Research area in the Strategic Objective “Establishing Technologies for Genome-scale DNA Synthesis and Functional Expression, and Creating Technology Seeds for Material Production and Medical Care”

Large-scale genome synthesis and cell programming

Research Supervisor: Haruhiko Siomi (Professor, Keio University School of Medicine)

Overview

This research area aims to elucidate basic principles in relation to the structure and function of genomes (the principle of genome function) and for the creation of a platform technology for the use of cells on the basis of such knowledge. In particular, we aim to control cells by using long-chain DNA and thus to develop this frontier in the field of life science, including genome science and cell engineering, and to establish a technology platform.

In recent years, research and development that use long-chain DNA has been accelerating globally, following paths developed by synthetic biology. In the U.S., China, and the UK, a certain number of genome synthesis centers have been established, where strategical investments have been made in fundamental research, technology developments, fostering venture enterprises, and more. However, when we look at the endeavors of each country, it seems that there are only a small number of research and development projects that proceed in the area genome programming for the autonomous control of cells.

This is why in this research area we will manage research and development for the purpose of solving the principle of functional genomics in view to establish a future platform technology for genome programming. From the point of view of making use of long-chain DNA, a field in which considerable development has been ongoing, we facilitate four project areas comprising "Elucidation of Genome Structure and Function," "A Platform Technology for Genome Design," "Genome Synthesis Technology," and "Producing artificial cells," which aim to generate knowledge in relation to the complex functions and structures of genomes, as well as establishing a new technology in relation to genome synthesis and artificial cells.
Research Supervisor’s Policy on Call for Application, Selection, and Management of the Research Area

1. Target of this Research Area
On the basis of the information highlighted above, the research area of “Large-scale genome synthesis and cell programming” we aim depends on technologies for writing, fathoming, and regulating the genome, which will lead to understanding of the principle of genome function and to accelerating the development of new technologies that enable us to manipulate cells and to design and synthesis genome-scale DNA. The goals of this research project are four-fold, which are indicated below.

- "Elucidation of Genome Structure and Function" that aims to understand the principle of functional genomics.
- "A Platform Technology for Genome Design" that aims to develop a technology to predict the genome sequences required for the emergence of a function in a cell.
- "Genome Synthesis Technology" that aims to synthesize artificial DNA at the megabase scale.
- "Producing Artificial Cells" that aims to modify and synthesize a considerable number of genomes to produce useful cells with novel functions.

In this research project, participants are highly encouraged to create interdisciplinary interactions and collaborations among researchers in a wide variety of principles, including genome science, chromosome engineering, virology, microbiology, plant sciences, medical science, and other life sciences, as well as nucleic acid chemistry, materials science, nanotechnology, measurement science, information science (including artificial intelligence (AI) and machine learning), engineering, and optical science in order to generate new technologies/new devices, new discoveries, and new ideas. As stated above, this research area is regarded as an area of budding knowledge. Therefore, we seek challenging and unique proposals for two types of project: CREST and PRESTO.

Presented below are some research and development endeavors we are looking for in this area. These are but examples and we are expecting challenging proposals by highly motivated researchers in new fields of research using a wide variety of organisms as models.

(1) "Elucidation of Genome Structure and Function": We invite proposals from a wide
range of fields for research and development in relation to elucidation of genome structure and function (including organelle genomes such as mitochondria and chloroplasts). Our expecting research fields include:

a. Understanding of relation between genome sequences and positions of (protein-coding) genes in the genome.

b. Developing new techniques that allow visualizing the structure of specific genomic regions.

c. Understanding of the cause and consequence of specific chromosome positions in the nucleus, and developing new technologies to regulate such chromosome positions.

d. Understanding of stable replication and segregation of chromosomes, and developing new technologies to facilitate the research field.

e. Understanding of interactions between the genome and environmental conditions, including extremophiles that adapt to extreme environmental conditions.

(2) "A Platform Technology for Genome Design": We invite proposals from a wide range of fields for research into hypothesis verification led by informatics approaches, and the use of informatics for the programming of artificial genomes. Our expecting research fields include:

a. Genome programming algorithms that enable genome functions to emerge by using databases and/or AI.

b. Predictions, models, simulations, and new technologies to activate the genome in heterologous systems.

c. New methods to calculate and compute possible functions of a specific genomic region based on a variety of genome data.

d. Comparative genomics that allow to identify genomic regions that determine speciation and developmental programs of organisms including uncultivated microorganisms.

(3) "Genome Synthesis Technology": We invite proposals from a wide range of fields for research on DNA synthesis technology to lead rapid progress in the fields of genome synthesis efficiency and total base length. Our expecting research fields include:

a. New technologies to synthesize long and accurate DNA molecules based on biology and/or organic chemistry.
b. DNA assembly technologies that enable to synthesize long-chain DNA.
c. Generation and use of new artificial chromosomes and/or artificial nucleic acids that facilitate synthesis of long-chain DNA.
d. Developing new devices to manipulate long-chain DNA.
e. Developing new methods to transfer genomes and artificial chromosomes into cells.
f. Generating new logic to manipulate chromosomes and long-chain DNA.

(4) "Producing Artificial Cells": We seek further research and development in relation to new cytoarchitectures based on the introduction of genomes and/or on the large-part alteration of chromosomes. Our expecting research fields include:
   a. Artificial cells that can replicate and proliferate with energy-yielding system.
   b. Artificial cells that have mutation-generating system to facilitate genome evolution and exhibit communal behavior. To communicate with each other by exchanging molecules.
   c. Introduction of heterologous gene sets or chromosomes into cells to create new phenotypes.
   d. Developing new technologies to transfer long-chain DNA into cells.
   e. Developing new technologies to transfer (long-chain) DNA into organelles.
   f. Generating new cells that adapt to transfer of long-chain DNA.

2. Principle of Project Invitation and Selection

To make your proposal, clarify your aims during the research period with preliminary results that help evaluate the feasibility of the proposal, and describe any bottlenecks of your research (unsolved scientific and/or technological problems) as well as the novelty of your methods (and a comparison with a similar technology (benchmark)) in the written proposal.

(1) CREST

In CREST, proposals by a large number of excellent researchers with considerable achievements have been adopted. However, in addition, in this research area, we are willing to adopt challenging proposals submitted by young researchers, in consideration to the characteristics of budding research. Further, we will examine each proposal based on the uniqueness of the concept. Therefore, we are expecting challenging proposals by highly motivated researchers in new fields
of research. As for such proposals that have a view to the rapid industrial application of research results, researchers are allowed to include those from private companies in their team.

(2) PRESTO

The research and the development aims included in this project are somewhat similar to the tasks in the CREST project stated above. However, in the PRESTO project in particular, we are willing to adopt challenging proposals that are based on novel concepts in the field of fundamental research or technology development (or both) including the proposals that contribute to solving a bottleneck in a fundamental research phase and/or are expected to bring a great progress in this field with a novel idea. We therefore want proposals from highly-motivated researchers who, in spite of current difficulty, are trying to find a new frontier, with fellow researchers adopting their proposals.

Based on the granted proposals in both CREST and PRESTO of 2018, we are expecting many more proposals on "A Platform Technology for Genome Design" in 2019.

3. Research Periods and Research Funds

(1) CREST

The research period is five and a half years or shorter.

Your research fund (for direct expenses) can be one of three types: small-scale with about 150 million yen in total, middle-scale with about 300 million yen, or large-scale with about 500 million yen. Clarify which one you wish to choose in your proposal. For the small-scale type, we are expecting unique proposals made by a group consisting of a small number of researchers as stated above. We will make an assessment including a decision on the continuity of the research within about three years regardless of the type of a task. In addition, we may reorganize the research tasks and teams if necessary on the basis of the result of our assessment.

(2) PRESTO

The research period is three and a half years or shorter, and the upper limit of the research fund is 40 million yen in total (excluding indirect expenses).

For those projects in which a considerable achievement and/or strong ripple
effect is expected, if the result of the research is further enhanced, we may extend the research period by two years at the most on the basis of the result of the assessment at the end of the research period.

4. Principle of Research Area Management

(1) Acceleration of Research Achievements and Progress-Based Reviews

a. The research funds will be reviewed on a fiscal year basis. Please note in advance that your research funding may be increased or decreased depending on the progress of the research.

b. For both CREST and PRESTO projects, we will examine the potential to grant further funds based on the discretionary expenses for research supervision or similar for further research acceleration and/or to promote the new applications based on the research achievements.

c. For the CREST project, we may demand the review, the reorganization, and/or similar changes of a research organization and/or the research funds if necessary. In the case of the review on a research organization, we may reorganize not only the organization in a team but also the organizations in two or more research teams.

(2) Information Sharing and Organization of Information Centers

We will encourage the participants in this research area to share scientific knowledge and new technologies at research area conferences or similar events. We appreciate your cooperation. In particular, in the development of genome programming technology, it is understood that the integrated analysis of the relevant data is necessary. Therefore, we may organize an integration center for the data acquired through the research in this research area. Therefore, if we determine that the information should be integrated at a research center in the period of this research and if we also determine that the information on the achievements in the research should be integrated, then we may ask the researchers participating in this research area to provide data. We assume that the applicants will cooperate with us on this matter.

(3) International Cooperation

We are in cooperation with research institutes in and outside Japan that are active in or associated with this research area and share technologies and exchange human resources. In particular, we place importance on sharing information with
international consortia and on publishing achievements. Your cooperation is appreciated.

(4) Managing ELSI (Ethical, Legal, and Social Implications)

While we advance our research in this area, it is important to consider the ethical, legal, and social implications (ELSI) for the application of any achievement. Therefore, on the basis of the state of the progress of an achievement, we make in-depth discussions with researchers in the field of relevant humanities and social sciences in a timely manner.

The researchers participating in this research area will be asked to cooperate in the activities mentioned above. We appreciate your cooperation in advance.

5. Other Important Information

When you make a proposal for the CREST project, please ensure that you write down which funding type you prefer in the "Research Type" column on Form 1 of the research area that you make a proposal in; that is, a small-scale type (about 150 million yen in total), a middle-scale type (about 300 million yen in total), or a large-scale type (about 500 million yen in total).

*The research proposal form for applying for this research area is different from that of other research areas, so to apply, download the correct form from the JST website of Call for Research Proposals.
*For the PRESTO program, please use the common form.