The changing face of protein production

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As consumers become more concerned about the impacts of their food choices on both their own health and the health of the planet, the need for innovative methods to produce foods that are not only nutritious but environmentally friendly and ethical is rising more than ever before. Alternative ways of supplying proteins into human diet have been one of the most controversial subjects over recent years, resulting in development of various methods to replace conventional animal-based products, such as milk and meat. With recent advancements integrating cell-culture, genetic engineering, and food science, producing meat or milk in a laboratory is no longer only a scene in science fiction movies.

According to the United Nations' World Population Prospects (UN, 2019), the world population will grow from 7.7 billion people in 2019 to 10.9 billion in 2100, with the countries of Sub-Saharan Africa accounting for more than 50% of the global population growth (Figure 1; Wood, 2019). Therefore, feeding a growing world population must first and foremost consider people living in those rapidly growing regions and not just Europe or the USA where population is projected to begin to decline before the end of this century. That said, are the current innovations in producing food for a growing population, such as lab-grown meats, ultra-processed plant-based products, precision fermentation and insect proteins applicable to the countries where food security and malnourishment are still major issues? We need solutions that work for these developing countries and their people not just middle-class Western consumers.

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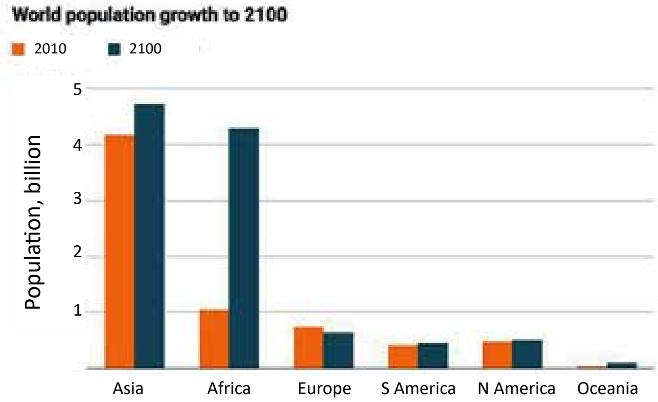

Figure 1. Projected world population growth from 2010 to 2100. (Adapted from: *The Conversation*)

The alternative protein challenge

Plant-based products for instance, such as plant milk replicates or plant-based fake meat, have gained considerable popularity over the past few years. Despite their nutritional value and environmental footprint being constantly scrutinised, it is predicted that the market size for these products in Australia alone will be $3.1 billion by 2030 (Admassu *et al.*, 2020). These products will not be the focus of this article; instead, we will discuss the less debated area of recombinant food proteins (precision fermentation), cell-based meat, and insect proteins.

One industry report speculates that: the cost of (recombinant) food proteins will be five times cheaper by 2030 and 10 times cheaper by 2035. By 2030, modern food production will be higher quality and cost less than half as much to produce as

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animal-derived products. By 2030, the number of cows in the USA will have fallen by 50% and the cattle farming industry will be all but bankrupt. The whole of the cow milk industry will collapse once these technologies are used to produce the individual proteins in milk and this industry will be bankrupt by 2030 (Tubb and Seba, 2021). These predictions are based solely on their view of advances in precision fermentation.

Precision fermentation (recombinant protein production)

Precision fermentation is 'a process that allows us to program micro-organisms to produce almost any complex organic molecule' (Tubb and Seba, 2021). In other words, we take the gene for a protein (say beta-lactoglobulin) that we want to produce and insert it into a plasmid and then transfect that plasmid into a cell that can produce this protein in a fermentation vessel (Figure 2). It all sounds fairly simple and today it is, but it is not cheap to do.

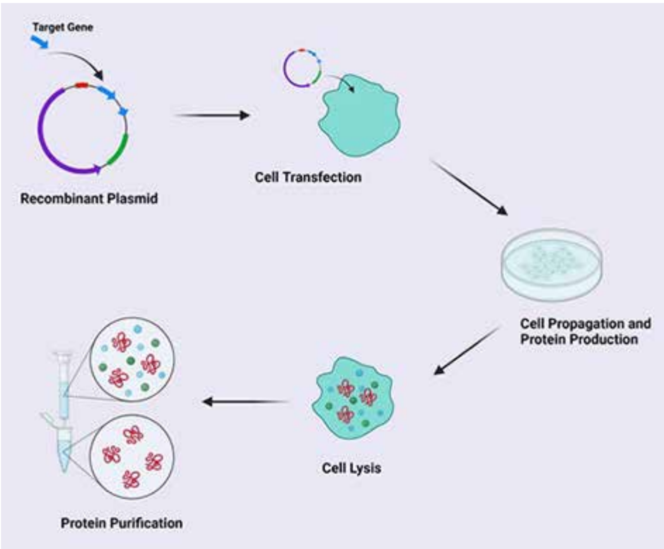

Figure 2. Processes involved in producing recombinant protein through precision fermentation. [Created through *BioRender.com*]

For example, how would we produce one billion litres of precision fermented milk using yeast cells? There are six key proteins in milk, and we would need to ferment each one separately, as each gene construct will perform differently in the laboratory. For milk with 3% protein content, we would need 30 million kilograms of protein. With yeast cultures producing around 10 grams of recombinant protein/litre that would require three billion litres of yeast culture media. Using 10,000 litre fermenters, we therefore require approximately 12,000 10-kilolitre bioreactors. If we assume that a production run takes two weeks, involving a set up phase, fermentation step and clean-up and re-sterilisation process, that would allow for 26 production runs each year. This would require $600 million in the cost of the fermentation equipment alone, not including staff, facilities, or materials.

Currently production costs for the many recombinant proteins used in medicine are hundreds of thousands of dollars per kilogram but a lot less for industrial-grade proteins like cellulase and beta-glucosidase, used in ethanol production (Puetz and Wurm, 2019). The major reasons for these large differences are the regulatory standards required and the extent of downstream processing needed to produce a highly pure and consistent final product. Assuming an estimated final cost of around $100/kg for the recombinant milk proteins, that would result in a cost of goods of $3/litre for protein alone in the final product. We would then need to add sterile water, fats, sugars, minerals, and vitamins to produce the final precision fermented milk. The last step would be some form of filtration or sterilisation before bottling the final product. Our estimate is that the likely cost of production of these products would be at least four times that of fresh milk. There are companies like *Perfect Day* already producing ice-cream with recombinant beta-lactoglobulin in limited amounts.

In an effort to revolutionise the infant nutrition industry, a Singapore-based startup, *TurtleTree Labs*, is producing human breastmilk by culturing mammalian cells in the lab. Although still in its infancy, the company has raised $3.2 million seed funding and managed to get closer to an economically viable price range by reducing their cultured milk price from $180 per litre to $30 per litre. Again, is this a solution for solving the food shortage issues outside the Western world?

Cell-based meat

Many high-tech companies are now shifting their focus to producing cell-based meat (e.g. *Memphis Meats*, *Eat Just*), also known as cultivated, *in vitro,* and cultured meat, referring to 'meat cells cultivated in cell culture bioreactors, as opposed to on a farm' (Vergeer *et al.*, 2021). A lot of the processes for production of cell-based meats will be the same as precision fermentation as explained above, except that you grow muscle cells from a cow in the same types of fermenters. However, mammalian cells are far more expensive to grow than yeast because they need special growth factors and nutrients. These essential cell-growth factors, such as insulin growth factor, will be produced as recombinant proteins as described above. In a recent report commissioned by the *Good Food Institute*, an estimated costing for cell-based meats was modelled for production of 10 kilotons of cell-based meat per year (Vergeer *et al.*, 2021). Their best estimate, which assumes some significant improvements in the final cost of media and facilities, was $133/kg. With ground beef at less than $5 per kilo there is a major challenge ahead. Their estimate for the cost of a cell-based meat production facility was US$450 million and 1000 of these facilities will be needed to replace the current beef production in the USA alone. In addition, all energy would need to be from fully renewable sources to be more sustainable than current meat production systems (Lynch and Pierrehumbert, 2019). The same group also discussed some possibilities to reduce the cost of producing cell-based meat by 2030 in order to bring it closer to a commercially viable alternative. These possibilities include: lowering the price of growth factors and recombinant proteins, increasing cell density, shortening production run time, and using larger cell volume, hence increasing production efficiency and minimising media, equipment and energy use. They estimated that by reducing the price of recombinant proteins and growth factors only, the production cost could potentially drop to $15/kg, whereas implementing all of the above-mentioned strategies for lowering costs will potentially reduce production costs to a price that is comparable to the traditional meat value ($2/kg).

In summary the estimates for cell-based meat production are currently 100- to 1000-fold that of conventional systems. Their major problem is that they assume that a cell-based facility can be run at a food-grade standard when in fact it will have to be a pharmaceutical-grade standard (see Figure 3)..

Figure 3. Contrasting a food-grade facility on the left with a pharmaceutical-grade facility on the right. [Credit: Getty Images]

In the USA, the Food and Drug Administration will regulate the fermentation process and the US Department of Agriculture the production of the final products, further complicating what could be a difficult regulatory environment (Watson, 2019). The growth cycle for a batch of cells will be a minimum of 42 days of continuous sterile culture, almost impossible to maintain without rigorous manufacturing standards. The optimism that cell-based protein costs of production can be decreased by over 1000-fold are unrealistic, given that after tens of billions of dollars of investment by the pharmaceutical industry over the last 20 years, the productivity of cell-based medicinal products was only improved by 10- to 20-fold. In essence, cell-based meats at best will be a high-value niche product servicing middle- to high-income consumers. The final product is also just a burger, not a prime steak, that will require a whole new set of technologies such as edible cell scaffolds and 3D printing of meat.

Insect proteins

Food waste is a significant problem, with over 30% of the food currently produced being wasted. Using insects such as soldier fly larvae and mealworms we can convert these waste streams into highly nutritious protein for pets, fish, and livestock. Over $600 million Euros have been invested and several facilities are already farming insects at large scale (6,000 tonnes per year) with *Protix* in Europe and *Enterra* in Canada (Niyonsaba *et al.*, 2021). Numerous insects are also already consumed whole by humans, with two billion people in 130 countries enjoying these products, and there is no reason in the long run why insect proteins, when produced in powdered form, cannot be used for human food manufacture.

Conclusion

All of these new technologies are technically viable. The challenge is whether they can be manufactured at scale and a cost of goods to be commercially viable. It is unlikely that these new protein sources will replace animal-sourced proteins, and there are significant questions about their environmental and nutritional claims. There are already restrictions in various countries on the use of terms like 'milk' and 'meat' on food labels for these alternative protein products, such as plant-based milk, and this could also be a problem for precision fermented and cell-based products. There are also challenges with consumer acceptance of products that will be produced with genetically modified organisms, cell-based culture systems, or insect farming. In most cases they will be niche products for high-value markets for consumers in developed countries.

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