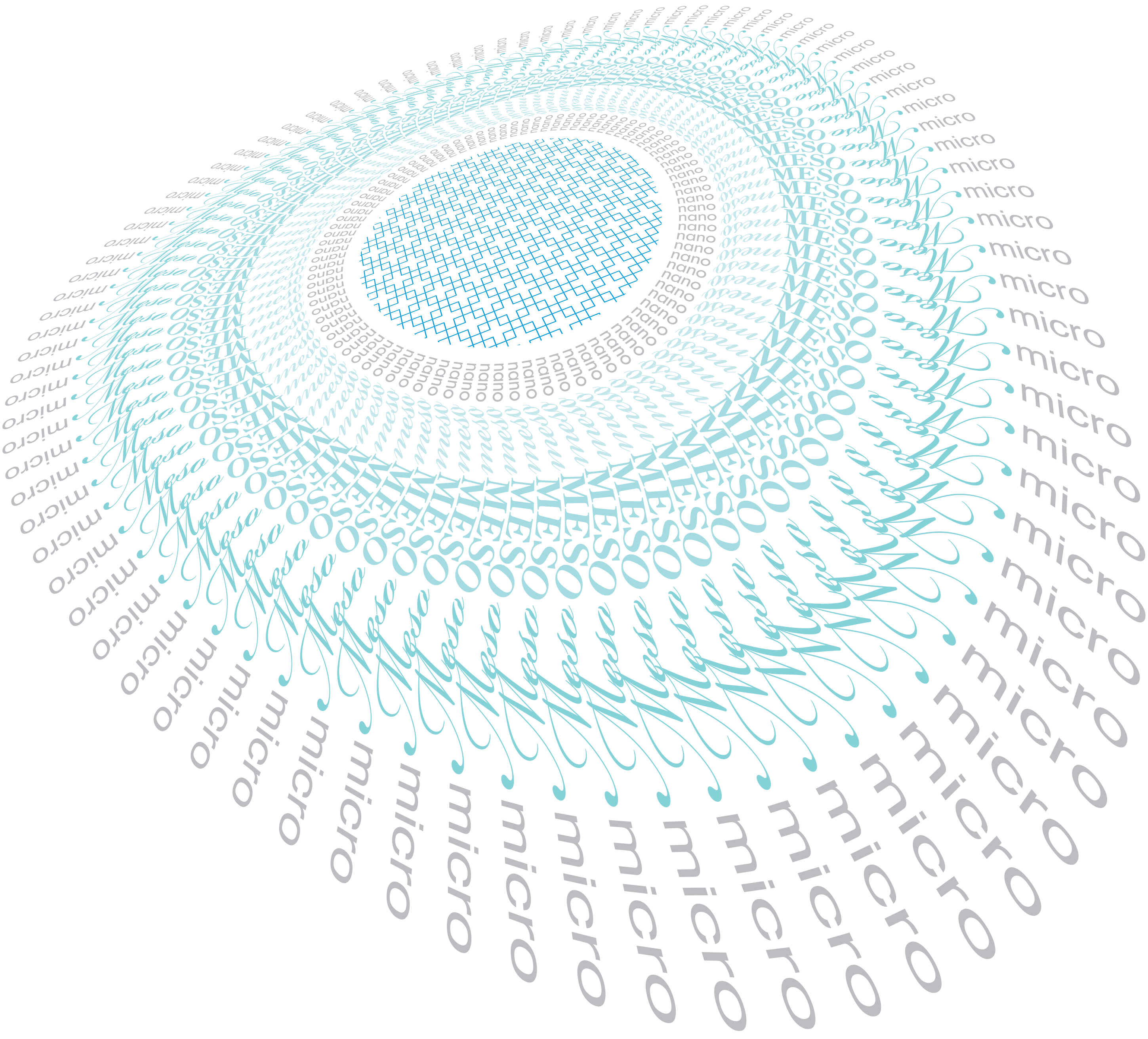


iCeMS
KYOTO UNIVERSITY
WPI Research Center

Institute for Integrated Cell-Material Sciences

President's Message: Kyoto University's International Strategy and High Hopes for iCeMS

Juichi Yamagiwa

President
Kyoto University

My name is Juichi Yamagiwa, President of Kyoto University as of October 1, 2014, in succession to former President Hiroshi Matsumoto.

Founded in October 2007, Kyoto University's Institute for Integrated Cell-Material Sciences (iCeMS) was established as one of five original World Premier International Research Center Initiative (WPI) institutes throughout Japan. Led by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), the mission of this program is to create world-class, interdisciplinary research centers that break new ground in their global outlook and openness to management reform that is unprecedented in Japan. In all these aspects, I am pleased to say that iCeMS has contributed significantly to making these goals a reality.

The research focus of iCeMS continues to be the mesoscopic domain between materials and cells, where we have accelerated ground-breaking research, including the synthesis of over 1,500 compounds to manipulate stem cells and cellular functions.

When looking at iCeMS contributions to not only Kyoto University but also society, iCeMS has played significant roles in swiftly advancing the establishment of CiRA which is led by Nobel Prize winner Shinya Yamanaka, launching the multidisciplinary journal Biomaterials Science in collaboration with the Royal Society of Chemistry, teaching a massive open online course (MOOC) at edX which was co-founded by Harvard and MIT, and making an impact on the science community.

iCeMS also serves as a blueprint for planned university-wide management reforms, with globalization being a key component. Measures already being undertaken by the institute include: English as the official language; having at least 30 percent overseas researchers; active international efforts in public relations and overseas networking; streamlined executive decision making; and implementation of flexible employment practices and merit-based pay. I am confident that these initiatives pioneered by iCeMS will have a profound, university-wide impact, helping the entire institution attain a higher level of excellence. Thus, it is my hope to spread these reforms throughout Kyoto University. Based on our "2 by 2020" initiative, we will establish the International Research Academy (tentative) with iCeMS as a core group within this new organization to advance necessary reforms.

Shortly after its establishment, iCeMS initiated an overseas visits program which has enabled a large number of young researchers — postdocs and graduate students — to travel abroad for career advancement and networking opportunities. In fact, the success of this program has strongly influenced Kyoto University initiatives aimed at increasing international indices by 2020, such as the John Mung Program, which similarly supports young researchers going overseas.

Faced with an aging society in Japan, increasing globalization, and the necessity to develop stronger ties between academia and industry, universities — in addition to its traditional role as an education and research institute — must improve how its management paves the way for future success. On the other hand, educational research and university management must be considered separately, as academic research and profit do not always mix. As such, achieving a sustainable management system by taking appropriate measures will enable us to preserve Kyoto University's fundamental philosophy of freedom that allows researchers to explore issues that they feel will ultimately benefit society. I believe that iCeMS' non-conformist ideas will serve as the perfect example of improved university management.

In closing, I look forward to your continued support and guidance.

Director's Vision for an Integrated Cell-Material Science

Susumu Kitagawa

Director
Institute for Integrated Cell-Material Sciences (iCeMS)
Kyoto University

All cellular processes can ultimately be comprehended as chemical events, and such a chemical understanding of cells should allow us to mimic cellular processes using chemical materials. Our institute seeks to illuminate precisely such a chemical basis of cells, **creating compounds to control processes in cells such as stem cells** *(materials for cell control)*, and further down the road spark **cellular processes to create chemical materials** *(cell-inspired materials)*. Combining Kyoto University's established strength in cell biology, chemistry, and physics to delve deeply into the world lying at the boundary of materials and life, we are making a concerted effort, through interdisciplinary research, to ultimately create a new research field of **integrated cell-material science**.

Efforts to explain cell functions using chemistry are not new. Biochemistry, for instance, uses proteins as a starting point in attempting this at a molecular level, and molecular biology, while also focused on molecules, takes a DNA-based approach. And in their own ways, both methods have yielded significant innovations in pharmaceuticals and biotechnology.

Meanwhile, cell biology has also seen substantial success by considering the cell as a whole, most notably in research related to embryonic stem (ES) cells and induced pluripotent stem (iPS) cells, which are beginning to make an impact on the biomedical industry.

Our institute seeks a middle ground: between the large, whole-cell approach of cell biology, and the small, protein and DNA approaches of biochemistry and molecular biology. We call this the mesoscopic realm, lying between a few tens and a few hundreds of nanometers, on the border between materials and living matter. Investigating this boundary region, we strive to explain the material-chemical basis of cells' living functions, ultimately using materials to create novel artificial systems with unique and tunable functions.

A study of the melded boundary between cells and materials based on a fusion of cell biology, chemistry, and physics is our goal. We seek to be the best in the world, with the fruits of our international, interdisciplinary labors bringing nourishment and fresh ideas to research in industries as diverse as medicine and the environment. Our efforts are focused on examining the following two questions:

1. Can we describe cellular processes in terms of chemistry, and create materials to control them?

Cells sustain life through properties of self-assembly and cooperative interactions among nearly countless chemical materials, moving ceaselessly in space and time. Broadening our scope beyond the narrow confines of nanoscale molecular interactions, we find it necessary to take a wider, mesoscopic view of molecular complexes. To accomplish this, we are pursuing the development of advanced imaging technologies and modeling, and physical and chemical technologies to dissect complex cellular events. Based on this analysis, we seek to investigate ***materials for cell control***. Research areas in this context are as follows:

- **Manipulation of Nucleus Information**: The nucleus memorizes and processes centralized information in the cell. We strive to elucidate the dynamics and mechanisms of chromatin organization and transcription regulation during cell differentiation as well as reprogramming. By doing so, we can develop synthetic functional molecules, including those with photoinducible properties, to visualize and manipulate nuclear information processing.

- **Manipulation of Membrane Compartments**: Cellular membrane compartments mediate condensation and selection: inward and outward signaling cascades, energy conversion, and exchange of matter. We seek to understand the molecular mechanisms of these membrane-domain reactions to develop molecular technologies for manipulating membrane functions by external stimuli such as light, magnetic field and heat.

- **Manipulation of Cell Communication**: Differentiation of stem cells into multicellular tissues is regulated by the communication between cells alone and cells with materials. We seek to uncover underlying mechanisms and develop scaffolds by molecular scale design for reconstruction of functional cell architectures such as brain, muscle and germline tissues.

2. Can we reproduce cellular structures with materials?

Renowned physicist Richard P. Feynman once wrote: "What I cannot create, I do not understand." In other words, only in the process of creation can we achieve true understanding.

In this spirit, our institute has a long-term goal to replicate cellular functions with designed materials (***cell-inspired materials***). This should be possible once a full understanding of such cellular processes (as described above) has been achieved. We therefore simultaneously advance analysis and synthesis, applying the resulting higher level of knowledge to further research, such as in the proposed creation of the following chemical materials:

- **Materials for Cell Membrane Functions**, such as the development of materials based on an understanding of the complex balance and interaction of processes on the cell membrane.

- **Energy Storage in Cells**, such as the creation of materials mimicking living systems' abilities to sort and store energy bearing ions and molecules, and materials to unlock the energy storage potential of carbon dioxide, carbon monoxide, and methane gas.

July 2015

About WPI

www.jsps.go.jp/wpi

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. The MEXT grants average ¥1.3–1.4 billion per center (up to \700 million each for centers selected in 2012) annually over 10–15 years, and interim evaluations are conducted at 5-year intervals. WPI centers are as follows (as of May 2015):

- Tohoku University Advanced Institute for Materials Research (AIMR) [selected 2007]
- The University of Tokyo Kavli Institute for the Physics and Mathematics of the Universe (Kavli IPMU) [selected 2007]
- Kyoto University Institute for Integrated Cell-Material Sciences (iCeMS) [selected 2007]
- Osaka University Immunology Frontier Research Center (IFReC) [selected 2007]
- National Institute for Materials Science International Center for Materials Nanoarchitectonics (MANA) [selected 2007]
- Kyushu University International Institute for Carbon-Neutral Energy Research (I^2CNER) [selected 2010]
- University of Tsukuba International Institute for Integrative Sleep Medicine (IIIS) [selected 2012]
- Tokyo Institute of Technology Earth-Life Science Institute (ELSI) [selected 2012]
- Nagoya University Institute of Transformative Bio-Molecules (ITbM) [selected 2012]

Timeline

2007	**Sep. 12**	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	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 iCeMS with Prof. Shinya Yamanaka as founding director.
	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 iCeMS with Prof. Akihiro Kusumi as founding director.
	Jun. 26	iCeMS Gifu University Satellite opening ceremony held.
	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 sister institute to 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	**Jul. 21–23**	Heidelberg University Collaborative Research Center SFB 873-Kyoto University iCeMS joint symposium held in Heidelberg.
2012	**Apr. 20–22**	Peking University and Tsinghua University Center for Life Sciences (CLS)-Kyoto University iCeMS joint symposium held in Beijing.
	Oct. 8	Prof. Shinya Yamanaka wins the Nobel Prize in Physiology or Medicine.
	Dec. 3–5	iCeMS co-organizes the World Stem Cell Summit in Florida with the Karolinska Institutet and other leading institutions.
2013	**Jan. 1**	Prof. Susumu Kitagawa succeeds Prof. Nakatsuji as director.
	Jan.	The first issue of *Biomaterials Science*, a joint venture between the Royal Society of Chemistry (RSC) and iCeMS, published.
	Jun. 6-9	WPI institutes co-host Japan-France workshop on materials science at iCeMS.
	Oct.	iCeMS Rakunan Shinto Laboratory opened.
2014	**Apr. 20**	Her Royal Highness Princess Maha Chakri Sirindhorn of Thailand visits iCeMS.

Organization Chart

As of July 2015

Executive Board


Susumu Kitagawa
Director


Ryoichiro Kageyama
Deputy Director


Motonari Uesugi
Deputy Director


Mineko Kengaku
Board of PIs Chairman


Shinji Tomita
Administrative Director

Scientific Advisor


Shinya Yamanaka
CiRA* Director

Principal Investigators (PIs)


Yong Chen


Mitsuru Hashida


Hiroshi Imahori


Ryoichiro Kageyama


Mineko Kengaku


Makoto Kiso
Gifu Univ Satellite


Susumu Kitagawa


Norio Nakatsuji
Founding Director


Mitinori Saitou


Hiroshi Sugiyama


Motomu Tanaka


Kazumitsu Ueda

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


Yoshie Harada
CeMI Director


John Heuser


Akihiro Kusumi


Koichiro Tanaka


Motonari Uesugi


Shinya Yamanaka


Peter Carlton


Franklin Kim


Tatsuya Murakami


Easan Sivaniah

NCBS-inStem Satellite Lab


Kenichi Suzuki

Science Communication


Kazuto Kato

iCeMS Kyoto Fellow


Dan Ohtan Wang

Administration

iCeMS

Admin Director Shinji Tomita　Deputy Admin Director Kazuyoshi Matsui

General Affairs & Planning	Research Planning	IT Strategy

Yoshida South Campus

Admin Director Takashi Kawahara

General Affairs	Overseas Planning & Public Relations	Accounting

Adjunct Professors

- Ryu Abe (Grad Sch Eng)
- Kazunari Akiyoshi (Grad Sch Eng)
- Itaru Hamachi (Grad Sch Eng)
- Hiroshi Kageyama (Grad Sch Eng)
- Hiroaki Kato (Grad Sch Pharm Sci)
- Hiroshi Kitagawa (Grad Sch Sci)
- Hidetoshi Kotera (Grad Sch Eng)
- Michiyuki Matsuda (Grad Sch Bio/Med)
- Yasuo Mori (Grad Sch Global Env/Eng)
- Miho Murayama (Wildlife Research Cntr)
- Eisuke Nishida (Grad Sch Bio)
- Takashi Shinohara (Grad Sch Med)
- Masahiro Shirakawa (Grad Sch Eng)
- Ryosuke Takahashi (Grad Sch Med)
- Hidehito Tochio (Grad Sch Sci)
- Fumiko Toyoshima (Inst Virus Rsch)
- Nagahisa Yoshimura (Grad Sch Med)

Academic Advisory Committee

- Barbara Baird (Cornell University)
- Daniel Choquet (Université de Bordeaux 2)
- Eng-Hin Lee (National University of Singapore)
- Laura Kiessling (University of Wisconsin-Madison)
- Keiji Morokuma (Kyoto University)
- Noriko Osumi (Tohoku University)
- Kenneth R. Poeppelmeier (Northwestern University)
- Ferdi Schüth (Max-Planck-Institut für Kohlenforschung)
- Fiona Watt (Kings College London)

Industrial Advisory Committee

- Stephen Minger (GE Healthcare)
- Sotirios Karathanasis (MedImmune)
- Tsuneaki Sakata (Shionogi & Company, Ltd.)
- Goemon Kurihara (JEOL Ltd.)
- Joydeep Goswami (Thermo Fisher Scientific)

*Kyoto University Center for iPS Cell Research and Application

Management

Adhering to the principles of the WPI program, iCeMS has implemented a new system of management which is unprecedented in a Japanese university.

Management Reform Initiatives

- Rapid, institute director-centered decision-making process
- A pay scale not based solely on seniority
- Hiring not limited by the retirement age

Initiatives Aimed at Meeting International Standards

- 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 with over 50% English-speaking administrative staff

Promoting Ground-Breaking, Interdisciplinary Research

- 18 world-class principal investigators (WPI PIs)
- iCeMS Kyoto Fellow (junior PI) and iCeMS Associate Kyoto Fellow positions
- Facilities Management Committee and the implementation of open offices and shared laboratories
- Promotion of interdisciplinary research through the common use of large facilities, such as apparatuses in the Center for Meso-Bio Single-Molecule Imaging (CeMI)
- Hosting international symposia (approx. 3 annually) and iCeMS Seminars regularly conducted by noted international researchers (approx. 30 seminars annually)
- Postdoc Seminar series “Learning Lounge” to facilitate cross-disciplinary research (approx. once a month)
- Annual iCeMS Retreats to aid interaction between labs (74 faculty and staff attended in 2009, 115 in 2010, 152 in 2011, 164 in 2012, 205 in 2013)

University-Industry-Government Collaboration

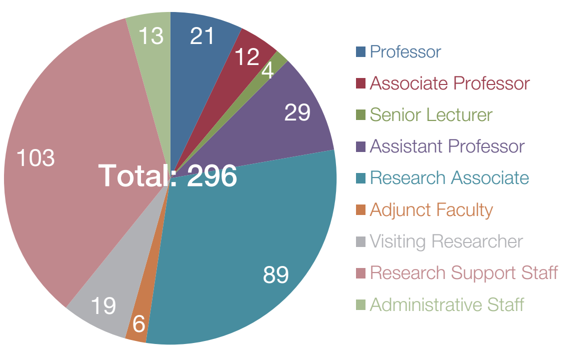
- Development of innovation management theory coupled with vigorous efforts to link the public and private sectors
- Industrial Advisory Committee
- Building closer ties with the Kyoto University URA office (KURA)

Local and Global Outreach

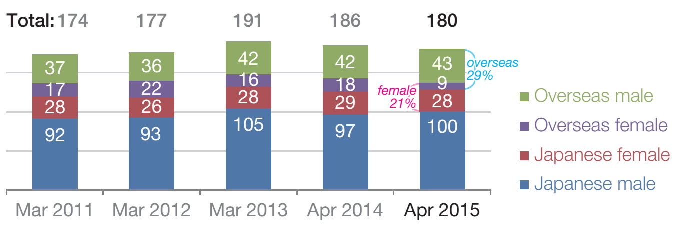
- Development of science communication theory hand-in-hand with active outreach programs (e.g. science cafés, hands-on stem cell workshops for high school students)
- WPI joint outreach efforts both at home (e.g. symposia for high school students) and abroad (e.g. AAAS annual meetings)

Facts and Figures

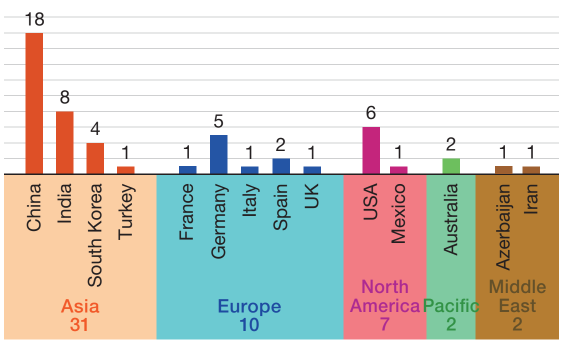
All staff (April 2015)



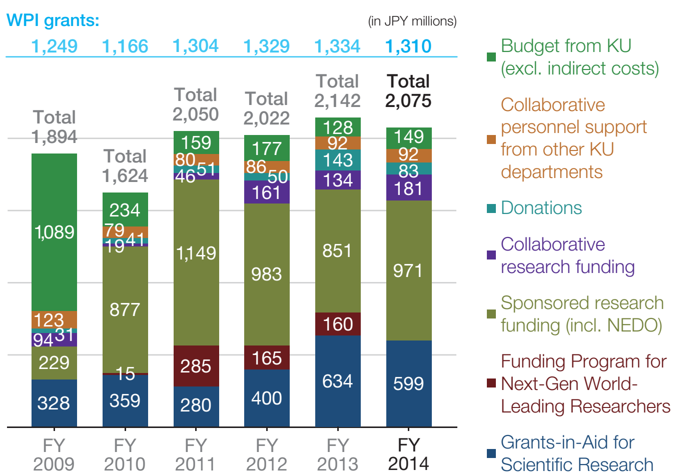
Researchers (April 2015)



Researchers from overseas (April 2015)



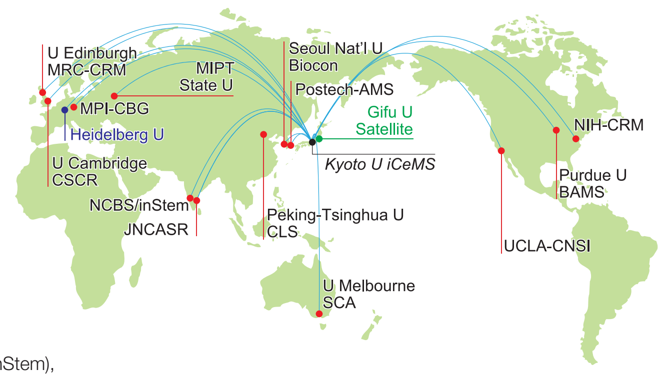
Finance (April 2015)



Honors and Awards

Month/Year	Award/Prize	Awardees
Apr 2015	Commendation for Science and Technology Prize (Young Scientists' Prize category)	Ryotaro Matsuda
Apr 2015	Marco Polo della Scienza Italiana	Susumu Kitagawa
Jul 2014	Rising Stars Award	Shuhei Furukawa
Jun 2014	2014 Thomson Reuters Highly Cited Researcher	Susumu Kitagawa
Jun 2014	The 6th German Innovation Award “Gottfried Wagener Prize 2014”	Hideki Hirori
May 2014	E.B. Wilson Medal of the American Society for Cell Biology	John Heuser
Mar 2014	Commendation for Science and Technology Prizes	Norio Nakatsuji, Kei Kano, Eri Mizumachi, Koichiro Tanaka
Feb 2014	Philipp Franz von Siebold Award	Motomu Tanaka
Feb 2014	PCCP Prize	Hiroshi Satou
Jan 2014	Japan Academy Medal	Mitinori Saitou
Sep 2013	Leo Esaki Award	Susumu Kitagawa
May 2013	RSC de Gennes Prize	Susumu Kitagawa
Jan 2013	Quadrant Award First Prize	Nobuhiro Yanai
Nov 2012	Order of Culture	Shinya Yamanaka
Nov 2012	Life-time Achievement Award (Journal of Drug Targeting)	Mitsuru Hashida
Oct 2012	Nobel Prize in Physiology or Medicine	Shinya Yamanaka
Oct 2012	The 7th Young Scientist Award of the Physical Society of Japan	Hideki Hirori
Mar 2012	Japan Society for Bioscience, Biotechnology, and Agrochemistry Award	Hiromune Ando
Nov 2011	AAAS Days of Molecular Medicine Young Investigator Award	Ganesh Pandian Namasivayam
Oct 2011	Member of the Science Council of Japan	Susumu Kitagawa
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
Sep 2010	2010 Thomson Reuters Citation Laureates	Susumu Kitagawa, Shinya Yamanaka
Mar 2010	Imperial and Japan Academy Prizes	Shinya Yamanaka
Mar 2010	ABC2010 Young Investigator Award	Koh Nagata
Mar 2010	Japan Bioscience, Biotechnology and Agrochemistry Society Award	Kazumitsu Ueda
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
Mar 2009	The Chemical Society of Japan Lectureship Award	Shuhei Furukawa
Jan 2009	The Chemical Society of Japan Award	Susumu Kitagawa
Apr 2008	Humboldt Research Award	Susumu Kitagawa
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

Partner Institutions & Satellite



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

- **iCeMS Satellite at Gifu University, Japan**
- **Heidelberg University, Germany (university-level MoU signed)**
- Institute for Stem Cell Biology and Regenerative Medicine (inStem), India*
- Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), India*
- Max Planck Institute of Molecular Cell Biology and Genetics (MPI CBG), Germany
- Moscow Institute of Physics and Technology (MIPT), Russia*
- NIH Center for Regenerative Medicine (NIH CRM), USA*
- Peking University and Tsinghua University Center for Life Sciences (CLS), China*
- Pohang University of Science and Technology Division of Advanced Materials Science (POSTECH AMS), South Korea*
- Purdue University Center for Basic and Applied Membrane Sciences (PUBAMS), USA
- Seoul National University Medicinal Bioconvergence Research Center (Biocon), South Korea*
- Tata Institute of Fundamental Research National Centre for Biological Sciences (NCBS), India*
- The University of Edinburgh Medical Research Council Centre for Regenerative Medicine (MRC CRM), UK*
- The University of Melbourne Stem Cells Australia (SCA)
- UCLA California NanoSystems Institute (CNSI), USA*
- University of Cambridge Wellcome Trust Centre for Stem Cell Research (CSCR), UK

*MoU (memorandum of understanding) partners

Yong Chen Lab

Nanobiotechnology, Nanofabrication, Microfluidics and Stem Cells

Faculty Members

Yong Chen (Professor)

Ken-ichiro Kamei (Associate Professor)

Li Liu (Assistant Professor)

Research Overview

We develop micro- and nano-engineering tools and methods for cell-based assays. In particular, we are interested in mimicking cellular microenvironments for the investigation and control of stem cell processes. As example, we produced nanofibers using natural and synthetic polymers to support **long-term expansion** of **human induced pluripotent stem cells** (hiPSC) as well as **tissue formation** of **cardiomyocytes** and **neurons**. In parallel, we set down a microfluidic platform for **high-throughput screening** of culture and differentiation conditions, offering unique advantages over conventional approaches in terms of efficiency, manpower and reagent economy. Finally, we contribute to the interdisciplinary approach on porous coordinate polymers based and **light controlled regulation** of cells functions. By carefully analyzing the cellular behaviors under different conditions, we were able to achieve a better understanding of the influence of physicochemical cues and microfluidic environments on stem cell culture and derived tissue formation, which impacts the future applications including drug discovery, medical diagnosis, cellular therapy and regenerative medicine.

At the present, we focus on the following research topics:

1. **Multilayer constructs** of hiPSC-derived cardiomyocytes for **drug screening** and **transplantation**, using nanofibers as cellular carriers and tissue formation cues. Multi-electrode arrays are employed for recording electrophysiological response of the tissue constructs.

2. **Three-dimensional patterning** of scaffolds to **recapture neurogenesis**, using both lineage-specific and coordinated neuronal subtypes. Multi-conduits microfluidic circuits and multi-electrode arrays are used with spatiotemporal stimuli and readout.

3. Microfluidic platforms for high-throughput screening of scaffold materials and processing parameters. Cell sorting and culturing devices are also fabricated to study and/or solve the problems of **heterogeneity** and **tumorigenicity** of hPSCs-derivatives.

Selected Papers

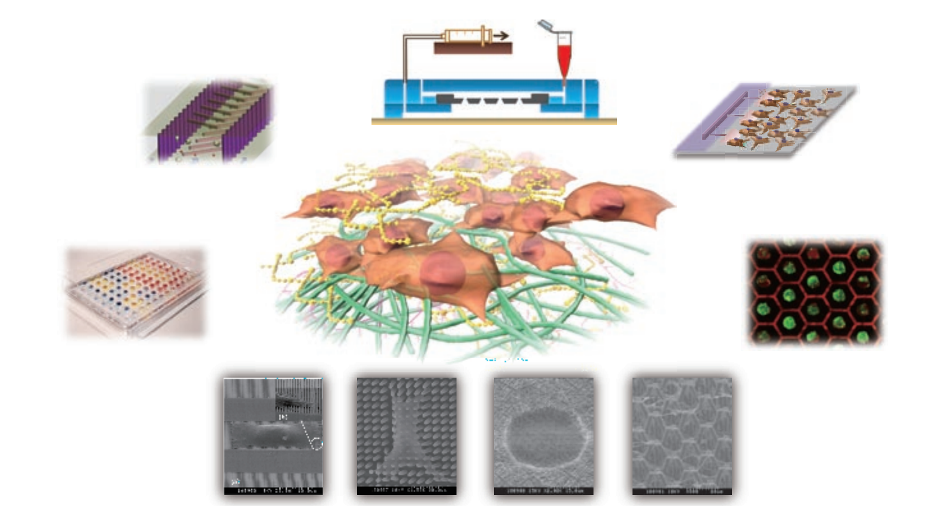
K. Kamei, Y. Mashimo, Y. Koyama, C. Fockenberg, M. Nakashima, M.Nakajima, J. Li, Y. Chen, 3D printing of soft lithography mold for rapid production of polydimethylsiloxane-based microfluidic devices for cell stimulation with concentration gradients. *Biomed. Microdev.* **17**, 36 (2015).

L. Liu, M. Yoshioka, M. Nakajima, A. Ogasawara, J. Liu, K. Hasegawa, S. Li, J. Zou, N. Nakatsuji, K. Kamei, Y. Chen, Nanofibrous gelatin substrates for long-term expansion of human pluripotent stem cells. *Biomaterials* **35**, 6259-6267 (2014).

S. Diring, D. O. Wang, C. Kim, M. Kondo, Y. Chen, S. Kitagawa, K. Kamei, S. Furukawa, Localized cell stimulation by nitric oxide using a photoactive porous coordination polymer platform. *Nat. Commun.* **4**, 8 (2013).

K. Kamei, Y. Hirai, M. Yoshioka, Y. Makino, Q. H. Yuan, M. Nakajima, Y. Chen, O. Tabata, Phenotypic and Transcriptional Modulation of Human Pluripotent Stem Cells Induced by Nano/Microfabrication Materials. *Adv. Health. Mater.* **2**, 287-291 (2013).

L. Liu, Q. Yuan, J. Shi, X. Li, D. Jung, L. Wang, K. Yamauchi, N. Nakatsuji, K. Kamei, Y. Chen, Chemically-defined scaffolds created with electrospun synthetic nanofibers to maintain mouse embryonic stem cell culture under feeder-free conditions. *Biotechnol. Lett.* **34**, 1951-1957 (2012).



Physicochemical cues and microfluidic environments for cells and tissues

Yoshie Harada Lab

Single-Molecule Physiology, Biophysics

Faculty Members

Yoshie Harada (Professor)
Takeharu Sekiguchi (Associate Professor)
Yong-Woon Han (Assistant Professor)
Takuma Sugi (Assistant Professor)

Research Overview

Biomolecules that function in our bodies come in a variety of sizes ranging from several to hundreds of nanometers. This size falls precisely in the "meso" domain, which lies at the junction between micro and macro levels. A key difference in the environments of humans and biomolecules is that it is impossible for biomolecules to ignore thermal fluctuations because they are constantly exposed to changes in heat. Thus, unlike artificial machines, biomolecules are able to make skillful use of thermal fluctuations while functioning. For example, RNA polymerase is one-dimensionally diffused on DNA when searching for a promoter site. Our ultimate goal is to elucidate the how biomolecules operate.

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 are developing new imaging technologies and use these techniques to investigate the molecular mechanisms of biomolecules.

Three main research directions are as follows:

1. Development of a novel single-molecule imaging technique using fluorescent diamond nanoparticles
2. Analysis of biomolecular interactions with zero-mode waveguides
3. Molecular mechanism of epigenetics

Selected Papers

Y. W. Han, Y. Tsunaka, , H. Yokota, T. Matsumoto, G. Kashiwazaki, H. Morinaga, K. Hashiya, T. Bando, H. Sugiyama, Y. Harada, Construction and characterization of Cy3-or Cy5-conjugated hairpinpyrrole-imidazole polyamides binding to DNA in the nucleosome. *Biomater. Sci.* **2**, 297-307 (2014).

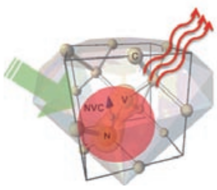
Y. Yoshinari, Z. Kalay, Y. Harada, Observing the rotational diffusion of nanodiamonds with arbitrary nitrogen vacancy center configurations. *Phys. Rev.* **B 88**, 8 (2013).

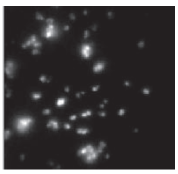
H. Yokota, Y. A. Chujo, Y. Harada, Single-Molecule Imaging of the Oligomer Formation of the Nonhexameric Escherichia coli UvrD Helicase. *Biophys. J.* **104**, 924-933 (2013).

R. Igarashi, Y. Yoshinari, H. Yokota, T. Sugi, F. Sugihara, K. Ikeda, H. Sumiya, S. Tsuji, I. Mori, H. Tochio, Y. Harada, M. Shirakawa, Real-time background-free selective imaging of fluorescent nanodiamonds in vivo. *Nano Lett.* **12**, 5726-5732 (2012).

Y. W. Han, T. Matsumoto, H. Yokota, G. Kashiwazaki, H. Morinaga, K. Hashiya, T. Bando, Y. Harada, H. Sugiyama, Binding of hairpin pyrrole and imidazole polyamides to DNA: relationship between torsion angle and association rate constants. *Nuc. Acids Res.* **40**, 11510-11517 (2012).

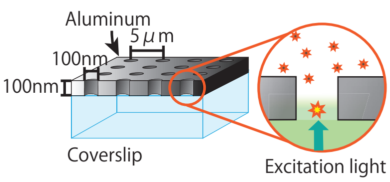
• Development of a novel single-molecule imaging technique using fluorescent diamond nanoparticles

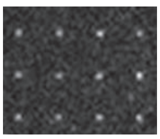




Fluorescence image of Nitrogen-Vacancy Center in diamond nanoperticles

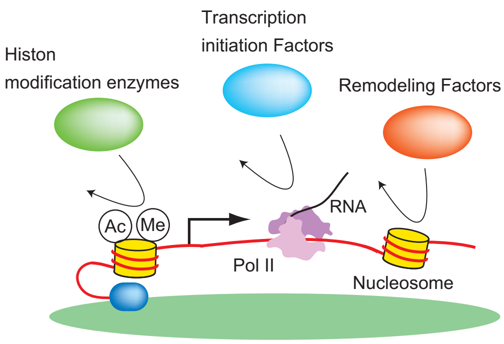
• Analysis of biomolecular interactions with zero-mode waveguides





Fluorescence image of fluorescent dye in nano holes

• Molecular mechanism of epigenetics



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

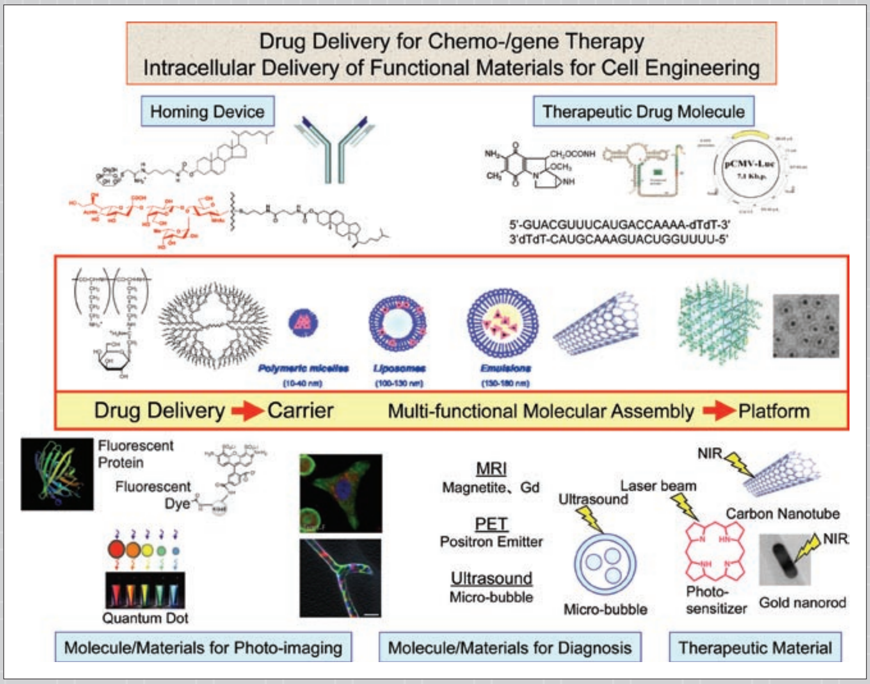
H. Babazada, F. Yamashita and M. Hashida, Suppression of experimental arthritis with self-assembling glycol-split heparin nanoparticles via inhibition of TLR4-NF-κB signaling. *J. Control. Release* **194**, 295-300 (2014).

H. Nakanishi, Y. Higuchi, F. Yamashita, and M. Hashida, Targeted gene integration using the combination of a sequence-specific DNA-binding protein and phiC31 integrase. *J. Biotechnol.* **186**, 139-147 (2014).

S. Zhou, Y. Hashida, S. Kawakami, J. Mihara, T. Umeyama, H. Imahori, T. Murakami, F. Yamashita, and M. Hashida, Preparation of immunostimulatory single-walled carbon nanotube/CpG DNA complexes and evaluation of their potential in cancer immunotherapy. *Int. J. Pharm.* **471** (1-2), 214-223 (2014).

Y. Kono, S. Kawakami, Y. Higuchi, K. Maruyama, F. Yamashita, and M. Hashida, Tumour-associated macrophages targeted transfection with NF-κB decoy/mannose-modified bubble lipoplexes inhibits tumour growth in tumour-bearing mice. *J. Drug Target.* **22** (5), 439-449 (2014).

Y. Hashida, H. Tanaka, S. Zhou, S. Kawakami, F. Yamashita, T. Murakami, T. Umeyama, H. Imahori, and M. Hashida, Photothermal ablation of tumor cells using a single-walled carbon nanotube-peptide composite. *J. Control. Release* **173**, 59-66 (2014).

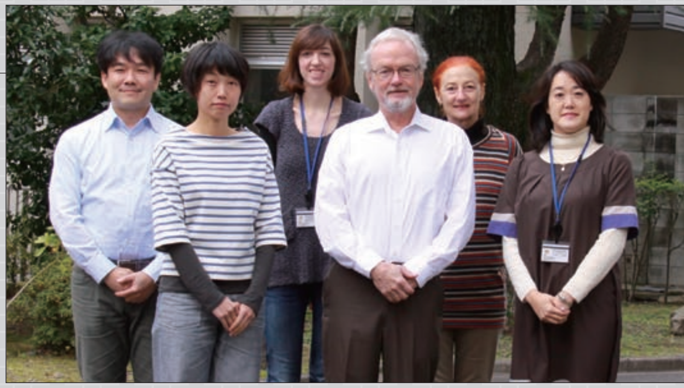


John Heuser Lab

Biophysics, Cell Biology

Faculty Members

John Heuser (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

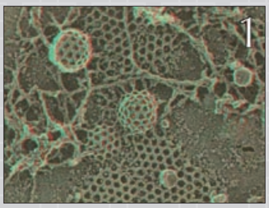
P. I. Hanson, R. Roth, Y. Lin, J. E. Heuser, Plasma membrane deformation by circular arrays of ESCRT-III protein filaments. *J. Cell Biol.* **180**, 389-402 (2008).

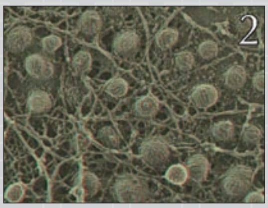
N. Morone, C. Nakada, Y. Umemura, J. Usukura, A. Kusumi, Three-dimensional molecular architecture of the plasma-membrane-associated cytoskeleton as reconstructed by freeze-etch electron tomography. *Methods Cell Biol.* **88**, 207-236 (2008).

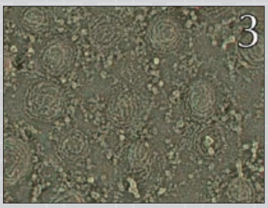
J. Heuser, Evidence for recycling of contractile vacuole membrane during osmoregulation in dicyostelium amoebae - a tribute to Gunther Gerisch. *Eur. J. Cell Biol.* **85**, 859-871 (2006).

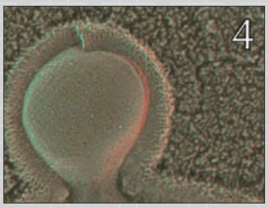
N. Morone, T. Fujiwara, K. Murase, R. S. Kasai, H. Ike, S. Yuasa, J. Usukura, A. Kusumi, Three-dimensional reconstruction of the membrane skeleton at the plasma membrane interface by electron tomography. *J. Cell Biol.* **174**, 851-862 (2006).

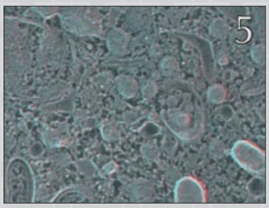
J. Heuser, Deep-etch EM reveals that the early poxvirus envelope is a single membrane bilayer stabilized by a geodetic "honeycomb" surface coat. *J. Cell Biol.* **169**, 269-283 (2005).











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

Hiroshi Imahori Lab

Organic Chemistry, Photochemistry, Drug Delivery Systems

Faculty Members

Hiroshi Imahori (Professor)

Yuta Takano (Assistant Professor)

Research Overview

Our laboratory has been working on **artificial photosynthesis** and **solar energy conversion**. 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 hybrid solar cells**. Currently, a power conversion efficiency of >10% has been achieved on our porphyrin-sensitized 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) **Light-harvesting meso-scale materials** for photodynamic and photothermal therapy (Murakami, Hashida, Takano labs)
2) **Light-emitting meso-scale materials** for cell imaging (Murakami, Hashida labs)
3) **Photoinduced charge separation meso-scale materials** for controlling cellular functions (Murakami, Mori, Heuser, Kengaku, Nakatsuji labs)

Selected Papers

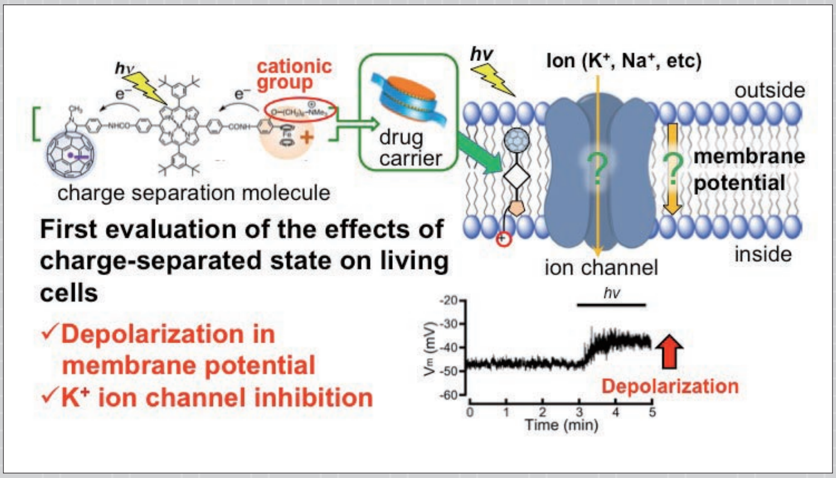
T. Umeyama, J. Baek, Y. Sato, K. Suenaga, F. Abou-Chahine, N. V. Tkachenko, H. Lemmetyinen, H. Imahori, Molecular interactions on single-walled carbon nanotubes revealed by high-resolution transmission microscopy. *Nat. Commun.* (2015), in press.

T. Higashino, Y. Fujimori, K. Sugiura, Y. Tsuji, S. Ito, H. Imahori, Tropolone as high-performance robust anchoring group for dye-sensitized solar cell. *Angew. Chem. Int. Ed.*, (2015), in press.

T. Numata, T. Murakami, F. Kawashima, N. Morone, J. E. Heuser, Y. Takano, K. Ohkubo, S. Fukuzumi, Y. Mori, H. Imahori, Utilization of photoinduced charge-separated state of donor-acceptor-linked molecules for regulation of cell membrane potential and ion transport. *J. Am. Chem. Soc.* **134**, 6092-6095 (2012).

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

H. Hayashi, I. V. Lightcap, M. Tsujimoto, M. Takano, T. Umeyama, P. V. Kamat, H. Imahori, 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).



Ryoichiro Kageyama Lab

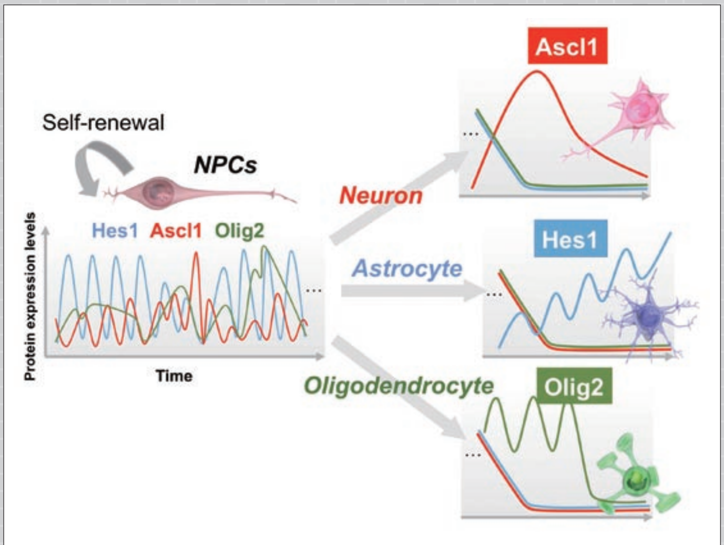
Developmental Biology, Neural Stem Cell Biology

Faculty Members

Ryoichiro Kageyama (Professor)
Hiromi Shimojo (Assistant Professor)

Research Overview

Neural stem cells are present not only in the embryonic but also in the adult brain and continuously produce new neurons, although at different rates. Decrease in number or depletion of neural stem cells leads to severe damage in brain morphogenesis or impairment of higher brain functions such as learning and memory. We are investigating the molecular mechanisms of proliferation and differentiation of neural stem cells, aiming at controlling these cells at will. Multipotent neural stem cells undergo self-renewal while giving rise to three cell lineages, neurons, astrocytes, and oligodendrocytes. It has been shown that the **basic-helix-loop-helix (bHLH) transcription factors** Ascl1/Mash1, Hes1, and Olig2 regulate fate choice of neurons, astrocytes, and oligodendrocytes, respectively. These same factors are coexpressed by neural stem cells. Here, we found by time-lapse imaging that these factors are expressed in an oscillatory manner by neural stem cells. In each differentiation lineage, one of the factors becomes dominant and sustained. We used a new **optogenetic** approach to control expression of Ascl1, and found that although sustained Ascl1 expression promotes neuronal fate determination, oscillatory Ascl1 expression maintains proliferating neural stem cells. Thus, the **multipotent** state correlates with **oscillatory** expression of several fate-determination factors, whereas the differentiated state correlates with sustained expression of a selected single factor. This optogenetic strategy will be useful for many medical purposes such as brain disease treatment and tissue regeneration.



Expression dynamics of bHLH factors in multipotency and cell fate choice.
The expression of multiple bHLH factors oscillates in multipotent neural stem cells, whereas that of a selected factor becomes up-regulated and sustained during cell fate choice.

Selected Papers

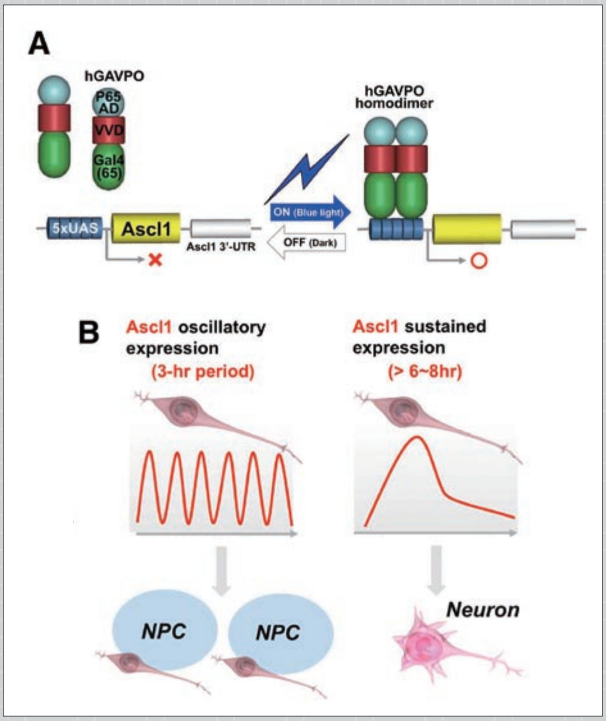
A. Isomura, and R. Kageyama, Ultradian oscillations and pulses: coordinating cellular responses and cell fate decisions. *Development* **141**, 3627-3636 (2014).

I. Imayoshi, and R. Kageyama, bHLH factors in self-renewal, multipotency, and fate choice of neural progenitor cells. *Neuron* **82**, 9-23 (2014).

I. Imayoshi, A. Isomura, Y. Harima, K. Kawaguchi, H. Kori, H. Miyachi, T.K. Fujiwara, F. Ishidate, and R. Kageyama, Oscillatory control of factors determining multipotency and fate in mouse neural progenitors. *Science* **342**, 1203-1208 (2013).

T. Tateya, I. Imayoshi, I. Tateya, K. Hamaguchi, H. Torii, J. Ito, and R. Kageyama, Hedgehog signaling regulates prosensory cell properties during the basal-to-apical wave of hair cell differentiation in the mammalian cochlea. *Development* **140**, 3848-3857 (2013).

Y. Harima, Y. Takashima, Y. Ueda, T. Ohtsuka, and R. Kageyama, Accelerating the tempo of the segmentation clock by reducing the number of introns in the Hes7 gene. *Cell Reports* **3**, 1-7 (2013).



Optogenetic approach to control neural stem cells. (A) hGAVPO activates Ascl1 gene expression by blue light illumination. (B) The hGAVPO system shows that oscillatory expression of Ascl1 activates the proliferation of NPCs, whereas sustained expression of Ascl1 promotes neuronal differentiation.

Mineko Kengaku Lab

Developmental Neurobiology, Cell Biology

Faculty Members

Mineko Kengaku (Professor)

Kazuto Fujishima (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** 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

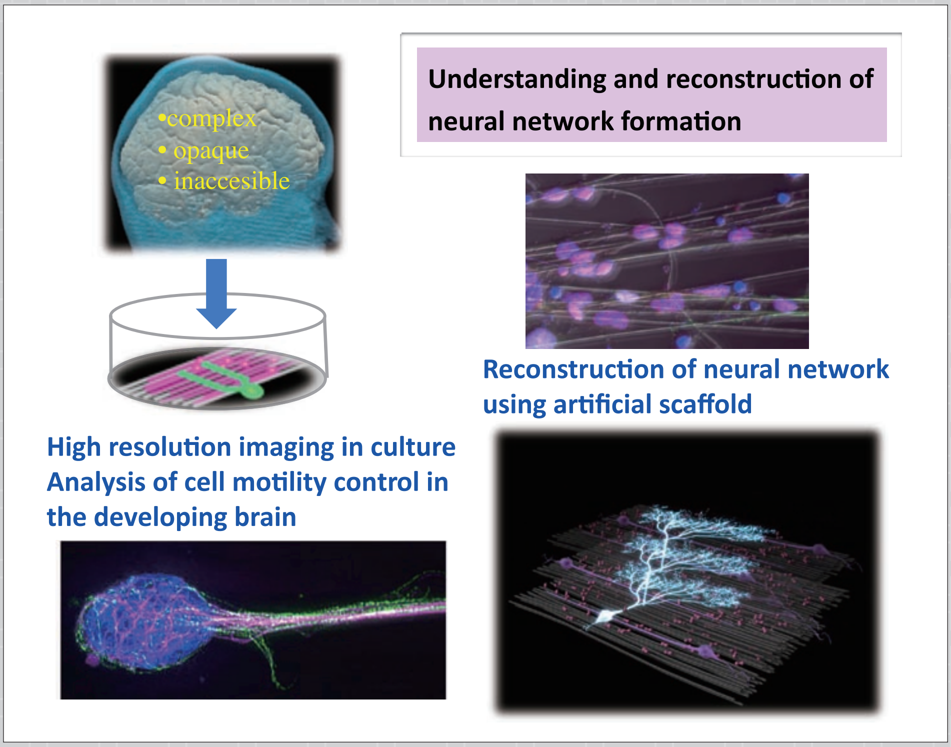
K. Nakashima, H. Umeshima, M. Kengaku, Cerebellar granule cells are predominantly generated by terminal symmetric divisions of granule cell precursors. *Dev. Dyn.* **244**, 748-758 (2015).

K. Fukumitsu, K. Fujishima, A. Yoshimura, Y.K. Wu, J. Heuser, M. Kengaku, Synergistic action of dendritic mitochondria and creatine kinase maintains ATP homeostasis and actin dynamics in growing neuronal dendrites. *J. Neurosci.* **35**, 5707-5723 (2015).

Y.K. Wu, K. Fujishima, M. Kengaku, Differentiation of apical and basal dendrites in pyramidal cells and granule cells in dissociated hippocampal cultures. *PLoS One* **10**, e0118482 (2015).

H. Umeshima, M. Kengaku, Differential roles of cyclin-dependent kinase 5 in tangential and radial migration of cerebellar granule cells. *Mol. Cell. Neurosci.* **52**, 62-72 (2013).

K. Fujishima, R. Horie, A. Mochizuki, M. Kengaku, Principles of branch dynamics governing shape characteristics of cerebellar Purkinje cell dendrites. *Development* **139**, 3442-3455 (2012).



Makoto Kiso Lab

Glycotechnology, Bio-active molecule chemistry

Faculty Members

Makoto Kiso (Professor)

Hiromune Ando (Associate Professor)

Research Overview

This satellite pursues the elucidation of the molecular basis underlying the multifunctions of carbohydrates (especially those called as "**glycans**") in various biological processes by chemical methods and its applications in medicine. Our research is focused on the development of versatile and powerful synthetic methodology of glycans, and the creation of the **Glycobank** possessing a wide spectrum of biologically-significant glycans and functionalized glycan probes. Utilizing the full entries of the Glycobank, we are going to conduct cross-disciplinary studies with molecular biology, developmental biology, structural biology, biophysics for the understanding and application of biological functions of glycans.

Our synthesized glycans have been utilized in diverse biological researches such as those on immune system, virus entry, cancer migration. At iCeMS, we have launched new cross-disciplinary projects using the entries of the Glycobank, which include:

1. Creation of the **glyco-director** system for stem cell engineering, which comprises of the arrays of homogenous synthetic glycans that (will) direct the differentiation, proliferation of stem cells (ES and iPS cells), by collaboration with the stem cell science (Nakatsuji G and Yamanaka G) and nanomaterial science (Kitagawa G).
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, by collaboration with single-molecule cell biophysics (Kusumi G, Suzuki G and Ueda G).
3. Innovation of **drug delivery system** (**DDS**) by creating new drug carriers using carbon nanotubes and liposomes functionalized with glycans by the collaboration with biopharmaceuticals (Hashida G).

Selected Papers

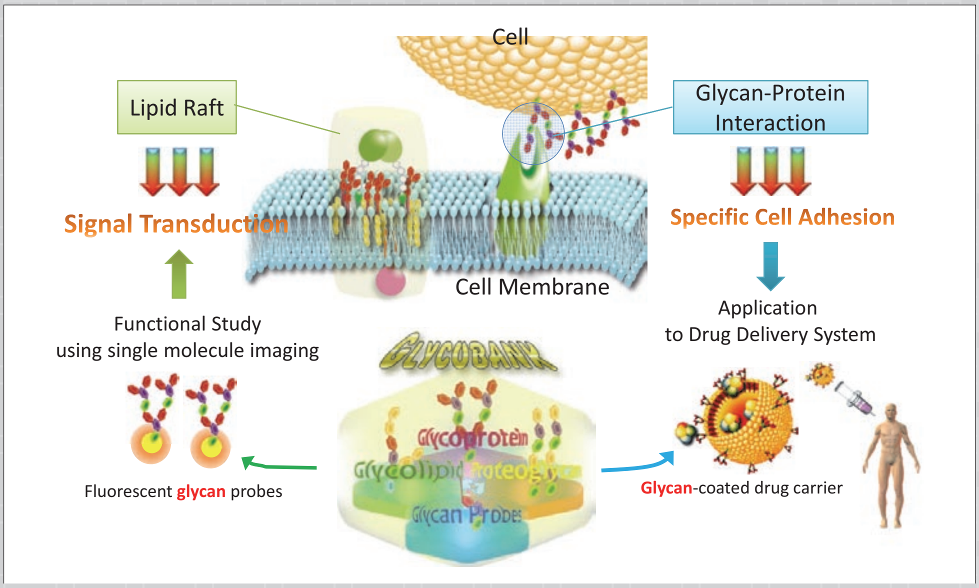
A. Ueki, K. Un, Y. Mino, M. Yoshida, S. Kawakami, H. Ando, H. Ishida, F. Yamashita, M. Hashida, M. Kiso, Synthesis and Evaluation of Glyco-coated Liposomes as Drug Carriers for Active Targeting in Drug Delivery Systems. *Carbohydr. Res.* **405**, 78-86 (2015).

S. Abe, Y. Tokura, R. Pal, N. Komura, A. Imamura, K. Matsumoto, H. Ijiri, N. J. M. Sanghamitra, H. Tabe, H. Ando, M. Kiso, H. Mori, S. Kitagawa, T. Ueno, Surface functionalization of protein crystals with carbohydrate using site-selective bioconjugation. *Chem. Lett.* **44**, 29-31 (2015).

T. Suzuki, H. Makyio, H. Ando, N. Komura, M. Menjo, Y. Yamada, A. Imamura, H. Ishida, S. Wakatsuki, R. Kato, M. Kiso, Expanded potential of seleno-carbohydrates as a molecular tool for X-ray structural determination of a carbohydrate–protein complex with single/multi-wavelength anomalous dispersion phasing. *Bioorg. Med. Chem.* **22**, 2090-2101 (2014).

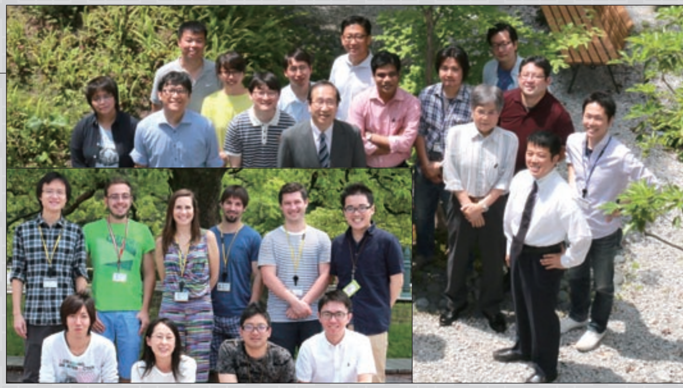
H. Tamai, H. Ando, H. Ishida, M. Kiso, First synthesis of a pentasaccharide moiety of ganglioside GAA 7 containing unusually modified sialic acids through the use of N Troc-sialic acid derivative as a key unit. *Org. Lett.* **14**, 6342-6345 (2012).

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



Susumu Kitagawa Lab

Coordination Chemistry



Faculty Members

Susumu Kitagawa (Professor)
Koji Tanaka (Professor)
Takaiku Yamamoto (Professor)
Shuhei Furukawa (Associate Professor)
Ryotaro Matsuda (Associate Professor)
Masakazu Higuchi (Assistant Professor)
Nobuhiko Hosono (Assistant Professor)
Katsuaki Kobayashi (Assistant Professor)
Shinpei Kusaka (Assistant Professor)
Reiko Sakaguchi (Assistant Professor)

Research Overview

1. Mesoscopic Coordination Chemistry: We focus on the development of new synthesis protocols of coordination materials known as PCPs/MOFs in the mesoscale (5-1000 nm) and the understanding of their unique properties. Our research is directed towards functionalizing these materials in multi-scale size domains, ranging from molecular-scale framework functionalization to manipulation of their physical form (size and morphology) in the mesoscale. The resulting new materials are further considered for microenvironmental applications, in particular, towards cell biology. By taking advantage of gas storage properties of PCPs/MOFs, our current target is to deliver bioactive gas molecules such as nitric oxide (NO) or carbon monoxide (CO) in a spatially and temporally controlled manner both in intracellular and extracellular microenvironments. Our goal is to establish gas biology using bioactive gas releasing PCPs.

2. Gas Conversion and Energy Storage: The main research themes of our group are gas conversion and energy storage. By taking a queue from nature's strategy **to store energy in the form of chemical bonds** — a process that has been refined over 3.5 billion years of evolution and is necessary for the survival of all living organisms— our goal is to develop an artificial energy storage system. To this end, we are developing new porous materials, such as porous coordination polymers (PCPs), that have high surface tunability and are structurally diverse, for potential industrial applications. PCP catalysts offer a promising approach for utilizing materials to convert important gases used in energy storage.

3. Gas capture and separation: We have been creating environmentally-responsive porous materials. For example, photo-responsive one enables us to trap and release gas molecules when and where we want. We also successfully developed flexible crystalline porous materials for highly effective and low-energy consuming separation of gaseous molecules. We aim to solve environmetal and energy problems through the development of new porous materials useful for the capture, separation, and conversion of gas molecules that are present abundantly in atmosphere.

Selected Papers

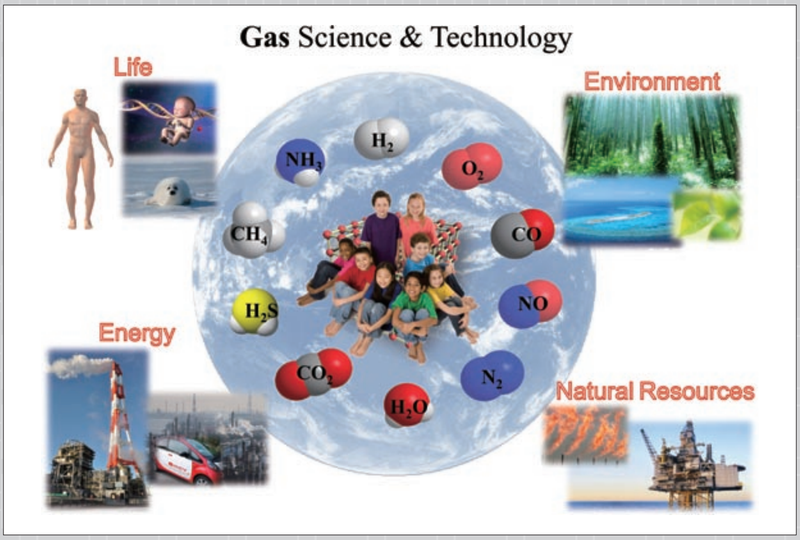
H. Sato, W. Kosaka, R. Matsuda, A. Hori, Y. Hijikata, R. V. Belosludov, S. Sakaki, M. Takata, S. Kitagawa, Self-accelerating CO sorption in a soft nanoporous crystal. *Science* **343**, 167-170 (2014).

Y. Sakata, S. Furukawa, M. Kondo, K. Hirai, N. Horike, Y. Takashima, H. Uehara, N. Louvain, M. Meilikhov, T. Tsuruoka, S. Isoda, W. Kosaka, O. Sakata, S. Kitagawa, Shape-memory nanopores induced in coordination frameworks by crystal downsizing. *Science* **339**, 193-196 (2013).

S. Diring, D. O. Wang, C. Kim, M. Kondo, Y. Chen, S. Kitagawa, K. Kamei, S. Furukawa, Localized cell stimulation by nitric oxide using a photoactive porous coordination polymer platform. *Nat. Commun.* **4**, 2684 (2013).

J. Reboul, S. Furukawa, N. Horike, M. Tsotsalas, K. Hirai, H. Uehara, M. Kondo, N. Louvain, O. Sakata, S. Kitagawa, Mesoscopic architectures of porous coordination polymers fabricated by pseudomorphic replication. *Nat. Mater.* **11**, 717-723 (2012).

S. Horike, S. Shimomura, S. Kitagawa, Soft porous crystals. *Nat. Chem.* **1**, 695-704 (2009).



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

Z. Kalay, T. K. Fujiwara, A. Otaka, A. Kusumi. Lateral diffusion in a discrete fluid membrane with immobile particles. *Phys. Rev. E.* **89**, 022724 (2014).

K. G. Suzuki, R. S. Kasai, K. M. Hirosawa, Y. L. Nemoto, M. Ishibashi, Y. Miwa, T. K. Fujiwara, A. Kusumi, Transient GPI-anchored protein homodimers are units for raft organization and function. *Nat. Chem. Biol.* **8**, 774-783 (2012).

A. Kusumi, T. K. Fujiwara, R. Chadda, M. Xie, T. A. Tsunoyama, Z. Kalay, R. S. Kasai, K. G. Suzuki, Dynamic organizing principles of the plasma membrane that regulate signal transduction: commemorating the fortieth anniversary of Singer and Nicolson's fluid-mosaic model. *Ann. Rev. Cell Develop. Biol.* **28**, 215-250 (2012).

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

K. A. Tanaka, K. G. Suzuki, Y. M. Shirai, S. T. Shibutani, M. S. Miyahara, H. Tsuboi, M. Yahara, A. Yoshimura, S. Mayor, T. K. Fujiwara, A. Kusumi, Membrane molecules mobile even after chemical fixation. *Nat. Methods* **7**, 865-866 (2010).

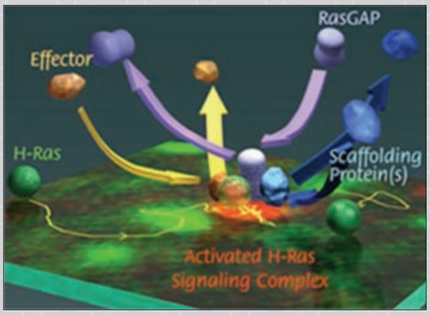


Fig. 2

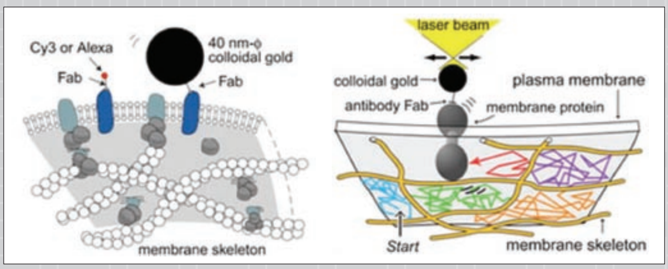


Fig. 1

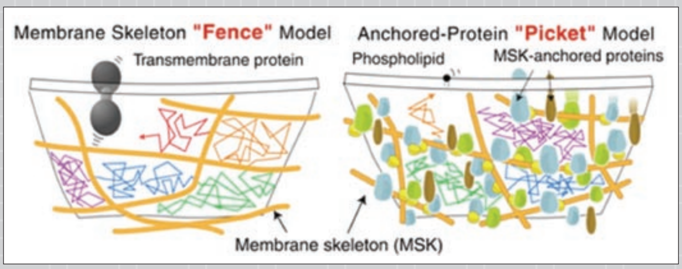


Fig. 3

Norio Nakatsuji Lab

Stem Cell Biology, Developmental Biology

Faculty Members

Norio Nakatsuji (Professor)
Kazuhiro Aiba (Associate Professor)
Takamichi Miyazaki (Assistant Professor)

Research Overview

Our research group has been working on the 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 developed 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.

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 in the iCeMS.
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). For example, we have identified novel small molecules which can induce efficient and robust cardiomyocyte differentiation from many human ES and iPS cell lines in totally defined xeno-free conditions.
3. Development of novel technologies for large-scale production of high-quality human pluripotent stem cells using 3D culture system. 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

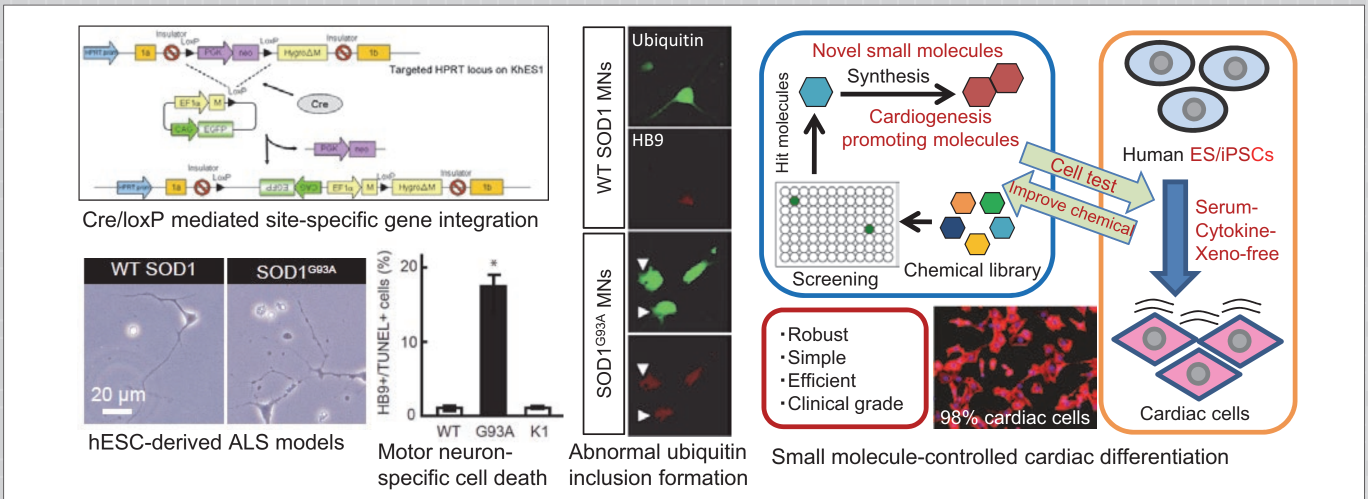
T. G. Otsuji, J. Bin, A. Yoshimura, M. Tomura, D. Tateyama, I. Minami, Y. Yoshikawa, K. Aiba, J. E. Heuser, T. Nishino, K. Hasegawa, N. Nakatsuji, A 3D Sphere culture system containing functional polymers for large-scale human pluripotent stem cell production. *Stem Cell Reports* (2014). DOI: http://dx.doi.org/10.1016/j.stemcr.2014.03.012

S. Kadota, I. Minami, N. Morone, J. E. Heuser, K. Agladze, N. Nakatsuji, Development of a reentrant arrhythmia model in human pluripotent stem cell-derived cardiac cell sheets. *Eur. Heart J.* **34**, 1147-1156 (2013).

T. Wada, S. K. Goparaju, N. Tooi, H. Inoue, R. Takahashi, N. Nakatsuji, K. Aiba, Amyotrophic lateral sclerosis model derived from human embryonic stem cells overexpressing mutant superoxide dismutase 1. *Stem Cells Transl. Med.* **1**, 396-402 (2012).

T. Miyazaki, S. Futaki, H. Suemori, Y. Taniguchi, M. Yamada, M. Kawasaki, M. Hayashi, H. Kumagai, N. Nakatsuji, K. Sekiguchi, E. Kawase, Laminin E8 fragments support efficient adhesion and expansion of dissociated human pluripotent stem cells. *Nat. Commun.* **3**, 1236 (2012).

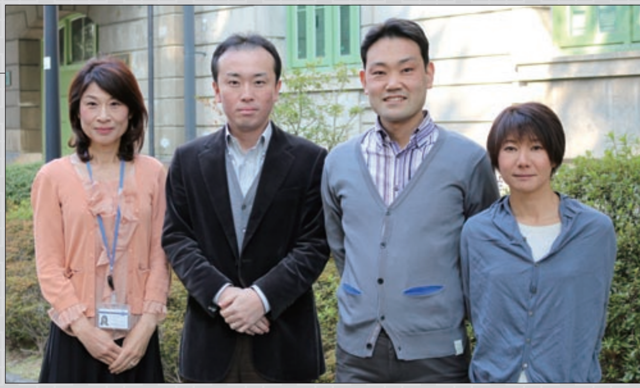
I. Minami, K. Yamada, T. G. Otsuji, T. Yamamoto, Y. Shen, S. Otsuka, S. Kadota, N. Morone, M. Barve, Y. Asai, T. Tenkova-Heuser, J. E. Heuser, M. Uesugi, K. Aiba, N. Nakatsuji, A small molecule that promotes cardiac differentiation of human pluripotent stem cells under defined, cytokine- and xeno-free conditions. *Cell Rep.* **2**, 1448-1460 (2012).



Mitinori Saitou Lab

Germ Cell Biology, Stem Cell Biology

Faculty Members
Mitinori Saitou (Professor)
Yoji Kojima (Assistant Professor)



Research Overview

The germ cell lineage ensures the creation of new individuals, perpetuating/diversifying the genetic and epigenetic information across the generations. We have been investigating the mechanism for germ cell specification and development in mice. Based on the knowledge obtained, using pluripotent stem cells [**embryonic stem cells (ESCs)** and **induced pluripotent stem cells (iPSCs)**], we have succeeded in precisely reconstituting the specification and subsequent development of germ cells in culture both in males and females: ESCs/iPSCs are induced into epiblast-like cells (EpiLCs) and then into **primordial germ cell-like cells (PGCLCs)**, which contribute to spermatogenesis and oogenesis and to fertile offspring. Based on this system, we have succeeded in inducing the germ-cell fate on EpiLCs by forced expression of key transcription factors and have clarified their mechanisms of action. We have also shown that a mesodermal factor, T, directly up-regulates the expression of germline determinants and plays an essential role in PGC specification. Furthermore, we have identified comprehensive quantitative chromatin-state dynamics during in vitro PGC specification, establishing the concept of epigenetic reprogramming at the outset of germ cell development. Our work serves as a foundation for the reconstitution of germ-cell development in other mammals, including humans.

Selected Papers

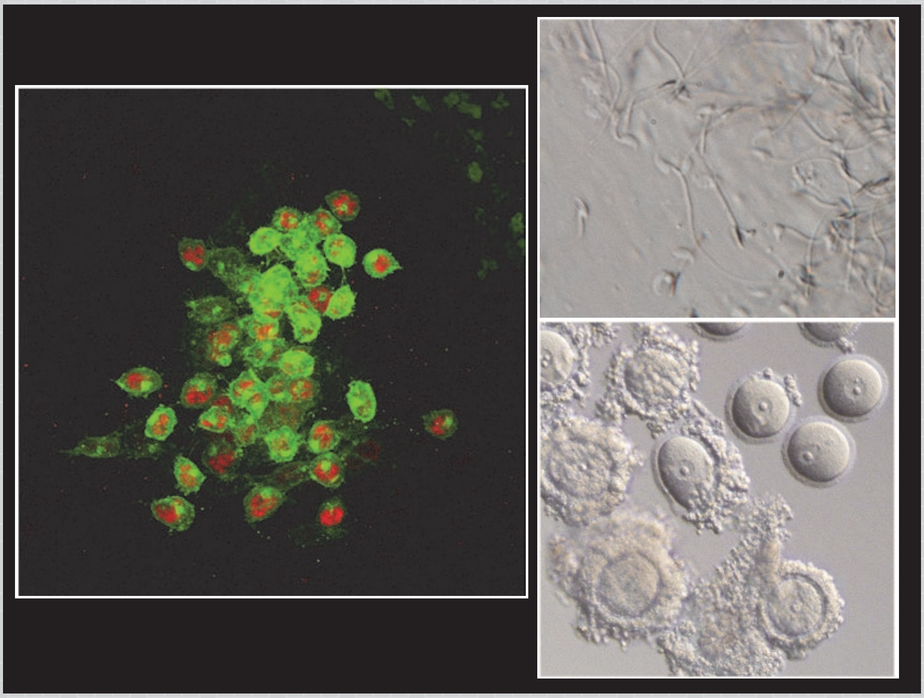
K. Kurimoto, Y. Yabuta, K. Hayashi, H. Ohta, H. Kiyonari, T. Mitani, Y. Moritoki, K. Kohri, H. Kimura, T. Yamamoto, Y. Katou, K. Shirahige, M. Saitou, Quantitative dynamics of chromatin remodeling during germ cell specification from mouse embryonic stem cells, *Cell Stem Cell* **16**, 517-532 (2015).

T. Nakamura, Y. Yabuta, I. Okamoto, S. Aramaki, S. Yokobayashi, K. Kurimoto, K. Sekiguchi, M. Nakagawa, T. Yamamoto, M. Saitou, SC3-seq: A method for highly parallel and quantitative measurement of single-cell gene expression, *Nuc. Acids Res.* **43**, e60 (2015).

Aramaki, S., Hayashi, K., Kurimoto, K., Ohta, H., Yabuta, Y., Iwanari, H., Mochizuki, Y., Hamakubo, T., Kato, Y., Shirahige, K., and Saitou, M. A mesodermal factor, T, specifies mouse germ cell fate by directly activating germline determinants, *Dev. Cell* **27**, 516-529 (2013).

F. Nakaki, K. Hayashi, H. Ohta, K. Kurimoto, Y. Yabuta, M. Saitou, Induction of the mouse germ cell fate by transcription factors in vitro. *Nature* **501**, 222-226 (2013).

M. Yamaji, J. Ueda, K. Hayashi, H. Ohta, Y. Yabuta, K. Kurimoto, R. Nakato, K. Shirahige, M. Saitou, PRDM14 ensures naïve pluripotency through dual regulation of signaling and epigenetic pathways in mouse embryonic stem cells, *Cell Stem Cell* **12**, 368-382 (2013).



(left) PGCs in mouse embryo at embryonic day 7.5. Green: Blimp1-mVenus, Red: AP2γ.
(right, top) Spermatozoa from PGCLCs from ESCs.
(right bottom) Oocytes from PGCLCs from ESCs.

Hiroshi Sugiyama Lab

Chemical Biology

Faculty Members

Hiroshi Sugiyama (Professor)
Masayuki Endo (Associate Professor)
Ganesh Pandian Namasivayam (Assistant Professor)

Research Overview

The Sugiyama group's research interests involve the chemical biology of nucleic acids. Using the tools of organic synthesis and molecular biology, the Sugiyama group is defining the chemical principles underlying the recognition, reactivity, and structure of nucleic acids. The group utilizes a chemical approach in following areas: design of highly efficient sequence-specific DNA acting agents, design of unnatural nucleic acid for understanding of nucleic acid structure and function, design of DNA nanostructures for control and observation of the single molecular dynamic and single reaction, and development of a general method probing DNA local conformation in vivo. Our long-term goals are to analyze the molecular behaviors involved in epigenetic regulation, and create **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 for cell biology. Using the 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, our research focuses on the following six topics: (1) Design and construction of novel multidimensional DNA nanostructures; (2) Programmed assembly of the DNA nanostructures and the functionalization; (3) Regulation of chemical and enzymatic reactions in the designed nanospace; (4) Single-molecule visualization and biophysical analysis of the behaviors and reactions of biomolecules in the designed nanostructure; (5) Development of novel delivery system for cellular applications; (6) Applications for molecular robotics.

Selected Papers

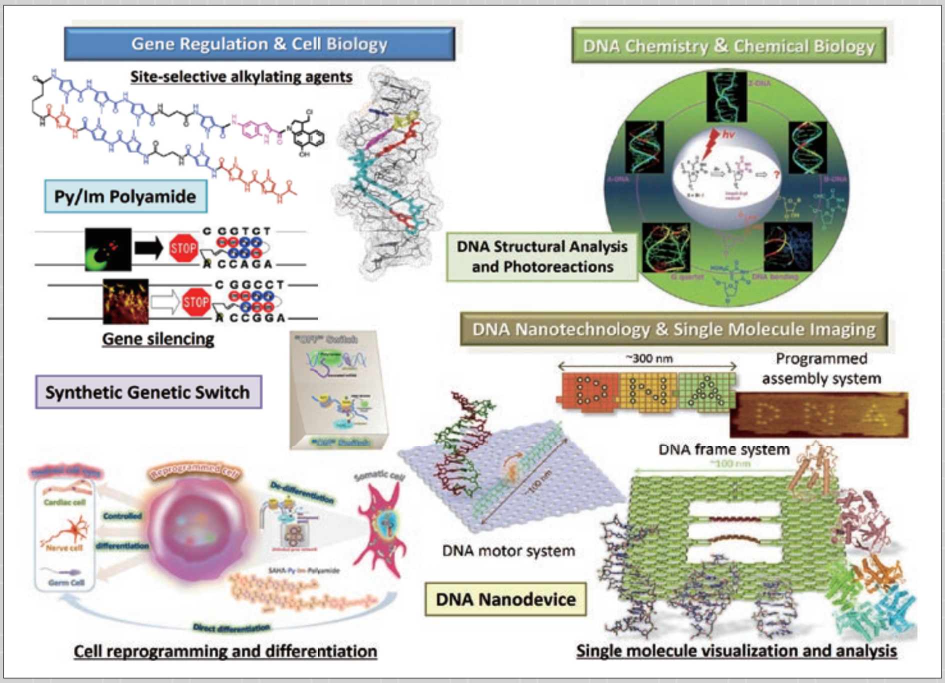
M. Endo, H. Sugiyama, Single-Molecule Imaging of Dynamic Motions of Biomolecules in DNA Origami Nanostructures Using High-Speed Atomic Force Microscopy. *Acc. Chem. Res.* **47**, 1645-1653 (2014).

Y. Suzuki, M. Endo, Y. Yang, H. Sugiyama, Dynamic Assembly/Disassembly Processes of Photoresponsive DNA Origami Nanostructures Directly Visualized on a Lipid Membrane Surface. *J. Am. Chem. Soc.* **136**, 1714-1717 (2014).

Y. Suzuki, M. Endo, Y. Katsuda, K. Ou, K. Hidaka, H. Sugiyama, DNA Origami Based Visualization System for Studying Site-Specific Recombination Events. *J. Am. Chem. Soc.* **136**, 211-218 (2014).

G. N. Pandian, J. Taniguchi, S. Junetha, S. Sato, L. Han, A. Saha, C. Anandhkumar, T. Bando, H. Nagase, V. Thangavel, R. D. Taylor, H. Sugiyama, Distinct DNA-based epigenetic switches trigger transcriptional activation of silent genes in human dermal fibroblasts. *Sci. Rep.* **4**, 3843 (2014).

Y. Kawamoto, T. Bando, F. Kamada, Y. Li, K. Hashiya, K. Maeshima, H. Sugiyama, Development of a New Method for Synthesis of Tandem Hairpin Pyrrole-Imidazole Polyamide Probes Targeting Human Telomeres. *J. Am. Chem. Soc.* **135**, 16468-16477 (2013).



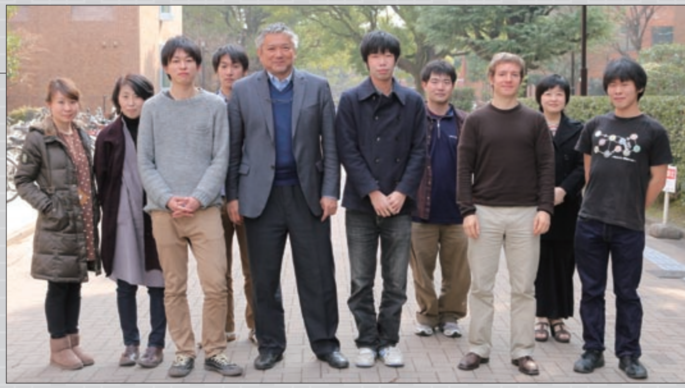
Koichiro Tanaka Lab

Teraherz Optical Science

Faculty Members

Koichiro Tanaka (Professor)

Hideki Hirori (Associate Professor)



Research Overview

Terahertz (THz) wave, 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 (3mJ/pulse). This has allowed us to generate an intense THz wave over 1 MV/cm in the electric field with the repetition rate of 1 KHz. Recently, our group has been exploring **non-linear optical responses** of semiconductors and mesoscopic 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-wave, the microscope will work at video rates. Biological applications are now possible and will be conducted in collaboration with Kusumi, Kitagawa, and Kengaku groups.

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

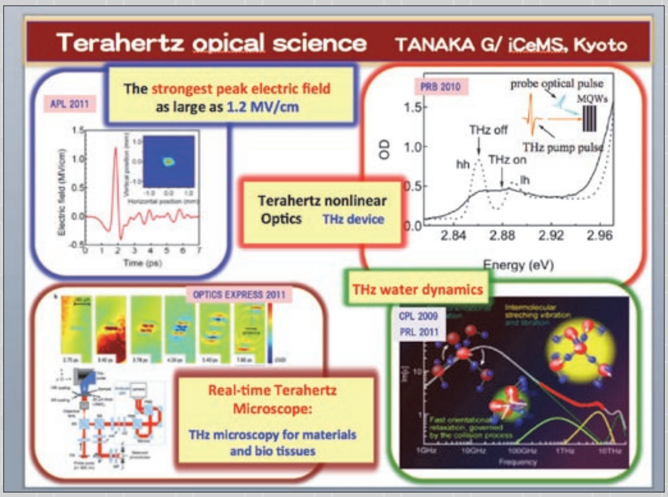
F. Blanchard, K. Sumida, C. Wolpert, M. Tsotsalas, T. Tanaka, A. Doi, S. Kitagawa, D. G. Cooke, S. Furukawa, K. Tanaka, Terahertz phase contrast imaging of sorption kinetics in porous coordination polymer nanocrystals using differential optical resonator. *Opt. Express* **22**, 11061-11069 (2014).

K. Shinokita, H. Hirori, K. Tanaka, T. Mochizuki, C. Kim, H. Akiyama, L. N. Pfeiffer, K. W. West, Terahertz-Induced Optical Emission of Photoexcited Undoped GaAs Quantum Wells. *Phys. Rev. Lett.* **111**, 067401 (2013). *Editor's Suggestion

T. Kampfrath, K. Tanaka, K. A. Nelson, Resonant and nonresonant control over matter and light by intense terahertz transients, *Nature Photonics* **7**, 680 (2013).

H. Hirori, K. Shinokita, M. Shirai, S. Tani, Y. Kadoya, K. Tanaka, Extraordinary carrier multiplication gated by a picosecond electric field pulse. *Nat. Commun.* **2**, 594 (2011).

H. Hirori, A. Doi, F. Blanchard, K. Tanaka, Single-cycle terahertz pulses withamplitudes exceeding 1 MV/cm generated by optical rectification in LiNbO3. *Appl. Phys. Lett.* **98**, 091106 (2011).



Motomu Tanaka Lab

Biological Physics, Interface Science, Active Bio-Matter

Faculty Members

Motomu Tanaka (Professor)

Marcel Hörning (Assistant Professor)

Research Overview

The Tanaka Laboratory is cultivating a new research field "**Physics of Cells and Tissues**" by the combination of (1) **tailor-made biointerface models** (such as "supported membranes", Tanaka and Sackmann, Nature, 437, 656 (2005)) and (2) **quantitative physical tools** both in real space (e.g. live-cell imaging and analysis) and reciprocal space (advanced X-ray and neutron scattering, diffraction imaging).

One of our focuses in the iCeMS is to shed light on the **interfaces**, "*where cells meet materials*". The reactions at soft, biological interfaces cannot be described only as a sum of individual molecular elements, which has been a common strategy in the past decades. In order to deal with *dynamic, stochastic processes out of equilibrium*, such as **diseases and development**, we must consider the cooperativity and fluctuation in *mesoscopic reaction spaces*. Thus, the introduction of concepts in statistical physics is a powerful strategy to extract **spatio-temporal correlations**. In addition to the development of new "*in house*" physical techniques to quantify the strength of cell-material interactions, we intensively perform cutting-edge research at synchrotron and neutron facilities to gain hierarchical-structures at soft interfaces over different length scales.

Our laboratory is a highly interdisciplinary, international team that consists of people with training backgrounds in physics, chemistry, and biology. The principal investigator (Prof. Motomu Tanaka) has developed his scientific career in Europe (Germany), serving as a full professor in chemistry and physics at the University of Heidelberg. Within the framework of Japanese-German University Partnership Program (HeKKSaGOn Alliance), he got a cross-appointment as the "First HeKKSaGOn Professor" at Kyoto University since April 2013. Our global challenge is to establish a new scientific discipline in iCeMS through tight collaboration with our main lab in the University of Heidelberg (Germany) and many collaborating partners in Europe and Japan.

Selected Papers

A. S. Burk, C. Monzel, H. Y. Yoshikawa, P. Wuchter, R. Saffrich, V. Eckstein, M. Tanaka*, A. D. Ho*, Quantifying Adhesion Mechanisms and Dynamics of Human Hematopoietic Stem and Progenitor Cells. *Sci. Rep.* **5**, 9370; DOI:10.1038/srep09370 (2015).

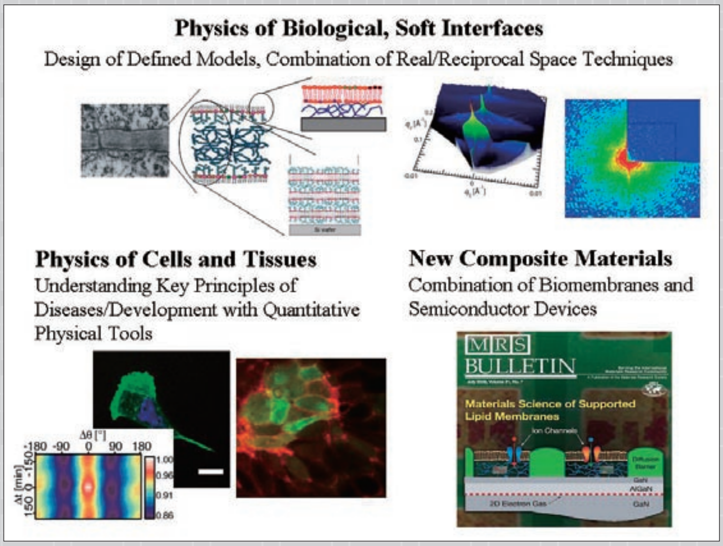
H. Rieger, H. Y. Yoshikawa, K. Quadt, M. A. Nielsen, C. P. Sanchez, A. Salanti, M. Tanaka*, M. Lanzer, Cytoadhesion of Plasmodium falciparum–infected erythrocytes to chondroitin-4-sulfate is cooperative and shear enhanced. *Blood* **125**, 383-391; DOI:10.1182/blood-2014-03-561019 (2015).

A. Yamamoto, W. Abuillan, A. S. Burk, A. Körner, A. Ries, D. B. Werz, B. Demé, M. Tanaka*, Influence of length and conformation of saccharide head groups on the mechanics of glycolipid membranes: Unraveled by off-specular neutron scattering. *J. Chem. Phys.* **142**, 154907; DOI: 10.1063/1.4918585 (2015).

A. Körner, C. Deichmann, F. F. Rossetti, A. Köhler, O. V. Konovalov, D. Wedlich, M. Tanaka*, Cell differentiation of pluripotent tissue sheets immobilized on supported membranes displaying cadherin-11. *PLoS ONE* **8** (2): e54749. DOI:10.1371/journal.pone.0054749 (2013).

T. Kaindl, H. Rieger, L-M. Kaschel, U. Engel, A. Schmaus, J. Sleeman, M. Tanaka*, Spatio-temporal patterns of pancreatic cancer cells expressing CD44 isoforms on supported membranes displaying hyaluronic acid oligomers arrays. *PLoS ONE* **7** (8): e42991. doi:10.1371/journal.pone.0042991 (2012).

*corresponding authors



Kazumitsu Ueda Lab

Cellular Biochemistry

Faculty Members

Kazumitsu Ueda (Professor)
Atsushi Kodan (Assistant Professor)
Koh Nagata (Assistant Professor)

Research Overview

Humans are made of materials, such as amino acids, carbohydrates and lipids. These materials are absorbed and circulated in the body via transporter proteins. **ABC (ATP-binding cassette) proteins** are membrane proteins, which mainly transport various lipids. **ABC proteins** work in the forefront of the interaction between cells and lipophilic materials and also generate physiologically important materials in the body, such as "good cholesterol". 48 **ABC proteins** in humans play physiologically important roles and their functional defects can lead to a variety of pathological conditions, including cardiovascular diseases, respiratory failure of infants, skin diseases, neuronal diseases, senile blindness, diabetes, and gout. Our research on **ABC proteins** will establish the basis for **Cell-Material interactions** and contribute to human health by exploring the cause of such diseases and finding ways to prevent them. At iCeMS, we are carrying out the following cross-disciplinary research projects:

1. We are revealing the physiological roles of **ABC proteins** in pluripotent **ES and iPS cells**, and developing small-molecule fluorescent probes specific for **ES and iPS cells**. These compounds can be used to identify pluripotent **ES and iPS cells** and will be a useful tool for basic cell biology research and stem cell therapy. (In collaboration with the Nakatsuji, Yamanaka, and Uesugi Labs.)

2. We have revealed the functional architectures of **ABC proteins** using X-ray crystal structure analysis at the best resolution, which will facilitate our understanding of the mechanism of **Material recognition by ABC proteins**.

3. ABCA1 and ABCG1 are key molecules for generating plasma **meso-particle** high-density lipoprotein (HDL), which is so-called "good cholesterol" and critical for cholesterol homeostasis. Furthermore, it is suggested that they reorganize some **meso-domains** on the plasma membrane and modulate immune and inflammation responses. We succeeded for the first time in visualizing **ABC proteins** in action on the plasma membrane in collaboration with the Kusumi and Heuser Labs at CeMI (Center for **Meso-Bio** Single-Molecule Imaging). We are revealing the mechanism of HDL formation, which is important to prevent atherosclerosis.

4. In collaboration with the Kengaku Lab, we are revealing the role of **ABC proteins** in **meso-domain formation** in neuronal cells.

5. The microenvironment surrounding cells is a critical factor for determining the fate of cells, including proliferation and differentiation. We are elucidating the mechanism by which cells sense their microenvironment through associations made with the extracellular matrix, which ultimately determines their fate.

Selected Papers

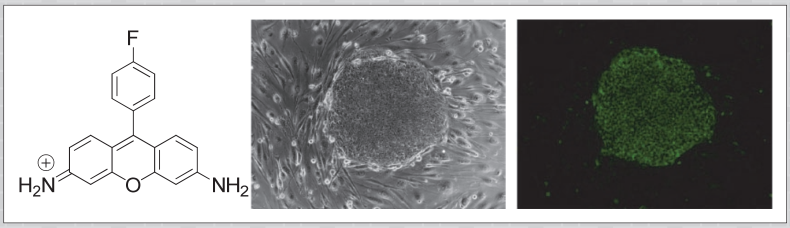
L. Tomiyama, T. Sezaki1, M. Matsuo. K. Ueda, N. Kioka, Loss of Dlg5 expression promotes the migration and invasion of prostate cancer cells via Girdin phosphorylation. *Oncogene* **24**, 1141-1149 (2015).

T.-F. Kuo, D. Mao, N. Hirata, B. Khambu, Y. Kimura, E. Kawase, H. Shimogawa, M. Ojika, N. Nakatsuji, K. Ueda, M. Uesugi, Selective elimination of human pluripotent stem cells by a marine natural product derivative. *J. Am. Chem. Soc.* **136**, 9798-801 (2014).

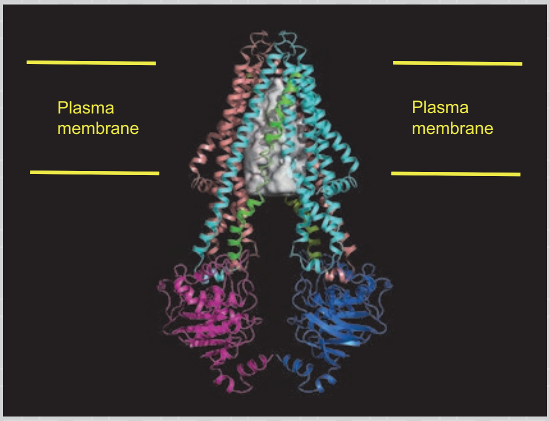
A. Kodan, T. Yamaguchi, T. Nakatsu, K. Sakiyama, C. J. Hipolito, A. Fujioka, R. Hirokane, K. Ikeguchi, B. Watanabe, J. Hiratake, Y. Kimura, H. Suga, K. Ueda, H. Kato, Structural Basis for Gating Mechanisms of a Eukaryotic P-glycoprotein Homolog. *Proc. Natl. Acad. Sci. U. S. A.* **111**, 4049-4054 (2014).

N. Hirata,N. M. Nakagawa, Y. Fujibayashi, K. Yamauchi, A. Murata, I. Minami, M. Tomioka, T. Kondo, T-F. Kuo, H. Endo, H. Inoue, H. S-i. Sato, S. Ando, Y. Kawazoe, K. Aiba, K. O. Nagata, E. Kawase, Y-T. Chang, H. Suemori, K. Eto, H. Nakauchi, S. Yamanaka, N. Nakatsuji, K. Ueda, K. M. Uesugi, A Chemical Probe Selective for Human Pluripotent Stem Cells. *Cell Reports* **6**, 1165-1174 (2014).

K.O. Nagata, C. Nakada, R. S. Kasai, A. Kusumi, K. Ueda, ABCA1 dimer-monomer interconversion during HDL generation revealed by single-molecule imaging. *Proc. Natl. Acad. Sci. USA*, **110**, 5034-5039 (2013).



1. Fluorescent probe for human ES/iPS cells



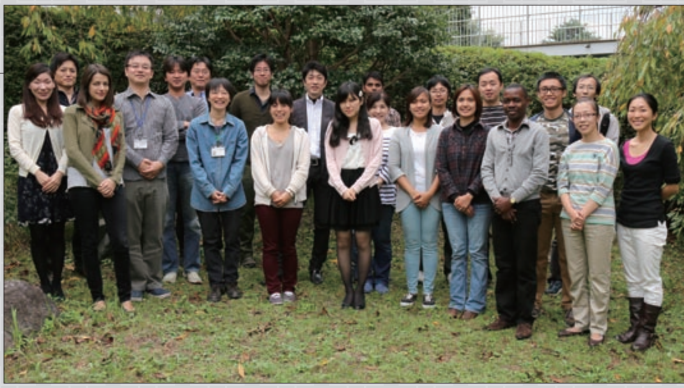
2. Multi-drug recognition mechanism by MDR1

Motonari Uesugi Lab

Chemical Biology

Faculty Members

Motonari Uesugi (Professor)
Shinichi Sato (Assosiate Professor)
Yasushi Takemoto (Assistant Professor)



Research Overview

Chemical biology is an interdisciplinary field of study that is often defined as "chemistry-initiated biology." As biological processes all stem from chemical events, it should be possible to understand or manipulate biological events by using chemistry. Our laboratory has been discovering or designing unique organic molecules that modulate fundamental processes in human cells. Such **synthetic organic molecules** often serve as tools for **basic cell biology** and **cell therapy**. Our mission is to create new world of bioactive synthetic molecules: their new way to use, their new shapes, and their new sizes. We hope to open new avenues for small-molecule applications in a range of fields, including future concepts in drug discovery and use of small molecules for cell therapy.

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

- **Small-molecule tools for basic cell biology**. Discovery or design of unique chemical probes that specifically control or detect biological process permits new approaches to exploring complex cellular events. Our main interests lie in modulation or detection of gene expression, cell interaction, and energy control.

- **Small molecule tools useful for cell therapy**. One potential problem of cell therapy is high cost. Small molecules 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 the ill-defined cell therapy.

Selected Papers

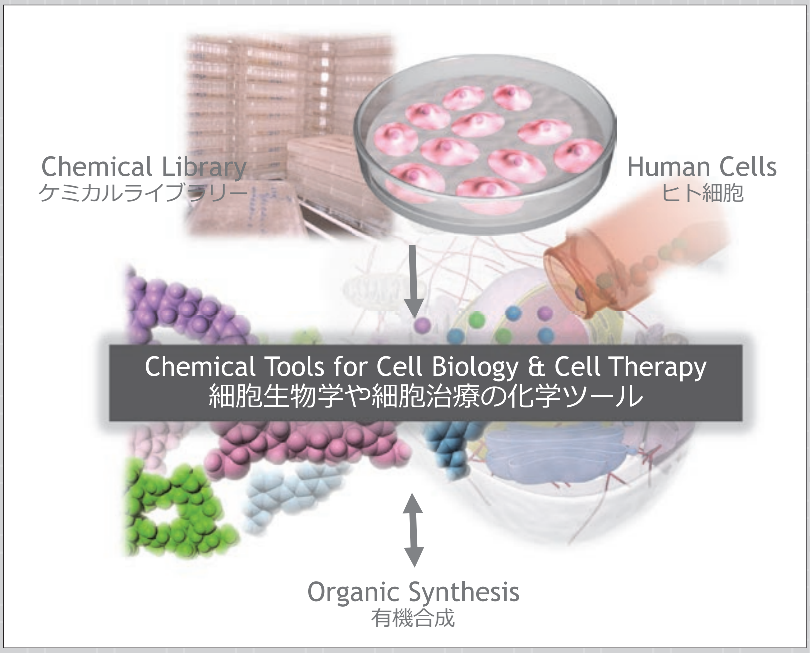
S. Sato*, M. Watanabe, Y. Katsuda, A. Murata, D. O. Wang, M. Uesugi, Live-cell imaging of endogenous mRNAs with a small molecule. *Angew. Chem. Int. Ed.* **54**, 1855-1858 (2015).

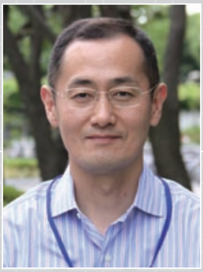
H.L. Frisco-Cabanos, M. Watanabe, N. Okumura, K. Kusamori, N. Takemoto, J. Takaya, S. Sato, S. Yamazoe, Y. Takakura, S. Kinoshita, M. Nishikawa, M. Koizumi, M. Uesugi, Synthetic molecules that protect cells from anoikis and their use in cell transplantation. *Angew. Chem. Int. Ed.* **53**, 11208-11213 (2014).

T. F. Kuo, D. Mao, N. Hirata, B. Khambu, Y. Kimura, E. Kawase, H. Shimogawa, M. Ojika, N. Nakatsuji, K. Ueda, M. Uesugi, Selective elimination of human pluripotent stem cells by a marine natural product derivative. *J. Am. Chem. Soc.* **136** (28), 9798-9801 (2014).

N. Hirata, M. Nakagawa, Y. Fujibayashi, K. Yamauchi, A. Murata, I. Minami, M. Tomioka, T. Kondo, T. F. Kuo, H. Endo, H. Inoue, S. Sato, S. Ando, Y. Kawazoe, K. Aiba, K. Nagata, E. Kawase, Y. T. Chang, H. Suemori, K. Eto, H. Nakauchi, S. Yamanaka, N. Nakatsuji, K. Ueda, M. Uesugi, A chemical probe that labels human pluripotent stem cells. *Cell Rep* **6**, 1165-1174 (2014).

N. Takemoto, T. Suehara, H. Frisco, S. Sato, T. Sezaki, K. Kusamori, Y. Kawazoe, S. Park, S. Yamazoe, Y. Mizuhata, R. Inoue, G. Miller, S. Hansen, G. Jayson, J. Gardiner, T. Kanaya, N. Tokitoh, K. Ueda, Y. Takakura, N. Kioka, M. Nishikawa, M. Uesugi, Small molecule-induced clustering of heparan sulfate promotes cell adhesion. *J. Am. Chem. Soc.* **135** (30), 11032-11039 (2013).





Shinya Yamanaka Lab

Stem Cell Biology, Developmental Engineering

Faculty Members

Shinya Yamanaka (Professor)
Yasuhiro Yamada (Professor)
Akitsu Hotta (Assistant Professor)
Akira Watanabe (Assistant Professor)
Takuya Yamamoto (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. However, it remains controversial whether iPS cells are distinguishable from 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 to achieve iPS cell-mediated cell transplantation therapy.

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

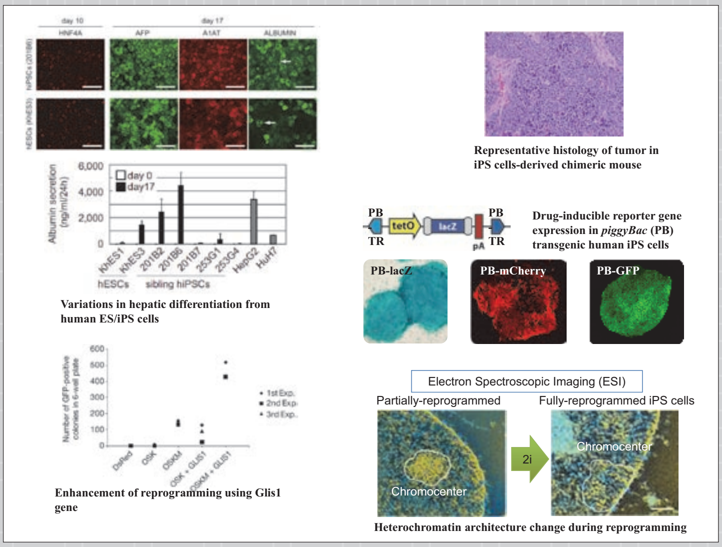
K. Okita, T. Yamakawa, Y. Matsumura, Y. Sato, N. Amano, A. Watanabe, N. Goshima, S. Yamanaka, An efficient nonviral method to generate integration-free human-induced pluripotent stem cells from cord blood and peripheral blood cells. *Stem Cells* **3**, 458-66 (2013).

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

K. Ohnishi, K. Semi, T. Yamamoto, M. Shimizu, A. Tanaka, K. Mitsunaga, K. Okita, K. Osafune, Y. Arioka, T. Maeda, H. Soejima, H. Moriwaki, S. Yamanaka, K. Woltjen, Y. Yamada, Premature termination of reprogramming in vivo leads to cancer development through altered epigenetic regulation. *Cell* **156**, 663-77 (2014).

H. Lisa Li, T. Nakano, A. Hotta, Genetic correction using engineered nucleases for gene therapy applications. *Dev. Growth Differ.* **56**, 63-77 (2014).

S. Ohta, E. Nishida, S. Yamanaka, T. Yamamoto, Global splicing pattern reversion during somatic cell reprogramming. *Cell Rep.* **5**, 357-66 (2013).



Peter Carlton

Pluripotent stem cells, Meiosis, Chromatin Biology, Superresolution Optical Microscopy

Faculty Members Peter Carlton (Associate Professor)

Research Overview

The Carlton lab focuses on understanding how chromosomes and chromatin are dynamically regulated for the correct expression and inheritance of the genome. Our research has two main areas:

Pluripotent stem cells have unique requirements for genome regulation: they must suppress all developmental pathways, while remaining competent to activate any given pathway. We are using **superresolution microscopy** and developing image analysis methods to investigate the chromatin dynamics of the pluripotent genome in three dimensions, and to discover changes in genome organization that accompany differentiation to lineage-committed cells.

Meiosis is an essential cell division process that creates haploid cells (e.g., sperm and eggs) from diploid precursors. Errors in meiosis cause many human reproductive problems, from infertility to birth defects. Using the nematode Caenorhabditis elegans as a model system for its excellent genetic and cytological qualities, we aim to find the mechanisms underlying correct pairing and synapsis of homologous chromosomes, as well as regulation of recombination. A major part of our efforts center around the phosphoregulation of proteins required for meiotic prophase.

Selected Papers

A. Sato-Carlton, X. Li, O. Crawley, S. Testori, E. Martinez-Perez, A. Sugimoto, P. M. Carlton, Protein phosphatase 4 regulates homologous chromosome pairing and synapsis, and maintains recombination competence with increasing age. *PLoS Genet.* **10**, e1004638 (2014).

P. M. Carlton, J. Boulanger, C. Kervrann, J. B. Sibarita, J. Salamero, G. Gordon-Messer, D. Bressan, J. E. Haber, S. Haase, L. Shao, L. Winoto, A. Matsuda, P. Kner, S. Uzawa, M. G. L. Gustafsson, Z. Kam, D. A. Agard, J.W. Sedat, Fast live simultaneous multiwavelength four-dimensional optical microscopy. *Proc. Acad. Natl. Acad. Sci. U. S. A.* **107**, 16016-22 (2010).

L. Schermelleh, P. M. Carlton‡, S. Haase, L. Shao, L. Winoto, P. Kner, B. Burke, M.C. Cardoso, D.A. Agard, M.G.L. Gustafsson, H. Leonhardt, J.W. Sedat, Subdiffraction multicolor imaging of the nuclear periphery with 3D structured illumination microscopy. *Science* **320**, 332-6 (2008).

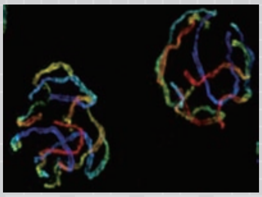


Figure 1. Meiotic chromosomes in C. elegans visualized with superresolution 3D-SIM microscopy. The two lateral elements of the synaptonemal complex, separated from each other at a distance of around 150 nanometers, are resolvable. This three-dimensional image is color-coded to represent depth.

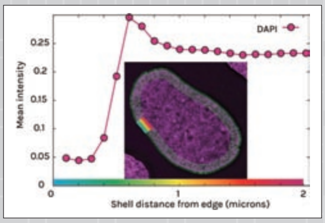


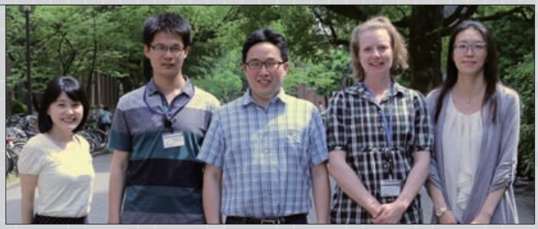
Figure 2. Automated quantitation of DNA intensity (detected with the DNA-specific dye DAPI) in a human embryonic stem cell showing a peak at the nuclear periphery. By detecting the nuclear edge and averaging the intensity over successively more distant shells, our program determines an unbiased radial intensity profile.

Franklin Kim

Synthetic Nano-/Meso-Chemistry, Self-Assembly

Faculty Members

Franklin Kim (Associate Professor)



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.

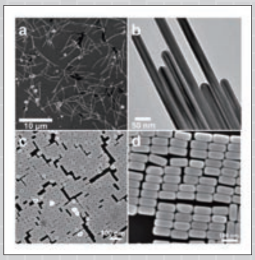
1. **Gold nanoparticles & nanowires**
   Due to their strong optical responses and biocompatibility, gold nanoparticles are used in a wide range of biological studies. Through precise control over the particle morphology and surface modification, we aim to develop structures that can be used for bio-sensing 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

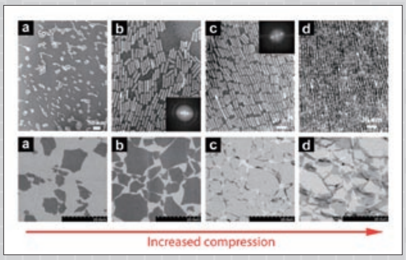
J. Zou, F. Kim, Diffusion driven layer-by-layer assembly of graphene oxide nanosheets into porous three-dimensional macrostructures. *Nat. Commun.*, DOI: 10.1038/ncomms6254 (2014).

J. Zou, F. Kim, Self-assembly of two-dimensional nanosheets induced by interfacial polyionic complexation. *ACS Nano* **6**, 10606-10613 (2012).

F. Kim, L. J. Cote, J. Huang, Graphene oxide: surface activity and two-dimensional assembly. *Adv. Mater.* **22**, 1954-1958 (2010).



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



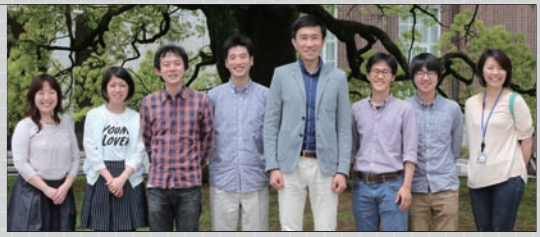
Two-dimensional (2D) assemblies of nanoscale building blocks prepared by Langmuir-Blodgett technique (top: $BaCrO_3$ nanorods, bottom: graphene oxide nanosheets)

Tatsuya Murakami

Protein Engineering, Cell Engineering

Faculty Members

Tatsuya Murakami (Associate Professor)



Research Overview

The Murakami group is aiming to develop novel cell engineering technologies and drug delivery systems against intractable diseases by **external stimuli–responsive materials**.

We previously showed that semiconducting single-walled carbon nanotubes are able to generate reactive oxygen species under near-infrared (NIR) illumination for the elimination cancer cells (*J. Am. Chem. Soc.* **2012**, *134*, 17862–17865), and a heavy metal ion-coordinated naphthalocyanine dimer was found to be a NIR dye capable of highly-sustained photothermal activity thanks to its unique structure (*ACS Nano* **2013**, *7*, 8908–8916). We also succeeded in developing a photocontrol method for plasma membrane potential by utilizing long-lived charge separation states of fullerene derivatives (*J. Am. Chem. Soc.* **2012**, *134*, 6092–6095), and extremely localized photothermal heating system by using gold nanorods and NIR laser (*ACS Nano* **2014**, *8*, 7370–7376). In all these cases, genetically and/or chemically engineered high-density lipoprotein (HDL) mutants (*Biotechnol. J.* **2012**, *7*, 762–767) were the key nanomaterials that enabled stabilization, detoxification, and site-specific delivery of the NIR-responsive nanomaterials.

HDL is a natural nanomaterial, consisting mainly of a lipid-binding serum protein, apoA-I and phospholipids, that mediates reverse cholesterol transport in our bodies, in other words, the good cholesterol. Recent studies have revealed broader functions of HDL, such as glucose metabolism acceleration and microRNA transport. In collaboration with medical and pharmaceutical research groups in Kyoto University and ETH Zürich, we are also developing HDL-based drug carriers by utilizing protein-engineering approaches.

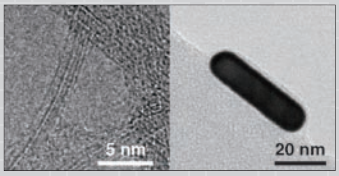
Selected Papers

T. Murakami, H. Nakatsuji, N. Morone, J. E.Heuser, F.Ishidate, M. Hashida, H. Imahori, Mesoscopic Metal Nanoparticles Doubly Functionalized with Natural and Engineered Lipidic Dispersants for Therapeutics. *ACS Nano* **8**, 7370-7376 (2014).

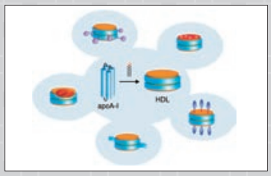
S. Mathew, T. Murakami, H. Nakatsuji, H. Okamoto, N. Morone, J. E. Heuser, M. Hashida, H. Imahori, Exclusive Photothermal Heat Generation by a Gadolinium (Bis(naphthalocyanine) Complex and Inclusion into Modified High-Density Lipoprotein Nanocarriers for Therapeutic Applications. *ACS Nano* **7**, 8908-8916 (2013).

T. Murakami, H. Nakatsuji, M. Inada, Y. Matoba, T. Umeyama, M. Tsujimoto, S. Isoda, M. Hashida, H. Imahori, Photodynamic and Photothermal Effects of Semiconducting and Metallic-Enriched Single-Walled Carbon Nanotubes. *J. Am. Chem. Soc.* **134**, 17862–17865 (2012).

1



2



1. Electron microscopy images of photoresponsive nanomaterials. Carbon nanotubes (left) and gold nanorods (right).
2. Schematic illustration of HDL and its engineering: The protein moiety, apoA-I, offers suitable sites for chemical modification, and can also be genetically fused with functional peptides and proteins. The surface charge of the lipid bilayer is controllable by using anionic and cationic lipids, and functional molecules with a hydrophobic domain are membrane-anchored. A phospholipid nanodisc reveals various hydrodynamic diameters dependent on the amount of the drug incorporated.

Research Groups 22

Easan Sivaniah

Polymer Science, Bionanotechnology

Faculty Members

Easan Sivaniah (Associate Professor)

Research Overview

The Sivaniah group manipulates materials with synthetic and biological approaches whilst seeking to establish a viable interface between the two.

In recent years we have delivered notable biomaterials research papers on intelligent scaffolds to interrogate the factors that influence cell migration. One example is well-defined scaffolds to determine the role of 3-D architectures on cell migration (*Biomaterials* **31**, 2201–2208, 2010). Another example is the controlled generation of spatially variant stiffness in 2D gels to interrogate cell mechanotaxis (*Advanced Materials* **24**, 6059–6064, 2012). Moreover our group studies the generation of bioplastics using bacterial and enzymatic tools.. Through such works, we will channel our experiences to develop practical principles that can support our vision of a grand challenge of generating industrially relevant processes via bionanotechnology.

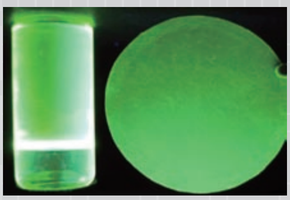
Although soft-matter bionanotechnology forms one key part of our research, our approach is to mix both synthetic and biosynthetic methods of materials development (with a current primary focus in achieving energy efficiency and environmental targets in separation technology). Examples include the report of a transformative platform technology for generating nanoporous materials (*Nature Materials* **11**, 53–57, 2012) and high performance microporous membranes for the separation of important environmental gases.

Selected Papers

Q. Song, S. Cao, R. H. Pritchard, B. Ghalei, S. A. Al-Muhtaseb, E. M. Terentjev, A. K. Cheetham, E. Sivaniah, Controlled thermal oxidative crosslinking of polymers of intrinsic microporosity towards tunable molecular sieve membranes. *Nat. Commun.* **5**, 4813 (2014).

Q. Song, S. Cao, P. Zavala-Rivera, L. P. Lu, W. Li, Y. Ji, S. A. Al-Muhtaseb, A. K. Cheetham, E. Sivaniah, Photo-oxidative enhancement of polymeric molecular sieve membranes. *Nat. Commun.* **4**, 1918 (2013).

P. Zavala-Rivera, K. Channon, V. Nguyen, E. Sivaniah, D. Kabra, R. H. Friend, S. K. Nataraj, S. A. Al-Muhtaseb, A. Hexemer, M. E. Calvo, H. Miguez, Collective osmotic shock in ordered materials. *Nat. Mater.* **11**, 53-57 (2012).



Green light for green membrane technology

The photo shows fluorescence of solution (left) and membrane (right) made of a polymer of intrinsic microporosity (PIM-1) under irradiation of ultraviolet light. The ultraviolet irradiation induces oxidation and surface densification of the polymeric molecular sieve membranes. These highly permeable and selective membranes would make gas separation process more energy efficient and environmental friendly.

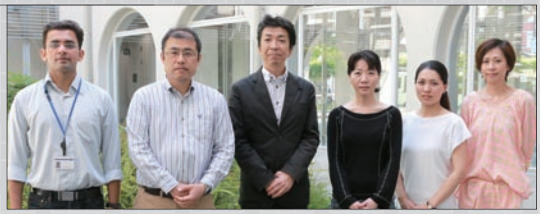
NCBS-inStem Satellite Lab Group

Kenichi 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 group's primary mission is to strengthen the international relationship among the iCeMS in Kyoto and the Tata Institute for Fundamental Research (TIFR), National Centre for Biological Sciences (NCBS) and the Institute for Stem Cell Biology and Regenerative Medicine (inStem) in Bangalore, India. This partnership includes not only research collaboration, but also joint symposia, researcher exchanges, and management of satellite facility and laboratories at both the iCeMS and at NCBS-inStem.

Our research is focused on **understanding how signal transductions regulate cell proliferation, migration, differentiation, and functions**. We are pursuing this primary goal using a variety of biological processes and samples including many types of cultured cells (such as human ES/iPS cells) as well as using laboratory mice. We are also employing various conventional and advanced tools in biophysics, chemistry, single molecule imaging, developmental biology, and cell and molecular biology. Our main projects are listed below:

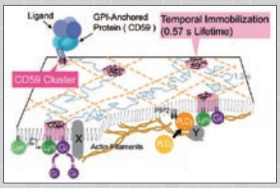
1. **Understanding dynamic mechanisms in cellular systems** using high-resolution and multicolor **single molecule imaging** of receptors and signaling molecules in living cells (Suzuki)
2. **Elucidation of molecular mechanisms in cell plasma membranes** using **single molecule imaging** with high temporal resolution (Suzuki)
3. Understanding how **signaling cascades regulate the pluripotent transcriptional network** and epigenetic reprogramming (Hasegawa)
4. Investigating **molecular mechanisms involved in cell fate determination** in early embryonic development and pluripotent stem cell differentiation (Hasegawa)

Selected Papers

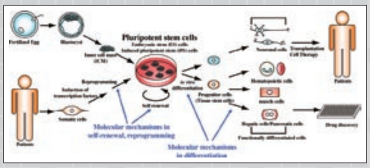
K. G. N. Suzuki, R. S. Kasai, K. M. Hirosawa, Y. L. Nemoto, M. Ishibashi, Y. Miwa, T. K. Fujiwara, A. Kusumi, Transient GPI-anchored protein homodimers are units for raft organization and function. *Nat. Chem. Biol.* **8**, 774-783 (2012).

K. Hasegawa, S. Y. Yasuda, J. L. Teo, C. Nguyen, M. McMillan, C. L. Hsieh, H. Suemori, N. Nakatsuji, M. Yamamoto, T. Miyabayashi, C. Lutzko, M. F. Pera, M. Kahn, Wnt signaling orchestration with a small molecule DYRK inhibitor provides long-term xeno-free human pluripotent cell expansion. *Stem. Cells Transl. Med.* **1**, 18-28 (2012).

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



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

Kazuto Kato (Science Communication Group)

Science Communication

Faculty Members

Kazuto Kato (Professor) Kei Kano (Associate 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. Since the Great East Japan Earthquake on 11 March, 2011, the influence of science communities on society has received attention, on the contrary, the influence of society on science communities has been growing.

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 dialogue skills** in a bid to build stronger mutual relations among researchers in different fields and between scientific communities, public, and policy makers. We also conduct research and development on "Science of Science, Technology and Innovation Policy".

Selected Papers

K. Kano, Toward achieving broad public engagement with science, technology, and innovation policies: trials in JAPAN Vision 2020. *International Journal of Deliberative Mechanisms in Science* **3**, 1-23 (2014).

J. Minari, T. Shirai, K. Kato, Ethical considerations of research policy for personal genome analysis: the approach of the Genome Science Project in Japan. *Life Sciences, Society and Policy* **10**, 4 (2014).

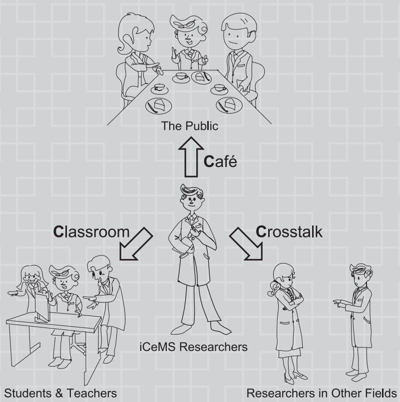
E. Mizumachi, K. Matsuda, K. Kano, M. Kawakami, K. Kato, Scientists' attitudes toward a dialogue with the public: a study using "science cafes". *Journal of Science Communication* **10**, 4, A02 (2011).

Cafés: As in "science cafés". Young iCeMS researchers engage in conversations with the public over tea and coffee in a relaxed, friendly atmosphere. The science cafés are designed to improve young researchers in dialogue skills.

Crosstalks: "How to challenge a new field?" "How should we collaborate with researchers in different fields or policy makers?" A young researcher of the iCeMS speaks with experts in various disciplines on their thoughts about research and science.

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

3C activities



Dan Ohtan Wang

Neuroscience, RNA Biology, Photochemistry

Faculty Members

Dan Ohtan Wang (Assistant Professor / iCeMS Kyoto Fellow)

Research Overview

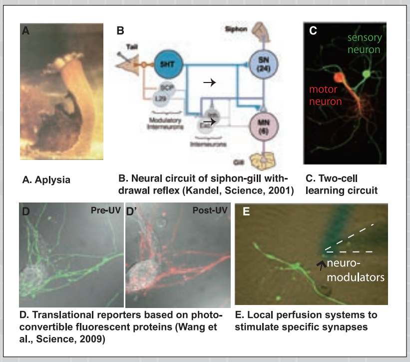
Our group studies the molecular and cell biological mechanisms of learning-related **neuronal plasticity**, a process in which the strength and the number of synaptic connections between neurons are altered by experience. Such structural and functional changes in our brain occur in an activity-dependent manner and are **mediated by highly orchestrated gene networks**. We are particularly interested in understanding how gene expression in the neural circuits is regulated in **space and time** during long-term neuronal plasticity, a critical molecular aspect of the formation and storage of lasting memories. To detect the learning-related changes in gene expression in situ with high spatiotemporal resolution, we are developing live-cell fluorescence imaging methods using gene-specific hybridization-sensitive probes. The nature of our research requires novel bioactive materials and innovative technical approaches, which drives us to conduct cross-disciplinary research projects inside and outside iCeMS.

Selected Papers

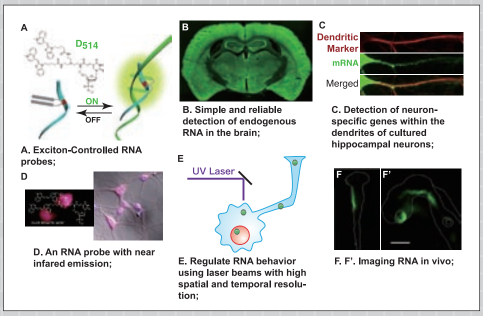
Oomoto I., Hirano-Suzuki A., Umeshima H., Y. W. Han, H. Yanagisawa, P. Carlton, Y. Harada, M. Kengaku, A. Okamoto, T. Shimogori, D. O. Wang, ECHO-liveFISH: in vivo RNA Labeling Reveals Dynamic Regulation of Nuclear RNA Foci in Living Tissues. *Nucl. Acids. Res.* doi:10.1093/narlgkv614 (2015).

S. Diring, D.O. Wang, C. Kim, M. Kondo, Y. Chen, S. Kitagawa, K. Kamei, S. Furukawa, Localized cell stimulation by nitric oxide using a photoactive porous coordination polymer platform. *Nat. Commun.* **4**, 2684 (2013).

D. O. Wang, H. Matsuno, S. Ikeda, A. Nakamura, H. Yanagisawa, Y. Hayashi, A. Okamoto, A quick and simple FISH protocol with hybridization-sensitive fluorescent linear oligodeoxynucleotide probes. *RNA* **18**, 166-175 (2012).



Imaging local protein synthesis at sensory-motor neuronal synapses in Aplysia



Visualizing endogenous RNA in highly sensitive and quantitative manner in living neuronal circuits.

Center for Meso-Bio Single-Molecule Imaging

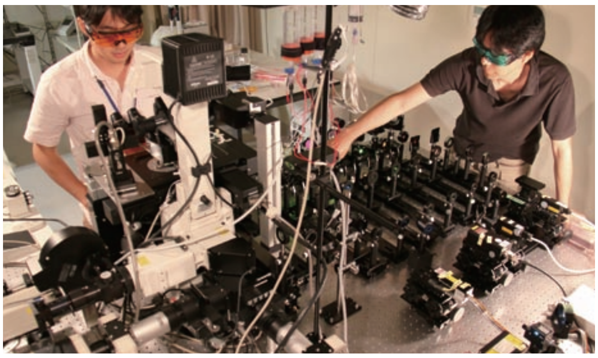
CeMI iCeMS Imaging Center

Director Yoshie Harada (Professor) | **Deputy Director** Takahiro Fujiwara (Associate Professor)

www.cemi.icems.kyoto-u.ac.jp

The CeMI was established on March 3, 2009, as the iCeMS' imaging innovation center for **cellular mesoscopic science**. Its key missions are: 1) 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 2) 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°C in 5% CO_2 atmosphere); a terahertz near-field microscope with the world's fastest image acquisition rate (500Hz) and highest spatial resolution (λ/30); and other advanced, commercial confocal/time- lapse fluorescence microscopes. The center will also hold symposia, seminars, workshops, and hands-on training sessions, open to the scientific community worldwide.



Industry Partners (alphabetical order): Carl Zeiss Microscopy Co., Ltd., Hamamatsu Photonics K.K., JEOL Ltd., Leica Microsystems K.K., Nikon Instech Co., Ltd., Nikon Instruments Co., Ltd., Olympus Corp., Photron Ltd.

RSC-iCeMS New Journal *Biomaterials Science*

In January 2013 the Royal Society of Chemistry (RSC) published the first issue of *Biomaterials Science*, a new multi-disciplinary journal launched in collaboration with iCeMS. Its founding director Norio Nakatsuji and Prof. Hiroshi Sugiyama serve as co-editor-in-chief and associate editor respectively. The broad scope of the journal ranges from the fundamental science of biomaterials to their biomedical applications. Main research areas include (but are not limited to):

- Mesoscopic science of cells and materials
- Molecular design of biomaterials
- Materials for nanomedicine and drug delivery systems
- Materials for stem cell research
- Tissue engineering and regenerative medicine
- Nanomaterials at the biointerface
- Biologically inspired and biomimetic materials
- Interfacial phenomena in biomineralization

www.rsc.org/biomaterialsscience

Collaboration with CiRA

In November 2007 Prof. Shinya Yamanaka, an iCeMS principal investigator (PI), reported that his team had successfully generated induced pluripotent stem cells (iPS cells) from human skin cells. In January 2008 then iCeMS Director Norio Nakatsuji appointed Prof. Yamanaka as founding director of the Center for iPS Cell Research and Application (CiRA), which was established under the auspices of iCeMS in order to advance iPS cell research. In April 2010 Kyoto University re-established CiRA as a full-fledged university research institute, with Prof. Yamanaka as its founding director.

Since that time, both institutes have continued to collaborate closely as sister institutes, with iCeMS aiming to integrate the cell and material sciences, contributing to the advancement of stem cell research such as with ES and iPS cells, and CiRA continuing its pioneering work in the areas of regenerative medicine and drug discovery using iPS cells.

CiRA

www.cira.kyoto-u.ac.jp

Yamanaka Wins Nobel Prize

Prof. Shinya Yamanaka, CiRA director and iCeMS PI, and Prof. Sir John Gurdon of the University of Cambridge shared the Nobel Prize in Physiology or Medicine 2012 for their discovery that mature cells can be reprogrammed to become pluripotent.

Sir John Gurdon (left) speaking at an iCeMS Seminar with Prof. Shinya Yamanaka (right) in the audience (November 2010, iCeMS)

Facilities

As of July 1, 2015

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 October 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

iCeMS Katsura Laboratory | Completed in April 2008

A 220 m² 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.

iCeMS Katsura Lab Adjunct 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)

iCeMS Rakunan Shinto Laboratory | Completed in October 2013

Advanced Chemical Technology Center in Kyoto (ACT Kyoto)

In October 2013, iCeMS established the Rakunan Shinto Laboratory in Kyoto City in an effort to bridge academia and industry. The facilities, built with maximum safety features in mind, are furnished with state of the art equipment, such as a gas measurement room and high-throughput machinery, to advance research on porous coordination polymers involved in gas separation and energy storage, both of which have a significant impact on the environment. This venture has led to a number of industry partners who share research space and collaborate on research projects.

17-minute walk from "Tamba-bashi" Station, Keihan or Kintetsu Line,
17-minute bus ride from "Kyoto" Station, JR Line Hachijo-guchi Exit

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

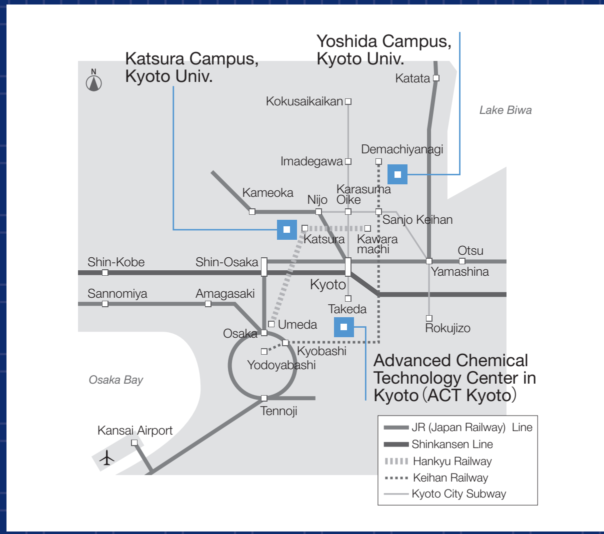
iCeMS Katsura Laboratory

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

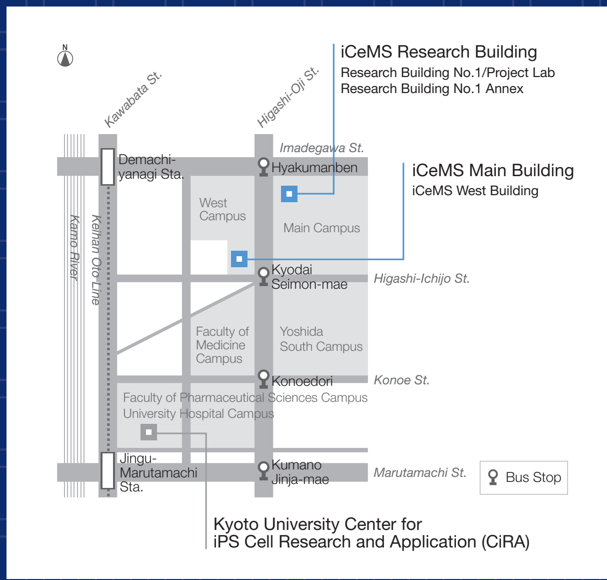
Advanced Chemical Technology Center in Kyoto (ACT Kyoto)

iCeMS Rakunan Shinto Laboratory

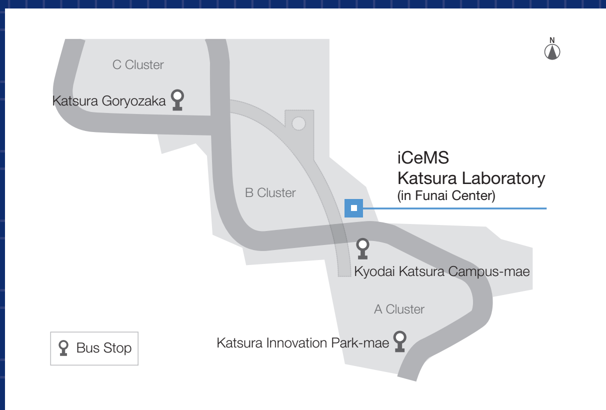
105 Jibe-cho, Fushimi-ku, Kyoto
17-minute walk from “Tamba-bashi” Station
(Keihan or Kintetsu Line)
Rakunan Express: 17-minute bus ride from "Kyoto" Station
(JR Line Hachijo-guchi Exit)



Directions to iCeMS, Kyoto University



Yoshida Campus, Kyoto University



Katsura Campus, Kyoto University

iCeMS Brochure | Issued: July 2015

Lab group information is current as of July 1, 2015.

Email: info@icems.kyoto-u.ac.jp
Phone: 81-75-753-9753 (Int'l) / 075-753-9753 (Domestic)
Fax: 81-75-753-9759 (Int'l) / 075-753-9759 (Domestic)
Address: Yoshida Ushinomiya-cho, Sakyo-ku, Kyoto 606-8501, Japan
URLs: www.icems.kyoto-u.ac.jp
facebook.com/Kyoto.Univ.iCeMS
twitter.com/iCeMS_KU