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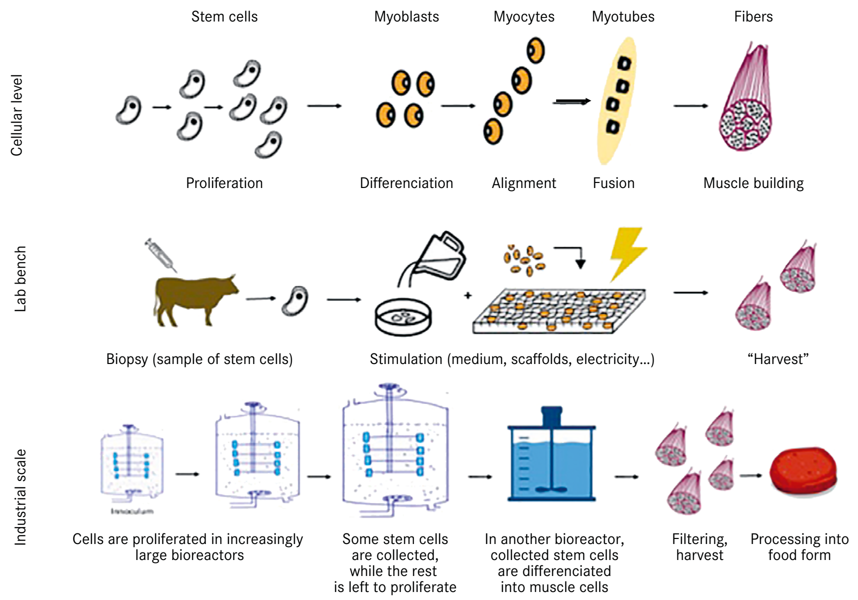
"*In vitro* meat": growing muscle cells for food

For the past 20 years, researchers have been trying to produce cultures of animal cells for food consumption. "*In vitro* meat" is framed as a disruptive innovation, and as a project addressing the many challenges related to animal farming. Where does it come from and who promotes it? What are the technical hurdles to industrial scale-up? The research strategies? And what will be the challenges when bringing it to the market? This note provides some answers*.

For the past thirty years, researchers and entrepreneurs have been discussing the possibility of making artificial steaks[1]. Many alternatives to meat based on protein crops and legumes have been developed, and marketed beyond traditional niches. More recently, the arrival of food products based on *in vitro* culture of animal cells has received a lot of attention[2]. The process is inspired by tissue engineering and medical organ regeneration techniques. It involves taking stem cells from an animal. Proliferating them in a nutrient medium made up of proteins, amino acids, hormones and other "growth factors". And then, forcing them to differentiate into muscle cells and attach to micro-supports or "scaffolds" - to, finally, form clusters of cells or fibers (image 1).

Image 1 - **The three scales for obtaining "*in vitro* meat" (cellular level, lab bench, industrial setting)**



Comment: As regards the industrial scale, the diagram presents the hypothesis of trains of culture moved from small to increasingly large bioreactors[4]. Other approaches aim for a less disturbing process for cells, easier to industrialize (proliferation / differentiation in a single step, with only one bioreactor)[5].

Source: author

At the end of 2020, the American company Just, Inc. received approval from the Singapore authorities to market, in a single restaurant, a paste of chicken cells, sold as a mixture with vegetable proteins in the form of "bites". Various startups are announcing mass production in the next five to ten years, mostly in the minced meat niche. In the longer term, others target the production of whole complex "pieces", interweaving muscle, fat, connective tissue, etc. For instance in February 2021, Aleph Farms announced that it had successfully replicated sirloin steak using a 3-D cell printing process (bioprinting)[3].

These prototypes stand out from other "alternative proteins" already on the market, such as vegetarian "burgers". Indeed, it is no longer just a question of reproducing the nutritional profile of farmed products, or even their texture and organoleptic qualities.

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1. Choudhury D. *et al.*, 2020, "Commercialization of plant-based meat alternatives", *Trends in plant science*, nov 25(11):1055-1058.
2. For a comparison of this important media coverage with the relative scarcity of scientific publications, see Chikri S. *et al* ., 2020, "Analysis of scientific and press articles related to cultured meat for a better understanding of its perception", *Front. Psychol.*, 25/08.
3. Peskett M., 2021, "Aleph Farms' 3D bioprinting delivers world's first cultivated ribeye steak", *Food and farming technology*.
4. Specht L., 2020, *An analysis of culture medium costs and production volumes for cultivated meat*, The Good Food Institute.
5. Bodiou V., Moutsatsou P., Post M., 2020, "Microcarriers for Upscaling Cultured Meat Production", *Front. Nutr.*, 7:10.

Because they are manipulating the building blocks of animal flesh, these entrepreneurs think they produce more than a substitute or than an analogue of "real" meat. According to them, these "*in vitro* meat"[6] projects would make it possible to solve a set of problems linked to intensive farming methods and meat consumption: greenhouse gas emissions, animal welfare, health risks, spread of zoonoses, and more.

Such an innovation would also support the nutritional transition of "emerging countries" towards a more meaty diet. Indeed, in theory, the exponential proliferation of cells from a single biopsy could produce the equivalent of the world's annual consumption of meat[7]. For some, reproducing meat in the laboratory would even make it possible to defend, in Western countries, a standard of commensality undermined by the growing conflicts around livestock products, the rise of special diets[8] and the spread of veganism.

This note gathers information on the cultivation of animal cells for human consumption. The first section reviews the history of projects to replace livestock products with alternative proteins. The second shows how food tech took on the "*in vitro* meat" project, and underlines its current technical limits. Finally, the last section addresses the challenges of its marketing and integration into the food supply.

1 - Replacing livestock products with "alternative proteins"

The current assemblage of *in vitro* culture techniques (cells + medium + controlled environment) has been known for a long time. Already in the 1940s, the appropriate techniques disseminated worldwide in medical research networks. However, until the 1990s and the swift developments in tissue engineering in human medicine, large-scale production of animal cells for human consumption did not appear feasible, and was not seriously considered.

On the other hand, the idea of replacing meat with an artificial equivalent, supposed to be of the same nutritional quality, has given rise to many - more or less successful - achievements. It appears as one of the solutions to make food production coincide with the nutritional needs of populations (together with others aiming at fixing the "food equation": regulation of births, increase in yields, cultivation of new lands, adjustment of rations, etc.). At the end of the 19th century, utopians and suffragists imagined how the *meal-in-a-pill* would undo the knot of injustice linking famine, poverty and capitalist, even patriarchal domination. "Artificial meat" therefore became a commonplace in the prophecies on the future of food[9]. After World War II, science fiction hijacked this humanitarian topic, delivering a pessimistic version, associating it with the triumph of marketing, industrialization and the exploitation of living things[10]. Advances in chemistry and biology nourished these imaginations, as did applied research in the food sector. The niche project to replace livestock products was carried by researchers linked, first, to vegetarian sects (such as the products of the Kellogg brothers around 1895), then, to the hippie counter-culture – and, thirdly, the military-industrial sector, concerned with ensuring the continuity of food in times of war. The words of "substitutes", "analogues" or "ersatz", were common then.

At the end of the 20th century, two sets of basic trends converged and renewed the terms of the debate, involving different dimensions and scales of food: nutrition, ethics, politics, and environment. Meat became central in diets. In Western countries, it occupied an important place in the ration from the years 1950-1960 on. The development of industrial farming allowed mass consumption at low prices. More recently, it has been developing very quickly in all the other continents. In addition, the relationship of consumers to food has evolved, with food increasingly reduced to providing protein and nutrients.

At the same time, this centrality of meat becomes problematic, at the junction of several challenges: nutritional and health consequences of eating "too much" of certain meats, environmental impacts of livestock (greenhouse gas emissions and contribution to climate change, imported deforestation), sensitivity to animal suffering and welfare, etc. Thus, debates on the food equation returned in the 2000s, the motto being to "feed the world" in 2050, under a set of renewed constraints.

In this context, the word "protein" is put forward commercially, when offering alternatives to meat. Some products result from the transformation of raw materials: soybeans, peas, and to a lesser extent, seaweed. It was the case, in the 2010s, with Impossible Foods or Beyond Meat "burgers", marketed by fast-food chains or supermarkets, sometimes by positioning them on the meat shelves. Others involve the use of genetically modified yeasts, such as the protein combinations or "milks" produced by Clara Foods and Perfect Day. Finally, the replacement strategy using "pure compounds"[11] (rather than ingredients drawn from animal and plant tissues) is re-activated by approaches akin to molecular cuisine, DIY cooking[12] and even formulation in animal feed.

"*In vitro* meat" entered this space of alternative proteins at the turn of the 2000s, with the spread of tissue engineering techniques. For its first appearances outside the laboratory, like the tests on a fish explant in a NASA-funded program[13], it remained incredible to many observers. Conducted by eccentric, if not marginal, researchers, this work seems unusual and provokes strong reactions. For instance, the first tasting of cultivated frog "flesh", by the artists Catts and Zurr, in Nantes in 2003, relays a critical discourse on biotechnologies[14]. The pioneers have to deconstruct, with great difficulty, the image of science fiction, while positioning themselves regarding the public problems and challenges of the moment. Embedded in a professional environment characterized by debates on GMOs and stem cells, they also anticipate questions of acceptance and marketing, and immediately set a "specification" formulated from the first patent filed by Dutch scientist Van Eelen in 1997[15] : the process and the final product should not pose the same problems as factory-farmed meat, nor give rise to new ones.

2 - Food tech and the technical challenges of "*in vitro* meat"

A shift to the economy of startups and venture capital took place at the beginning of the 2010s. After vegetating for ten years in academia, the "*in vitro* meat" project found an echo in the Silicon Valley, a milieu oscillating between technological optimism and ecological catastrophism. M. Post, professor of physiology involved in the Dutch project, receives funding from S. Brin, co-founder of Google. In 2013, in London, the public tasting of the first "burger" made from cells grown *in vitro* took place, at an estimated cost of 250,000 euros.

6. While other terms tend to spread internationally, such as "cultured meat", the words *in vitro* remain commonly used in French public debate.
7. Post M. *et al.*, 2020, "Cultured beef: from small biopsy to substantial quantity", *Journal of the science of food and agriculture*, july.
8. Fischler C. (dir.), 2013, *Les alimentations particulières*, O. Jacob.
9. Churchill W., 1931, "Fifty years hence", *Popular mechanics.*
10. Kornbluth P., Pohl F., 1952, *The space merchants*, Ballantine.
11. This H., 2016, "What can 'artificial meat' be? Note by note cooking offers a variety of answers", *N3AF*, 6.
12. On Soylent, see Widdicombe L., 2014, "The end of food. Has a tech entrepreneur come up with a product to replace our meals?", *New Yorker.*
13. Benjaminson M. *et al.*, 2002, "*In vitro* edible muscle protein production system (mpps): stage 1, fish", *Acta Astronautica*, p. 879-889.
14. Catts O., Zurr I., 2013, "Disembodied livestock: the promise of a semi-living utopia", *Parallax*, p. 101-113.
15. https://patents.google.com/patent/WO1999031222A1/en

"*In vitro* meat" then flows into the form and chronology of disruptive *food tech* projects. This term refers to all food startups offering innovations (products, distribution, etc.), using information technology and biotechnology. The 2013 "burger" positions as a *proof of concept*. Subsequently, many startups, most of them new, take their first steps in incubators or receiving significant funding during venture capital rounds.

The companies involved are mainly located in California, then in the Netherlands and Israel with, for this country, commercial agreements signed with China in the area of *clean tech* (innovations aimed at reducing the ecological footprint). In France, there are at least three projects linked to "*in vitro* meat" (Gourmey for the production of an equivalent of foie gras, Vitalmeat for chicken cells, Core-Biogenesis for the bioproduction of growth factors, necessary to regulate the life cycle of cells)[16]. At the end of 2019, the venture capital sector supports 32 initiatives worldwide, at various stages of progress, for an amount of 166 million euros[17]. The total workforce is approaching 80 companies and is growing steadily[18]. The presence of Asian investors is noticeable, as well as the contribution of the pharmaceutical group Merck to Mosa Meats, or that of the multinational meat companies Tyson and Cargill, in January 2020, to a record fundraising of $ 161 million by Memphis Meats intended for the creation of a pilot production site. While they do exist, partnerships with public research organizations are not often to the fore[19]. The projects aim to imitate the flesh of different animals: beef, chicken, fish, crustaceans. Some adopt a premium orientation (wagyu, red tuna, foie gras), but most are positioned on the niche of minced, weakly structured, "meat".

While searching for technical solutions and competing for the processes, these actors "storytell" a narrative of *in vitro* "meat" and cooperate in conferences, presenting each year the scope of the work carried out, the next steps, the pitfalls, etc. Several books formulate the challenges of the project[20] and exhibit a trend, an overall movement[21]. In addition, NGOs linked to the vegan movement (New Harvest, The Good Food Institute), together with researchers in psychology or marketing, study the "social acceptability" and the ways in which this innovation is delivered to consumers. Public opinion and strategic considerations thus determine the terms that are used: "cultured", "clean", "cell-based", etc. Beyond the variations, all names assume that the product has the qualities of farmed meat, without its drawbacks.

When it comes to processes, there are many challenges, and progress is difficult to assess (Box 1). Biology works by trial and error[22]: many tests are necessary to mimic natural processes[23], to substitute elements that are too expensive, unfit for human consumption, ethically troublesome, etc., with virtuous equivalents, and finally to optimize them. The difficulties are even greater since the *in vivo* formation of muscle coordinates many biological processes. This tedious work at the laboratory bench is rarely mentioned, except to underline the contribution of automated tools (metabolic modeling and bioinformatics), which may ensure control and acceleration.

The sector obtains its supplies from pharmaceutical companies, which produce inputs compatible with human medicine, with very high health requirements and prices. Recently, the funding boom has sparked the emergence of second-generation startups, providing services to production-oriented startups, which could help lower costs.

All in all, a cloud of uncertainties still surrounds the technologies chosen and the results obtained on a pre-industrial scale - a fairly typical situation in a universe torn

Box 1 - **The technical challenges of "*in vitro* meat"**

The challenges concern the four components of the cultivation system.

- **Cell lines**
  The origin of stem cells determines their ability to proliferate. The number of divisions is naturally constrained (Hayflick limit). To go beyond 50 generations and take advantage of the exponential growth of cells, it would be necessary to adjust the knowledge obtained on model animals in the laboratory, to real life / farm animals, and to develop "immortalized" lines through genetic engineering. Such an option based on the principle of GMOs is controversial, but tempting to bypass certain technical dead-ends and win the "race to the market".
- **The culture medium**
  Classically used in culture media, fetal bovine serum provides hormones and other growth factors necessary for the proliferation and differentiation of cells. Some say it represents more than 90% of the production costs, and its use must therefore be lowered. In addition, ethical problems arise with this serum, as it is necessary to slaughter pregnant cows, not to mention matters of composition and consistency. While the development of media that do not use this serum seems possible, scientific publications on the subject remain scarce. It should be remembered, that the use of hormones and growth factors is prohibited in Europe for animal breeding.
- **Micro-supports or scaffolds**
  At the stem cell differentiation stage, the development of cultures in 3D, as opposed to those in 2D on Petri dishes, raises questions about the choice of materials. Coatings, topographies, and hydrophilic characters are instrumental in the adhesion of the cells. Separation techniques from cells during "harvest", and the compatibility with food consumption, are still an issue.
- **Bioreactors**
  Scaling up beyond the small formats commonly used in labs, poses problems of mixing and oxygenation in incubators (or, failing that, of cell necrosis), i.e. issues in fluid mechanics. Different schemes are conceivable, depending on the type of final product targeted (more or less structured). In a theoretical cost study conducted by the Good Food Institute[24], cell proliferation occurs with a bioreactor change every 10 days, up to a 20,000 liters tank. At this stage, 50 to 90% of the cells are harvested for differentiation into muscle fibers. The non-transferred part continues to multiply, with these successive "culture trains" taking advantage of exponential growth to obtain up to 19 tons of material from a 2.5 ml inoculum. According to statements from Just Inc., the basis of chicken bites marketed in Singapore is grown in 1,200 liter bioreactors. Note, however, that in the field of allogeneic cell therapy, in human medicine, the jump to bioreactors with a capacity of 35 to 50 liters, currently still in progress - i.e. volumes much lower than those envisaged for industrial production of "*in vitro* meat" - is described as difficult by some publications[25].

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16. Pons H., 2020, « En France, la viande artificielle se tient encore loin de nos assiettes », *Maddyness*, décembre.
17. Choudury D. *et al.*, 2020, "The business of cultured meat", *Trends in biotechnology*, june, 38.
18. Good Food Institute, 2020, *2019 State industry report. Cultivated meat.*
19. Mosa Meats is, however, linked to Maastricht University, and Aleph Farms to the Technion, the Israel Institute of Technology.
20. For instance, Shapiro P., 2018, *Clean meat. How growing meat without animals will revolutionize dinner and the world,* Gallery books.
21. Stephens N. *et al.*, 2020, "Making sense of making meat: moments in the first 20 years of tissue engineering muscle to make food", *Frontiers in sustainable food systems*, july.
22. Knorr-Cetina K., 1996, « Le "souci de soi" ou les "tâtonnements" : ethnographie de l'empirie dans deux disciplines scientifiques », *Sociologie du travail,* 1996, pp. 311-330.
23. Post M., Hocquette J.-F., 2017, "New sources of animal proteins: Cultured meat", in Purslow P. (dir.), *New aspects of meat quality,* Elsevier.
24. Specht L., 2020, *op. cit.*
25. Allan S. J. *et al.*, 2019, "Bioprocess design considerations for cultured meat production with a focus on the expansion bioreactor", *Frontiers in sustainable food systems*, june.

between the requirements of disruption, the principle of transparency and the secrecy of the processes[26]. More detailed information should gradually become available, at the initiative of startups, providing the benchmarks that are currently lacking.

3 - An imminent arrival on the market, but still a lot of questions

Some players already consider "*in vitro* meat" to be an equivalent in characteristics to minced meat, which represents 50% of the world meat market. This new production would replace factory farming, which would then become "obsolete". Several historical antecedents are summoned to show that such a quick, far-reaching change is possible: decline of the whaling industry with the development of kerosene, abandonment of horse traction with the mass production of automobiles, etc.

Yet, for such a trajectory to gain momentum, a series of conditions should be met: product equivalence (in terms of technical-functional properties), price level, convenience, and a trust of eaters at least equivalent to the one granted to the natural referent[27]. Beyond the technical difficulties relating to product development, many uncertainties remain before considering large-scale commercialization. Several parameters, in particular the choices of public regulation, will condition this dissemination, potentially leading to contrasting situations across the world.

Marketing is first and foremost subject to obtaining marketing authorizations. In Europe, the files within the framework of the Novel Food regulation require, among other things, to remove doubts about the use of synthetic hormones or GMOs, and "to demonstrate that the material used (plastic, biomaterials), the culture medium with its many components and compounds, the animal cells used, etc., present no danger"[28]. The protection of public health is a prerequisite. Unless it abides such requirements, "*in vitro* meat" cannot be produced or distributed on European markets.

A second uncertainty concerns the right to call the substitute "meat". US law appears to be moving towards such recognition, under certain conditions, but it could be different in Europe, where regulations require demonstration of nutritional equivalence, and involve assessments based on habits and customs[29]. Among the elements expected from a meat product, the protein content of cultured cells (e.g. essential amino acids) is not yet known, nor their iron or vitamin B12 content[30]. Another rarely mentioned challenge is the texturing of the final product. Right now, one gets more of a clump of cells, shaped like a paste, than a textured muscle. Only the Aleph Farms project aims at the direct production of a whole piece, such as sirloin steak or duck aiguillettes, while others rather seek to improve the palatability of the product by co-culturing different types of cells, including adipocytes in addition to myocytes. It should be noted that in France, the law relating to the transparency of information on agricultural and food products, prohibits any animal name for products made from plant compounds. "*In vitro* meat" will therefore meet the same name restrictions as previous generations of alternative proteins, when they intend to use animal denominations, such as for example "milk", "meat" or "steak".

In addition, the rules on consumer information will weigh, in particular to demonstrate secondary qualities. For example, while the first life cycle analyzes announced a drastic reduction in the ecological footprint, coupling with renewable energies now appears necessary to achieve these performances[31]. Likewise, while formulation is in progress, the use of fetal bovine serum, as in the case of chicken bites marketed in Singapore, is an obstacle for *animal free* labelling.

Another uncertainty relates to the development of a viable business model. The low level of texturing positions the products in the Fast-Moving Consumer Goods (FMCG) segment, where price is the main determinant of the purchasing decision. The natural meat replacement scenario is then unlikely to happen if prices do not approach parity. However, we can also consider a niche positioning, with products marketed towards young tech-savvy consumers, who increasingly consider meat as a mere protein intake. Co-formulation scenarios of hybrid *in vitro*-plant protein products are also very likely.

Finally, the trajectory and success of these products will depend on considerations on the social model associated with *in vitro* cultures. Critics of the technological headlong rush are increasing, warning against health risks[32] or defending traditional breeding and gastronomy[33]. The shift from a logic of controversy to a situation of open conflict[34] could have a dissuasive effect on the development of these products and severely limit their place in food systems. In France, an article relating to the prohibition of "cellular meat" in school canteens was adopted in first reading during the debates at the National Assembly on the Climate and Resilience Act[35]. In the event of production accidents on the markets where "*in vitro* meat" is approved, as today in Singapore, and more generally in case of unexpected effects, a front of opposition to these biotechnologies may precipitate, as happened with GMOs.

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A number of players aim to replace livestock products with substances obtained in a controlled environment. The first achievements of "artificial meat" struck a chord, attracting substantial funding. Even if the techniques currently used could benefit from medical advances in tissue engineering, considerable uncertainties remain, however, as regards both the processes and the products: use of growth hormones in culture media, ecological footprint, nutritional properties, costs, consumer interest, etc. In addition to these technological uncertainties, social issues are very important. As such, the positions taken by the Minister of Agriculture and Food and by members of the French Parliament show that the public authorities are already addressing these issues.

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26. Guthman J., Biltekoff C., 2020, "Magical disruption? Alternative protein and the promise of de-materialization", *Environment and Planning E: Nature and Space.*
27. Burton R., 2019, "The potential impact of synthetic animal protein on livestock production. The new 'war against agriculture'?", *Journal of rural studies*, 68.
28. Hocquette J.-F. *et al.*, 2020, « Viande *in vitro*. Intérêts, enjeux et perception des consommateurs », *Techniques de l'ingénieur,* décembre.
29. Seehafer A., Bartels M., 2019, "Meat 2.0. The regulatory environment of plant-based and cultured meat", *EFFL*, 4, pp. 323-331.
30. Fraeye I. *et al.*, 2020, "Sensorial and nutritional aspects of cultured meat in comparison to traditional meat: Much to be inferred", *Frontiers in nutrition*, 7:35.
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32. Muraille E., 2019, « La "viande cultivée" en laboratoire pose plus de problèmes qu'elle n'en résout », *The Conversation,* 11/8.
33. For instance, Luneau G., 2020, *Steak barbare,* Editions de l'Aube. Porcher J., 2019, *Cause animale, cause du capital,* Le bord de l'eau.
34. Chateauraynaud F. *et al.*, 2010, *Les OGM entre régulation économique et critique radicale*, GSPR.
35. See https://www.assemblee-nationale.fr/dyn/15/dossiers/lutte_contre_le_dereglement_climatique. And the position of the French association for cellular agriculture: Rolland N., 2021, « Agriculture : La viande cultivée se voit déjà privée de cantine », *Le Monde,* 04/21.

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