Title of Project : New frontier for ubiquitin biology driven by chemo-technologies

Yasushi Saeki
(Tokyo Metropolitan Institute of Medical Science, Department of Advanced Science for Biomolecules, Associate Director)

Research Project Number : 18H05497 Researcher Number : 80462779

【Purpose of the Research Project】

Ubiquitin research today is deeply connected with almost all areas of life science research. The diversity of ubiquitin's functions can be attributed to the structural variety of ubiquitin modification, called the 'ubiquitin code'. However, these ubiquitin codes are more diverse and dynamic than expected, and the decoder molecules are also diverse, making it difficult to see the overall principles of ubiquitin codes. In addition, an increasing number of ubiquitin-associated diseases have been identified, but pathogenetic mechanisms have been elucidated for only a limited number. Hence, the research methods and tools for analyzing each ubiquitin-dependent pathway are in urgent demand.

This research project employs chemo-technologies as a new research tool to decipher, manipulate, and create ubiquitin codes. The objective is to elucidate as-yet-unknown principles of ubiquitin function in detail, as well as to establish novel techniques for ubiquitin-mediated regulation of cellular function.

【Content of the Research Project】

In close collaboration with life scientists and organic chemists, the project will progress on two fronts: understanding the mechanisms of ubiquitin codes using chemo-technologies (A01), and developing chemo-technologies for analyzing ubiquitin codes (A02) (Fig.1). The research group will be equipped with an extensive research support system that includes tools and equipment for compound screening, peptide synthesis, state-of-the-art proteomics analysis, and protein structure analysis. Specifically, to elucidate the mechanisms of ubiquitin code in each ubiquitin-dependent pathway, we will develop small-molecule compounds or stapled peptides that enable immediate inhibition of the particular function of each ubiquitin modification or decoder molecule. Also, by combining chemo-technologies with state-of-the-art proteomics analysis, this project will explore novel ubiquitin codes and decoder molecules, and simultaneously enable direct analysis of the higher-order structure of ubiquitin chains. On the other hand, by manipulating ubiquitin codes with small-molecule compounds, we will explore methodology for not only degradation, but also localization and activation of particular proteins.

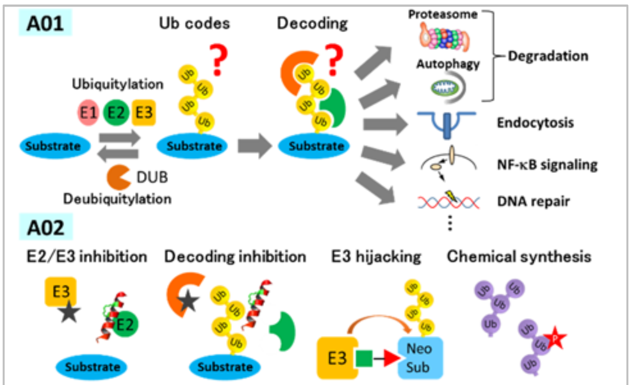


Fig. 1. Next generation ubiquitin research by chemo-technology

【Expected Research Achievements and Scientific Significance】

Our research project will markedly improve our understanding of the mechanisms of ubiquitin codes. The chemical tools developed in this project can be applied to discovery of new biology pathways involving ubiquitin and correct understanding of the pathogenesis of ubiquitin-associated diseases, as well as drug development. Our project will also promote a new collaborative style between biologists and chemists.

【Key Words】

Ubiquitin code: Information about various functions coded in the higher-order structure of various ubiquitin modifications.
Chemo-technology: Chemical techniques including the development and use of small-molecule compounds, stapled helical peptides, and agents that induce targeted protein degradation.

【Term of Project】 FY2018-2022

【Budget Allocation】 1,170,100 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.ubiquitin.jp/

Title of Project : Chronogenesis: how the mind generates time

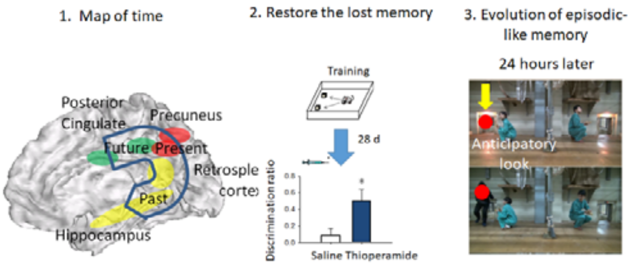
Shigeru Kitazawa
(Osaka University, Graduate School of Frontier Biosciences, Professor)

Research Project Number : 18H05520 Researcher Number : 00251231

【Purpose of the Research Project】

We discriminate the present from the past and the future while we live our daily lives. Where does the awareness of time, which we term “mental time”, come from? In our previous five-year project, “The Science of Mental Time”, we achieved three major goals as follows.

1) We successfully drew a map of mental time



over the medial surface of the cerebral cortex.

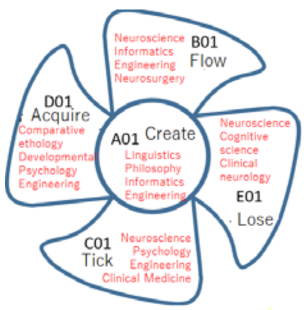
2) We developed methods for manipulating mental time in lab animals, and initiated clinical applications

3) We clarified the ontogeny and the phylogeny of the episodic-like memory.

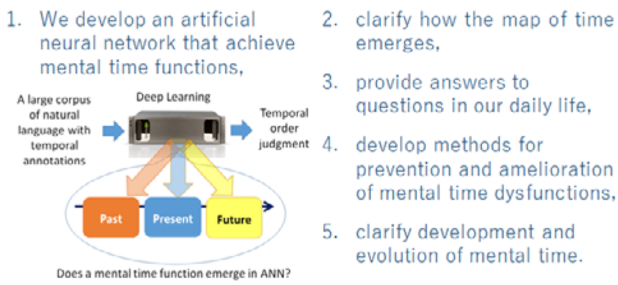
To make a further step forward, we “creates” an artificial neural network that achieves mental time functions, and use it as a control to be compared with the brain. Through the comparison, we address four critical question. 1) How does a sense of continuous “temporal flow” emerge? 2) How are rhythmic brain activities related with our awareness of time? 3) How do we “acquire” time through development and evolution? 4) How do we “lose” our time in neurological and mental diseases?

【Content of the Research Project】

This project consists of five sub-projects. Sub-project A01, located in the center of the five, “creates” an artificial neural network that outputs the order of two events when it receives multiple sentences sampled from a text corpus. The other four sub-projects, characterized by key words such as “Flow” (B01), “Tick” (C01), “Acquire” (D01), and “Lose” (E01), address each of the four above-mentioned questions.



【Expected Research Achievements and Scientific Significance】



Five achievements are expected from our collaborative and interdisciplinary studies.

1) We will develop artificial neural networks that achieve our mental time functions.

2) We will clarify how the map of time functions and emerges.

3) We will provide solid scientific answers to naive questions like “Why do we feel nostalgic for the past?”, and “Why does time fly when we have fun?”.

4) We will develop new methods for evaluating and manipulating mental time, and initiate clinical applications for screening and ameliorating the symptoms of diseases with mental time dysfunctions like dementia.

5) We will clarify similarities and differences in the mental time functions between the human and the other species, and between adults and children.

【Key Words】

Mental time: an awareness of time as being past, present, and future, specifically evolved in humans. Mental time is constructed by the brain and does not therefore necessarily coincide with time in the physical world.

【Term of Project】 FY2018-2022

【Budget Allocation】 1,157,200 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.chronogenesis.org/
kitazawa@fbs.osaka-u.ac.jp

Title of Project : Science of Soft Robot: interdisciplinary integration of mechatronics, material science, and bio-computing

Koichi Suzumori
(Tokyo Institute of Technology, School of Engineering, Professor)

Research Project Number : 18H05465　Researcher Number : 00333451

【Purpose of the Research Project】

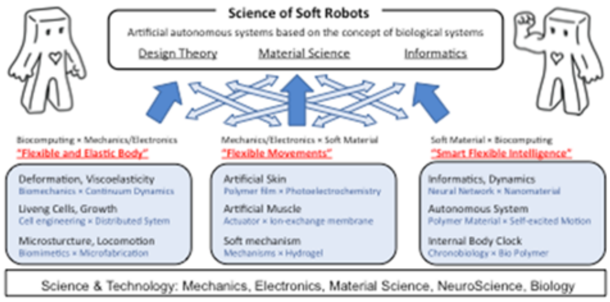
In this area, we focus on "softness" peculiar to organisms as the platform of life phenomena. In various fields, academic studies that refer to softness occur individually. The international trend of science and technology "from hard to soft" is the background toward science and technology that is close to human and living things. A science that organically bundles biology, information science, material science, and mechanical/electronic engineering is an unexplored area, and integration is desired. Introduction of softness brings an essential change accompanying the construction of a new academic area and we believe that a vast knowledge will be opened.

In this project, we propose "artificial autonomous systems based on the concept of biological systems" with the features of living organisms and define them as "soft robots" anew. The soft body of a living thing, its form, structure, mechanism, and information processing are fundamentally different from artificial things we can build at the present day. We call this frontier the new academic area "Science of Soft Robots." The aim of this area is to integrate new academic challenges in each field and to create an active academic trend toward science of soft robots.

【Content of the Research Project】

The new academic area "Science of Soft Robots" not only imitates and reproduces organisms but also learns from living things, but also to learn from biological systems and to make artificial systems beyond living things. The framework consists of "soft robot design theory", "soft robot material science", and "soft robot informatics".

Soft Robot Design Theory aims to blend mechatronics and biomechanics. It aims to allow flexible and elastic body. Also included is a biohybrid device incorporating living cells. Soft Robot Material Science creates flexible movements by smart material that has never been used on machines. We focus on soft mechanisms, electronics with extreme softness/elasticity, artificial muscle comparable to biological muscle using polymer material. Soft Robot Informatics aims to design smart and flexible intelligence in which software and hardware are inseparably combined. By utilizing the soft material dynamics as an information processing device, we aim to break through the limits of conventional information processing. In addition, by introducing a chemical reaction system on a soft body, we obtain spontaneous periodic motion and chemical body clock.



【Expected Research Achievements and Scientific Significance】

Through collaboration among interdisciplinary researchers who have never before met, the following academic outcomes are expected. First of all, it is possible to reveal principles of skillful soft mechanisms found in the animals and realization by artificial systems. From the viewpoint of material science, we can provide new actuators, flexible sensors, and soft energy source utilizing a functional polymer material and an electrochemical phenomenon. As a contribution to robotics, it is possible to provide a theoretical framework of continuum dynamics that handles nonlinearity and large deformation of soft materials. It is also expected to have soft mechanics using a functional hydrogel. For information processing technology, we will show that soft behavior of complex body can be used as a computational resource different from semiconductor chip.

As a social return of academic outcomes, various applications utilizing safety due to softness, biocompatibility are conceivable. Soft robots that can coexist with humans are expected to develop into safe and intellectual physical exercise support in an aging society, realization of safe mobility, monitoring robots without discomfort.

【Key Words】

Soft Robot, Soft Actuator, Soft Mechanism, Flexible Sensor, Biohybrid, Biocomputing

【Term of Project】 FY2018-2022

【Budget Allocation】 1,194,200 Thousand Yen

【Homepage Address and Other Contact Information】

http://softrobot.jp

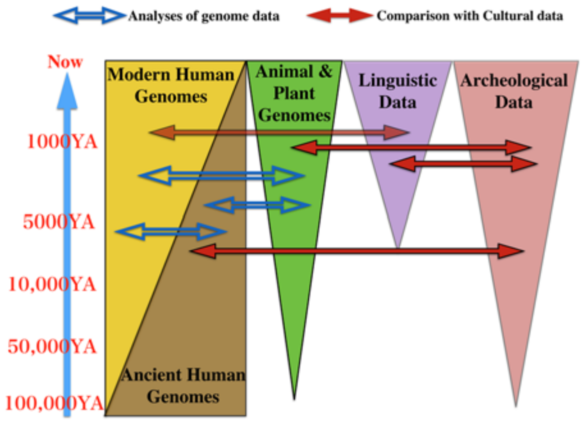
Title of Project : Deciphering Origin and Establishment of Japonesians mainly based on genome sequences date

Naruya Saitou
(National Institute of Genetics, Division of Population Genetics, Professor)

Research Project Number : 18H05505 Researcher Number : 30192587

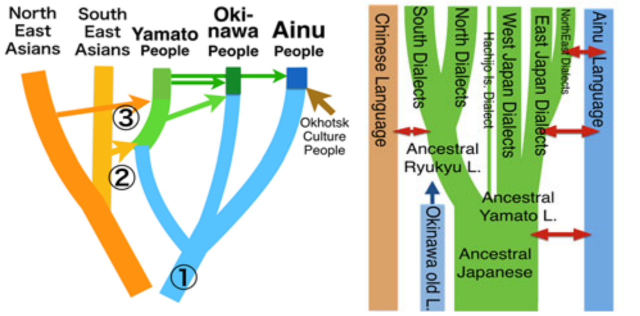
【Purpose of the Research Project】

People reached Yaponesia (Japanese Archipelago) around 40,000 years ago for the first time, and many waves of migration occurred after that time. Within this framework, we seek to decipher the genomic history of Yaponesians (people on Japanese Archipelago) through determination and comparative analyses of many modern and ancient human genomes. We also analyze genome data of animals and plants which moved to Yaponesia with Yaponesians. Temporal changes of population size are also estimated from genome sequence data by using existing methods and newly developed methods. Because we need to examine history of Yaponesians from many aspects, archeology with special reference to age estimation (dating) of artifacts and ancient organisms and linguistics with special reference to dialect analyses of Japanese and Ryukyuan languages will have collaborative fusion study with evolutionary genomics. We aim to establish new discipline, "genome history" of Yaponesians, through integration of these various analyses.



【Content of the Research Project】

Collect modern Yaponesian DNA samples from various geographical area, and examine the three-migration hypothesis by analyzing their genome sequences (A01 and B03 groups). Extract DNAs from ancient Yaponesian of archeological sites in various periods and area, and compare their genome sequences with modern ones including analyses on natural selection and disease related genomic changes (A02, A01, B03 groups). Analyze genome sequences of animal and plant species and use them for estimating timings of human migrations to Yaponesia and interactions with continental people (A03 and B03 groups). Examine artifacts found from archeological sites of various periods and area with special reference of



detailed dating (B01 and A02 groups). Examine dialect data of Japanese and Ryukyuan languages in detail and also infer phylogenetic relationship of Japanese by comparing genome data (B02, A01, A02, B03 groups). Develop new theories to estimate population size change and selection coefficient changes during very short time scale (B03, A01 groups). Study different area of interdisciplinary researches not covered by A01-A03 and B01-B03 groups in A04 and B04 publicly offered groups. We publish magazine "Yaponesian", as well as supporting global collaborations and assisting career development of young researchers.

【Expected Research Achievements and Scientific Significance】

Clarify periods and source populations of Yaponesia within the framework of Out-of-Africa dispersal of anatomically modern humans.
Clarify population size changes of Yaponesians and their ancestors and estimate major migration times.
Estimate locations and periods of migrants to Yaponesia.
Clarify correlations between arrivals of cultural elements and human migrations from comparison of archeological data and mutational changes of genomic DNA.
Estimate the rate of changes of languages spoken in Yaponesia and narrow down language family that may be phylogenetically closer to Japanese.

【Key Words】

Yaponesia, Japanese Archipelago, human evolution, genome, archeology, linguistics, human history

【Term of Project】 FY2018-2022

【Budget Allocation】 658,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://yaponesian.org/
come-together@yaponesian.org/

Title of Project : Elucidation of the strategies of mechanical optimization in plants toward the establishment of the bases for sustainable structure system

Taku Demura
(Nara Institute of Science and Technology, Graduate School of Science and Technology, Professor)

Research Project Number : 18H05484 Researcher Number : 40272009

【Purpose of the Research Project】

As environmental and population issues are worsening at the global level, efforts to build up a sustainable society are accelerating. The creation of a sustainable living space, in harmony with the surrounding environment, is one of society's most important endeavors, even in the fields of manufacturing, architectural design, and urban planning.

In recent years, approaches in engineering using biomimetics have been pursued. Additionally, studies on plant cell walls have demonstrated that plants are excellent structural systems that autonomously optimize their mechanical properties in response to various environmental factors.

Based on the above background, this research project aims to understand the mechanical optimization of plants on a multi-scale (molecular, cellular, tissue, and individual) level. Also, we aim to sublimate the mechanical optimization strategy of plants into new energy-saving / material-saving building designs, new material models, and to create a base for the next-generation of sustainable structural systems (Figure 1).

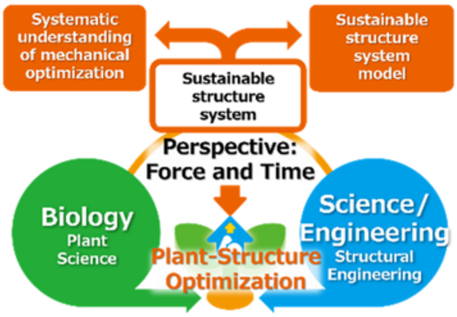


Figure 1. Research strategy and expected achievement

【Content of the Research Project】

In this area, we will create a foundation for a new principle of architectural structure system based on the "mechanical optimization strategies" hidden in various phenomena operated by plants. For this purpose, three research groups are set. Group A01 "System" will aim to understand the mechanical phenomenon at the organ-individual scale and will propose the new "building system". Group A02 "Module" will elucidate the mechanical phenomenon on the cell-tissue scale and will provide new module designs. Group A03 "Unit" will analyze the mechanical properties on the subcellular scale and will develop units (building materials) in construction.

【Expected Research Achievements and Scientific Significance】

One of the expected outcomes is the development of a new "structural system model" based on the mechanical optimization strategy of plants. We will thus utilize the knowledge of the structural-mechanical features that give plant cell walls their strength and plasticity to build up a next generation material model. It is also expected that "mechanical optimization" will be added to our knowledge of the growth strategies of plants, especially our insight into the fundamental principles for stable growth of organisms in harmony with the internal and external environments, which may rewrite the basic principles of biology. In addition, this research area is looking forward to the creation of a new scientific field that can directly contribute to the construction of a sustainable society. The academic achievement of this area will be relayed to social implementation technologies in the future. Particularly, we are expecting sustainable construction in harmony with various environmental factors unique to this country (earthquake, typhoon, temperature difference of the four seasons, etc.).

Furthermore, this research will contribute to the establishment of next-generation bio-based technologies, through the engineering of the functionalization of plant and their capabilities to respond to environmental stresses, thus generating plants that can withstand global environmental changes.

【Key Words】

Mechanical optimization: To change the body structure of living organisms into a mechanically optimized form during development and environmental response.

Sustainable structural system: A space structure with high sustainability even in exhaustion of resources and energy with constant changes in the environment.

【Term of Project】 FY2018-2022

【Budget Allocation】 1,180,500 Thousand Yen

【Homepage Address and Other Contact Information】
http://bsw3.naist.jp/plant-structure-opt/

Title of Project : Molecular Engine: Design of Autonomous Functions through Energy Conversion

Kazushi Kinbara
(Tokyo Institute of Technology, School of Life Science and Technology, Professor)

Research Project Number : 18H05418 Researcher Number : 30282578

【Purpose of the Research Project】

In this research area, we define a molecular device that causes a mechanical structural change by receiving external energy and converts it into another form of energy, as "molecular engine." It is aimed at establishing basic scientific disciplines for building molecular engines. For this purpose, experts in synthetic chemistry, molecular biology, biophysics, soft matter physics, computer science, which have been developed independently as different fields, work together to unite wisdom and thereby create a new research field for nanoscale molecular devices and systems. Looking to construct social implementable devices, we explore the availability of various energy sources (Figs. 1 and 2).

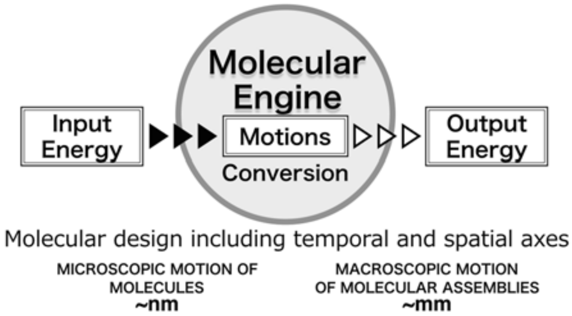


Fig. 1 Concept of “molecular engine.”

【Content of the Research Project】

In this area, in order to establish the concept of "molecular engine", small molecules with a relatively simple structure, macromolecules capable of forming a higher order structure such as a protein, molecular aggregates in which these are integrated. In each of the different hierarchies, we aim to construct disciplines to realize energy conversion via mechanical motion. For this purpose, the following four research groups are organized, including experimental, computational, and theoretical science with artificial molecular machines, biomolecular machines and molecular assemblies. A01: Rational design of molecular units for energy conversion, B01: Movement of molecular assemblies with energy conversion function, C01: Detection and measurement of molecular engines, C02: Theoretical analysis of energy conversion by molecular engines.

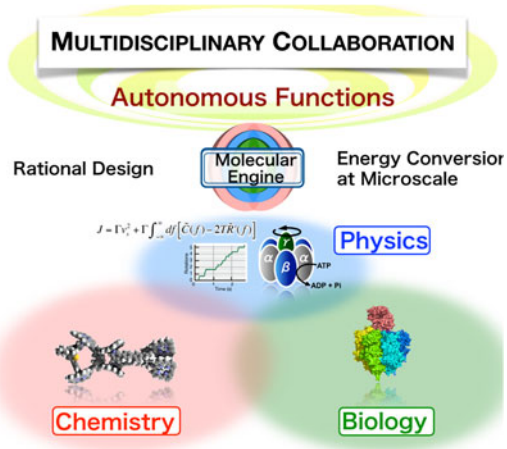


Fig. 2 Multidisciplinary collaboration.

【Expected Research Achievements and Scientific Significance】

Design principles for the energy conversion by the mechanical motion of molecular systems, that highly efficiently converts various energies such as chemical-bond, electrical, mechanical and, light energy to other usable energies is established. It is expected that new possibilities of energy conversion systems will be proposed.

【Key Word】

Molecular Machine: molecule that moves physically like a machine by applying external stimuli

【Term of Project】 FY2018-2022

【Budget Allocation】 1,193,600 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.molecular-engine.bio.titech.ac.jp

Title of Project : Singularity biology

Takeharu Nagai
(Osaka University, The Institute of Scientific and Industrial Research, Professor)

Research Project Number : 18H05408 Researcher Number : 20311350

【Purpose of the Research Project】

There exist critical moments, such as the 'Big Bang' where "something out of nothing gets created" or in the future, when artificial intelligence might become greater than human intelligence. These points are called *singularities*. In the field of biological science, discontinuous critical phenomena are broadly seen, for example, the emergence of life from the primordial soup, or the evolution and outbreak of diseases. It has been indicated that only a small number of core elements are required to bring about discontinuous changes to an entire multi-component system. However, the mechanism-of-action that generates such singularity phenomena is not yet certain. In our research project, to look deeply into singularity cells, we are developing an imaging platform that will achieve both wide field-of-view high-resolution imaging and high-speed long-term imaging, and corresponding information analysis methods. This will enable us to be at the cutting edge of new scientific fields, where we uncover the underlying mechanisms for the generation of singularity cells as well as their biological functions.

【Content of the Research Project】

In order to study the processes that singularity cells, considered as minority entities, bring criticality to an entire system (ex: an organ or whole body), it is necessary to measure, analyze, and examine such biological systems in a holistic spatial-temporal manner. For this purpose, an imaging system is required for visualization of *molecules, cells, and organs* across different length scales. In order to achieve this, we will organize a core team under a research management team to develop a unique machine we call **AMATERAS** (**A**spired **M**ultimodal **A**nalytical **T**ools for **E**very **R**are **A**ctivities in **S**ingularity) which allows us to capture macroscopic spatiotemporal dynamics with microscopic precision: *not only the composite trees but also the whole forest*. In addition, we will organize the following three groups to develop authentic trans-scale analysis that plays a role to *seamlessly link from micro to macro*. Group A01 will develop and integrate techniques to measure and control singularity cells from the stand point of optics and molecular engineering. Group A02 will construct a theoretical framework to identify singularity cells and to verify the causality based on information science. Group A03 will unravel the biological significance of singularity cells by verifying causality which is elicited from individual biological models. By conducting this kind of circulative collaborative research, we will create the research field "singularity biology", with reference to its universality.

【Expected Research Achievements and Scientific Significance】

We will develop an unprecedented integrative device for measurement and analysis, **AMATERAS**, and will establish a research platform covering not only academia but also several relevant companies. From the effective operation of **AMATERAS**, which includes the acceleration of large scale cross field research among optics, molecular engineering, mathematical biology, information science, biology, and medicine, we expect to largely contribute to the development of innovative devices, the construction of a new information processing theory, and early diagnosis to facilitate and intervention in the case of disease. By creating an alliance network with **AMATERAS** at its core, we will promote industry-academia collaborations. Moreover, this network will contribute to the development of human resources and foster next generation young leaders with full knowledge in different fields through holding international training courses and symposiums specializing in trans-scale measurements and analyses.

【Key Words】

Singularity phenomena: Phenomena that discontinuously and dramatically change the dynamics of an entire system in multi-cell society, where organs and individual bodies are constructed from large number of cells. We call the minority cells that trigger the changes "singularity cells".

【Term of Project】 FY2018-2022

【Budget Allocation】 1,210,100 Thousand Yen

【Homepage Address and Other Contact Information】

http://singularity-bio.jp