Title of Project：Development of Molecular Robotics based on DNA Nanoengineering

Satoshi Murata
(Tohoku University, Graduate School of Engineering, Professor)

Research Area：Comprehensive fields

Keyword：Autonomous Decentralized Systems, DNA Nanoengineering, Molecular robotics

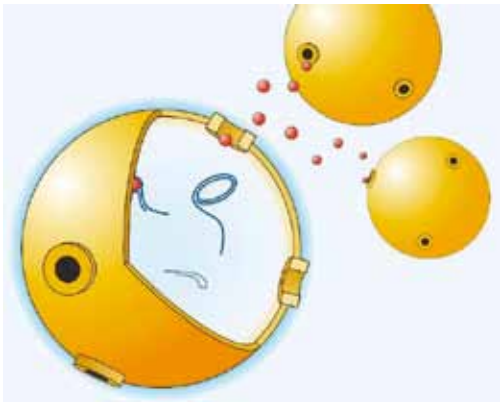
【Purpose and Background of the Research】

The new field called "DNA Nanoengineering" is focused on designing various molecular devices out of synthesized DNA. It emerged at the intersection of computer science, biochemistry, material science, and engineering. As the result of recent efforts, DNA has established as an important building block for the bottom-up self-assembly in nanotechnology, with various nanostructures and nanodevices. Recent progress indicates that the field is now heading beyond structural elements and towards complex systems that integrate sensing, information processing, and actuation, all realized within DNA-based devices. This project aims at developing fundamental methodology to integrate those DNA devices to build functional systems, in other words, the "Molecular Robots."

【Research Methods】

There are several approaches to realize molecular robots. The approach we have adopted is to mimic the structure of living organisms, namely the cellular structure. The key technology we use is the special method to grow DNA nanostructure on a surface of templates such as micro-sized gel bead, called "substrate-assisted self-assembly." This method enables us to build capsules made of DNA with known base sequences. These capsules not only can contain various DNA molecular devices, but also integrated with various channel devices which functions as interface for the molecular robot like channel proteins on the lipid bilayer.

In our project, we focus on development of the following four technologies. (1) Construction of DNA compartment to store molecular devices (2) Construction and implementation of interface device that enables molecular input /output through the compartment (3) Method to control reactions in the molecular robot and also molecular communication between molecular robots (4) Rule design for the swarm of molecular robots to emerge cooperative behavior through the interaction by the communication.



【Expected Research Achievements and Scientific Significance】

This project is expected to be a breakthrough that extends the robotics to the world at the molecular scale. Technologies developed here can be used as fundamental tools for varieties of artificial molecular machines, therefore, it will make a large impact for both academic and industrial fields. For instance, a super-drug delivery system in which a group of molecular robots beats the diseased part like the immune system will be one of the future applications of the molecular robotics.

【Publications Relevant to the Project】

・Hamada S, Murata S, Substrate-assisted assembly of interconnected single duplex DNA nanostructures, *Angewandte Chemie (Int. Ed.).* **48**, 6820-6823, 2009
・Fujibayashi K, Hariadi R, Park SH, Winfree E, Murata S, Toward Reliable Algorithmic Self-Assembly of DNA Tiles: A Fixed-Width Cellular Automaton Pattern, *NanoLetters*, **8**-7, 1791-7, 2008

【Term of Project】 FY2010-2014

【Budget Allocation】 164,700 Thousand Yen

【Homepage Address and Other Contact Information】

URL http://www.molbot.mech.tohoku.ac.jp
EMAIL murata@molbot.mech.tohoku.ac.jp

Title of Project：Understanding and construction of developmental process from body-babbling to sociality acquisition

Minoru Asada
(Osaka University, Graduate school of Engineering, Professor)

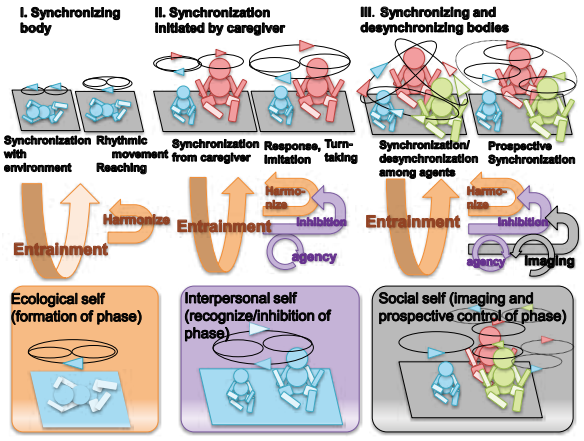
Research Area：Comprehensive fields

Keyword：Intelligent robot, Sensory behavior system, Sensation/Perception/Attention, Communication

【Purpose and Background of the Research】

We, the project leader's group, have been intensively promoting the study aiming at understanding human cognitive development process based on the design theory of humanoid robots with computational brain model, and achieved the excellent results in both individual development and the development between individuals. One of the big issues we have not attacked is how infants can acquire the representations of the self and others through the various kinds of experiences. In this project, we are going to attack this issue based on cognitive developmental robotics [1] through designing and working of humanoid robots and also infant behavior observations. We especially focus on the developmental process from body babbling to sociality acquisition. Applying the concept of synchronization/desynchronization, we reveal the developmental process of self/others representation, and realize make-believe play by seamlessly connecting them.

【Research Methods】



The first three years, we separate an acquisition process of self/others concepts into ecological, interpersonal, and social selves, and construct a computational model for each phase. (1) In the neonatal period, synthetic construction of body babbling, and synchronization/association between behavior and objects are realized (ecological self). (2) In the infant period, based on scaffolding from a caregiver expected to synchronize with the infant (robot), inhibition of synchronization is introduced. As a result, turn-taking can be realized (interpersonal self). (3) In early childhood, active control of synchronization/ desynchronization can be realized based on an interaction model among three agents (social self).

In parallel with the above, design and construction of infant robots and psychological experiments with real infants are used to verify the computational models. The last two years, these models are connected to emerge make-believe play as a result of the development.

【Expected Research Achievements and Scientific Significance】

This project enables us to understand the early process of self/others concept formation. As a result, this will impact the existing disciplines such as developmental psychology, cognitive science, and neuroscience, and accelerate the integration with these disciplines, that may lead the emergence of new science. On the other hand, the design theory for communication robots that infers the internal states of others will be given for artifacts symbiotic with senior people.

【Publications Relevant to the Project】

[1] M. Asada et al., "Cognitive developmental robotics: a survey" IEEE Trans. on Autonomous Mental Development, Vol.1(1), pp. 12--34, 2009.
[2] H. Sumioka et al. "Reproducing Interaction Contingency Toward Open-Ended Development of Social Actions: Case Study on Joint Attention". IEEE Trans. on Autonomous Mental Development, Vol.2(1), pp.40--50, 2010.

【Term of Project】 FY2010-2014

【Budget Allocation】 167,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.er.ams.eng.osaka-u.ac.jp/English/Welcome.html

Title of Project : Unveiling Social Brain by Analyzing Prefrontal Brain Network: Applying Methodological from Microelectrode to fMRI

Naoyuki Osaka
(Kyoto University, Professor Emeritus)

Research Area : Comprehensive fields

Keyword : Cognitive Science, Social Brain, Working Memory

【Purpose and Background of the Research】

Previous studies on higher brain function has been focused on the "biological brain", while present study focused on the "social brain" which works in highly interactive social context. We assumed unveiling the workings of prefrontal brain network may reveal properties of the "social brain". By applying various techniques and subjects (from microelectrode to fMRI (functional Magnetic Resonance Imaging); from monkey to human), we explore how the executive function of the working memory controls social neuronal network (see Figure 1).

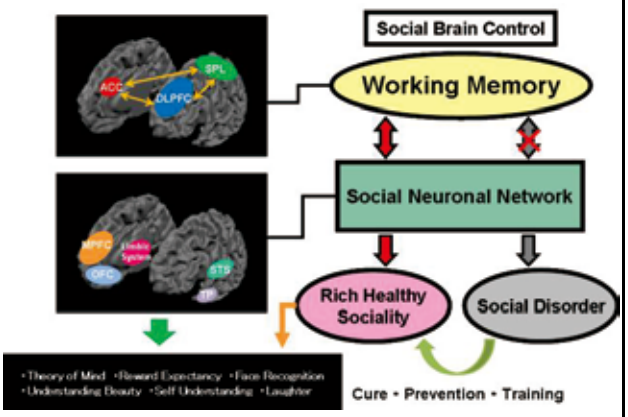


Figure 1. Diagram showing how the working memory's executive function controls social neuronal network (social brain).

We investigate the brain mechanism which makes for social consciousness (and its disorder) and understanding the self and the others (ToM) by interdisciplinary approach integrating cognitive neuroscience and humanities.

【Research Methods】

Seven major and multiple international scientists work together to unveil how the executive system of the prefrontal cortex controls the "social brain" using fMRI, TMS (transcranial magnetic stimulation), ERP (event-related potentials), tDCS (transcranial direct current stimulation) and microelectrode from monkey to human. Special interests are on the issues of cooperative/competitive behavior in relation to reward; understanding self and others (Theory of Mind) from the standpoint of social neuroscience; understanding beauty and laughter from neuroaesthetics; social economical behavior from neuroeconomics.

Moreover, we explore how the malfunction of the prefrontal network results in social disorder. Finally, neuronal network model controlling "social brain" will be presented.

【Expected Research Achievements and Scientific Significance】

Unveiling the neuronal dynamics of the "social brain" will provide us how the "social brain" developed from social environment.

Furthermore, we expect to develop the ways to cure and prevent social disorder and keep healthy sociality by training.

【Publications Relevant to the Project】

Osaka N, Osaka M, Morishita M, Kondo H, Fukuyama H, Shibasaki H: The neural basis of executive function in working memory: an fMRI study based on individual differences. Neuroimage, **21**: 623-631, 2004.

Osaka N, Logie R, D'Esposito M (Eds) Cognitive Neuroscience of Working Memory. Oxford University Press, 2007.

Osaka N. (Ed) Brain Representation of the Working Memory. Kyoto University Press, 2008.

Yaoi K, Osaka M, Osaka N: Is the self special in DMPFC? : An fMRI study. Social Neuroscience, **4**: 455-463, 2009.

Osaka N (Ed) Brain Imaging. Baihukan Publisher, 2010.

【Term of Project】 FY2010-2014

【Budget Allocation】 165,700 Thousand Yen

【 Homepage Address and Other Contact Information】

http://www.social-brain.bun.kyoto-u.ac.jp/

Title of Project : Mechanism governing the positioning and synaptic contacts of cortical inhibitory neurons

Fujio Murakami
(Osaka University, Graduate school of Frontier Biosciences, Professor)

Research Area : Comprehensive field

Keyword : Molecular and cellular neuroscience, Developmental and regenerative neuroscience, Neural development and its abnormality, Neurocytology

【Purpose and Background of the Research】

Higher brain functions of the cerebral cortex depend on neural networks consisting of both excitatory and inhibitory neurons. Although inhibitory neurons account for only 20% of all neurons in the cortex, they are highly diverse in their morphology, functions and molecular expression. Due to this diversity, the complicated local network containing inhibitory neurons has not been clarified yet. The goal of this project is to clarify the molecular mechanism regulating the final position of inhibitory neurons, and to comprehend the origin of the diversity of inhibitory neurons. We focus on the postulated role of environment including synaptic activity, especially from the surrounding excitatory pyramidal neurons.

【Research Methods】

This project aims for thorough understanding of the cellular mode of inhibitory neuron migration by *in vivo* real-time imaging, focusing on a late phase of migration from the marginal zone into the cortical plate. Based on these results, we plan to dissect the underlying molecular mechanisms, specifically, the role of chemoattraction / repulsion by meningeal or cortical cells. We also plan to analyze the participation of environmental factors including synaptic contacts with excitatory neurons in determining the final position of inhibitory neurons. By experimentally delaying the migration of excitatory neurons, and examine its influence on the position of inhibitory neurons, we will clarify the relationship between the synaptic contacts and the position of inhibitory neurons.

【Expected Research Achievements and Scientific Significance】

In spite of postulated importance in the information processing, studies of inhibitory neuron lag behind due to the diversity and the lack of regularity in their anatomical positions. Comprehension of the rule governing the construction of local circuits obtained through this project will shed light on the information processing in the cerebral cortex. Furthermore, the obtained knowledge will contribute to the elucidation of the etiology of the brain deficits in higher brain function.

【Publications Relevant to the Project】

Tanaka, D.H., Yanagida, M., Zhu, Y., Mikami, S., Nagasawa, T., Miyazaki, J., Yanagawa, Y., Obata, K. and Murakami, F. Random walk behavior of migrating cortical interneurons in the marginal zone: time-lapse analysis in flat-mount cortex. J. Neurosci. 29, 1300-1311, 2009

Tanaka, D.H., Maekawa, K., Yanagawa, Y., Obata, K. and Murakami, F. Multidirectional and multizonal tangential migration of GABAergic interneurons in the developing cerebral cortex. Development. 133, 2167-2176, 2006

【Term of Project】 FY2010-2014

【Budget Allocation】 166, 400 Thousand Yen

【 Homepage Address and Other Contact Information】

http://square.umin.ac.jp/murakami-lab/

Title of Project: Molecular studies of motor learning and maturation of the cerebellar network

Shigetada Nakanishi
(Osaka Bioscience Institute , Director)

Research Area : Integrated Science and Innovative Science

Keyword : cerebellum, motor learning, neural network, neural maturation, intracellular signaling

【Purpose and Background of the Research】

The organization and the integrative regulation of the neural network are fundamental subjects for a better understanding of mechanisms underlying brain function and dysfunction. The cerebellum is the key neural substrate that controls motor coordination and learning. The research projects using the reversible neurotransmission blocking (RNB) technique are directed toward the following subjects:

1) how the cerebellar network controls motor coordination and motor learning.
2) how the functional cerebellar network is established in an activity-dependent manner during development.

【Research Methods】

1. Regulatory mechanisms of the cerebellar circuit

We developed a novel RNB technique that allowed us to selectively and reversibly block a particular neural transmission in the neural network and to dissect sequential processes of motor learning at different cerebellar circuits. The mechanisms underlying different processes of motor learning (expression of motor learning at Purkinje cells and acquisition/storage of motor learning at the interpositus and vestibular nuclei) will be investigated by various approaches combining in vivo Ca^{2+} imaging, electrophysiology, molecular biology and microarray analysis of the RNB model mice.

2. Maturing mechanisms of the cerebellar circuit

The cerebellar granule cells mature at the postnatal period. The gene expression in maturing processes is controlled by a master transcription factor via a sequential activity-dependent mechanism involving the stimulation of glutamate receptors, Na^{+} and Ca^{2+} channels and intracellular Ca^{2+} signaling. This investigation will explore the regulatory mechanisms of gene expression and Ca^{2+} signaling in granule cell maturation.

【Expected Research Achievements and Scientific Significance】

1. This project deals with the central theme of brain science as to how neural information is processed and integrated in the neural network and how memory and learning are acquired, expressed and stored by integrative mechanisms of the different neural circuits.
2. The mechanisms that govern maturation of the neural network in an activity-dependent manner largely remain elucive and are being explored in this project.

【Publications Relevant to the Project】

1. Nakanishi, S. Genetic manipulation study of information processing in the cerebellum. Neuroscience 162:723-731(2009)
2. Okazawa, M., Abe, H., Katsukawa, M., Iijima, K., Kiwada, T. and Nakanishi, S. Role of calcineurin signaling in membrane potential-regulated maturation of cerebellar granule cells. J.Neurosci. 29: 2938-2947 (2009)
3. Wada, N., Kishimomto, Y., Watanabe, D., Kano, M., Hirano, T., Funabiki, K. and Nakanishi, S. Conditioned eyeblink learning is formed and stored without cerebellar granule cell transmission. Proc.Natl.Acad.Sci.USA 104: 16690 -16695 (2007)

【Term of Project】 FY2010-2014

【Budget Allocation】 167,400 Thousand Yen

【 Homepage Address and Other Contact Information】

http://www.obi.or.jp/

Title of Project：Saliency detection by the "unconscious" visuo-motor system

Tadashi Isa
(National Institute for Physiological Sciences,
Department of Developmental Physiology, Professor)

Research Area：Neuroscience

Keyword：awareness, superior colliculus, attention, saccade, blindsight

【Purpose and Background of the Research】

When the primary visual cortex (V1) is damaged, visual awareness in the affected visual field is impaired. However, it has been reported that some patients can localize the objects in the affected visual field either by reaching or saccadic eye movements when they are forced to do so. Such dissociation of visual awareness and ability of goal directed movements has been termed "blindsight" and attracted attention of wide variety of scientists, from clinician, physiologists to psychologists and philosophers. The midbrain structure superior colliculus (SC) has been supposed as the center of such "unconscious" visuo-motor system, however why and how the superior colliculus can detect salient visual stimuli is still elusive. In this project, we will clarify the neural mechanism of saliency detection in the unconscious visual system with behavioral neurophysiological experiments in a non-human primate model of blindsight and analysis of local circuit structure of the superior colliculus by using in-vitro slice preparations obtained either from the rodents or common marmosets.

【Research Methods】

①Saliency detection in a monkey model of blinsdsight---we have been studying the saccadic eye movements in macaque monkeys with unilateral lesion of the V1. In this project, we will combine the brain imaging with functional MRI and single unit recording and reversible pharmacological blockade to clarify the whole picture of the visual pathways for the visuo-motor processing after the V1 lesion. In addition to the SC, the pulvinar, the parietal cortex and frontal eye fields will be the primary targets of the study. We will also analyze the saliency detection under the free viewing condition based on the "saliency model" proposed by Itti and Koch (2000).

②Saliency detection mechanism in the local circuit of the superior colliculus---We have reported that in the horizontal slices of the superior colliculus which contains all the elements of the local structure for the spatial map that stimulation of a particular site induces typical center excitation and surround inhibition, which can be the basis for the winner-take-all type of saliency detection. We will study how the individual neurons in the local circuits, both excitatory and inhibitory neurons, behave to form the winner-take-all or vector summation activation field by applying Ca^{2+} imaging in the 2-photon laser microscopy and whole cell patch clamp recordings in *in vitro* slice preparation of the Sc obtained from the mouse and marmosets.

【Expected Research Achievements and Scientific Significance】

We may be able to clarify the whole picture of the saliency detection by the subconscious visual system, which might also be useful for designing the neuro-rehabilitational therapy for the patients with cortical blindness.

【Publications Relevant to the Project】

1. Weiskrantz L, Blindsight--a case study spanning 35 years and new developments. 2nd edition, Oxford Univ Press.
2. Yoshida M, Takaura K, Kato R, et al. (2008) Striate cortical lesions affect deliberate decision and control of saccade: implication for blindsight. *J Neurosci*, 28: 10517-10530.
3. Isa T, Hall WC (2009) Exploring the superior colliculus in vitro. *J Neurophysiol*, 102: 2581-2593 (review).
4. Isa T, Yoshida M. (2009) Saccade control after V1 lesion revisited. *Curr Opin Neurobiol,* 19: 608-614 (review).
5. Ikeda T, Yoshida M, Isa T. (2010) Functional differences between cortical and subcortical visual pathway in spatial attention: inhibition of return and attention capture. *J Cogn Neurosci, Online Early Access,*

【Term of Project】 FY2010-2014

【Budget Allocation】 160,000 Thousand Yen

【 Homepage Address and Other Contact Information】

http://www.nips.ac.jp/hbfp/English/index.html
tisa@nips.ac.jp

Title of Project : Development of experimentation systems related to personalized medicine using humanized NOG mice

Mamoru Ito
(Central Institute for Experimental Animals, Laboratory Animal Research Department, Principle Investigator)

Research Area : Comprehensive fields, Laboratory animal science

Keyword : laboratory animals, immunodeficient mice, NOG mice, humanized mice, personalized medicine

【Purpose and Background of the Research】

Severe immunodeficient NOG (NOD/Shi-scid, IL-2Rg KO) mice reported by us in 2002 are well known to support engraftment and differentiation of transplanted human cells and tissues without rejection. Therefore, these mice are considered extremely useful for generating "humanized mice", and humanized mice using NOG mice are actually widely used in various research fields of medicine and biology, especially as human disease models.

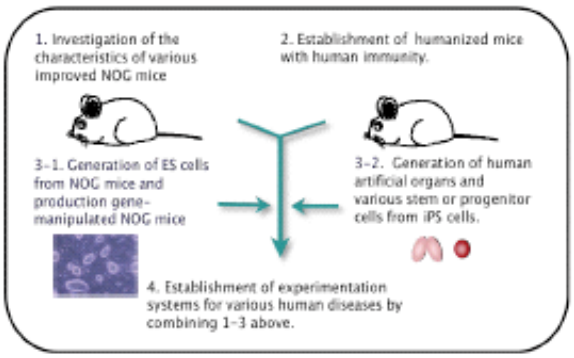
We have developed 30 or more improved NOG mice in the period from 2006 to 2009 under a previous Grant-in-Aid for Scientific Research (S) to improve NOG mice more appropriate for generating humanized mice.

The purpose of this project is to generate more useful humanized mice with human immunity corresponding to various human diseases using the improved NOG mice. In addition, new technologies using human iPS cells for personalized medicine will be investigated for application of humanized mouse models.

【Research Methods】

Based on the results of the previous Grant-in-Aid for Scientific Research (S) from 2006 to 2009 under, the following research will be undertaken.

1. Investigation of the characteristics and usefulness of various improved NOG mice as humanized mice



2. Establishment of the technologies to generate humanized mice with human immunity
3. Investigation of generation of human artificial organs and various stem or progenitor cells from human induced puriopotent stem (iPS) cells
4. Establishment of experimentation systems for various human diseases by combining 1to 3 above

【Expected Research Achievements and Scientific Significance】

Humanized mice are considered to be very useful to study the mechanisms of human diseases and to develop therapeutic agents. The generation of humanized mice with human immunity attempted in this project may contribute to vaccine development for human infectious diseases, such as malaria and HIV-1. Human artificial organs or various stem and progenitor cells generated from human iPS cells may help overcome the limitation of human resources, and may be applied on the personalized medicine.

【Publications Relevant to the Project】

・Ito, M., K. Kobayashi, and T. Nakahata. 2008. NOD/Shi-scid IL2rgamma(null) (NOG) mice more appropriate for humanized mouse models. *Curr Top Microbiol Immunol* 324:53-76.
・Ito, M., H. Hiramatsu, K. Kobayashi, et al. 2002. NOD/SCID/gamma(c)(null) mouse: an excellent recipient mouse model for engraftment of human cells. *Blood* 100:3175-3182.

【Term of Project】 FY2010-2014

【Budget Allocation】 124, 300 Thousand Yen

【 Homepage Address and Other Contact Information】

http://ciea.or.jp
mito@ciea.or.jp

Title of Project : Development of a Nano-Micro Platform for Tissue Engineering Applications

Koji Ikuta, Ph. D.
(The University of Tokyo, Graduate School of Information Science and Technology, Professor)

Research Area : Biomedical Engineering - Biomedical engineering/Biological material science

Keyword : Medical micromachines, nanomachines

【Purpose and Background of the Research】

Tissue engineering is a research field thriving at an immense speed globally. However, most research concentrates only on the cellular level, such as establishing stem cell lines and investigating differentiation inducing techniques. In order to boost tissue engineering to a clinically applicable level, it is inevitable for tissue regeneration technologies to be developed, not at the cellular level, but at the tissue/organ level. Still, to regenerate 3-dimensional tissue with thicknesses ranging in the mere millimeter scale remains too high a challenge.

We aim to contribute to the field by integrating originally developed root technologies such as 3-D nano-fabrication, micro-actuators, super-small force sensing, and nano-functional materials (Fig. 1).

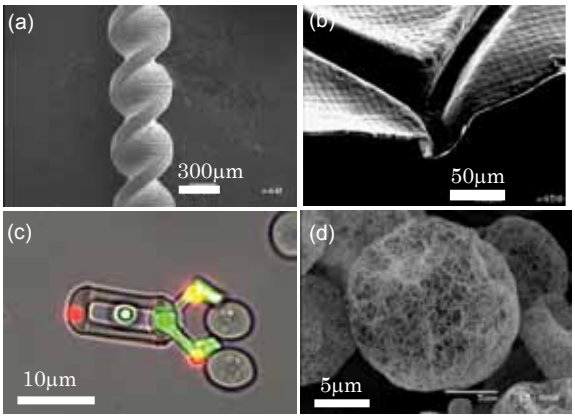


Figure 1. Originally developed root technologies (a) Magnetic micro-machine (b)Biodegradable membrane micro-channel (c)Optically-driven cell manipulating robot (d) Biodegradable nanofiber capsule.

【Research Methods】

The tissue engineering platform to be developed is composed of 3 differently scaled classes: mm, μm and nm. The largest class will be a cell culture chip no larger than a square centimeter containing a culturing chamber, medium providing vessels, heat and CO_2 control units. The middle class will be a micro-channel network placed within the culturing chamber. The micro-channels will function as an inlet for gene transfection and differentiation inducement. The lowest class will be a nano-actuator that can apply stimuli to individual cells enabling the inducement of differentiation via mechanical stimuli. Accordingly to the above three classes, single cells to mass tissue can be controlled, and inducing differentiation along with 3-D tissue culturing will be realized.

【Expected Research Achievements and Scientific Significance】

The described tissue engineering platform aims to regenerate multiple functioning 3-D tissues. As it being a basic technology, the formation of intellectual property and the origination of new industries / venture businesses can also be expected.

For future plans we are aiming to develop clinically functional, implantable tissues through thorough animal experiments. By combining conventional stem cell technology with the tissue engineering platform we pursue a radical solution to the chronicle problem of lacking donors seen in transplantation medicine today.

【Publications Relevant to the Project】

・K. Kobayashi, K. Ikuta, Three-dimensional magnetic microstructures fabricated by microstereolithography, Appl. Phys. Lett., 92, 262505 (3pp), 2008
・A. Yamada, F. Niikura, K. Ikuta, A three-dimensional microfabrication system for biodegradable polymers with high resolution and biocompatibility, J. Micromech. Microeng., 18, 025035 (9pp), 2008
・M. Ikeuchi and K. Ikuta, Membrane Micro Emboss (MeME) Process for 3-D Membrane Microdevice, Micro Electronic and Mechanical Systems, IN-TECH, pp.1-14, 2009

【Term of Project】 FY2010-2014

【Budget Allocation】 167,200 Thousand Yen

【 Homepage Address and Other Contact Information】

http://www.keisu.t.u-tokyo.ac.jp/lab/lab_ipc/ikutalab.htm

Title of Project : Creation of Binding Growth Factors by Molecular Evolutionary Engineering and their Medical Applications

Yoshihiro Ito
(RIKEN ,Nano Medical Engineering Laboratory, Chief Scientist)

Research Area : Biomaterials
Keyword : Regenerative Medicine, Tissue Engineering

【Purpose and Background of the Research】

To achieve regenerative medicine, it is necessary to create bioactive materials. We found that chemically immobilized growth factor proteins could control the growth and differentiation of cells on material surfaces. In the present study we will create new binding growth factors for development of new medical materials.

We will develop and establish peptide evolutionary engineering method for creation of new proteins binding to organic, metallic, ceramic, and biological materials. The proteins will be employed for modifications of medical materials or drugs.

In addition, extended molecular evolutionary engineering will be accomplished by using non-canonical amino acids. By utilizing this technology, we will obtain more specific and highly binding growth factors.

【Research Methods】

First we will establish peptide evolutionary engineering and will prepare new binding growth factor proteins by the developed methodology. Subsequently the biological activity will be investigated using cell lines culture and animal experiments.

Preparation of new binding growth factors

Random sequence peptide library will be produced by transcription and translation using cell-free system from random sequence DNA library.

From this library some specific sequences will be determined by in vitro selection for target substrata including synthetic polymer, natural polymer, ceramic, metal, cell, and tissue.

Extended molecular evolutionary engineering

Extended peptide evolutionary engineering using non-coding amino acids will be established for selection of highly and selectively binding affinity.

Biological evaluation of novel proteins

The binding affinity of prepared proteins to organic, ceramic, metallic, and biological materials will be precisely investigated by physico-chemical methods.

The biological activities such as growth enhancement and differentiations control of prepared growth factors will be investigated using several cell lines. In addition, the biding domains and growth factor domains will be variously combined for optimal effect. Finally the binding growth factors will be investigated by animal experiments and considered for medical applications.

【Expected Research Achievements and Scientific Significance】

For regenerative medicine it is important to precisely control of stem cells and construct matrices for tissue formation. In this study a new peptide evolutionary engineering and its extension will be achieved by incorporation of artificial amino acids. By the new methodology we will stabilize growth factors for a long time and allow the materials bio-active for new medical applications.

【Publications Relevant to the Project】

T. Kitajima, H. Hasuda, M. Sakuragi, T. Ozu, and Y. Ito, “A chimeric epidermal growth factor with fibrin-affinity promotes repair injured keratinocyte sheets,” ***Acta Biomater.***, **5**, 2623-2632 (2009)

Y.Ito, “Covalently immobilized biosignal molecule materials for tissue engineering,” ***Soft Matter***, **4**, 46-56 (2008)

【Term of Project】 FY2010-2014

【Budget Allocation】 167,600 Thousand Yen

【 Homepage Address and Other Contact Information】

http://www.riken.jp/engn/r-world/research/lab/wako/medical/index.html

Title of Project : Development of an innovative PET technique using Geiger-mode APDs for future medical application

Jun KATAOKA
(Waseda University, Research Inst. for Science and Engineering, Associate Professor)

Research Area : Imaging and Instrumentation for Nuclear Medicine
Keyword : medical imaging, PET, avalanche photodiode, MPPC

【Purpose and Background of the Research】

Positron emission tomography (PET) is an effective method of evaluating the distribution of radio-labeled tracers in vivo, and is rapidly gaining acceptance as an important tool for use in nuclear medicine. The use of dual modality PET/CT imaging, however, suffers from poor soft-tissue contrast, with patients also subjected to a significant radiation. Although Magnetic Resonance Imaging (MRI) is free from such problems, the Photo-Multiplier Tube (PMT) incorporated in a PET scanner is difficult to use within the MRI high magnetic field. Moreover, the spatial resolution attainable with a PMT-based PET (typically >5mm) is far from the theoretical limit of the PET resolution (≤ 1mm). An APD is a compact, high performance light-sensor that could also be used in the MRI. Moreover, given the advantage of pixel miniaturization, we have successfully developed a high-resolution PET technique with sub-millimeter spatial resolution. Our goal in this research is to further extend an innovative PET technique using Geiger-mode APDs for future application in (1) depth-of-interaction (DOI)-PET, (2) MRI-PET, and also used in a Time-Of-Flight (TOF) capable PET scanner.

【Research Methods】

This is a 5-year research project starting from FY2009. As a high performance light sensor, several types of Geiger-mode APD-arrays will be designed and developed in cooperation with Hamamatsu Photonics K. K. We will make a prototype gamma-ray camera consisting of a MPPC-array optically coupled to a DOI matrix consisting of either LYSO or LuAG scintillators. To read the MPPC signals with an amplification gain of $10^{5\text{-}6}$, a high speed, low-noise, analog ASIC will be developed that includes pulse height and timing discriminators for TOF measurements. A versatile MPPC-based PET module will be fabricated by combining all the detector components, which is expected to be less than 50x50x100 mm^2 in size. A pair of module and coincidence circuits will be assembled into an experimental prototype gantry to evaluate the spatial resolution. Capability as a TOF and MRI-PET scanner will be also tested in the final stage of the development.

【Expected Research Achievements and Scientific Significance】

Recent developments in photo detector have induced the family of multi pixel silicon detectors such as Si-PM and MPPC, operated in Geiger mode. Such sensors are extremely compact, robust and easy to operate, and immediately found broad application in the various fields of experimental physics and nuclear medicine. However, the sensor itself is still in research and development (R&D) phase, and our project will be the first case/trial of providing "on-demand" detectors that could be easily applicable to future PET scanner. Also development of all detector units in domestic may increase the PET market share in Japan.

【Publications Relevant to the Project】

・J.Kataoka *et al.,* "Development of an APD-based PET Module and Preliminary Resolution Performance of an Experimental Prototype Gantry", *IEEE, Trans. Nucl. Sci.*, in press, 2010
・J. Kataoka *et al.,* "Development of large-area, reverse-type APD –arrays for high-resolution medical imaging," *Nucl. Inst. and Meth. A*, vol.604, pp.323–326, Jun. 2009
・J. Kataoka *et al.,* "An active gain-control system for Avalanche photo-diodes under moderate temperature variations," *Nucl. Inst. and Meth. A*, vol.564, pp.300–307, Jun. 2006
・J. Kataoka *et al.,* "Recent progress of avalanche photodiodes in high-resolution X-rays and gamma-rays detection," *Nucl. Inst. and Meth. A*, vol.541, pp.398–404, Jun. 2005.

【Term of Project】 FY2010-2014

【Budget Allocation】 68,400 Thousand Yen

【Homepage Address and Other Contact Information】
http://www.spxg-lab.phys.waseda.ac.jp/

Title of Project : Development of International Geospatial Data Sharing System for the Understanding of Land Environment

Ryutaro Tateishi
(Chiba University, Center for Environmental Remote Sensing, Professor)

Research Area : Remote sensing
Keyword : Remote sensing, Geographic information system, Environmental information

【Purpose and Background of the Research】

As the recognition of the importance of global environment spreads, many researchers/ research organizations have been produced different types of environmental data in different academic fields. However most of the produced data are used only in a limited research community. In order to understand our environment more, we need to analyze the environment by integrating existing data. This idea was published by Tateishi and Hastings (2000).

The purpose of this project is to develop international data sharing system for further understanding of land environment. The requirements of the developed system are 1) capability to overlay researcher's own data on other researchers' data, 2) capability to browse images by any person, 3) Theoretically unlimited expansion of servers.

【Research Methods】

The main part of the project is system development and the other part is applications using the developed system. Two applications are planned: the production of global land cover data and environmental analysis of Asia.

The steps of the system development are as follows. 1) Survey of existing data distribution systems, 2) Design of the system, 3) Development of minimum system in Japan within two years, 4) improvement of the system and international expansion in the following three years.

【Expected Research Achievements and Scientific Significance】

The main expected achievement is the development of an international free-access cluster-type geospatial data sharing system (Fig. 1) which allows users (researchers who use geospatial data) view others' data, overlay his/her data with others, and register/download data freely. Scientific significance of the project is that this system can promote to discover new research subjects and to analyze relationships among different geospatial data by overlaying his/her data with other data easily and freely. The system will be maintained and used even after the 5-year project period.

Though the developed system can be used for any geospatial analysis, two applications will be expected in this project. One is the production of high-accuracy global land cover data. The other one is the understanding of environmental changes in East and South-east Asia for 100 years using by satellite data and old maps.

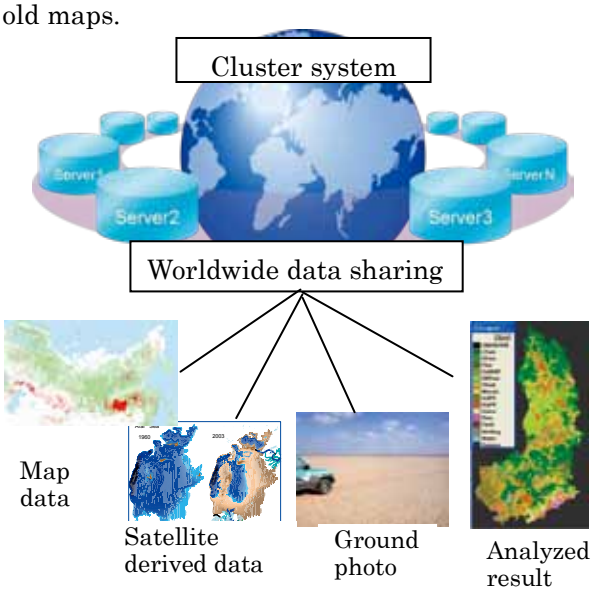


Fig. 1 International geospatial data sharing system

【Publications Relevant to the Project】

・Tateishi, R. and D. Hastings (Ed.), Global Environmental Databases, ISPRS WG IV/6 (1996-2000), 250p., July 2000
・Chandra Giri, David Hastings, Bradley Reed and Ryutaro Tateishi, Chapter 9, Status and Future of Global Databases, Manual of Geographic Information Systems, pp.113-139, ASPRS, 2009

【Term of Project】 FY2010-2014

【Budget Allocation】 83,100 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.cr.chiba-u.jp/~tateishi-lab/home.htm

Title of Project : Telomere Functions in Cancer Development

Fuyuki Ishikawa
(Kyoto University, Graduate School of Biostudies, Professor)

Research Area : Cancer Biology

Keyword : Genetic Instability, Telomere, Next-generation Sequencer

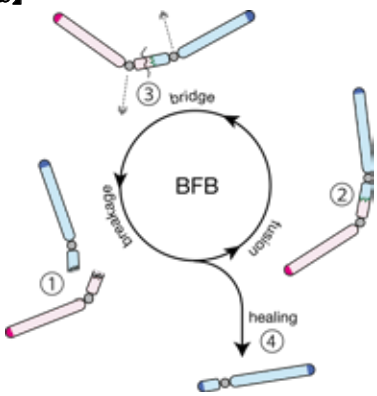
【Purpose and Background of the Research】

In Japan, cancer is the leading cause of death. However, the current measures for cancer treatment is not satisfying.

Genetic instability is uniquely possessed by cancer cells, but not by normal cells. Cancer cells acquire a broad range of random genetic abnormalities. Recently, it is recognized that variable numbers and composition of chromosomes contribute to the progression of cancer. However, the molecular details of how aberrant chromosomes are formed in cancer cells are not well understood.

It has been proposed that the insufficient functions of telomeres, the end of chromosomes, play a key role in chromosome aberration. However, this hypothesis has not been examined experimentally. The aim of this study is to elucidate whether telomere dysfunctions lead to genetic instability in cancer cells, and how this pathway is important for the progression of cancer.

【Research Methods】



Telomeres cap the end of chromosomes, thereby preventing the fusion of two chromosomes. Dysfunctional telomeres promote the formation of fusion chromosomes (step one to two in the figure), which possess two kinetochores and thus called dicentric chromosomes (step three). In M phase, two spindles emanating from the opposite poles can simultaneously attach and pull the two kinetochores on the dicentric chromosomes, which eventually lead to a break between the two kinetochores. Thus formed broken chromosomes lack the telomere and again follow the steps one to three. However, when telomerase is active, it can heal the broken end by adding telomeric DNA sequence and the healed abnormal chromosomes may be stabilized (step four). This hypothesis was proposed more than fifty years ago to explain how chromosomes dysfunctional for telomeres produce abnormal chromosomes, but experimental tests of the scenario have never conducted before.

We will first identify the presence of fusion chromosomes in cells and organisms defective in telomere functions. Toward this goal, we will exploit the next-generation sequencer and sequence the fusion points by massive sequencing.

Once it has been proved that fused chromosomes play a role in chromosomal instability in cancer cells, we will test the role of telomerase using telomerase-knockout mice.

【Expected Research Achievements and Scientific Significance】

Molecular elucidation of how telomeres and telomerase facilitate chromosomal instability will help us to prevent the progression of cancer cells by targeting key molecules in telomeres.

【Publications Relevant to the Project】

Ishikawa, F. Telomere crisis, the driving force in cancer cell evolution. Biochem. Biophys. Res. Commun., 230, 1-6 (1997)

Miyoshi, T., Kanoh, J., Saito, M., and Ishikawa, F. Fission yeast Pot1-Tpp1 protects telomeres and regulates telomere length. Science, 320, 1341-1344 (2008)

【Term of Project】 FY2010-2014

【Budget Allocation】 167,400 Thousand Yen

【 Homepage Address and Other Contact Information】

http://www.lif.kyoto-u.ac.jp/labs/fish

Title of Project : Regulatory Mechanisms of Tumor Microenvironment

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

Research Area : Integrated Science and Innovative Science, Comprehensive fields, Oncology, Tumor biology

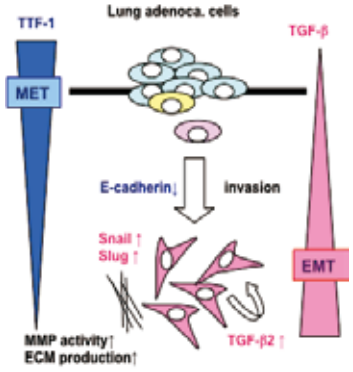
Keyword : Tumor microenvironment, Signaling, Pathology, Development/Differentiation

【Purpose and Background of the Research】

Tumor microenvironment is composed of fibroblasts, inflammatory cells, immune cells, and blood and lymphatic vascular cells. In this project, we will elucidate the roles of TGF-beta family proteins and some transcription factors, including Snail and Prox1, in induction of epithelial-mesenchymal transition (EMT), differentiation of cancer-associated fibroblasts (CAFs) and their interaction with cancer stem cells, and regulation of homeostasis of blood and lymphatic vasculatures. Through these studies, we will uncover the molecular mechanisms of invasion and metastasis of cancer, and try to develop new strategies for treatment of cancer. For these purposes, we will study 1) the mechanisms of EMT induced by TGF-beta. We also study 2) the roles of growth factors and transcription factors in the induction of CAFs, 3) molecular mechanisms of angiogenesis and lymphangiogenesis and identification of novel lymphangiogenic molecules using diffuse-type gastric cancer models, and 4) identification of BMP-target genes involved in angiogenesis and lymphangiogenesis.

【Research Methods】

1) Regulation of TGF-beta-induced EMT. We will find molecule(s), which are downstream components of Ras signaling and cooperatively act with TGF-beta for induction of EMT. We also identify Snail-target genes involved in EMT using Panc1 and A549 cells, and study mechanisms of action of TTF-1, focusing on the Smad-binding sites on the Snail promoter.



2) Induction of CAFs and their functional characterization. We will investigate the functional properties of CAFs induced by FGF, TNF-alpha, or HGF using various technologies.
3) Regulation of angiogenesis and lymphangiogenesis. We will study the mechanisms of (lymph)angiogenesis using diffuse-type gastric cancer models in mice. We also study the function of novel Prox1-binding protein(s) in lymphangiogenesis.
4) Functions of BMPs in tumor microenvironment. We will identify novel BMP-9 target genes in endothelial cells by ChIP-Seq. We also study the function of BMP-9 in lymphangiogenesis.

【Expected Research Achievements and Scientific Significance】

This project will facilitate the establishment of novel strategies for treatment of cancer. Since cancer therapy targeting tumor micro-environment may not induce critical side effects, findings obtained in this project may become useful in the future. Since studies on micro-environment are important not only for cancer progression but also for normal developmental processes, our project may also be valuable for biological processes other than cancer.

【Publications Relevant to the Project】

1) Ikushima H, Miyazono K. (2010) TGF-beta signalling: a complex web in cancer progression. Nat Rev Cancer. 10 (6): 415-24.
2) Komuro A, et al. (2009) Diffuse-type gastric carcinoma: progression, angiogenesis, and transforming growth factor beta signaling. J Natl Cancer Inst. 101 (8): 592-604.

【Term of Project】 FY2010-2014

【Budget Allocation】 167,400 Thousand Yen

【 Homepage Address and Other Contact Information】

http://beta-lab.umin.ac.jp/

Title of Project：Study of MT1-MMP in cancer

Motoharu Seiki, Ph.D.
(The University of Tokyo, Institute of Medical Science, Professor)

Research Area：Oncology

Keyword：Characteristics of cancer cells, Invasion, Metastasis, Cell adhesion and movement

【Purpose and Background of the Research】

Cancer arises from epithelial cells that cover surface of tissues and organs. During tumor progression epithelial phenotype of cancer cells is frequently lost and mesenchymal phenotype becomes apparent. This phenotypic conversion is called as epithelial-mesenchymal transition (EMT) and it accompanies acquisition of invasive and metastatic ability of cancer cells.

My group has been studying on membrane-type 1 matrix metalloproteinase (MT1-MMP) since we discovered it in 1994. MT1-MMP is frequently expressed in malignant cancer cells and promotes invasion and metastasis by degrading pericellular proteins. Regulation of MT1-MMP expression in cancer cells is tightly linked to the EMT program. Once MT1-MMP was expressed in cancer cells it regulates not only invasion but also diverse functions of malignant cancer cells such as growth, motility, and VEGF expression etc. The diverse biological outcomes of MT1-MMP action depends on substrates of which functions are modified by MT1-MMP-dependent processing.

The aim of this study is to identify new substrates that are important to regulate cancer cell functions and regulators of cell functions that are tightly linked to the use of MT1-MMP by cells.

【Research Methods】

We took mass spectrometry analysis to identify MT1-MMP-associating proteins. We isolated MT1-MMP-containing complexes from malignant carcinoma and sarcoma cells and subjected them to the analysis. Identified proteins contained membrane protein substrates as about half of the proteins were indeed cleaved by MT1-MMP at least in vitro or by cell-based assay. Through the analysis of MT1-MMP-associaitng membrane proteins, we already identified HB-EGF is a new substrate of MT1-MMP. Processing of HB-EGF by MT1-MMP converted HB-EGF to a potent growth factor that does not require heparin as a co-factor.

Many cytoplasmic proteins were also identified and most of them were confirmed to be co-immunoprecipitaed with MT1-MMP. We already characterized that one of them has an ability to bind $p27^{kip1}$ that is a well-known cell cycle regulator. Recently $p27^{kip1}$ is known to localize in cytoplasm as well to inhibit activation of RhoA by binding to GDP-RhoA and preventing RhoA to bind GEFs for activation. We named this protein as p27RF-Rho and demonstrated that it localizes at inner surface of cell-ECM interaction sites. Upon stimulation of cells RhoA activation was observed at the sites where p27RF-Rho localizes and invadopodia were formed accompanying MT1-MMP on the outer surface. We are extending this line of study to identify new substrates and regulators that promotes cancer progression by using MT1-MMP.

【Expected Research Achievements and Scientific Significance】

This study will contribute to further understanding cellular strategy to use MT1-MMP during cancer progression and the results are expected to provide clues to develop new strategies for treatment of cancer patients and finding biomarkers to monitor the patients.

【Publications Relevant to the Project】

Itoh, Y. and Seiki, M. MT1-MMP: a potent modifier of pericellular microenvironment. J Cell Physiol 2006;*206*: 1-8.

Sato, H., Takino, T., Okada, Y., Cao, J., Shinagawa, A., Yamamoto, E., and Seiki, M. A matrix metalloproteinase expressed on the surface of invasive tumour cells. Nature 1994;*370*: 61-5.

【Term of Project】 FY2010-2013

【Budget Allocation】 164,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.ims.u-tokyo.ac.jp/cancercell/index.html

【Grant-in-Aid for Scientific Research(S)】

Integrated Science and Innovative Science (New multidisciplinary fields)

Title of Project : Elucidation of thermohaline/biogeochemical circulation systems connecting the Sea of Okhotsk with subarctic North Pacific Ocean

Masaaki Wakatsuchi
(Hokkaido University, Professor Emeritus)

Research Area : New interdisciplinary fields, Environmental science

Keyword : Ocean thermohaline circulation

【Purpose and Background of the Research】

One of primary processes that foster abundant production in the Oyashio area is due to the fact that dissolved iron is transported from the northwestern continental shelves in the Sea of Okhotsk to the remote Oyashio area. The iron transportation is made with thermohaline circulation in the Sea of Okhotsk driven by dense shelf water (DSW), which is formed when sea ice is produced over the northwestern shelf. DSW production and intensity of thermohaline circulation depends on competitive processes between fresh water input from Amur River and saline water from the North Pacific Ocean. However, estimation of the saline water transport, which is a key parameter for determining the thermohaline circulation intensity, has been lacking because there are almost no in-situ measurements in the area spanning between the East Kamchatka Current and the eastern Sea of Okhotsk. In this project, we will conduct intensive observations in this data-vacant area to elucidate subtle and miracle mechanisms of the iron transport system from the Sea of Okhotsk to the North Pacific Ocean. Specifically:

(1) Measurement of thermohaline transport in the area of the East Kamchatka Current and the eastern Sea of Okhotsk.
(2) Quantitative description of iron circulation in the North Pacific by investigating a potential source of iron off the Kamchatka Peninsula.
(3) Elucidating entire system of thermohaline and material circulation spanning between the Sea of Okhotsk and the North Pacific Ocean.

【Research Methods】

Intensive observations will be conducted in the eastern Sea of Okhotsk and the East Kamchatka Current areas in 2011 and 2012 using Russian vessels. The observations include:

- Measurements of thermohaline transport by mooring systems that measure temperature, salinity and current velocity.
- Lagrangian measurement of temperature and salinity by profiling floats.
- Measurements of various nutrients and biological parameters in several sections across the East Kamchatka Current by Russian vessels, including iron transport processes originating from the continental shelves off the Kamchatka Peninsula.

Based on the above in-situ observations, numerical simulations, hydrographic dataset produced by a Russian institution and satellite measurements are integrated to elucidate entire system of thermohaline and material circulation spanning between the Sea of Okhotsk and North Pacific Ocean.

【Expected Research Achievements and Scientific Significance】

It is the scientific merit of this project that is to elucidate thermohaline circulation processes whose strength is controlled by the consequence of competitive processes between fresh water input from Amur River and saline water flux from North Pacific. Our target is to understand the miracle processes of the Okhotsk thermohaline circulation quantitatively which fosters abundant fishery resources of this area. We are convinced that completion of this project, which concludes the Japanese-origin, decade-long exploration of this miracle system, will be a first step for further understanding of the earth system in depth.

【Publications Relevant to the Project】

Wakatsuchi, M., 2009, A mystery of rich ocean. Trends in the Sciences (JSC Forum), 54-59, December issue.

Ohshima, K.I., T. Nanowatari, S. Riser, M. Wakatsuchi (in press), Seasonal variation in the in- and outflow of the Okhotsk Sea with the North Pacifc, *Deep-Sea Res., II.*

【Term of Project】 FY2010-2014

【Budget Allocation】 167,700 Thousand Yen

【 Homepage Address and Other Contact Information】

http://wwwoc.lowtem.hokudai.ac.jp/

Title of Project : Warming events and their impacts during the past 150,000 years viewed from Greenland ice

Kumiko Goto-Azuma
(National Institute of Polar Research, Division of Research and Education, Associate Professor)

Research Area : New multidisciplinary fields

Keyword : Global warming

【Purpose and Background of the Research】

To improve the projection of future Arctic climate and environment changes associated with global warming, including retreat of Greenland ice sheet, advancement in ice sheet and climate modeling is required. For this goal, long-term records of the past Arctic warmings and their impacts, and the understanding of the mechanisms are necessary. An international ice coring project NEEM (North Greenland Eemian Ice Drilling) was initiated to obtain the oldest ice core in the northern hemisphere, covering the last interglacial period Eemian, which is thought to be 3-5 °C warmer than today.

Under the NEEM project, we aim at reconstructing the climatic and environmental changes during the last interglacial (Eemian), early Holocene, and the abrupt climate changes in the last glacial period (DO events). Based on an accurate chronology, relative timing of changes in Greenland air temperature, greenhouse gases, sea level, global ocean temperature, Antarctic temperature and orbital parameters will be investigated. Results of this project will shed light on the mechanisms of climate and ice sheet changes, and also provide important data for improving climate and ice sheet models.

【Research Methods】

The NEEM ice core will be analyzed to reconstruct the climate and environment during early Holocene warming, abrupt warming events in the last glacial period, and entire Eemian with unprecedentedly high time-resolutions. An accurate chronology will be produced by O_2/N_2 ratio measurements. Xe and Kr in extracted air will be analyzed to reconstruct mean ocean temperature. Microscopic and DNA analyses of microbes, analysis of air content, and analyses of ions using a continuous flow analysis system and ion chromatographs will be also carried out to investigate changes of Greenland ice sheet, vegetation, sea ice, mineral dust, and atmospheric circulation. These data will be analyzed along with other data including greenhouse gases and stable water isotopes, which will be obtained by the Japanese and international collaborators.

【Expected Research Achievements and Scientific Significance】

The accurate chronology determined by O_2/N_2 ratio measurements will be able to constrain the relative timing of changes in Greenland air temperature, greenhouse gases, sea level, Antarctic air temperature, global mean ocean temperature, and orbital parameters. The results will provide new insights into the mechanisms of glacial cycles. The data will also contribute to evaluate the impacts of warmings, such as glacial terminations and DO events, on global ocean temperature, ice sheet retreat, vegetation, sea ice, aridity in Asian deserts, and atmospheric circulation. The project will also produce valuable data to test and improve climate and ice sheet models.

【Publications Relevant to the Project】

・Steffensen, J.P, K.K. Andersen, M. Bigler, H.B. Clausen, D. Dahl-Jensen, H. Fischer, K. Goto-Azuma and 13 others, High resolution Greenland ice core data show abrupt climate change happens in few years, Science, 321, 680, DOI:10.1126/science.1157707, 2008.

・Kawamura, K. et al. Northern Hemisphere forcing of climatic cycles in Antarctica over the past 360,000 years. Nature, 448, 912-917, 2007.

【Term of Project】 FY2010-2014

【Budget Allocation】 168, 100 Thousand Yen

【 Homepage Address and Other Contact Information】

http://polaris.nipr.ac.jp/~NEEM
kumiko@nipr.ac.jp

Title of Project : Catastrophic reduction of sea-ice in the Arctic Ocean – its impact on the marine ecosystems in the polar region –

Naomi Harada
(Japan Agency for Marine-Earth Science Technology, Research Institute for Global Climate, Team-Leader)

Research Area : New multidisciplinary fields, Environmental science, Environmental dynamic analysis
Keyword : Environmental monitoring of the polar regions

【Purpose and Background of the Research】

The marine ecosystem surrounding the Arctic Ocean is complicated and difficult to predict the future because "disadvantage" phenomena such as ocean acidification and "advantage" phenomena such as improving light condition for marine organisms, respectively, are simultaneously progressing. The aims of this study are 1) to estimate the recent changes in sea-ice thickness and sea-ice covering area, and temporal changes in primary production, 2) to understand the physiological response of marine phyto- and zooplanktons having carbonate tests on warming or freshening associated with sea-ice melting, 3) to develop a new model for marine ecosystems in the Arctic Ocean, to reproduce the primary production by using the model and to understand the response of marine ecosystems on the catastrophic environmental changes caused by rapid sea-ice reduction (Fig.1: Inside the black circle).

【Research Methods】

This study will be investigated by three groups of observation by research vessel and satellite, culture and breeding of planktons, and marine ecosystem model. The specific research outlines are as follows:

- Estimation of changes in sea-ice thickness and covering area, and water mass structure to understand annual changes in physical oceanographic environment associated with sea-ice expansion or reduction in the Arctic Ocean
- Detection of seasonal and annual changes in primary production and organisms composition
- Understand of changes in physiological response of coccolithophorid and foraminifer on environmental changes caused by sea-ice melting by culture / breeding experiments
- Development of new model for marine ecosystems in the Arctic Ocean based on the NEMURO, which has already been used for the prediction of fish resources in the North Pacific, to reproduce the primary and secondary production and to predict the distribution area of fish resources.

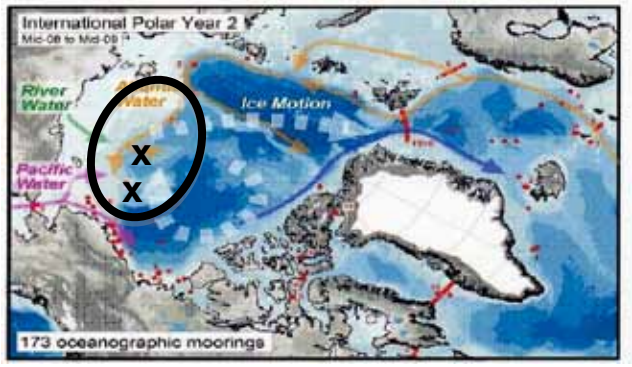


Fig. 1 Location map of observation area (black circle) and deployment sites of sediment trap and physical oceanographic mooring systems (black crosses)

【Expected Research Achievements and Scientific Significance】

It is expected that we can obtain new prediction of marine ecosystems not only low trophic level organisms but also fish resources in this area. The prediction of fish resources in the Arctic Ocean would contribute to the planning of Japanese policy for fisheries.

【Publications Relevant to the Project】

Nishino, S. et al. (2009) Vertical double silicate maxima in the sea-ice reduction region of the western Arctic Ocean: implications for an enhanced biological pump due to sea-ice reduction. J. Oceanogr., 60, 871–883.
Yamamoto-Kawai M. et al. (2009) Aragonite undersaturation in the Arctic Ocean: effects of ocean acidification and sea ice melt, Science, 326, 1098–1100.

【Term of Project】 FY2010-2014

【Budget Allocation】 152, 300 Thousand Yen

【 Homepage Address and Other Contact Information】

Title of Project : Molecular pathology and regulatory mechanisms involved in the breakdown of nucleotide pool homeostasis under environmental stress

Yusaku Nakabeppu
(Kyushu University, Medical Institute of Bioregulation, Professor)

Research Area : New multidisciplinary fields

Keyword : damage, nucleotide pool, DNA, RNA

【Purpose and Background of the Research】

For living organisms, maintaining the integrity of their genomic DNA harboring the genetic information and transmitting them precisely from parents to offspring or from cell to cell are essential biological functions in order to maintain the species and individuals, respectively. DNA is always in danger of modification by reactive molecules generated by environmental factors such as radiation or by cellular metabolisms such as respiration. We have demonstrated that DNA lesions cause mutations or cell death if not repaired, and the former may initiate carcinogenesis while the latter may result in various degenerative diseases. We have unveiled that genomic damage is caused not only by direct lesions generated in DNA, but also by modification of its precursor mononucleotides. Given that more than ten-billion molecules of mononucleotides are required for an entire replication of human genome, the quality control of nucleotide pool – "a source of mononucleotides" – is undoubtedly important for maintaining the integrity of genomic DNA. Moreover, mononucleotides are essential for various cellular functions such as energy transfer and signal transduction.

The aim of this project is to identify and investigate the molecules essential for the maintenance of the nucleotide pool homeostasis.

【Research Methods】

We explore biological phenomena caused by the breakdown of nucleotide pool homeostasis:

(1) We identify modified nucleotides generated by radiation or chemicals using LC-MS/MS. We then establish methods to quantify the modified nucleotides in cells and tissues. Using these methods, we evaluate effects of the modified nucleotides generated in cells as well as in tissues under various environmental stresses.

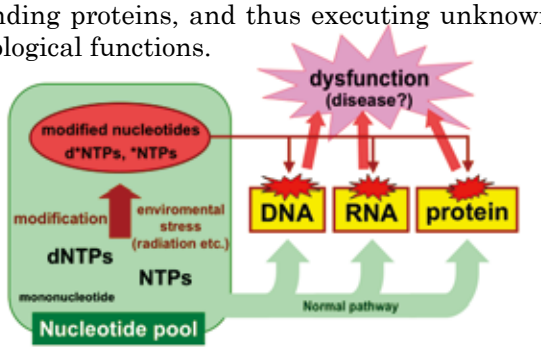
(2) Using affinity chromatography with modified nucleotide-immobilized resins, we purify and identify proteins whose functions are affected by various modified nucleotides, or which degrade modified nucleotides. We then clone and characterize genes for these proteins.

(3) We examine biological effects of modified nucleotides on cultured cells and mouse. Using strategies based on disruption/knockdown or over-expression of genes identified in (2), we clarify roles of these genes *in vivo*.

(4) Using mouse models for Alzheimer's disease and cancer, we explore the mechanisms how modified nucleotides modulate the pathologies.

【Expected Research Achievements and Scientific Significance】

Mononucleotides are important not only as precursors of DNA, but also as precursors of RNA and regulatory ligands for various proteins. Elucidation of mechanisms for quality control of nucleotide pool may lead to the development of new research fields. For example, it is likely that the modified nucleotides derived from ATP/GTP interact with many kinds of well-known ATP/GTP binding proteins, and thus executing unknown biological functions.



【Publications Relevant to the Project】

- Oka S, Tsuchimoto D, Sakumi K, Nakabeppu Y *et al.* Two distinct pathways of cell death triggered by oxidative damage to nuclear and mitochondrial DNAs. *EMBO J*, 27: 421-432 (2008)
- Behmanesh M, Sakumi K, Abolhassani N, Oka S, Tsuchimoto D, Nakabeppu Y *et al.* ITPase-deficient mice show growth retardation and die before weaning. *Cell Death Differ*, 16: 1315-1322 (2009)

【Term of Project】 FY2010-2014

【Budget Allocation】 167, 000 Thousand Yen

【 Homepage Address and Other Contact Information】

http://www.bioreg.kyushu-u.ac.jp/nfg/

Title of Project：Signal toxicity mediated through nuclear receptors of new generation bisphenols

Yasuyuki Shimohigashi
（Kyushu University, Faculty of Sciences, Professor）

Research Area：New multidisciplinary fields
Keyword：Endocrine disruptors, Bisphenols, Nuclear receptors, Signal toxicity

【Purpose and Background of the Research】

Our discovery of the specific receptor of endocrine disruptor bisphenol A (BPA), namely, estrogen-related receptor γ (ERRγ), has impacted the studies on BPA's low-dose effects. Meanwhile, novel polycarbonate plastics made from new generation bisphenols (AF, B, C2, E, and Z as replacement of BPA) have been newly developed, and their possible and potential endocrine disruptions are now worried greatly.

Fig. 1. Bisphenol A in the most stable conformation.

Because of high ERRγ expression in the fetal brain, BPA is likely concerned with adverse effects on development and differentiation of the central nervous system. We recently found the feedback system in which ERRγ regulates a number of nuclear receptors and transcription factors. The present objectives are to clarify the molecular mechanisms of signal toxicity mediated through nuclear receptors of diverse bisphenols.

【Research Methods】

The investigation of molecular machinery of the fetal brain is to shed light on the influence of BPA and other bisphenols in the central nerve system. Those include the identification of ERRγ's target genes by ChiP, real-time PCR analysis of gene expression in BPA-feeding animals, the structural and cellular analyses of signal toxicity mediated by nuclear receptors, and many other intrinsic experimentations.

【Expected Research Achievements and Scientific Significance】

A special concern is signal toxicity in the cranial nerve. High expectation is due to the establishment of the molecular basis of intrinsic risk assessment of bisphenols.

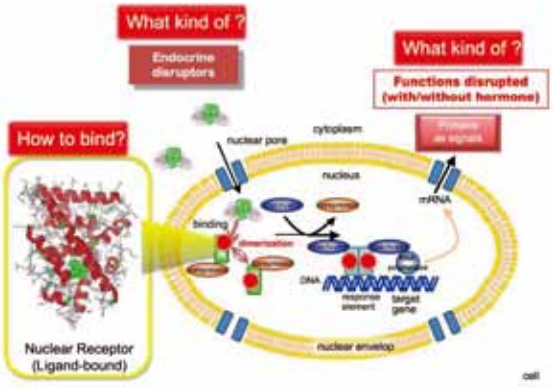


Fig. 2. Schematic diagram of signal toxicity mediated through nuclear receptors of new generation bisphenols.

【Publications Relevant to the Project】

A. Matsushima, X. Liu, H. Okada, M. Shimohigashi, and Y. Shimohigashi: Bisphenol AF is a Full Agonist for the Estrogen Receptor ERα, but a Highly Specific Antagonist for ERβ. *Environ. Health Perspect.*, in press. Online 28 4 2010 | doi:10.1289/ehp.0901819

A. Matsushima, Y. Kakuta, T. Teramoto, T. Koshiba, X. Liu, H. Okada, T. Tokunaga, S. Kawabata, M. Kimura, and Y. Shimohigashi: Structural Evidence for Endocrine Disruptor Bisphenol A Binding to Human Nuclear Receptor ERRγ. *J. Biochem.*, **142(4)**, 517-524 (2007).

【Term of Project】 FY2010-2014

【Budget Allocation】 120, 600 Thousand Yen

【Homepage Address and Other Contact Information】

http://lsfb.scc.kyushu-u.ac.jp/
E-mail: shimo@chem.kyushu-univ.jp

Title of Project : Creation and Evaluation of Complex Nanostructures Comprising Multi-Atom Species at Room Temperature by Atom-by-Atom Imaging, Chemical Identification and Manipulation

Seizo Morita
(Osaka University, Graduate School of Engineering, Professor)

Research Area : Compound New Area
Keyword : Nano Probe

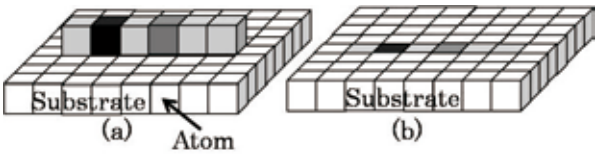
【Purpose and Background of the Research】

Complex nanostructures comprising multi-atom species show strong quantum confinement effect and, hence, we can design the confined electron energy. Atom manipulation and chemical identification of individual atoms are, however, critical to construct such complex nanostructures. Conventional nanostructures have been constructed from metal atoms and molecules weakly adsorbed on metal substrate by scanning tunneling microscope (STM) at low temperature (LT).

In this project, we will create and evaluate complex nanostructures comprising multi-atom species at room temperature (RT) by atom-by-atom imaging, chemical identification and manipulation of single atoms based on atomic force microscopy (AFM) combined with scanning tunneling microscopy (STM) [AFM/STM].

【Research Methods】

Using nanospace, we will investigate how to build up complex nanostructures supported on the semiconductor substrate at RT [Fig.(a)] by atom manipulation method. By atom interchange manipulations, we will also investigate how to build up complex nanostructures embedded in the semiconductor surface at RT [Fig.(b)].



Then we will evaluate various physical properties of created complex nanostructures with both functionality and quantum effects at RT using AFM/STM. Here, using AFM we will evaluate mechanical property, while using STM we will evaluate electronic property of complex nanostructures at RT. Moreover we will compare the nature of embedded complex nanostructures at RT with those supported on the surface at RT.

【Expected Research Achievements and Scientific Significance】

Multi-atom species are the origin of functionality of materials, while the nanostructure is the origin of quantum effects. Accordingly, complex nanostructures comprising multi-atom species combine the functionality of materials with the quantum effects and, hence, are the source of abundant novel nanomaterials and nanodevices. Using only the atom manipulation method, we can arbitrarily assembly complex nanostructure atom-by-atom. Thus, using AFM atom manipulation and AFM/STM characterization, we can create and evaluate complex nanostructures to search for valuable, novel complex nanostructures. Therefore, such investigations will open the gates to the novel field of physics and chemistry of complex nanostructures.

【Publications Relevant to the Project】

・ S.Morita, F.J.Giessibl, R.Wiesendanger (Eds.), "Noncontact Atomic Force Microscopy (Volume 2)", Springer, ISBN: 978-3-642-01494-9, pp.1~401 (2009).
・ Y.Sugimoto, P.Pou, O.Custance, P.Jelinek, M.Abe, R.Pérez and S.Morita, "Complex Patterning by Vertical Interchange Atom Manipulation Using Atomic Force Microscopy", Science, Vol.322, pp.413~417 (2008).
・ Y.Sugimoto, P.Pou, M.Abe, P.Jelinek, R.Pérez, S.Morita and O.Custance, "Chemical identification of individual surface atoms by atomic force microscopy", Nature, Vol.446, pp.64~67 (2007).

【Term of Project】 FY2010-2014

【Budget Allocation】 159, 600 Thousand Yen

【 Homepage Address and Other Contact Information】

http://www.afm.eei.eng.osaka-u.ac.jp/
smorita@eei.eng.osaka-u.ac.jp

Title of Project : Spin-polarized Lasing in Quantum Dots

Akihiro Murayama
(Hokkaido University, Graduate School of Information Science and Technology, Professor)

Research Area : New multidisciplinary fields

Keyword : Nanostructure fabrication, Quantum dot, Nano-optical devices, Spin devices

【Purpose and Background of the Research】

A spin-polarized laser is a new optical device emitting coherent lights with circular polarizations reflecting electron-spin states in solid state circuits. This spin laser is expected to be a coherent light source to transfer the electron-spin states which are important in future electronics into the circular polarization properties of the light. Electron-spin relaxation can be significantly suppressed in semiconductor quantum dots (QDs), therefore, the spin states can be temporally conserved. This means that a spin laser with active gain media consisting of the semiconductor QDs can realize efficient transfer from electron-spin states in solid state circuits to circular polarizations in laser lights.

We study the spin-polarized laser structure, where the QD active media with sufficiently long spin-relaxation times and metallic ferromagnetic electrodes are employed (Fig. 1).

The purpose of this study is first to fabricate metallic ferromagnetic electrodes for the injection of spin-polarized electrons. Next, we study atomic-scale hetero-epitaxial growth of the ferromagnetic thin film on the surface of a semiconductor layer for the purpose of achieving efficient electron-spin injection, where electron-spin relaxation induced by electron scattering due to defects and impurities during the injection is sufficiently suppressed. Finally, we identify the physical mechanism responsible for spin-polarized lasing in semiconductor QDs.

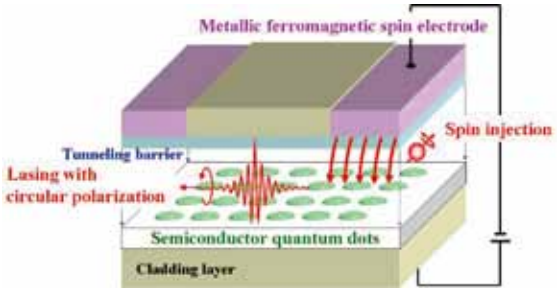


Fig. 1 A schematic drawing of the spin-polarized laser structure with active media of semiconductor QDs and metallic ferromagnetic electrodes.

【Research Methods】

Metallic ferromagnetic nanostructures will be fabricated as electron-spin-injection electrodes by using a lithography technique. Next, epitaxial growth of the ferromagnetic thin film on the surface of a compound semiconductor layer will be studied for the purpose of eliminating interfacial defects which induce electron-spin relaxation during the spin injection across the interface. Additionally, ultrafast spin-polarized electron tunneling will be studied based on coupled spin-polarized wave functions of electrons, which enables to realize efficient spin injection with the injection time faster than the spin-relaxation time.

【Expected Research Achievements and Scientific Significance】

The physical mechanism to realize spin-polarized lasing in QDs will be established. In addition to this main achievement, the following scientifically significant points will be clarified; epitaxial growth of defect-free interfaces between semiconductor surfaces and ferromagnetic ultrathin films, coupled wave functions of spin-polarized electrons between a ferromagnetic layer and QDs, efficient ultrafast tunneling of spin-polarized electrons into QDs with the discrete density of states.

【Publications Relevant to the Project】

・A. Murayama, T. Asahina, K. Nishibayashi, I. Souma, and Y. Oka,
"Efficient spin injection into self-assembled quantum dots via LO-phonon-assisted resonant electron tunneling",
Appl. Phys. Lett. **88**, 023114 (2006).

・A. Murayama, T. Furuta, K. Hyomi, I. Souma, Y. Oka, D. Dagnelund, I. A. Buyanova, and W. M. Chen,
"Dynamics of exciton-spin injection, transfer, and relaxation in self-assembled quantum dots of CdSe coupled with a diluted magnetic semiconductor layer of $Zn_{0.80}Mn_{0.20}Se$",
Phys. Rev. **B 75**, 195308 (2007).

【Term of Project】 FY2010-2014

【Budget Allocation】 150,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://mars-ei.eng.hokudai.ac.jp/

Title of Project：Development and deployment of the radar network at high resolution

Zen-Ichiro Kawasaki
(Osaka University, Graduate School of Engineering, Professor)

Research Area：New multidisciplinary fields

Keyword：Meteorological disasters

【Purpose and Background of the Research】

Social vulnerability has become a major concern in recent years for the modern highly sophisticated society, particularly in terms of natural disaster. In order to prevent the meteorological disaster, the radar system has been widely used and the most effective tool, because the system can remotely sense the meteorological targets over the wide area in a short time. Most conventional radars for both operation and research are S-, C-, and X-band radars covering 100–450 km in radius with a range resolution of more than 100 m and a time resolution of 5 min roughly, which are appropriate for the precipitation system of macro- or mesoscale. On the other hand, it is difficult for conventional radars to detect smaller scale weather phenomena such as localized scattered thunderstorms, tornadoes, and microbursts, which often damage our lives seriously. In addition to these, while the radar system can detect the motion of the hydrometors, it is not possible to detect the electrical signature of thunderstorms. In this project, using the recently developed small radar systems and lightning location system, the life cycle of the thunderstorm and lightning activity are observed with high resolution, and the way to predict the meteorological disaster will be developed.

【Research Methods】

In this research project, based on the developments of the 3 dimensional lightning mapping system and the broad band radar system, we are going to 1) develop the radar network and assess its effectiveness, 2) construct the data processing and distribution system, 3) analyze the thunderstorm behavior using both the broad band radar data and lightning location data from the digital broad band interferometer, and 4) develop the prediction model for meteorological disaster.

【Expected Research Achievements and Scientific Significance】

The two main instrument used in this research project, the broad band radar and the broad band digital interferometer, have been both developed in Osaka University. The Ku-band broadband radar (BBR), with fast scanning capability for meteorological application can accurately measure the radar reflectivity factor with a range resolution of several meters and a time resolution of 55 s per volume scan from the nearest range of 50 m to 15 km for 10-W power using pulse compression. On the other hand, the broad band digital interferometer is a system to locate sources of VHF impulses based on the digital interferometric technique. The basic idea of the technique is to estimate the phase differences between the EM pulses received by a pair of spatially separated broadband antennas at various frequencies. By doing so, the location of the VHF sources emitted by lightning is determined and the 3 dimensional structure of lightning progression is reconstructed with at least 2 sites. Using these instruments, the electrical and dynamical nature of storms are observed and analyzed to predict the natural disasters.

【Publications Relevant to the Project】

・Yoshida, S., C. J. Biagi, V. A. Rakov, J. D. Hill, M. V. Stapleton, D. M. Jordan, M. A. Uman, T. Morimoto, T. Ushio, Z-I. Kawasaki, Three-dimensional imaging of upward leaders in triggered lightning using VHF broadband digital interferometers, *Geophys. Res. Lett.*, VOL. 37, L05805, doi:10.1029/2009GL042065, 2010.3

・Yoshikawa, E., Tomoaki Mega, Takeshi Morimoto, Tomoo Ushio, Zen Kawasaki, Katsuyuki Imai, and Shin'ichiro Nagayama, Development and Initial Observation of High Resolution Volume Scanning Radar for Meteorological Application, *IEEE Trans. Geosci. Remote Sens.*, in press

【Term of Project】 FY2010-2014

【Budget Allocation】 77,600 Thousand Yen

【 Homepage Address and Other Contact Information】

http://www1a.comm.eng.osaka-u.ac.jp/index.html.ja

【Grant-in-Aid for Scientific Research(S)】
Integrated Science and Innovative Science (New multidisciplinary fields)

Title of Project：A novel approach for the understanding of basic structure and behavior of human chromosomes

Katsuhiko Shirahige
(The University of Tokyo, Institute of Molecular and Cellular Biosciences, Professor)

Research Area：Genome Science

Keyword：Chromosome Informatics, Chromosome Dynamics, Chromosome Structure

【Purpose and Background of the Research】

Chromosome is a platform of life and various functions are integrated into a single chromosome molecule (Figure1). To understand the molecular mechanism that guarantees the proper function of chromosome, it is essential to study the process of chromosome dynamics (i.e., replication, recombination, repair, and partition) using a genomic approach. Genetic and biochemical approaches have so far identified hundreds of proteins that function in some aspects of chromosome dynamics. Now, genomic

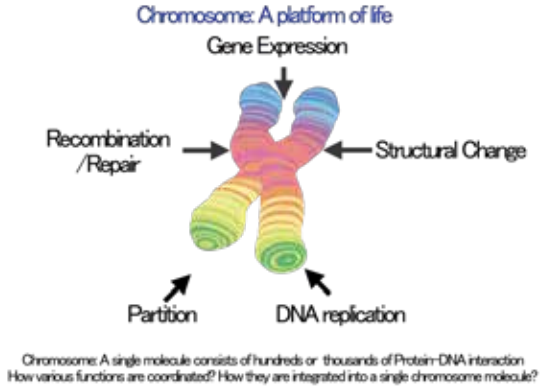


Figure1: Chromosome is a platform of life

approaches are able to show us how these proteins are integrated in the process of whole chromosomal dynamics, that is, how each elemental process is connected to make a complex network in order to guarantee the faithful maintenance of genomes. The goal of this proposal is to build up an analytical system to understand the structure and function of the human chromosome through a genomic approach. Our genomic approach (ChIP-seq technology; Chromatin Immuno-precipitation combined with next generation sequencer technology) has made us to know how protein-DNA interactions are actually integrated into the chromosome functions, and how each function is connected to make a huge network for the faithful maintenance of genome.

【Expected results】

The system we develop will tell us not only the molecular basis of functional elements of human chromosomes (replication origins, cohesin sites, centromeres and so on.), but also how these functional elements are organized to construct the flexible, dynamic, and huge chromosome structure, that is a specific feature of mammalian chrmosome (Figure2).

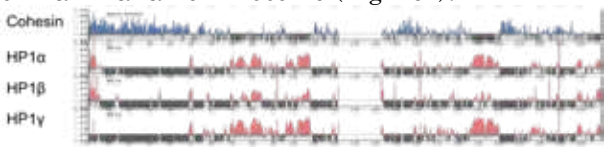


Figure2: Binding profiles of cohesin, HP1α, β, and γ on human chromosome1 revealed by ChIP-seq methods. Large heterochromatic (HP1) and euchromatic (cohesin) domain on chromosome1 are visualized.

【Research Methods】

Using HeLa and RPE cell lines, we will explore cell cycle dependent and senescence dependent changes of chromosome structure by monitoring binding profiles of more than 40 proteins by ChIP-seq. 3D chromosome folding structure will be examined by Hi-C technique. We will newly develop an algorithm to interpret ChIP-seq data and to investigate the correlation among protein binding profile and Hi-C maps. New chromosome functions and functional networks will be predicted and proved experimentally.

【Expected Research Achievements and Scientific Significance】

An entirely new picture for the molecular basis of human chromosome structure and dynamics will be revealed. The analytical system constructed in this study will open to public and be useful not only to basic fields of biosciences but to applied scientific fields like regenerative medicine and predictive medicine.

【Publications Relevant to the Project】

・T. Sutani, et al.. Curr. Biol. 19, 492-497, (2009)
・K. S. Wendt et al. Nature (article). 451, 796-801, (2008)

【Term of Project】 FY2010-2014
【Budget Allocation】 172,700 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.iam.u-tokyo.ac.jp/chromosomeinformatics/
kshirahi@iam.u-tokyo.ac.jp

Title of Project : Multi-disciplinary Study of Southeast Asian Planted Forests and Local Societies

Noboru Ishikawa
(Kyoto University, Center for Southeast Asian Studies, Associate Professor)

Research Area : Area Studies
Keyword : Biomass Society, Plantation, Multi-disciplinary Field Science

【Purpose and Background of the Research】

The equatorial zone has accumulated the highest concentration of biomass due to greater solar radiation energy and heavier rainfall. The region under study has also been a most fertile ground for resource commodification. Such a tropical zone has gone through fast-paced metamorphoses in the past several decades with the changing status of biomass from jungle produce, cultivated rubber, timber, to oil palm and acacia mangium as potential energy sources in the post-petroleum era.

The fundamental transformation of biomass is a common feature of societies of insular Southeast Asia. The landscape of rainforest-cum-plantation fields offers an analytical locale to examine a biomass shift under the organizational power of the state and structural power of capitalism, with new projects of time-space compression, where deforestation, plantation, and reforestation are simultaneously at work, with green agendas for the global energy crisis and climate change. The formula for co-existence of *planted forest* (acacia mangium and oil palm plantation) with the sound socio-economic base for the survival of local communities can only be figured out by cross-disciplinary studies composed of social and natural sciences.

【Research Methods】

The proposed project is a multi-sited, multi-disciplinary empirical study, a strategic combination of field sciences. To understand the transformation of biomass society in the tropics, the research seeks to examine the articulation points between social systems and natural systems. Both social and natural sciences have long engaged in the study of connections. From community, region, nation-state, to empire --- or from patch to landscape, scaling and rescaling the units of analysis in time and space to comprehend how constituent parts of a system are related, and distant places linked. Such engagements in the study and theorization of interconnections, however, have usually been pursued without connecting their thoughts to other attempts, and a common ground for the confluence between geosphere, biosphere and human habitat has not been fully investigated. While the science of nature and technology deals with material flows such as water, gases, and minerals through physical and biological processes, social science looks into commodity chains and levels of socio-cultural, economic, and political integrations and disintegrations.

The development of Bornean plantation field is morally endorsed and financially backed up by the international community in search of a sustainable development path for human society. Planted forests of oil palm and acacia mangium as a potential energy source are regarded as good for carbon emissions, and people on Wall Street produce products for the securitization of tropical biomass under the newly proposed REDD (*Reducing Emissions from Deforestation and Degradation*) initiative. The threshold between nature and non-nature is now being arbitrarily manipulated by capitalists, the states, and international organizations.

Articulating the field study of local peoples, cultures, and landscapes, namely anthropology, geography, history, political economy, environmental economics, plant and animal ecology, hydrology, soil science, area informatics, and forest ecology, a research team is organized for examining the multi-dimensional driving forces of change in human/non-human interactions in a heterogeneous landscape consisting of oil/acacia plantations, primary and secondary forests, and swidden fields.

【Expected Research Achievements and Scientific Significance】

To examine whether or not societies located along the equator can find an alternative path toward their own sustainability needs further investigation. The transformation of Southeast Asian biomass society may be a common feature among the equatorial zones of the world. Insular Southeast Asia will serve as an important locale where it may be possible to combine historical research and fieldwork with other sciences in order to examine whether or not the resilience of local communities of mankind, fauna, and flora is yet to find another strategy in response to the emergent geo-political conditions that bring qualitative and quantitative transformations.

【Publications Relevant to the Project】

Ishikawa, Noboru. 2010. *Between Frontiers: Nation and Identity in a Southeast Asian Borderland.* Athens/Singapore/Copenhagen: Ohio University Press /National University of Singapore Press/NIAS Press.

Ishikawa, Noboru (ed.) 2010. *Flows and Movements in Southeast Asia: New Approaches to Transnationalism*. Kyoto University Press (2nd ed.).

Ishikawa, Noboru Denyse Snelder, and Wil de Jong (eds.) 2010 *Transborder Governance of Forests, Rivers and Seas*, London: Earthscan.

【Term of Project】 FY2010-2014

【Budget Allocation】 149, 800 Thousand Yen

【Homepage Address and Other Contact Information】

A website linked to the following URL will be set up: http://www.cseas.kyoto-u.ac.jp/