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Recent progress of cultivated meat in Asia

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Abstract

Accelerated by recent technological advancements, alternative proteins (AP) offer new opportunities to produce meat alternatives in a more sustainable, efficient, and secure way compared to conventional animal agriculture. As a primary category of AP, cultivated meat (CM), which is grown *in vitro* from animal cells, rather than raising livestock, provides a new approach to creating meat that is identical to conventional meat. Although Asia was not the first region to invest in CM research, scientists and technologists have made significant strides across the continent in recent years. This article summarizes some of the most notable CM developments and advancements in four Asian countries (China, Japan, South Korea, and Singapore) spanning the areas of research and education, commercialization, and policy and regulation. Moreover, key insights into the challenges and opportunities that Asia's cultivated meat industry will encounter in the years ahead are also provided.

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Introduction

While cultivated meat (CM) has been drawing significant attention in recent years, the fundamental technology behind it was developed by French biologist Alexis Carrel^[1] more than a century ago. As far back as 1931, Winston Churchill brought up the first assumption that humanity should grow chicken breast or wing for food with a suitable media rather than raising a whole chicken. Nevertheless, it was not until Dutch researcher Mark Post showcased the world's first hamburger with a patty made of CM in 2013 that the awareness of CM started to grow around the world, triggering a wave of CM innovation^[2]. As of 2021, according to The Good Food Institute (GFI, Washington, DC, USA), Ark Biotech, and Agency for Science, Technology and Research (A*STAR), there are at least 107 CM companies in operation, 170 academic publications, and 49 patents that are directly relevant to CM worldwide^[3-5].

CM is one of the three primary pillars of the alternative protein (AP) space, which also includes meat, eggs, and dairy products produced from plants and enabled by fermentation technologies. Alternative proteins offer a scalable solution to many of the most pressing environmental and food security challenges. According to a comprehensive life cycle assessment commissioned by the GFI and conducted by research consultancy firm CE Delft (Netherlands), CM requires significantly less land than conventional meat and has a lower carbon footprint when produced using renewable energy^[6]. For example, CM could reduce beef production's climate footprint and land use by up to 92% and 95%, respectively. Additionally, CM shows higher efficiency in terms of its feedto-meat ratio. As a result, CM can aid in building a more sustainable and efficient food system that can provide sufficient volumes of meat to satisfy the projected 50% increase in global meat demand by 2050. Furthermore, CM can make

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global food supply chains less vulnerable by eliminating the risks of zoonotic diseases and strengthening the food production system and food security when being disrupted.

In general, there are four main steps to creating CM^[7,8]. Firstly, a suitable cell line needs to be developed, preferably stem cells that maintain the ability to differentiate in vitro into the muscle cells, adipose cells, and fibroblasts that meat is composed of. Then, the cells are cultured in a bioreactor and harvested when reaching sufficient quantity. Next, the cells can be further cultured in a bioreactor for maturation using scaffolds or via scaffold-free approaches. Lastly, the matured tissues are processed into food products. This hypothesis has been proved technically viable in the lab by scientists, but large-scale production of CM will require huge levels of investment to overcome technical challenges, reduce costs, and scale-up infrastructure. Moreover, as a novel food source, consumer acceptance and implementation of forward-thinking regulatory frameworks are both crucial for the continued development of CM.

As the CM industry has grown rapidly, its geographical distribution has also expanded. In 2021 alone, CM attracted \$62 million (USD) in invested capital in the Asia Pacific region^[3]. Although that only accounts for 4.5% of the global CM investment total, the Asia Pacific is one of the world's fastest-growing regions. Currently, Singapore is also the only country that has approved commercial sale of CM products, which has helped motivate Asian innovation hubs in accelerating cellular agriculture research and development. The rapid regional development of CM has been accelerated by the efforts and breakthroughs from different countries, China, Japan, South Korea, and Singapore in particular. This article summarizes the current state of CM and highlights the many challenges and opportunities the industry faces in these countries, including research and education, commercialization, policy and regulation.

Research and Education

Robust growth in CM publications

As shown in Fig. 1a, the total number of academic papers focusing on CM from researchers in China, Japan, South Korea, and Singapore is 65. As of March 2022, the statistics are based on searches of commonly used keywords, such as 'cultured meat', 'cultivated meat', 'lab-grown meat', and 'cellbased meat', in the Web of Science, PubMed, and Science-Direct databases (if a paper was jointly published by several researchers within these four countries, it was counted as one paper). The earliest article was published in 2015, titled 'The environmental prospects of cultured meat in China', which compared the energy use and greenhouse gas emissions associated with producing CM, livestock products, and crops^[9]. It was not until 2017 that the first research article addressing the industry's technical needs was published, by Nanjing Agricultural University (Nanjing, China)^[10]. This study, for the first time, successfully purified porcine muscle stem cells with the fluorescence-activated cell sorting method, which is of great importance for obtaining seed cells for CM. In 2019, a research team from the University of Tokyo (Tokyo, Japan) developed a fiber-shaped microcarrier for cell encapsulation, which can be used as a three-dimensional (3D) culture system to support large-scale cell expansion for CM^[11]. Following this, the number of publications by research teams from these four countries grew robustly to 14 in 2020 and increased nearly three fold in 2021. More than half of these papers are original research articles (Fig. 1b); while 48 articles focus on science and technologies, and the rest are either commercialization insights, such as market analysis and consumer acceptance, or general topics like environmental impacts, food security, and nomenclature (Fig. 1c).

Establishing a suitable cell line is a fundamental step for CM. As shown in Fig. 1d, most of the original scientific research articles reported significant findings in cell line development. For example, magnetic activation was tested for cell sorting, the feasibility of smooth muscle cells was evaluated as an alternative to commonly used satellite cells, and activating the yes-associated protein (YAP) of porcine muscle stem cells was evidenced to enhance cell proliferation and differentiation capacities at high cell density^[12-14]. Secondly, in recent years, many teams have reported the successful fabrication of structured meats, particularly in Japan. For example, Waseda University and Tokyo Women's Medical University research teams successfully developed a 6 $mm \times 6 mm$, 0.8 mm thick tissue using a self-developed net mould method with fibroblasts spheroids^[11]. Additionally, researchers at the University of Tokyo stacked matured tissue developed with the cylindrical molding method into a macroscale tissue^[15]. Furthermore, researchers from the University of Tokyo and the University of Tsukuba jointly bioprinted a 3D tissue consisting of 72 fibers made of bovine cells^[16]. Utilizing bioprinting technologies, China Meat Research Center's researchers also successfully created tissues up to six layers thick with bioinks containing porcine skeletal muscle satellite cells, and sodium alginate-gelatin and gelatin-methacrylatesilk fibroin as the biomaterials^[17].

Meanwhile, many studies have contributed to lowering the cost of CM, such as demonstrating the feasibility of using *Chlorella Vulgaris* extract or blue algae-derived C-phycocyanin as the nutrient source in culture media or developing a polysaccharide film-based platform for cell sheet



Fig. 1 Recent papers on cultivated meat from China (CN), Japan (JP), South Korea (KR), and Singapore (SG). (a) The total number of papers referencing cultivated meat from the four countries. (b) The number of research article types from the four countries. OR: original research, RA: review article, Others include discussion, editorial, and perspectives. (c) The number of papers with a focus on technology (Tech), commercialization (CE), and others. (d) The topic distribution of the scientific original research articles published from the four countries.

formation^[18,19]. Some findings increased bioprocess production scale by validating an airlifted reactor design via computational fluid dynamics modeling or investigating the hydrodynamics and mass transfer characteristics of a spinner flask^[20,21]. These inspiring research findings were also shared at international conferences and events such as the 7th International Cultivated Meat Conference. Currently, most of the publications from the CM research groups in these four countries focus on the upstream part of the CM value chain, such as studying relevant pathways and developing suitable immortalized cell lines for CM. Some of these studies investigated feasible methods for constructing a whole-cut meat in the lab-scale. There are a lack of studies on the midstream and downstream value chain (large-scale bioprocessing and food manufacturing) due to the nascent state of the industry. With rising commercial interest, it is anticipated that more midstream- and downstream-focused research findings will be reported, for example, topics like bioprocessing optimization and media for cost control and scaling to meet the needs in this growing industry. Research findings and innovations are also highly encouraged for publication in open-access journals or patented so as to share the advancement with the larger scientific community and accelerate industry growth.

Funding support for CM research

The research projects mentioned above are supported by both government and private grants. In Singapore, the Singapore Food Agency (SFA) and A*STAR established the Singapore Food Story (SFS) R&D Grant, which includes AP as a theme^[22]. The grant aims to encourage researchers to address technical challenges that may slow the national agenda of strengthening Singapore's food security and to ultimately achieve the '30 by 30' goal: producing 30% of Singapore's nutritional needs locally by 2030 through a productive and sustainable transformation. In China, CM research projects are mostly supported by the National Natural Science Foundation and the Key R&D Program of China or the local province. In 2020, a collaborated CM project by Nanjing Agricultural University and Joes Future Food was approved by Jiangsu Science and Technology Department. In the same year, plantbased and CM manufacturing was included as a theme in the 'Green Biological Manufacturing' program, a National Key R&D program launched by the Ministry of Science and Technology of China. Jiangnan University's three-year research project titled 'High-efficiency biological manufacturing technology of artificial meat' (https://news.jiangnan.edu.cn/ info/1048/74730.htm) was selected for funding. In addition, the 'Starry Night Science Fund Zhejiang University Shanghai Institute for Advanced Study' (http://fanxing.zju.edu.cn/#/), established by Zhejiang University and the Starry Night Foundation, which funded a cultivated fish project and a cultivated pork project focusing on muscle and fat generation. Meanwhile, GFI Consultancy, an AP promoting agency in China, also launched the first research grant dedicated specifically to AP research in China. In South Korea, in addition to the Innovative Cultured Meat Technology Development Alchemist Project launched by the National Research Foundation of Korea, CM research was also supported by the Korea Institute of Planning and Evaluation for Technology in

Food, Agriculture, and Forestry (IPET) through the Development of High Value-Added Food Technology Program. As for Japan, in 2017, the Japan Science and Technology Agency launched the JST-Mirai R&D program (www.jst.go.jp/mirai/ en/index.html) with eight prioritized themes set by the Ministry of Education, Culture, Sports, Science and Technology (MEXT). The program aims to facilitate R&D that can move the local industry closer to the 'proof-of-concept' stage. Three projects aiming to develop CM technologies were adopted as 'feasibility studies' under the innovation food production technologies of the 'Sustainable Society' mission in 2018. These three projects have been integrated into a fullscale R&D project ('Development of the production technology for next generation-meat using 3D tissue engineering techniques') since 2020. Although more research funding has been devoted to CM research in Asian countries, the support is still insufficient and needs to be strengthened to keep pace with western countries, where CM research began earlier. Governmental support is believed to help create a robust ecosystem and promote multidisciplinary research collaborations.

Research centers and educational courses

In recent years, increasing numbers of new research programs, research centers, and university modules have been established by governments, research institutes, and universities. For example, in 2019, Jiangnan University in China established the Science Center for Future Foods (http://future foods.jiangnan.edu.cn/) with multidisciplinary expertise in synthetic biology, sensory science, and biotechnology to leverage future food development. In 2021, the Bioprocessing Technology Institute (BTI, www.a-star.edu.sg/bti) of A*STAR in Singapore launched a new government-funded research program: The CentRe of Innovation for Sustainable banking and Production of cultivated Meats (CRISP Meats). BTI has over 19 years of experience in bioprocess science and biomedical engineering, which would aid CM innovation such as designing growth factors for media development and bioprocess development. In addition to these research developments, the first AP university module in Southeast Asia debuted at Singapore's Nanyang Technological University in 2021^[23]. The undergraduate elective module was developed in collaboration with scientists from The Good Food Institute Asia Pacific (GFI APAC), an alternative protein think tank. Subsequently, the National University of Singapore also worked with GFI APAC and A*STAR to introduce a graduatelevel course titled 'Introduction to Advanced Meat Alternatives'^[24]. These vital educational resources provide the next generation of scientists and technologists with a more comprehensive and systematic understanding of the science of AP.

Commercialization

Company and investment overview

According to GFI, the total capital investment in APAC's AP sector in 2021 was \$312 million USD, arising from 40 recorded deals^[3]. In particular, 19.9% of that total (\$62 million USD) was dedicated to CM, which was an increase from \$44 million USD in 2020 (Fig. 2a). Also in 2021, the world's first cultivated



Fig. 2 Commercialization landscape of cultivated meat. (a) APAC annual alternative protein invested capital and deal count from 2015 to 2021 (reproduced from GFI). (b) The number of CM companies in China, Japan, South Korea, and Singapore (excluding ingredients and equipment suppliers).

crustacean meat company, Singapore-based Shiok Meats (www.greenqueen.com.hk/shiok-meats-funding-seafood), achieved a total accumulated funding amount of \$30 million USD. Similarly, Joes Future Foods (www.joesfuturefood.com/ newsinfo/2046159.html), the first CM company in mainland China, raised \$10.9 million USD in their Series A round to focus on scaling up and building a pilot production line. Soon after, SeaWith, a South Korea-based cultivated seafood startup announced in February 2022, the completion of a \$5.43 million USD Series A investment round^[25]. The huge potential of Asia's CM sector has also motivated more entrepreneurs into this space so that the total number of CM companies in these four countries has now climbed to 17, with five newly formed CM startups launching in 2021 alone (Fig. 2b).

From prototype demonstration to the real taste

Since Asia's first batch of CM prototypes were successfully developed in 2019, versatile CM products have been showcased and tasted throughout the region (Fig. 3). The NISSIN FOODS Group and University of Tokyo created a 3D muscle tissue cube (www.nissin.com/en_jp/sustainability/feature/ cultured-meat) of 1.0 cm \times 0.8 cm \times 0.7 cm (the prototype was not edible due to the use of research materials). A research team at Nanjing Agricultural University (https:// kxyjy.njau.edu.cn/info/1062/8879.htm) successfully produced 5 g of cultivated pork after 20 days of culture^[26]. At the same time, CM was gradually moving beyond a laboratory setting and into small-scale tasting events. In 2019, Shiok Meats presented a traditional Chinese dim sum dish called 'Siew Mai' made of cultivated shrimp meat at the Disruption in Food and Sustainability Summit^[27]. Similarly, Avant Meats, a Hong Kong-based cultivated fish company, demonstrated the world's first cultivated fish maw products at the Asia Society's Future Food Summit^[28]. More CM seafood products were subsequently developed and tasted after that, including cultivated lobster meat, crab meat, and fish fillets. In addition to seafood, cultivated pork and beef products have also been created by Joes Future Food, CellX, and SeaWith, and sampled by invited guests at exclusive tasting events. It was until December 2019, when California-based startup Eat Just (https://goodmeat.co) obtained the world's first regulatory

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approval from SFA for commercial sales of a cultivated meat product, the first ever cultivated meat product was debuted on the menu at a local restaurant. After that, Eat Just's cultivated chicken bites were soon offered in limited quantities through a food delivery service and were even featured on a pop-up menu at an iconic Singapore hawker stall.

The need to leap over hurdles—cost reduction and scaling-up

The CM industry has made tangible progress in overcoming many complex scientific obstacles, such as increasing production rates and yield. Nevertheless, if the cost of CM remains as high as it was for the first cultivated shrimp 'Siew Mai', which cost more than \$3,500 USD, large-scale commercialization of CM will not be possible. Since CM has been developed by borrowing technologies from the biopharmaceutical field, a primary challenge for the whole industry is to reduce the overall production cost to make CM comparable in price to conventional meat products currently available in the market. It is generally agreed that the high cost of CM can be largely attributed to the growth factors and serum used in the culture media; hence, multiple solutions are being explored in media development.

Using serum-free culture media is one approach, by reducing the amount or eliminating the use of serum. South Korean startup CellMEAT has demonstrated that its exclusive serum-free media can maintain cell viability and accelerate cell proliferation^[29]. According to Avant Meats, they have reduced 90% of their production costs compared to the company's initial production runs by using serum-free media. To further reduce the production costs, Avant partnered with QuaCell, a biotechnology company in China equipped with ISO and GMP accredited facilities and large-scale bioreactors, to investigate using food-grade ingredients in the optimized formulation for large-scale production^[30]. Alternatively, Sea-With developed a proprietary technology of cultivating lowiodine brown algae seaweeds to produce a low-cost serumfree media. They also uses microalgae-based technology in scaffolding fabrication for its cultivated beef prototype^[31]. More recently, KCell Biosciences, a cell culture media startup, partnered with South Korean food company CJ CheilJedang to build facilities in Busan, South Korea, aiming to produce



Fig. 3 Milestones of the cultivated meat industry in China, Japan, South Korea, and Singapore from 2019.

low-cost cell culture media for the cellular agriculture supply chain^[32].

Partnerships between CM startups, large corporations, biotechnology companies, and research centers play an essential role in solving industry bottlenecks. Japanese food giant Ajinomoto recently announced a partnership with Israeli CM startup SuperMeat to contribute its strength in biotechnology and fermentation for culture media development^[33]. Similarly, Japanese startup IntegriCulture organized the 'CulNet Consortium', which gathers together company collaborators in the supply chain specializing in scaffolding, bioreactors, and media development, aiming to create an infrastructure platform — the 'CulNet System[™] (https://integriculture.com/ en/technology/) — to address cost, safety, and scale-up challenges in CM. This new platform has demonstrated the ability to supply serum components and facilitate faster liverderived cell proliferation than conventional animal serum.

Moving CM production from lab scale to commercial scale is another challenge. In Asia, Shiok Meats has taken an early lead in the scaling-up process. The company's mini-pilot plant is now operating in Singapore to support cultivated seafood R&D^[34]. Shiok Meats is also planning to establish a satellite lab in Thailand in the near future. Meanwhile, Avant Meats has started a collaboration with A*STAR's BTI, aiming to scale up the production of food-grade cultivated fish by identifying the critical factors affecting fish cell growth and optimizing process design through joint research^[35]. Additionally, Singapore-based Esco Aster's cGMP AsterMavorsTM platform has received SFA's approval for CM manufacturing and supports research labs and companies in cellular agriculture process development and validation from small scale to pilot scale (up to $1.2-1.6 \times 10^{12}$ cells)^[36].

Developing regional and global strategic partnerships

Among all the continents, Asia has the highest fish consumption with a major proportion accounted for by China and Japan^[37]. Growing demand for seafood and rising challenges fulfilling that demand has helped drive strategic partnership development. Avant Meats has partnered with Vietnam's top seafood exporter, Vinh Hoan Corporation, to promote the commercialization of cultivated fish products^[38]. Similarly, California-based cultivated fish company BlueNalu (www.bluenalu.com) also signed Memorandums of Understanding (MOUs) with global food giants Thai Union and Mitsubishi to accelerate market research, consumer insight collection, regulatory frameworks, and exploration of business and product opportunities for Asia's cultivated fish market.

Global collaboration is not limited to cultivated seafood. Israel-based CM startup Aleph Farms (www.aleph-farms.com) has partnered with Mitsubishi, Thai Union, and CJ CheilJedang to develop market and commercialization strategies to sell cultivated beef in Asia. In addition to surging regional demand for protein, Asian markets are also appealing because of greater consumer acceptance of novel foods. According to a cross-country study conducted by Singapore Management University, CM's acceptance was higher among Singaporean participants than those from the US^[39]. A previous peer-reviewed study similarly reported that consumers' willingness to purchase CM is higher in China and India than in the US^[40].

Policy and Regulation

Singapore has been an early leader by allowing some CM products to be sold within the country. SFA was also the first

regulatory agency in the world to grant a food processing license to a contract development and manufacturing organization for CM manufacturing. In late 2021, SFA updated its 'Requirements for the Safety Assessment of Novel Foods and Novel Food Ingredients', which provides guidance for food companies on required safety assessments for novel foods and novel food ingredients^[41]. In the same year, SFA approved new types of cultivated chicken products to be sold in the market in 2022. These progressive actions have helped successfully establish Singapore as an active cellular agriculture innovation hub.

In other countries, efforts are also being made to facilitate pre-market approval and post-market supervision. For example, in Japan, an industry-academia-government coalition called the 'Japan Association for Cellular Agriculture' (JACA, https://crs-japan.org/en/programs/cellular-agriculture) is developing rule creation protocols for CM commercialization. Through in-depth discussion with different stakeholders. JACA is working on developing industry guidelines and recommendations, including safety and quality control frameworks and food labeling standards that can be used as an advisory for new law implementation. In South Korea, it is reported that Korea's Ministry of Food and Drug Safety plans to lay the foundation for reviewing the safety evaluation of AP foods by 2024, including CM. Meanwhile, 'obtaining calories and protein from plants, animals and microorganisms' was advocated during the Fifth Session of the 13th Chinese People's Political Consultative Conference in China, which underlined the importance of diversifying protein sources. Apart from this, China has also taken proactive steps to support its domestic CM sector, which include demonstrating a strategic plan for 'future food manufacturing' in the nation's latest five-year agricultural plan as part of China's blueprint for food security, and advocating the exploration of 'synthetic proteins' for novel food in the '14th Five-Year Bioeconomy Plan'.

Since CM is commonly regarded as a novel food source, it is necessary to establish clear guidelines and assessments to ensure safety. Indeed, even in Singapore, CM regulatory approvals have so far been granted on a case-by-case basis. In China, there is currently no comprehensive guideline on CM regulation beyond a standard legal document titled 'Administrative Measures for the Safety Review of New Food Raw Materials', which regulates the use of raw materials without consumption history in China^[42,43]. The rapid development of CM technologies makes it important for national authorities to begin a dialogue with different stakeholders and obtain a comprehensive understanding of CM production, so that they can prepare regulatory frameworks accordingly. In the meantime, the Food and Agriculture Organization of the United Nations has actively discussed the CM-associated food safety implications in a foresight report, which provides insights into potential food safety hazards from cell lines, media components, and food safety assessment needing to be performed for the end products^[44].

Conclusions and Perspectives

There is no doubt that the CM industry possesses enormous potential in Asia. Although this article summarizes only some of the many major achievements that have taken place in recent years across China, Japan, South Korea, and Singapore, it illustrates the tangible progress being made throughout the region's thriving CM sector, including scientific research breakthroughs, increasing investments, global partnerships, and support from forward-thinking governments and regulatory agencies. Stakeholders of all shapes and sizes are collaborating to create an ecosystem that is greater than the sum of its parts.

Still, much more progress is needed at all levels to address the CM sector's remaining challenges. CM innovators in Asia can also learn experiences and knowledge from the industry's forerunners. As an emerging and multidisciplinary field, the CM sector needs experts from a wide range of scientific and technical backgrounds to collectively utilize their skills to advance CM scientific innovations. Continued efforts are needed to motivate scientists in relevant fields to realize the potential of applying their expertise to the CM sector, such as holding CM-focused sessions at international conferences, and establishing not only private funding, but also public funding to support fundamental and scientific research.

Additionally, it is crucial to advocate resource-sharing and harness the strengths of academia and industry to tackle bottlenecks and push forward CM towards industrialization. Secrecy is a hurdle that slows down the development of CM globally. Increasing the transparency of newly developed technologies via patents and open-access publications would protect intellectual properties while allowing more data sharing among the community. The scientific analysis in this article shows that there are intensive studies focusing on CM's various needs, cell line development, in particular, which is a fundamental part of CM, has the most publications among the four selected countries so far. Also, many companies have developed solutions for cheaper culture media. Imagine if these findings could be publicly accessed in resources similar to the government-funded UK Stem Cell Bank (www.nibsc. org/ukstemcellbank) and the nonprofit American Type Culture Collection (www.ncbi.nlm.nih.gov/books/NBK209072) that provides open-access cell lines for research and clinical purposes, more rapid progress in CM scientific research would be expected to happen. Sharing technical advancements can help scale up CM production, accelerate progress on producing products that can satisfy and even exceed Asian consumers' expectations, and realize CM's many societal benefits.

As Asian countries move ever closer to embracing CM and other AP, raising awareness and deepening the societal understanding of CM science can help build a more openminded environment for novel foods to thrive. Joint efforts on public education and promotion by the industry are encouraged. Developing specialized courses would also help prepare talent with knowledge and skills for the future. We are witnessing the blooming of the CM industry, but the process of maturing CM technologies has only just begun. Facilitated dialogue between various stakeholders and key decision-makers is needed to ensure that information can be transferred smoothly, avoid misunderstandings, and increase transparency. Recent examples of such gatherings include a CM-focused webinar co-hosted by JACA and GFI APAC, and a roundtable discussion co-organized by Merck Innovation Hub China and GFI Consultancy. Additionally, industry organizations like the APAC Society for Cellular Agriculture, JACA, and the Korean Society of Cellular Agriculture serve as convenient platforms to connect different players and nurture a healthier CM ecosystem. These steps and actions, when combined with thoughtful and fair approval frameworks from policymakers and regulatory authorities, would pave the way for CM industrialization.

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Conflict of interest

The authors declare that they have no conflict of interest.

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