Very high density of CHO cells in perfusion by ATF or TFF in WAVE Bioreactor™ - part I. Effect of the cell density on the process. *Biotechnol. Prog.* 29, 754–767