Title of Project： Glia decoding: deciphering information critical for brain-body interactions

OKABE Shigeo
(The University of Tokyo, Graduate School of Medicine, Professor)

Number of Research Area：20A301　Researcher Number： 60204012

【Purpose of the Research Project】

The internal state of an animal changes continuously in response to the environment. The internal condition of the animal body also affects brain functions. Traditionally the sensory organs have been taken as the main route of interaction between the nervous system and the environment. However, recent studies proposed that glial cells play a central role in the interaction between the brain and peripheral tissue as a bidirectional interface. Internal conditions of the body are presented to the brain via the glial interface. Reciprocally, glial cells transmit signals of the brain status to the peripheral organs and tissues. The development of new methods for decoding the signals in glial cells (glia decoding) will help a full understanding of brain-body interactions.

This research program achieves comprehensive decoding of glial cell functions by recruiting researchers with new analytical methods or interest in peripheral organs. To this end, we set three goals as follows:

(1) Understand the information processing between glia and neural circuits, with particular reference to the dynamics of metabolic, cardiovascular, and immunological responses.

(2) Clarify the various interaction mechanisms between the environment, internal body state, and brain function, especially those operating via the glia-derived signals.

(3) Develop methods of decoding glial cell state, function, and intercellular signaling (glia decoding), which facilitate the understanding of signal integration in the brain-body interactions.

These approaches will clarify the functional correlation between brain and body, leading to a new research field beyond the current brain science.

【Content of the Research Project】

We set the following three research aims in this program.

(A01) Brain functions based on the integration of glia and neural network.

The research topics include glial regulation of developing neural circuits, energy consumption and metabolic processes regulated by glia and blood vessels, and intercellular signaling between glia and other cell types visualized by FRET biosensor. These experiments will clarify the functional integration of glia and neural networks.

(A02) Regulation of the brain-body interaction by glia.

Information of noxious stimuli in the peripheral tissue is transmitted to the brain via multiple pathways. In this context, mechanisms other than the fast signal transmission through the classical peripheral sensory system are likely to be operated. The possible involvement of glial and immune cells in this process is explored.

(A03) Comprehensive analysis and manipulation of glia-mediated brain-body interactions.

New methods that enable comprehensive decoding and manipulation of glial functions in the whole brain will be developed. New replacement technology of glial cells in the entire brain will be tested. Also, new tissue-clearing technology for the imaging of total glial cells in the brain will be applied to the analysis of glial functions. We try to identify the possible roles of long-range cellular communications via exosomes in the brain-body interactions.

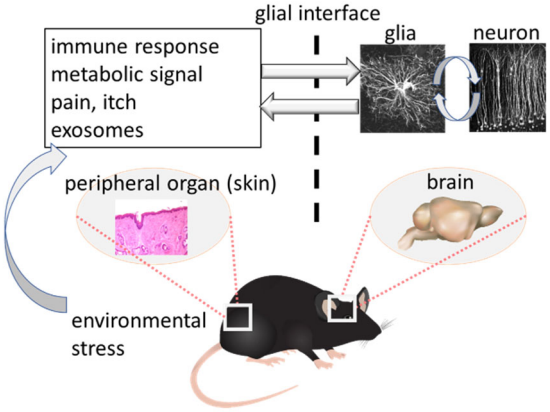


Figure 1. Glial interface regulates brain-body interactions

【Expected Research Achievements and Scientific Significance】

Neural circuit study is supported by large brain projects in the US and EU. It is necessary to establish systematic research programs in the study of glia and brain-body interaction. The new research program will discover multiple functions of glia at the interface between brain and peripheral organs, together with the development of cutting-edge technologies for the deciphering of "glial code." The data produced in this program will expand the glial research field beyond the current neuroscience. Moreover, this research program will help identify the core pathology of neurological and psychiatric disorders.

【Key Words】

Brain-body interaction: mechanism of homeostasis and integrated function of the whole body through the elaborate interaction of the peripheral organs and the brain.

【Term of Project】 FY2020-2024

【Budget Allocation】 1,222,400Thousand Yen

【Homepage Address and Other Contact Information】

http://gliadecode.com /

【Grant-in-Aid for Transformative Research Areas（A）】

Section Ⅲ

Title of Project： Multi-layered regulatory system of plant resilience under fluctuating environment

MATSUSHITA Tomonao
(Kyoto University, Graduate School of Science, Professor)

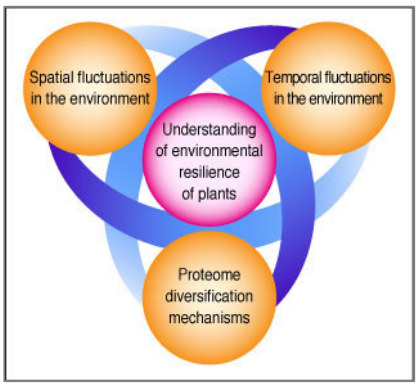
Number of Research Area：20A302　Researcher Number：20464399

【Purpose of the Research Project】

Plants are exposed to constantly fluctuating environments where they sprout. Attributes of their environment, such as soil nutrients and leaf-filtered sunlight, display mosaic-type spatial fluctuations, and are accompanied by irregular fluctuations across time, such as in degree of dryness. Moreover, it is not unusual for attributes of a real natural environment to fluctuate in a compound manner. To survive in such environments, plants are equipped with characteristic resilience mechanisms that enable them to adapt robustly and flexibly to environmental changes across a wide dynamic range. However, research to date has been limited to analysis of single-environment response under uniform conditions, and has not elucidated multi-layered adaptive mechanisms in intrinsically fluctuating, compound environments. In particular, most phenomena and molecular mechanisms whose actions can be observed only under fluctuating environmental conditions remain to be elucidated. By focusing on molecular mechanisms that regulate fluctuating temporal and spatial environmental information, and the proteome diversification mechanisms supporting them, this research project will seek to elucidate the nature of plant environmental resilience, and revolutionize research into biological adaptation to the environment.

【Content of the Research Project】

This transformative research project will seek to understand the robust as well as the characteristically flexible dynamic adaptive capacity that plants demonstrate under fluctuating environmental conditions—that is, their environmental resilience mechanisms—by going a step beyond research to date into plant environmental response under uniform conditions, to effect a revolution in research methods and concepts relating to plant environmental response, by introducing three original perspectives actually seen in natural environments: 1) spatial fluctuations; 2) irregular fluctuations over time; and furthermore, 3) multi-layered proteome diversification mechanisms, including changes in transcription start sites, as a molecular basis supporting adaptive capacity in fluctuating temporal and spatial environments. In addition, plant environments in the natural world are thought to consist of multiple, overlapping and fluctuating environmental layers, and an understanding of plant responses to complex natural environments such as this has so far been almost entirely lacking. In this research project, specialists engaged in different types of environmental stimulus response research will collaborate to elucidate response mechanisms in compound environments of various configurations.



Three original perspectives in this project

【Expected Research Achievements and Scientific Significance】

Elucidation of the molecular mechanisms supporting plant environmental resilience should establish concepts that give rise to new research currents. Moreover, this research project will promote the development of young researchers who can play active international roles. In addition, it should generate results that will contribute to structuring basic technologies for solving food supply and energy problems in the future. These researches could also facilitate understanding of biological systems for regulating a wide range of environmental information.

【Key Words】

Resilience: Commonly signifies dynamic adaptive capacity incorporating flexibility and robustness with respect to a continuously changing environment. This can truly be said to exemplify the survival strategy of plants, which have chosen a strategy of immobility, in contrast to animals, which move about seeking environments optimized for survival.

【Term of Project】 FY2020-2024

【Budget Allocation】 1,204,200 Thousand Yen

【Homepage Address and Other Contact Information】

https://plant-resilience.jp
mat@gr.bot.kyoto-u.ac.jp

Title of Project： Inducing lifelong plasticity (iPlasticity) by brain rejuvenation: elucidation and manipulation of critical period mechanisms

KANO Masanobu

(The University of Tokyo, Graduate School of Medicine, Professor)

Number of Research Area：20A303　Researcher Number：40185963

【Purpose of the Research Project】

Brain function is greatly influenced by experience during postnatal development. Early in life, neural wiring is dramatically reorganized to reflect input from the environment in such "critical periods (CPs)" – restricted times during which plasticity of neuronal connectivity is particularly high. (Fig. 1). Salient CP experiences are etched into neural circuits that persist throughout life. For example, if juvenile animals are deprived of vision through one eye, that eye becomes virtually blind for the remainder of the animal's life if not corrected during their CP. It is then anticipated that CP reopening in adulthood might enable recovery of impaired neural function or the acquisition of additional brain functionality. Indeed, recent studies have demonstrated the possibility to advance or delay CP onset as well as to reopen them in adulthood. (Fig. 1). Furthermore, after brain injury, neural circuit plasticity seems to be transiently enhanced to facilitate functional recovery, analogous to a "CP" seen in normal development. In our Transformative Research Area, we therefore redefine CP as a limited time window of elevated capacity for plasticity and reorganization of neural circuits potentially throughout life. We aim to deepen our understanding of the development of brain and mind by pursuing basic mechanisms of CPs and to induce lifelong plasticity (iPlasticity) by brain rejuvenation.

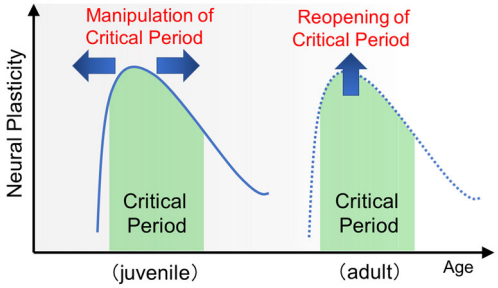


Figure 1. Critical Period and Its Manipulation and Reopening

【Content of the Research Project】

We established two research categories, A01: "Mechanisms of neural circuit reorganization in CPs during development" and A02: "Manipulation and reopening of CPs and mechanisms of CPs after brain injury". In A01, the investigators will pursue the mechanisms of CPs in the developing nervous system in relation to synapse pruning, E/I balance (i.e., ratio of excitatory and inhibitory inputs) and social interaction. Masanobu Kano investigates how neural activity regulates synapse pruning during postnatal cerebellar development in mice. Mariko Miyata examines the difference between synapses that are strengthened and survive throughout life from those that are weakened and eventually eliminated by synapse pruning in the developing sensory thalamus. Kenichi Ohki investigates how neurons in the primary and higher visual cortices acquire response diversity during their CPs in developing mice. Motokazu Uchigashima examines structural plasticity of dendritic spines that leads to neural circuit reorganization in visual cortical neurons during the CP. Sho Tsuji performs quantitative analyses on the influence of language experience in the CP for native language acquisition in human infants.

In A02, investigators pursue how to manipulate timing and duration of CPs in the developing nervous system, how to reopen CPs in adulthood, and how to facilitate recovery from brain injury. Takao Hensch elucidates the mechanisms by which attention and arousal influence neural circuit plasticity during CPs and how to develop the means to reopen CPs in adult mice. Takashi Kanamaru theoretically investigates how neural networks acquire nonlinear dynamics such as stable attentional states during the CP. Takuya Takahashi measures the density and distribution of AMPA receptors and $GABA_A$ receptors and estimates the E/I balance in the human brain after stroke by using PET. Junichi Ushiba develops means to facilitate the formation of compensatory neural circuits in post-stroke subacute brains by using brain-machine interface (BMI) technology.

【Expected Research Achievements and Scientific Significance】

Our knowledge about the mechanisms of neural circuit reorganization during CPs of the developing nervous system will be greatly advanced. Discovery of the means to manipulate and reopen CPs may lead to novel therapy of neurodevelopmental disorders such as amblyopia, speech and hearing disorders. Developing effective rehabilitation procedures alongside methods for monitoring E/I balance in the human brain is expected to facilitate functional recovery after stroke. Furthermore, the outcome of our research area may give insights into infant care, education and clues to develop novel brain- inspired Artificial Intelligence.

【Key Words】

critical period: restricted time during which plasticity of neuronal connectivity is particularly high and neural wiring is reorganized to reflect input from the environment

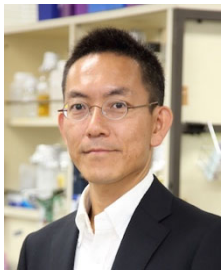
【Term of Project】 FY2020-2024

【Budget Allocation】 1,247,500 Thousand Yen

【Homepage Address and Other Contact Information】

http://iplasticity.umin.jp/

rinkaiki@m.u-tokyo.ac.jp



Title of Project： Multifaceted Proteins: Expanding and Transformative Protein World

TAGUCHI Hideki
(Tokyo Institute of Technology, Institute of Innovative Research, Professor)

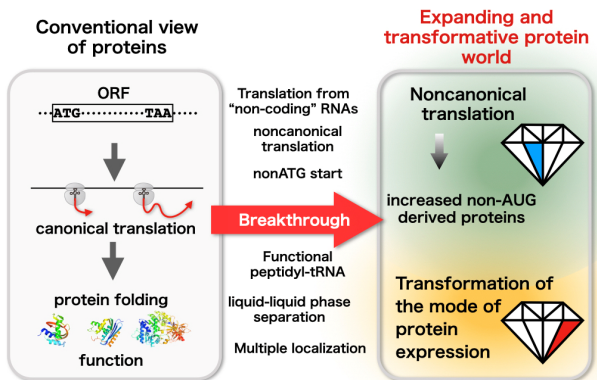
Number of Research Area：20A304　Researcher Number：40272710

【Purpose of the Research Project】

Over the past few years, the traditional view of proteins has been updated. Current protein science has been based on the premise that the ribosome synthesizes the polypeptide from the start codon to a stop codon of the open reading frame (ORF) in the mRNA. The completed polypeptide chain folds into a three-dimensional structure, and then functions. However, recent breakthroughs in various discoveries and technological innovations have revealed novel aspects of protein science. For example, translation does not always initiate from the AUG start codon of the annotated ORFs. Translation often starts from a codon other than AUG, and sometimes stalls during the translation elongation, independent of stop codons. Accumulating evidence shows that a number of non-coding RNAs, which, by initial definition, do not code for proteins, is translated into physiologically relevant proteins. The repertoire of proteins that shape the proteome increases due to innovations in mass spectrometry-based proteomics. In addition, it has become clear that proteins do not always function by folding, and that they do not only function at specific locations. Furthermore, such noncanonical translation is closely related to diseases such as neurodegenerative disorders.

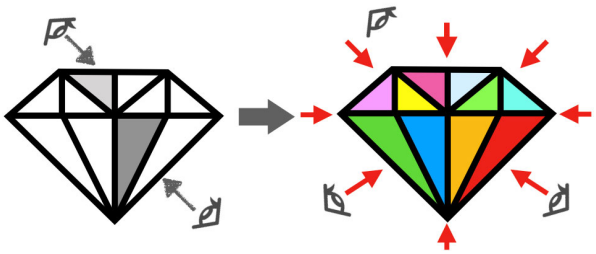
Thus, the "protein world" is expanding and transforming (Fig. 1). In other words, to truly understand the real protein world, it is necessary to update the conventional view on the translation, the repertoire, and modes of function.

Fig. 1 Expanding and Transformative Protein World



This project aims to construct a new paradigm by redefining the protein world from multifaceted perspectives, and to update the conventional view of proteins (Fig. 2).

Fig. 2 Concept of Multifaceted Proteins



【Content of the Research Project】

The following research will be conducted to achieve the aim.

1. Generality and function of proteins produced from noncanonical translation dynamics.
2. Exploration of previously unappreciated proteomes and their physiological functions.
3. Noncanonical translation involved in neurodegenerative diseases and its relation to pathology.
4. Novel aspect of protein function in the cell.
5. Development and application of new methodologies

【Expected Research Achievements and Scientific Significance】

The paradigm shift in protein science, achieved by this project, will have a great impact on basic science, but it will not be limited to the protein science. In addition, this field is expected to lead to seamless connections to the medical and industrial fields, such as the elucidation of the pathogenesis of neurodegenerative diseases, biomarkers for diseases, and *de novo* design protein research.

【Key Words】

Noncanonical translation: Translation that does not just initiate from the AUG start codon and end at stop codons in open reading frames. Also, noncanonical translation includes disease-related repeat-associated non-AUG-dependent translation (RAN translation).

【Term of Project】 FY2020-2024

【Budget Allocation】 1,211,200 Thousand Yen

【Homepage Address and Other Contact Information】

http://proteins.jp

Title of Project： Genome modality: understanding physical properties of the genome

NISHIYAMA Tomoko
(Nagoya University, Graduate School of Science, Associate Professor)

Number of Research Area：20A305　Researcher Number：90615535

【Purpose of the Research Project】

Since the discovery of DNA double helix, genome study has been expanded and our knowledge of the genome was enormously progressed; Meanwhile whole genome has been sequenced in many model organisms and nowadays genome editing technology is widely and rapidly spread. The past genome researches have mainly forced on its informational aspects, such as replication, repair, recombination, and division of the genomic information and further highlighted epigenetic regulations to explain genetic phenomena. On the other hand, physical properties of the DNA, such as stiffness, torsion, supercoiling and so on, have been much less understood, although it is the most important properties directly affecting the genome structure. In this project, we will focus on physical properties of genome/DNA to understand how the genome builds its structure and how it functions. We define "genome modality" as a multi-dimensional mode to organize the structure and function of the genome. We will uncover bona fide figure of the genome from the perspective of genome modality. To this end, we utilize methods of biochemistry, cell biology, genome science, and polymer physics and create new field to study "genome modality."

【Content of the Research Project】

Objects of this project range from nano-scale DNA/nucleosome structures to organisms (Figure 1). Regulators of genome modality would include nucleoplasmic/cytoplasmic environments, physical properties of proteins, and physicochemical reactions such as liquid-liquid phase separation, as well as physical properties of DNA. How do they regulate genome modality in each scale and define chromosome- or chromatin-dynamics, and how does dysfunction of the factors result in disorganization of cellular functions and causes diseases? We will address these questions from different approaches including theoretical physics, measurements of biophysical properties, reconstitutions, and genomics as well.

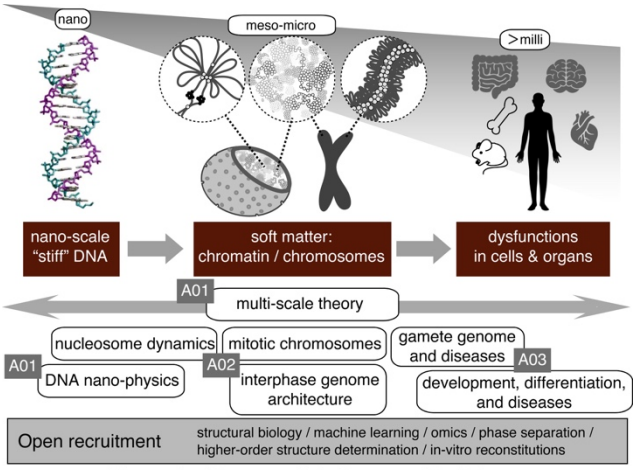


Figure 1　Framework in Genome Modality

In the framework, there are 3 major categories as follows. A01: Physics of genome modality, where we uncover nano-scale genome structure and properties, and also build multi-scale theoretical model of the genome. A02: Meso-scale genome modality, where we focus on meso-scale structure including nucleosome, DNA loops, and chromatin fibers/domains, and figure out how these structures are formed. A03: Disorders of genome modality, where we address the questions how dysfunction of genome modality-regulating factors causes diseases.

【Expected Research Achievements and Scientific Significance】

First, we will discover novel genome organizers, which can regulate physical properties of DNA. This will be possible only when both genome biology and polymer physics fields work together collaboratively in our consortium, and will establish a novel concept of genome organization based on physical properties of DNA. Second, we will create "Genome Modality Suite", an integrative platform, where all new information coming from this project are combined, so that nano-scale disorders of the genome can be linked to whole-genome behavior and resulting diseases. This platform will be opened for public as a useful tool in the future.

【Key Words】

Genome modality: A multi-dimensional mode to organize/regulate the structure and function of the genome.

【Term of Project】

FY2020-2024

【Budget Allocation】

1,140,400 Thousand Yen

【Homepage Address and Other Contact Information】

https://www.genome-modality.com
nishiyama@bio.nagoya-u.ac.jp

Title of Project： Material properties determine body shapes and their constructions

INOUE Yasuhiro
(Kyoto University, Graduate School of Engineering, Professor)

Number of Research Area：20A306　Researcher Number：80442929

【Purpose of the Research Project】

When building a house, it is important to choose the appropriate building materials. This is because the physical properties of the building materials determine how they are manufactured and assembled, which in turn determines the final shape of the house. This factor can be linked to the morphogenesis of living organisms. Since cells alone are not rigid enough to build and maintain the physical body, support materials (calcium, collagen, chitin, etc.) are used. For building "bodies," cells must choose construction methods depending on materials.

In this area, we aim to reveal the principle of morphogenesis by demonstrating a new paradigm for processing non-cellular materials. By viewing the essence of morphogenesis as "body = workpiece, cell = worker," we believe that mathematical modeling and large-scale simulation will become easier whereby the relationship between "macroscopic shape" and "cellular behavior" will become clearer at a stroke. In addition, since this paradigm is engineering itself, we can expect the application of industrial design technologies to living organisms, as well as the industrial application of discoveries obtained from living organisms.

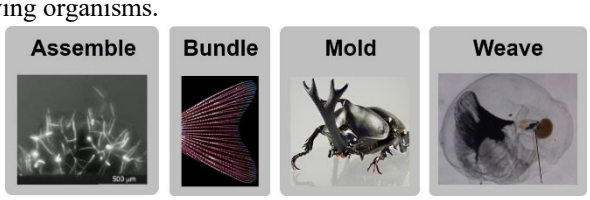


Fig. 1 Processing of support materials.

【Content of the Research Project】

In this area, three research groups will be promoted with the support of Administrative group. Research group A01 consists of biological researchers who have experimental systems suitable for elucidating new principles. Although the phenomena are diverse, the principle of morphogenesis will be approached from the viewpoint of the processing non-cellular materials. In research group A02, the formation of the body is modeled and simulated in terms of the processing of materials, and the principles of morphogenesis are studied theoretically. In research group B01, we will promote the above projects by developing measurement and manipulation techniques for materials and cells, and conversely, we will apply the principles of biological morphogenesis to theoretical engineering and technological development. We aim to develop new engineering applications that have been inspired from the principles and processes by which the shapes of living organisms are constructed.

【Expected Research Achievements and Scientific Significance】

By understanding the morphogenesis based on a new paradigm of "processing of non-cellular materials," we expect to revolutionize our understanding of developmental biology in general, beyond the subject matter covered in this research area. The contribution of cells will be viewed as more than just a part of the body, cellular behaviors will be viewed as "workers" processing and assembling the support materials that determines the shape of the body.

This research focus has a high affinity with engineering since morphogenesis is defined as the processing of materials. In this regard, we will explore engineering applications of the discovered biological principles. For example, the principle of manufacturing and storing 3D structures as compact planes, as seen in the formation of a house of Larvacea, is expected to lead to new design and manufacturing technologies for architecture and machinery. The cellular behaviors as workers in sponges can also be expected to lead to the development of new decentralized control theories for systems such as drones that operate in many occupational capacities.

Furthermore, since research in this area will be conducted through collaboration among a wide range of disciplines, we expect that it will lead to the development of young researchers who can discover and solve problems from a variety of perspectives by having an overview of all contributing factors, from basic science to its complex applications.

【Key Words】

Support material: A pyramid shape stacked with soft dumplings will collapse under their own weight. With skewers, you can make a tower like this. In this case, the skewer, a support material, makes the shape.

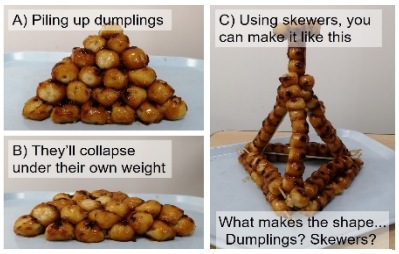


Fig. 2 Making the shape.

【Term of Project】

FY2020-2024

【Budget Allocation】

1,147,300 Thousand Yen

【Homepage Address and Other Contact Information】

https://www.architect-bio.info