# Developmental brain sciences toward understanding of origin of intelligence

**Gentaro Taga**
(The University of Tokyo, Graduate School of Education, Associate professor)

**【Outline of survey】**

The aim of our project is to understand the developmental origin of human intelligence. The intelligence involves generation of adaptive behaviors in the physical and social environment and acquisition of knowledge, which enriches one's mind and produces individual diversity. To detect emergence of and developmental changes in various types of intelligence, we conduct multidisciplinary studies involving brain imaging using near infrared optical topography, measurement of eye and body movements, psychological testing and dynamical systems modeling. We focus on the issues of domain specificity/generality of development, U-shaped development, sensitive periods and plasticity, interference of learning and development over different time scales, and the origin of rational thinking. We try to capture dynamic changes in behaviors and functional brain activations in early infancy and construct a new framework for system-level understanding of innateness and development of human intelligence.

**【Expected results】**

We expect to gain a deeper understanding of the relationship between the innate constraints and experience-dependent mechanisms for the acquisition of intelligence on behavioral and neural levels. This project will not only add new findings in special fields of cognitive science, behavioral science, neuroscience and developmental psychology, but also provide a new vision of development in pediatrics, childcare, education, engineering and philosophy, each of which pursues essential understanding of human being.

**【References by the principal investigator】**

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| 【Term of project】 FY2008− 2012 | 【Budget allocation】 **80,000,000 yen** (direct cost) |
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**【Homepage address】** http://www.p.u-tokyo.ac.jp/~taga/

# Activity-dependent mechanisms regulating dendritic morphology and function

**Haruhiko Bito**

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

**【Outline of survey】**

A fundamental question is how an ensemble behavior of 100 billion neurons can possibly give rise to a coherent and integrated "brain" that controls the whole human organism. Our central nervous system is physically wired and organized based on evolutionary and developmental principles that are primarily encoded into the genome and that are highly conserved in mammals from rodents to primates. This neural network, however, is also able to recognize and memorize external and internal events as they occur, and flexibly act based on memories of experienced events. We aim to address the basic signal transduction mechanisms which mediate the interaction between electrical and chemical signaling in the dendritic compartments and which allows information to be written and re-written into the neuronal circuits.

Specifically, we will examine: 1) the mechanisms underlying the formation and maturation of the dendritic morphology; and 2) the mechanisms by which local synaptic events can induce neuron-wide global changes via activation of transcriptional, translational and cytoskeletal processes; 3) the mechanisms that instruct individual synapses to alter or to maintain its responsiveness upon establishment of a global neuron-wide change in input-output function.

**【Expected results】**

Through this research project, we expect to better understand the precise nature and the whole spectrum of the molecular changes, both local and global, in the neurons undergoing profound modifications of the synaptic wiring, during development and in adult animals. Furthermore, we will identify key molecular and cellular mechanisms and principles that govern information processing and storage in active neuronal circuits.

**【References by the principal investigator】**

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| 【Term of project】 FY2008－2012 | 【Budget allocation】 80,600,000 yen (direct cost) |
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【Homepage address】 http://www.neurochem.m.u-tokyo.ac.jp/Homepage.html

# Molecular mechanisms for neuronal function via vesicular trafficking

**Michiko Shirane**
(Kyushu University, Medical institute of Bioregulation, Associate Professor)

## 【Outline of survey】

In cells, proteins, lipids, or several molecules can travel via membrane-enclosed compartments, which are referred to transport vesicles. This membrane traffic flows along highly organized, directional routes, which allow the cell to secrete, eat, and remodel its plasma membrane.

A neuron is extraordinary above all for its enormously extended shape, with a long axon and branching dendrites connecting it through synapses to other cells. The axon and dendrites, known as neurites, enable neuron to receive, conduct, and transmit signals. To perform the specific task, neuron seems to possess a special system for vesicular trafficking. However, little is known about the precise mechanism for the neuron-specific vesicular trafficking.

During the neurite formation, membrane components are transported in a directional manner within the cell by a membrane recycling system, resulting in expansion of the cell surface area in the region of neurite formation. We isolated a novel protein protrudin, which promotes neurite formation through regulation of the membrane recycling system. It was recently shown that protrudin is also related to neuronal function as it is mutated in a neurodegenerative disease.
In this research project, we aim to elucidate the mechanisms for the regulation of the neuron-specific vesicular trafficking and the related neurodegenerative disease.

## 【Expected results】

This project will contribute to understanding the biological relevance of neuron-specific vesicular trafficking in neuronal function. Through this project, it is also expected the practical use of the knowledge for the clinical application in neurodegenerative disease.

## 【References by the principal investigator】

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| 【Term of project】 FY2008− 2012 | 【Budget allocation】 **77,000,000 yen** (direct cost) |
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【Homepage address】 http://www.bioreg.kyushu-u.ac.jp/saibou.html

# Multi-dimensional Omics on Brain Anatomy

**Mitsutoshi Setou**
(Hamamatsu University School of Medicine, Molecular Imaging Frontier Research Center, Professor)

**【Outline of survey】**

Immunohistochemistry for proteins and *in situ* hybridization for mRNA are used for the observation of biomolecules with a microscope. However, these techniques can only observe the already-identified biomolecules. We developed a new mass spectrometric microscopy which can observe various biomolecules at once with molecular weight. Our preliminary data showed dynamic distribution of the lipids, glycolipids, and proteins. In this study, we will make mouse brain mass imaging ATLAS. In addition, we will try to analyze mouse development, aging, sex, feeding, and the response for physiological stimulations. We use neurodegenerative disease model mice to establish our analytical system. Further, analysis of human postmortem brain will be in scope. Finally, we will try pathological analysis of postmoterm brains of human psychiatric diseases patients.

**【Expected results】**

The constituent elements of brain are water, lipids, proteins, glycolipids, nucleic acids, and others in the order of weight percentage. Because the techniques for observing the distribution of lipids and glycolipids had been limited, these distributions were hardly described. Our preliminary data with mass microscopy shows that lipids and glycolipids distributed dynamically. Thus, our survey will open a new field. Moreover, we can expect the discovery of new biomolecules by analyzing human neuronal diseases including schizophrenia.

**【References by the principal researcher】**

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| 【Term of project】 FY2008－2012 | 【Budget allocation】 **78,100,000 yen** (direct cost) |
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**【Homepage address】**

http://www2.hama-med.ac.jp/w3a/mifrc/mole-ana/setou/ja/index.html

# Synaptic regulatory mechanisms by novel AMPA receptor modulators

**Masaki Fukata**
(National Institute for Physiological Sciences, Department of Cell Physiology, Professor)

**【Outline of survey】**

AMPA receptors (AMPARs) mediate most fast excitatory synaptic transmission in brain. The activity dependent changes of AMPAR-mediated synaptic transmission are thought to be critical for learning and memory. Therefore, the regulatory mechanisms of AMPAR functions are the foremost issue in modern neuroscience. In this project, we clarify the regulatory mechanisms of synaptic transmission by focusing on novel regulators of AMPARs: 1) the PSD-95 palmitoylating enzyme, which determines the synaptic position of PSD-95 scaffold, and 2) the epilepsy-related ligand/receptor, LGI1/ADAM22. We also elucidate the relationship between AMPARs and Alzheimer's disease-related proteins. Taken together, we clarify regulatory mechanisms for synaptic function and dysfunction.

**【Expected results】**

The misregulation of synaptic transmission causes various neurological disorders, including dementia and epilepsy. Because AMPARs mediate most excitatory synaptic transmission in brain, clarifying the regulatory mechanisms of AMPARs should contribute to understanding the pathogenesis of above neurological disorders. Because enzymes and ligands/receptors are targets for about two-third of all drugs in use today, our originally identified palmitoylating enzymes and epilepsy-related ligand/receptor could become therapeutic targets for synaptic disorders.

**【References by the principal investigator】**

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| 【Term of project】 FY2008− 2012 | 【Budget allocation】 **78,100,000 yen** (direct cost) |
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【Homepage address】 http://www.nips.ac.jp/fukata/

## In vivo gene function analysis using lentiviral vector

**Masahito Ikawa**
(Osaka University, Research Institute for Microbial Diseases, Associate Professor)

**【Outline of survey】**

Lentiviral (LV) vectors are efficiently integrated into the host genome and stably express the transgene for life-time so that they have been successfully used in biological and biomedical studies. We have previously demonstrated that lentiviral vector transduction of fertilized eggs is a facile and efficient method to generated transgenic animals (LV-Tg method). In this project, we are going to develop an "*in vivo* gene function analysis system" using LV-Tg method. For this purpose, tissue specific gene modification with cre/loxP system, targeted gene knockdown with RNAi system, and inducible gene expression with tet on/off system will be examined in combination with lentiviral vector mediated gene trap mutagenesis. Throughout the project, we investigate the gene trapped mice and elucidate the mechanism of reproduction at molecular basis. All the mice obtained will be distributed through public bioresource center.

**【Expected results】**

Combination with LV-Tg method with other techniques will provide a novel gene function analysis system that promotes biological science in the post-genome project. Since the knockout mice will be distributed through bioresource center, the individual researcher need not to generate mutant mice by themselves. Elucidation of the mechanism of reproduction and its clinical applications might help the couples suffered from infertility.

**【References by the principal investigator】**

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| 【Term of project】 FY2008－2012 | 【Budget allocation】 74,500,000 yen (direct cost) |
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**【Homepage address】**

http://kumikae01.gen-info.osaka-u.ac.jp/members/ikawa/index.htm

# Inhibitory effects on the growth of cancer cells using surface topography

**Masaru Tanaka**
(Tohoku University, Institute of Multidisciplinary Research for Advanced Materials, Associate Professor)

**【Outline of survey】**

Three-dimensional (3D) porous scaffolds fabricated from biodegradable polymers have widely been used as temporary extracellular matrices, and play critical roles in tissue engineering. We have already known that nano-micro patterns on the surface of the scaffold have significant influences on the morphology, proliferation, differentiation and functions of various normal cells. However, effects of the scaffolds on cancer cells are not known yet. We have reported a honeycomb-patterned polymer film (honeycomb film) with highly regular pores that is formed by self-organization. The honeycomb films exerted a strong influence on cell morphology, proliferation, cytoskeleton, focal adhesion, and ECM production profiles. On the other hand, we have found the growth inhibition on the honeycomb film. In this study, we will examine the influence of the surface topography on the behavior of cancer cells, such as cell adhesion, detachment, cell-cycle, and motility on the honeycomb films as well as on a flat film in order to clarify the growth inhibition of cancer cells and how the cell recognize the surface topography.

**【Expected results】**

The design of nano- and microstructures based on self-organization would be a key area of research in the search for new materials, and it has a variety of potential applications in cancer and tissue engineering scaffolds. These results would have the potential benefit of honeycomb film in cancer research. This is the first study to propose novel concept of anti-cancer strategy using surface topography.

**【References by the principal investigator】**

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| 【Term of project】 FY2008－2012 | 【Budget allocation】 74,500,000 yen (direct cost) |
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【Homepage address】 http://poly.tagen.tohoku.ac.jp/Site/Top.html

# Neural processes underlying motor control and learning of bimanual movement

**Daichi Nozaki**
(The University of Tokyo, Graduate School of Education, Associate Professor)

## 【Outline of survey】

As symbolized by skillful movement during playing musical instruments and sports activity, human has an ability to perform a variety of movements by combining the movements of body parts such as arms and legs. A conventional research question is what neuronal mechanisms are involved in the spatial and/or temporal coordination of elemental movements. However, it seems necessary to reconsider the premise of the research question, because we have recently shown that compound movement is not constructed from the elemental movements. Specifically, distinct neuronal processes are likely to be involved in the control of the same left (right) arm movement across unimanual and bimanual movements. This new concept opens several novel research questions about the functional role, brain representation, process of selection, and acquisition of such multi-neuronal processes. This study aims to clarify the principle of how the CNS controls bimanual (or compound) movement by clarifying these questions using various methods such as motor learning experiment, brain functional imaging, and mathematical modeling.

## 【Expected results】

My hypothesis is that well-coordinated bimanual movement is achieved by mechanisms that flexibly switch neuronal processes for a limb control according to the kinematics of another limb. I believe that the exploration of the hypothesis will lead to a novel understanding for the bimanual movement control. Furthermore, the knowledge of the present research will provide a new rehabilitation technique for stroke patients and an efficient training program to develop bimanual motor skills.

## 【References by the principal investigator】

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| 【Term of project】 FY2008− 2012 | 【Budget allocation】 **66,900,000 yen** (direct cost) |
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# Atmospheric aerosol properties inferred from their external mixing state

**Michihiro Mochida**
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**【Outline of survey】**

Global climate change is a serious environmental problem confronted by world societies. To date, some important factors regulating the Earth's climate remain unclear, which hinders prediction of future climate and determination of effective countermeasures. One factor is the relationship between airborne particles in the atmosphere (aerosol particles) and climate. Aerosol particles act as nuclei of cloud droplets and ice crystals; they are therefore closely related to cloud and precipitation processes. Moreover, aerosol particles and cloud droplets scatter and/or absorb solar radiation and influence the atmospheric energy balance. This study is designed to elucidate characteristics of aerosol particles according to differences in individual particles and the external mixing state. To achieve this, field observations are undertaken to segregate aerosol particles according to their size and hygroscopicity; then the physical and chemical properties are determined. The importance of the external mixing state of atmospheric aerosols and their relation to climate processes are discussed.

**【Expected results】**

This study will establish a method to determine both the external mixing state of atmospheric aerosols and the physical and chemical properties of the particles (composition, cloud condensation nuclei activity, and ice nucleation activity). This approach will reveal characteristics of atmospheric aerosol types (e.g., urban and marine) and their underlying aerosol processes. It is expected that the results of this project will contribute to future development of climate models.

**【References by the principal investigator】**

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| 【Term of project】 FY2008－2012 | 【Budget allocation】 80,100,000 yen (direct cost) |
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【Homepage address】 http://www.iar.nagoya-u.ac.jp/~mochida/

# Architectonics of metallic nano-materials and infrared plasmons

**Tadaaki Nagao**
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## 【Outline of survey】

In metallic material, electron system oscillates in a collective manner with ultrahigh frequencies. This oscillation is called plasmon and the world-wide active research field has emerged recently that aims at controlling the propagation, scattering, and the polarization of light in nanometer scale, by utilizing the coupling between the plasmon near the surface and external photon field. Normally, the plasmon frequency lies in visible to ultraviolet regime, but when the object shape becomes atomically thin, and the interaction between the objects becomes significant, the oscillation frequency shifts downwards to the infrared regime or lower with tiny nano-scale propagation wavelength.

In this project, we will establish the way for applying this novel knowledge for the realization of new classes of optical materials. We will explore various nano-metallic architecture, by adopting nanofabrication, colloidal process, as well as molecular atomic-layer epitaxy. In this way, we will establish a new methodology, which can be called as “nano-plasmotectonics”, for realizing innovative infrared optical materials.

## 【Expected results】

The optical functional properties explored here fits to the spectral region which is important in the field of environment, bio-sensing, and energy, and also matches to the requirement for the miniaturization of the future opto-electronic devices. Therefore, the outcomes from this project are highly expected to be applied in various fields as the evolution of nanotechnology proceeds. In the present project, along with the materials development, we will also develop new nano-measurement techniques and will feedback these results bidirectionally which should be highly effective in establishing the original methodology for developing innovative optical materials. In this way, we believe we can open the way for designing and realizing novel low-frequency plasmonic materials.

## 【References by the principal investigator】

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| 【Term of project】 FY2008－2012 | 【Budget allocation】 88,900,000 yen (direct cost) |
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## 【Homepage address】

http://www.nims.go.jp/mana/members/young_scientist/t_nagao/index.html