Towards Biomanufacturing of Cultured Meat

Yap Wee Swan, Deepak Choudhury*, Ratima Suntornnond

Biomanufacturing Technology, Bioprocessing Technology Institute (BTI),
*Agency for Science, Technology, and Research (A*STAR), 20 Biopolis Way, Singapore 138668*

**Correspondence: Deepak_Choudhury@bti.a-star.edu.sg*
Twitter: @biodreamz
Lab website: [Biomanufacturing Technology]

Keywords: Cultured meat, Cultivated meat, Cell-based Meat, Alternative Protein, Cellular agriculture, Biomanufacturing

Abstract

Cultured meat has emerged as a promising alternative to conventional meat due to its potential to be healthier, more humane and sustainable. The development of serum-free media by Messmer et al. and the adaptation of soy protein as edible scaffolds by Ben-Arye et al. highlight innovations in this nascent field.

Cultured meat/Cultivated Meat (CM) is being intensively explored as an alternative meat source as limited existing resources will be unable to meet the needs of a burgeoning population in the long run. As the over dependence of meat production using conventional methods often entails a significant environmental footprint, CM appears rather promising due to its potential to mitigate some of these environmental ramifications [1]. Although the sector has only gained prominence in the last decade following the historical showcase of the world's first cultured hamburger in 2013 [2,3], the earliest references to CM date back to the 1900s [4]. A summary of the significant milestones guiding CM history can be found in **Figure 1A**. Notably, CM's commercialisation was recognised in 2020 with the launch of first cultured chicken in Singapore [5].

Since the field is still evolving rapidly, more focus needs to be placed on issues such as tangible scalability and sustainability, else the success would be limited. In addition, numerous studies have outlined four key challenges/research pillars for this sector: cell line development, serum-free media, edible scaffoldings and bioprocess design [1,4,6]. In this spotlight, we are highlighting key recent publications which rigorously attempted to address the media and scaffolding challenges (**Figure 1B**).

Fetal bovine serum (FBS) is traditionally used to promote cell proliferation in cell culture media, but drastic reductions in its concentrations promote muscle cell differentiation. With commercial products still using FBS in their manufacturing process, eliminating serums is undoubtedly a significant step towards sustainable CM production, reducing the reliance on animal-based components. A study that stood out among those investigating serum-free media was by Messmer and colleagues, who examined the gene expression profiles of bovine satellite cells undergoing serum-starvation-induced myogenic differentiation [7]. The study uncovered previously unknown mechanisms behind the differentiation process, which is beneficial for developing serum-free cell culture techniques. The initial phase of differentiation was associated with an upregulation of surface receptors such as insulin-like growth factor 1 receptor (IGF1R), transferrin receptor (TFRC) and lysophosphatidic acid receptor 1 (LPAR1). It was found that by supplementing the serum-free media with ligands capable of binding to these receptors, differentiation can be induced without serum starvation by using similar mechanisms. Furthermore, the serum-free media were even observed to promote the formation and maturation of myotubes within collagen/Matrigel hydrogels over an eight-day period, allowing the fabrication of three-dimensional muscle models. Although the muscle model currently comprises hydrogels made from animal components, it serves as a proof of concept for the efficacy of the developed serum-free media and suggests its potential application in CM.

Despite the benefits of the developed media accords, their scalability and reproducibility are crucial for extensive adoption. As culture media is a significant contributor to CM prices, it is vital to drive this cost down to scale. Precision fermentation could be a cost-effective method of producing the active ligands necessary for the developed media at scale by leveraging existing fermentation infrastructure [8]. Additionally, it is imperative to verify if differentiation mechanisms are conserved across various organisms to facilitate the development of more diverse CM products. By doing so, we would be able to ensure the versatility of the developed media and its application in the CM industry.

In another highly-cited study by Ben-Arye and colleagues, the team found that textured soy proteins (TSP) were suitable scaffolds for CM applications due to their porosity, versatility, and palatability [9]. Despite its extensive use in producing plant-based meat alternatives for its texture and protein content, its potential as a tissue engineering scaffold was not explored until this work. The team of researchers demonstrated that TSP could support cell growth and facilitate tissue formation by conferring mechanical support similar to the native extracellular matrix (ECM). This is particularly important when producing thicker CM cuts than existing minced and processed products. The sensory panel in the study also highlighted the product’s palatability with positive descriptors such as “pleasant meaty flavour” during the tasting process. As one of the first studies to examine the sensory characteristics of CM products with a human tasting panel, it opens CM products up to the realms of food-related research and illustrates how sensory profiles play a pivotal role in understanding consumer acceptance of CM products.

With its sustainable and scalable origins (i.e., from food waste valorisation), TSP’s potential as a scaffold is varied. However, since this study used the serum in the culture process, we believe the research will benefit greatly from integrating insights from other serum-free media research to create a more sustainable product and contribute to the sector’s collective growth.

Aside from the current cell, media, scaffolding and bioprocessing challenges; safety remains a crucial issue for consumer acceptance of CM products. The recent expert consultation organised jointly by FAO and WHO in Nov 2022 on cell-based food was one of the first sincere attempts to openly discuss, debate and collate information on various safety aspects of cell-based food production process [10]. The formation of cellular agricultural societies across various geographical locations is a welcome move to initiate closer deliberations and fine-tune the common agenda [11]. The best way forward is to address safety concerns through an ecosystem similar to the aforementioned event that encourages more collaboration and effectively establishes industry standards for collective progress [12]. Ultimately, whichever the area of CM research, researchers and start-ups should not lose sight of the goal of developing reproducible and evidence-based CM technologies to alleviate the growing risks posed by our current food system and build a more resilient one [13].

Acknowledgement

This work is supported by the National Research Foundation, Singapore, and the Agency for Science, Technology and Research (A*STAR), under the Singapore Food Story R&D Programme (Grant Number H20H8a0003 awarded to Deepak Choudhury). Any opinions, findings, conclusions, or recommendations expressed in this material are those of the author(s). They do not reflect the views of the National Research Foundation, Singapore and the Agency for Science, Technology and Research (A*STAR). The authors would also like to thank Dr Quang Bach Le, Research Scientist at BTI A*STAR for feedback on the manuscript.

Declaration of interests

The authors declare no conflict of interest.

References

1. Post, M.J. (2012) Cultured meat from stem cells: Challenges and prospects. *Meat science* 92, 297-301
2. Choudhury, D. *et al.* (2020) The business of cultured meat. *Trends in biotechnology* 38, 573-577
3. Ng, E.T. *et al.* (2021) Cultured meat-a patentometric analysis. *Critical Reviews in Food Science and Nutrition*, 1-11
4. Edelman, P. *et al.* (2005) Commentary: In vitro-cultured meat production. *Tissue engineering* 11, 659-662
5. Tan, A. (2020) *THE STRAITS TIMES*
6. Stephens, N. *et al.* (2018) Bringing cultured meat to market: Technical, socio-political, and regulatory challenges in cellular agriculture. *Trends in food science & technology* 78, 155-166
7. Messmer, T. *et al.* (2022) A serum-free media formulation for cultured meat production supports bovine satellite cell differentiation in the absence of serum starvation. *Nature Food* 3, 74-85
8. Singh, S. *et al.* (2021) Cultivated meat production propelled by fermentation. *Trends in Food Science & Technology*,
9. Ben-Arye, T. *et al.* (2020) Textured soy protein scaffolds enable the generation of three-dimensional bovine skeletal muscle tissue for cell-based meat. *Nature Food* 1, 210-220
10. FAO (2023). Cell-based food.

11. GFI (2023). Leading APAC Cellular Agriculture Stakeholders Announce Historic Agreement in Singapore.
12. Ong, S. *et al.* (2020) Cell-based meat: current ambiguities with nomenclature. *Trends in Food Science & Technology* 102, 223-231
13. Holmes, D. *et al.* (2022) Cultured meat needs a race to mission not a race to market. *Nature Food* 3, 785-787

Figures

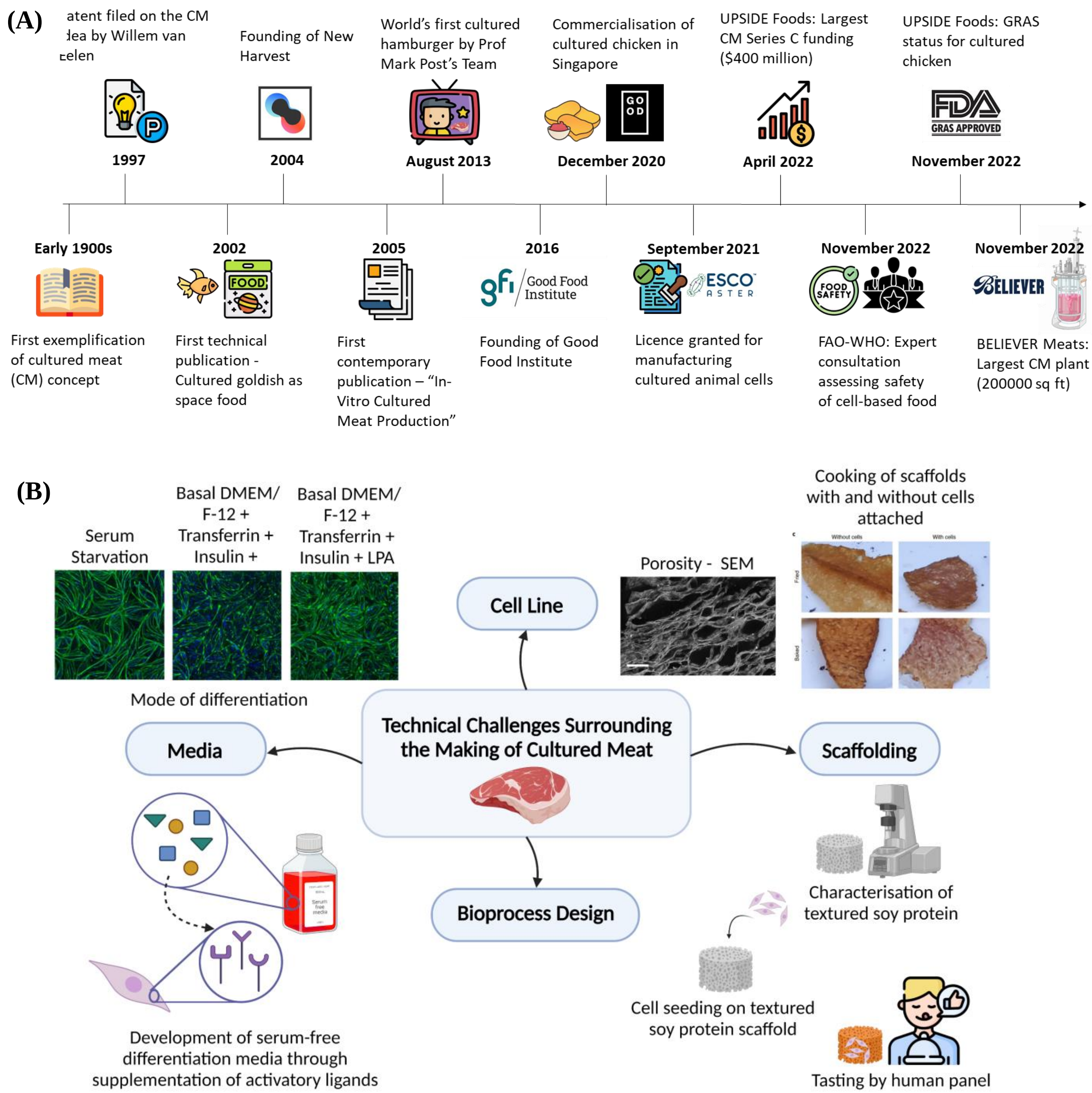

Figure 1. **(A)** A brief overview of the major milestones in the history of cultured meat (CM). This figure was created using icons from Flaticon (flaticon.com). **(B)** The figure was adapted from two major research initiatives exploring the development of serum-free differentiation media [7] and textured soy protein as scaffolds [9] and created using BioRender (http://biorender.com/).