Title of Project : Refinement and Extension of Higher-Order Model Checking

Naoki Kobayashi
(The University of Tokyo, Graduate School of Information Science and Technology, Professor)

Research Project Number : 15H05706 Researcher Number : 00262155
Research Area : Theoretical Computer Science
Keyword : Program theory, Formal verification

【Purpose and Background of the Research】

As a lot of important infrastructures are nowadays controlled by computers, it is important to guarantee the reliability of computer software. Higher-order model checking, the main subject of this project, is an extension of model checking, which has been considered a promising method for system verification. Higher-order model checking has more potentials than the traditional, finite state model checking.

We have already constructed the first higher-order model checker in the world, and implemented a fully automatic verifier for functional programs on top of it. We have also shown that by compressing data in the form of a program that generates them, we can use higher-order model checking to apply a variety of operations (such as pattern matching) to the compressed data without decompression.

The goal of this project is to significantly extend the previous results on higher-order model checking. We aim to establish more solid theoretical foundations for higher-order model checking, and significantly improve the size and properties of programs that can be automatically verified, and the quality of data compressions and manipulations based on higher-order model checking.

【Research Methods】

We set up the following four sub-topics, and study them in parallel.

(1) Theoretical foundations of higher-order model checking: Higher-order model checking is concerned about properties of the (possibly infinite) tree that is generated by a higher-order tree grammar. We plan to attack important open problems about the higher-order grammars. We also plan to provide a theoretical justification of why many instances of higher-order model checking can be solved in practice, despite the extremely high worst-case complexity of higher-order model checking. Based on these theoretical results, we also plan to develop a more efficient higher-order model checker.

(2) Applications to automated verification of functional programs: We have already constructed an automated program verification tool MoCHi for functional programs. We plan to improve it, so that much larger programs and a wider range of specifications can be handled

(3) Extended higher-order model checking and its applications to verification of object-oriented and concurrent programs: We plan to develop a better extended higher-order model checker, and construct fully-automated verification tools for object-oriented/concurrent programs on top of it.

(4) Applications to data complexity: We plan to improve data compression/manipulation methods based on higher-order model checking. We also plan to investigate their applications to knowledge discovery.

【Expected Research Achievements and Scientific Significance】

This project will contribute to the improvement of the reliability of computer software. Applications to data compression will also help solving the recent problem of the information explosion.

From an academic viewpoint, as higher-order model checking is related to a broad range of theoretical computer science, including program theory, formal languages, and complexity theory, the success of the project would have a big impact on the whole area of theoretical computer science. Applications to data complexity will also have an impact on other areas such as natural language processing and bioinformatics.

【Publications Relevant to the Project】

Naoki Kobayashi, Model Checking Higher-Order Programs, Journal of the ACM, 60(3), 62 pages, 2013.

Naoki Kobayashi, Kazutaka Matsuda, Ayumi Shinohara, Kazuya Yaguchi, Functional Programs as Compressed Data, Higher-Order and Symbolic Computation, 25(1), pp.39-84, 2012.

【Term of Project】 FY2015-2019

【Budget Allocation】 149,200 Thousand Yen

【Homepage Address and Other Contact Information】

http://www-kb.is.s.u-tokyo.ac.jp/~koba/

Title of Project : Establishing Theoretical Foundations for Mathematical Modeling of Pathological Biosystems and its Applications to Personalized Medicine

Kazuyuki Aihara
(The University of Tokyo, Institute of Industrial Science, Professor)

Research Project Number : 15H05707 Researcher Number : 40167218
Research Area : Informatics
Keyword : Mathematical system theory, Complex systems, Biological information

【Purpose and Background of the Research】

Since spatio-temporal big data are recently available in the field of biological and life sciences, mathematical informatics researches on how to analyze such data are becoming important more and more. In particular, our research aims at developing mathematical modeling of pathological biosystems and its applications to personalized medicine. By this project, we will establish theoretical foundations for personalized medicine that can be widely used in real practice.

【Research Methods】

For studies of complex systems, it is useful to mathematically derive and analyse their models. Thus, we will develop methods of such mathematical modeling and analysis by focusing mainly on hormone therapy for prostate cancer and the Dynamical Network Biomarkers (DNB) theory, a new concept for biomarkers. By analysing physiological big data of various diseases and validating these methods, we will construct mathematical theory with real applicability for realizing personalized medicine (Fig. 1).

【Expected Research Achievements and Scientific Significance】

(1) Hormone Therapy Based on Mathematical Models for Prostate Cancer and its Expansion to Other Diseases

We will explore possibility of personalized medicine by using tailor-made mathematical models constructed with clinically observed time series data of biomarkers such as prostate specific antigen (PSA). Our mathematical methods, especially based on short time series data in clinics, will enable to judge which is more appropriate, continuous or intermittent androgen suppression (IAS), and schedule IAS optimally for each patient when IAS is chosen. Deciding optimal treatment schedules can be also made possible for various other diseases that will acquire treatment resistance.

(2) Dynamical Network Biomarkers Theory: Developments and its Applications

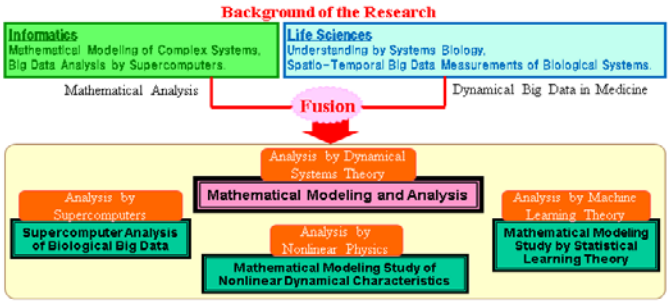


Figure 1 Summary of this research.

DNBs aim at identifying the critical pre-disease state between healthy and disease states, rather than distinguishing healthy and disease states. Thus, this research characterizes the state transitions from healthy to disease attractors. We will enable to diagnose and start treating various diseases at their very early stages near but before the bifurcation points leading to disease states.

【Publications Relevant to the Project】

・L. Chen, R. Liu, Z.-P. Liu, M. Li, and K. Aihara: "Detecting Early-warning Signals for Sudden Deterioration of Complex Diseases by Dynamical Network Biomarkers," Scientific Reports, Vol.2, Article No.342, pp.1-8 (2012).
・Y. Hirata, N. Bruchovsky, and K. Aihara: "Development of a Mathematical Model that Predicts the Outcome of Hormone Therapy for Prostate Cancer," Journal of Theoretical Biology, Vol.264, No.2, pp.517-527 (2010).

【Term of Project】 FY2015-2019

【Budget Allocation】 148,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.sat.t.u-tokyo.ac.jp/index.html
aihara@sat.t.u-tokyo.ac.jp

Title of Project : Research on Information Infrastructure Platform for Sustainable Smart Mobility

Akira Fukuda
(Kyushu University, Faculty of Information Science and Electrical Engineering, Professor)

Research Project Number : 15H05708 Researcher Number : 80165282
Research Area : Informatics
Keyword : Information Network

【Research Aim and Background】

Research on smart mobility has started to change its focus to new domains, not only on transport systems. Although approaches from information science have been applied, most approaches conduct R&D on separated techniques such as sensing, acquisition and visualization of automobile probe data etc. There is a lack of systematic/foundational research on design, development, and construction of an info infrastructure platform for smart mobility. The current smart mobility society has evidenced new progress about emergence/utilization of novel sensing techniques or services focusing on ITS, and further development can be anticipated. A dynamic architecture which can embrace these factors becomes important. Discover malfunctions in the operation phase after system's construction, and feed-back the discovered malfunctions to design phase. A feedback mechanism based on this process

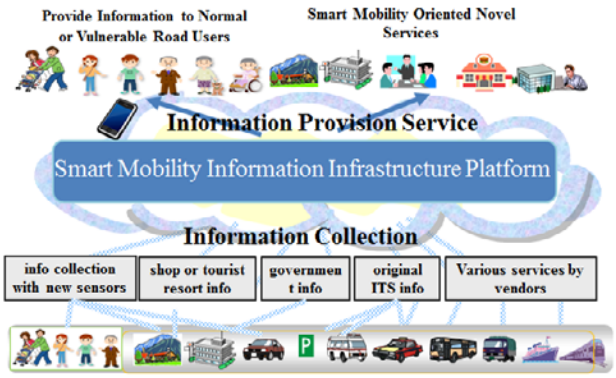


Figure 1. Smart Mobility Info Infrastructure Platform

or experience/knowledge obtained in this process is indispensable. Establishing such a mechanism enables construction of sustainable systems. This research investigates architecture for design, development, and construction techniques of an info infrastructure platform, targeting on smart mobility and is life-cycle oriented, i.e., covering all phases until system's deployment and operation.

【Research Methods】

Unlike most previous research which stops at a close cycle of system design, development, and construction, the most significant feature of this research is to establish 1) systematic techniques that can actualize problems discovered during system's operation and feedback them flexibly for platform's redesign/reconstruction; 2) sustainable smart mobility info infrastructure platform. In particular, through extending previous research achievements, this research is to establish 1) architecture of life-cycle oriented smart mobility systems, 2) feedback technologies from system's operation to design, 3) reliable design/verification techniques. ITS is a central target field now, but smart energy will also be considered in the future.

The research aims at practical results, and thus, industrial cooperation is indispensable. To this end, the research plans to establish close cooperation with ITS and smart energy communities.

【Expected Research Achievements and Scientific Significance】

Smart mobility society is to become important in the future. In such a society, through operation, we are able to construct sustainable and improvable systems, and to stabilize social infrastructure. Also, through exporting the accomplished infrastructure platform to developing countries as a social infrastructure, industrial competitiveness of our country can be strengthened.

【Publications Relevant to the Project】

・W.Kong, L.Liu, T.Ando, H.Yatsu, K.Hisazumi, and A.Fukuda : Facilitating Multicore Bounded Model Checking with Stateless Explicit-State Exploration, The Computer Journal, 2014.
・T. Ando, H.Yatsu, W.Kong, K.Hisazumi, and A. Fukuda : Translation Rules of SysML State Machine Diagrams into CSP# toward Formal Model Checking, Int. J. of Web Information System 2014.

【Term of Project】 FY2015-2019

【Budget Allocation】 153,600 Thousand Yen

【Homepage Address and Contact Information】

https://www.f.ait.kyushu-u.ac.jp/projects/KakenKibanS

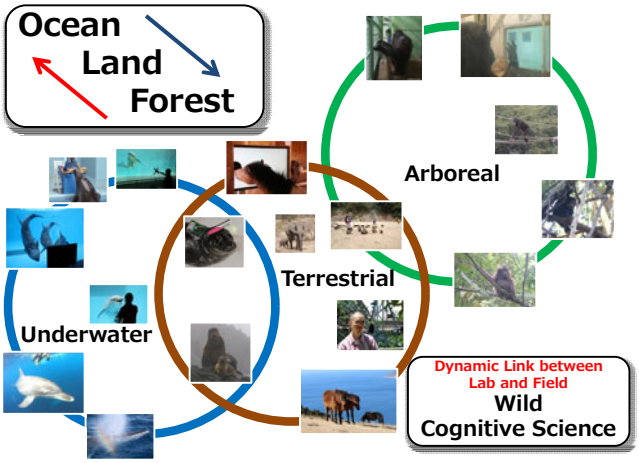
Title of Project : Wild Cognitive Science : Comparative–Cognitive Approach toward Understanding Evolution and Diversity of Mind

Masaki Tomonaga
(Kyoto University, Primate Research Institute, Associate Professor)

Research Project Number : 15H05709 Researcher Number : 70237139
Research Area : Cognitive Science
Keyword : Primates, Mammals, Evolution of Mind, Adaptation, Comparative Cognitive Science

【Purpose and Background of the Research】

Purpose of this research project is to understand "How" and "Why" our human minds have evolved. For this purpose, it is necessary to compare cognitive abilities not only between humans and evolutionarily closest species such as nonhuman great apes, but between us and various species of mammals who have adapted to completely different environments from ours, such as dolphins, seals, and horses. We focus on the aspect of "adaptation" of our minds and try to compare among minds underwater, minds on the land, and minds in the forest. Especially our approaches include dynamic interactions between cognitive experiments in the laboratory and behavioral observations in the wild. "Inspired by wild, and examine in the lab, and vice versa." Through these efforts, we try to establish a new interdisciplinary science named as "Wild Cognitive Science".



【Research Methods】

In this project, we study primates (humans, nonhuman great apes, etc.), cetaceans (dolphins, belugas, etc.), pinnipeds (seals, sea lions, etc.), and terrestrial mammals (horses, etc.). Using and expanding innovative techniques established through the comparative-cognitive studies with great apes (touchpanel, eye-tracker, etc.) in the studies with other mammals, we will try to make a breakthrough for the comparative cognitive science in nonprimate mammals. Research topics are categorized into 2 major topics, cognition of physical and social worlds. Concurrently with the laboratory study, we actively introduce innovative techniques to the field studies, such as biologging, camera-trap network, drone-based observations, etc.

【Expected Research Achievements and Scientific Significance】

Uniqueness of research project is a dynamic interaction of studies among variety of species adapted to different environments, and interaction between the laboratory and the wild. Our unique attempt, "Wild Cognitive Science" will provide new perspectives to the evolution of mind, and shed light on the importance of biodiversity which is the basis for diversity and convergence of the evolution of mind.

【Publications Relevant to the Project】

・Tomonaga et al. (2014). How dolphins see the world. Sci. Rep., 4, 3717.
・Yu & Tomonaga (2015). Interactional synchrony in chimpanzees. Sci. Rep., 5, 10218.

【Term of Project】 FY2015-2019

【Budget Allocation】 152,700 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.pri.kyoto-u.ac.jp/koudou-shinkei/shikou/staff/tomonaga/indexj.html
tomonaga.masaki.4m@kyoto-u.ac.jp

Title of Project：Neural Basis of Mental Images

Yukiyasu Kamitani
(Kyoto University, Graduate School of Informatics, Professor)

Research Project Number：15H05710　Researcher Number：50418513
Research Area：Informatics
Keyword：Cognitive Neuroscience

【Purpose and Background of the Research】

Mental images constitute an essential part of our experience. Images are not only induced by external stimulation but are also internally generated as volitional imagery or dreaming. Although the phenomenal similarity between these types of images suggests a common neural basis, it remains elusive. In this project, we aim to reveal common neural representations for these images using machine learning-based pattern analysis of brain activity data.

Our group have developed methods for "brain decoding" for the last decade. Brain decoding predicts detailed mental contents from brain activity patterns using machine learning algorithms. We have shown that visual features such as orientation and motion direction can be reliably decoded from visual cortical activity, and that even the reconstruction of seen images (Figure 1, left) and the decoding of dreamed visual objects (Figure 1, right) are possible.

【Research Methods】

In this project, we collect brain activity data using functional MRI (fMRI) while participants are seeing images (Perception), having mental imagery (Imagery), or having dreams (Dreaming) (Figure 2). In addition to decoding analyses within each dataset, we perform generalization analyses in which a decoder trained on a dataset is tested on another dataset. Using the generalization

Figure 1　Neural decoding of visual information

performance as an index for the similarity of neural representation, we systematically and exhaustively quantify the similarity across image features and brain regions.

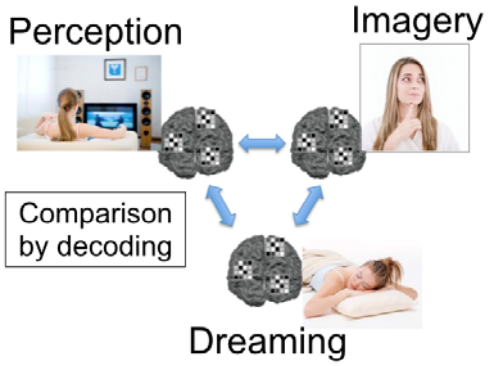


Figure 2　Our approach

【Expected Research Achievements and Scientific Significance】

This project will reveal the common neural basis for the different types of images, and provide insights into the mechanisms that generate mental experiences.

【Publications Relevant to the Project】

- Horikawa, T., Tamaki, M., Miyawaki, Y., and Kamitani, Y. (2013). Neural decoding of visual imagery during sleep. Science *340*, 639-642.
- Miyawaki, Y., Uchida, H., Yamashita, O., Sato, M. A., Morito, Y., Tanabe, H. C., Sadato, N., and Kamitani, Y. (2008). Visual image reconstruction from human brain activity using a combination of multiscale local image decoders. Neuron *60*, 915-929.

【Term of Project】FY2015-2019

【Budget Allocation】153,700 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.cns.atr.jp/dni/

Title of Project : Research on Core Algorithms for Discrete Structure Manipulation Systems

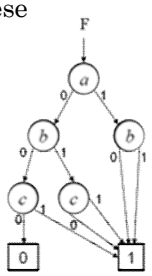
Shin-ichi Minato
(Hokkaido University, Graduate School of Information Science and Technology, Professor)

Research Project Number : 15H05711 Researcher Number : 10374612
Research Area : Informatics
Keyword : Discrete Structure Manipulation System, Algorithm

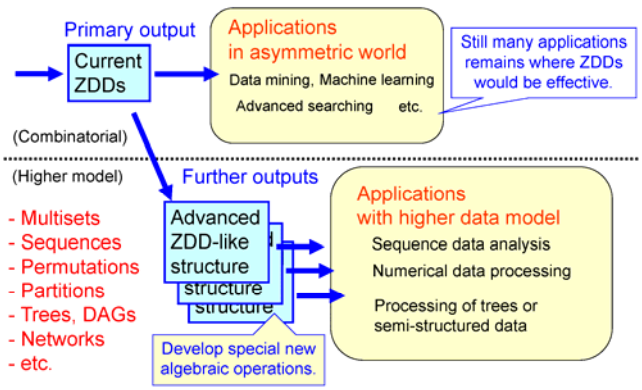
【Purpose and Background of the Research】

Discrete structures are foundational material for computer science and mathematics. Many problems solved by computers can be decomposed into discrete structures using simple primitive algebraic operations. It is very important how to represent large-scale discrete structural data and to execute their operations efficiently.

The project leader has been leading "JST ERATO Minato Discrete Structure Manipulation System Project" for five years. In this project, he has studied discrete structure manipulation systems using Zero-suppressed Binary Decision Diagrams (ZDDs) and their practical applications. As the results of the project, they developed novel techniques for enumerating, compressing and indexing large-scale data based on ZDDs, and they are very effective for real-life problems. Many researchers are now interested in these techniques, and several number of related research projects has been started. This research project focus on the core algorithms of discrete structure manipulation, and we will continue to maintain a firm research community in the center of the other related research projects.



(ZDD)



【Research Methods】

As a primary research output, we first apply the current ZDD techniques to many practical applications where ZDDs would be effective. In the other hand, we also consider the higher-level data models, such as multisets, sequences, permutationsm trees, etc. We will develop ZDD-like data structures for them, and not only the data structures but also their algebra will provide fruitful applications. This project will study such core algorithms for discrete structure manipulation systems, and will provide their efficient software implementations for related application engineers in academia and industory. More specifically, our research topics include 1) development of core algorithms for discrete structure manipulation and providing software implementation, 2) Development of efficient searching, enumerating, and indexing methods, and 3) Promoting the researcher's community and collaboration with other related national projects.

【Expected Research Achievements and Scientific Significance】

Computer science and technology consists of a layer of foundational theory and a layer of engineering customized for each application. Our research area of discrete structure manipulation is located in the middle of the two layer, called "the Art" layer, to connect "Science" and "Engineering." Our project will provide a research community where theoretical people and application people collaborate together. It may create the seeds of technology.

【Publications Relevant to the Project】

- Takeru Inoue, Hiroaki Iwashita, Jun Kawahara, and Shin-ichi Minato: "Graphillion: software library for very large sets of labeled graphs," International Journal on Software Tools for Technology Transfer (STTT), Springer, DOI 10.1007/s10009-014-0352-z, Oct. 2014.

【Term of Project】 FY2015-2019

【Budget Allocation】 103,400 Thousand Yen

【Homepage Address and Other Contact Information】

http://www-erato.ist.hokudai.ac.jp/

Title of Project : Plankton in Polar Regions—toward an Understanding of their Characteristics

Naomi Harada
(Japan Agency for Marine-Earth Science and Technology, Research & Development Center for Global Change, Deputy Director of R&D Center)

Research Project Number : 15H05712 Researcher Number : 70344281
Research Area : Environmental Science
Keyword : Marine biology, Arctic Ocean, Ocean Acidification

【Purpose and Background of the Research】

The decline of biodiversity (the biomass, composition, and distribution of species) on Earth reflects the fact that the ability of Earth to sustain biodiversity in a dynamic environment has been seriously compromised by environmental stressors such as climate change and ocean acidification. Furthermore, the reduction of sea ice in the Arctic Ocean, which has progressed more rapidly than previously predicted, could exacerbate several environmental stresses, including ocean warming, acidification, and stratification. How do marine organisms in polar regions respond to ocean warming and acidification? This study focuses on phytoplankton and zooplankton, which constitute the base of the food chain in the Arctic Ocean. The goals of the research are to understand 1) the influence of ocean acidification on calcifiers; 2) the warming-associated changes of the biomasses of major and minor species; and 3) the specific functions of plankton that live in the Arctic.

【Research Methods】

The target area of this study is the western Arctic Ocean, where the reduction of sea ice is especially serious (Fig. 1). A time series sediment trap mooring system will be deployed at Station NAP (75°N, 162°W), a biological hotspot, to collect settling biogenic particles. We will also measure temperature, salinity, dissolved oxygen and nutrient concentrations, and pH by using sensors deployed on the mooring system. The micro X-ray computer tomography technique (MXCT) will be developed to evaluate the impact of ocean acidification on calcifiers. We will analyze the assemblage of settling biogenic particles by using 18S rRNA sequences to detect temporal changes in major and minor species. Whole-genome analyses of specific phytoplankton will reveal how the phytoplankton produce various aliphatic hydrocarbons.

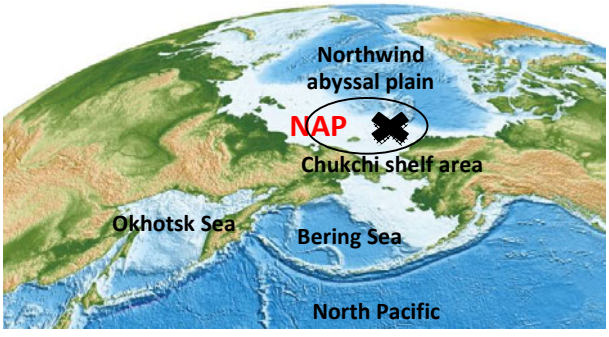


Figure 1. Observation area (black oval) and Station NAP (×), which is where the time series sediment trap mooring system is to be deployed..

【Expected Research Achievements and Scientific Significance】

Analyses of settling biogenic particles and environmental data at Station NAP will enable us to understand seasonal and annual changes in the composition and biomass of lower-trophic-level organisms in the western Arctic Ocean and their responses to environmental stressors, especially ocean warming and acidification. Because no standard method for quantifying responses of marine organisms to ocean acidification currently exists, then the MXCT technique could become the standard method for evaluating the impact of ocean acidification on marine calcifiers

【Publications Relevant to the Project】

・ Watanabe, E. et al. (2014) Enhanced role of eddies in the Arctic marine biological pump, Nature Comm., doi: 10.1038/ncomms4950.
・ Onodera, J. et al., (2015) Diatom flux reflects water-mass conditions on the southern Northwind Abyssal Plain, Arctic Ocean. Biogeosciences, 12, 1373–1385.

【Term of Project】 FY2015-2019

【Budget Allocation】 151,900 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.jamstec.go.jp/arctic-eco/

Title of Project : Mechanism of Genome Integrity Maintenance in Tissue Stem Cell

Takeshi Todo
(Osaka University, Graduate School of Medicine, Professor)

Research Project Number : 15H05713 Researcher Number : 90163948
Research Area : Biological Effects of Radiation and Chemicals
Keyword : Damage Response

【Purpose and Background of the Research】

Maintenance of genome integrity is crucial for all organisms. However genome stability is continuously challenged by a diverse array of mutagenic forces. To maintain the genome integrity several mechanisms have evolved. Multiple DNA repair pathways minimize the mutagenic consequences of DNA damage and erroneous DNA replication. Cell cycle checkpoint assures the efficient elimination of errors during DNA replication and chromosome segregation. Apoptosis is the most effective way to eliminate potentially deleterious cells carrying DNA damage. Each process has been well characterized at molecular level. However, how each process contributes to the induction of genome instability is still unclear. In this study we will clarify the role of each process on mutagenesis.

Another important issue for the study of damage response is the type of target cell. Tissues of our body consist of heterogenous population of cells, which include slowly dividing stem cells, extensively proliferating cells and differentiated function cells. Communication between these cells and the niche surrounding the stem cell play an important role on the maintenance of each tissues as well as the damage response. Among these cells, tissue stem cell is exceptional because it stays on the tissue for long time, and thus has strong impact on the late effects of genome damage, carcinogenesis and aging. In this study we will focus on tissue stem cells, and damage response in these cells will be studied *in vitro* and *in vivo*. Culture cell provides a uniform population of cells, thus suitable for the precise study of the gene function. On the other hand, *in situ* study of cell in tissue provides a lot of information about cell-cell interaction. In this study, we use rat mesenchymal stem cell or tissues of small fish medaka *Oryzias latipes* as *in vitro* or *in vivo* system, respectively.

【Research Methods】

Basic tool for the present study is genome analysis by Next Generation Sequencer (NGS). Rapid progress in NGS diffusion enables a direct approach to the genome stability. Rearrangement induced *in vitro* and/or *in vivo* cells will be determined by NGS. Another novel approach is mosaic analysis. The mosaic tissue, consisting of cells in which gene of the interest is either on or off, will provide a system for precise analysis of gene function. Two methods will be used for establishing mosaic tissues, IR-Lego (Infrared laser-Evoked Gene Operator) and transposon mediated efficient trans-genesis.

【Expected Research Achievements and Scientific Significance】

Maintenance of genome integrity is indispensable for the tissue stem cells. This study will clarify the nature of damage response expressed in stem cells. Another expected result is the quality control of stem cells. Recently stem cell competition has been noticed as a stem cell quality control system. Whether or how this system play a role on damage response will be clarified.

【Publications Relevant to the Project】

・Kamei Y, Suzuki M, Watanabe K, Fujimori K, Kawasaki T, Deguchi T, Yoneda Y, Todo T, Takagi S, Funatsu T, Yuba S. Infrared laser-mediated gene induction in targeted single cells in vivo. *Nature Methods*. (2009) 6(1):79-81.
・Ishikawa T, Kamei Y, Otozai S, Kim J, Sato A, Kuwahara Y, Tanaka M, Deguchi T, Inohara H, Tsujimura T, Todo T. High-resolution melting curve analysis for rapid detection of mutations in a Medaka TILLING library. *BMC Mol Biol.* 2010 15;11(1):70

【Term of Project】 FY2015-2019

【Budget Allocation】 153,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.med.osaka-u.ac.jp/pub/radbio/www/index.html

Title of Project : Molecular Mechanism for Toxic Effect of Methylmercury

Akira Naganuma
(Tohoku University, Graduate School of Pharmaceutical Sciences, Professor)

Research Project Number : 15H05714 Researcher Number : 80155952
Research Area : Environmental sciences, Environmental and hygienic pharmacy
Keyword : Methylmercury, Toxicology, Transcriptional regulation, Signal transduction, Autocrine

【Purpose and Background of the Research】

Methylmercury is an environmental pollutant that causes serious central nervous system disorder. However, molecular mechanisms for the selective damage to the central nervous system caused by methylmercury remain poorly understood.

Aiming to understand the molecular mechanisms, we have carried out a study to search proteins affecting the methylmercury toxicity by using a comprehensive gene screening method. We identified the transcription factor-like protein HOXB13 as an intracellular factor that enhances the toxicity of methylmercury. We also found that methylmercury induced synthesis of cytotoxic factors, such as TNFα, through the action of HOXB13, and then released TNFα from the cell, and that these cytotoxic factors induced cell death. By administering methylmercury in mice, we confirmed that the induction of TNFα expression was specific to brain tissue; this finding can be considered a breakthrough for understanding the onset mechanisms for methylmercury toxicity. Thus, in this study, we aim to clarify the overall molecular mechanisms behind this phenomenon.

【Research Methods】

In this study, using cultured nervous system cells derived from humans or mice, we will analyze the mechanisms for activation of HOXB13 by methylmercury, as well as the mechanisms for synthetic derivation of secretory cytotoxic factors including TNFα via HOXB13. We will also examine in detail the mechanisms for inducing cell death or methylmercury toxicity enhancement by secretory cytotoxic factors. In addition, using TNFα- and HOXB13-knockout mice, we will examine the role of TNFα and HOXB13 in the central nervous system toxicity of methylmercury, as well as describing the importance of HOXB13 in TNFα induction by methylmercury in the brain.

【Expected Research Achievements and Scientific Significance】

This study may provide a clear and logical explanation for the brain-specific onset mechanisms for methylmercury toxicity that have remained unknown for more than half a century. The study will make it possible to develop prophylactic measures for methylmercury poisoning, and genetically identify groups that are highly susceptible to methylmercury.

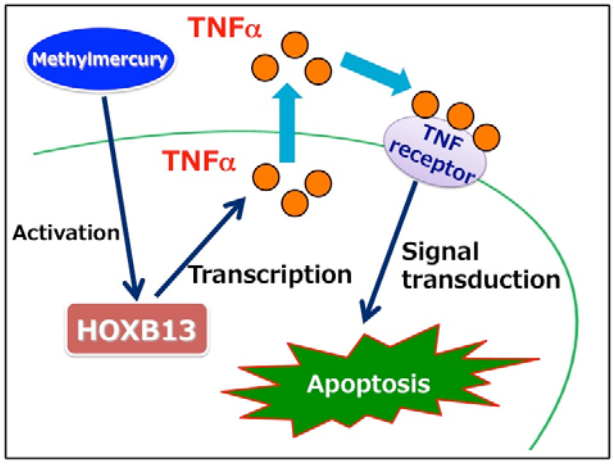


Figure 1 Transcription of TNFα induced by methylmercury through activation of HOXB13, and apoptosis induced by TNFα

【Publications Relevant to the Project】

1. Hwang, G. W., Ryoke, K.,Takahashi, T. and Naganuma, A.: Silencing of the gene for homeobox protein HOXB13 by siRNA confers resistance to methylmercury on HEK293 cells. J. Toxicol. Sci., 35, 941-944 (2010).
2. Hwang, G. W., Murai, Y., Takahashi, T. and Naganuma, A.: The protein transportation pathway from Golgi to vacuoles via endosomes plays a role in enhancement of methylmercury toxicity. Sci. Rep., 4, 5888 (2014).

【Term of Project】 FY2015-2019

【Budget Allocation】 151,400 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.pharm.tohoku.ac.jp/~seitai/seitai-index.html

Title of Project : Physical Photochemical Functionalization of Oxide Nanotubes through Hierarchical Structure Tuning

Tohru Sekino
(Osaka University, The Institute of Scientific and Industrial Research, Professor)

Research Project Number : 15H05715 Researcher Number : 20226658
Research Area : Environmental Science
Keyword : Sound material recycle system

【Purpose and Background of the Research】

The present researcher repoted that titania nanotube (TiO_2 nanotube, TNT) with open-end nano-tubular structure, typically 8-10 nm in outer-diameters, could be successfully synthesized by simple and low temperature solution chemical route without using any template. Because of synergy combination of low-dimensional nanostructure and physicochemical aspect of TiO_2, the TNTs exhibited various excellent physical and photochemical functions such as coexistence of photocatalytic properties and high molecular adsorption function, showing the TNT is a real multifunctional nanomaterial. High potential not only environmental functions but also energy havesting functions such as solar cell electrode has confirmed, implying it opens a new window to oxide semicondoctors as advanced environmental, energy creation and biocompatible materials and systems.
In this project, novel nanostructural tuning will be attempted to the oxide nanotubes to enhanse their phsycal photochemical multifunction further through processing development and optimization. Final goal is thus to develop hyper-multifunctional low-dimensional oxide nanotubes for advanced next generation environemtal cleaning materials, energy havesting/materials conversion catalysts, and biocompatible functional nanomaterials.

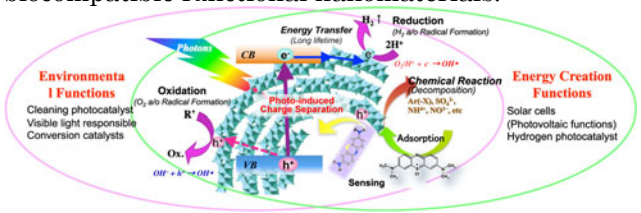


Fig.1 Materials characteristics of oxide nanotubes and development concdept of the project.

【Research Methods】

To achieve research goals, this project will focus on hierarchical materials tuning and synthesis, structure and function analysis, and clarifying the roles of low-dimensional nanostructures on various physical photochemical functions. In detail, lattice-level modification of nanotubes by ion doping and immobilization of metals, compounds and organic molecules and polymers will be carried out. As the example, titania nanotubes (TNTs) will be modified by ion doping based on the band engineering to tune their semiconductive properties. One of the goals of this tuning lies in the development visible-light responsible photocatalyst. On the other hand, immobilizing various materials will be carried out to realize 0-dimensional and 1-dimentional heterogeneous low-dimensional nanocomposites, which would exhibit better photochemical performance.

【Expected Research Achievements and Scientific Significance】

Through the project, we will develop novel low-dimensional oxides with excellent physical photochemical functions, which might become next generation high-performance environmental and energy materials. In addition, systemization of science and engineering of oxide nanotube materials would be achieved through the detailed investigation on the synthesis, nanostructure and functions. Through the study, we will demonstrate materials tuning methodology that contributes realization of advanced friendly nanomaterials.

【Publications Relevant to the Project】

・ D. J. Park, T. Sekino, S. Tsukuda, S.-I. Tanaka, *Res. Chem. Intermed.,* **39**, 1581-1591 (2013).
・ T. Sekino, *Ceram. Jpn.*, **41**[4], 267-271(2006).
・ T. Kasuga, M. Hiramatsu, A. Hoson, T. Sekino, K. Niihara, *Langmuir*, **14**, 3160-63(1998).

【Term of Project】 FY2015-2019

【Budget Allocation】 153,700 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.sanken.osaka-u.ac.jp/labs/mmp/

Title of Project : Design for Driving Automation and Legal Systems Conforming to Characteristic Features and Limitations of Cognition and/or Decision Making of Human Drivers

Toshiyuki Inagaki
(University of Tsukuba, Faculty of Engineering, Information and Systems, Professor)

Research Project Number : 15H05716 Researcher Number : 60134219
Research Area : Social/Safety System Science
Keyword : Automated driving, Human factors, Authority and responsibility, Negligence liability

【Purpose and Background of the Research】

Automated driving has been attracting the attention from wide variety of people expecting a bright future for the vehicle of the next generation. It should be noted, however, that automation has both positive and negative sides, as we have learnt through accidents of glass-cockpit aircraft. We need to work unflinchingly on unsolved technical as well as non-technical problems in order to realize sensible automated driving systems that can be accepted by the society.

This project aims to develop theories and methodologies for design of driving automation and legal systems reflecting characteristic features and limitations of cognition and/or decision of human drivers. More precisely, this project tries to identify mismatches between humans' understanding of and/or expectation on driving automation and humans' responsibility that are assumed by the machine. This project also tries to propose a new legal system suitable for the age of driving automation.

【Research Methods】

To accomplish the above-mentioned goals, the following three Research Aspects are set up in this project: Human Factors (HF) Research Aspect, Engineering Design (ED) Research Aspect, and Authority and Responsibility (AR) Research Aspect.

The HF Research Aspect's goals are: (1) to identify human factors in driving automation with solutions, (2) to formulate guidelines for design of human-machine interface, and (3) to develop training programs for enhancing driver's resilience in cases of unexpected events.

The ED Research Aspect's goals are: (1) to develop systematic methods for finding out 'missing levels of automated driving' in the list by NHTSA, SAE, or BASt, (2) to identify an optimal level of automation for performing safe and smooth transfer of control authority from the automated driving system to the human driver when the system requests, and (3) to develop safety control mechanisms for cases of traffic conditions which the automated driving systems may not be able to cope with.

The AR Research Aspect's goals are: (1) to identify problems of the current legal system when the automated driving systems are put into the real world, (2) to develop a new legal theory for analyzing negligence liability when using driving automation, and (3) to propose a new system for driver's license in the age of driving automation.

【Expected Research Achievements and Scientific Significance】

This project investigates driving automation from various viewpoints including human factors, trust in and reliance on automation, systems reliability, safety control, human-machine interface design, criminal law, and civil law. New theories and methodologies developed in this project will be used in some government-initiated programs, such as CAO's SIP program for automated driving and MLIT's ASV program.

【Publications Relevant to the Project】

・T. Inagaki & T.B. Sheridan. Authority and responsibility in human-machine systems: Probability theoretic validation of machine initiated trading of authority. Cognition Technology & Work 14 (29-37) 2012.
・T. Inagaki & M. Itoh. Human's overtrust in and overreliance on advanced driver assistance systems: A theoretical framework. Int'l J Vehicular Tech, doi:10.1155/2013/951762

【Term of Project】 FY2015-2019

【Budget Allocation】 153,400 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.risk.tsukuba.ac.jp/~inagaki/eng/coagency.html

Title of Project : Urgency Evaluation of the Nankai Great Earthquake and Tsunami by Scientific Ocean Drilling

Gaku Kimura
(The University of Tokyo, Graduate School of Science, Professor)

Research Project Number : 15H05717 Researcher Number : 80153188
Research Area : Complex Systems (Social/Safety system science)
Keyword : Seismic hazard, Tsunami

【Purpose and Background of the Research】

Our scientific objective is to quantitatively evaluate the urgent state of the great subduction-zone earthquake in the Nankai Trough off SW Japan, which is a site where great subduction-zone earthquakes have repeatedly occurred more than 1,300 years, lost tremendous amount of lives and properties, and the hazard risk to occur in 30 years is high. To realize our goal, our strategy consists of the following three tactics.
(1) quantify the in-situ stress state and pore fluid pressure of the hanging wall of the plate boundary fault and the fault itself (2) evaluate the effective strength of the plate boundary fault together with fault structure, and (3) continuous and repeating observation of the physical properties and state of the plate boundary fault by seismic study. Integrating these researches, we will quantitatively evaluate the urgency status of the coming Nankai earthquake and tsunami.

【Research Methods】

(1) To obtain the stress and effective stress, we conduct logging of the drilling borehole, anelastic stress measurement for the core sample, and their integrations for the seismic reflection survey.

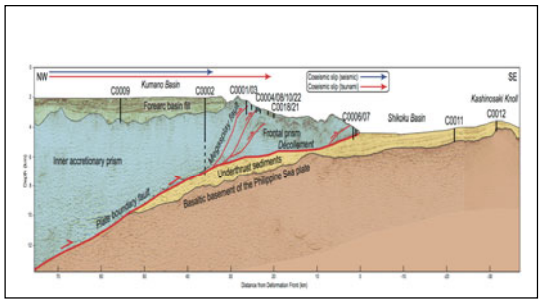


Figure 1 seismic reflection profile and its interpretation with drilling sites of the Nankai Trough off the Kii Peninsula, SW Japan

(2) To obtain effective strength of the plate boundary fault, friction experiments for the plate boundary fault and hanging wall are conducted under the in-situ condition and their results will be compared with in-situ stress state.
(3) To obtain the space-temporal change in effective stress condition in the hanging wall and plate boundary fault, we conduct 3D vertical seismic reflection experiment in the borehore and repeat surrounding seismic reflection survey around the borehole observatories.

【Expected Research Achievements and Scientific Significance】

Achievement of the goal will pave a road of new science and technology to quantitavely evaluate the urgency of the subduction zone earthquake and tsunami. Its societal relevance for the hazard risk management is clear. The research is conducted under the collaboration with International Ocean Discovery Program (IODP), and will suggest a new Japanese international initiative for the science and technology in this field.

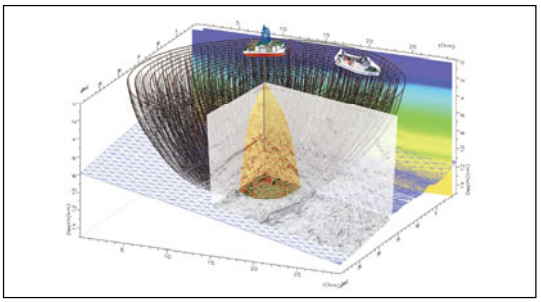


Figure 2 Surrounding 3D vertical seismic reflection survey around seismometer array in the borehole

【Publications Relevant to the Project】

・Kimura, G., Hamahashi, M., et al., (2013), J. Struct. Geol., 52, 136–147.
・Accretionary prism and seismogenic zone of the great earthquakes, 2009, Kimura G. and Kinoshita M. Eds, Tokyo Univ. Press, 281pp.

【Term of Project】 FY2015-2019

【Budget Allocation】 153,500 Thousand Yen

【Homepage Address and Other Contact Information】

http://www-solid.eps.s.u-tokyo.ac.jp/~gaku/
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Title of Project : Toward Mitigating Tsunami Hazards from Outer-rise Earthquakes: Mapping Potential Earthquake Faults and Constructing a Tsunami Database

Shuichi Kodaira
(Japan Agency for Marine-Earth Science and Technology, R&D Center for Earthquake and Tsunami, Director)

Research Project Number: 15H05718 Researcher Number: 80250421
Research Area : Natural Disaster
Keyword : Tsunami, Outer-rise Earthquake

【Purpose and Background of the Research】

Following great megathrust earthquakes, large normal-faulting earthquakes commonly occur in the outer rise, seaward of subduction zones (Fig. 1). These seismic events, which may occur decades after megathrust earthquakes, present large tsunami hazards. The tsunami inundation early warning system that is now used for megathrust events functions by comparing observed tsunami waves to a database of synthetic tsunamis that could be generated by numerous well-located potential earthquake faults. However, there is little information about potential earthquake faults in the outer rise seaward of the Japan Trench. Therefore, the main purposes of this project are to gather the necessary data for the tsunami inundation early warning system by 1) compiling a map of potential earthquake faults in the outer rise based on active-source seismic data and earthquake activity of the oceanic plate, and 2) compiling a database of simulated tsunamis caused by earthquakes on these outer-rise faults.

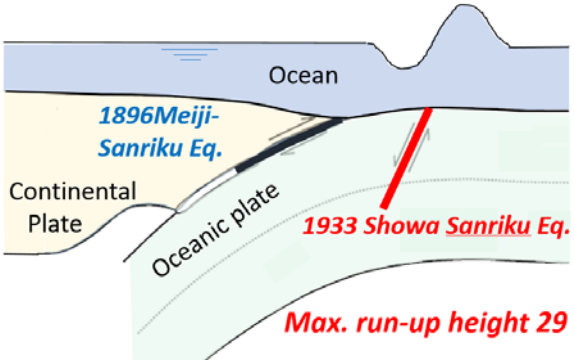

Fig. 1 Schematic diagram of outer-rise earthquake and tsunami wave on the ocean surface.

【Research Methods】

This project uses two research methods: 1) marine geophysical observations to map potential earthquake faults and 2) tsunami simulations to construct a tsunami database. In the marine geophysical observation program, we will conduct large-scale seismic imaging, earthquake monitoring and fine-scale seismic imaging in the outer rise by using JAMSTEC's seismic exploration system and an ultra-deep ocean-bottom seismometer that we has developed. In the second part of this project, we will compile a map of potential faults capable of generating large earthquakes (M>7.5) and perform a series of tsunami simulations to construct a tsunami database. A tsunami simulation code developed by our research team will be run on the Earth Simulator supercomputer.

【Expected Research Achievements and Scientific Significance】

As specialists in deep-sea marine geophysical observations, we has been implementing a tsunami inundation early warning system for Nankai Trough earthquakes based on a seafloor earthquake and tsunami observation network in the Nankai Trough. In this project we will map potential faults of outer-rise earthquakes in the Japan Trench and expand the existing tsunami inundation early warning system. Moreover, this project will yield fundamental data to more fully utilize the Japan Trench seafloor earthquake and tsunami observation system, which will make a significant contribution to future research in hazard mitigation and prevention.

【Publications Relevant to the Project】

・Fujie, G., S. Kodaira, M. Yamashita, T. Sato, T. Takahashi and N. Takahashi (2013), Systematic changes in the incoming plate structure at the Kuril trench, *Geophys. Res. Lett.*, DOI: 10.1029/2012GL054340
・Obana, K., Kodaira, S., Nakamura, Y., Sato, T., Fujie, G., Takahashi, T., & Yamamoto, Y. (2014). Aftershocks of the December 7, 2012 intraplate doublet near the Japan Trench axis. *Earth, Planet. Space*, *66*, doi:10.1186/1880-5981-66-24.

【Term of Project】

FY2015-2019

【Budget Allocation】

154,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.jamstec.go.jp/donet/e/

Title of Project : Evaluation and Control of Epilepsy Dynamics Based on Multimodal Brain Signals and Thermal Neuromodulation Using Focal Brain Cooling

Michiyasu Suzuki
(Yamaguchi University, Graduate School of Medicine, Professor)

Research Project Number : 15H05719 Researcher Number : 80196873
Research Area : Neurosurgery
Keyword : Thermal neuromodulation, Epilepsy, Low-invasive implantable devices

【Purpose and Background of the Research】

Epilepsy is a common chronic neurological disorder characterized by recurrent unprovoked seizures. The condition is usually treated with medication, but even the best agents do not provide seizure control in over 30% of patients with epilepsy. Surgical treatment is performed for such patients, but is not always successful because of proximity to eloquent areas.

Electrical stimulation of the brain has been proposed as a replacement for surgical resection such as VNS and RNS. However, the role of electrical stimulation in treatment of epilepsy is still unclear and several clinical studies have not achieved satisfactory results.

Focal cooling of the epileptogenic region of the brain is an attractive and nondestructive approach for treatment of patients with epilepsy. Focal brain cooling (FBC) was proposed approximately 50 years ago as an effective method for treatment of impaired brain conditions and recent research has shown suppression of abnormal electrical brain activity (epileptic discharges) using FBC. In the first clinical study performed worldwide, we showed that FBC has neuroprotective and anticonvulsant effects in patients intraoperatively.

Improved measurement methods have suggested that both EEG and other kinds of brain activity are related to the pathology of epilepsy Therefore, we have developed a thermal neuromodulation system based on focal brain cooling using epilepsy dynamics analysis of multimodal brain signals, in collaboration with a medical and engineering team.

【Research Methods】

The research plan is divided into three parts, with the goal of development of a low-invasive implantable thermal neuromodulation system. In part A, a novel implantable sensor will be developed for detection of multimodal brain signals such as EEG, brain temperature, NIRS signal, intracranial pressure, and head motion, using flexible printed circuit technology. In part B, the pathological brain dynamics of epilepsy will be examined using statistical analysis and mathematical neural modeling. In part C, we will develop a FBC apparatus that can modulate the pathologic brain on demand under a minute power load.

【Expected Research Achievements and Scientific Significance】

Surgery is effective for treatment of some patients with epilepsy, but other patients are not candidates for resection and many are refractory to treatment. These patients experience physical or mental disabilities in their lives that compromise social interactions, employment, and overall health and quality of life.

In the near future, it is likely that our research will open new horizons in neuromodulation devices. These new devices will have important roles in treatment of epilepsy and stroke. This treatment will be transformative for patients who currently cannot be treated effectively.

【Publications Relevant to the Project】

・Nomura S, Inoue T, Maruta Y, Imoto H, Suzuki M. Changes in glutamate concentration, glucose metabolism, and cerebral blood flow during focal brain cooling of the epileptogenic cortex in humans. Epilepsia, 2014;55(5):770-776
・Yamakawa T, Inoue T, Suzuki M, Niwayama M. Development of an Implantable Flexible Probe for Simultaneous Near-Infrared Spectroscopy and Electrocorticography. IEEE Transaction on Biomedical Engineering, 2014;61(2):388-395

【Term of Project】 FY2015-2019

【Budget Allocation】 152,600 Thousand Yen

【Homepage Address and Other Contact Information】

http://ds.cc.yamaguchi-u.ac.jp/~neuro-w1/
neurosur@yamaguchi-u.ac.jp

Title of Project : Toward New Frontiers in High-Resolution 3D Color Radiology Imaging

Jun Kataoka
(Waseda University, Faculty of Science and Engineering, Professor)

Research Project Number : 15H05720 Researcher Number : 90334507
Research Area : Radiological physics and technology
Keyword : Medical imagin system, 3D imaging, Compton camera

【Purpose and Background of the Research】

3D image processing is commonly used in projection mapping, stereo vision, and even printers. In contrast, only monochromatic 2D static images are currently available for radiology imaging applications such as radiographs and X-ray CT. Our challenge is to obtain high-resolution, color X-ray/gamma-ray images in real time in order to visualize the 3D structure and materials of a subject as well as the dynamic evolution of phenomena of interest. In this research, we realize three innovations: (A) high-precision X-ray and gamma-ray imaging technology, (B) 3D medical Compton imager, and (C) wide-field 3D monitor for applications to environmental surveys.

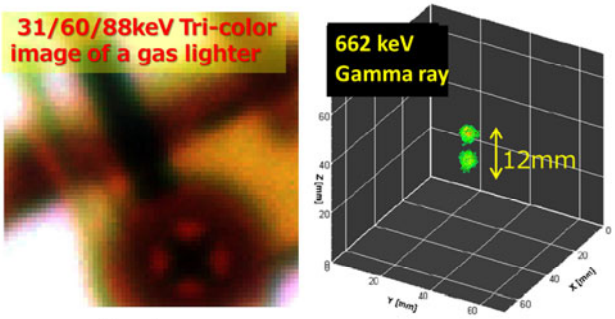

Fig.1: (left) Tri-color image using diced scintillaotr array (right) 3D gamma-ray image using Compton camera.

【Research Methods】

As a high-precision X-ray image sensor, we fabricate various scintillator plates that are cut using a microdicing saw. We aim to demonstrate improved SNR (signal to noise ratio) in the photon counting image in order to reduce the radiation dose in the X-ray CT scan. With regard to gamma-ray energies, we use two approaches: (1) 3D Compton imaging of multiple radionuclides and (2) beam-online monitor for proton/ion beam therapy. By using our prototype Compton camera, we optimize the detector design to achieve a high-resolution handheld medical Compton camera. This camera can also be used for applications to environmental surveys; for example, it can serve as the payload of a helicopter to measure the radiation dose in the forests near Fukushima or as a wearable gamma camera for performing effective decontamination operations.

【Expected Research Achievements and Scientific Significance】

Since Roentgen's discovery of X-rays in the 19th century, the visualization of "invisible" radiation has remained a challenge. The image sensor developed in this study is very simple, cost effective, and versatile. To date, we have developed a novel method to localize the incident gamma rays three dimensionally with 1-mm precision. While this technique has already been implemented in a PET (511 keV) detector, we will now apply it to the 3D measurements of gamma rays with arbitrary energy (up to 2 MeV) that is not limited to 511 keV.

【Publications Relevant to the Project】

・J.Kataoka *et al.*, "Recent progress of MPPC based scintillation detectors in high precision X-ray and gamma-ray imaging", *Nucl. Instr. and Meth. A.*, vol.784, pp.248-254 (2015)
・T.Fujita, J.Kataoka *et al.*, "Two dimensional diced scintillator array for innovative, fine resolution gamma camera", *Nucl. Instr. and Meth. A.*, vol.765, pp.262-268 (2014)
・J.Kataoka *et al.*, "Handy Compton camera using 3D-position sensitive scintillators coupled with large-area monolitic MPPC-arrays", *Nucl. Instr. and Meth. A.*, vol.732, pp.404-407 (2013)

【Term of Project】 FY2015-2019

【Budget Allocation】 112,200 Thousand Yen

【Homepage Address and Other Contact Information】

http:// www.spxg-lab.phys.waseda.ac.jp
kataoka.jun@waseda.jp

Title of Project : Therapeutic Drug Discovery and Elucidation of RNA Disease Pathogenesis by Use of CRISPR-Based Disease iPS Cells and Animal Models

Masatoshi Hagiwara
(Kyoto University, Graduate School of Medicine, Professor)

Research Project Number : 15H05721 Researcher Number : 10208423
Research Area : Chemical biology
Keyword : Postgenomic drug discovery, CRISPR, iPS, Splicing

【Purpose and Background of the Research】

RNA is vulnerable to intervention due to its characteristics as a mediator of genetic information. RNA is more extensively and dynamically regulated by modification and processing compared to DNA, where genetic information is stored. Many RNA-binding proteins etc. are involved in RNA processing, and abnormalities in this process cause disease (RNA disease). In this project, we aim to determine the "compound intervening splicing rules" from transcriptome data of cells treated with lead chemical compounds. Using RNA disease model iPS cells and animal models constructed by CRISPR-Cas9, we wish to establish a novel field of chemical biology where postgenomic drugs to RNA disease are generated.

【Research Methods】

In this project, we will follow five steps (Figure 1) to reach our goal. 1) Elucidating "intervening rules" of each splicing intervening compound, 2) Categorizing "abnormal splice codes" of each RNA disease. 3) Matching each RNA disease with appropriate splicing intervening compound and 4) Structure optimization of the compound. We will use a splicing reporter and feedback the information for further optimization of the compound. 5) Using RNA disease model iPS cells and models animals constructed by CRISPR-Cas9, we will verify, secondary screen, and test the efficacy of the compounds to evaluate the effectiveness to RNA disease at whole-body level.

【Expected Research Achievements and Scientific Significance】

This project is completely original from two points of view. First, establishing "intervening rules" of splicing intervening compounds will make it possible to efficiently seek compounds that correct aberrant splicing of RNA diseases with no cure at the moment. Second, using phenotypically relevant RNA disease models of iPS cells and animals constructed by CRISPR/Cas9 in order to verify and optimize structure will help identify compounds closer to clinical application.
We believe this project will develop a new field of chemical biology, where genetic diseases are treated by chemical compounds.

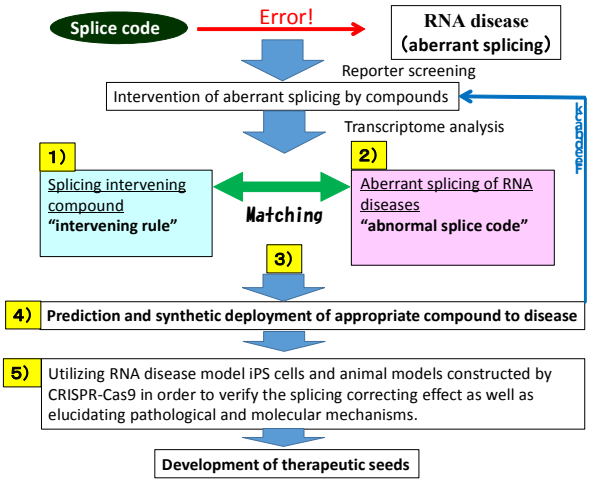

Figure: Matching "splicing intervening compound" and "RNA disease"

【Publications Relevant to the Project】

・Ohe K and Hagiwara M. Modulation of alternative splicing with chemical compounds in new therapeutics for human diseases. ACS Chem. Biol. 10(4):914-924, 2015.
・Yoshida M, Kataoka N, Miyauchi K, Ohe K, Iida K, Yoshida S, Nojima T, Okuno Y, Onogi H, Usui T, Takeuchi A, Hosoya T, Suzuki T, Hagiwara M. Rectifier of aberrant mRNA splicing recovers tRNA modification in familial dysautonomia. Proc Natl Acad Sci U S A. 112(9):2764-2769, 2015.
・Nishida A, Kataoka N, Takeshima Y, Yagi M, Awano, H, Ota, M, Itoh K, Hagiwara M, and Matsuo M. Chemical treatment enhances skipping of a mutated exon in the dystrophin gene. Nature Commun 2, 308, 2011.

【Term of Project】 FY2015-2019

【Budget Allocation】 153,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.anat1dadb.med.kyoto-u.ac.jp/Anat1DADB/TOP.html

Title of Project : Cellular Programming Using Synthetic RNP Nanosystems

Hirohide Saito
(Kyoto University, Center for iPS Cell Research and Application, Professor)

Research Project Number : 15H05722 Researcher Number : 20423014
Research Area : Complex Systems
Keyword : Functional RNA, Synthetic biology, Cellular programming, Regenerative medicine

【Purpose and Background of the Research】

RNA- protein complexes (RNP) are one of the most important biomolecular complexes to form living systems. If we can create synthetic RNP-based gene regulatory systems, it could expand the field of basic life science and medical applications. In this research, we aim to program mammalian cell fate precisely and autonomously, by integrating our developed RNA synthetic biology techniques. To achieve this objective, three research topics are set as below: ① Development of a new method that allows us to precisely detect and purify live target cells, ② Design and construction of artificial RNP nanostructures that control intracellular protein localization and cell signaling, ③ and finally development of experimental evolution techniques to generate functional RNP devices in cells. By achieving these three topics, we aim to establish synthetic RNA-mediated genetic manipulation technologies that control cell fate according to intracellular conditions.

【Research Methods】

① **Development of a new method for detecting and purifying live target cells**:
In order to accelerate regenerative medicine to the clinic, it is important to develop a method that enables to detect and purify target cells safely and precisely, and remove undesired cells autonomously. Therefore, to accomplish this task, we aimed to develop a new method, by introducing synthetic RNA-based gene switches and synthetic circuits into target cell populations.

② **Design and construction of functional RNP nanostructures within cells**:
To control the accumulation and localization of intracellular proteins, we introduce designed RNA nanostructures in mammalian cells. We have recently succeeded in constructing synthetic nanostructures composed of RNA and protein (RNP nano-triangles). Thus, by expanding our RNP molecular design technology, it is possible to generate RNP nanomachines that function in mamalian cells.

③ **Directed evolution system to generate functional RNP devices**:
For realizing the genetic manipulation according to the expression of any target protein factor, it is important to obtain synthetic RNA sequences that bind to any target agent. Therefore, we will develop a new method that enables us to evolve synthetic RNA and control target gene expression (such as a cell death-inducing factor) in live cells.

【Expected Research Achievements and Scientific Significance】

If we can develop new technologies that freely program target cells in accordance with the intracellular environment, it is possible to open up new frontiers in life sciences. In addition, if we can safely and precisely generate a variety of cells derived from pluripotent cells, it will accelerate and contribute to the field of regenerative medicine. Thus, the developed technologies will be a promising tool for both basic life science and clinical stem cell research and medical applications.

【Publications Relevant to the Project】

- Kenji Miki, Kei Endo,…, *Hirohide Saito, and *Yoshinori Yoshida. “Efficient Detection and Purification of Cell Populations Using Synthetic MicroRNA Switches”. ***Cell Stem Cell***, 16, 699-711 (2015)
- Eriko Osada, Yuki Suzuki, Kumi Hidaka, Hirohisa Ohno, Hiroshi Sugiyama, Masayuki Endo, and *Hirohide Saito, “Engineering RNA-protein complexes with different shapes for imaging and therapeutic applications”. ***ACS Nano***, 8130–8140 (2014)

【Term of Project】 FY2015-2019

【Budget Allocation】 124,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.cira.kyoto-u.ac.jp/saito/
hsaito-g@cira.kyoto-u.ac.jp

Title of Project : Development of Fluorescent Probes with Molecular Evolution Engineering

Junichi Nakai
(Saitama University, Graduate School of Science and Engineering, Professor)

Research Project Number : 15H05723 Researcher Number : 80237198
Research Area : Complex Systems
Keyword : Fluorescent probe

【Purpose and Background of the Research】

Since Green fluorescent protein (GFP) has been cloned, the fluorescent proteins and the imaging techniques are getting important for biological and medical research. We have been developing genetically encoded calcium indicators (GECIs) such as G-CaMPs and R-CaMPs (Figure 1). Nowadays, these GECIs are widely used in many model animals for reporting cellular activities. On the other hand, peptide aptamers are peptides that bind to molecules with high specificity. In recent years, because of the molecular recognition capability of peptide aptamars of biological material, biotechnological and medical application of peptide aptamers has been studied. In this research, we are going to combine our fluorescent reporter technology and the peptide aptamars, so that new fluorescent probes that have high-affinity binding to a variety of substrates can be rapidly generated.

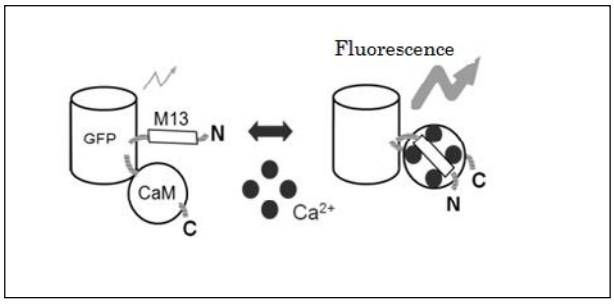

Figure 1 G-CaMP

【Research Methods】

This research has three parts, (1) development of fluorescent probe with functional peptide aptamers, (2) development of fluorescent probes with random peptide aptamers, (3) development of new screening techniques.

The fluorescent reporter moiety of G-CaMP will be fused with the peptide aptamers that are known to be functional as binding proteins or the random peptide aptamars, that will be selected with new screening technique afterword.

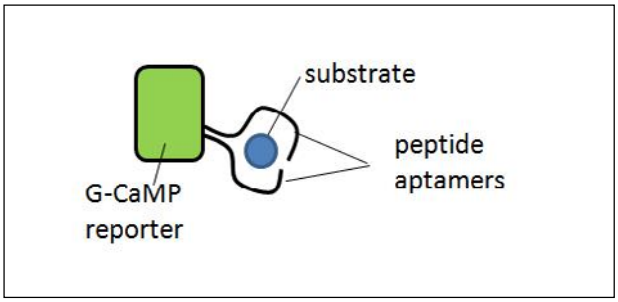

Figure 2 New probe

【Expected Research Achievements and Scientific Significance】

Imaging techniques are getting more and more important in biology, medicine, and pharmacology. In this research, we are going to establish new techniques for developing fluorescent probes. With the new methodology, high-performance fluorescent probes will be rapidly generated. These fluorescent probes will be able to be used in biology, basic research in medicine, and drug discovery, so that this research makes contribution to development of human society.

【Publications Relevant to the Project】

Nakai J, Ohkura M, Imoto K: A high signal-to-noise Ca^{2+} probe composed of a single green fluorescent protein. Nat Biotechnol 19, 137-141, 2001.

Inoue M, Takeuchi A et al: Rational design of a novel high-affinity, ultrafast, red calcium indicator R-CaMP2. Nat Methods 12, 64-70, 2015.

【Term of Project】 FY2015-2019

【Budget Allocation】 154,500 Thousand Yen

【Homepage Address and Other Contact Information】

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Title of Project： Neuroendocrinology of Social Behavior

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Research Project Number：15H05724　　Researcher Number：50396610
Research Area：Neuroscience, Behavioral Neuroendocrinology
Keyword：Social Behavior, Steroid Hormone Receptors, Optogenetics, Sexual Differentiation, Individual Differences, Neural Network

【Purpose and Background of the Research】

It is essential for human beings to establish and maintain emotional bonding with other people. However, it has become more and more difficult to form and maintain stable social relationships in a highly industrialized/computerized world. This has brought about a number of negative traits, such as neglect, child abuse, impulsive violence, etc. The main goal of our research is to understand the neurobiological basis of social and affective behaviors. Since gonadal steroids play a central role in the regulation of sex-typical social behaviors throughout life, we will study brain mechanisms of their time-, sex-, and brain site-specific action. We aim to understand: (1) how hormones act on the development of neural network for social behavior; (2) how they regulate adaptive expression of behavior; and (3) how they determine sex and individual differences.

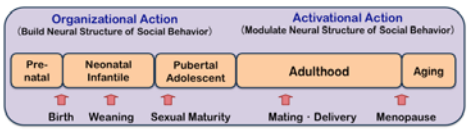

Fig. 1 Life-Long Action of Steroid Hormones on the Regulation of Social Behavior

【Research Methods】

We will focus on organizational and activational action of gonadal steroid hormones to determine the role of the two types of estrogen receptors, ERα and ERβ, and their mechanisms of action. Using several different approaches, we will determine critical site, time and mechanisms of steroid action for the sex-typical (both male and female) regulation of sexual, aggressive, and parental behavior as well as social recognition, preference, and anxiety, in mice. Particularly, we will use siRNA-mediated knockdown of ERs, optogenetic manipulation on neural network of social behavior, and neuroanatomical and physiological assays. We will also analyze ER-related genetic polymorphisms to identify determinants of individual differences in social behaviors.

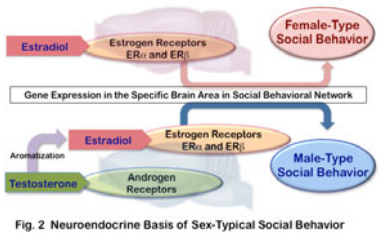

Fig. 2 Neuroendocrine Basis of Sex-Typical Social Behavior

【Expected Research Achievements and Scientific Significance】

Our goal will be to establish "a comprehensive brain map of hormonal action for the regulation of social behaviors" by collaborative interactions with neuroscientists with various expertise. These studies will advance our knowledge of how social-behavioral networks are regulated by gonadal steroids via ERα and ERβ for sex-typical behavioral expression. The outcome of the studies is expected to provide scientific insights of the nature and causes of disruption of human social and affective behaviors, and determine a possible neuroendocrine basis of sex- and individual-differences. Ultimately the findings should contribute greatly to human well-being.

【Publications Relevant to the Project】

- Tsuda MC, …Ogawa S. Modification of female and male social behaviors in estrogen receptor β knockout mice by neonatal maternal separation. *Front Neurosci*, **8**, 274, 2014.
- Sano K, …Ogawa S. Differential effects of site-specific knockdown of estrogen receptor α in the medial amygdala, medial preotic area, and ventromedial nucleus of the hypothalamus on the sexual and aggressive behavior of male mice. *E J Neurosci*, **37**,1308-1319, 2013.
- Musatov S, …Ogawa S. Knockdown of estrogen receptor α using viral-mediated RNA interference abolishes female sexual behavior. *PNAS, U.S.A.*, **103**, 10456-10460, 2006.

【Term of Project】

FY2015-2019

【Budget Allocation】

151,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.kansei.tsukuba.ac.jp/~ogawalab/?lang=en