Vol. 18, pp. 13–15 (2021)
doi: 10.2142/biophysico.bppb-v18.002

Biophysics and Physicobiology
https://www.jstage.jst.go.jp/browse/biophysico/

Commentary and Perspective

Expanding horizons of biosciences by light-control

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Received December 28, 2020; accepted January 28, 2021; Released online in J-STAGE as advance publication February 2, 2021

The recent remarkable advances in optogenetics made it possible to deepen our understanding of many biological systems and functions, especially in brain research [1]. The findings and engineering of various light-sensitive proteins expand the possibility of optogenetics [2]. In addition to optogenetics, various other techniques with the use of light have also been developed one after another such as imaging and monitoring techniques of cellular activity with novel genetically encoded indicators based on fluorescent and/or luminescent proteins including calcium- or voltage-sensitive probes [3–7]. The application of light in biology, hereafter referred to as "light-control," requires the improvement in three major elements: observation and imaging, manipulation and control, and their application to biological systems such as optogenetics. Based on the recent progress of this attractive field, we organized a symposium on "New horizons of bio-function studies by light-control" at the 58th annual meeting of the Biophysical Society of Japan (BSJ) in September 2020. The symposium was co-organized by a research area of the Precursory Research for Embryonic Science and Technology program (PRESTO), Japan Science and Technology Agency (JST), "Optical Control," directed by Prof. Yoshinori Shichida (Ritsumeikan University). We invited 4 PRESTO members and 2 senior society members whose studies are quite unique and novel in this developing field. Three lecturers are developing unique and novel methods or techniques, and the rest 3 lecturers are applying light manipulation to unique systems, including medical application. We covered wide areas of the researches with light-control in the symposium (Fig. 1).

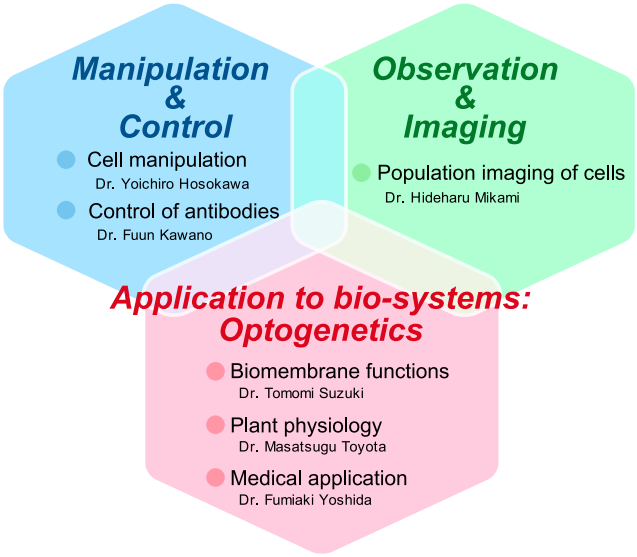

Figure 1 Three elements of bio-function studies by light-control techniques. The topics covered in the symposium are listed.

In the symposium, each speaker presented their unique and pioneering researches that enlarge the fields of light-control for biological sciences. Dr. Fuun Kawano (The University of Tokyo, PRESTO) presented the development of light-controllable antibodies called optobody. The specificity of interaction between optobody and its target is guaranteed by antibody-antigen recognition and association is controlled by light. With this unique light-controllable antibody, he discussed the possibility of manipulation and

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control of the activity of a specific functional biomolecule. The method would be more effective than the available light-control system such as LOV2-helix in terms of targeting endogenous biomolecules. We can expect the success because he experienced the development of a highly efficient photoactivatable Cre recombinase [8]. Prof. Yoichiro Hosokawa (NAIST) showed a new technique for cell manipulation using a femto-second laser system [9]. He applied the laser ablation method to cell adhesion. His experimental system is unique because the cell-cell adhesion of a limited area can be broken while keeping the rest areas intact. He estimated the adhesion force of cells by using this technique and the aid of an atomic force microscope. These two studies will provide new and powerful methods to allow for an expansion of the functions to be manipulated with light. Prof. Hideharu Mikami (Hokkaido University, PRESTO) talked about a new high-speed microscopic method for imaging a large population of neurons, which will allow researchers to understand how biological systems work based on the activities of individual cells. With the highly efficient light-sheet microscope, he aimed to achieve an ultrafast data acquisition speed of 1,000 volumes/sec overwhelming the retained speed of a high speed laser-scanning confocal system [10]. At present, the imaging system achieves a volume rate over 100 volumes/sec. The volume rate can be further improved by replacing scanning devices in the microscope.

Dr. Tomomi Suzuki (Kyoto University, PRESTO) presented her unique study about optogenetic control of phospholipids and regulation of biomembrane functions [11]. She intended to control the activity of yeast flippase with light. Since the activity of flippase is regulated by phosphorylation with flippase kinase, she introduced phototropin (CrPHOT) into the flippase-kinase-knock-out yeast and succeeded to control flippase by light in a kinase activity-dependent manner. This technique would contribute to the elucidation for the mechanisms of various cellular functions and the significance of biomembrane lipids alteration. Prof. Masatsugu Toyota (Saitama University) talked about his pioneering optogenetic research on plant physiology, especially on the mechano-sensing system [12]. With the unique calcium imaging system, he showed how signals are transmitted from the stimulation point to the overall plant. The protection from the eating leaves by insect larva is essential for the whole plant maintenance. It was known that the leaf damage rapidly activates defense responses in distant parts of the plant. He showed the signal of the first bite by larvae is spread over the whole plant with the dynamic calcium imaging, which is similar to the mechano-signal (touch etc.) transmission. Dr. Fumiaki Yoshida (Saga University, PRESTO) showed the medical potential of optogenetic techniques. The deep brain stimulation (DBS) is an effective therapy for the movement disorders such as Parkinson's disease or dystonia [13]. He is trying to develop a new method for DBS with light stimulation [14]. Light is considered to be better than the widely used electric stimulation because of a lower probability of brain damage due to a higher localization of stimuli. Many patients would expect the success of the trials.

Biology is the science of complex systems because biological systems exhibit great diversity and complexity. There are many species that are quite different in structures and functions, including animals, plants, fungi, and so on (Fig. 2). In addition, single organisms have a hierarchy composed of many levels from molecules to individual organisms. Nevertheless, previous studies using conventional light-control techniques only cover a limited range; a small population of cells was observed and limited cellular functions such as neural responses were subject to control with simple optogenetic tools in model animals. The recent advances including topics introduced in the symposium clearly indicated the directions to overcome the limitation. The acquired knowledge and developed techniques would be essential and effective to understand the diversity and complexity as well as the universality in biological systems (Fig. 2).

The studies presented in the symposium are some of the typical examples that are currently broadening the range of light-control of bio-functions. Since those studies might not be familiar yet to the members of BSJ, we believe that the symposium could provide an opportunity for attendees to broaden the understanding about this field. We omitted presentation of researches about light observation systems

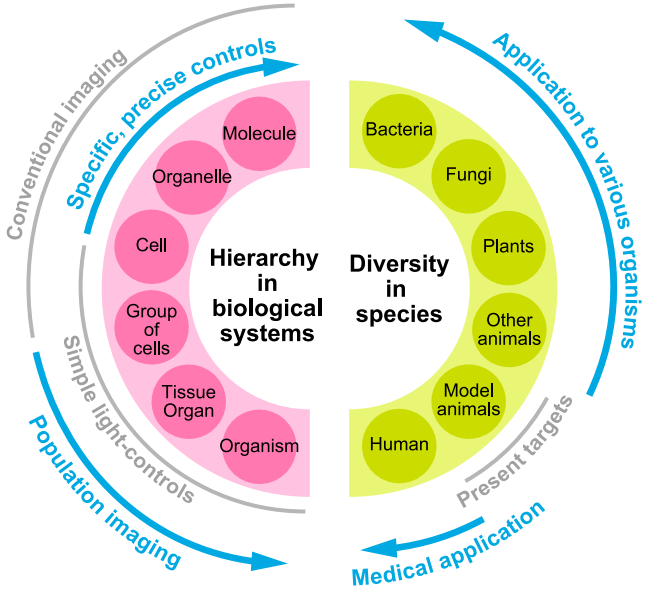

Figure 2 Expansion of light-control researches over the complexity and diversity of biological systems.

with the use of fluorescent proteins as well as fluorescent dyes and caged compounds, because such researches are already among the most popular and successful fields in BSJ, and are occasionally taken as a symposium at annual meetings. Based on the studies presented in the symposium as well as popular imaging studies in BSJ, light-control techniques will be applied more widely to various organisms and also to humans for medical purposes (Fig. 2). On the other hand, the development of new observation techniques and new optogenetic tools will enable researchers to observe a larger population of cells and specific, precise control of more cellular functions. Such expansion of the range of application of light-control in both the dimension will lead to new horizons of observation and control of bio-functions.

Due to the serious epidemic influence of COVID-19, the symposium was held as a remote style. Despite of the new style of symposium, we counted more than 100 participants reflecting the significance and expectation of the light-control techniques in many areas of biology and biophysics.

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(*Edited by Haruki Nakamura*)