NEW FIELDS OF TECHNOLOGY AND APPLICATION PIONEERED BY SYNTHETIC BIOLOGY

– THE HISTORY OF MICROBIAL FERMENTATION IN JAPAN AND THE POTENTIAL OF CREATING NEW INDUSTRIES BASED ON THAT EXPERTISE –

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SUMMARY

- Synthetic biology is receiving greater recognition as a technological field that produces substances beneficial to human society, including synthetic cells, by leveraging knowledge gained through biological research as well as engineering methods such as genetic modification.
- High growth is expected in the synthetic biology market in the future, and significant investments are being made in various countries, particularly in Europe, the US, and China. Meanwhile, there are concerns about the impact on the global and biological environment resulting from the ability to create biomaterials and genetically modified organisms that do not exist in nature. Although international conventions have been established regarding genetically modified microorganism and other biomaterials, the interpretation and execution of regulations differ from country to country. Therefore, regulations and oversight that apply to the entire supply chain are considered necessary for cross-border business.
- Owing to Japan's history of fostering fermentation technologies such as miso and soy sauce, the country has the potential to create new industries through synthetic biology due to its accumulation of basic research on microorganisms, genetic engineering, and other related topics.

1. WHAT IS SYNTHETIC BIOLOGY?

Biology is a natural science that analyzes a broad range of living organisms to solve the mysteries of life relating to organisms inhabiting the Earth and sheds light on the structures and functions of cells, the mechanism of heredity, and other matters. Since ancient times, the study of biology has enabled great advancements in medicine, agriculture, and other fields. Molecular biology made great progress in the 1950s, leading to the development of technologies (e.g., genetic recombination, genome editing, DNA/RNA synthesis technologies) that make it possible to artificially recreate some of the functions possessed by living organisms, including artificial cells as well as genes with genetic sequences that do not exist in nature.

A major characteristic of synthetic biology is that it attempts to shed light on the mysteries of life from a different angle than biology, while at the same time making full use of the biological research findings accumulated to date. One example of this type of synthetic biology research is an artificial cell developed by the Tokyo Institute of Technology in 2019 that is capable of absorbing the energy required for protein synthesis from light.[1] All of the synthetic cells prototyped up until that point had been externally supplied with the energy necessary to sustain life, and used that energy to synthesize proteins from DNA. Such synthetic cells cease all activity when they run out of energy. In other words, they are merely pseudo-cells incapable of sustaining themselves.

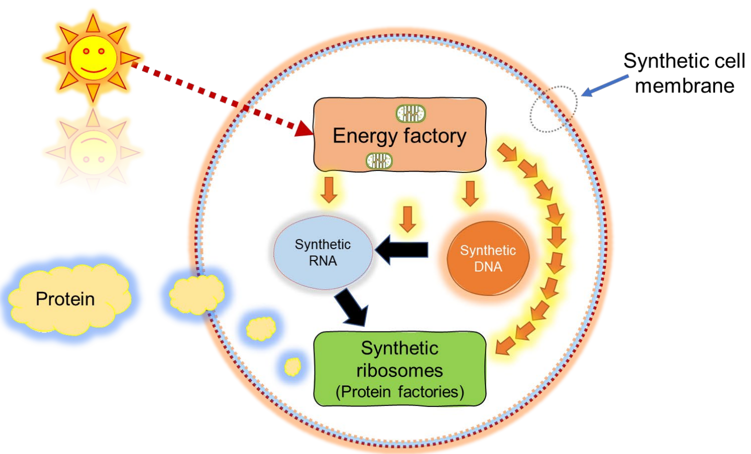
[1] Tokyo Institute of Technology, "ELSI Scientist Constructs Artificial Photosynthetic Cells" https://www.titech.ac.jp/english/news/2019/043911 (Last accessed on September 2, 2022; the same applies hereinafter)

Creating artificial cells for industrial applications requires that they be able to produce energy internally, just like actual living cells.

The research group at the Tokyo Institute of Technology developed an artificial organelle that synthesizes proteins by absorbing energy from externally irradiated light, similar to chloroplasts in plants. This has paved the way for the creation of synthetic cells that can provide their own energy. Such self-sustaining synthetic cells (Figure 1) can be used, as in the case of COVID-19 gene therapy drugs, to partially produce spike proteins from mRNA information using the synthetic cell's own energy without taking over human cells like a virus.[2] This will enable the body's own immune response system to produce antibodies.

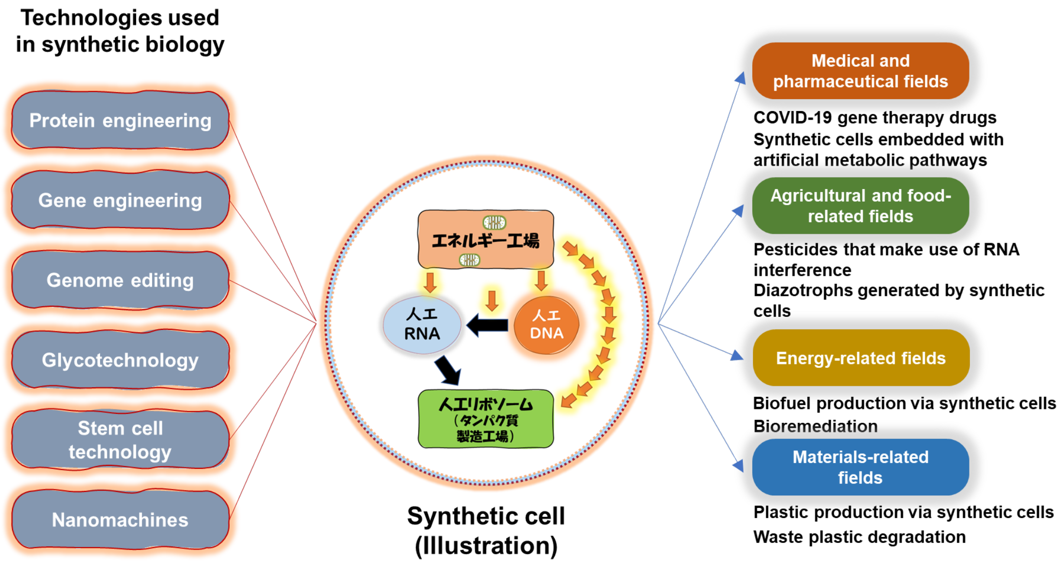
Technologies created by the field of synthetic biology are already being applied to solve various social issues, and active investments in research and development as well as attempts to implement the technologies in society are underway in Europe, the US, China, and other countries (Figure 2). This report examines the current state of affairs, while also presenting the challenges facing synthetic biology and the field's future prospects.

Figure 1. Synthetic cell capable of providing its own energy (illustration)



Source: Prepared by MGSSI based on related materials

Figure 2. Industrial applications of synthetic biology



Source: Prepared by MGSSI based on related materials

[2] According to research conducted by Osaka University and the Japan Agency for Medical Research and Development, the development of mRNA vaccines that encode only receptor binding domains (RBD) instead of whole spike proteins could suppress the production of infection-enhancing antibodies.
https://www.amed.go.jp/news/release_20210525-02.html Incidentally, Pfizer's BNT162b1 vaccine encodes only the RBD.

2. THE SYNTHETIC BIOLOGY MARKET AND FIELDS OF TECHNOLOGY AND APPLICATION

2-1. Market Overview

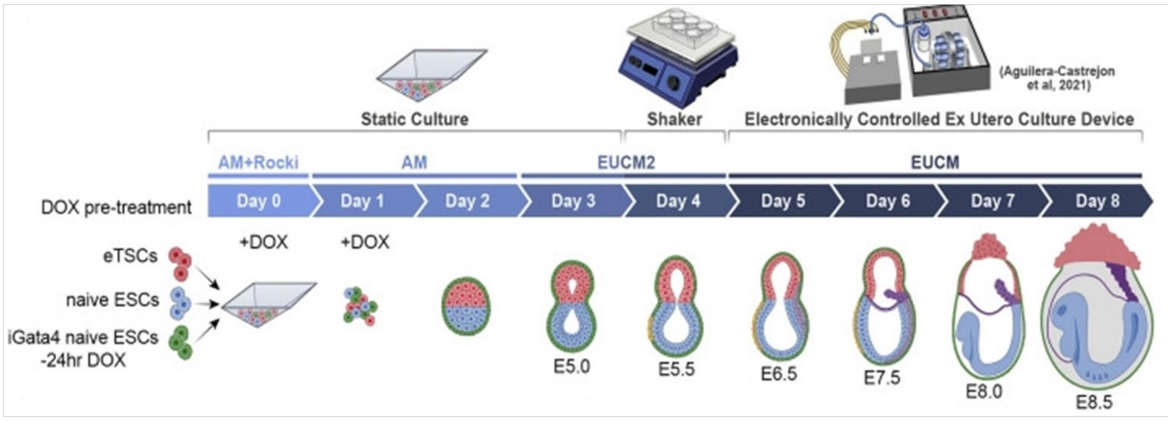
The field of synthetic biology is expected to achieve high growth in the future, and significant investments are being made in various countries, particularly in Europe, the US, and China. According to SynBioBeta, a network for the promotion and advancement of synthetic biology, while funding in the field only totaled around $7.8 billion in 2020, it surged to approximately $18 billion in 2021.[3] In addition, the global market, which came to $8 billion in 2020 and $9.5 billion in 2021, is projected to reach approximately $33.2 billion by 2026. The following sections introduce topics in the medical, agricultural, and materials-related fields in which the application of synthetic biology-derived technologies shows particular promise.

2-2. Fields Applying these Technologies

(1) Medicine

In the medical field, basic technologies for artificially growing organs that can be transplanted into humans are expected to emerge in the future. Professor Jacob H. Hanna and his colleagues at the Weizmann Institute of Science (Israel) have developed a synthetic embryos technology by which stem cells are cultured in an artificial uterus and grown into specific organs.[4] This research makes use of stem cells from mice, and researchers observed a beating heart, blood flow, the beginnings of brain tissue, and eyeballs within the artificial uterus (Figure 3). In the future, the research team intends to take on the challenge of growing organs using the ability of human cells to self-organize, and to extend human healthy life expectancy by enabling transplants of fully functioning organs. To this end, it is important to grow synthetic human embryos in the early stage of gestation (40 to 50 days). Synthetic embryos at this stage might be grown and produced as an important biomaterial for

Figure 3. Synthetic embryo technology using mouse stem cells and artificial uteruses



Source: Cell "Post-Gastrulation Synthetic Embryos Generated Ex Utero from Mouse Naïve ESCs", August 01, 2022
https://www.cell.com/cell/fulltext/S0092-8674(22)00981-3?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867422009813%3Fshowall%3Dtrue#%20

[3] SynBioBeta, Built with Biology "4Q 2021 Synthetic Biology Venture Investment Report"
http://uploads.builtwithbiology.com/BWB%20Q4%202021%20Final.pdf

[4] Jacob H. Hanna et al. "Ex utero mouse embryogenesis from pre-gastrulation to late organogenesis", 17 March 2021
https://www.nature.com/articles/s41586-021-03416-3
and Jacob H. Hanna et al. "Post-Gastrulation Synthetic Embryos Generated Ex Utero from Mouse Naïve ESCs," August 1, 2022
https://www.cell.com/cell/fulltext/S0092-8674(22)00981-3#relatedArticles

synthetic biology-related companies in the future, as they have the potential to self-organize not only into livers, kidneys, and other organs but even into hands and feet. This technology has already been licensed to RenewalBio (Israel). The company is not only cultivating organs but also propagating hematopoietic stem cells, which produce blood, aiming to commercialize treatments for blood-related illnesses and technologies for regenerating immune systems.

(2) Agriculture

One hot topic in the field of agriculture is nitrogen fertilizer, the main ingredient of which is anhydrous ammonia produced from natural gas. International conflicts have caused a massive surge in the price of natural gas, which has hampered the production of nitrogen fertilizers. Synthetic biology-related companies are exploring the possibility of transitioning to forms of agriculture that do not make use of nitrogen or other chemical fertilizers. Within the field of synthetic biology, much attention has been focused on the mechanism by which legumes and their symbiotic microorganisms (diazotrophs) take in nitrogen from the air and produce ammonia. There is a long history of research into whether or not that mechanism can be applied to corn, wheat, rice, and other major crops. If these DNA modifications can reduce dependence on nitrogen fertilizers, it will be good news for agricultural producers.[5]

(3) Materials

This section introduces efforts aimed at solving plastic-related issues in the field of materials. In 2016, a strain of bacteria was discovered to be capable of breaking down polyethylene terephthalate (PET), which is mass produced in Japan as a material for making plastic bottles.[6] These bacteria have the ability to break PET down into terephthalic acid and ethylene glycol, which are ultimately converted back into carbon dioxide and water. In 2020, the practical applications of this research were significantly advanced by modifying these bacteria through genome editing to be able to break down waste PET six times faster than previously possible. After these PET-degrading bacteria were discovered in Japan, others around the world began similar research. Now, microorganisms capable of breaking down materials other than PET have been discovered.[7] Research and development are underway to improve the efficiency of the degradation process, among other goals.

3. SYNTHETIC BIOLOGY COMPANIES TO WATCH

Many of the synthetic biology-related companies of note are based in the US. Particularly well-known companies include Ginkgo Bioworks, Caribou Biosciences, and ZBiotics. Japanese companies include Bio Palette Co., Ltd., which has developed a type of genome editing that does not involve DNA cleavage; Setsuro Tech, a venture company from Tokushima University; and Bacchus Bio innovation, which produces biomaterials necessary in the study of synthetic biology. Figure 4 provides an overview of some major synthetic biology-related companies, including those just listed.

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5 Mitsui & Co. Global Strategic Studies Institute "Biologicals Hold Promise for Sustainable Agriculture – Biotechnology Enables Development of Alternatives to Pesticides and Chemical Fertilizers – ," Oct 2021
https://www.mitsui.com/mgssi/en/report/detail/__icsFiles/afieldfile/2021/11/27/2110t_sato_e.pdf

6 Shosuke Yoshida et al. "A bacterium that degrades and assimilates poly (ethylene terephthalate)", Science, 11 March 2016
https://www.science.org/doi/10.1126/science.aad6359
These PET-degrading bacteria were discovered at a plastic bottle processing plant in Sakai City.

7 Jan Zrimec et al. "Plastic-Degrading Potential across the Global Microbiome Correlates with Recent Pollution Trends", ASM Journals, 26 October 2021
https://journals.asm.org/doi/10.1128/mBio.02155-21

Figure 4. Major synthetic biology companies

Company	Country	Overview
Ginkgo Bioworks	US	A leading company in the field of synthetic biology. Creates innovations in the production of pharmaceuticals, chemicals, fertilizers, and other synthetic biomaterials by leveraging synthetic biology to program cells and then artificially create some of the functions of living organisms.
Caribou Biosciences	US	A pioneering company in genome editing using CRISPR. Promotes genome-edited cell therapy that makes use of chRDNA (CRISPR hybrid RNA-DNA) technology.
ZBiotics	US	Developed the world's first genetically modified probiotic (using Bacillus subtilis var. natto; relieves hangovers). Develops innovative products, such as microorganisms designed to combat infectious diseases.
Twist Bioscience	US	Develops DNA data storage technologies that make use of synthetic DNA, and conducts research to identify and promote the development of drug discovery targets based on genetic differences between ethnic groups and other factors.
Bacchus Bio innovation	Japan	An integrated biofoundry. Cooperates with Bio Palette Co., Ltd. (genome editing) and Synplogen Co., Ltd (DNA synthesis), both startups from Kobe University.
Amyris	US	A synthetic biology company producing raw materials for the flavors and fragrances (F&F) market. Has work on COVID-19 vaccine development in collaboration with the US National Institute of Allergy and Infectious Diseases.
National Resilience	Canada	A synthetic biology company that advertises itself as a next-generation life science company. Develops and produces pharmaceuticals and biologics.
Codex DNA	US	Develops gene synthesis technologies that generate synthetic DNA/synthetic mRNA from DNA sequence information, as well as fully automated systems to produce peptides with short amino acid sequences.
Zymergen	US	Makes use of software engineering and AI-integrated automation systems to produce chemicals and biomaterials in half the time and at less than 1/10th the cost of conventional systems.
Apeel Sciences	US	Produces plant-derived coatings that keep perishables fresh throughout the entire supply chain. Aims to reduce (minimize) food waste.
Precigen	US	Uses its proprietary ActoBiotics platform to develop AG019, a microbe-based diabetes drug, as well as immunotherapies and other treatments for infectious diseases, cancer, leukemia, etc.
Renewal Bio	Israel	Grows organs for transplantation by growing artificial embryos in artificial uteruses using stem cell technology. Provides state-of-the-art organoid technology, which does not require sperms or eggs.

Source: Prepared by MGSSI based on each company's website

4. CHALLENGES FACING SYNTHETIC BIOLOGY

One of the challenges facing synthetic biology is the field's potential impact on the global and biological environment resulting from the ability to create biomaterials and genetically modified organisms that do not exist in nature. Biomaterials such as synthetic DNA/RNA, synthesis kits, chemical agents, and other materials often used in synthetic biology are available on the Internet, and in theory, it is possible to create artificial cells and synthetic viruses with relatively simple equipment. If such synthetic viruses are inadvertently leaked into the natural world, the impact on humans, animals, and plants would be immeasurable. The potential of this resulting in irreversible consequences is undeniable.

The Cartagena Act (also known in Japan as the Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms) is an international agreement regarding genetically modified microorganisms and other biomaterials used in synthetic biology.[8] The purpose of the Cartagena Act is to prevent adverse effects on biodiversity by establishing measures to regulate the use of genetically modified organisms. However, the interpretation and execution of regulations differ from country to country. In order for all possible measures to be in place, it is important to agree upon matters internationally.

[8] Ministry of Agriculture, Forestry and Fisheries "What is the Cartagena Act?" https://www.maff.go.jp/j/syouan/nouan/carta/about/

Genetically modified organisms are currently being used for business purposes in ways that cross national borders, and regulations and oversight that apply to the entire supply chain are necessary. Oxitec, in the UK, is releasing genetically modified mosquitoes into the wild with the permission of the government and local authorities in order to combat malaria, Zika fever, and other mosquito-transmitted other diseases. Considering that genetically modified foods are already a part of people's lives, risks are present when the results of research in synthetic biology are tested in biological environments; there is an urgent need to assess the risks and formulate countermeasures.

5. FUTURE PROSPECTS

For significant achievements to be made in the field of synthetic biology, it is important to foster and integrate companies (biofoundries) that produce synthetic DNA/RNA, microbial cultures, synthetic cells, stem cells, and other biomaterials. The importance of biofoundries has even been pointed out by the Cabinet Office's "Council of New Form of Capitalism Realization." The Department of Information Technology and Human Factors at the National Institute of Advanced Industrial Science and Technology (AIST) has established the Industrial Cyber-Physical Systems Research Center, which—in addition to research aimed at advancing the manufacturing industry—also conducts research into integrating biotechnology and IT. This provides an environment where researchers and developers can attempt integrating the technologies of different industries and fields. In order for industries in Japan to have access to the field of synthetic biology, the focus should be on fostering clusters of synthetic biology-related companies by funneling funds to these sorts of development environments and human resources.

Japan has a long history of producing foods that make use of microbial fermentation, such as miso and soy sauce. Most recently, uridine produced by Yamasa Corporation's Biochemicals Division is being used as an mRNA material in COVID-19 gene therapy medications. Also, actinomycetes discovered in the soil in Ito City, Shizuoka Prefecture, are being used in Ivermectin, an antiparasitic drug that was brought into practical use by Satoshi Omura, professor emeritus at Kitasato University who, along with two others, was awarded the Nobel Prize for his work in 2015. These and other factors suggest that Japan is where creating the synthetic biology industry makes the most sense.