Research area in the Strategic Objective "Development of optical control technologies and elucidation of biological mechanisms"

6.1.5 Development and application of optical technology for spatiotemporal control of biological functions

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Overview

This research area promotes the development of optical control technologies and their applications.

Recently, optical control technologies such as optogenetics, have caused revolutionary advances in life-science research by virtue of their characteristic ability for control with extreme spatiotemporal resolution. Given their reversibility, as well as their amenability to real-time monitoring, these technologies are expected to be adopted rapidly in the diverse fields of biology and medicine.

On the other hand, these technologies still require improvements to enable better understanding of biological mechanisms: cellular toxicity of blue light, undesired effects of the transgene, development of long wavelength photoreceptor proteins, among others. In addition, the invasiveness associated with implanted light probes or transgenes should be overcome for clinical applications.

Thus, the aim of this research area is the development of optical control technologies to overcome the aforementioned problems, and the elucidation of the mechanism of biological functions by means of these technologies. To understand and regulate intricate biological systems, we solicit research proposals in the fields of neuroscience, immunology, developmental biology, regenerative medicine, and cancer research among others.

Research Supervisor's Policy on Call for Application, Selection, and Management of the Research Area

1. Background

Since the development of optogenetics in 2005, optical control technologies in the field of life sciences have developed as a novel research technique for generating photoreceptor proteins in specific nerve cells, artificially controlling neural activities, and clarifying the nerve-cell operation principle and functions of behavior. These technologies, which can control target cells spatiotemporally, have developed to the point of transcriptional control, and a trend of expanding the application of these techniques in other life science fields, beyond the brain science, has been recognized. However, in Japan, such technological development is still limited, and notable expansion has been observed only in specific fields, such as the neuroscience. Therefore, in this research field, we aim to create innovative technologies to control the vital functions for sustaining life by expanding and applying the innovative light-used technologies to various biological activities including neuroscience fields.

2. Expected Targets and Examples of Research and Development Projects

CREST is a top-down research and development program targeted at social and economic needs. To execute CREST, research proposals, aiming at such future goals and objectives, must be prepared instead of simply extending the applicants' own research. For preparing these proposals, please consider the research directions and the examples of research and development program described below.

By considering future technological development in the medical care and biological production fields, the research and development will be focused on the following three main activities: (1) Development of optical control technologies characterized by superminimal invasion and superior spatiotemporal resolution, (2) development of optical control technologies for observing biological activities at the tissue, organ, and whole individual/organism level, and (3) development of optical control technologies for the analysis and spatiotemporal control of biological functions.

(1) Development of optical control technologies characterized by superminimal invasion and superior spatiotemporal resolution

An example of the problems that need to be addressed for the current optical control technologies is the biological invasiveness due to biological toxicity of the used light source, which is caused by using viruses for transferring genes and by embedding a probe, fiber, etc. for light irradiation and observation of deep parts. In such cases, this research project will advance the innovative technological development to reduce biological invasiveness. In addition, this research project will develop novel technologies for the optical control of near-infrared light to address the issues of biological toxicity and reachability of the light-source. Once these novel technologies are established, they can be combined with the conventional approaches using observation probes in the visible light region. Furthermore, this research project can include the development of new technologies for controlling functions by using DDS and light irradiation, and the development of novel nontransgenic technologies for combining chemical compounds (such as caged compounds) with light. Specific examples of the research and development projects are listed below. In addition to these examples, proactive proposals of other innovative technologies are expected.

- Development of optical control technologies using near-infrared light
- Development of target-specific gene transfer technologies
- Development of target delivery technologies of optically controllable drugs
- Development of technologies that can improve the efficiency of photoreceptor-protein introduction and expression

(2) Development of optical control technologies for observing biological activities at the tissue, organ, and whole individual/organism level

The current optical technologies such as optogenetics and imaging have locality problems, that is, observation

conditions such as resolution and the observable range are restricted. For example, the observable range in the central nervous system of mammals is of the order of several hundred micrometers, and no currently available technology can enable observation of the whole tissue under investigation. However, future technologies need to be developed such that the observable range of the target phenomenon can be expanded with optical control and a wide range of biological activities can be observed with a high degree of accuracy in real time. To address these issues, this research project aims to develop technologies that can expand the real-time imaging and observational range of biological responses during optical control. The breakthrough observation technologies for realizing live imaging at the tissue, organ, and individual/organismic level will be developed by combining Japan's conventionally strong optical technologies (such as probe and microscope development technologies) with engineering technologies for their systemization.

(3) Development of optical control technologies for the analysis and spatiotemporal control of biological functions

Optogenetics, which is an optical control technology for analyzing biological functions, has developed to control target molecules with high spatiotemporal accuracy, and permeated the field of life sciences rapidly. However, as its operation and observation ranges are limited, novel analytical technologies with higher accuracy and a wider range are needed. This research project aims to advance the research and development for understanding biological activities at the level of cells, tissues, organs, and individuals by using diverse technologies based on optical characteristics.

The main trend in life science research in recent years has been the integrated research of components, which has its roots in systems biology. However, although the research for the spatiotemporal analysis of functions generated by interaction between proteins or between cells are an important part of integrated life sciences, it cannot be said that research in this direction has been sufficiently performed.

Therefore, this research project aims to analyze multiple factors spatiotemporally by using optical control technologies to understand biological activities comprehensively and to develop the fundamental technologies for controlling and applying biological functions.

Specific biological activities that need to be covered are neuronal functions, immunity, embryonic development, regeneration, cancers, and microbes, etc., and innovative optical technologies for controlling diseases and biological functions need to be developed. Examples of the research and development handled by this project are listed below. In addition to these examples, proactive proposals of other innovative technologies for multifactor control and multifactor analysis are expected.

- Research and development of technologies for analyzing the entire pathway of reactions by remarkably improving the spatiotemporal resolution of optical control of nerve cells and by widening the observation range
- Research and development of technologies for understanding the molecular correlation and operation principle of biological activities (by optical control of multiple factors such as signal molecules and transcriptional

factors) and for controlling biological functions and disease states

3. Team Building for Proposal

* A proposal consisting of the above three main development activities is recommended for this CREST research project/study.
* (1) “Development of optical control technologies characterized by superminimal invasion and superior spatiotemporal resolution” or (2) “Development of optical control technologies for observing biological activities at the tissue, organ, and whole individual/organism level” should be performed by the team that demonstrates the usefulness of (3) “Development of optical control technologies for the analysis and spatiotemporal control of biological functions”

4. Other Considerations

When submitting proposals for this research area, please clearly indicate the following two items:

(1) Objectives to be achieved three years and five years after selection

(2) Ripple effects of the results after the conclusion of the program

The upper limit for total research expenses will be 500 million yen (except overhead expense). For proposals that exceed 300 million yen (except overhead expense), please clearly indicate the breakdown of the expenses in the proposal. In addition, please note that research expenses will be revised for each fiscal year, and expenses may increase or decrease in accordance with the progress of research

5. Collaboration with Other Research Areas

Administration of this research project will include collaboration with the CREST research area “Pioneering of Next-Generation Photonics by Discovering and Applying Novel Optical Functions and Properties,” the PRESTO research area, “Optical Control Technologies for Understanding Biological Mechanisms” and “Fully-Controlled Photons and their Proactive Usage for New Era Creation (FRONTIER)," and the hosting collaborative conferences and workshops when required. Additionally, we will promote collaboration with related academic societies and research institutes and will occasionally hold symposiums and integrated studies for the purpose of expanding activity in new research areas.

6. General comments (abstract) on the FY 2016 selections and the expectations for FY 2017

In the FY 2016 selections, the proposals that met the following three criteria were selected.

- Inclusion of life functions that can be explored only by the proposed observation technology or optical manipulation technology.
- Development and utilization of new technologies instead of existing technologies.

- The research system is well-organized and –equipped, and the information necessary for realizing the research concept is provided.

Among the proposals that were not selected, there were many excellent proposals, such as those that included analysis on important life functions, those based on highly original ideas, etc. However, the proposals that lacked the development of new technology, preliminary data, realizability, or focus on the elucidation of life functions, were not adopted. In this second year of selections, we expect innovative proposals that will lead to the understanding and control of life phenomena that cannot be analyzed with existing technologies.

○ Please refer to the following website when preparing a submission, as it includes video briefings on the submission process last year: http://senryaku.jst.go.jp/teian/top/setsumeikai.html