Title of Project : Comprehensive research on statistical methodologies and their applications for development of personalized medicine

Shigeyuki Matsui
(Nagoya University, Graduate School of Medicine, Professor)

Research Project Number : 16H06299 Researcher Number : 80305854
Research Area : Statistical science
Keyword : genomic data analysis, personalized medicine, design and analysis of clinical studies

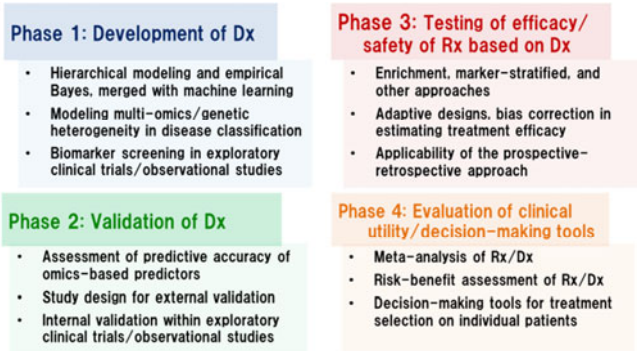
【Purpose and Background of the Research】

Recent advances in biotechnology have accelerated the development of personalized medicine, which uses patient-specific molecular characteristics to optimize diagnosis and treatment. In oncology, for example, molecularly targeted therapies have become the mainstay, often yielding better outcomes than conventional chemotherapies. Such treatments frequently involve substantial inter-patient variation in clinical effects. Consequently, traditional approaches to efficacy assessment based on average benefit across the patient population are often inappropriate, elevating the risk of overtreatment or loss of therapeutic opportunities.

To promote personalized medicine, we must seek new paradigms for the development of diagnostics (Dx) that are capable of identifying patient-specific drug responses (e.g., molecular biomarkers).

【Research Methods】

The development of personalized medicine is



divided into four phases, as shown below.

We will create new interventional and observational clinical study designs, as well as statistical methods and tools for data analysis, to assist at each of these stages.

Specifically, we will focus on case studies of a variety of cancers, rheumatoid arthritis (autoimmune disease), diabetes mellitus, and other types of disorders. Interdisciplinary collaborations will play key roles in this wide-ranging project. The work builds on a coordinated network of biostatisticians, statistical scientists, and physicians/biomedical researchers.

【Expected Research Achievements and Scientific Significance】

The novel statistical methods that will be generated over the course of this project will help to achieve a paradigm shift in clinical development. We expect that the methodologies that we create during this project will significantly increase the likelihood of successfully bringing personalized medicine to clinical practice.

In relation to biostatistics and clinical epidemiology, our efforts will help establish "personalized evidence–based medicine" (pEBM), a new therapeutic framework that takes advantage of individualized diagnostic assessment. pEBM will improve the therapeutic risk–benefit profile and help reduce health care costs to society.

From the perspective of statistical science, this project will open a new methodological arena in which statistical or causal inference will meet predictive analysis. Heretofore, these topics have been addressed independently of each other.

【Publications Relevant to the Project】

- Matsui S, Buyse M, Simon R. (2015). Design and Analysis of Clinical Trials for Predictive Medicine. Chapman & Hall/CRC Press.
- Matsui S, Simon R, et al. (2012). Developing and validating continuous genomic signatures in randomized clinical trials for predictive medicine. Clin Cancer Res. 18, 6065-73.

【Term of Project】 FY2016-2020

【Budget Allocation】 87,500 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.nagoya-biostat.jp

Title of Project : Basic Research of a Dark-Silicon-Based Logic-LSI Technology for Brainware Computing

Takahiro Hanyu
(Tohoku University, Research Institute of Electrical Communication, Professor)

Research Project Number : 16H06300 Researcher Number : 40192702
Research Area : Information Science
Keyword : Computer Systems

【Purpose and Background of the Research】

We study on dark-silicon logic-LSI technology for brainware (brain-inspired) computing. The brainware computing that mimics the human-brain function has a possibility to realize ultra-low power computation for real-time objection recognitions. In order to realize the brainware computing in LSI, extremely fine-grain power gating (EFGPG) techniques are required, where the EFGPG techniques allow LSIs to consume power only on circuits operated.

In this study, we focus on asynchronous control essentially used in the human-brain information processing and exploit it with the dark-silicon approach. Hence, we research and develop asynchronous circuits with EFGPG techniques for real-time brainware computing.

【Research Methods】

We develop the dark-silicon asynchronous logic LSI technologies that can control the gate-level power gating. To verify the functionality of the dark-silicon asynchronous logic LSI in a fabricated chip, we study three main topics as follows:

1) FY2016-2017
Dark-silicon asynchronous basic logic blocks are designed for small-scale circuits. In addition, equivalent CMOS integrated circuits are designed and fabricated to verify the basic function.
2) FY2017-2018
Hybrid CMOS/Magnetic tunnel junction (MTJ)-based dark-silicon asynchronous logic circuits are designed and fabricated to verify the gate-level power gating for brainware computing.
3) FY2018-2020
Based on the experimental results from the CMOS/MTJ hybrid chip, a low-level vision chip based on the dark-silicon asynchronous logic gates are designed and evaluated for real-time brainware computing.

【Expected Research Achievements and Scientific Significance】

To the best our knowledge, it is the first research to combine asynchronous-circuit technologies and MTJ-based gate-level power gating techniques for ultra-low power computation in both domestic and overseas.

The asynchronous circuits exhibit an intrinsic function that autonomously detects circuit operations using local signals. We exploit the function to reduce unnecessary power consumption wasted as much as possible for ultra-low power computation. In addition, using the MTJ-based nonvolatile devices, the gate-level power gating can be applied to the whole chip because of the nonvolatility.

For applications other than brainware computing, the proposed dark-silicon logic-LSI techniques can be used for Internet-of-Things (IoT) devices consisting of sensors and integrated circuits. As the number of IoT devices is expected to be 80 billions in 2025, the proposed ultra-low power technique would be a key technology in future computing systems.

【Publications Relevant to the Project】

T. Hanyu, et al., "Spintronics-Based Nonvolatile Logic-in-Memory Architecture Towards an Ultra-Low-Power and Highly Reliable VLSI Computing Paradigm," *Proc. 2015 DATE Conference*, pp. 1006-1011, Mar. 2015 (invited).

T. Hanyu, et al., "Standby-Power-Free Integrated Circuits Using MTJ-Based VLSI Computing," *Proc. of the IEEE*, 2016 (to appear).

【Term of Project】 FY2016-2020

【Budget Allocation】 127,100 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.ngc.riec.tohoku.ac.jp
hanyu@riec.tohoku.ac.jp

Title of Project : Acquisition of the independence of mind: Evolution and development of the mind liberated from the current external environments

Kazuo Fujita
(Kyoto University, Graduate School of Letters, Professor)

Research Project Number : 16H06301 Researcher Number : 80183101
Research Area : Cognitive Science, Comparative Cognitive Psychology
Keyword : Evolution, development, learning; Thought, inference, problem solving

【Purpose and Background of the Research】

Humans can imagine time and place distant from here and now. They solve problems by manipulating mental images and simulate future events flexibly. Evidence in nonhuman animals for tools, culture, and language, etc. has led some researchers to propose this "ability to transcend time and space" as the ultimate defining feature of humans. We challenge this view.

I have demonstrated forms of higher-order mental functions such as metacognition, episodic memory retrieval, and causal inference in nonhuman primates, carnivores and birds. Central to such cognitive performances is the ability to "voluntarily manipulate mental representations, liberated from environmental stimuli."

We call this "the independence of mind" in our project: the critical mental function for "the ability to transcend time and space." Our goals include: (1) empirical study of phylogeny and ontogeny of "the independence of mind" by comparative and developmental analyses across species and human infants, and (2) investigation of understanding of social others derived from this critical function.

【Research Methods】

Testing human infants, nonhuman primates, rodents, companion animals, zoo animals, and birds, we will study: (A) functions that require active and flexible manipulation of mental representations, such as thoughts and inferences, (B) metacognition and mental time travel as components to realize (A), and (C) understanding others, social intelligence, and theory of mind as an application of the functions above. Below we present a few concrete experimental plans.

Mental rehearsal. Subjects solve simple puzzles, which are sometimes pre-exposed before they manipulate the devices. Subjects will solve the task more easily with pre-exposure if they can freely manipulate mental representations.

Preparatory behavior. Subjects perform memory tasks of varying difficulty. They may choose an option to obtain a hint before they actually solve the task. Will they adaptively choose this option in advance when they predict future difficulty?

Understanding others by projection. Can subjects translate their own experience of peeking into another room to infer that other people will the same, to gain advantage in a task simulating a treasure-hunting game?

The experimental procedures will be modified whenever necessary. We will start with a few species and gradually expand the tests to more.

【Expected Research Achievements and Scientific Significance】

Our intuitive and sophisticated experiments will demonstrate rudimentary "independence of mind" in multiple species.

The most important scientific significance lies in providing answers to the most essential question of what humans are, from comparative cognitive science, to renew conception of humans. The project also addresses neural correlates, and provides hints to understand and help socially handicapped people.

【Publications Relevant to the Project】

Fujita, K. (ed.) (2015). *Doubutsu tachi wa nani wo kangaete iru: doubutsu shinrigaku no chosen.* Gijutsu Hyoronsha, 303pp.

Takagi, S., Arahori, M., Chijiiwa, H., Tsuzuki, M., Hataji, Y., & Fujita, K. (2016). There's no ball without noise: cats' prediction of an object from noise. *Animal Cognition*, in press. (DOI 10.1007/s10071-016-1001-6)

【Term of Project】 FY2016-2020

【Budget Allocation】 142,900 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.psy.bun.kyoto-u.ac.jp/kibanS_fujita2016/
kfujita@bun.kyoto-u.ac.jp

Title of Project : Communication System for Defending against Attacks of Media Clones

Noboru Babaguchi
(Osaka University, Graduate School of Engineering, Professor)

Research Project Number : 16H06302 Researcher Number : 30156541
Research Area : Human informatics, Perceptual information processing
Keyword : Visual Media Processing, Speech Information Processing, Privacy Protection

【Purpose and Background of the Research】

Distribution of non-authentic media has become a potential threat in our daily life. Its typical example is a fraud by voice impersonation of family members or friends. It is therefore of great importance to protect the receivers of such non-authentic but skillfully fabricated replicas of authentic media, called media clones, by means of media processing technologies towards safe and reliable society. The purpose of this research project is to realize a communication system that can defend against attacks of media clones.

【Research Methods】

Figure 1 shows a framework of this research. A sender Alice sends her authentic media such as video or audio to a receiver Bob through physical and cyber channels. At this time, a malicious sender Eve stealthily acquires privacy, biological, and environmental information of Alice, to make fake information. Based on the fake information, she generates Alice's media clones and sends them to Bob to deceive him.

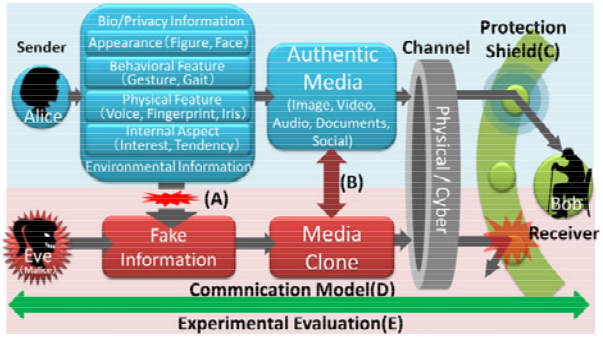


Figure 1 Framework of this research.

To realize a communication system for defending the receivers attacked by the media clones, we pursue the following five topics. (A) Development of methods for protecting the privacy, biological, and environmental information to prevent fake information generation. (B) Verification of the capability of generating various types of media clones such as audio, visual, text, and social media derived from the fake information. (C) Realization of a protection shield for media clones' attacks by recognizing them. We focus on analysis of liveness resulting from biological living features. (D) Modeling of the proposed communication system. (E) Experimental evaluation for a total system and its components. We build benchmark databases of both authentic media and media clones, and open them to the public.

【Expected Research Achievements and Scientific Significance】

This research will realize a safe, reliable, and easy-to-use means of communication even for the aged and infirm. The technologies for generating and recognizing media clones can lead to production of media beyond time, space, and culture, to novel innovations in diverse areas such as media art and medical welfare engineering, and to a paradigm shift in recognizing subtle difference and qualitative change that support the authenticity in media expression. The research is further expected to contribute to the data and open science by systematic collection of diverse media data, as well as to creation of a new academic field that lies in the boundary of media processing, security, and communication.

【Publications Relevant to the Project】

・Y. Nakashima, T. Ikeno, and N. Babaguchi: "Evaluating Protection Capability for Visual Privacy Information," IEEE Security & Privacy, Vol. 14, No. 1, pp. 55-61, 2016.
・N. Babaguchi and Y. Nakashima: "Protection and Utilization of Privacy Information via Sensing," Invited Paper, IEICE Transactions on Information and Systems, Vol. E98-D, No. 1, pp. 2-9, 2015.

【Term of Project】 FY2016-2020

【Budget Allocation】 120,700 Thousand Yen

【Homepage Address and Other Contact Information】

http://www2c.comm.eng.osaka-u.ac.jp/proj/mc/index.html

Title of Project : Systematic Study on Human Response to Noncontact Distributed Haptic Stimulation and Its Applications

Hiroyuki Shinoda
(The University of Tokyo, Graduate School of Frontier Sciences, Professor)

Research Project Number : 16H06303 Researcher Number : 40226147
Research Area : Human interface and interaction
Keyword : Haptics, Human-computer interaction, Virtual reality

【Purpose and Background of the Research】

Non-contact midair haptic display using airborne ultrasound can stimulate any positions on a skin at any moment without constraining human motions, in principle, but currently, only small workspaces of applications have been examined as shown in Figure 1. In this study, we first expand the workspace so that the upper half of a human body can move freely in it. Large areas of airborne ultrasound phased arrays (AUPA) are synchronized and precisely control the force distributions on the body while suppressing acoustic stream and avoiding the occlusion problem. Using the developed system, we systematically clarify the human response to haptic stimulation and apply it to 3D interfaces and communication systems.

Figure 1 Aerial touch panel with haptic feedback

【Research Methods】

In order to realize such a large workspace as shown in Figure 2, we first develop AUPA units that are serially connected and can form large areas of AUPA keeping one-microsecond synchronization.
Using this device, we examine a midair 3D interface where we can handle and shape aerial 3D images with tactile feedback. We also realize human motion guidance by noncontact haptic stimulation in midair, which enables efficient interfaces with less load on vision as well as direct instruction of complex motions.
At the same time, we clarify the emotional effects of haptic stimulation by systematically changing the stimulations with visual/auditory ones in various context. The scientific results enabled by the highly repeatable haptic stimulations are applied to the researches of stress control, extension of perceived body ownership and future communication systems.

【Expected Research Achievements and Scientific Significance】

Midair haptics is a new tool to produce haptic sensation with high repeatability and controllability, free from the conventional problems caused from mechanical contact. The research clarifies the nature of haptics and open up a new field of computer interface and interaction.

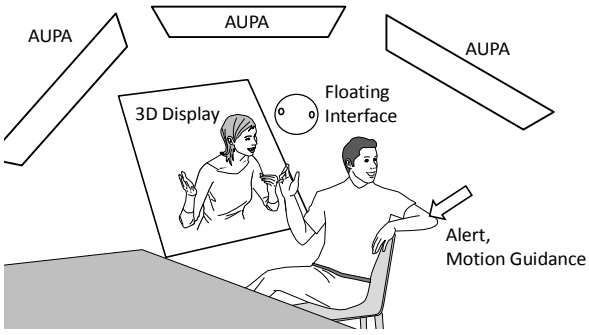


Figure 2 Midair haptics test bench

【Publications Relevant to the Project】

・Y. Monnai, K. Hasegawa, M. Fujiwara, S. Inoue, H. Shinoda, “HaptoMime: Mid-Air Haptic Interactions with a Floating Virtual Screen,” Proc. UIST2014, pp.663-667, 2014.
・Y. Makino, Y. Furuyama, S. Inoue, H. Shinoda, “HaptoClone (Haptic-Optical Clone) for Mutual Tele-Environment by Real-time 3D Image Transfer with Midair Force Feedback,” Proc. CHI 2016, pp. 1980-1990, 2016.

【Term of Project】 FY2016-2020

【Budget Allocation】 130,700 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.hapis.k.u-tokyo.ac.jp/?lang=en

Title of Project : Educational Cloud Platform for Improving Education and Learning by Using Educational Big Data

Hiroaki Ogata
(Kyushu University, Faculty of Arts and Science, Professor
Learning Analytics Center, Director)

Research Project Number : 16H06304　Researcher Number : 30274260
Research Area : Learning Management Systems
Keyword : Learning Analytics, Digital textbook, e-Book, Educational Big Data, Learning Logs

【Purpose and Background of the Research】

This research aims at developing an "educational cloud platform" that enables leaners and teachers to capture teaching and learning activities in both formal and informal learning setting, to organize an educational big data, and to reuse the data for improving teaching and learning processes. We will apply the educational could platform in K12, higher education, and adult learning settings. That is, lifelong learning logs will be accumulated and be provided as an open data. By analyzing the data, "educational data science" will be established.

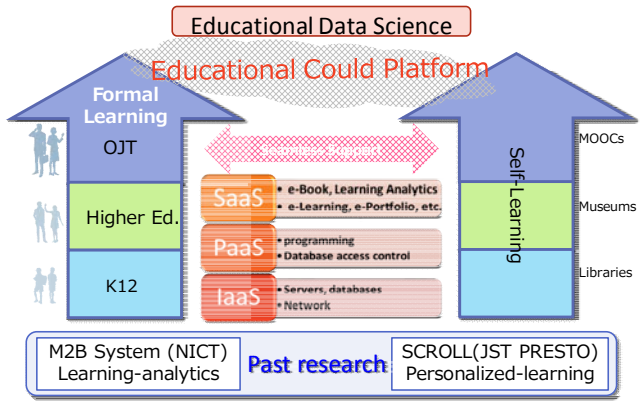


Figure 1　Overview of this research.

【Research Methods】

To improve teaching and learning, we will introduce an educational cloud platform by combining (1) M2B system (called Mitsuba) that consists of a learning management system (Moodle), an e-portfolio system (Mahara), and an e-book system (BookLooper), with (2) SCROLL (System for Capturing and Reuse Of Learning Logs). M2B system has been supported in the line of "Research and Development on Fundamental and Utilization Technologies for Social Big Data" by the National Institute of Information and Communications Technology (NICT). SCROLL is developed by the support of JST PRESTO.

【Expected Research Achievements and Scientific Significance】

In educational technology and learning science research, there is still an unsolved problem, how to construct educational big data, how to use it and how to analyze and evaluate it. This research tackles these issues and lead a research filed called educational data science.

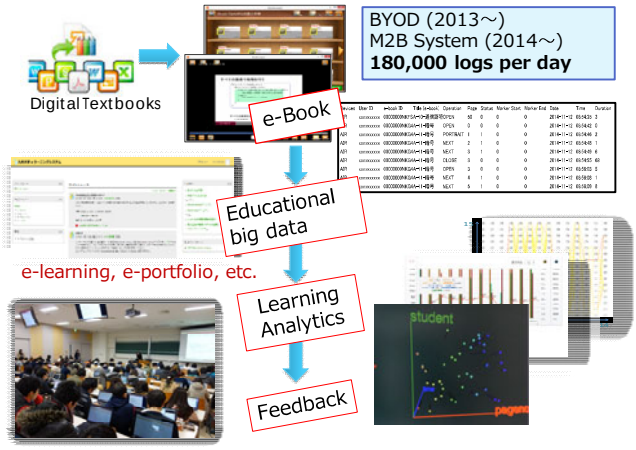


Figure 2　Data flow.

【Publications Relevant to the Project】

・Ogata, H., et al., Ubiquitous Learning Project Using Life-logging Technology in Japan, Educational Technology and Society Journal, Vol.17, No.2, pp.85-100, 2014.
・Ogata, H., et al., Learning Analytics Towards the usage of Educational Big Data, Journal of Japanese Society for Information and Systems in Education, Vol.33, No.2, pp.58-66, 2016.

【Term of Project】 FY2016-2020

【Budget Allocation】 140,900 Thousand Yen

【Homepage Address and Other Contact Information】

http://lac.kyushu-u.ac.jp/members/e_ogata.html
ogata@artsci.kyushu-u.ac.jp

Title of Project : Precise analysis of HOx cycle in the air by novel techniques and new development of oxidants and aerosols chemical dynamics

Yoshizumi Kajii
(Kyoto University, Graduate School of Global Environmental Studies, Professor)

Research Project Number : 16H06305 Researcher Number : 40211156
Research Area : Environmental analysis
Keyword : HOx cycle, Ozone, Oxidants, PM2.5, Air pollution

【Purpose and Background of the Research】

Photochemical oxidants and PM2.5 are one of most important issues of environment. In spite of reductions of ozone precursors ozone abundance still has positive trend in most of area in Japan. Scientific evidence for mitigation strategy of these issues is required. The fact that modeling studies systematically underestimate for prediction of oxidants and secondary organic aerosols (SOA) abundances implies a lacking of scientific understanding for the formation mechanism of these secondary pollutants. For the reduction strategy and precise prediction of these oxidants, further understanding of atmospheric processes is necessary.

In order to explore the cause of underestimation for secondary pollutants, the following sub themes are set as follows, 1.Establishment of the methodology to determine the cycle number of HOx cycle and HOx yields in the ambient air, 2. Determination of productions rates for oxidants driven by HOx cycle, 3.Comparison of production rates between observation and prediction by HOx cycle analysis, 4.Photochemical chamber studies for growth and aging of SOA induced by HOx cycle and establishment of synthetic modeling system for the predictions of these oxidants, 5.Evaluation of the contributions of unknown reactivity for the formation of oxidants and aerosols.

【Research Methods】

Instruments for HO_2 and RO_2 reactivity measurements by laser spectroscopy will be constructed. The yield determination system for OH, HO_2 and RO_2 will be developed. Ozone and UV-lights induced HOx radical production rate measurement system will be constructed. Semi-volatile compounds driven by HOx cycle will be developed. Photochemical chamber studied for growth and aging of SOA and variation of chemical and physical properties induced by HOx cycles will be performed and synthetic modeling system for the prediction of secondary pollutants will be improved. Intensive field study of HOx cycle, semi-volatile compounds, and SOA will be planed in the final year and the theory of HOx cycle system will be tested.

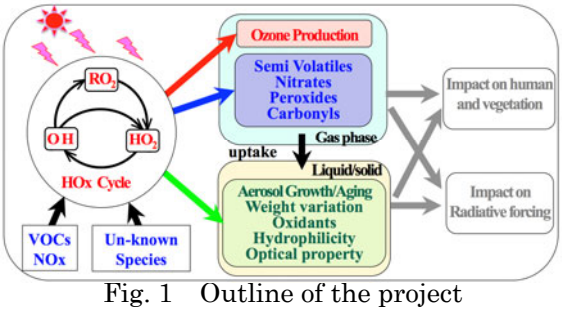


Fig. 1 Outline of the project

【Expected Research Achievements and Scientific Significance】

Quantitative analysis of HOx cycles will be capable and prediction of secondary pollutants such as ozone, organic nitrates and SOA will become more precisely through this project. Understanding of growth/aging processes of SOA induced by HOx cycle is quite important to consider its atmospheric behavior such as its residence time, physical properties.

Since oxidants and SOA are considered to provide significant impact on both human and vegetation and on radiative forcing, prediction of such secondary pollutants will contribute for social demand greatly.

【Publications Relevant to the Project】

A laser-flash photolysis and laser-induced fluorescence detection technique for measuring total HO_2 reactivity in ambient air;□ Miyazaki et al.. *Rev. Sci. Inst.*, 84, 076106 (2013).

【Term of Project】

FY2016-2020

【Budget Allocation】

139,600 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.atmchem.ges.kyoto-u.ac.jp

Title of Project : Establishment of Novel Bioassays for in vivo Genotoxicity Prediction and Mechanism Characterization

Shunichi Takeda
(Kyoto University, Graduate School of Medicine, Professor)

Research Project Number : 16H06306 Researcher Number : 60188191
Research Area : Environmental analyses and evaluation, Risk sciences of radiation and chemicals
Keyword : Toxicology, Toxic chemical compounds

【Purpose and Background of the Research】

Why you must establish a new bioassay to control genotoxic chemical products?

Every developed country requires companies to demonstrate the safety of chemical products before introducing to the market using methods specified by law. The methods of detecting genotoxicity were developed more than 30 years ago, and have the two weaknesses; (i) limited sensitivity and specificity (Ref. *Mutat. Res.* 588:47, 2005), and (ii) no information about the type of DNA lesions, such as DNA-strand breaks, hydrolysis of bases, and crosslink of nucleotides, generated by individual chemicals. The limited sensitivity is due to the usage of DNA-repair-proficient wild-type cells, which is capable of accurately repairing DNA damage caused by genotoxic chemical products.

Requirement of in silico genotoxicity test

A large number of chemicals are in the market without checking their genotoxicity if they had been sold before the law started controlling genotoxic products in 1973. In addition, genotoxicity tests are expensive. Thus, we need *in silico genotoxicity* tests, the computer-based prediction of genotoxicity from the structure of individual chemicals. To this end, you must have the study data that include minimum false-negative and false-positive data. The study data must also include information about the type of DNA lesions, the product of chemical reactions between DNA and genotoxic chemicals.

Purpose of our research

The aim of this research is to solve the above (i) and (ii) problems. To this end, we previously created a novel bioassay using the chicken DT40 cells, and tested its validity in National Institute of Health (NIH), US., using a golden-standard chemical library containing ~10,000 chemicals provided National Toxicology Program in US (see Publications Relevant to the Project).

【Research Methods】

(1) Development of new genotoxicity bioassays using the human TK6 cell line. The usage of the TK6 cell line is recommended by the OECD guideline. Our proposal is to include (a) TK6 mutant clones deficient in individual DNA-repair pathways generated by the gene-editing method, in addition to (b) wild-type TK6 cells for the genotoxicity test. If one of the mutant clones shows a more prominent response, such as higher micronuclei formation, to chemicals than do wild-type cells, we judge the chemicals as genotoxicity-positive. Bioassays with wild-type cells serve as a negative control, and would ensure the high specificity of our genotoxicity test.
(2) We will test the validity of the new bioassay in collaboration with NIH. US.
(3) We will explore novel mutagenic mechanisms.

【Expected Research Achievements and Scientific Significance】

Expected achievement is to significantly improve the current method of detecting mutagenic chemicals. Another achievement is to establish a new method of identifying the type of lesions induced by mutagenic chemicals. Identifying the type of lesions induced by a large number mutagenic chemicals would make the computer learn the quantitative relationship between the structure of chemicals and the type of DNA lesions induced by them.

【Publications Relevant to the Project】

・ Nishihara K, Huang R, Zhao J, Shahane SA, Witt SK, Smith-Roe SL, Tice RR, Takeda S, Xia M. (2016) Identification of genotoxic compounds using isogenic DNA repair deficient DT40 cell lines on a quantitative high throughput screening platform. Mutagenesis 31 (1): 69-81.

【Term of Project】 FY2016-2020

【Budget Allocation】 140,900 Thousand Yen

【Homepage Address and Other Contact Information】

http://rg4.rg.med.kyoto-u.ac.jp/
stakeda@rg.med.kyoto-u.ac.jp

Title of Project : Molecular mechanisms underlying higher-order regulation of DNA damage recognition for nucleotide excision repair

Kaoru Sugasawa
(Kobe University, Biosignal Research Center, Professor)

Research Project Number : 16H06307 Researcher Number : 70202124
Research Area : Risk sciences of radiation and chemicals
Keyword : DNA damage recognition, nucleotide excision repair, xeroderma pigmentosum

【Purpose and Background of the Research】

Genomic DNA is highly susceptible to damage derived from various sources. Nucleotide excision repair (NER) eliminates diverse DNA lesions caused mainly by environmental agents, such as ultraviolet light (UV) and chemical compounds, thereby playing a crucial role in preventing various diseases including cancer.

In mammalian NER, the xeroderma pigmentosum-related factors, XPC and DDB2, recognize and bind to sites of damage and initiate the repair reaction. Although these damage recognition factors exhibit specific binding affinities for damaged DNA *in vitro*, precise molecular mechanisms still remain to be elucidated, by which a relatively small number of lesions can be efficiently recognized *in vivo* within the huge genomic DNA.

This project is aimed to elucidate novel molecular mechanisms underlying higher-order regulation of the intiation step in NER, particularly by focusing on intracellular dynamics and interactions of XPC and DDB2 proteins. This research will contribute to understanding of the molecular basis that enables efficient surveillance of genomic DNA in response to various environmental stresses.

【Research Methods】

This project undertakes three approaches to identify novel factors and molecular mechanisms involved in regulating the initiation of NER; 1) comprehensive identification of interacting partners of XPC and DDB2, 2) search for siRNA and chemical compounds that affect recruitment of XPC or DDB2 to local UV damage (Fig. 1), 3) identification of biochemical activities that stimulate the cell-free NER reaction reconstituted with purified NER factors and damaged DNA substrates organized into chromatin structures. Candidate factors obtained from these approaches will be tested for their functions in NER by up- or down-regulation of their expression. Finally, the underlying molecular mechanisms will be analyzed with the defined cell-free NER system.

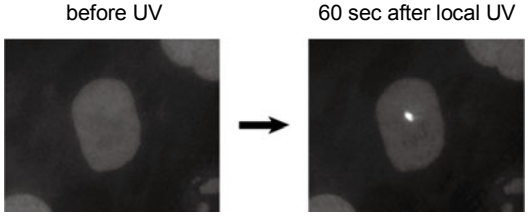


Fig. 1. Visualized accumulation of EGFP-tagged XPC in the area of local UV damage

【Expected Research Achievements and Scientific Significance】

DNA damage recognition is a crucial, rate-limiting step regulating the entire repair process. Identification of novel factors and mechanisms that stimulate this critical step would be expected to lead to enhancement of our intrinsic NER capacity, which will be applied to developing strategies for protection against UV and chemicals, and also for prevention of various diseases including cancer.

【Publications Relevant to the Project】

Akita M, Tak YS, Shimura T, Matsumoto S, Okuda-Shimizu Y, Shimizu Y, Nishi R, Saitoh H, Iwai S, Mori T, Ikura T, Sakai W, Hanaoka F, Sugasawa K: SUMOylation of xeroderma pigmentosum group C protein regulates DNA damage recognition during nucleotide excision repair. Sci. Rep. 5, 10984 (2015).

Matsumoto S, Fischer ES, Yasuda T, Dohmae N, Iwai S, Mori T, Nishi R, Yoshino K, Sakai W, Hanaoka F, Thomä, NH, Sugasawa K: Functional regulation of the DNA damage-recognition factor DDB2 by ubiquitination and interaction with xeroderma pigmentosum group C protein. Nucleic Acids Res. 43, 1700-1713 (2015).

【Term of Project】 FY2016-2020

【Budget Allocation】 133,500 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.research.kobe-u.ac.jp/brce-sugasawa

Title of Project : Comprehensive and systematic study for control/eradication of allergic diseases via environmental and medical approaches

Hirohisa Takano
(Kyoto University, Graduate School of Engineering, Environmental Health Division, Professor)

Research Project Number : 16H06308 Researcher Number : 60281698
Research Area : Environmental Science
Keyword : Allergy/asthma, environment, hygiene, social medicine, immunology

【Purpose and Background of the Research】

Allergic diseases including bronchial asthma, pollinosis, atopic dermatitis and food allergies have been dramatically increasing worldwide, especially in the developed countries and urban areas. Changes in environmental factors, rather than those in genetic factors, are thought to be responsible for the increase in allergic diseases. An increase in environmental pollutants is involved in the recent changes in the environment and is thought to be responsible, at least partly, for the increase in allergic diseases. We have previously reported that environmental pollutants such as diesel exhaust particles, representatives of ambient fine particles (PM2.5), environmental chemicals including plasticizers, and nanomaterials can enhance allergic diseases. To control allergic diseases in modern society, not only medical approach but also environmental approach should be considered, because environmental pollution or pollutants are ubiquitous in our living environment. The aim of our comprehensive and systematic study is to control allergic diseases via environmental and medical approaches.

【Research Methods】

Our systemic study using *in vitro*, *ex vivo*, and *in vivo* procedures will analyze the underlying essential and fundamental mechanisms through which environmental pollutants enhance allergic diseases such as bronchial asthma and atopic dermatitis. Especially, we will focus on the important cells including epithelial cells, antigen presenting cells and a variety of immune cells and their intercellular interactions in the enhancing effects of environmental pollutants. Our targets include brain and bone marrow in addition to local inflammatory sites. Furthermore, we will identify the critical intracellular molecules, cell surface molecules and humoral mediators which play pivotal roles in the important cells and intercellular interactions. On the other hand, we will identify the possible enhancing factors and/or substances for allergic diseases by creating the evaluation system, where test samples will be applied to the *in vivo* evaluation using animal models on the basis of the results in the simple *in vitro* screening test using the identified cells and molecules.

【Expected Research Achievements and Scientific Significance】

We will elucidate the essential and fundamental mechanisms by which environmental pollutants enhance allergic diseases at the original source of biological/immunological responses and cell development/differentiation. Especially, we will identify the critical molecules as the possible targets for the new medicines or the medical approach to allergic diseases under the combined exposure to environmental pollutants and allergens which we usually suffered in daily life. On the other hand, we will identify the possible enhancing factors and/or substances for allergic diseases by testing a variety of environmental samples and consumer products. Finally, we would like to control allergic diseases via environmental and medical approaches.

【Publications Relevant to the Project】

・Takano H, et al.: Diesel exhaust particles enhance antigen-induced airway inflammation and local cytokine expression in mice. ***Am J Respir Crit Care Med*** 156: 36-42, 1997.
・Takano Hirohisa : Sick building syndrome, chemicals and allergies. ***Japan Medical Journal*** 4742: 18-22, 2015.

【Term of Project】 FY2016-2020

【Budget Allocation】 139,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://health.env.kyoto-u.ac.jp/environmental_health_division/index.html

Title of Project : Advanced Interdisciplinary Research on Coastal Areas based on Shallow Seafloor Geomorphology: Development of a Paradigm through 3D Seafloor Mapping

Hironobu Kan
(Kyushu University, Graduate School of Integrated Sciences for Global Society, Professor)

Research Project Number : 16H06309 Researcher Number : 20294390
Research Area : Geography
Keyword : seafloor investigation, geomorphology, coral reef, mapping, environment

【Purpose and Background of the Research】

Coastal zones have always had a close relationship with the human society since the beginning of human civilization. However, there is very little scientific knowledge on coastal areas despite their closeness to human settlements. The coastal seafloor at depths shallower than ~130 m was subjected to alternating subaerial erosion and sedimentation during Quaternary sea-level change. However, the coastal seafloor is rarely discussed in conventional geomorphology.

A wideband multibeam echosounder (MBES: R2Sonic 2022) was introduced to our laboratory through a JSPS Grant-in-Aid for Scientific Research (A) in 2010 to observe high-resolution (1 to 2 m grid size) bathymetry of seafloor from 1 to 400 m depth. Snippet/TruePix options were also embedded in the system to observe backscatter data in 2013. We conducted MBES surveys in Kume, Ishigaki, Kikai and Okinawa Islands in the Ryukyus to develop seafloor geomorphology.

【Research Methods】

In this research, we are planning to introduce a POS/MV to improve accuracy of our bathymetric surveys. We are also planning to create high-resolution coastal map from photography using SfM software. New perspectives and new field of research will be developed through collaborative field research in geomorphology, geology, sedimentology, marine environment, disaster prevention, biology, nature conservation, culture, anthropology, and archaeology.

【Expected Research Achievements and Scientific Significance】

We discovered submerged tropical karst features and abundant living corals in Nagura Bay on Ishigaki Island in the southern Ryukyu Islands, Japan (Kan *et al.* 2015). As reported by the Ministry of Environment, Nagura Bay is believed to be influenced by the influx of a terrestrial red soil and nutrient load induced by land-use change and less coral coverage. Our discoveries suggest that scientific exploration and research are urgently needed in the coastal areas because these areas are prone to development and also easily affected by land development. We expect to make many discoveries during the period of this study and to create a paradigm by improving the evaluation of the coastal seafloor.

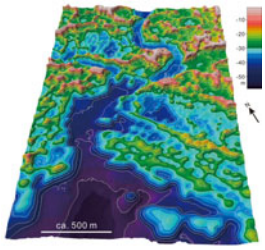


Figure 1 Submerged karst in Nagura Bay

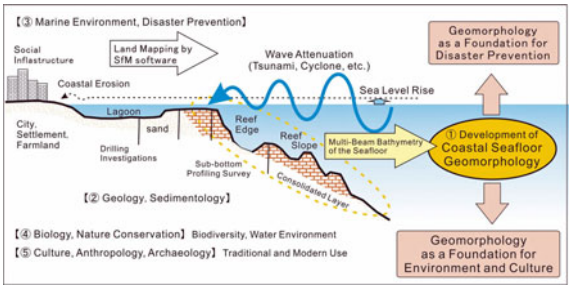


Figure 2 Conceptual diagram of this study

【Publications Relevant to the Project】

Kan, H., Urata, K., Nagao, M., *et al.* (2015) Submerged karst landforms observed by multibeam bathymetric survey in Nagura Bay, Ishigaki Island, southwestern Japan. Geomorphology, 229, 112-124.

Ono, R., Katagiri, C., Kan, H., Nagao, M., *et al.* (2016) Discovery of Iron Grapnel Anchors in Early Modern Ryukyu and Management of Underwater Cultural Heritages in Okinawa, Japan. International Journal of Nautical Archaeology, 45, 75-91.

【Term of Project】 FY2016-2020

【Budget Allocation】 126,600 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.scs.kyushu-u.ac.jp/kan

Title of Project : A challenge to develop GNSS buoy system for high-functional tsunami monitoring and continuous observation of ocean-bottom crustal movements

Teruyuki Kato
(The University of Tokyo, Earthquake Research Institute, Professor)

Research Project Number : 16H06310 Researcher Number : 80134633
Research Area : Tsunami, ocean-bottom crustal movements
Keyword : Tsunami, ocean-bottom crustal movements

【Purpose and Background of the Research】

The research team lead by the Project Leader of this proposal have developed GNSS buoy for monitoring tsunami at coastal area. Given the success of preliminary experiment of precise measurements of sea-surface heights at far offshore, this research plan is proposed, in which we try to conduct operational experiments for high accurate real-time monitoring of sea-surface height measurements at far offshore. In addition, we tackle a new experiment of continuous measurements of ocean-bottom crustal movements using GNSS-acoustic system using the same GNSS buoy. If this experiment is successful, the GNSS buoy system will open a new era of exploring continuous observation of ocean-floor, which will lead to bring us detailed information on inter-plate coupling and its temporal change, process of slow slip events, etc. Moreover, as the GNSS buoy data will be utilized to monitoring troposphere and ionosphere, deployments of GNSS buoy array in the ocean will be a powerful infrastructure for a synthetic disaster mitigation technology.

【Research Methods】

We will rent a fishery buoy off Kochi Prefecture for our experiments. A GNSS system and acoustic transducer, together with apparatus for satellite transmission, will be set on the buoy.

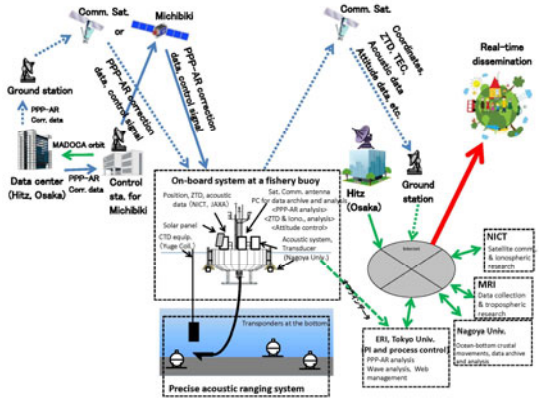


Fig. 1 Detailed design of experiment.

We conduct continuous experiments using satellite communication link. Precise orbits are transmitted from the ground and precise positioning and estimation of ZTD and TEC are conducted on-board of the buoy. Continuous acoustic ranging between buoy and ocean-bottom will also be conducted. Evaluation of data quality will be made as well. Quality of ZTD and TEC data will be examined and their impact to the atmospheric and ionospheric researches will be evaluated. Finally, the final plan of GNSS buoy array in outer ocean and the specification for necessary communication satellite will be documented.

【Expected Research Achievements and Scientific Significance】

A new research developments utilizing the GNSS buoy or buoy array will be expected in the following fields; tsunami including sea-waves, ocean-bottom crustal movements – in particular, related to inter-plate coupling and slow slip events -, atmospheric and ionospheric researches. Moreover, the GNSS buoy array, if it is realized in the future, will be a powerful infrastructure for a synthetic disaster mitigation technology related to the field stated above.

【Publications Relevant to the Project】

Terada, Y., T. Kato, T. Nagai, S. Koshimura, N. Imada, H. Sakaue, K. Tadokoro, Recent developments of GPS tsunami meter for a far offshore observations, in Proceedings of the IAG Symposium GENAH2014, vol. 145, 2015 (in press)

Kato, T., Global Positioning System: Toward the next dream – from the view point of the Japanese University Consortium for GPS Research (JUNCO) -, 59(3), 87-97, 2013. (in Japanese)

【Term of Project】 FY2016-2020

【Budget Allocation】 141,900 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.tsunamigps.com/

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

Integrated Disciplines (Complex Systems)

Title of Project : Dynamical, thermodynamical and cloud-microphysical studies of violent wind and heavy rain-producing tropical cyclones: Quantitative improvement of intensity estimations/forecasts

Kazuhisa Tsuboki
(Nagoya University, Institute for Space-Earth Environmental Research, Professor)

Research Project Number : 16H06311 Researcher Number : 90222140
Research Area : Social/Safety system science, Natural disaster/Disaster prevention science
Keyword : Meteorological disasters, Natural disaster prevention, typhoon, aircraft observation

【Purpose and Background of the Research】

Typhoons are the most devastating weather system. Violent wind and heavy rainfall associated with a typhoon cause huge disaster in East Asia including Japan. In 2013, Supertyphoon Haiyan struck the Philippines caused a very high storm surge and more than 7000 people were killed. In 2015, two typhoons approached the main islands of Japan and severe flood occurred in the northern Kanto region. Moreover, many researches have projected increase of typhoon intensity with the climate change. However, the historical data of typhoon include large uncertainty. In particular, intensity data of the most intense typhoons have larger error after the US aircraft reconnaissance of typhoon was terminated in 1987. Addressing the problem of the typhoon intensity is the main objective of the present study. We perform aircraft observation of typhoon to improve intensity estimation, and also in-situ observation of thermodynamical and cloud-microphysical processes of typhoons to improve numerical model. According to the observational results, intensity estimations and forecasts will be improved.

【Research Methods】

As shown in Fig. 1, we will perform aircraft observations of typhoons. Using dropsondes from the aircraft, temperature, humidity, pressure, and wind are measured in the surrounding region of the typhoon center. The dropsonde data are assimilated to the numerical cloud-resolving model which has been developed in Nagoya University and we make efforts to realize accurate estimations and forecasts of the typhoon intensity as well as typhoon track. Furthermore, we will utilize a ground-based balloon with microscope camera, X-band precipitation radar, Ka-band cloud radar, aerosol sonde, and drone to observed typhoon and associated clouds and precipitation. After the test flight in 2016, typhoon observations will be made for the next 4 years; 2017-2020. The main target area of observation is the south of Okinawa where a typhoon turns.

【Expected Research Achievements and Scientific Significance】

This research will advance aircraft observation technique of typhoon in Japan. The aircraft observation will be the breakthrough to improve typhoon intensity estimations. Assimilation of the aircraft observation data to the cloud-resolving model will improve intensity estimations and forecasts of typhoons. This is the first step for the future advanced aircraft observation and will contribute to prevention or reduction of typhoon disasters.

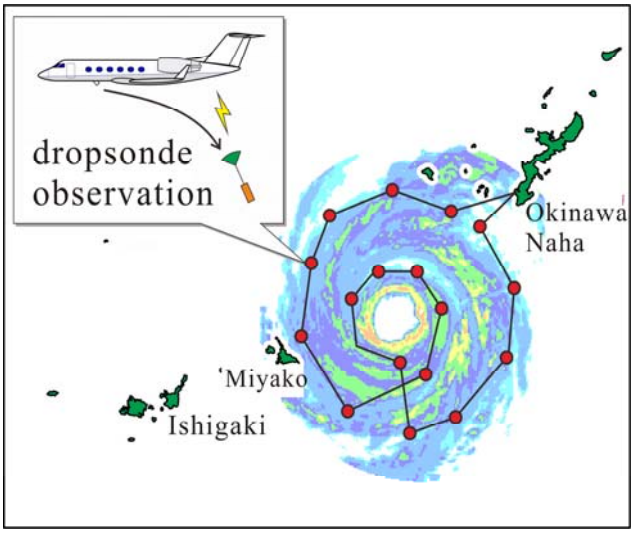


Figure 1 Flight plan for dropsonde observation. Closed circles are positions of dropsonde launch.

【Publications Relevant to the Project】

Tsuboki, K., M. K. Yoshioka, T. Shinoda, M. Kato, S. Kanada, and A. Kitoh (2015), Future increase of supertyphoon intensity associated with climate change, *Geophys. Res. Lett.*, **42**, 646–652, doi:10.1002/2014GL061793.

【Term of Project】 FY2016-2020

【Budget Allocation】 136,600 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.rain.hyarc.nagoya-u.ac.jp/~tsuboki/kibanS/index_kibanS_eng.html

Title of Project : Development of "4-dimensional scaffold system" that integrates signaling factors and 3-dimensional structural biomaterials

Yuichi Tei (Ung-il Chung)
(The University of Tokyo, Graduate Schools of Engineering and Medicine, Professor)

Research Project Number : 16H06312 Researcher Number : 30345053
Research Area : Complex Systems
Keyword : Regenerative medicine/Tissue engineering

【Purpose and Background of the Research】

Recent progress in stem cell biology helps elucidate signaling network for tissue and organ regeneration and also develop delivery system of signaling factors to target cells. In addition, emergence of 3D printer promotes control technology for 3D shape of scaffold materials. However, an individual element is insufficient to realize clinical regeneration; development of the interface that integrates both signaling factors and scaffold materials is essential.

This proposal attempts to develop high-performance hydrogel unit that retains signaling factors to enable their spatial placement and then degrades at desired timing to deliver the signaling factors to target cells. Such hydrogel system integrates signaling factors and scaffold materials to create "4D scaffold system" that controls differentiation and proliferation of local cells in time and space.

【Research Methods】

First, optimize signaling network for bone/cartilage regeneration and delivery of signaling factors in appropriate molality. Second, optimize the performance of scaffold materials for bone/cartilage by controlling 3D shape on various scales. Third, based on hydrogel design/fabrication method studied so far, develop new hydrogel unit that meets 5 demand characteristics for integrating interface of signaling factors and scaffold materials: ①Suppression of gel swelling in aqueous condition; ②Retention of mechanical strength in aqueous condition; ③Control of network size; ④Control of degradation in coordination with degradation; ⑤ Biocompatibility. Then, prototype "4D scaffold system" that enables spatial and temporal control of cell differentiation and proliferation. Forth, implant the prototyped "4D scaffold system" into bone/ cartilage-defect model to test its performance and elucidate detailed mechanism of regeneration.

【Expected Research Achievements and Scientific Significance】

Integration of 3D shape control, signaling network for bone/cartilage regeneration, signal delivery system using high-performance hydrogel unit as an interface to create novel "4D scaffold system". By controlling both timing and 3D location of signal release, construct science and technology platform for precise regulation of differentiation and proliferation of local cells. In addition, using genome-wide analysis, investigate the mechanism of regeneration from molecular biology/epigenome viewpoint, study the interface of scaffold materials and living body, and obtain genome-level molecular basis for practical applications that guarantees efficacy and safety.

This proposal plans to create "4D scaffold system" using high-performance hydrogel unit that integrates scaffold materials and signaling factors and to provide proof of concept in bone and cartilage regeneration. This system may provide versatile science and technology platform for not only regeneration of other organs, but also prevention/diagnosis/treatment of various diseases.

【Publications Relevant to the Project】

Kondo S, Sakai S, Chung U, et al. Reliable hydrogel with mechanical 'fuse link' in an aqueous environment. Adv Mater 27:7407-7411, 2015.
Kanke K, Ohba S, Chung U, et al. Stepwise differentiation of pluripotent stem cells into osteoblasts using four small molecules under serum-free and feeder-free condition. Stem Cell Rep 2:751-760, 2014.

【Term of Project】 FY2016-2020

【Budget Allocation】 126,600 Thousand Yen

【Homepage Address and Other Contact Information】

http:// www.tetrapod.t.u-tokyo.ac.jp/
tei@tetrapod.t.u-tokyo.ac.jp

Title of Project : Development of nanogel hybrid materials for medical application

Kazunari Akiyoshi
(Kyoto University, Graduate School of Engineering, Professor)

Research Project Number : 16H06313 Researcher Number : 90201285
Research Area : Complex Systems
Keyword : Nano-biomaterials

【Purpose and Background of the Research】

Developments of novel biomaterials related to delivery and sustained releases of biologics (such as antibodies, cytokines, nucleic acids, and extracellular vesicles) have become essential in the progress of advanced medical care. The objective of this study is to design novel hybrid gel materials based on nanogels as the building blocks (tectons) for effective utilization of biologics in drug delivery system and tissue engineering. Functional nanogels are constructed by hybrids with biopolymers or metallic/inorganic materials, or extracellular vesicles. A hierarchical gel-biomaterials wherein the structure is controlled from the nano to the macro level were obtained by hybrid nanogel tectonics. The nanogel technology provides a novel method for developing biomaterials whereby spatial and temporal responses can be controlled.

【Research Methods】

The topics of our projects are as folows.
1) Development of functional nanogels and nanogel tectonic materials: design of new glycomaterials as nanogel tectons 2) Construction of nanogel hybrid materials for DDS and tissue engineering: hybrid of nanogel tectonic materials (porous, microspherical, fibrous gel) with proteins, nucleic acids, inorganic / metal nanoparticles, extracellelar vesicles. 3) Nanogel-tectonic materilas for cancer immunotherapy: development of a new nanogel carrier for effective antigen and adjuvant delivery and a nanogel/exosome hybrid that can control the cancer microenvironment.

【Expected Research Achievements and Scientific Significance】

The project proposes a new strategy for designing novel hierarchical hybrid biomaterials as building blocks for functional nanogels (new research field called “Hybrid Nanogel Engineering”). We have successfully developed self-assembled nanogels that prevent irreversible protein aggregation, and can permit sustained release as native form via a chaperone-like mechanism. We believe that our study will be a breakthrough, particularly in the field of protein delivery.

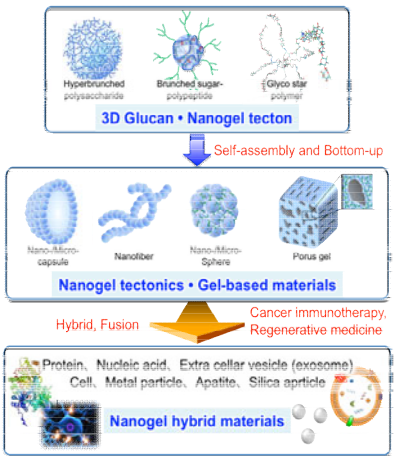


Figure 1 Invention and medical application of nanogel hybrid materials

【Publications Relevant to the Project】

・Tahara Y, Mukai S, Sawada S, Sasaki Y, Akiyoshi K, Nanocarrier-integrated microspheres: Nanogel tectonic engineering for advanced drug delivery systems, Advanced Materials, 27, 5080-5088(2015)
・Hashimoto Y, Mukai S, Sawada S, Sasaki Y,Akiyoshi K, Nanogel tectonic porous gel loading biologics, nanocarriers and sells for advanced scaffold, Biomaterials, 37, 107-115(2015)

【Term of Project】 FY2016-2020

【Budget Allocation】 133,100 Thousand Yen

【Homepage Address and Other Contact Information】

http:// www.akiyoshi-lab.jp

Title of Project : Development of Neo-Bionanocapsules: Drug and Gene Delivery System to Wide Range Tissues with Virus-derived Functional Domains

Shun'ichi Kuroda
(Osaka University, The Institute of Scientific and Industrial Research, Professor)

Research Project Number : 16H06314 Researcher Number : 60263406
Research Area : Drug Delivery System
Keyword : Nanomedicine, Virus, Automated Single-cell Analysis and Isolation System

【Purpose and Background of the Research】

Conventional synthetic nanocarriers for drug delivery system (DDS) have hardly accomplished to harbor the following three functions simultaneously: *in vivo* active targeting ability, stealth ability for escaping from immune system, and cell entering ability. We have focused on hepatitis B virus (HBV) envelope L protein, indispensable for human liver-specific infection, and then generated bio-nanocapsule (BNC) by expressing L protein in yeast cells. So far, we have demonstrated that BNC functions as a human liver-specific DDS nanocarrier by the above three abilities in the ectodomain of L protein (Figure 1).

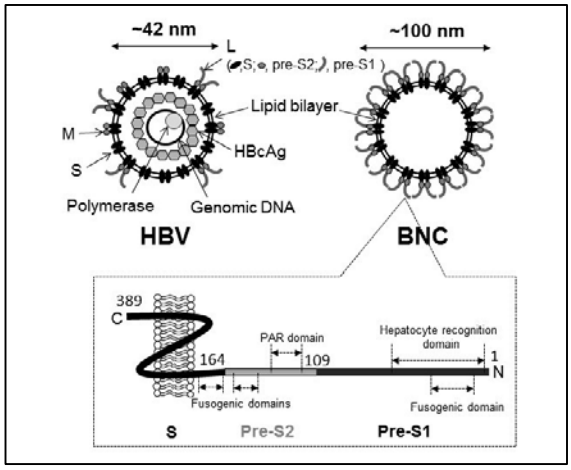


Figure 1 HBV, BNC, and Their Domains

Considering the use of BNC as a forthcoming DDS nanocarrier in clinical sites, it is very hard to produce BNC under current good manufacturing practice (GMP), because BNC is a hybrid of chemical drug and biological drug. In this project, we will reconstitute the above three abilities on the conventional synthetic DDS nanocarriers (e.g., liposomes, nanomicelles) by using chemically defined materials exclusively.

【Research Methods】

In FY2016, we will develop short peptides exhibiting stealth ability and cell entering ability, which show equal activity of HBV. Meanwhile, we will establish affibodies recognizing various tissues and cells (including cancers) specifically by using an automated single-cell analysis and isolation system (our original robot). After FY2017, we will elucidate the mechanism how the peptides with stealth ability and cell entering ability work on the molecular basis. Furthermore, we will optimize the immobilization of affibody, stealth peptide, and cell entering peptide on the conventional synthetic DDS nanocarriers by the realtime observation under high-speed atomic force microscopy (our original method). Finally, we will obtain versatile "Neo-BNC" consisting of chemically defined materials exclusively, which harbors stringent and strong *in vivo* active targeting ability, strong stealth ability without using polymers, and efficient cell entering ability.

【Expected Research Achievements and Scientific Significance】

Neo-BNC will contribute to the development of forthcoming nanomedicines as a platform technology. Especially, the issues occurred in current RNA medicines will be addressed.

【Publications Relevant to the Project】

Nanoparticles for the Delivery of Genes and Drugs to Human Hepatocytes. Yamada T, et al., Nature Biotechnol. 21 (2003) 885-890.
Development of a Virus-mimicking Nanocarrier for Drug Delivery Systems: The bio-nanocapsule. Somiya M, and Kuroda S. Adv. Drug Delivery Rev. 95 (2015) 77-89.

【Term of Project】 FY2016-2020

【Budget Allocation】 139,100 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.sanken.osaka-u.ac.jp/labs/smb/
skuroda@sanken.osaka-u.ac.jp

Title of Project : Dynamic structure and domain formation of membrane lipids in model bilayer systems

Michio Murata
(Osaka University, Graduate School of Science, Professor)

Research Project Number : 16H06315 Researcher Number : 40183652
Research Area : Complex systems
Keyword : Conformational mobility, domain structure, lipid bilayer, sphingomyelin, lipid rafts

【Purpose and Background of the Research】

Lipid-lipid and lipid-protein interactions have been recently revealed to play key roles in cell physiology such as signal transduction and substance transportation. Because lipids are highly flexible molecules, the elucidations of their 3D structures surrounding membrane proteins and self-assembly called 'lipid rafts' are extremely difficult even with the use of X-ray and NMR. We have studied to elucidate the active structure of lipids in and around proteins by using solid-state NMR techniques combined with ultrahigh-resolution X-ray crystallography, organic synthesis and protein engineering. This breakthrough is expected to advance our knowledge in biological and biomedical sciences over the next decade, and also contribute the researches and developments for medical and pharmaceutical applications.

【Research Methods】

a) Conformation of lipid molecules in lipid rafts: The pair of ^{2}H and ^{13}C is site-specifically introduced to a fatty acyl chain. Magnetic dipole-dipole interaction is determined by REDOR, which provides the mobility and orientation of a labeled segment that has not been obtainable from conventional ^{2}H NMR. In addition, we focus on saponin aglycone mimicking the Cho structure to evaluate structural factors that are responsible for Cho-ordering effects.

b) Lipid molecules in rafts in atomic resolution molecular interaction: we attempt the direct observation of molecular interactions using solid state NMR. A ^{13}C-^{15}N pair in the SM amide induces greater relaxation, by which the correlation time can be determined with much higher precision. Correlation time and domain size as experimental data are compared with those from molecular simulation results.

c) Interactions between proteins and lipids: Bacteriorhodopsin (bR) as a model membrane proteins is used for investigating lipid-protein interactions. We try to establish a methodology to evaluate the conformation of surrounding lipids based on molecular dynamics simulations (Figure 1) and NMR measurements of a biomembrane model containing integral proteins.

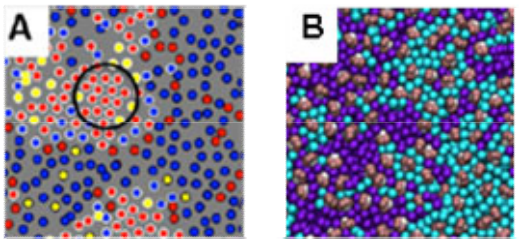


Figure 1. Molecular simulations of raft domains by two groups. Red in A and cyan in B are raft lipid molecules to segregate from the other lipids (the circled lipids is forming raft-like structure).

【Expected Research Achievements and Scientific Significance】

The molecular mechanism underlying the selective recruitment of proteins to lipid rafts plays an important role in the intracellular signal transduction. By this research, a deeper understanding of lipid-protein interactions could be achieved and the structure and functions of lipids in biological membranes would help promote the understanding of the molecular basis of biological membranes, and eventually lead to drug discovery and diagnostic development.

【Publications Relevant to the Project】

・Nakagawa, Y., Umegawa, Y., Tsuchikawa, H., Hanashima, S., four coauthors、Murata, M. *Biochemistry* (2016). Published online.
・Matsumori, N.; Yamaguchi, T.; Maeta, Y.;Murata, M. *Biophys. J.* 108(12), 2816-2824 (2015).

【Term of Project】 FY2016-2020

【Budget Allocation】 140,600 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.chem.sci.osaka-u.ac.jp/lab/murata/
murata@chem.sci.osaka-u.ac.jp

Title of Project : Integrative Biology of Autism Spectrum Disorder

Toru Takumi
(RIKEN, Brain Science Institute, Senior Team Leader)

Research Project Number : 16H06316 Researcher Number : 00222092
Research Area : Brain Sciences
Keyword : Autism, CNV, Cell model, Neural circuit, Brain gut axis

【Purpose and Background of the Research】

Psychiatric diseases were thought to be psychologically disturbed without any morphological abnormality in the brain and different from neurological diseases. However, recent advance in neuroscience provides a general concept of mental diseases as a biological disorder that is equivalent to other neurological and complex diseases. The same or similar pathological mechanisms as other diseases may underlie at the spine/synapse where classical neuropathology was unable to reach and detect its anomaly.

In Japan autism spectrum disorders (ASD) has been mainly studying in an aspect of educational psychology such as how to educate kids with autisms. Now research on ASD can lead the field on neuropsychiatric disorders as a spectrum, partly because the genetic contribution of ASD is higher than that of other psychiatric diseases.

We generated a mouse model for human chromosome 15q11-q13 duplication by using a chromosome-engineering technique based on Cre-loxP system as the first CNV (copy number variant) mouse model of ASD. The duplication of 15q11-q13 is the most frequently associated with cytogenetic abnormality of ASD. Recent advance in genome science has provided thousands of CNV and hundreds of those closely linked to ASD.

【Research Methods】

(Cell, Synapse) We have developed a next-generation chromosome engineering technique using CRISPR/Cas9 system. Using the next-generation chromosome engineering technique, we develop ES cell models with CNV seen in ASD. After neural differentiation from ES cells, we characterize them by transcriptome analysis such as RNA-seq and by morphological analysis.

(Circuit, Behavior) We examine neural circuits for social behavior by using virtual reality system or in vivo freely moving mice combined with optogenetics.

(Environment) To see brain-gut axis, we examine microbiota of patients with ASD and mouse model of ASD.

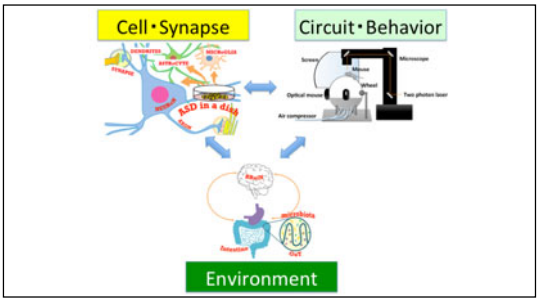


Figure 1 ASD

【Expected Research Achievements and Scientific Significance】

This study consists of three different approaches. PI attempts to understand the complex ASD pathophysiology by combination of the results of these different approaches.

Research achievements by this study will be expected not only to develop new diagnosis and treatment of ASD but also to contribute the understanding of social brain development.

【Publications Relevant to the Project】

・Nakatani, J., et al. Abnormal behavior in a chromosome-engineered mouse model for human 15q11-13 duplication seen in autism. ***Cell*** 137, 1235-1246, 2009.
・Isshiki, M., et al. Enhanced synapse remodeling as a common phenotype in mouse models of autism. ***Nat. Commun.*** 5, 4742, 2014.

【Term of Project】 FY2016-2020

【Budget Allocation】 139,200 Thousand Yen

【Homepage Address and Other Contact Information】

http:// takumi.brain.riken.jp

Title of Project : Neural circuit mechanisms controlling social conflicts

Hitoshi Okamoto
(RIKEN, Brain Science Institute, Deputy Director and Senior Team Leader)

Research Project Number : 16H06317 Researcher Number : 40183769
Research Area : Basic and Social Brain Science
Keyword : Social conflict, habenula, zebrafish, mouse, interpeduncular nucleus

【Purpose and Background of the Research】

All vertebrates fight among conspecifics for larger territories or better reproductive partners. Such social conflicts terminate not by killing of the loser but when one of the fighting pairs surrenders and both fighting animals accept the dominant-subordinate relationship between them. Until now, nothing has been known as to how the termination of social conflicts is regulated. We have obtained the evidence supporting that the two adjacent neural circuits connecting the habenula (Hb) to the interpeducular nucleus (IPN) are deeply involved in the regulation of this process. In this study, based on such discovery of our own, we will elucidate the neural mechanisms regulating the decision of the winner-loser relationship in the social conflicts of the vertebrates.

【Research Methods】

The lateral and medial subnuclei of the dorsal habenula in the zebrafish are evolutionary homologs of the dorsal and ventral subnuclei of the medila habenula, respectively. In this study, we use both zebrafish and mouse by taking advantage of this evolutionary conservation. We will also use various cutting-edge technology such as genetic manipulation, optogenetics and neural activity imaging to elucidate the functions of the neural pathways including the Hb-IPN connections in the regulation of the social conflicts.

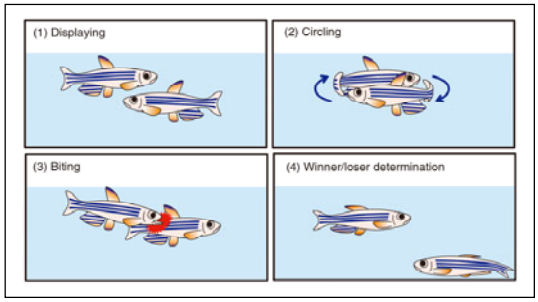


Figure 1 Social conflict of two male zebrafish

【Expected Research Achievements and Scientific Significance】

Social conflicts are common in any animals including human beings. It is also common between animals and humans that the losers defeated in the social conflicts increase the probability of loss in the successive fights. Therefore, the knowledge obtained through our study will cast important insights into human social behaviors and give clues for the treatment of the behavioral disorders such as social shut-in.

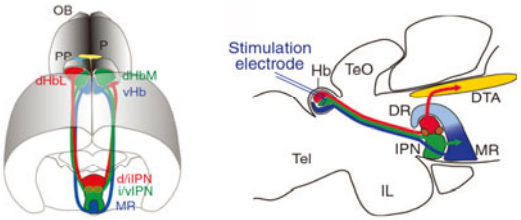


Figure 2. The habenulo-interpeduncular pathways and their efferents.
dHbL & dHbM, lateral and medial subnucleus of the dorsal habenula; vHb, ventral habenula; d/i/v IPN, dorsal/intermediate, ventral interpeduncular nucleus; MR & DR, medial and dorsal raphe; OB, olfactory bulb; P, pineal gland; PP, parapineal gland; Tel, telencephalon; IL, inferior lobe of the hypothalamus; TeO, optic tectum; DTA,

【Publications Relevant to the Project】

・Chou M, Amo R, Kinoshita M, and **Okamoto H** et al. (2016) Social conflict resolution regulated by two dorsal habenular subregions in zebrafish. Science 352:87-90
・Amo R, Fredes F, Kinoshita M, and Okamoto H et al. (2014) The habenulo-raphe serotonergic circuit encodes an aversive expectation value essential for adaptive active avoidance of danger. Neuron, 84:1034-1048.
・Agetsuma M, Aizawa H, and Okamoto H. et al. (2010) The habenula is crucial for experience-dependent modification of fear responses in zebrafish. Nat Neurosci. 13:1354-1356.

【Term of Project】 FY2016-2020

【Budget Allocation】 142,900 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.brain.riken.jp/jp/faculty/details/37