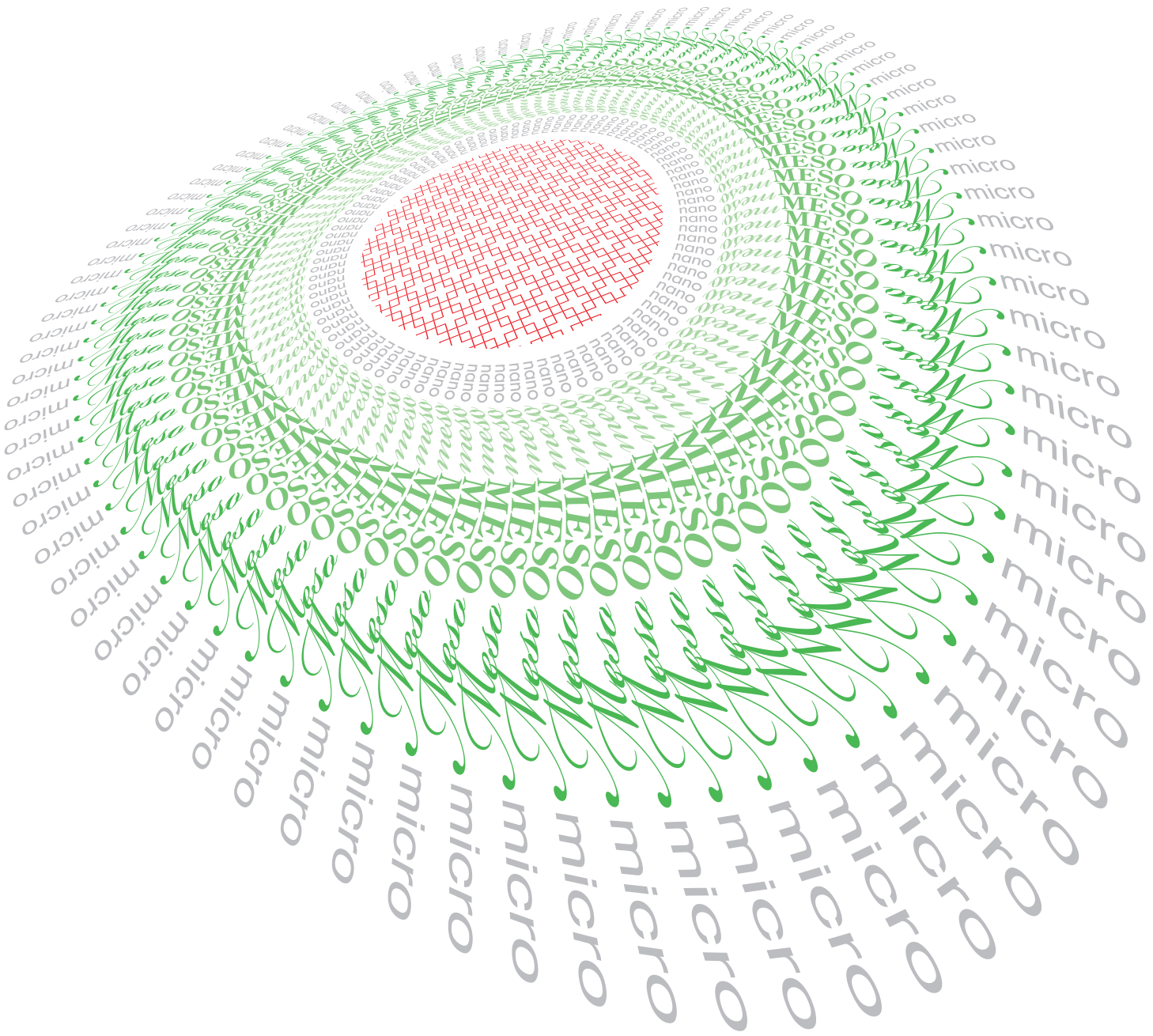

iCeMS
KYOTO UNIVERSITY
WPI Research Center

Institute for Integrated
Cell-Material Sciences

KYOTO UNIVERSITY
FOUNDED 1897
KYOTO JAPAN

wpi
World Premier International
Research Center Initiative

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From the Director

The Institute for Integrated Cell-Material Sciences (iCeMS) at Kyoto University was established in October 2007 as one of the World Premier International Research Center Initiative (WPI) centers, which together aim to forge a new model for scientific institutions to advance leading edge research, create new interdisciplinary domains, establish truly international research environments, and reform existing research organizations.

Here in Kyoto, we have so far successfully achieved three important aims of the WPI initiative. The first is the highest level of research and science. For example, we have had 547 research papers published during our first 4 years, 70 in leading journals with an impact factor of 10 or more. The second is internationalization. As many as 30% of our scientists are from various countries around the world. English is the official language for meetings and official communications. Additionally we have an extensive and growing network of international partner institutions, with which we are actively exchanging scientists, organizing joint symposia, and establishing mutual satellite laboratories.

Third is the promotion of interdisciplinary fields. Our founding concept is the **integration of cell and material sciences**, providing the potential for a wide variety of novel research and innovation. Among these, we are particularly channelling our efforts into the rapidly growing area of **stem cell science and technology**, along with building on our pioneering work in the new, developing field of **mesoscopic science and technology**. Our current work has already produced ground-breaking, internationally recognized results, with such cross-disciplinary research anticipated to lead to innovations in medicine, pharmaceuticals, the environment, and industry.

We have succeeded in developing many new methods and approaches through productive collaboration between cell and material scientists. These include chemical probes and synthetic transcription factors for stem cell research, imaging probes and devices relevant to next-generation cell biology, and functional porous coordination polymer (PCP) materials for controlled release of bioactive molecules. We now aim to advance the biological and material sciences by applying such novel methods and approaches. Particular emphasis is placed on advancement of stem cell science and technology, investigation of cellular mesoscopic architectures and functions, and creation of smart materials inspired by cellular mesoscopic architectures and functions.

Finally, I consider our most important aim to be the establishment of an institution attracting the best young scientists from around the world, where superb, cross-disciplinary, integrated research will flourish and the great researchers of tomorrow can be trained and nurtured.

These future scientific leaders must possess not only specialized research skills and scientific excellence, but they must also have broad knowledge and wisdom to make the best decisions for society as a whole. They will face numerous problems present and emerging around the world. Hence our institute seeks to have its researchers acquire communication skills and social literacy to work together with other disciplines and society at large, along with maintaining the highest level of our own scientific, ethical, and social integrity. We consider it our mission to identify the role that scientists should play in this restless world, and train ourselves and future scientists to exercise sound judgment accordingly.

October 2011

Norio Nakatsuji

Director
Institute for Integrated Cell-Material Sciences,
Kyoto University

WPI Initiative

Launched in 2007 by the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) in order to establish globally visible research centers, the WPI program seeks to 1) advance leading edge research, 2) create new interdisciplinary domains, 3) establish truly international research environments, and 4) reform existing research organizations.

wpi World Premier International Research Center Initiative

The MEXT grants average ¥1.4 billion (approximately US$14 million) annually per center over 10–15 years, and interim evaluations are conducted at 5-year intervals. Each center is required to meet the following global visibility criteria: 1) 10–20 world-class principal investigators, 2) over 30% overseas researchers, and 3) a staff of over 200 total.

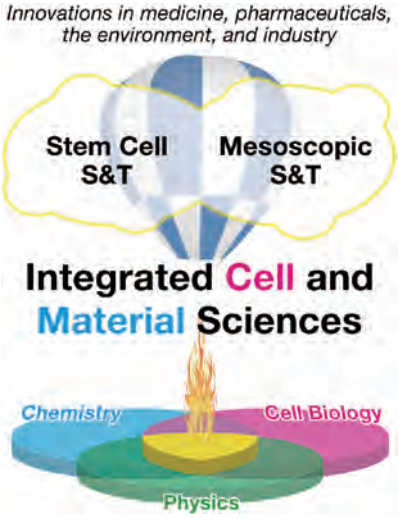
WPI research centers (as of Sep 2011)

- Advanced Institute for Materials Research (AIMR), Tohoku University
- Institute for the Physics and Mathematics of the Universe (IPMU), Todai Institutes for Advanced Study, The University of Tokyo
- Institute for Integrated Cell-Material Sciences (iCeMS), Kyoto University
- Immunology Frontier Research Center (IFReC), Osaka University
- International Center for Materials Nanoarchitectonics (MANA), National Institute for Materials Science
- International Institute for Carbon-Neutral Energy Research (I^2CNER), Kyushu University

Research Areas and Objectives

The iCeMS aims to create new cross-disciplinary fields through the **integration of cell and material sciences**.

Investigating the control mechanisms of multimolecular structures within cells and artificial materials, the iCeMS pioneers the development of **stem cell science and technology and mesoscopic science and technology**. These are anticipated to lead to **innovations in medicine, pharmaceuticals, the environment, and industry**.



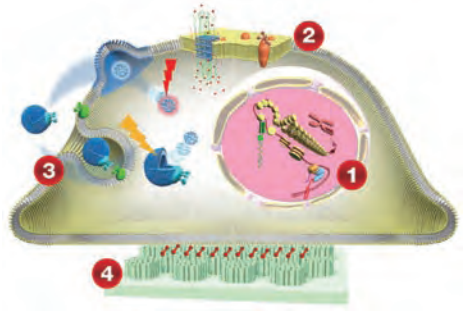
Mesoscopic domains lie between 1 nm and 1 μm, a realm where materials and life meet and interact. Physicists explore this domain using “mesoscopic physics”. We seek to expand this research area by developing “mesoscopic sciences”, a truly interdisciplinary study applying physics, chemistry, and cell biology.

Stem cell science and technology include:

1. Reprogramming with chemical compounds for iPS cell derivation
2. Chemical probes for stem cell research
3. Control of ES/iPS cell growth and differentiation with chemicals and materials
4. Creation and applications of stem cell-derived model cells in medicine and drug discovery

Mesoscopic science and technology include:

1. Imaging and probing meso-complexes in living cells
2. Production of functional mesoscopic materials, including porous coordination polymers (PCPs)
3. Integration of mesoscopic materials and living cells
4. Modeling, simulation, and physics theories of mesoscopic events in materials and living cells



❶ Chromatin architecture/function
➢Gene expression control with bio-functional chemicals/materials

❷ Cell membrane architecture/function
➢Ion channel/transporter/receptor with bio-functional chemicals/materials

❸ Intracellular delivery of bio-functional materials
➢Control by external signals

❹ Cellular environment architecture/function
➢Nano/meso/micro-engineered materials with bio-functional molecules

Timeline

2007	**Sep. 12**	The iCeMS is selected for the World Premier International Research Center (WPI) Initiative by the Ministry of Education, Culture, Sports, Science and Technology (MEXT).
	Oct. 1	The iCeMS is established at Kyoto University with Prof. Norio Nakatsuji as founding director.
2008	**Jan. 22**	The Center for iPS Cell Research and Application (CiRA) is established under the auspices of the iCeMS with Prof. Shinya Yamanaka as founding director.
	Feb. 19	iCeMS inauguration ceremony held at the Kyoto University Clock Tower Centennial Hall.
	Apr. 28	New iCeMS laboratory opened on the Katsura Campus of Kyoto University.
2009	**Mar. 3**	The Center for Meso-Bio Single-Molecule Imaging (CeMI) is established within the iCeMS with Prof. Akihiro Kusumi as founding director.
	Apr. 28	iCeMS Complex 1 opening ceremony held at the iCeMS Main Building.
	Jun. 26	iCeMS Gifu University Satellite opening ceremony.
	Nov. 1	Chemical Screening Center opened in the Main Building.
2010	**Apr. 1**	The Center for iPS Cell Research and Application (CiRA) is re-established as a sibling institute to the iCeMS with Prof. Shinya Yamanaka as founding director.
	Dec.17	India's Tata Institute for Fundamental Research's National Centre for Biological Sciences (NCBS) and the Institute for Stem Cell Biology and Regenerative Medicine (inStem) Satellite Laboratory opening ceremony held at the iCeMS.
2011	**Apr. 17**	iCeMS Satellite Laboratory opening ceremony held at the NCBS-inStem in Bangalore.

Management

According to the principles of the WPI program, the iCeMS is implementing a new system of management which is unprecedented for a Japanese university.

Management Reform Initiatives

- Rapid, institute director-centered decision-making process
- An Executive Board, Board of PIs, and committee structure supporting the director
- A pay scale not based solely on seniority
- Hiring not limited by the retirement age

Initiatives Aimed at Meeting International Standards

- Establishment of the Internationalization Committee
- Use of English as the official language
- Global staff recruitment and over 30% non-Japanese researchers
- Strengthening of International Public Relations and Overseas Affairs and Planning staff
- Establishment of the Overseas Researchers Support Office
- Over 50% English-speaking administrative staff
- Active exchange with many overseas partner institutions
- Active overseas outreach via the Institutional Program for Young Researcher Overseas Visits
- iCeMS Seminars regularly conducted by noted international researchers (approx. 30 annually)

Promoting Ground-Breaking, Cross-Disciplinary Research

- 18 world-class principal investigators (PIs)
- iCeMS Kyoto Fellow (junior PI) positions
- Strategic Committee for Cross-Disciplinary Research
- Facilities Management Committee and the implementation of open offices and shared laboratories
- A research environment including break areas designed to promote active exchanges across disciplines
- Promotion of cross-disciplinary research through the common use of large facilities, such as apparatuses in the Center for Meso-Bio Single-Molecule Imaging (CeMI)
- A Cross-Disciplinary Seminar series
- International symposia (approx. 3 annually)
- Exploratory Grants for Junior Investigators, promoting cross-disciplinary research among young iCeMS scientists
- Support for collaborative projects with other young Kyoto University researchers via the iCeMS Cross-Disciplinary Research Promotion Project

Other Efforts

- Development of science communication theory hand-in-hand with an active outreach program
- Development of innovation management theory coupled with a vigorous public and private sector linkage effort
- Establishment of the hESC Ethics Committee
- English-language workshops on obtaining competitive grants

Organization Chart

As of April 2012

Executive Board


Norio Nakatsuji
Director


Susumu Kitagawa
Deputy Director


Koichiro Tanaka
Chairman of the Board of PIs


Shinji Tomita
Administrative Director

Principal Investigators (PIs)


Konstantin Agladze


Yong Chen


Mitsuru Hashida


Takashi Hiiragi


Hiroshi Imahori


Mineko Kengaku


Makoto Kiso
Gifu Univ Satellite


Susumu Kitagawa


Norio Nakatsuji


Hiroshi Sugiyama


Kazumitsu Ueda


Motonari Uesugi


Yoshie Harada
CeMI Director


John Heuser


Akihiro Kusumi


Koichiro Tanaka

Center for Meso-Bio Single-Molecule Imaging (CeMI)


Shinya Yamanaka
CiRA* Director

**Kyoto University Center for iPS Cell Research and Application*


Mikio Takano**

***Program-Specific Research Center Professor*

iCeMS Kyoto Fellows (Junior PIs)


Peter Carlton


Ziya Kalay


Franklin Kim


Tatsuya Murakami


Takuya Yamamoto
CiRA PI

iCeMS Associate Kyoto Fellows


Kaoru Sugimura


Dan Ohtan Wang

NCBS-inStem Satellite Lab


Kenichi Suzuki

Innovation Management


Shintaro Sengoku

Science Communication


Kazuto Kato

Administration

Management Strategy Division: Takashi Kawahara, Deputy Admin Director

General Affairs	Finance	Funding Management	Facilities and Environment
Kohta Noda	Takashi Kawahara	Shunji Ohi	Sadako Katayama

International Strategy Division

International Public Relations	Overseas Affairs and Planning	Research Planning	IT Strategy
Yutaka Iijima	Daisuke Yamada Overseas Researchers Support	Takashi Asada hESC Research Ethics Committee Support	Yoshitaka Morimura

Adjunct Professors (Kyoto University)

- Kazunari Akiyoshi (Grad Sch Eng)
- Itaru Hamachi (Grad Sch Eng)
- Hiroshi Kageyama (Grad Sch Eng)
- Ryoichiro Kageyama (Inst Virus Rsch)
- Hiroshi Kitagawa (Grad Sch Sci)
- Hidetoshi Kotera (Grad Sch Eng)
- Michiyuki Matsuda (Grad Sch Bio/Med)
- Yasuo Mori (Grad Sch Global Env/Eng)
- Mitinori Saitou (Grad Sch Med)
- Takashi Shinohara (Grad Sch Med)
- Masahiro Shirakawa (Grad Sch Eng)

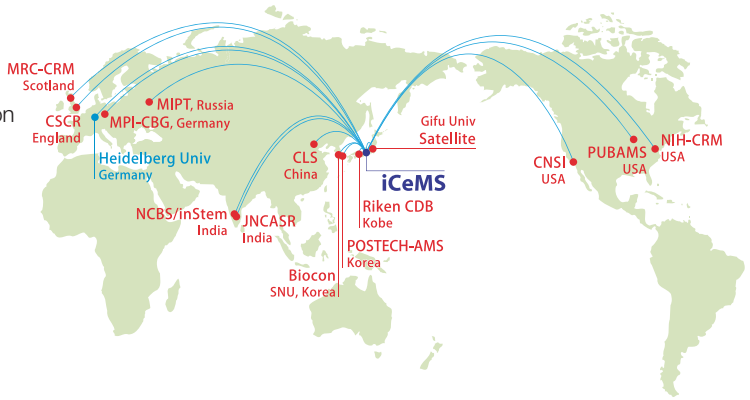
Advisory Committee

- Barbara Baird (Cornell University)
- Daniel Choquet (Université de Bordeaux 2)
- Mark Haw (The University of Strathclyde)
- Eng-Hin Lee (The University of Singapore)
- Keiji Morokuma (Kyoto University)
- Noriko Osumi (Tohoku University)
- Kenneth R. Poeppelmeier (Northwestern University)
- Ferdi Schüth (Max-Planck-Institut für Kohlenforschung)
- Fiona Watt (The University of Cambridge)

Partner Institutions & Satellite

The iCeMS enriches its research through close contact with the following domestic and international partners:

- Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR)
- Max Planck Institute of Molecular Cell Biology and Genetics (MPI CBG)
- Moscow Institute of Physics and Technology (MIPT)
- National Centre for Biological Sciences (NCBS), India
- Institute for Stem Cell Biology and Regenerative Medicine (inStem), India
- NIH Center for Regenerative Medicine (NIH CRM)
- Peking University and Tsinghua University Center for Life Sciences (CLS)
- Pohang University of Science and Technology Division of Advanced Materials Science (POSTECH AMS)
- Purdue University Center for Basic and Applied Membrane Sciences (PUBAMS)
- Riken Center for Developmental Biology (CDB)
- Seoul National University Medicinal Bioconvergence Research Center (Biocon)
- The University of Edinburgh MRC Centre for Regenerative Medicine (MRC CRM)
- UCLA California Nanosystems Institute (CNSI)
- University of Cambridge Wellcome Trust Centre for Stem Cell Research (CSCR)
- **Satellite at Gifu University**



Institutional Program for Young Researcher Overseas Visits

With support from the Japan Society for the Promotion of Science (JSPS), the iCeMS funds two initiatives intended to assist scientists seeking to expand their future career possibilities. During their time overseas, participants are also expected to act as evangelists for the iCeMS.

(1) Long-Term:

International Seminar Tour Mainly for Senior Lecturers and Assistant Professors

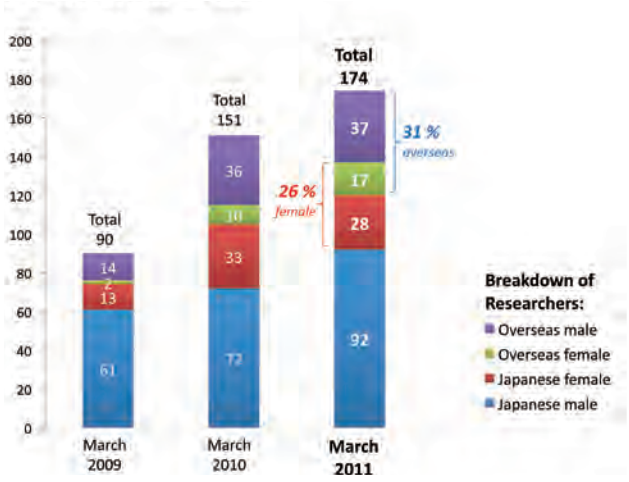
4–7 researchers annually, 2–3 month overseas stays each, for the purpose of promoting collaborative work and building networks. Supporting those seeking to become truly global scientists by planting and nurturing the seeds of international cooperation.

(2) Short-Term:

Overseas Interview Tour Mainly for Research Associates and Graduate Students

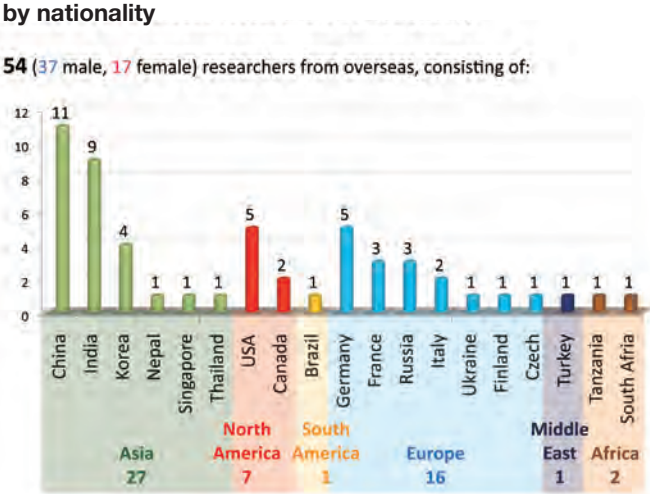
6–9 researchers annually, 2–3 week overseas stays each, for the purpose of an interview tour to enhance future overseas job prospects. Participants receive thorough pre-departure presentation training as well as post-return debriefings.

Breakdown of researchers



Breakdown of overseas researchers by nationality

As of March 2011



Konstantin Agladze Lab

Biophysics, Non-Linear Science

Faculty Members

Konstantin Agladze (Professor)

Nobuyuki Magome (Assistant Professor)

Research Overview

Our highly diverse group of researchers includes biophysicists, chemists, biochemists, material scientists, as well as computational scientists, advancing the interdisciplinary field of physics and **bio-physics** of **excitable** and **self-organizing systems**. Special attention is paid to the mechanisms of **transition to a chaotic state** in cardiac tissue, which might be lethally dangerous. Understanding how a heart can lose its orchestrated function allows for the development of efficient methods to **fight cardiac arrhythmia**. As a rule, the precursors of such a dangerous state in the heart muscle are rotating **spiral waves** or **reentries**. Currently, the following four directions of study are being developed:

1. Study of fundamental mechanisms of reentry (or spiral waves) originating in the heart based on the **curvature-related failure** of the propagating wave.

2. Development of a novel method for controlling cardiac activity based on **reversible sensibilization** of voltage-gated ion channels of cardiomyocytes to **light** and subsequent **meso-scale changes** in **membrane-protein complexes** responsible for cardiomyocytes functioning.

3. Development of **nanofiber-based scaffolds** for **cardiac tissue engineering** employing a meso-scale approach in investigation of single-cell and single-fiber attachment. These scaffolds will allow us to construct functional artificial cardiac tissue patches with **well-controlled structures**.

4. Study of **interaction** and **common network formation** of **primary** culture cardiomyocytes with cardiomyocytes descended from **pluripotent stem cells**, as a generic experimental model for cardiac tissue repair.

Selected Papers

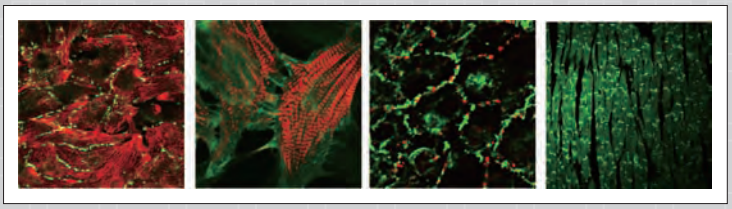
Orlova, Y., Magome, N., Liu, L., Chen, Y., and Agladze, K., "Electrospun nanofibers as a tool for architecture control in engineered cardiac tissue", *Biomaterials,* **32**, 5615–24 (2011).

Magome, N., Kanaporis, G., Moisan, N., Tanaka, K., and Agladze, K., "Photo-Control of Excitation Waves in Cardiomyocyte Tissue Culture" *Tissue Eng Part A,* in press.

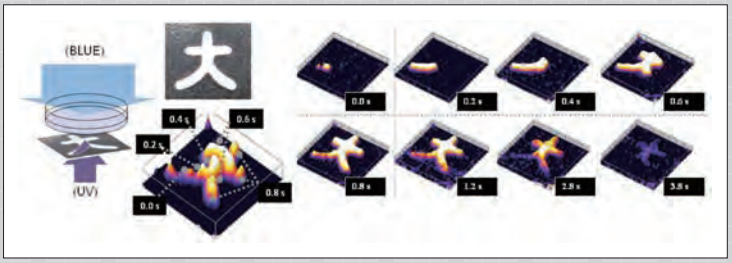
Erofeev, I.S., Magome, N., and Agladze, K., "Digital photo-control of the network of live excitable cells", *J. Exp. Theor. Phys. Lett.*, **94**, 513–516 (2011).

Magome, N. and Agladze, K. Patterning and excitability control in cardiomyocyte tissue culture. *Phys. D* **239**, 1560–1566 (2010).

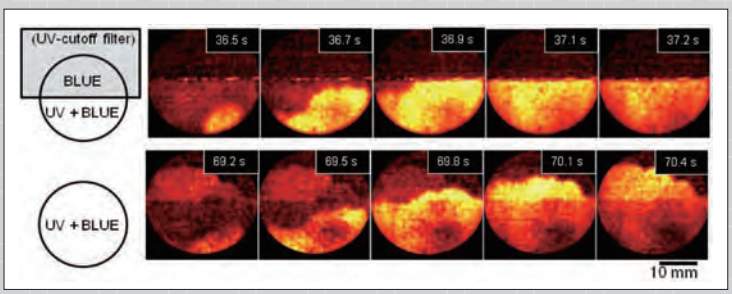
Horning, M., Isomura, A., Agladze, K. and Yoshikawa, K. Liberation of a pinned spiral wave by a single stimulus in excitable media. *Phys. Rev. E* **79**, 026218 (2009).



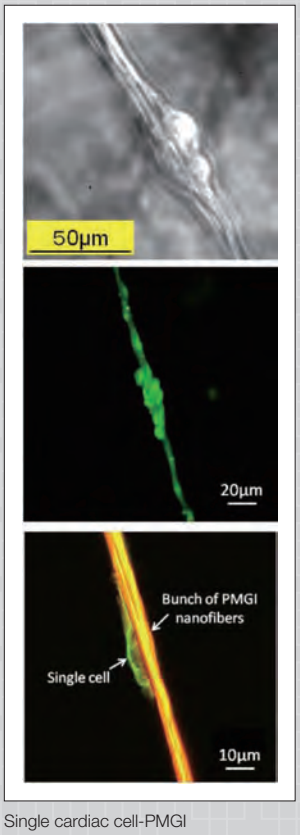
Cardiac tissue culture – immunostaining



Fluorescence images of propagating excitation waves in a light-controlled path



Light controlled excitation in a cardiac tissue culture



Single cardiac cell-PMGI nanofiber interaction

Yong Chen Lab

Nanobiotechnology

Faculty Members

Yong Chen (Professor)
Ken-ichiro Kamei (Assistant Professor)
Kaoru Sugimura (Assistant Professor)

Research Overview

Our main research interests are to develop new tools and methodologies based on **microfluidic** and **nanofabrication technologies**, which offer unique advantages over the conventional biological experimental settings, for applications in cell biological studies. Especially, Chen group has focused on to create in vitro cellular microenvironments (or niche), which have been revealed their important roles to regulate cellular functions in vivo (i.e., human pluripotent stem cells, neurons and cardiomyocytes). Indeed, our developing methods allow establishing well-defined artificial regulatory cellular environments at nm~μm scales. By utilizing our developed environments, we will be able to understand cellular environmental cues in detail and precisely controlling cellular functions. Such new methodological development leads us to apply stem cells for future applications in drug screening, cell-based therapy and regenerative medicine.

Our current research projects are listed below:

1. **Nanofabricated cellular scaffolds for maintaining pluripotent stem cell self-renewal and inducing differentiation**. We are developing nanostructured substrates and nanofibers for culturing pluripotent stem cells at an undifferentiated status and inducing lineage-specific differentiation.

2. **Microfluidic platforms for high-throughput screening**. Microfluidics are based on microfabrication technologies and used for chemical synthesis and gene analysis. Now, we are trying to develop new microfluidic platforms to screen drug candidates by using stem cells in a high-throughput fashion.

3. **Mechanical control of morphogenesis**. We are using our new method for estimating cell pressure and the tension of cell adhesion surfaces in vivo to understand how mechanical forces regulate the morphogenetic behaviors of cells (i.e., self-renewal and differentiation of stem cells).

At the iCeMS, we have been collaborating with other research groups on a variety of interdisciplinary projects:

1. Nano-substrates in conjunction with microfluidic platforms to perform hPSC culture and differentiation (Nakatsuji Lab).
2. Integration of meso-porous materials with nanoenfineered substrates for controlling bioactive small molecules in a spatial and temporal fashion (Kitagawa Lab).
3. Micro- and nanofluidic tools for guided growth of neural cells (Kenkagu Lab).
4. Nanoinjectors to stimulate cells in a high spatial resolution and image at a subcellular level (Kusumi Lab).
5. Nanofibers cooperated with magnetic nanoparticles for cell manipulation (Takano Lab).

Selected Papers

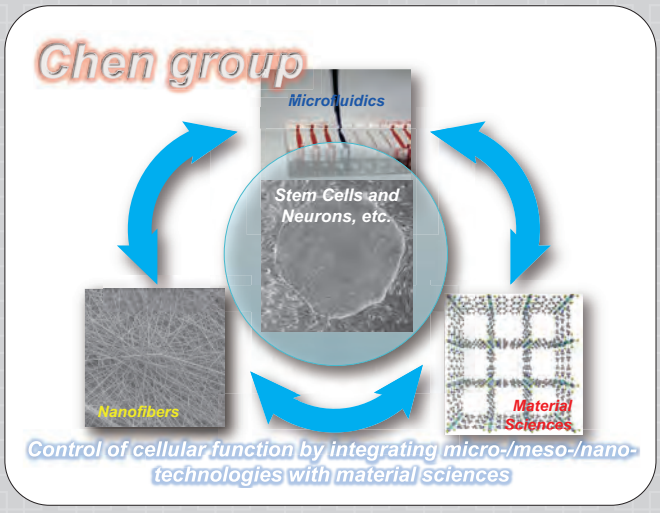
Li X., Liu L., Wang L., Kamei K., Yuan Q., Zhang F., Shi J., Kusumi A., Xie M., Zhao Z. and Chen Y. Integrated and diffusion-based micro-injectors for open access cell assays. *Lab Chip* **11**, 2612–2617 (2011).

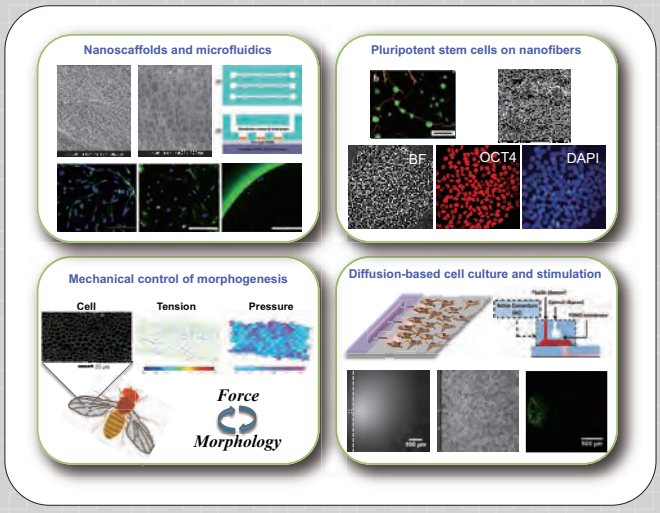
Liu Y., Wang H., Kamei K., Yan M., Chen K.J., Yuan Q., Shi L., Lu Y., Tseng H.R. Delivery of intact transcription factor by using self-assembled supramolecular nanoparticles. *Angew. Chem. Int. Ed. Engl.* **50**, 3058–3062 (2011).

Liu L., Luo C. X., Ni X. F., Wang L., Yamauchi K., Nomura S. M., Nakatsuji N. and Chen Y. A micro-channel-well system for culture and differentiation of embryonic stem cells on different types of substrate. *Biomed. Microdev.* **12**, 505–511 (2010).

Luo, C. X., Ni, X. F., Liu, L., Nomura, S. M. and Chen, Y. Degassing-Assisted Patterning of Cell Culture Surfaces. *Biotechnol. Bioeng.* **105**, 854–859 (2010).

Zhou, X. T., Shi, J., Zhang, F., Hu, J., Li, X., Wang, L., Ma, X. M. and Chen, Y. Reversed cell imprinting, AFM imaging and adhesion analyses of cells on patterned surfaces. *Lab Chip* **10**, 1182–1188 (2010).





Yoshie Harada Lab

Single-Molecule Physiology

Faculty Members

Yoshie Harada (Professor)
Mariko Ariyoshi (Associate Professor)
Yohsuke Yoshinari (Associate Professor)
Hiroaki Yokota (Senior Lecturer)
Yong-Woon Han (Assistant Professor)

Research Overview

The biomolecules functioning in our bodies vary in size from several nanometers to several hundreds of nanometers. This size is exactly the "meso" range at the junction between micro and macro. The critical difference between the environment in which biomolecules live and the environment in which we live is that biomolecules cannot ignore thermal fluctuations. Biomolecules are constantly exposed to large thermal fluctuations. Therefore, biomolecules differ from artificial machines in that they make skillful use of thermal fluctuations while functioning. For example, RNA polymerase is one-dimensionally diffused on DNA when searching for a promoter site on DNA. Our ultimate goal is to understand these skilled molecular functions of biomolecules.

Observing the motions of individual molecules and manipulating molecules directly are very useful for learning the working mechanisms of biomolecules. Therefore, we have developed techniques such as **single-molecule imaging microscopy** capable of directly observing the motion and structural changes of individual molecules, a method of manipulating molecules by grabbing molecules with **optical** or **magnetic tweezers**, and an apparatus for measuring the minute forces generated by molecules. Today, we use these techniques to investigate the functions of proteins related to **DNA replication**, **repair**, and **recombination**.

DNA replication, repair, and recombination are the most important mechanisms for guaranteeing the genetic continuity of a species. DNA replication is surprisingly complex because DNA information must be transmitted accurately to descendents. The dynamics of how various proteins actually interact when replicating DNA to catalyze a reaction quickly and with exquisite precision are not understood.

Therefore, our goal is to further develop **single-molecule measurement** techniques to understand DNA replication, repair, and recombination at the single-molecule level by single-molecule imaging of interactions between DNA and proteins, among different proteins, and simultaneous mechanical measurement of one interacting DNA molecule.

Selected Papers

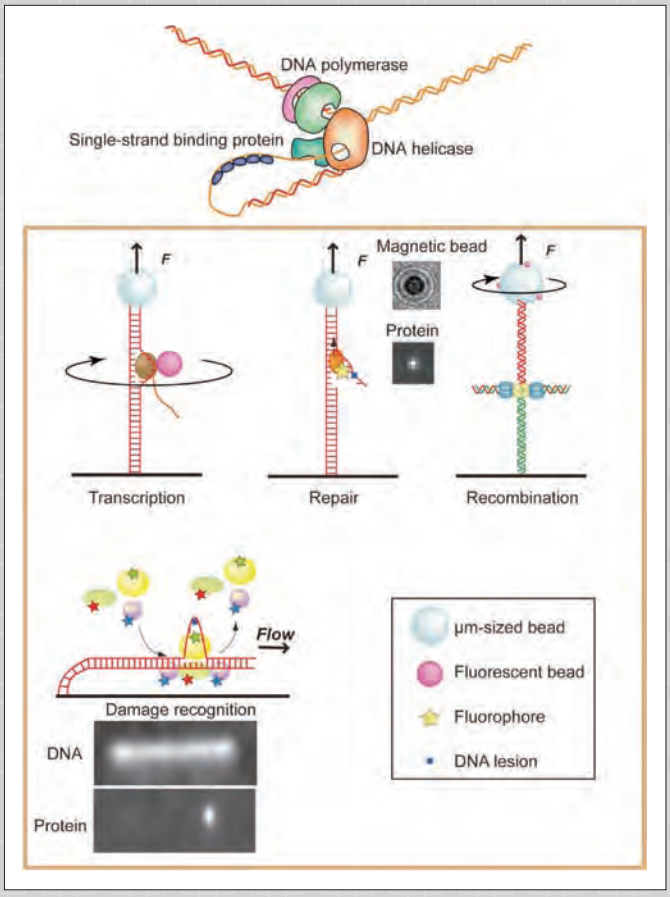
Miyazono, Y., Hayashi, M., Karagiannis, P., Harada, Y. and Tadakuma, H. Strain through the neck linker ensures processive runs: a DNA-kinesin hybrid nanomachine study. *EMBO J.* **29**, 93–106 (2009).

Sasuga, Y., Iwasawa, T., Terada, K., Oe, Y., Sorimachi, H., Ohara, O. and Harada, Y. Single-cell chemical lysis method for analyses of intracellular molecules using an array of picoliter-scale microwells. *Anal. Chem.* **80**, 9141–9149 (2008).

Hayashi, M. and Harada, Y. Direct observation of the reversible unwinding of a single DNA molecule caused by the intercalation of ethidium bromide. *Nucleic Acids Res.* **35**, e125 (2007).

Han, Y., Tani, T., Hayashi, M., Hishida, T., Iwasaki, H., Shinagawa H. and Harada, Y. Direct observation of DNA rotation during branch migration of Holliday junction DNA by Escherichia coli RuvA-RuvB protein complex. *Proc. Natl. Acad. Sci. U.S.A.* **103**, 11544–11548 (2006).

Sasuga, Y., Tani, T., Hayashi, M., Yamakawa, H., Ohara, O. and Harada, Y. Development of a microscopic platform for real-time monitoring of biomolecular interactions. *Genome Res.* **16**, 132–139 (2006).



Mitsuru Hashida Lab

Drug Delivery Systems (DDS)

Faculty Members

Mitsuru Hashida (Professor)

Research Overview

The use of **drug delivery systems** is a novel concept involving administration technology for optimizing chemotherapy to control the distribution of drugs. It is one of the most important fields and basic technologies supporting drug discovery and development in the pharmaceutical sciences associated with biomedicine and gene medicine. One of the main emphases of this group is **the development of drug and gene carriers** using new materials with unique characteristics. We are also studying the application of **carbon nanotubes (CNTs)** to drug delivery systems. One of the key steps in using CNTs *in vivo* is solubilization of this material into water, and we employ the approach using peptides as a dispersing agent to clear this subject. Currently, we are working on functionalization of CNTs for drug delivery. In this study, the physicochemical evaluation of CNTs is carried out collaboratively with the Imahori Lab, and functionalization of CNTs with sugar moiety is conducted in collaboration with the Kiso Lab. We are also developing new drug carrier collaborations with the Kiso Lab. A carbohydrate-cholesterol conjugate was synthesized through an electronically neutral linkage and is applied to the development of new drug carriers with improved cell-specific targeting properties.

Our current research projects are listed below:

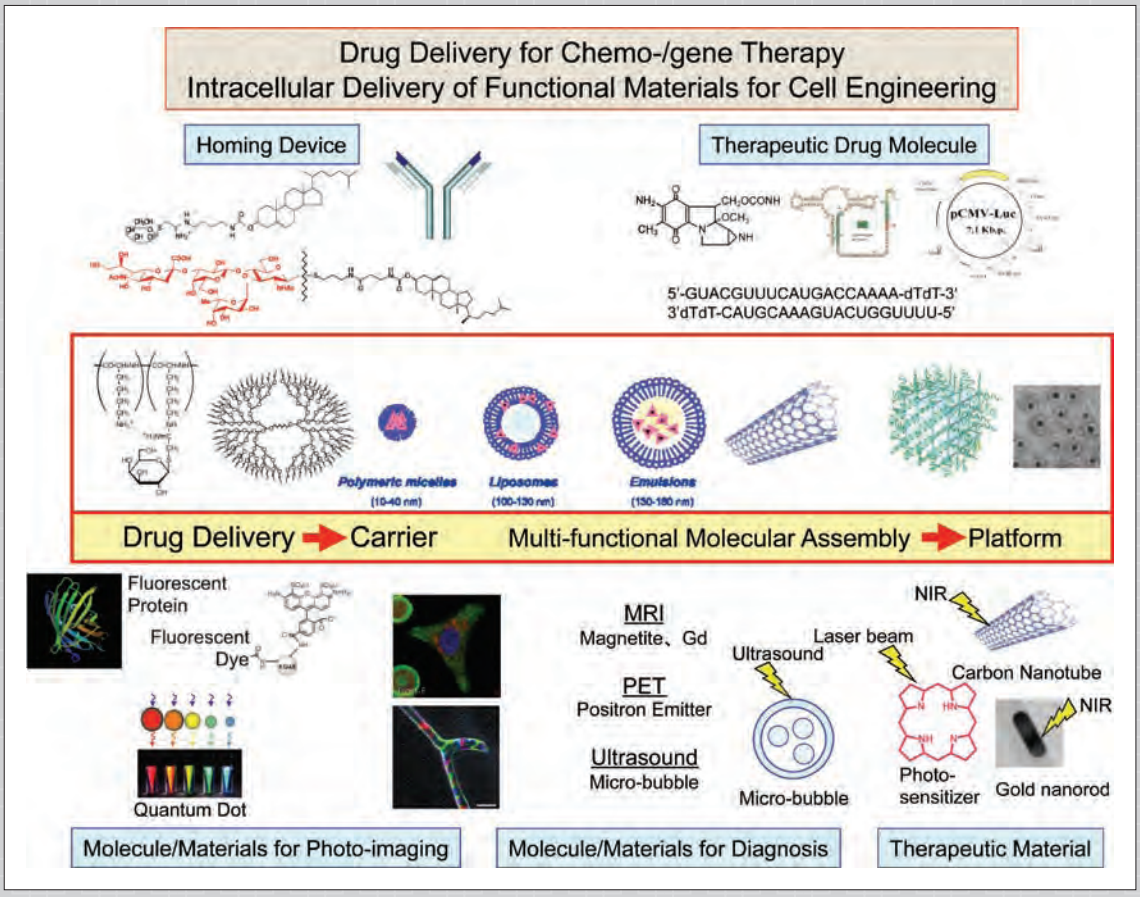
1. Rational design of macromolecular and particulate carriers for drug targeting
2. *In vivo* disposition control and targeting of proteins by chemical modification
3. Cell specific delivery of genes
4. Development of carrier systems employing new materials such as carbon nanotubes
5. *In silico* prediction of mucosal and skin absorption of drugs

Selected Papers

Higuchi, Y., Wu, C., Chang, K. L., Irie, K., Kawakami, S., Yamashita, F. and Hashida, M. Polyamidoamine dendrimer-conjugated quantum dots for efficient labeling of primary cultured mesenchymal stem cells. *Biomaterials* **32(28)**, 6676–82 (2011).

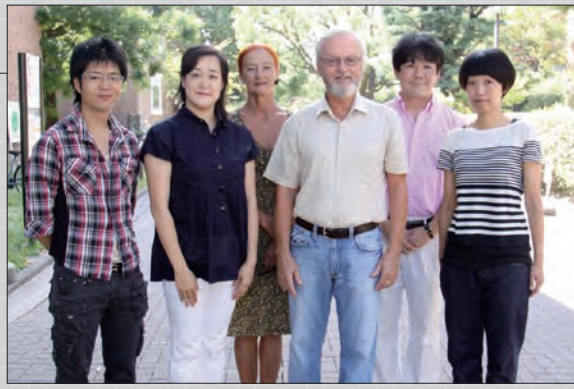
Un, K., Kawakami, S., Suzuki, R., Maruyama, K., Yamashita, F. and Hashida, M. Development of an ultrasound-responsive and mannose-modified gene carrier for DNA vaccine therapy. *Biomaterials* **31(30)**, 7813–26 (2010).

Nakanishi, H., Higuchi, Y., Kawakami, S., Yamashita, F. and Hashida, M. PiggyBac transposon-mediated long-term gene expression in mice. *Mol. Ther.* **18**, 707–14 (2010).



John Heuser Lab

Biophysics, Cell Biology



Faculty Members

John Heuser (Professor)
Nobuhiro Morone (Senior Lecturer)
Tatyana Tenkova-Heuser (Assistant Professor)

Research Overview

The key goal of this laboratory has long been to develop advanced new procedures for preserving the living appearance of the **meso-scaled molecular machinery** found inside cells. Our basic procedure is the "**quick-freeze/deep-etch**" method of **electron microscopy**, which we originally developed to visualize the mechanisms involved in the quantal release of neural transmitter substances from brain synapses and neuromuscular junctions. This we found involved secretion of the **meso-scaled entities** called "**synaptic vesicles**". Subsequently, our freeze-etch techniques were disseminated and reproduced all around the world, as other electron microscopists sought to visualize the structures and living dynamics of many different **meso-machines** found inside cells, including receptor and signaling complexes, cytoskeletal actomyosin networks, and a whole variety of cell-membrane differentiations, including clathrin-coated pits, caveolae, and endocytotic organelles of all sorts.

Overall, our "**quick-freeze/deep-etch**" techniques have been used to capture, visualize, and understand several important cellular processes that occur far too rapidly, and on too small a scale, to visualize in any other way – not only neural transmission, but also muscular contraction, viral infection, immune-cell synapse formation, vesicular transport, and cell migration during neurogenesis.

Additionally, we have modified the "**quick-freeze/deep-etch**" technique so that we can visualize isolated and purified protein and DNA macromolecules, in order to better understand the molecular mechanisms that underlie cellular functioning on the **meso-scale**. In all of our studies of macromolecules, as well as our studies of cell organelles, our TEM and SEM-imaging techniques have provided exceedingly true-to-life views that retain the full meso-architecture of cells and organelles, and thus are best viewed by modern methods of 3D-imaging including **tomography** and **stereology**.

At the present, we are well along in a further development of **cryo-scanning electron microscopy** for directly visualizing frozen cells without any further manipulation. In this way, we intend to make our EM laboratory in the iCeMS the world leader in 3D electron microscopy at the **meso-scale**.

The cross-disciplinary projects that we have already initiated with other iCeMS researchers include the following:

1. EM visualization of the pathological **meso-scale entities** that form in and around nerve and glial cells in various neurodegenerative diseases, including the "**plaques and tangles**" that develop in Alzheimer's disease, as well as the various other intracellular-fibril "**amyloid**" aggregates that form in Parkinson's disease, Huntington's disease, ALS, etc. Here we are working closely with the Nakatsuji Lab to develop and analyze various **ES and iPS** cell-lines that are genetically engineered to recapitulate these diseases by forming intracellular fibril-aggregates, with the goal of determining what can be done to prevent their formation or assist the affected cells in ridding themselves of them.

2. The above project also involves close collaboration with the Kusumi Lab, in order to **correlate our EM observations with their high-speed single-molecule imaging of fibril-formation**, in a further effort to determine the effects this has on membrane and organellar dynamics in living cells. Indeed, we are seeking to determine the EM-equivalents of many different aspects of the advanced high-speed single-molecule imaging that is always being done, on many different fronts, in the Kusumi Lab.

3. Finally, we are seeking to provide EM support for a number of other multidisciplinary research projects going on within the iCeMS, including the development of "**smart nanoporus materials**" with the Takano and Kitagawa Labs, the development of new imaging methods to visualize lipid transport and the formation of **mesoscale lipid-assemblies** with the Ueda and Kusumi Labs, and the spatial and temporal organization of organelles (everything from the mundane mitochondria to the most mysterious bit of 'nuage'), which the Hiiragi, Kengaku, and Nakatsuji Labs are studying to determine the special roles they play during **embryonic and neural development**.

Selected Papers

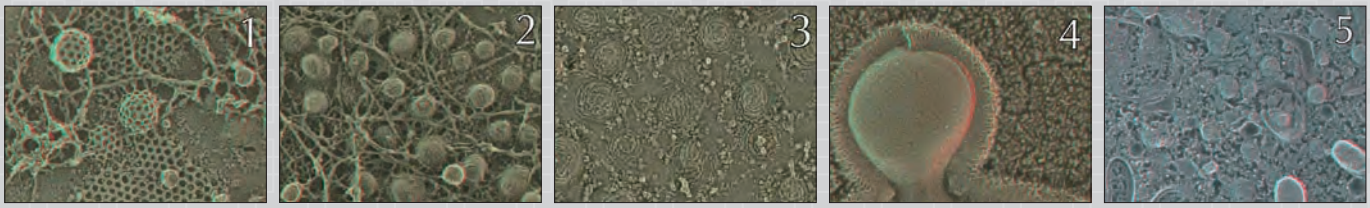
Hanson, P. I., Roth, R., Lin, Y. and Heuser, J. E. Plasma membrane deformation by circular arrays of ESCRT-III protein filaments. *J. Cell Biol.* **180**, 389–402 (2008).

Morone, N., Nakada, C., Umemura, Y., Usukura, J. and Kusumi, A. Three-dimensional molecular architecture of the plasma-membrane-associated cytoskeleton as reconstructed by freeze-etch electron tomography. *Methods Cell Biol.* **88**, 207–36 (2008).

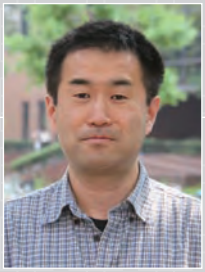
Heuser, J. Evidence for recycling of contractile vacuole membrane during osmoregulation in Dictyostelium amoebae – A tribute to Gunther Gerisch. Eur. *J. Cell Biol.* **85**, 859–871 (2006).

Morone, N., Fujiwara, T., Murase, K., Kasai, R. S., Ike, H., Yuasa, S., Usukura, J. and Kusumi, A. Three-dimensional reconstruction of the membrane skeleton at the plasma membrane interface by electron tomography. *J. Cell Biol.* **174**, 851–862 (2006).

Heuser, J. Deep-etch EM reveals that the early poxvirus envelope is a single membrane bilayer stabilized by a geodetic "honeycomb" surface coat. *J. Cell Biol.* **169**, 269–283 (2005).



Samples: 1. Clathrin-coated pits, 2. Actin MSK/Cavelae, 3. Caveolae, 4. Yeast, 5. Intestine



Takashi Hiiragi Lab

Developmental Biology

Faculty Members
Takashi Hiiragi (Professor)
Takeshi Matsui (Assistant Professor)

Research Overview

The goal of the research in our laboratory is the understanding of **totipotency**: what defines totipotency and what makes a cell totipotent. Our current research focuses on understanding the principles underlying early mammalian development. We have characterized the following key features: a. mechanical context plays a key role in **embryonic patterning** (Motosugi et al. 2005); b. asymmetry may emerge autonomously in an equivalent cellular population (Honda et al. 2008); c. early mouse development involves **stochastic processes** (Dietrich and Hiiragi 2007). These features suggest that, in order to understand the mechanisms of early mammalian development, it will be essential to address how diverse inputs acting on every individual cell are integrated in the embryo **at the systems level**. We thus adopt a variety of experimental approaches; 4D live-imaging, fluorescence-based gene-trap screens, gene expression profiling of individual blastomeres and computer simulation. An emerging hypothesis is that early mammalian embryogenesis may be a stochastic process in a particular structural context that eventually leads to **self-organization**. This principle may underlie the highly regulative capacity that is unique to mammalian pre-implantation embryos.

At iCeMS, we explore multi-disciplinary approaches including:

1. Characterization of the stochastic patterning process at the meso-scale level. While gene expression profile of the individual blastomeres is established, its spatio-temporal expression patterns will be visualized by Fluorescence Correlation Spectroscopy. This collaboration may identify a shift from “stochastic” to “consolidated” patterns of gene expression upon lineage commitment in vivo (with Harada Lab, CeMI, and Saitou Lab).
2. Evaluation of potential impact of cellular geometry on cell fate specification. **Mechanical constraint** will be applied to the embryo at a cellular level using a micro-device, in order to examine if geometrical information can influence gene expression (with Chen Lab).

Another research interest is the "epithelial evolution". About 360 million years ago, the first terrestrial vertebrate amphibians emerged from the water and adapted to life on land. In consequence, their surface epithelium evolved into multilayered stratified epithelia. Placing particular emphasis on this original epithelium, we intend to uncover the mystery of this epithelial evolution. We have produced evolutionally integrated skin-specific gene-deficient mice to reconstitute the ancient epidermis. We intend to analyze the mechanism of adaptive evolution of vertebrate skin through this reconstituted epidermis.

Selected Papers

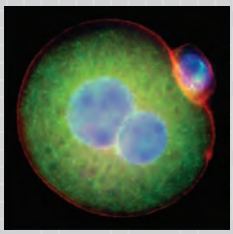
Matsui, T., Miyamoto, K., Kubo, A., Kawasaki, H., Ebihara, T., Hata, K., Tanahashi, S., Ichinose, S., Imoto, I., Inazawa, J., Kudoh, J., Amagai, M: SASPase regulates stratum corneum hydration through profilaggrin-to-filaggrin processing. *EMBO Mol. Med.* **3**, 320–333 (2011).

Honda, H., Motosugi, N., Nagai, T., Tanemura, M. and Hiiragi, T. Computer simulation of emerging asymmetry in the mammalian blastocyst. *Development* **135**, 1407–1414 (2008).

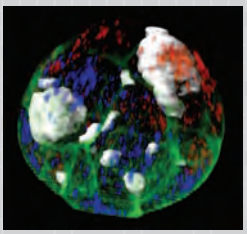
Dietrich, J. E. and Hiiragi, T. Stochastic patterning in the mouse pre-implantation embryo. *Development* **134**, 4219–4231 (2007).

Matsui T, Kinoshita-Ida Y, Hayashi-Kisumi F, Hata M, Matsubara K, Chiba M, Katahira-Tayama S, Morita K, Miyachi Y, Tsukita S: Mouse homologue of skin-specific retroviral-like aspartic protease (SASPase) involved in wrinkle formation. *J. Biol. Chem.* **281**, 27512–25 (2006).

Motosugi, N., Bauer, T., Polanski, Z., Solter, D. and Hiiragi, T. Polarity of the mouse embryo is established at blastocyst and is not prepatterned. *Gene. Dev.* **19**, 1081–1092 (2005).

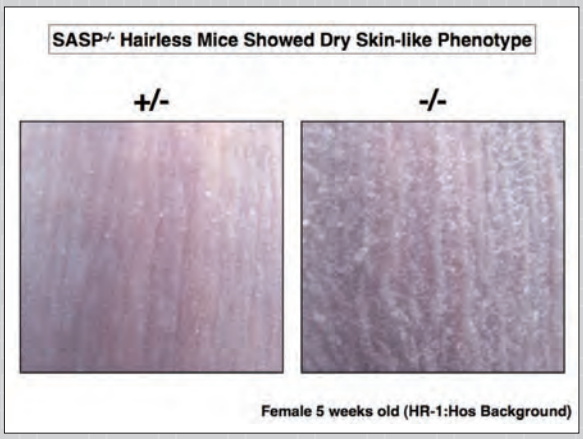


Totipotent egg

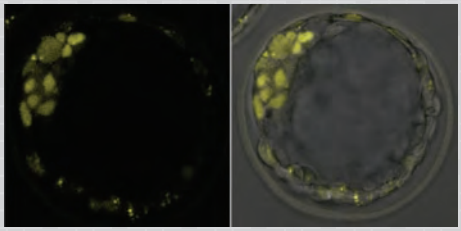


Blastocyst morphogenesis

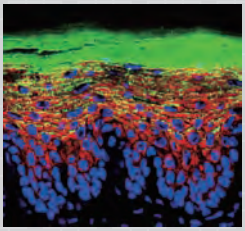
Computer simulation of blastocyst morphogenesis



Retroviral-like protease, SASPase was integrated into the genome of terrestrial vertebrates.



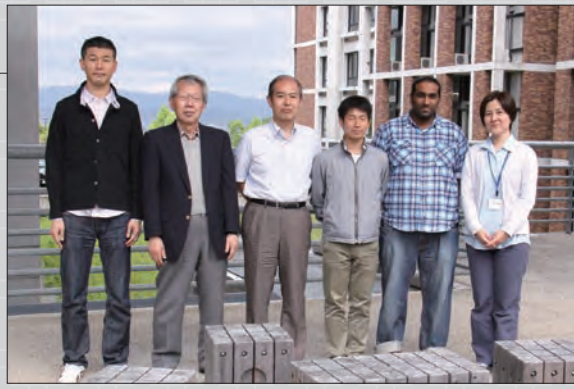
ICM-specific reporter expression in a gene-trap mouse



Localization of stratified epithelia-specific secreted peptide, dermokine in mouse epidermis

Hiroshi Imahori Lab

Organic Chemistry, Photochemistry, Drug Delivery Systems



Faculty Members

Hiroshi Imahori (Professor)

Kei Kurotobi (Assistant Professor)

Research Overview

Our laboratory has been working on development of **artificial photosynthetic** and **solar energy conversion systems**. In particular, we have demonstrated small reorganization energies of fullerenes, which is favorable for efficient solar energy conversion. Namely, they have made it possible to produce a long-lived charge-separated state with a high quantum yield in donor-acceptor systems. The elucidation of basic electron transfer properties of fullerenes has provided us with an important basis for high performance of fullerene-based organic electronics including organic solar cells. The papers published during this period are highly cited in the fields of chemistry and material science.

The shortage of fossil fuels and the degradation of the global environment have focused research attention on solar cells, which can convert sustainable solar energy into electricity. However, the cost of electricity from inorganic solar cells (silicon-based photovoltaics) is presently much higher than that generated by hydroelectric power and nuclear or fossil fuels. Therefore, it is necessary to develop low-cost, durable solar cells with high power conversion efficiencies. **Organic solar cells** would be promising candidates if they fulfill their potential, especially as they bear unique advantages over inorganic solar cells, that is, they are flexible, lightweight, and colorful.

Our group has been creating various organic solar cells including **dye-sensitized**, **bulk heterojunction**, and **novel organic solar cells**. Specifically, we have developed a novel hybrid solar cell possessing both characteristics of dye-sensitized and bulk heterojunction devices. Currently, a power conversion efficiency of >8% has been achieved on our solar cells.

At the iCeMS, we have initiated new multidisciplinary research projects based on organic chemistry and photochemistry through collaboration with other research groups of the institute, including:

1. Development of **light-harvesting mesomaterials** for phototherapy and multifunctional **light-emitting mesomaterials** for cell imaging (Murakami Fellow and Hashida Lab).

2. Development of **artificial transporters** made by photofunctional mesomaterials to elucidate cellular functions and control stem cells (Murakami Fellow, Heuser lab, and Mori Lab).

Selected Papers

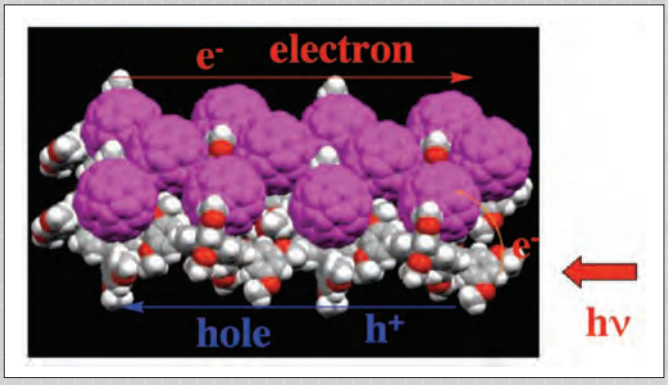
Hayashi, H., Nihashi, W., Umeyama, T., Matano, Y., Seki, S., Shimizu, Y., and Imahori, H. Segregated donor-acceptor columns in liquid crystals that exhibit highly efficient ambipolar charge transport. *J. Am. Chem. Soc.* **133**, 10736–10739 (2011).

Umeyama, T., Tezuka, N., Kawashima, F., Seki, S., Matano, Y., Nakao, Y., Shishido, T., Nishi, M., Hirao, K., Lehtivuori, H., Tkachenko, N. V., Lemmetyinen, H. and Imahori, H. Carbon nanotube wiring of donor-acceptor nanograins by self-assembly and efficient charge transport. *Angew. Chem. Int. Ed.* **50**, 4615–4619 (2011).

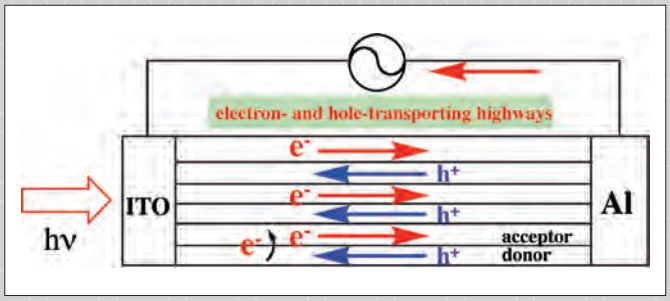
Hayashi, H., Lightcap, I. V., Tsujimoto, M., Takano, M., Umeyama, T., Kamat, P. V. and Imahori, H. Electron transfer cascade by organic/inorganic ternary composites of porphyrin, zinc oxide nanoparticles, and reduced graphene oxide on a tin oxide electrode that exhibits efficient photocurrent generation. *J. Am. Chem. Soc.* **133**, 7684–7687 (2011).

Imahori, H., Umeyama, T. and Ito. S. Large π aromatic molecules as potential sensitizers in dye-sensitized solar cells. *Acc. Chem. Res.* **42**, 1809–1818 (2009).

Kira, A., Umeyama, T., Matano, Y., Yoshida, K., Isoda, S., Park, J.-K., Kim, D. and Imahori, H. Supramolecular donor-acceptor heterojunctions by vectorial stepwise assembly of porphyrins and coordination-bonded fullerene arrays for photocurrent generation. *J. Am. Chem. Soc.* **131**, 3198–3200 (2009).



Highly efficient hole and electron transportation by molecule-level bicontinuous donor-acceptor network



Schematic illustration of ideal bulk heterojunction solar cell

Photocurrent generation in porphyrin-sensitized solar cell

Mineko Kengaku Lab

Developmental Neurobiology, Cell Biology

Faculty Members
Mineko Kengaku (Associate Professor)
Dan Ohtan Wang (Assistant Professor)

Research Overview

Control of **cell shapes and positions** is critical for the formation and function of multicellular tissues in living organisms. In the mammalian brain, 10–100 billion **neurons** with intricate branches are orderly arranged for integration into specific neural circuits. Differentiating neurons are highly motile cells that migrate long distances from the germinal layer to their destinations within the brain. They then extend cellular processes and arborize well-patterned dendrites and axons in order to contact their specific synaptic counterparts. These dynamic cellular movements are regulated by conformational and biochemical activity changes in **cell membranes** and **cytoskeletal proteins**. However, the spatiotemporal dynamics of molecules in motile neurons are largely unknown. The major goal of our research is to clarify the dynamics and mechanisms of **molecular interaction in meso-space** during **neuronal migration** and **dendrite branching**. We also aim to develop imaging techniques for real-time observation of molecular and cellular dynamics of neurons in the developing brain.

Three main research directions are as follows:

1. Live imaging analyses of **cytoskeletal dynamics** during **organelle transport** in migrating neurons
2. Biological and physical bases of **branch patterning** in differentiating dendrites
3. Development of **imaging techniques** for molecular analysis of neuronal motility

Selected Papers

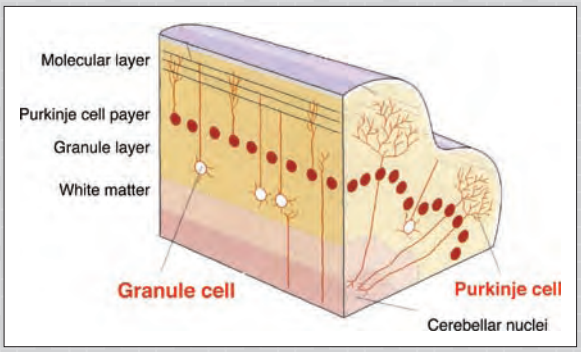
Kaneko, M., Takata, N., Eiraku, M., Kiyohara, Y., Aida, T., Hirase, H., Hashikawa, T. and Kengaku, M. Monoplanar arborization of Purkinje cell dendrites is regulated by afferent climbing fiber inputs. *PLoS ONE* **6**, e20108 (2011).

Sasaki, N., Kurisu, J. and Kengaku, M. Sonic hedgehog signaling regulates actin cytoskeleton via Tiam1-Rac1 cascade during spine formation. *Mol. Cell Neurosci.* **45**, 335–344 (2010).

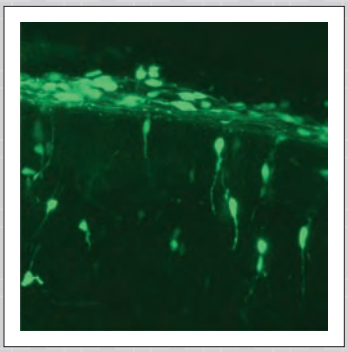
Kurisu. J., Fukuda. T., Yokoyama. S., Hirano, T. and Kengaku, M. Polarized targeting of DNER into dendritic plasma membrane in hippocampal neurons depends on endocytosis. *J. Neurochem.* **113**, 1598–1610 (2010).

Fukazawa, N., Yokoyama, S., Eiraku, M., Kengaku, M. and Maeda, N. Receptor type protein tyrosine phosphatase zeta-pleiotrophin signaling controls endocytic trafficking of DNER that regulates neuritogenesis. *Mol. Cell. Biol.* **28**, 4494–4506 (2008).

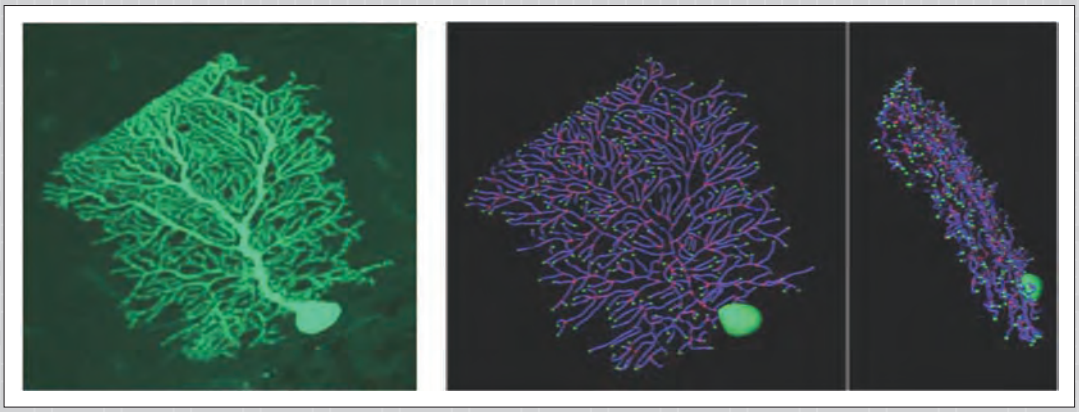
Umeshima, H., Hirano, T. and Kengaku, M. Microtubule-based nuclear movement occurs independently of centrosome positioning in migrating neurons. *Proc. Natl. Acad. Sci. U.S.A.* **104**,16182–7 (2007).



Cytoarchitecture of the cerebellar cortex of mammals



Time-lapse imaging of migrating granule cells in the developing cerebellum



Microscopic and graphic images of the cerebellar Purkinje cell transduced with GFP gene

Makoto Kiso Lab

Glycotechnology

Faculty Members
Makoto Kiso (Professor)
Hiromune Ando (Associate Professor)
Akihiro Imamura (Assistant Professor)

Research Overview

The iCeMS Gifu University satellite pursues the elucidation of the molecular basis underlying the multifunctions of carbohydrates (especially those called "**glycans**") in various biological processes by chemical methods and their applications in medicine. Our research is focused on the development of a versatile and powerful synthetic methodology of glycans, and the creation of a **Glycobank** possessing a wide spectrum of biologically-significant glycans and functionalized glycan probes. Utilizing the full entries of the Glycobank, we will conduct cross-disciplinary studies with molecular biology, developmental biology, structural biology, and biophysics in order to understand and apply the biological functions of glycans.

Our synthesized glycans have been utilized in diverse biological research such as those related to immune systems, virus entry, and cancer migration. At the iCeMS, we have launched new cross-disciplinary projects using the entries of the Glycobank, including:

1. Creation of the **glyco-director** system for stem cell engineering, which is comprised of arrays of homogenous synthetic glycans that direct the differentiation and proliferation of stem cells (ES and iPS cells), in collaboration with stem cell science (Nakatsuji and Yamanaka Labs) and nanomaterial science (Chen Lab).
2. Development of glycan probes for **single molecule tracking** of cell membranes to understand the formation and functions of **raft domains**, a functionalized complex of membrane constituents, in collaboration with single-molecule cell biophysics (Kusumi Lab).
3. Innovation of **drug delivery systems** (**DDS**) by creating new drug carriers using carbon nanotubes and lyposomes functionalized with glycans, in collaboration with biopharmaceuticals (Hashida Lab) and nanomaterial and biomaterial sciences (Kitagawa and Imahori Labs).

Selected Papers

Nakashima, S., Ando, H., Imamura, A., Yuki, N., Ishida, H. and Kiso, M. A first total synthesis of a hybrid-type ganglioside associated with amyotrophic lateral sclerosis-like disorder. *Chem. Eur. J.* **17**, 588–597 (2011).

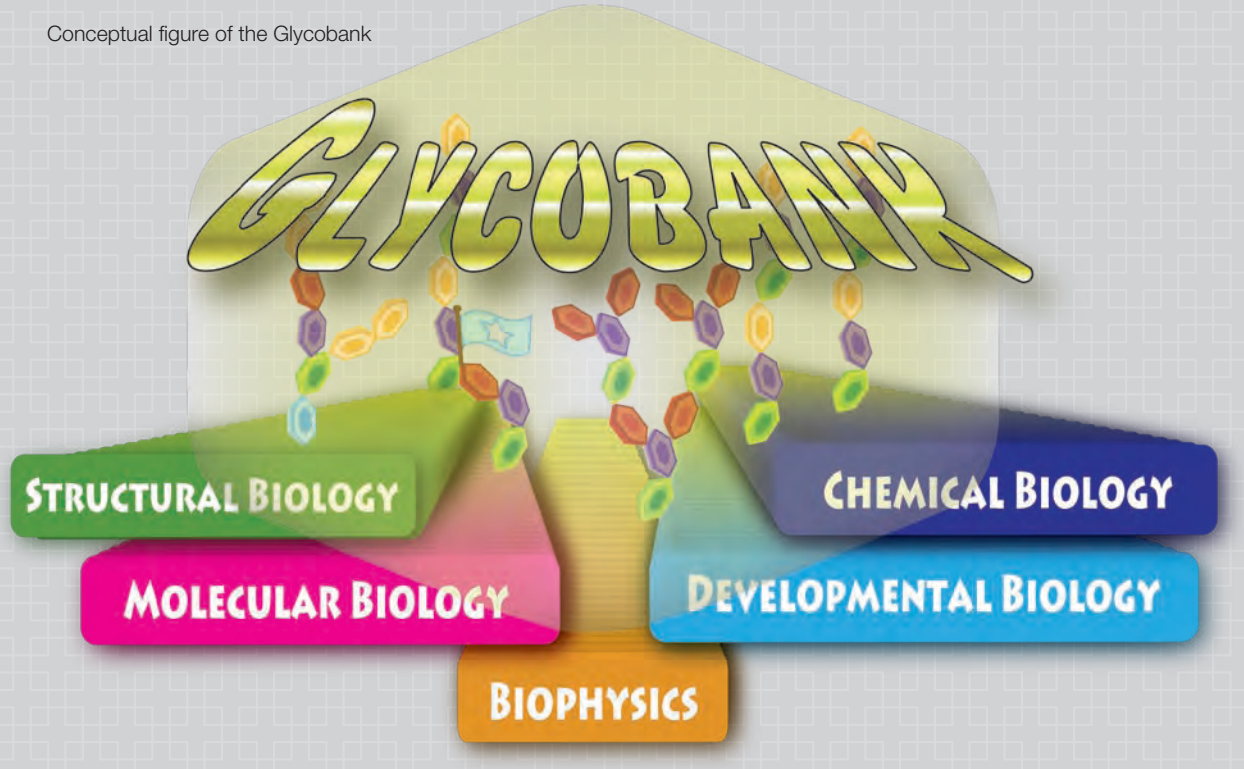
Tamai, H., Ando, H., Tanaka, H., Hosoda-Yabe, R., Yabe, T., Ishida, H. and Kiso, M. The total synthesis of the neurogenic ganglioside LLG-3 isolated from the starfish *Linckia laevigata*. *Angew. Chem. Int. Ed. Engl.* **50**, 2330–2333 (2011).

Fujikawa, K., Nohara, T., Imamura, A., Ando, H., Ishida, H. and Kiso, M. A cyclic glucosyl ceramide acceptor as a versatile building block for complex ganglioside synthesis. *Tetrahedron Lett.* **51**, 1126–1130 (2010).

Iwayama, Y., Ando, H., Ishida, H. and Kiso, M. A first total synthesis of ganglioside HLG-2. *Chem. Eur. J.* **15**, 4637–4648 (2009).

Stenmark, P., Dupuy, J., Imamura, A., Kiso, M. and Stevens, R. C. Crystal structure of botulinum neurotoxin type a in complex with the cell surface co-receptor GT1b–insight into the toxin–neuron interaction. *PLoS Pathog.* **4**, 1–10 (2008).

Conceptual figure of the Glycobank



Susumu Kitagawa Lab

Coordination Chemistry, Biological Inorganic Chemistry, Biomaterial Science

Faculty Members

Susumu Kitagawa (Professor)
Takafumi Ueno (Associate Professor)
Shuhei Furukawa (Associate Professor)
Ryotaro Matsuda (Associate Professor)
Hirokazu Kobayashi (Assistant Professor)
Stéphane Diring (Assistant Professor)
Masakazu Higuchi (Assistant Professor)
Hiroshi Sato (Assistant Professor)

Research Overview

We are developing a chemistry of new organic-inorganic porous materials with pores or also channels in a scale ranging from tenths of nanometers to several nanometers in size. So-called **smart microporous materials**, these have controllable properties *ad arbitrium* adjustable in response to surrounding environments. This new field will likely contribute to the alleviation of energy and environment issues as well as to an increase in human welfare by developing (a) low-pressure gas storage and high-efficiency separation systems, (b) molecular- and ion-transport and controlled-release microvessels working in cells, and (c) environmentally friendly chemical reaction systems. These materials being studied in our lab are called **Porous Coordination Polymers** (**PCPs**) and **Metal-Organic Frameworks** (**MOFs**). Moreover, we are interested in **mesoscale** (5-100nm) crystals of our materials because these have properties unique from their bulk counterparts. The mesoscale domain is particularly important in that vital physical and chemical phenomena of cells occur in this range. Our materials open the door to a new field combining cell biology and porous material science.

1. Development of PCPs: We synthesize functional PCPs not only for gas storage but also for separations with higher capacity than conventional materials. Low molecular weight molecules, such as carbon dioxide (CO_2), methane (CH_4), and alkanes (C_2-C_3) are important gases for sustaining life, and are contained in natural gas and biogas as well. In order to obtain highly purified CH_4, the key question is how to separate CH_4 from a mixture gas containing carbon dioxide (CO_2) impurities without expending a large amount of energy. Succeeding in this would provide us with a new industrial technology independent of petroleum oil resources.
2. Delivery of functional molecules, such as drugs and ions, using porous materials: carbon monoxide (CO), nitric oxide (NO), and ammonia (NH_3) have attracted attention as important molecules involved in many physiological and pathological processes. We are synthesizing new porous materials which can absorb and release these gas molecules and ions in physiological environments for detoxication and control of cell functions.
3. Porous materials integrated with cell membranes: We are working to construct new artificial membranes conjugated with porous materials having various functions such as gas storage and ion channels. These bio-integrated materials can serve as new drug delivery systems and bio-imaging reagents, as well as aiding in the elucidation of cell functions.
4. Bio-compatible materials using proteins: In many biological systems, protein assembly cages and channels can deliver various organic molecules and metal ions. We are working on reconstruction of porous materials made from protein assemblies or protein crystals for development of highly biocompatible materials.

Selected Papers

Takashima. Y., Martinez, M. V. Furukawa, S., Kondo, M., Shimomura, S., Uehara, H., Nakahama, M., Sugimoto, K., Kitagawa, S. Molecular decoding using luminescence from an entangled porous framework. *Nat. Commun.*, **2**, 168 (2011), DOI: 10.1038/ncomms1170.

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Koshiyama, T., Shirai, M., Hikage, T., Tabe, H., Tanaka, K., Kitagawa, S., Ueno, T. Post-Crystal Engineering of Zinc-Substituted Myoglobin to Construct a Long-Lived Photoinduced Charge-Separation System. *Angew. Chem. Int. Ed.* **50**, 4849–4852 (2011).

Sato, H., Matsuda, R., Sugimoto, K., Takata, M., Kitagawa, S. Photoactivation of a nanoporous crystal for on-demand guest trapping and conversion. *Nat. Mater.* **9**, 661–666 (2010).

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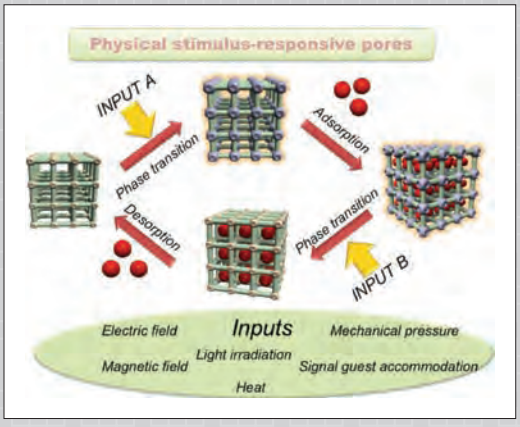
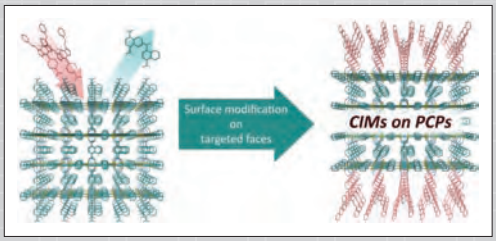
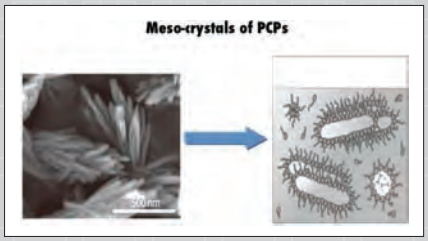


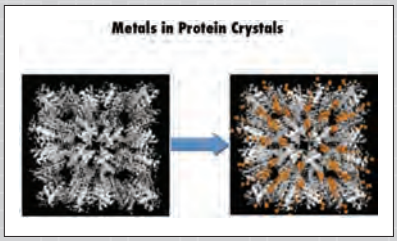
External stimuli for controlling PCP functions



Surface modification of PCPs



Functions of meso-crystals of PCPs



Accumulation of metal ions in porous protein crystals

Akihiro Kusumi Lab

Single-Molecule Cell Biophysics

Faculty Members

Akihiro Kusumi (Professor)

Research Overview

Our laboratory is dedicated to understanding **membrane mechanisms** and developing ultra-speed **single-molecule** observation and manipulation nano-methodologies applicable to the studies of living cells. These methodologies are initially employed to reveal the structures, dynamics, and functions of mesoscale (1–100 nm, slightly expanded from the iCeMS' definition of 5–100 nm) domains in the plasma membrane, which are investigated in the context of cellular **signal transduction** and **neuronal network remodeling**. A smooth melding of physics, engineering, and biomedicine is the key to the research conducted in our laboratory. Based on these single-molecule insights into mesoscale processes occurring in the cell, we intend to develop **systems molecular biology** to understand the mechanisms for the formation and function of meso-scale membrane domains, including membrane compartments, raft domains, and transient protein oligomers.

Fig. 1, left. **Single-molecule tracking** techniques. A fluorescent or colloidal gold tag is attached to a specific target membrane protein or lipid, and its movements in the cell membrane are visualized. **The fastest imaging** ever has been achieved for single gold particles and single fluorescent molecules (6 and 100 microseconds/frame with a spatial precision of 17 and 35 nm, respectively).

Fig. 1, right. Using laser tweezers, a gold-tagged membrane molecule is moved at will along the membrane.

Fig. 2. A signaling molecule, a small G protein Ras (green), undergoes diffusion on the cytoplasmic surface of the plasma membrane (yellow trajectories). The activation of this single Ras molecule was imaged (green color changed to red, center of this image), which entails the first successful observation of the activation of a single molecule. Furthermore, many other cytoplasmic molecules are recruited to this activated Ras molecule to form activated Ras signaling complexes, which last, surprisingly, for only a fraction of a second, suggesting the possibility that the basic unit of the cellular signal occurs like a digital pulse in such transient molecular complexes.

Fig. 3. A paradigm shift in the concept of plasma membrane structure and function, proposed by us. The entire plasma membrane is partitioned into many small compartments of 30–200 nm due to the actin-based membrane skeleton (membrane-skeleton “fence” model, left) and various transmembrane proteins anchored to the membrane skeleton (anchored transmembrane-protein pickets, right).

Transmembrane proteins anchored to the membrane skeleton and immobilized, lining the membrane skeleton fence, effectively act like rows of diffusion barriers, due not only to the steric hindrance effect but also to the hydrodynamic friction effect at the surfaces of immobile molecules.

Selected Papers

Kusumi, A., Suzuki, K. G. N., Kasai, R. S., Ritchie, K, and Fujiwara, T. K. Hierarchical mesoscale domain organization of the plasma membrane. *Trends Biochem. Sci.* (2011) in press.

Kasai, R. S., Suzuki, K. G. N., Prossnitz, E. R., Koyama-Honda, I., Nakada, C., Fujiwara, T. K., and Kusumi, A. Full characterization of GPCR monomer-dimer dynamic equilibrium by single molecule imaging. *J. Cell Biol.* **192**, 463–480 (2011).

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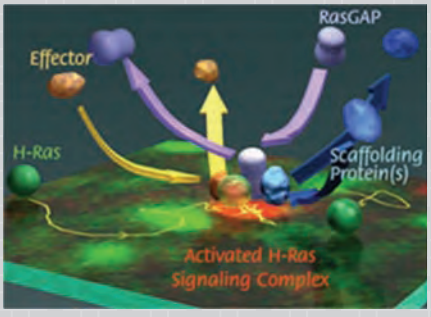

Fig. 2

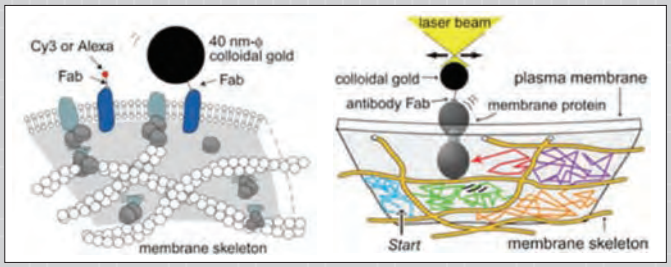

Fig. 1

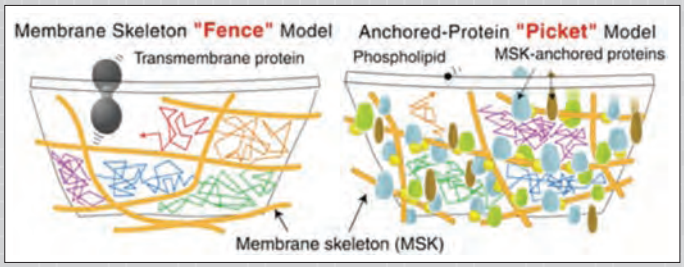

Fig. 3

Norio Nakatsuji Lab

Stem Cell Biology, Developmental Biology

Faculty Members

Norio Nakatsuji (Professor)
Dongju Jung (Senior Lecturer)
Kazuhiro Aiba (Senior Lecturer)

Research Overview

Our research group has been working on development and differentiation of **embryonic stem cells** and **germ cells** in mammals. In particular, we have established mouse, cynomolgus monkey, and **human embryonic stem (ES) cell lines**, and we have been carrying out various aspects of basic and application research using **pluripotent stem cells, including human ES and iPS cells.**

We have been developing methods of **genetic modification** in primate and human pluripotent stem cells, including conditional expression such as the Tet-On/Off system, expression of multiple transgenes, and the homologous recombination method. More recently, our group has created normal and disease **model cells** for disease mechanism research and drug discovery tools, which are important applications of pluripotent stem cell lines. These include production of neurodegenerative disease model cells by introduction of mutated genes, toxicology studies using cardiomyocytes, and **chemical screening** for stem cell control. We have initiated multidisciplinary research projects using **ES and iPS cell lines** in collaboration with other research groups of the iCeMS, as follows:

1. Creation and analysis of model cells from human ES and iPS cell lines. They include **neurodegenerative disease model** cells, such as Alzheimer, ALS and Huntington disease models, which are produced by genetic modification of stem cell lines and differentiation into relevant cells in each disease. Production of abnormal protein/peptides and disease mechanisms will be examined in collaboration with other research groups including the meso-imaging CeMI groups.

2. Control of stem cells with **chemical compounds** and **nano/meso/micro-fabricated materials** for growth and differentiation of ES/iPS cells in collaboration with chemical biology groups (such as the Uesugi and Sugiyama Lab) and nano/meso/micro-engineering groups (such as the Chen Lab). As the first example, we have identified novel small molecules which can induce efficient and robust cardiomyocyte differentiation from many human ES and iPS cell lines.

3. Development of novel technologies for large-scale production of high-quality human pluripotent stem cells. It is a government-supported project for medical and pharmaceutical application of stem cells, and carried out by collaboration with several high-technology companies in addition to the collaboration with many academic research groups.

Selected Papers

Tanaka, T., Hosokawa, M., Vagin, V. V., Reuter, M., Hayashi, E., Mochizuki, A. L., Kitamura, K., Yamanaka, H., Kondoh, G., Okawa, K., Kuramochi-Miyagawa, S., Nakano, T., Sachidanandam, R., Hannon, G. J., Pillai, R. S., Nakatsuji, N. and Chuma, S. Tudor domain containing 7 (Tdrd7) is essential for dynamic ribonucleoprotein (RNP) remodeling of chromatoid bodies during spermatogenesis. *Proc Natl Acad Sci U.S.A.* **108**, 10579–10584 (2011).

Otsuji, T.G., Minami, I., Kurose, Y., Yamauchi, K., Tada, M. and Nakatsuji, N. Progressive maturation in contracting cardiomyocytes derived from human embryonic stem cells: Qualitative effects on electrophysiological responses to drugs. *Stem Cell Res.* **4**, 201–213 (2010).

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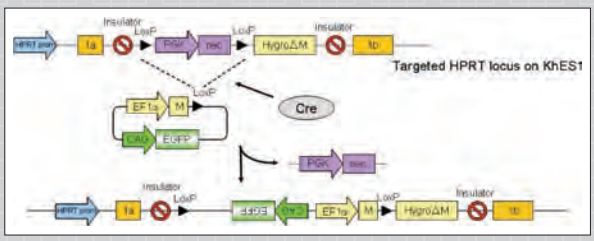
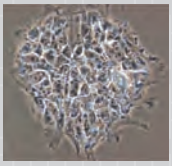
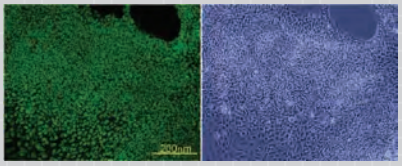
Shoji, M., Tanaka, T., Hosokawa, M., Reuter, M., Stark, A., Kato, Y., Kondoh, G., Okawa, K., Chujo, T., Suzuki, T., Hata, K., Martin, S. L., Noce, T., Kuramochi-Miyagawa, S., Nakano, T., Sasaki, H., Pillai, R. S., Nakatsuji, N. and Chuma, S. The TDRD9-MIWI2 complex is essential for piRNA-mediated retrotransposon silencing in the mouse male germline. *Dev. Cell* **17**, 775–787 (2009).



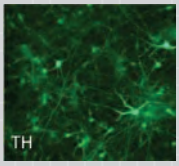
Cre/loxP mediated site-specific gene integration



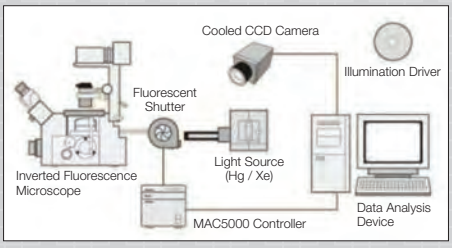
hES cells

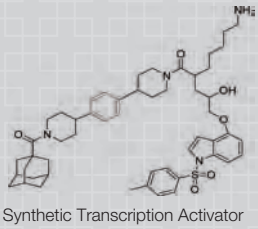


Neural stem/progenitor cells

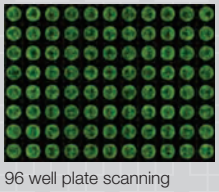


Dopaminergic Neurons

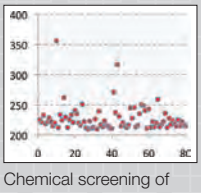




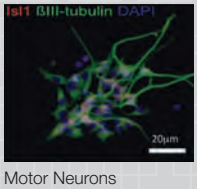
Synthetic Transcription Activator optimized "Wrenchnolol"



96 well plate scanning image GFP fluorescence



Chemical screening of effective compounds



Motor Neurons

Hiroshi Sugiyama Lab

Chemical Biology

Faculty Members
Hiroshi Sugiyama (Professor)
Masayuki Endo (Associate Professor)

Research Overview

The Sugiyama Lab's research interests involve the chemical biology of nucleic acids. Using the tools of organic synthesis and molecular biology, our group seeks to define the chemical principles underlying the recognition, reactivity, and structure of nucleic acids. We utilize a chemical approach in the following areas: design of highly efficient sequence-specific DNA acting agents, design of unnatural nucleic acids to elucidate nucleic acid structures and functions, design of DNA nanostructures to control and observe single molecule dynamics and single reactions, and development of a general method for probing DNA local conformation *in vivo*. Long-range goals are analysis of molecular behaviors involved in epigenetic regulation, and creation of **artificial genetic switches** for iPS cell production and targeted cell differentiation, and treatment of various diseases.

1. Sequence-specific DNA binder pyrrole-imidazole polyamides are developed and applied in cell biology. Using synthetic polyamides, specific gene regulations including gene suppression and activation are carried out by conjugating with alkylating agents and transcription activating small molecules. By constructing the gene regulation system, the method is expanded to create artificial synthetic molecules for cell reprogramming and differentiation.

2. Using the DNA self-assembly system “DNA origami” method, research focuses on the following points: (1) programmed assembly of DNA scaffolds; (2) design and construction of novel 2D and 3D DNA nanostructures; (3) control of biomolecular reactions in the designed nanostructures; and (4) biophysical analysis of single molecule behavior in the designed nanostructure. A real-time AFM imaging system is employed for the analysis of single molecule dynamics and single reactions in the designed nano-space.

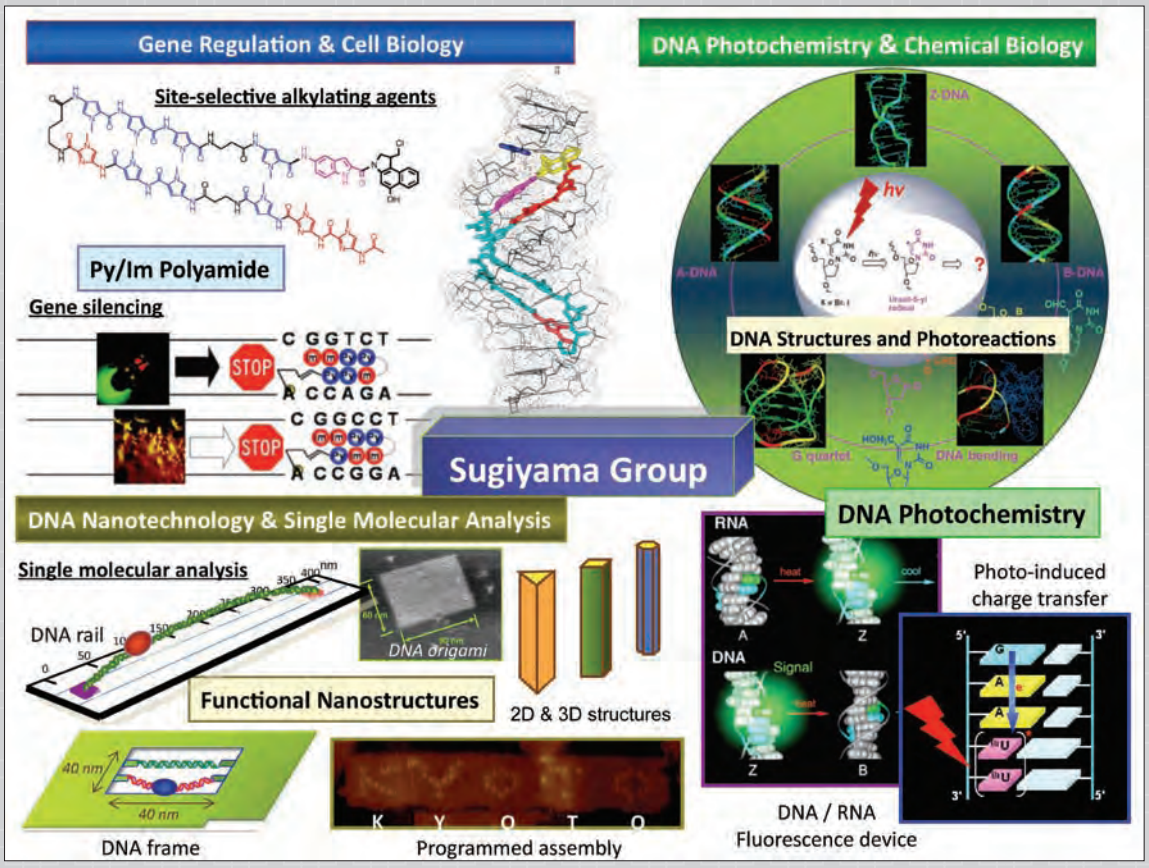
Selected Papers

Endo, M., Sugita, T., Katsuda, Y., Hidaka, K. and Sugiyama, H. Programmed-Assembly System Using DNA Jigsaw Pieces. *Chem. Eur. J.* **16**, 5362–5368 (2010).

Shinohara, K., Sannohe, Y., Kaieda, S., Tanaka, K., Osuga, H., Tahara, H., Xu, Y., Kawase, T., Bando, T. and Sugiyama, H. A Chiral Wedge Molecule Inhibits Telomerase Activity. *J. Am. Chem. Soc.* **132**, 3778–3782 (2010).

Endo, M., Katsuda, Y., Hidaka, K. and Sugiyama, H. Regulation of DNA Methylation Using Different Tensions of Double Strands Constructed in a Defined DNA Nanostructure. *J. Am. Chem. Soc.* **132**, 1592–1597 (2010).

Endo, M., Hidaka, K., Kato, T., Namba, K. and Sugiyama, H. DNA Prism Structures Constructed by Folding of Multiple Rectangular Arms. *J. Am. Chem. Soc.* **131**, 15570–15571 (2009).



Mikio Takano Lab

Solid State Chemistry

Faculty Members

Mikio Takano (Professor)
Seiji Isoda (Visiting Professor)
Hideki Koyanaka (Associate Professor)
Shinpei Yamamoto (Assistant Professor)

Research Overview

We are carrying out **solid state chemistry** (synthesis, structural analysis, and clarification of physical and chemical properties) on materials containing **3d transition metals** such as titanium (Ti), manganese (Mn), iron (Fe), and nickel (Ni). These elements are relatively rich in the earth's crust and, therefore, relatively cheap and easily obtained. Thanks to their high chemical activity there exist an uncountable number of compounds. Human society has made use of their superior functionalities as coloring materials (α-Fe_2O_3, for example), catalysts (TiO_2, Ni), dielectrics ($BaTiO_3$), magnets (α-Fe, Fe_3O_4), superconductors ($Bi_2Sr_2Ca_2Cu_3O_{10}$), battery electrodes (MnO_2, $LiCoO_2$), etc. We have used various artificial synthetic techniques to find out new such materials, but very recently a natural iron oxide produced by a species of water-habitant bacteria has attracted us very much. Its compositional, structural, and morphological features, which are somewhat beyond our imaginings, are suggestive of unique functionalities (collaboration with Prof. J. Takada's group, Okayama Univ.).

Our activity is multilayered. At the core, or at the most basic level, is the **search for unknown materials** using various synthetic techniques. On the surface are efforts to apply known and new materials to **cross-disciplinary research** with bioscience groups such as the Chen and Harada Labs. Our research ideal is that a new discovery by us will lead to a truly innovative, actual material.

The following are two typical topics included in our studies:

1. Nano-Sized Magnets

We have created nano-sized particles of strong magnets like the iron metal (**α-Fe**) and an iron nitride, **$Fe_{16}N_2$**, coated with organic layers providing biocompatibility and bio-functionality (see Fig.1). We note here that this nitride, being made of ubiquitously available elements only, is the most promising candidate for the next generation, resource conflict-free magnet.

2. Analysis of composition, structure, and morphology

Functionality of a material essentially depends upon its chemical composition, arrangement of constituent atoms (structure) and morphology. While there are many tools to analyze them, electron microscopy is employed extensively for analyses of nano-scale materials developing in Takano group as well as in collaborative groups such as the Imahori, Hashida, and Kitagawa Labs. Studies are being conducted on nano-magnetic particles, nanomaterials modified with light sensitive molecules or proteins, and also products of nano-space reactions.

Selected Papers

Yamamoto, S., Gallage, R., Tamada, Y., Kohara, K., Kusano, Y., Sasano, T., Ohno, K., Tsujii, Y., Kageyama, H., Ono, T., and Takano, M., Transformation of Nano- to Mesosized Iron Oxide Cores to α-Fe within Organic Shells Preserved Intact. *Chem. Mater.* **23**, 6, 1564–1569 (2011).

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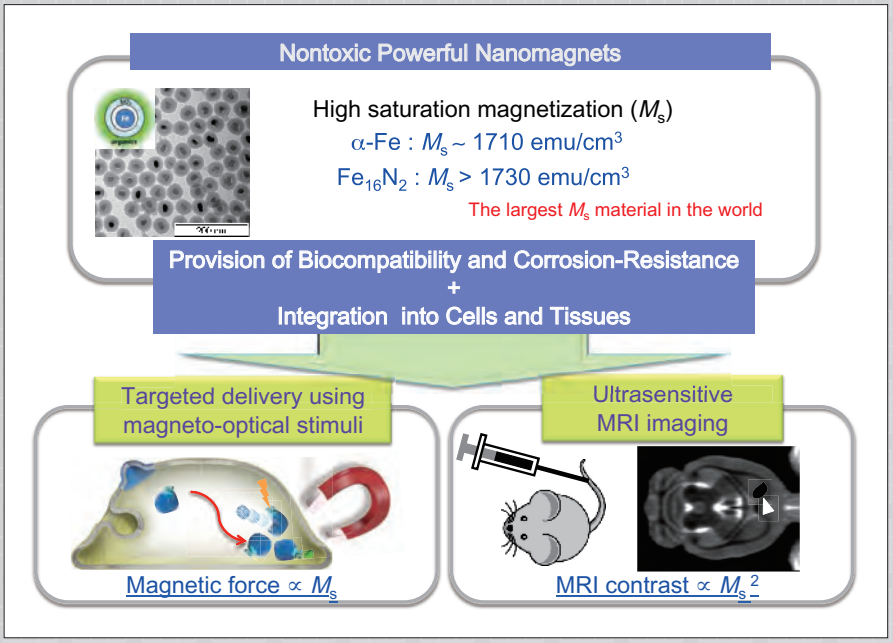

Fig.1
Nontoxic powerful nanomagnets prepared in our group, which are being employed for progressive applications such as spatiotemporally controlled intracellular release of physiologically active substances and ultrasensitive MRI imaging.

Koichiro Tanaka Lab

Teraherz Optical Science

Faculty Members
Koichiro Tanaka (Professor)
Masanobu Shirai (Assistant Professor)
Hideki Hirori (Assistant Professor)

Research Overview

Terahertz (THz) waves, electromagnetic radiation in the frequency region from 0.1 to 10 THz, is the next frontier in optical science and technology*. THz waves have been used to characterize the electronic, vibrational, and compositional properties of solid, liquid, and gas phase materials. In particular, biological sensing and imaging are the most highly anticipated applications of THz waves. Important features of THz waves for biological applications are summarized as follows:

- **Fingerprints**: Many biological molecules have their rotational and vibrational modes in the THz frequency range.
- **Water-sensitivity**: THz radiation is quite sensitive to water and its dynamic behaviors depending on temperatures and interaction with various kinds of solutes.
- **Safety**: THz radiation has low phonon energies (4 meV @ 1 THz) and, therefore, does not ionize biological tissue.

However, compared to well-developed visible light optical technologies and electronics in the microwave region, basic research, new approaches, and advanced technology development in the THz band have been only limited, as THz wave emitters and receivers are not as well developed compared to microwave and optical equipment.

We are developing high-power THz wave generation techniques and their application to the biological sciences. Our method of high power THz wave generation is based on the Cherenkov-type rectification process in $LiNbO_3$ crystals, or the four-wave-mixing process in laser induced gas-plasma with amplified femtosecond lasers (4mJ/pulse). This has allowed us to generate an intense THz wave over 200 kV/cm in the electric field in the repetition rate of 1 KHz. Recently, our group has been exploring **non-linear optical responses** of semiconductors and biological materials and we have found various novel phenomena that have never before been observed. Simultaneously we are developing a near-field THz microscope working at video rate. These technologies will open the doors to new THz sensing and **imaging** applications in the near future.

At the iCeMS, we have initiated new multidisciplinary research projects using high-power THz waves and related THz science and technologies including:

1. Biological applications of **THz near-field microscopy**. We have developed a special sensing crystal that enables us to convert the THz near-field image to a visible image using a non-linear optical process inside the sample mount. The current target for special resolution is below 5 micrometers. Thanks to our high power THz-waves, the microscope will work at video rates. Biological applications are now possible and will be conducted in collaboration with the Harada and Kusumi Labs.
2. Development of novel techniques to control materials with intense THz waves. Intense THz waves have the potential to modify or control optical and electrical properties in various functional materials. For example, non-linear properties in the THz frequency region are important in semiconductors for high-speed switching devices and future hopes in biological materials for new sensing and imaging technologies. Serious photo-blinking and darkening problems in fluorescent semiconductor quantum-dots may be overcome in part using resonant excitation of intense THz waves ranging from hidden dark levels to luminescent levels.
3. Water-material interaction in meso-space is important to understand biological activities in living cells. We are developing a special THz spectrometer with **attenuated total reflection** (ATR) devices to measure accurately the response function in the THz frequency region including optical permittivity and conductivity. We intend to elucidate the dynamic properties of liquids, especially hydration effects in small molecules, proteins, and lipid layers.
4. Ultrafast dynamics in **meso-space**. We have developed a **time-resolved optical measurement** system with femtosecond time-resolution to monitor light-induced chemical reactions. Using this technique, we are preparing to elucidate how molecules in meso-space behave under light irradiation. Along these same lines, we are studying porous materials developed by the Kitagawa Lab.

* In the different units, 1THz=1ps=300μm=33cm^{-1}=4.1meV=47.6 K.

Selected Papers

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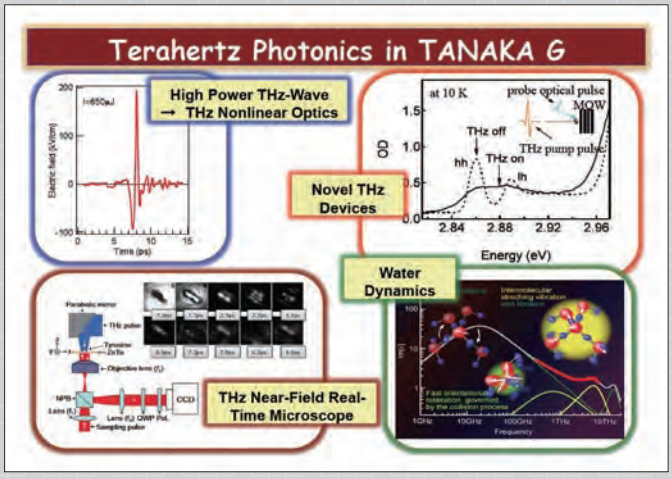
Jewariya, M., Nagai, M., and Tanaka, K., Ladder Climbing on the Anharmonic Intermolecular Potential in an Amino Acid Microcrystal via an Intense Monocycle Terahertz Pulse., *Phys. Rev. Lett.* **105**, 203003 (2010).

Brefuel, N., Watanabe, H., Toupet, L., Come, J., Matsumoto, N., Collet, E., Tanaka, K. and Tuchagues, J.P. Concerted Spin Crossover and Symmetry Breaking Yield Three Thermally and One Light-Induced Crystallographic Phases of a Molecular Material. *Angew. Chem., Int. Ed.* **48**, 9304–9307 (2009).

Watanabe, H., Hirori, H., Molnar, G., Bousseksou, A. and K. Tanaka. Temporal decoupling of spin and crystallographic phase transitions in $Fe(PTZ)_6(BF_4)_2$. *Phys. Rev. B* **79**, 180405 (2009).

Bousseksou, A., Molnar, G., Real, J. A. and Tanaka, K. Spin crossover and photomagnetism in dinuclear iron(II) compounds. *Coord. Chem. Rev.* **251**, 1822–1833 (2007).



Kazumitsu Ueda Lab

Cellular Biochemistry

Faculty Members

Kazumitsu Ueda (Professor)

Research Overview

ABC (ATP-binding cassette) proteins comprise the largest membrane transporter family, which transports various compounds in an ATP-dependent manner. They play important physiological roles in almost all cells of all species from bacteria to humans. About 50 **ABC proteins** in humans function to defend our bodies against toxic compounds in the environment, circulate various metabolites, and maintain homeostasis of glucose, cholesterol, and other compounds. Functional defects in these proteins can lead to a variety of pathological conditions, including cardiovascular diseases, diabetes, senile blindness, respiratory failure of infants, skin diseases, and neuronal diseases. Our research on **ABC proteins** will contribute to human health by exploring the cause of such diseases and finding ways to prevent them.

At the iCeMS, we are carrying out the following cross-disciplinary research projects:

1. Analyzing the expression profile of **ABC proteins** in **ES and iPS cells**, and developing synthetic small molecules which can modulate the functions of **ABC proteins**. These compounds will facilitate the study of the physiological roles of **ABC proteins** in **ES and iPS cells** as well as finding ways to prevent various diseases. (In collaboration with the Nakatsuji, Yamanaka, and Uesugi Labs.)

2. ABCA1 and ABCG1 are key molecules for generating high-density lipoprotein (HDL), which is so-called “good cholesterol” and critical for cholesterol homeostasis. However, their functional mechanisms are still unclear. Furthermore, it is suggested that they reorganize some **meso-domains** on the plasma membrane and modulate immune and inflammation responses. We are trying to reveal the functions of these **ABC proteins** by visualizing them on the plasma membrane in collaboration with the Kusumi and Heuser Labs at the **CeMI** (Center for Meso-Bio Single-Molecule Imaging).

3. We are analyzing the **functional architectures** of **ABC proteins** using single molecule analysis and X-ray crystal structure analysis. We are trying to develop synthetic artificial transporters and channels, which can modulate cell functions and behaviors in response to chemical or physical stimuli, based on the knowledge of **functional architectures** of **ABC proteins**. (In collaboration with the Kitagawa and Imahori Labs.)

Selected Papers

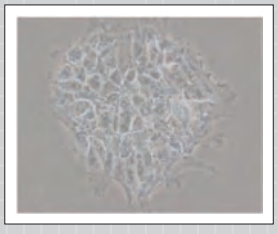
Nagao, K., Tomioka, M., and Ueda, K. Function and regulation of ABCA1- Membrane meso-domain organization and re-organization, *FEBS J.* **278**, 3190-3203 (2011).

Hozoji-Inada, M., Munehira, Y., Nagao, K., Kioka, N., and Ueda, K. LXRβ directly interacts with ABCA1 to promote HDL formation during acute cholesterol accumulation. *J Biol Chem.* **286**, 20117–24 (2011).

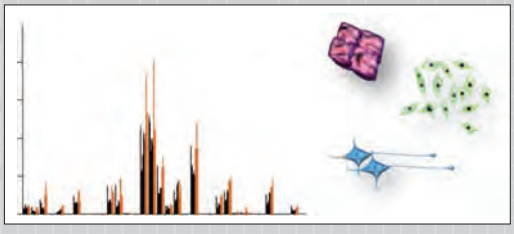
Yamashita H, Ueda K, and Kioka N. WAVE2 forms a complex with cAMP-dependent protein kinase (PKA) and is involved in PKA enhancement of membrane protrusions. *J Biol Chem.* **286**, 3907–3914 (2011).

Nagao, K., Takahashi, K., Hanada, K., Kioka, N., Matsuo, M. and Ueda, K. Enhanced apoA-I-dependent cholesterol efflux by ABCA1 from sphingomyelin-deficient CHO cells. *J Biol Chem.* **282**, 14868–74 (2007).

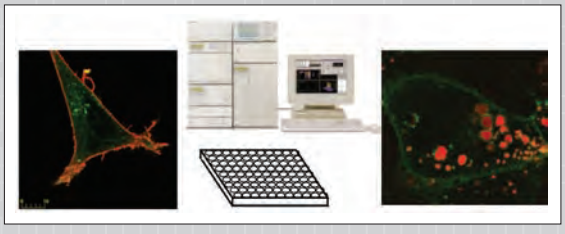
Morita, S.-y., Kobayashi, A., Takanezawa, Y., Kioka, N., Handa, T., Arai, H., Matsuo, M. and Ueda, K. Bile Salt-Dependent Efflux of Cellular Phospholipids Mediated by ATP Binding Cassette Protein B4. *Hepatology* **46**, 188–199 (2007).



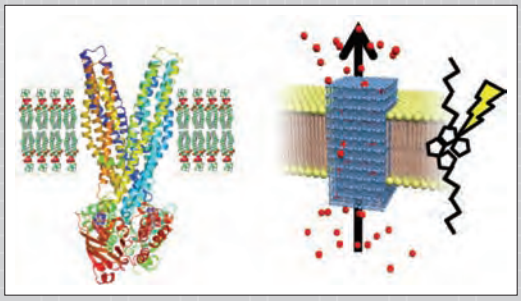
hES cells



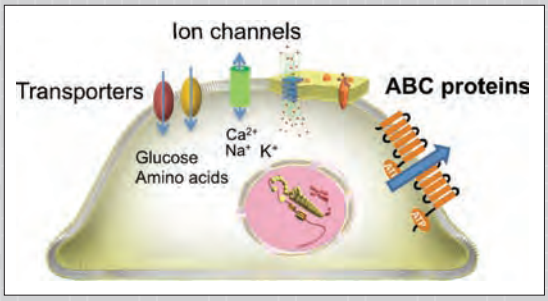
Physiological functions of ABC proteins in ES cells



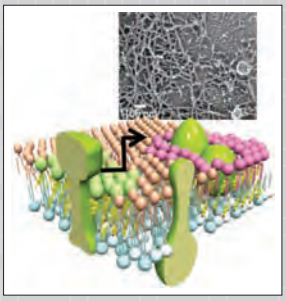
Development of activators and inhibitors of ABC proteins



Functional architectures



Transporters and channels



Membrane meso-domain formation

Motonari Uesugi Lab

Chemical Biology

Faculty Members
Motonari Uesugi (Professor)
Shinichi Sato (Assistant Professor)

Research Overview

Chemical biology is often defined as "chemistry-initiated biology," in which scientists start with chemistry and end up understanding biology by utilizing chemical tools. Our laboratory has been discovering or designing small-molecule tools that modulate fundamental processes in human cells. Such small organic molecules often serve as tools for basic cell biology and/or for cell therapy. Discovery or design of small molecules with unique biological activity permits small-molecule initiated exploration of complex cellular events, and may also contribute to the realization of cell therapy. Although our primary goal is to provide chemical tools for biological investigations, we also hope to open new avenues for small-molecule applications in a range of fields.

Below are a few examples of projects in our research group.

- Discovery and development of small-molecule fibronectin mimics. Cells in the human body form tissues and organs by attaching to the extracellular matrix. Cell attachment is mediated by the large protein, fibronectin. We have been designing small molecules that mimic this 440 KDa protein. "Small molecule fibronectins" may facilitate cost-effective culture, proliferation, and transplantation of human cells, and may be useful in both in basic cell biology and in cell therapy.
- Discovery and development of small molecule tools useful for cell therapy. One potential problem of cell therapy is high cost. Small molecule tools for cell therapy offer the advantage of cost-effective mass production. Thus, using small molecules in cell therapy will increase the affordability and accessibility of cell therapy worldwide. Most importantly, the use of stable and well-defined synthetic small molecules may compensate for ill-defined cell therapy.
- External control of transcription by small molecule transcription factors. Regulation of gene expression by transcription factors touches every process in eukaryotic biology. Our group previously showed that it is possible to create a functional transcription factor out of completely organic components. More precise mimics of naturally occurring transcription factors may serve as tools for cell biology and stem cell biology.

Selected Papers

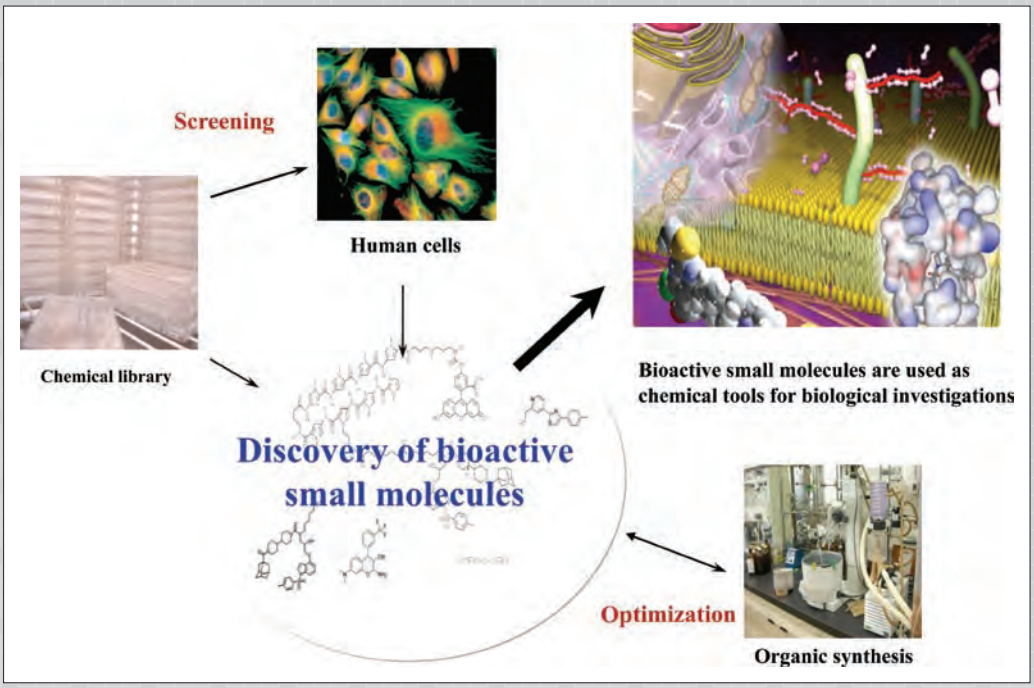
Kawazoe, Y., Shimogawa, H., Sato, A., and Uesugi, M. A Mitochondrial Surface-Specific Fluorescent Probe Activated by Bioconversion. *Angew. Chem. Int. Ed.* **50**, 5478–81 (2011).

Kamisuki, S., Mao, Q., Abu-Elheiga, L., Gu, Z., Kugimiya, A., Kwon, Y., Shinohara, T., Kawazoe, Y., Sato, S., Asakura, K., Choo, H., Sakai, J., Wakil, S. J. and Uesugi, M. A Small Molecule that Blocks Fat Synthesis by Inhibiting the Activation of SREBP. *Chem. Biol.* **16**, 882–892 (2009).

Yamazoe, S., Shimogawa, H., Sato, S., Esko, J. D. and Uesugi, M. A Dumbbell-Shaped Small Molecule that Promotes Cell Adhesion and Growth. *Chem. Biol.* **16**, 773–782 (2009).

Jung, D., Shimogawa, H., Kwon, Y., Mao, Q., Sato, S., Kamisuki, S., Kigoshi, H. and Uesugi, M. Wrenchnolol Derivative Optimized for Gene Activation in Cells. *J. Am. Chem. Soc.* **131**, 4774–4782 (2009).

Sato, S., Kwon, Y., Kamisuki, S., Srivastava, N., Mao, Q., Kawazoe, Y. and Uesugi, M. Polyproline-rod approach to isolating protein targets of bioactive small molecules: Isolation of a new target of indomethacin. *J. Am. Chem. Soc.* **129**, 873–880 (2007).



Shinya Yamanaka Lab

Stem Cell Biology, Developmental Engineering

Faculty Members

Shinya Yamanaka (Professor)
Yasuhiro Yamada (Professor)
Yoshinori Yoshida (Senior Lecturer)
Akitsu Hotta (Assistant Professor)
Akira Watanabe (Assistant Professor)
Knut Woltjen (Assistant Professor)

Research Overview

Our research group is focused on stem cell biology and developmental engineering. In particular, we have established mouse and human induced pluripotent stem cells (**iPS cells**), and we are carrying out various aspects of basic and applied research using **iPS cell** technology.

iPS cells can be generated from a wide range of somatic cell types, and many different methods have been developed for their generation. It is believed, however, that iPS cells are not in fact completely identical with ES cells. Using cell biology methods, including in vitro differentiation induction, and molecular biology methods, we plan to evaluate the pluripotency and safety of these cell types. By expanding our understanding of the mechanisms that underlie **reprogramming** and pluripotency, we aim to generate and culture iPS cells compatible for use in clinical applications. We also seek to use patient-specific iPS cells to study disease mechanisms and applications in drug development.

Using the viral vector transgene delivery system which drives the undifferentiated pluripotent stem cell-specific expression of GFP and drug-resistance genes as a high-efficiency method of selecting human iPS cells, we have facilitated the derivation of various patient-specific iPS cell lines and investigated the intra-nuclear changes that accompany the **reprogramming** process. With this platform, we will develop techniques for the generation and selection of safer human iPS cells, aiming for a novel iPS-based gene therapy approach to the treatment of hemophilia and other genetic disorders.

Using a drug-regulated transgenic mouse system, we are examining the role of iPS cell reprogramming factors in various somatic cells. Prematurely terminated reprogramming reverts cells back towards their original state, suggesting retention of an epigenetic memory. We are examining the chromatin changes induced by transcription factors leading to repression of key differentiation genes and stabilization of pluripotency. Understanding this mechanism may help to enhance reprogramming efficiencies and generate higher quality iPS cells. Also we have developed transposons as non-viral transgene delivery vectors for iPS cell reprogramming. Now, we are applying modifications of transposon technology to address genetic modification, gene discovery (functional annotation) and disease modeling in human iPS cells.

In order to apply iPS cells in a clinical setting, the risk of tumorigenesis from iPS cell-derived cells is to be eliminated. We are now trying to understand the mechanisms how tumor cells arise from iPS cell-derived cells to develop the safer methods of clinical application of iPS cells. We also expand the iPS cell research to understand the cancer biology, by applying the technology for inducing iPS cells to cancer cells in order to change the epigenetic status of cancer cells. Such epigenetically modified cancer cells may be useful to uncover the role of epigenetic control in cancer development.

Selected Papers

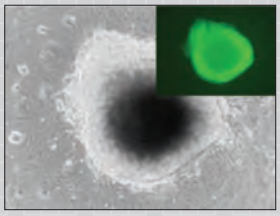
Maekawa, M., Yamaguchi, K., Nakamura, T., Shibukawa, R., Kodanaka, I., Ichisaka, T., Kawamura, Y., Mochizuki, H., Goshima, N., and Yamanaka, S. Direct reprogramming of somatic cells is promoted by maternal transcription factor Glis1. *Nature* **474**, 225–229 (2011).

Yamada, Y., Aoki, H., Kunisada T., and Hara, A. Rest promotes the early differentiation of mouse ESCs but is not required for their maintenance. *Cell Stem Cell* **6**, 10–15 (2010).

Woltjen, K., Michael, I.P., Mohseni, P., Desai, R., Mileikovsky, M., Hämäläinen, R., Cowling, R., Wang, W., Liu, P., Gertsenstein, M., Kaji, K., Sung, HK., and Nagy, A. piggyBac transposition reprograms fibroblasts to induced pluripotent stem cells. *Nature* **458**, 766–770 (2009).

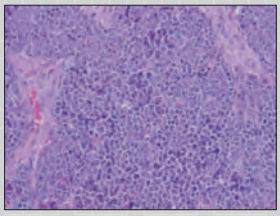
Hotta, A., Cheung, A. Y., Farra, N., Vijayaragavan, K., Seguin, C. A., Draper, J. S., Pasceri, P., Maksakova, I. A., Mager, D. L., Rossant, J., Bhatia, M., and Ellis, J. Isolation of human iPS cells using EOS lentiviral vectors to select for pluripotency. *Nat. Methods* **6**, 370–376 (2009).

Yoshida, Y., Takahashi, K., Okita, K., Ichisaka, T., and Yamanaka, S. Hypoxia enhances the generation of induced pluripotent stem cells. *Cell Stem Cell* **5**, 237–241 (2009).

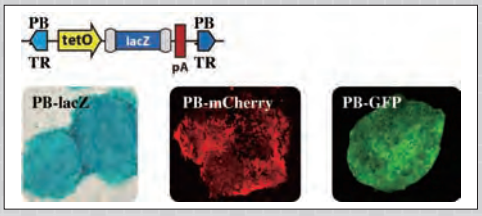


Mouse iPS cells

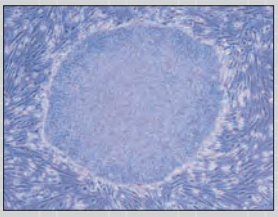
Progeny of chimeric mice derived from Nanog-iPS cells



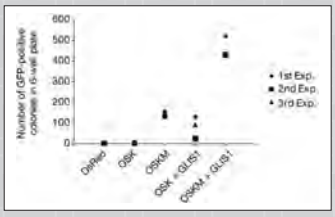
Representative histology of tumor in iPS cells-derived chimeric mouse



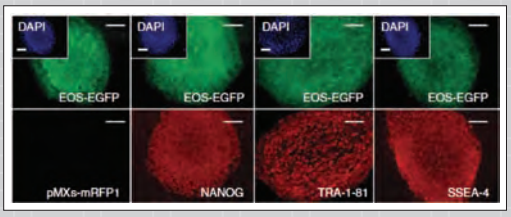
Drug-inducible reporter gene expression in piggyBac (PB) transgenic human iPS cells



Human iPS cells



Enhancement of reprogramming using Glis1 gene



EOS lentiviral vector selection system for human iPS cells

NCBS-inStem Satellite Lab Group

Kenichi G. N. Suzuki

Single-Molecule Cell Biophysics, Membrane Biology

Kouichi Hasegawa

Stem Cell Biology, Developmental Biology

Faculty Members Kenichi G. N. Suzuki (Associate Professor) Kouichi Hasegawa (Senior Lecturer)

Research Overview

Our mission is solidification and progression of international relationship between our iCeMS and the Tata Institute for Fundamental Research's National Centre for Biological Sciences (NCBS) and the Institute for Stem Cell Biology and Regenerative Medicine (inStem), Bangalore, India. The relationship between iCeMS and NCBS-inStem is, of course, is not limited in research collaborations. We are holding joint symposium, exchanging researchers, and conducting NCBS-inStem Satellite Facility in iCeMS and iCeMS Satellite Laboratory in NCBS-inStem.

Our study is focused on understanding how **signal transductions** regulate cell proliferation, migration, differentiation and function. We are working on this big aim in variety of biological processes and samples including a variety of cultured cells including human ES/iPS cells and mouse. We are also using various tools from conventional to most current techniques in biophysics, chemistry, single molecule imaging, developmental biology, cell and molecular biology. Our current and main projects are listed below.

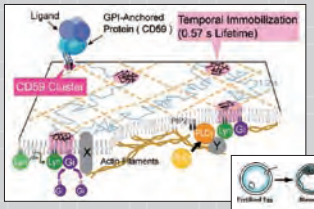
1. **Unraveling of dynamic mechanisms in cellular systems** by high-resolution and multicolor single molecule imaging of receptors and signaling molecules in live cells.
2. **Elucidation of molecular mechanisms** in cell plasma membranes by single molecule imaging with high temporal resolution.
3. **Signaling cascades regulate the pluripotent transcriptional network** and epigenetic reprogramming.
4. **Molecular mechanisms involved in cell fate determination** in early embryonic development and pluripotent stem cell differentiation.

Selected Papers

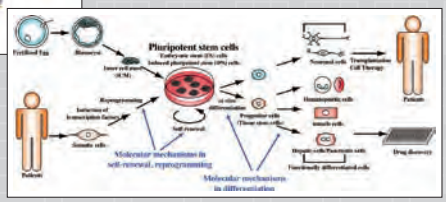
Tanaka, K. A. K*, Suzuki, K. G. N* (*equal contribution), Shirai, Y. M., Shibutani, S. T., Miyahara, M. S., Tsuboi, H., Yahara, M., Yoshimura, A., Mayor, S., Fujiwara, T. K., and Kusumi, A. Membrane molecules mobile even after chemical fixation. *Nature methods*, **7**, 865–866 (2010).

Hasegawa K., Pomeroy J. E. and Pera M. F. Current technology for the derivation of pluripotent stem cell lines from human embryos. *Cell Stem Cell*, **6**, 521–531 (2010).

Suzuki, K. G. N., Fujiwara, T. K., Sanematsu, F., Iino, R., Edidin, M. and Kusumi. A. GPI-anchored receptor clusters transiently recruit Lyn and G alpha for temporary cluster immobilization and Lyn activation: single molecule tracking study 1. *J. Cell Biol.* **177**, 717–730 (2007).



Single molecule observation enabled us to propose a working model showing how liganded CD59 clusters may function as a transient platform to transduce the extracellular signal to the intracellular signal.



Research objective in regenerative medicine

Shintaro Sengoku (Innovation Management Group)

Innovation Management, Science & Technology Management

Faculty Members

Shintaro Sengoku (Associate Professor) Takashi Asada (Professor) Nobuo Uotani (Professor)

Research Overview

In addition to being institutions for advanced learning and research, present day universities are increasingly expected to provide knowledge applicable to society. Consequently, an institutional effort must be undertaken to manage the mindsets of university personnel in order to realize for society the promises of their leading edge inventions and discoveries.

Our group promotes a fusion approach for international, interdisciplinary and industrial collaborations and explores a novel **management** model which aims to achieve true innovation.

Selected Papers

Sengoku, S., Sumikura, K., Oki, T., Nakatsuji, N. Redefining the Concept of Standardization for Pluripotent Stem Cells. *Stem Cell Reviews and Reports,* **7(2)**, 221–226 (2011).

Sengoku, S., Yoda, T., Seki, A. Assessment of Pharmaceutical Research & Development Productivity with a Novel Net Present Value-Based Project Database. *Drug Information Journal,* **45(2)**, 175–185 (2011).

Kusama R., Shime, T., Sengoku, S., Kawai, H., Kunieda, K., Yamada, K., Suematsu, C. Intellectual Productivity Management in Research Projects: Theoretical and Observational Approaches. Proceeding of PICMET 2011 Conference (2011).

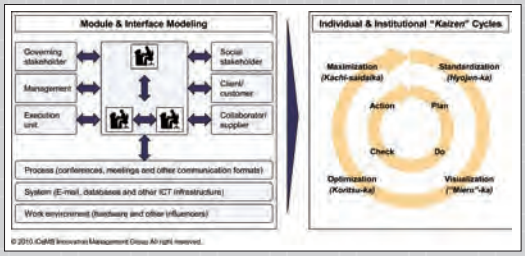


Fig. 1
Schematic diagram of a transaction-based approach for the management of collaborations

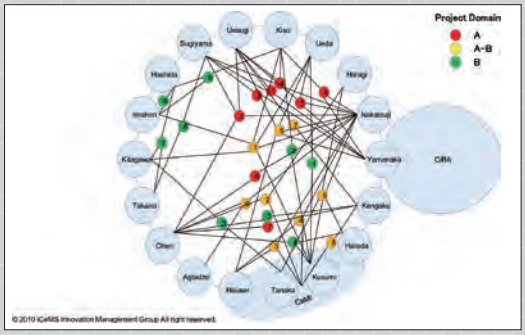


Fig. 2
Example network analysis of scientific integration and cross-disciplinary collaboration in the iCeMS. (preliminary version, 2009)

Kazuto Kato (Science Communication Group)

Science Communication

Faculty Members

Kazuto Kato (Adjunct Associate Professor) Kei Kano (Assistant Professor)

Research Overview

Science's rapid development and ever growing influence on society make it imperative that researchers recognize the social impact and meaning of their research, as well as actively engage with the general public.

Our group has been developing and evaluating three kinds of science communication activities, which we call the 3Cs (see figure). Through these, we aim to develop a **teaching program for researchers to enhance science communication skills** in a bid to build stronger mutual relations among researchers in different fields and between scientific communities and society.

Selected Papers

Kato, K., Kano, K. and Shirai, T. Science Communication: Significance for Genome-Based Personalized Medicine – A View from the Asia-Pacific. *Curr. Pharmacogenomics Pers. Med.* **8**, 92–96 (2010).

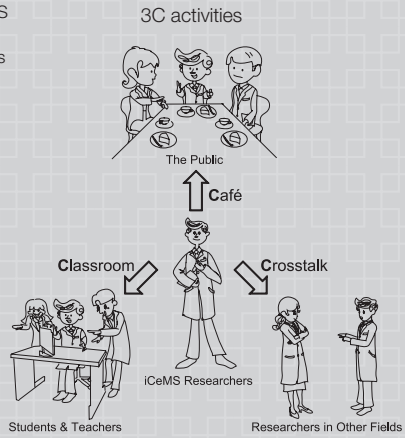
Zarzeczny, A., Scott, C., Hyun, I., Bennett, J., Chandler, J., Chargé, S., Heine, H., Isasi, R., Kato, K., Lovell-Badge, R., McNagny, K., Pei, D., Rossant, J., Surani, A., Taylor, P. L., Ogbogu, U. and Caulfield, T. iPS Cells: Mapping the Policy Issues. *Cell* **139**, 1032–1037 (2009).

Kano, K., Yahata, S., Muroi, K., Kawakami, M., Tomoda, M., Miyaki, K., Nakayama, T., Kosugi, S. and Kato, K. Multimedia presentations on the human genome: Implementation and assessment of a teaching program for the introduction to genome science using a poster and animations. *Biochem. Mol. Biol. Educ.* **36**, 395–401 (2008).

Cafés: As in "science cafés". iCeMS principal investigators (PIs) and colleagues engage in conversations with the public over tea and coffee in a relaxed, friendly atmosphere.

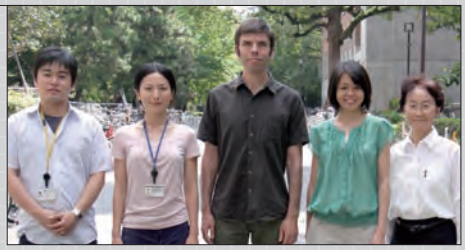
Crosstalks: A young researcher of the iCeMS speaks with one of the iCeMS PIs of his or her choice on the PI's thoughts about research and science.

Classrooms: Young iCeMS researchers collaborate with school teachers on cutting-edge educational programs. These hands-on research seminars include both laboratory work as well as extensive group discussions.



Peter Carlton

Meiosis, Chromosome Biology, Optical Microscopy



Faculty Members

Peter Mark Carlton (Assistant Professor / iCeMS Kyoto Fellow)

Research Overview

Our research group studies how the structure and dynamic behavior of **chromosomes** in **meiosis** control pairing, recombination, and the correct transmission of the genome. Errors in meiosis cause many human health problems, from infertility to birth defects. We use the nematode Caenorhabditis elegans as a model system for its excellent genetic and cytological qualities. A main focus of the lab is the use of **superresolution** techniques such as **3D structured illumination** and **single-molecule composition microscopy** to assess chromosome structure at the mesoscale. We aim to find the mechanisms underlying the recognition of chromatin as paired or unpaired, and understand why **meiotic** recombination occurs between homologs rather than sister chromatids. An additional area of interest is the study of dynamic processes such as **chromosome** movement with fast three-dimensional multiwavelength fluorescence imaging under conditions that preserve full viability. Collaborative efforts within iCeMS will apply advanced optical microscopy to questions of nuclear organization in mammalian stem cells, meiosis in mammalian systems, and neural development.

Selected Papers

Wang, C. J. R.*, Carlton P. M.*, Golubovskaya, I. and Cande, W. Z. Interlock formation and coiling of meiotic chromosome axes during synapsis. *Genetics* **183**, 905–915 (2009).

Schermelleh, L.*, Carlton, P. M.*, Haase, S., Shao, L., Winoto, L., Kner, P., Burke, B., Cardoso, M. C., Agard, D. A., Gustafsson, M. G., Leonhardt, H. and Sedat, J. W. Subdiffraction multicolor imaging of the nuclear periphery with 3D structured illumination microscopy. *Science* **320**, 1332–1336 (2008).

Carlton, P. M. Three dimensional structured illumination microscopy and its application to chromosome structure. *Chromosome Res.* **16**, 351–365 (2008).

*co-first authors

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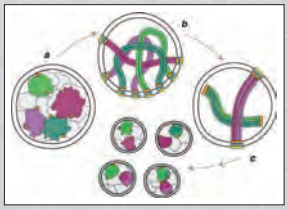

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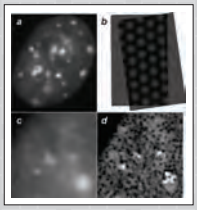
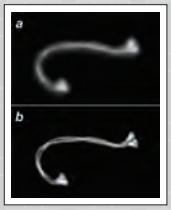


3



1. Meiosis creates haploid gametes from diploid precursor cells by an intricately coordinated reorganization of chromosomes. Chromosomes elongate (*a*) and attach their ends to the nuclear envelope. The ends undergo dynamic movement thought to contribute to the pairing process. Paired chromsomes (*b*) undergo recombination, exchanging genetic material. After two cell divisions (*c*), newly arranged chromosomes are contained in haploid gametes.

2. 3D Structured Illumination Microscopy (3D-SIM) has twice the resolution of optical microscopy. A striped pattern of light (*a*) interacts with the sample, allowing detection of fine details due to the moiré effect (*b*). Two views of mouse interphase chromatin at the nuclear periphery demonstrate increased resolution: (*c*), a conventional image, and (*d*), the same region with 3D-SIM. The exclusion of chromatin from the nuclear pore complexes appears as holes less than 150nm in diameter. (See Schermelleh, et al. 2008)

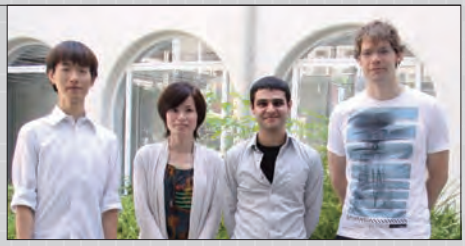
3. Conventional (*a*) and 3D-SIM (*b*) immunofluorescence images of a mouse meiotic chromosome synaptonemal complex (α-Sycp3 immunostaining). The separation and twisting of the synaptonemal complex can only be seen in the 3D-SIM image. Material provided by Dr. Shinichiro Chuma, Institute for Frontier Medical Sciences, Kyoto University.

Ziya Kalay

Statistical Physics

Faculty Members

Ziya Kalay (Research Associate / iCeMS Kyoto Fellow)



Research Overview

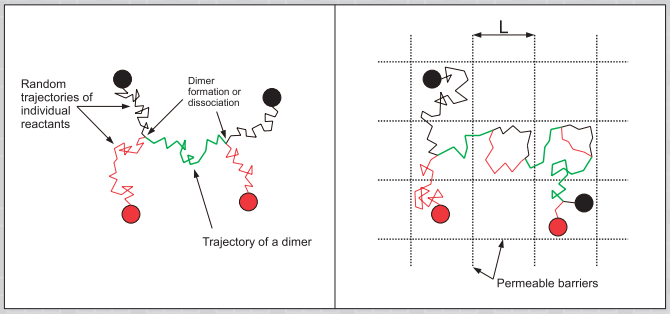
In predicting the state of a system in the future, system size and the number of constituents often determine the way we proceed. For just a few atoms, we can use quantum mechanics. For a collection involving multiples of Avogadro's number of them, we have statistical theories at our disposal. In between, there are many meso-scale systems of interest, for which well-established theories are not available. We are mainly interested in filling this gap by finding answers to questions such as the following: Can **mesoscopic structures** found in biological systems make use of thermal fluctuations to perform their functions? If so, how? How does **confinement** of membrane molecules **in mesoscale** (30–300 nm) **compartments** modify their reaction rate? This is one of the many questions we would like to answer to understand the hierarchical organization of the plasma membrane of live cells that spans the nano-meso-micron scales. In many cases, biological systems can be modeled by a collection of coupled oscillators, e.g. a network of neurons. To what extent can we predict the **response** of a collection of **coupled oscillators** to varying stimuli?

Selected Papers

Kalay, Z. Fundamental and functional aspects of mesoscopic architectures with examples in physics, cell biology, and chemistry. *Critical Reviews in Biochemistry and Molecular Biology*, **46**, 310–326 (2011).

Kalay, Z., Fujiwara, T. and Kusumi, A. "Cytoskeleton-induced mesoscale domains" in Cellular domains, edited by Nabi I. R. chapter 1. Wiley-Blackwell (Hoboken, NJ) (2011).

Uehara H., Diring, S., Furukawa, S., Kalay, Z., Tsotsalas, M., Nakahama, M., Hirai, K., Kondo, M., Sakata, O. and Kitagawa, S. Porous Coordination Polymer Hybrid Device with Quartz Oscillator: Effect of Crystal Size on Sorption Kinetics. *JACS*, **133**, 11932–11935 (2011).



Schematic illustration of the kinetics of dimer formation involving two diffusing reactants in free space (left), and in the presence of an array of partially permeable barriers (right). Partial confinement can enhance reaction efficiency by increasing the chances of collision after dissociation. In the plasma membrane of various live cells, lipids and proteins are observed to be partially confined in regions with L ~ 30-300 nm (Kusumi et al., Annu. Rev. Biophys. Biomol. Struct. 34 (2005), 351).

Franklin Kim

Synthetic Nano-/Meso-Chemistry, Self-Assembly

Faculty Members

Franklin Kim (Assistant Professor / iCeMS Kyoto Fellow)

Research Overview

Our group is interested in using various **nanomaterials as building blocks** for **constructing novel functional nano/mesoscale structures**, either through chemical synthesis or self-assembly. We focus on developing strategies which will allow precise control over the property of the produced structures, with emphasis in applications for cell-biological studies. Not only are we interested in using such materials for applications such as sensing and drug delivery, but also in gaining fundamental understanding on how they interact within the biological system in the molecular level. The multidisciplinary and strong collaborative environment of iCeMS makes it an excellent place to pursue such research that intersects materials science and biology.

We are currently exploring the following topics.

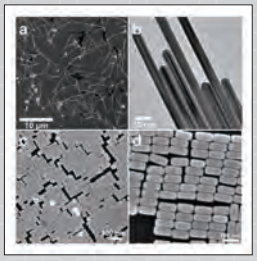
1. **Gold nanoparticles & nanowires**
   Due to their strong optical responses and biocompatibility, gold nanoparticles are used in a wide range of biological studies. Through precise control over the particle morphology and surface modification, we aim to develop structures that can be used for bio-sensing and therapeutics.
2. **Graphene-based composites**
   Graphene has gained much recent interest due to their high surface area, impressive electrical and mechanical properties, and chemical stability. We aim to utilize these sheets as a substrate for loading functional materials such as biomolecules and nanoparticles, which can then be integrated into cells.
3. **Self-assembly using Langmuir-Blodgett technique**
   Langmuir-Blodgett is a powerful method for preparing well-controlled two-dimensional assembly of nanoscale building blocks. Through assembly of biomolecules such as DNA, we plan to develop platforms for studying cell growth and proliferation.

Selected Papers

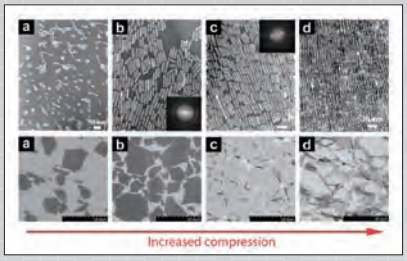
Kim, F., Cote, L., and Huang, J. Graphene oxide: surface activity and two-dimensional assembly. *Adv. Mater.* **22**, 1954 (2010).

Kim, F., Sohn, K., Wu, J., and Huang, J. Chemical synthesis of gold nanowires in acidic solutions. *J. Am. Chem. Soc.* **130**, 14442 (2008).

Kim, F., Crux-Silva, R., Luo, J., Cote, L., Sohn, K., and Huang, J. Self-propagating solid state reactions in oxidized graphite. *Adv. Funct. Mat.* **20**, 2867 (2010).



Shape controlled synthesis of gold nanoparticles (a and b: nanowire, c: nanocube, d: square cuboid)



Two-dimensional (2D) assemblies of nanoscale building blocks prepared by Langmuir-Blodgett technique (top: $BaCrO_3$ nanorods, bottom: graphene oxide nanosheets)

Tatsuya Murakami

Cell Engineering, Protein Engineering

Faculty Members

Tatsuya Murakami (Assistant Professor / iCeMS Kyoto Fellow)

Research Overview

Recent progress in the field of nanotechnology has enabled the creation of various nanostructures, including nanoparticles, nanodiscs, nanocubes, nanorods, and nanofibers. Some of these can be made responsive to **external stimuli**, and used, for instance, to kill cancer cells. When size-controlled at the mesoscale, they have potential as vehicles for cellular uptake and allow prolonged blood circulation, the latter being an essential function in drug delivery systems. To utilize these properties, however, it is necessary to refine the surface of the nanostructures to make them biocompatible and give them useful functions.

We have developed methods for modifying the surface of carbon nanomaterials for use in double **photodynamic and photothermal** cancer chemotherapy. We have also published papers on strategies for size control of protein-lipid nanodiscs at the **mesoscale**, and on a biocompatible carrier for **intracellular delivery** of various materials.

In the interests of making further progress based on these experiences, we have now started multidisciplinary research projects on biological applications of functionalized nanostructures in collaboration with other research groups in- and outside the iCeMS:

1. Development of **biocompatible dispersants** using protein engineering approaches
2. **Manipulation of cell function and fate** with external stimuli-responsive nanostructures
3. **Spatiotemporal regulation of drug therapy** with external stimuli-responsive nanostructures

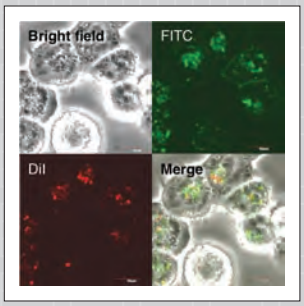
Selected Papers

Murakami, T., Kashiwagi, K., Shiba, K. Creation of novel signalling modulators from existing cytokine using scanning motif-programming. *Chem. Commun.* **47**, 9357–9359 (2011).

Murakami, T., Wijagkanalan, W., Hashida, M. and Tsuchida, K. Intracellular drug delivery by genetically engineered high density lipoprotein nanoparticles. *Nanomed (Lond)* **6**, 867–879 (2010).

Murakami, T., Tsuchida, K., Hashida, M. and Imahori, H. Size control of lipid-based drug carriers by drug loading. *Mol. BioSyst.* **6**, 789–791 (2010).

Cell-penetrating protein-lipid nanodisc



Confocal images of cells treated with cell-penetrating nanodisc

Carbon nanomaterials

Takuya Yamamoto

Molecular Biology, Bioinformatics

Faculty Members

Takuya Yamamoto (Assistant Professor / iCeMS Kyoto Fellow)

Research Overview

Elucidation of the molecular mechanisms of iPS cell induction processes is an important step toward applications of iPS cells for regenerative medicine. Analytical techniques (dry), such as bioinformatics, as well as molecular- and cell-biological experimental techniques (wet) are essential to extract biologically meaningful information from the enormous amounts of data acquired by such analytical devices as **microarrays and the next-generation sequencers**.

Our primary objective is to perform exhaustive analysis of the entire genome through multilateral approaches, fuse the dry and wet techniques by feedback, and elucidate the molecular mechanisms during iPS cell induction in an integrative way. Through our research, we would like to improve the efficiency and shorten the time needed to generate iPS cells.

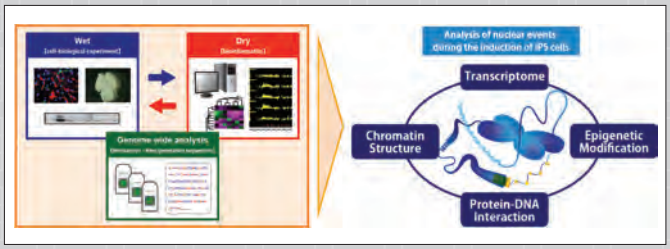
1. By using microarrays and next generation sequencers, we will perform **whole-transcriptome analysis** in iPS and ES cells to clarify the overall picture for gene expression controlling pluripotency.
2. By using next generation sequencers, we will perform **genome-wide analysis of epigenetic modifications, chromatin structures, and protein-DNA interaction** to shed light on the regulatory mechanisms in the nuclei of pluripotent stem cells.

Selected Papers

Sunadome, K., Yamamoto, T., Ebisuya, M., Kondoh, K., Sehara-Fujisawa, A., and Nishida, E. ERK5 Regulates Muscle Cell Fusion through Klf Transcription Factors. *Dev. Cell* **20**, 192–205 (2011).

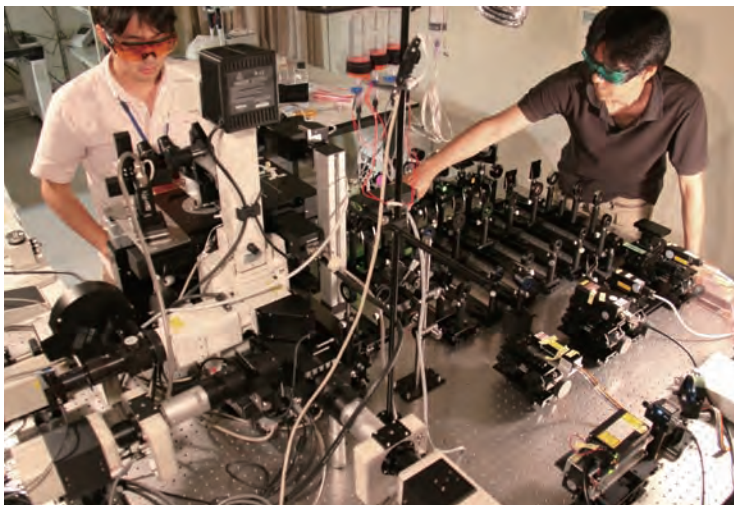
Honjoh, S., Yamamoto, T., Uno, M. and Nishida, E. Signalling through Rheb mediates intermittent fasting-induced longevity in C. elegans. *Nature* **457**, 726–730 (2009).

Yamamoto T., Ebisuya M., Ashida F., Okamoto K., Yonehara S. and Nishida E. Continuous ERK activation downregulates antiproliferative genes throughout G1 phase to allow cell-cycle progression. *Curr. Biol.* **16**, 1171–1182 (2006).



Research on the elucidation of iPS cell induction by comprehensive genome-wide analysis

Center for Meso-Bio Single-Molecule Imaging (CeMI)



CeMI
iCeMS Imaging Center

The CeMI was established on March 3, 2009, as the iCeMS' imaging innovation center for **cellular mesoscopic science**. Its key missions are:

- develop new, powerful technologies for imaging the *restless* nano- to meso-scale universe of biomolecular complexes in living cells, at the spatiotemporal resolutions of functioning single molecules, and
- make these technologies available quickly to the scientific community worldwide for the further advancement of cellular mesoscopic science.

The center places special emphasis on **single-molecule imaging** and **tracking**, and on **terahertz spectroscopy and microscopy**.

The following CeMI-built stations are currently in operation: four, single fluorescent-molecule tracking (SFMT) stations, each with various specific capabilities, including simultaneous three-color SFMT (unique in the world; see photo above), photoactivation, and the world's fastest frame-rate at 10 kHz (all operable for live cells at 37℃ in 5% CO_2 atmosphere); and a one terahertz microscope with the world's fastest image acquisition rate (10 Hz). Other advanced, commercial confocal/time- lapse fluorescence microscopes are also available.

The center has the following four specific areas of activity:

1. **Core Research**: Technology development and initial applications. These are conducted both in the laboratories of the core PIs as well as in the CeMI.
2. **Collaborative Research**: Following the development of new, pilot technologies and instruments by CeMI's core members, the first instruments for practical applications will be installed at the CeMI and then made available to all interested parties on a collaborative research basis. New, broad applications are expected to lead to further ground-breaking technologies and instruments. In addition, selected new technologies developed elsewhere will be implemented at the CeMI so that important advances can be incorporated as soon as possible.
3. **Education and Training**: The center will hold symposia, seminars, workshops, and hands-on training sessions, open to the scientific community worldwide.
4. **Services**: On a limited basis, CeMI personnel are available to obtain data for interested users, but only when the users are physically present. Commercial instruments, including those with both standard and advanced capabilities, are available to iCeMS scientists as well as to researchers outside of the iCeMS wishing to use the instruments for collaborative studies with iCeMS scientists.

The CeMI's aim is to become a world hub, where scientists from across the globe can gather to engage in **meso-bio**, **single-molecule imaging**, and to develop the mesoscopic science of cells.

www.cemi.icems.kyoto-u.ac.jp/e_index.php

Core Members

Participating PIs:	Yoshie Harada, John Heuser, Akihiro Kusumi (CeMI Director), and Koichiro Tanaka
Affiliated Researchers:	Peter Carlton and Ziya Kalay
Scientific Manager:	Takahiro Fujiwara (Senior Lecturer)
Visiting Professors:	Fumiyoshi Ishidate, Yoshihiro Oikawa, and Satoshi Ijuin
Imaging Technologists:	Hiroko Hijikata, Hisae Tsuboi, and Aiko Kondo

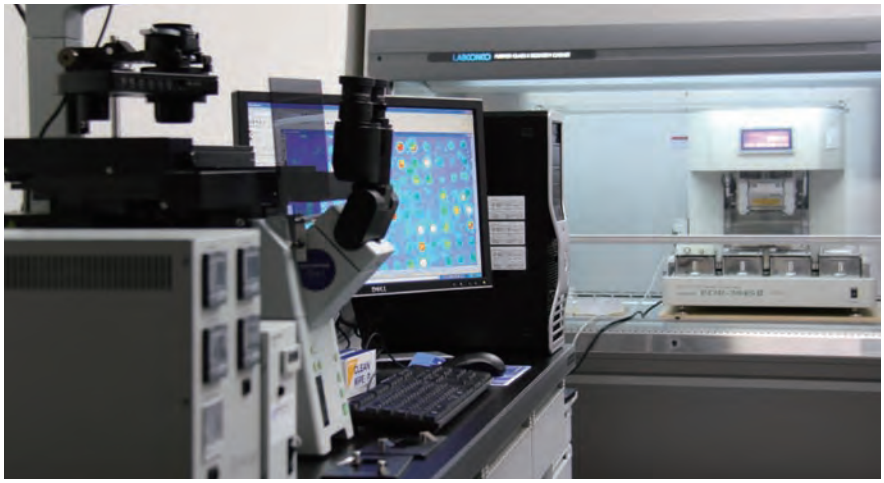
Industry Partners: Carl Zeiss Miocroscopy Co., Ltd., Hamamatsu Photonics K.K., JEOL Ltd., Leica Microsystems K.K., Nikon Instech Co., Ltd., Nikon Instruments Co., Ltd., Olympus Corp., Photron Ltd.

Dr. Fujiwara (second from left) and the CeMI staff

Visiting Professors (from left):
Prof. Ishidate, Prof. Oikawa, and Prof. Ijuin

iCeMS Chemical Screening Center

Including an automated screening system, cell culture equipment, and a chemical library of over 20,000 compounds, this center in the iCeMS main building serves as a core facility for discovering novel small organic molecules that modulate fundamental characteristics in mammalian cells, including ES/iPS cells. These resources are available to all iCeMS scientists, as well as to non-iCeMS researchers working in collaboration with iCeMS scientists.



The Chemical Screening Center in the iCeMS main building

iCeMS Katsura Laboratory

A 220 m^2 shared-use laboratory on Kyoto University's Katsura campus, with collaboration by four professors of the university's Graduate School of Engineering at its core. Research includes work on smart polymers whose phase transition (gel to solution) can be triggered by external stimuli. Such polymers can be combined, for example, with porous coordination polymers (PCPs) to enhance their functionality and compatibility with living cells.

The Funai Center housing the iCeMS Katsura Laboratory

Katsura Lab iCeMS Adj. Professors (from left):
Kazunari Akiyoshi (Department of Polymer Chemistry)
Itaru Hamachi (Department of Synthetic Chemistry and Biological Chemistry)
Yasuo Mori (Department of Synthetic Chemistry and Biological Chemistry)
Masahiro Shirakawa (Department of Molecular Engineering)

Initiatives Promoting Cell-Material Integration

Open laboratories and office spaces

Designed to encourage interaction and a natural, free flow of information among researchers from varying backgrounds.

Startup grants for cross-disciplinary collaboration

- iCeMS Exploratory Grants for Junior Investigators promote cross-disciplinary research among young iCeMS scientists. Selected so far: 13 projects (2009), 29 projects (2010), and 41 projects (2011).
- Funding for Kyoto University scientists collaborating with the iCeMS. So far selected: 19 (2010) and 15 (2011) joint projects with 12 university departments (2010).

Strategic Task Force for Cross-Disciplinary Research

Led by the institute deputy director and consisting of relevant PIs and younger researchers, providing strong institutional support for cross-disciplinary research.

Cross-Disciplinary Journal Club

Director-led web-based initiative, taking a lead role in interaction among fields. Including an online databank of scientific papers particularly useful in sparking ideas for new joint research projects.

Annual retreats for all research staff

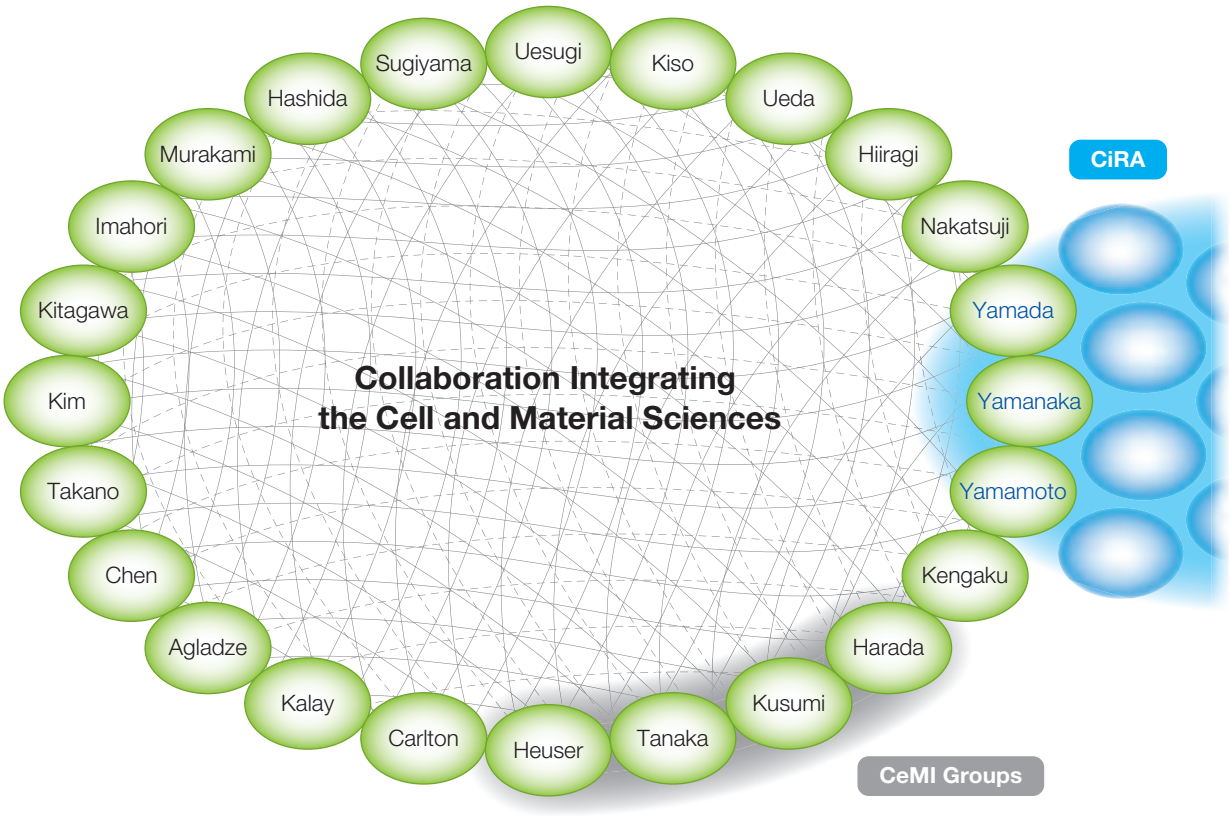
Enabling researchers to further interact through workshops, poster sessions, and recreational activities.
2009: 80 attended, 39 posters presented; **2010**: 121 attended, 74 posters presented; **2011**: 152 attended, 97 posters presented

iCeMS Seminars

A world-class series of invited speakers (90 total as of October 2011) including Prof. Kai Simons of the Max Planck Institute of Cell Biology and Genetics, Sir John Gurdon of the University of Cambridge, and Sir Ian Wilmut of the University of Edinburgh.

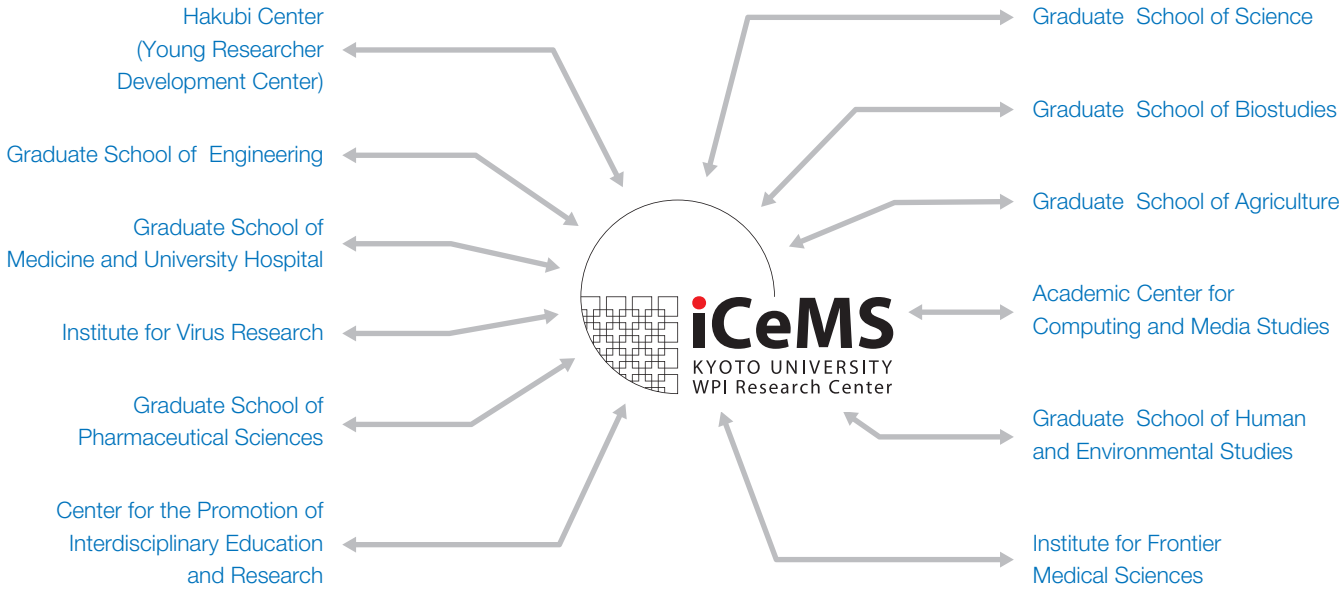
Joint Lab Meetings

Facilitating effective interaction among scientists from various fields of study.



University-Wide Cross-Disciplinary Collaboration

iCeMS exploratory cross-disciplinary grants supporting joint projects with other Kyoto University departments.

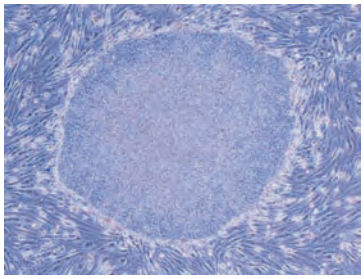


Collaboration with the Kyoto University Center for iPS Cell Research and Application (CiRA)

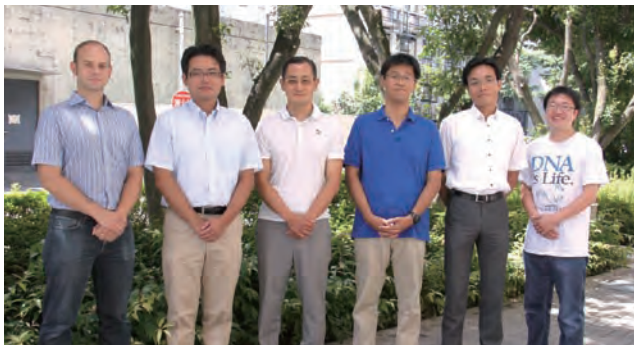
Following Prof Shinya Yamanaka's successful generation of induced pluripotent stem (iPS) cells from human fibroblasts in 2007, the Center for iPS Cell Research and Application (CiRA) was established in 2008 under the auspices of the iCeMS in order to further advance iPS cell research. The institute Director Norio Nakatsuji appointed iCeMS Prof Yamanaka as director of the CiRA.

In 2010 Kyoto University reestablished the CiRA as an independent institute under its jurisdiction. Prof Yamanaka serves both as director of the new center while continuing in his iCeMS professorship. The two sister institutes continue to be closely tied in their cooperative investigations involving basic research related to iPS cells.

www.cira.kyoto-u.ac.jp/e



iPS cells derived from
adult human dermal fibroblasts



From left: Drs. Woltjen, Yamada, Yamanaka, Yoshida, Hotta, and Watanabe

Kyoto University Center for iPS Cell Research and Application

People

As of Sep 1, 2011

Professor	18
Associate Professor	11
Senior Lecturer	7
Assistant Professor	20
Research Associate	67
iCeMS Kyoto Fellow	5
Adjunct Faculty	12
Visiting Faculty	42
Research Support Staff	73
Administrative Staff	32
Total	**287**

Finance

As of Sep 1, 2011
US $1 = 100 yen

WPI Grant	1 million USD / 100 million yen
FY 2007	**6.8**
FY 2008	**15.6**
FY 2009	**13.5**
FY 2010	**13.5**
FY 2011	**13.0**

Competitive Research Grant	
FY 2007	**6.4**
External Research Funding	4.8
MEXT/JSPS Grant-in-Aid for Scientific Research	1.5
Donations	0.1
FY 2008	**35.6**
External Research Funding	23.6
MEXT/JSPS Grant-in-Aid for Scientific Research	5.6
Donations	6.3
FY 2009	**56.4**
External Research Funding	46.1
MEXT/JSPS Grant-in-Aid for Scientific Research	9.7
Donations	0.6
FY 2010	**53.6**
External Research Funding	48.0
MEXT/JSPS Grant-in-Aid for Scientific Research	4.7
Donations	0.9
FY 2011	**38.2**
External Research Funding	34.8
MEXT/JSPS Grant-in-Aid for Scientific Research	3.2
Donations	0.2

MEXT: Ministry of Education, Culture, Sports, Science and Technology
JSPS: Japan Society for the Promotion of Science (a non-profit, independent administrative institution under the auspices of the MEXT)

Honors and Awards

Month/Year	Award/Prize	Awardee
Jun. 2011	Medal of Honor with Purple Ribbon 2011	Susumu Kitagawa
May. 2011	Member of National Academy of Sciences	John Heuser / Shinya Yamanaka
Mar. 2011	German Innovation Award Gottfried Wagener Prize (1st Prize)	Motonari Uesugi
Feb. 2011	Wolf Foundation Prize in Medicine	Shinya Yamanaka
Oct. 2010	Person of Cultural Merit (MEXT)	Shinya Yamanaka
Sep. 2010	2010 Thomson Reuters Citation Laureates	Susumu Kitagawa / Shinya Yamanaka
Aug. 2010	International Pharmaceutical Federation (FIP) Fellow Award	Mitsuru Hashida
Jul. 2010	American Society for Cell Biology (ASCB) Council Member	Akihiro Kusumi
Jun. 2010	2010 Kyoto Prize in Advanced Technology	Shinya Yamanaka
Mar. 2010	Japan Bioscience, Biotechnology and Agrochemistry Society Award	Kazumitsu Ueda
Mar. 2010	ABC2010 Young Investigator Award	Koh Nagata
Mar. 2010	Imperial and Japan Academy Prizes	Shinya Yamanaka
Jan. 2010	March of Dimes Prize in Developmental Biology	Shinya Yamanaka
Nov. 2009	Award for the Best Research Paper (Asian Association for Biology Education)	Kei Kano
Sep. 2009	Albert Lasker Basic Medical Research Award	Shinya Yamanaka
Apr. 2009	Canada Gairdner International Award	Shinya Yamanaka
Mar. 2009	The Chemical Society of Japan Lectureship Award	Shuhei Furukawa
Jan. 2009	The Chemical Society of Japan Award	Susumu Kitagawa
Nov. 2008	Medal of Honor with Purple Ribbon 2008	Shinya Yamanaka
Jul. 2008	Incentive Award for Young Scientist, Tokai Branch of The Society of Synthetic Organic Chemistry, Japan, 2008	Hiromune Ando
Apr. 2008	Humboldt Research Award	Susumu Kitagawa
Apr. 2008	Young Scientists' Prize for Science and Technology by the Japanese Minister of Education, Culture, Sports, Science and Technology	Takafumi Ueno
Feb. 2008	Robert Koch Prize 2008	Shinya Yamanaka
Dec. 2007	2007 NISTEP Prize (by the National Institute of Science and Technology Policy of the Japanese Ministry of Education, Culture, Sports, Science and Technology)	Hiroshi Imahori
Nov. 2007	American Association of Pharmaceutical Scientists, Research Achievement Award in Pharmaceutics and Drug Delivery	Mitsuru Hashida
Nov. 2007	The 25th Osaka Science Prize	Hiroshi Imahori

Facilities

As of May 1, 2012

iCeMS Main Building | Completed in March 2009

iCeMS West Building | Completed in September 2008

Approx. 5,000 m² of floor space

The iCeMS Main Building serves as the headquarters. In addition to ample shared laboratory space, it includes a seminar hall, a lounge for informal researcher get-togethers, and an exhibition room that doubles as a meeting space.

iCeMS Main Building:
Located at the "Higashiyama-Higashiichijo" intersection, across from the university headquarters

iCeMS Research Building | Completed in November 2010

Research Building No.1/Project Lab | Completed in September 2008

Research Building No.1 Annex | Completed in July 2009

Approx. 6,000 m² of floor space

Researchers from different groups collaborate with each other in extensive shared laboratory and office spaces to advance cross-disciplinary research.

iCeMS Research Building:
Located at the "Hyakumanben" intersection, about 200 meters from the iCeMS Main Building

Shared laboratories and open offices:
Designed to be shared by research groups from various fields in order to promote cross-disciplinary research

Directions

Yoshida Campus, Kyoto University

iCeMS Main Building

iCeMS West Building

Yoshida Ushinomiya-cho, Sakyo-ku, Kyoto
One-minute walk from “Kyodai Seimon-mae” Stop
(Kyoto City Bus)

iCeMS Research Building

Research Building No.1/Project Lab
Research Building No.1 Annex

Yoshida Honmachi, Sakyo-ku, Kyoto
One-minute walk from “Hyakumanben” Stop
(Kyoto City Bus)

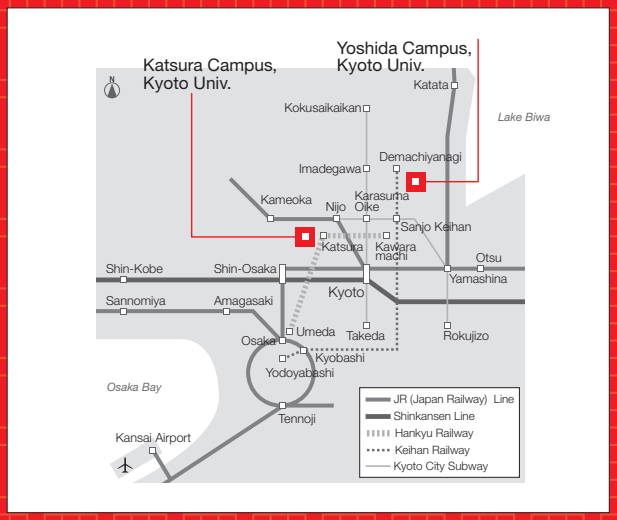
Kyoto University Center for iPS Cell Research and Application (CiRA)

53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto
Five-minute walk from “Jingu-Marutamachi” Station
(Keihan Railway)

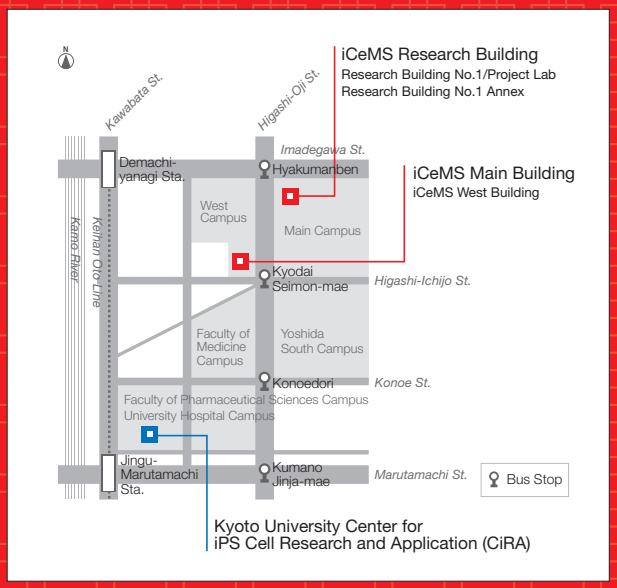
Katsura Campus, Kyoto University

iCeMS Katsura Laboratory

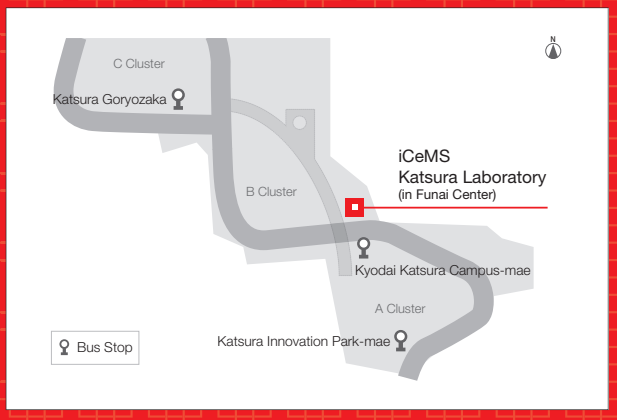
Kyoto University Katsura, Nishikyo-ku, Kyoto
Three-minute walk from “Kyodai Katsura Campus-mae”
Stop (Kyoto City Bus / Keihan Kyoto Kotsu Bus)



Directions to iCeMS, Kyoto University



Yoshida Campus, Kyoto University



Katsura Campus, Kyoto University

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