Establishing Technologies for Genome-scale DNA Synthesis and Functional Expression, and Creating Technology Seeds for Material Production and Medical Care

1. Objective:
Establishing Technologies for Genome-scale DNA Synthesis and Functional Expression, and Creating Technology Seeds for Material Production and Medical Care

2. Overview

Genomic DNA sequencing and genome-editing technologies constitute important foundational technologies that underpin advances in life sciences research. Recently, in particular, genome-editing technologies have received a plenty of attention as technologies that will transform the life sciences through the use of CRISPR-Cas9, and practical research on this topic is rapidly advancing in the breeding and healthcare fields. As part of this strategy, reforms are occurring in DNA synthesis technologies, which serve as a novel technology that will support the process. Research is also ongoing to elucidate genome-related functions and their underlying principals using the synthesis of long-chain DNA that is tens of thousands of base pairs long or longer, and analyzing its functional expression in cells.

With this strategic objective, MEXT aims to continue working together with those involved in information science, materials science, and other such fields with a primary focus on the life sciences to establish technologies for programming and synthesizing genomes and inserting them into cells to express gene/proteins with desired functions.

3. Objectives

This strategic objective is targeted at establishing technologies for synthesizing genome-scale length of DNA, as well as elucidating the essential nature of genomic functions using the synthesized DNA and control cellular function. Specifically, MEXT aims to achieve the following.

(1) Understand the functions of genomes, discover the basic underlying principles for artificially designing genomic sequences, and create techniques to achieve these goals.
(2) Develop technologies for programming and synthesizing genome-scale length of DNA, which will be introduced into to cells, leading to the expression of the desired functions.
(3) Create technologies for controlling cellular function using the programmed and synthesized DNA.

4. Future Vision of Society to Be Focused on When Promoting Research

By achieving the goals listed in “3. Objectives,” MEXT will contribute to developing the type of society listed below by establishing a technical foundation for modulating and controlling cells via an engineered approach without relying on biological species.

- A society that substantially reduces energy consumption in the manufacture of products and refining, and ensures sustainable patterns of production and consumption by eliciting unused biological functions to the utmost extent.
- A society that makes progress by substantially improving the production efficiency of biopharmaceuticals and establishing cells for use in research into illnesses and drug discovery research. Furthermore, these achievements will also promote research into and the establishment of treatment techniques for illnesses resulting from multiple causes.
- A society that promotes the transformation of the chemical industry processes to biological industry processes, which will provide Japan with a strong industrial competitive edge in this field.

5. Specific Research Examples

(1) Understanding genomic functions, discovering the basic underlying principles of artificially programmed genomic sequences and creating relevant techniques to achieve these aims.

The research will be carried out targeted at understanding genomic functions and establishing specific techniques for artificially programming novel genomic sequences. Examples of this include research to clarify genomic functions involving extracting or synthesizing genomic regions with currently unknown functions, to analyze these variants. Furthermore, research into using long-chain DNA to freely reconstitute higher order structures for genomes and clarify the role played by their

structure in cellular and biological functions. Other such research focuses include the development of information processing algorithms for extracting the desired functions in the form of specific DNA sequence information. Furthermore, strategies for experimentally validating these processes, as well as research into substituting genomic DNA from mitochondria and chloroplast with synthetic long-chain DNA to elucidate its functionality.

(2) Develop base technologies for programming and synthesizing genome-scale length of DNA, which will be introduced into cells to enable the expression of the desired functions in the cell.

MEXT will cultivate and innovate current underlying technologies related to DNA program, synthesis, and functional expression, and will develop foundational technologies that will enable the program, synthesize, and functional expression of long-chain DNA. For example, it will develop technologies related to analyzing big data to design genomic sequences, synthesize long-chain DNA to dramatically extend the upper limits of the DNA length that can be synthesized. This will facilitate the achievement of physical stability of long-chain DNA, as well as its introduction into cells, and host cells to which it can easily be introduced to express its functionality.

(3) Create technologies for controlling cellular function using the DNA the programmed and synthesized DNA.

MEXT will undertake research aimed at introducing programmed and synthesized long-chain DNA into cells, which will clarify its genomic sequences and the corresponding relationship with their functions, and control cellular function based on this process. For example, it will research using DNA to introduce new functions into cells, as well as for redesigning cellular genomes to use long-chain DNA and control cellular function.

Concerning the research and development (R&D) of items pertaining to the specific research examples in (1-3), consideration must be given to any hypothetical ethical, legal, or social problems that could arise from their practical implementation in the future. Therefore, research into these must incorporate advice and proposals from researchers in related humanities and sociological fields.

6. Research Trends in Japan and Overseas

(Trends in Japan)

The Cabinet Office held policy discussions on the challenges with and formulation of strategies for promoting innovation via biotechnology in October 2017 and hosted a bio-strategy review working group that started later in December. As part of this strategy, enormous interest was expressed in synthetic biology not only from the academia, but also from the bio-industry, and there were demands to establish a basic foundation for this process. Moreover, at the 85th meeting of the Life-Science Committee, Subdivision on Research Planning and Evaluation, Council for Science and Technology, Genome-Write technology was introduced as an important theme related to genomic medicine.

Japan continues to produce the foundational technology seeds for genome-scale long-chain DNA synthesis. Long-chain DNA synthesis is an area in which Japan retains the global advantage, as evidenced by the fact that it has reported techniques for using *Bacillus subtilis* for DNA accumulation, as well as techniques for reconstituting genome replication mechanisms of *Escherichia coli* in vitro (ImPACT "Artificial Cell Reactor"). As such, there are high hopes that new developments in academic research and its industrial applications resulting from the increasing sophistication and dissemination of long-chain DNA synthesis technology will serve as a growth engine for Japan in the future.

(Overseas Trends)

An international consortium on genome-scale DNA synthesis (GP-write) was launched in the US, where half of the participants at a kick-off meeting of the consortium consisted of companies, indicating the strong interest from both the industry and academia. In addition, this was adopted as a theme meriting attention in a 2017 edition of *Nature* magazine. In China, Shenzhen City, Tianjin University, and the Chinese Academy of Sciences are taking the lead in promoting the installation and expansion of world-class research laboratories in the synthetic biology field (which includes genome-scale length of DNA synthesis) with a multibillion yen budget. Therefore, many of their young

researchers are acquiring skills in the US and then returning home to China. However, it is the community in the US that provides coordination for international consortiums overall and, so, the US is still the frontier for such research. The UK formed a synthetic biology consortium starting in the latter half of the 2000s, but since the country is not an academic world-leader, it has been emphasizing industrialization through venture companies.

7. Details of the Examinations
The examinations were carried out as follows based on the Policy for Formulating Strategic Objectives (approved by the Expert Panel on Strategic Basic Research, Council for Science, Technology, and Innovation in July 2015).

(Drafting analytical materials related to research trends in Japan and overseas via scientometrical techniques using the Grants-in-Aid for Scientific Research Database and other similar platforms)

Analytical materials related to research trends in Japan and overseas were drafted using scientometrical techniques such as analyses of co-citation relations and direct-citation relations for research papers via the Grants-in-Aid for Scientific Research Database.

(Administering questionnaires to experts using analytical materials and drafting research trends that merit attention)

Questionnaires related to research trends that merit attention in the future were administered using the analytical materials that were drafted. These questionnaires were administered to the sectoral units of the Center for Research and Development Strategy, Japan Science and Technology Agency (JST), the program directors and others at the Japan Agency for Medical Research and Development, and the experts participating in the expert network of the Science and Technology Foresight Center, National Institute of Science and Technology Policy. Subsequently, the results of the questionnaires were analyzed, and trends related to this objective were designated as research trends that merit attention.

(Hosting workshops and drafting strategic objectives)

Workshops have been held by assembling experts from the industry and academia involved in research trends that merit attention. At these workshops, discussions were held on topics such as trends in Japan and overseas that merit particular attention, the social and economic effects of advances in research and technical development, and visions of a future society in which the results of this can be achieved. In addition, objectives that must be achieved during the research phase were addressed. Based on the discussions at the workshops, the strategic objectives were drafted.

8. Related Mentions Found in Texts Approved by the Cabinet, and other related tasks
5th Science and Technology Basic Plan (approved by the Cabinet in January 2016)

Chapter 3 (1) <1> ii)

Furthermore, we will undertake R&D on technologies for the production and utilization of fuels and chemicals from biomass and waste, and on waste treatment technologies.

Chapter 3 (3) <2> ii)

Hence, Japan will consolidate the following fundamental technologies in particular, which will function as core technologies in the real world for new value creation in individual systems.

・Biotechnology: technology transforming sensor and actuator technologies

Chapter 3 (1) <3>

Utilizing computer and data science, we will also pursue the creation of innovative functional and structural materials with dramatically shorter development lead times.

Comprehensive Strategy on Science, Technology, and Innovation for 2017 (approved by the Cabinet in June 2017)

Chapter 2 (2) [C] <2> ii)

・Strengthen R&D related to biotechnology in areas such as digitizing bioinformation, artificial

intelligence (AI), combining genome-editing technologies, and other such New Plant Breeding Techniques (NBT), as well as creating new value using high-level agricultural and biological functions

9. Other activities

One measure related to this strategic objective is the ImPACT "Artificial Cell Reactor." This program combines measurement and production, promotes long-chain DNA synthesis in cell-free systems, and promotes industrialization aimed at channeling the results of its research back to society. This strategic objective aims to clarify genomic functions by designing, synthesizing, and confirming the functions of long-chain DNA. Since it exists in a complementary relationship with this program, it must be promoted through close coordination.

Regarding the international strategy, MEXT will partner with the GP-write international consortium on genome-sized DNA synthesis to proactively promote the development of young human resource and the overseas deployment of technologies originating from Japan. It will also partner with companies who use these technologies to channel the R&D results back into the society.

The expectation is that initiatives for promoting research efficiently and effectively will be undertaken. For example, initiatives such as laying a foundation for further deploying research via databases and other similar strategies by partnering with the Life Science Database Integration Project (which began in FY2011) of the Japan Science and Technology Agency (JST) over the data obtained through research carried out under this R&D objective will be encouraged.