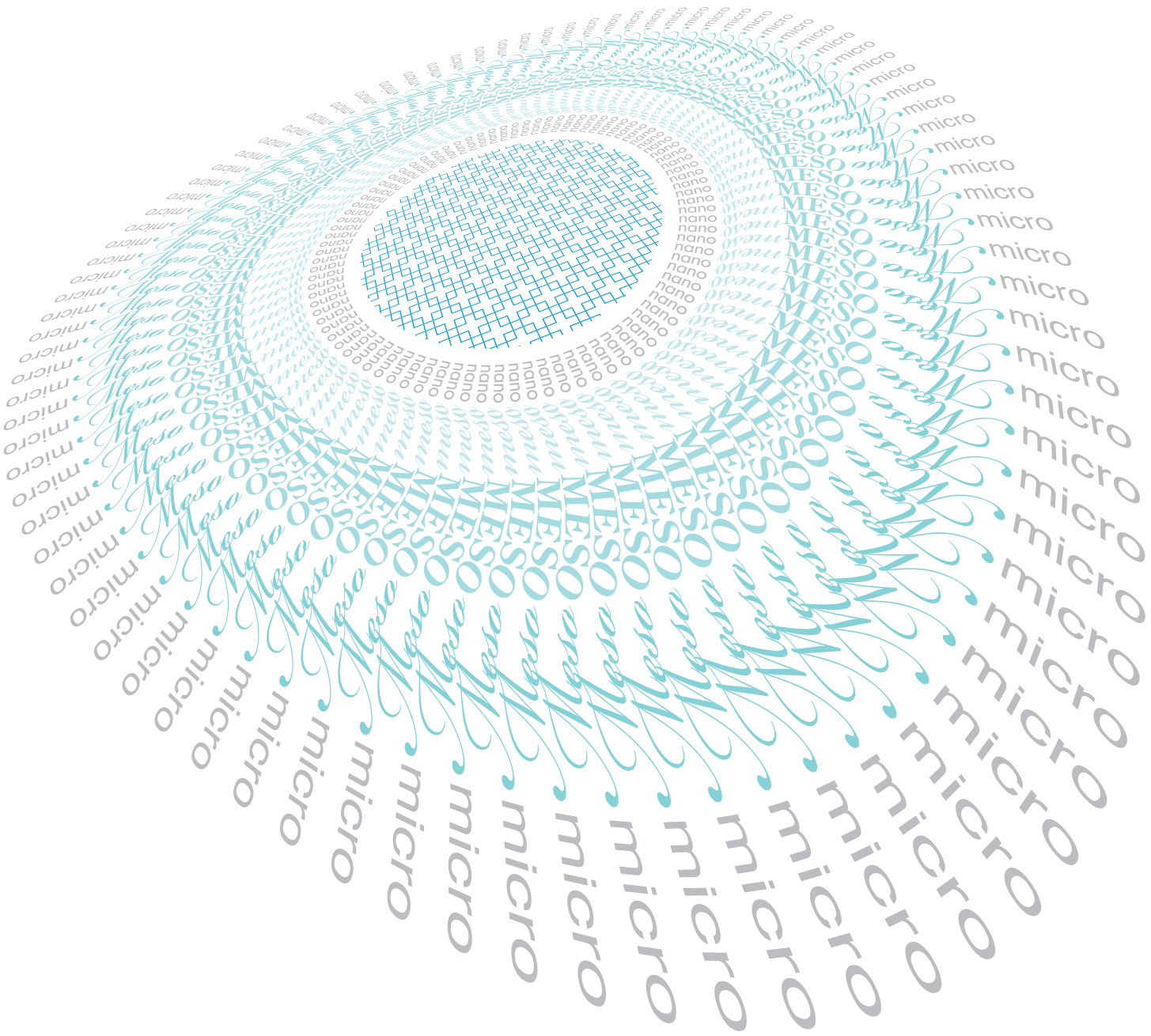


iCeMS
KYOTO UNIVERSITY
WPI Research Center

Institute for Integrated Cell-Material Sciences

KUIAS

wpi

Inspiring Creativity

Unlocking Life's Secrets, Transforming Our Lives

About iCeMS

At iCeMS we believe, as scientists, we live in exciting times. Time to discover, time to create, together.

Our mission is to explore the secrets of life by creating compounds to control cells, and further down the road to create life-inspired super materials that confront the myriad problems that afflict modern society.

Our approach is radical and new. At iCeMS we are not simply rewriting the rule-book, we are throwing it out of the window. Global warming. Pollution. Disease. Aging. These major concerns can no longer be countered by traditional single discipline-based research. Innovative solutions to the most pressing scientific and societal challenges of our time demand we adopt a multi-disciplinary, syncretic approach. Thus at iCeMS cell biologists, biophysicists, chemists, material scientists, physicists, and bioengineers share ideas and work together to devise new ways to integrate cells and materials, all for the greater good. Inspiration through collaboration.

The wider scientific community is slowly awakening to multi-disciplinary research, christening it 'convergence' and heralding it as the next revolution in science. We have been 'convergent' for nearly a decade. Results have been impressive. In our relatively short life iCeMS' collaborative research has resulted in a number of significant cutting-edge scientific discoveries, and the creation of over 1500 unique materials. And yes, we have a Nobel laureate too.

Not that anyone at iCeMS intends to rest on our laurels. In the years to come we strive to even greater levels of scientific excellence. Simultaneously we will leverage our critical mass of scientific and technological knowledge into purposeful, transformative innovations for the practical benefit of society.

Contents

Director's Vision for Integrated Cell-Material Sciences

Susumu Kitagawa
Director
Institute for Integrated Cell-Material Sciences (iCeMS)
Kyoto University Institute for Advanced Study

Cells comprise chemical materials, such as nucleic acids, proteins, lipids, and sugars. This ultimately means that all cellular processes are interpretable as chemical events, and accordingly that a chemical understanding of cells should allow us to mimic cellular processes using chemical materials. Our institute seeks to **develop materials to comprehend cellular functions** (materials for understanding cells), **produce materials to control processes in cells** (materials for controlling cells), and eventually to **create functional materials inspired by cellular processes** (cell-inspired materials). Combining Kyoto University's established strengths in cell biology, chemistry, physics, and mathematics to delve deeply into this field at the boundary of materials and life, we make concerted efforts through interdisciplinary research to pioneer **the new research domain of integrated cell-material sciences**.

What is needed to that end? A large collection of researchers studying both cells and materials? In my view, truly interdisciplinary research **grows out of friendly competition under one roof among outstanding talents with a great trail-blazing spirit and skills in their respective areas of expertise**. In other words, a new discipline can evolve only out of coexistence and interaction between researchers—those with a real understanding of cells and those with mastery of materials. **Participation by young, creative, and flexible researchers will also be important in addition to mature researchers who have already established their research areas**. These researchers should not only explore their individual areas but also possess a broad vision. At the same time, their research environment should facilitate awareness of other fields of study. We at iCeMS have conquered the former challenge by aggressively seeking out qualified researchers to build our organization, and our research environment itself serves as a gateway for researchers to other disciplines in regards to the latter task.

To give a more concrete example, iCeMS provides open offices so researchers in different disciplines can sit side by side and inspire each other. And almost all iCeMS events, including symposiums and retreats, are attended by researchers in the two fields of cells and materials. These researchers are required to make their expertise understood by those in other fields while also convincing their own peers with the content of their studies. This means that iCeMS researchers must identify and transmit, precisely and comprehensively, the originality and essence of their respective studies. Only after such information is successfully conveyed can we inspire other researchers and develop an environment for generating ideas.

One can certainly make the argument that information and values cannot be shared among researchers in different fields. At iCeMS, however, we have overcome this difficulty and turned it to our advantage by appreciating different views and values, and all members share a strong will to explore new research horizons to achieve the goals of our institute. As a result, **we have a keen sense of our groundbreaking attitudes and values**. In the iCeMS research environment we focus our efforts 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 self-assembly and cooperative interactions among great numbers of chemical materials. **To understand these cellular events, we must create chemicals and materials for observational study** and use them to advance cell analysis. Based on our findings in these analyses, we seek to investigate **materials for cell control with a special focus on stem cells**.

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. **The replication of cellular functions with designed materials should be possible once a full understanding of cellular processes has been achieved**. We are simultaneously working to advance analysis and synthesis, applying the resulting higher level of knowledge to further research, and striving for the creation of new materials.

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**	• The first issue of *Biomaterials Science*, a joint venture between the Royal Society of Chemistry (RSC) and iCeMS, published.
	Jan 1	• Prof. Susumu Kitagawa succeeds Prof. Nakatsuji as director.
	Jun 6-9	• WPI institutes co-host Japan-France workshop on materials science at iCeMS.
	Oct	• iCeMS Rakunan Shinto Laboratory opened.
2016	**Feb 29**	• iCeMS ties MoU with Vidyasirimedhi Institute of Science and Technology (VISTEC) of Thailand
2017	**Feb 2-4**	• iCeMS organizes Kyoto University International Symposium in Rayong and Bangkok, Thailand.
	Apr 1	• iCeMS becomes a research center of Kyoto University Institute for Advanced Study.
	May 24	• iCeMS was certified as a WPI Academy center by MEXT.

Organization Chart

Kyoto University Institute for Advanced Study

KUIAS

- Director-General
- Executive Board
- Deputy Director-General
- Planning and Co-ordination Office
- Center for Distinguished Professors

Research Centers

KUIAS facilitates itself as a hub for world-class researchers, with the pre-eminent researchers and research centers at its core.

Research Center

Executive Board


Susumu Kitagawa
Director


Ryoichiro Kageyama
Deputy Director


Motonari Uesugi
Deputy Director


Shuhei Furukawa
PI Board Chair


Jun Suzuki
Future Vision Task Force Chair


Mitsuru Hashida
Research Administrative Director

Research Groups

Academic Advisory Committee

iCeMS
KYOTO UNIVERSITY
WPI Research Center

Collaborative Research Center

- Administrative Office

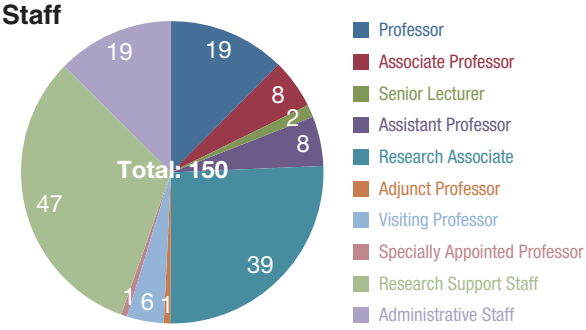
Management

- English used as the official Language, and strong support for non-Japanese researchers provided to meet the international standards
- Open offices and common labs designed to encourage interaction
- Hosting international symposia (approx. 2 annually) and iCeMS Seminars regularly conducted by noted international researchers (approx. 10 seminars annually)
- Strengthening the network with industry and partnership with overseas institutions
- Building closer ties with the Kyoto University URA office (KURA)
- Communicating to the public (Providing Internet videos of research presentations for non-scientists, and holding events for high school students)

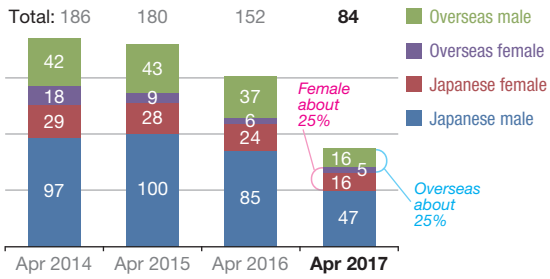
Fact and Figures

As of April 2017

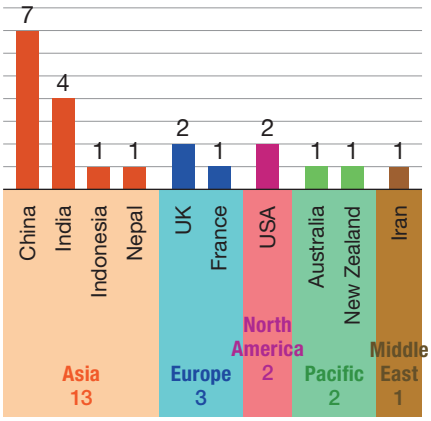
All Staff



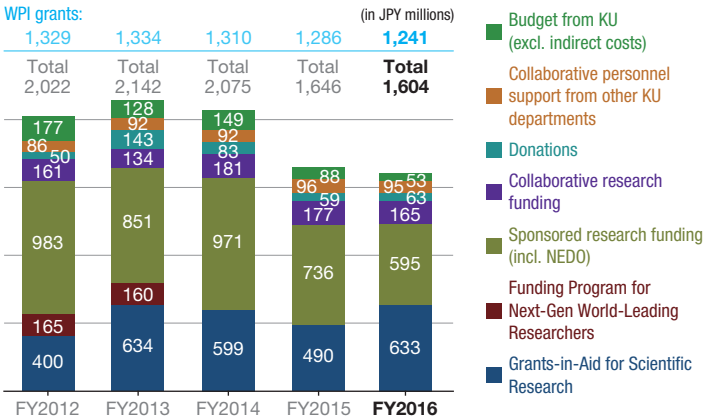
Researchers



Researchers from Overseas



Finance



Honors and Awards

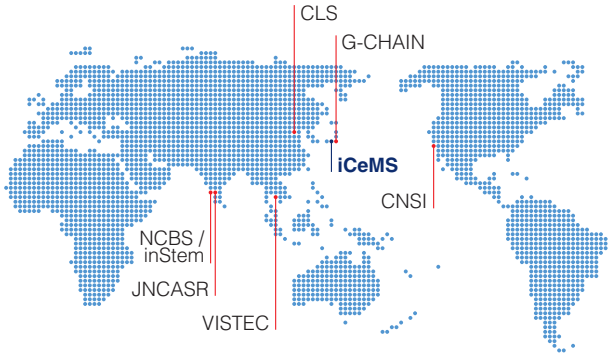
(Affiliations as of the time of the award)

Year/Month		Award / Prize	Awardees
2017	Sep	2017 Chemistry for the Future Solvay Prize	Susumu Kitagawa
	Jun	Fujihara Award	Susumu Kitagawa
	Apr	Ichimura Academic Award	Motonari Uesugi
	Apr	Commendation for Science and Technology Prize (Young Scientists' Prize category)	Shuhei Furukawa
2016	Oct	Basolo Medal	Susumu Kitagawa
	Sep	Takeda Prize for Medical Science	Mitinori Saitou
	Jun	Japan Academy Prize	Susumu Kitagawa
	Apr	Commendation for Science and Technology Prize (Young Scientists' Prize category)	Hideki Hirori, Akitsu Hotta
2015	Apr	Commendation for Science and Technology Prize (Young Scientists' Prize category)	Ryotaro Matsuda
	Apr	Marco Polo della Scienza Italiana	Susumu Kitagawa
2014	Jun	German Innovation Award Gottfried Wagener Prize (3rd Prize)	Hideki Hirori
	May	E.B. Wilson Medal of the American Society for Cell Biology	John Heuser
	Mar	Commendation for Science and Technology Prizes	Norio Nakatsuji, Kei Kano, Eri Mizumachi, Koichiro Tanaka
	Feb	Philipp Franz von Siebold Award	Motomu Tanaka
	Jan	Japan Academy Medal	Mitinori Saitou
2013	Sep	Leo Esaki Award	Susumu Kitagawa
	May	RSC de Gennes Prize	Susumu Kitagawa
2012	Nov	Order of Culture	Shinya Yamanaka
	Nov	Life-time Achievement Award (Journal of Drug Targeting)	Mitsuru Hashida
	Oct	Nobel Prize in Physiology or Medicine	Shinya Yamanaka
2011	Nov	AAAS Days of Molecular Medicine Young Investigator Award	Ganesh Pandian Namasivayam
	Jun	Medal of Honor with Purple Ribbon 2011	Susumu Kitagawa
	May	Member of National Academy of Sciences	John Heuser, Shinya Yamanaka
	Mar	German Innovation Award Gottfried Wagener Prize (1st Prize)	Motonari Uesugi
	Feb	Wolf Foundation Prize in Medicine	Shinya Yamanaka
2010	Sep	2010 Thomson Reuters Citation Laureates	Susumu Kitagawa, Shinya Yamanaka
	Mar	Imperial and Japan Academy Prizes	Shinya Yamanaka
	Mar	Japan Bioscience, Biotechnology and Agrochemistry Society Award	Kazumitsu Ueda
2009	Sep	Albert Lasker Basic Medical Research Award	Shinya Yamanaka
	Jan	The Chemical Society of Japan Award	Susumu Kitagawa
2008	Apr	Humboldt Research Award	Susumu Kitagawa
2007	Dec	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	American Association of Pharmaceutical Scientists, Research Achievement Award in Pharmaceutics and Drug Delivery	Mitsuru Hashida

Partner Institutions

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

- UCLA California NanoSystems Institute (CNSI), USA
- Tata Institute of Fundamental Research National Centre for Biological Sciences (NCBS), India
- The Institute for Stem Cell Biology and Regenerative Medicine (inStem), India
- Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), India
- Peking-Tsinghua Center for Life Sciences (CLS), China
- Vidyasirimedhi Institute of Science and Technology (VISTEC), Thailand
- Center for Highly Advanced Integration of Nano and Life Sciences, Gifu University (G-CHAIN), Japan



Principal Investigators (PIs)

At iCeMS, researchers from different fields work together to devise groundbreaking ideas.

Chemical Biology

Motonari Uesugi

Materials Science

Shuhei Furukawa

Easan Sivaniah

Susumu Kitagawa

Cell Biology

Dan Ohtan Wang

Jun Suzuki

Ryoichiro Kageyama

Itaru Hamachi

Fuyuhiko Tamanoi

Hiroshi Imahori

Satoshi Horike

Hiroshi Kageyama

Peter Carlton

Mineko Kengaku

Kazumitsu Ueda

Ryu Abe

Hiroshi Kitagawa

Michiyuki Matsuda

Eisuke Nishida

Kouichi Hasegawa

Hiroshi Sugiyama

Yasuo Mori

Daniel Packwood

Koichiro Tanaka

Mitinori Saitou

Ken-ichiro Kamei

Kaoru Sugimura

Tissue Engineering

Biophysics

The red frames are PIs and the others are Adjunct PIs.

Ryu Abe Lab

Artificial Photosynthesis,
Solar Hydrogen Production,
Photocatalysts

Faculty Members

Ryu Abe (Adjunct PI)

Research Overview

Depletion of fossil resources and other environmental issues have become a matter of serious concern, and researchers are now expected more strongly than ever to contribute to the realization of sustainable development - a society that balances the economy with the natural environment. It has been estimated that the amount of available solar energy on the surface of the Earth is much higher than the total energy consumption by humankind. Therefore, the development of an efficient **solar-light energy conversion** system could be of tremendous help in meeting our future energy need. Among such systems, **photocatalytic (or photoelectrochemical) water splitting** into H_2 and O_2 using semiconductor photocatalysts (or photoelectrodes) has received much attention recently due to the potential of this method for the **clean production of H_2 from water** utilizing solar energy. Because almost half of all incident solar energy at the Earth's surface falls in the visible region, the efficient utilization of visible light remains indispensable for realizing practical H_2 production based on photocatalytic water splitting. Our research group has recently developed a new type of photocatalytic water splitting system, mimicking the mechanism of photosynthesis in green plants, and demonstrated water splitting under visible light for the first time. In this system, the water splitting reaction is broken up into two stages: one for H_2 evolution and the other for O_2 evolution; these are combined by using a shuttle redox couple in the solution. This system reduces the energy required to drive each photocatalysis process, allowing visible light to be utilized more efficiently than in conventional water splitting system. We have also demonstrated efficient water splitting under visible light by using porous oxynitrides film photoelectrodes that were prepared via simple and scalable procedures. Our group also has developed highly efficient highly efficient visible-light-responsive photocatalysts for **environmental purification** and organic synthesis.

Selected Papers

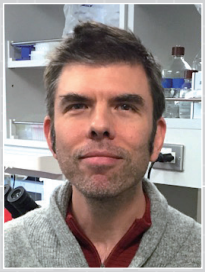
H. Fujito, H. Kunioku, D. Kato, H. Suzuki, M. Higashi, H. Kageyama, R. Abe, Layered Perovskite Oxychloride Bi_4NbO_8Cl: A Stable Visible Light Responsive Photocatalyst for Water Splitting. *J. Am. Chem. Soc.* **138**, 2082-2085 (2016).

G. Sahara, H. Kumagai, K. Maeda, N. Kaeffer, V. Artero M. Higashi, R. Abe, O. Ishitani, Photoelectrochemical Reduction of CO_2 Coupled to Water Oxidation Using a Photocathode With a Ru(II)–Re(I) Complex Photocatalyst and a CoO_x/TaON Photoanode. *J. Am. Chem. Soc.* **138**, 14152-14158 (2016).

R. Abe, K. Shinmei, N. Koumura, K. Hara, B. Ohtani, Visible-Light-Induced Water Splitting Based on Two-step Photoexcitation between Dye-Sensitized Layered Niobate and Tungsten Oxide Photocatalysts in the Presence of Triiodide/Iodide Shuttle Redox Mediator. *J. Am. Chem. Soc.* **135**, 16872-16884 (2013).

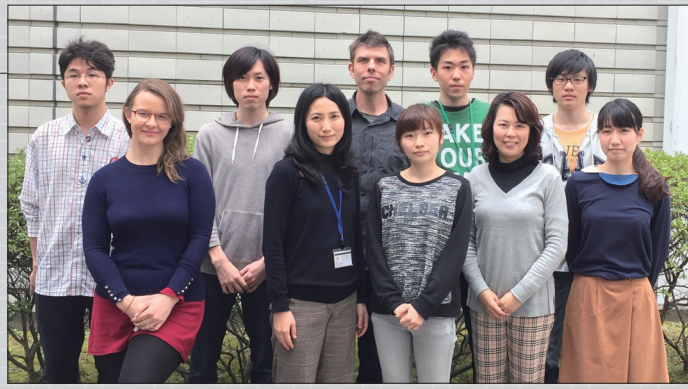
M. Higashi, K. Domen, R. Abe, Fabrication of an Efficient $BaTaO_2N$ Photoanode Harvesting a Wide Range of Visible Light for Water Splitting. *J. Am. Chem. Soc.* **135**, 10238-10241 (2013).

R. Abe, Recent Progress on Photocatalytic and Photoelectrochemical Water Splitting under Visible Light Irradiation. *J. Photochem. Photobiol. C: Photochemistry Reviews (Invited review)* **11**, 179-209 (2010).



Peter Carlton Lab

Meiosis, DNA Damage and Repair, Epigenetics, Superresolution Microscopy



Faculty Members

Peter Carlton (Adjunct PI)

Research Overview

Our research group studies the mechanisms cells use to accurately transmit their genetic information across cell divisions and across generations. We study the mechanisms of chromosome pairing, genetic recombination, and correct transmission of the genome in **meiosis** (the cell division that produces sperm and eggs in sexually reproducing organisms). Errors in meiosis are responsible for many human health problems, from infertility to birth defects. Using the nematode worm *Caenorhabditis elegans* as a model system, we are studying the roles of conserved meiotic proteins that may shed light on human **reproductive health**.

Additionally, we are researching mechanisms that mammalian cells use to repair DNA when it is damaged. Our DNA is under constant attack from sources such as UV irradiation, errors during replication, or chemical poisons, and our cells must routinely repair this **DNA damage** to avoid death or transformation into cancer. We are currently investigating the covalently modified DNA base **5-hydroxymethylcytosine**, which becomes actively enriched at sites of DNA damage, to understand the roles of epigenetics in genome integrity.

In addition to standard cell biological methods of genetics and biochemistry, our group heavily uses advanced microscopy techniques such as **3D structured illumination** and deconvolution microscopy, combined with **quantitative image analysis**, to understand the dynamic regulation of proteins and DNA inside the cell.

Selected Papers

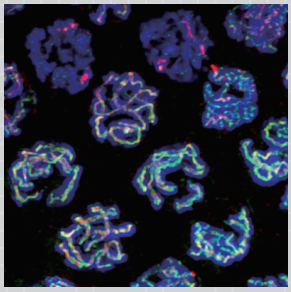
G. R. Kafer, X. Li, T. Horii, I. Suetake, S. Tajima, I. Hatada, P.M. Carlton, 5-Hydroxymethylcytosine Marks Sites of DNA Damage and Promotes Genome Stability. *Cell Rep.* **14**, 1283-1292 (2016).

Y. Mishima, C. D. Jayasinghe, K. Lu, J. Otani, M. Shirakawa, T. Kawakami, H. Kimura, H. Hojo, P. Carlton, S. Tajima, I. Suetake, Nucleosome compaction facilitates HP1γ binding to methylated H3K9. *Nucleic Acids Res.* **43**, 10200-10212 (2015).

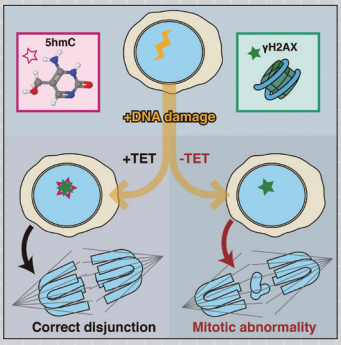
A. Sato-Carlton, X. Li, O. Crawley, S. Testori, E. Martinez-Perez, A. Sugimoto, P. M. Carlton, Protein phosphatase 4 promotes chromosome pairing and synapsis, and contributes to maintaining crossover competence with increasing age. *PLoS Genet.* **10**, e1004638 (2014).

W. Zhang, N. Miley, M. S. Zastrow, A. J. MacQueen, A. Sato, K. Nabeshima, E. Martinez-Perez, S. Mlynarczyk-Evans, P. M. Carlton, A. M. Villeneuve, HAL-2 promotes homologous pairing during Caenorhabditis elegans meiosis by antagonizing inhibitory effects of synaptonemal complex precursors. *PLoS Genet.* **8**, e1002880 (2012).

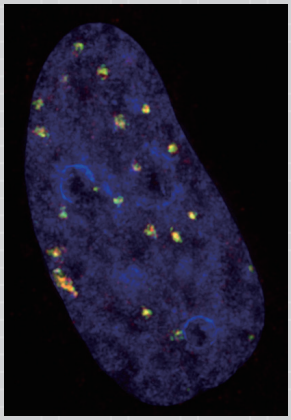
P. M. Carlton, J. Boulanger, C. Kervrann, J.-B. Sibarita, J. Salamero, S. Gordon-Messer, D. Bressan, J. E. Haber, S. Haase, L. Shao, L. Winoto, A. Matsuda, P. Kner, S. Uzawa, M. Gustafsson, Z. Kam, D. A. Agard, J. W. Sedat, Fast live simultaneous multiwavelength four-dimensional optical microscopy. *Proc. Natl. Acad. Sci. U. S. A.* **107**, 16016-16022 (2010).



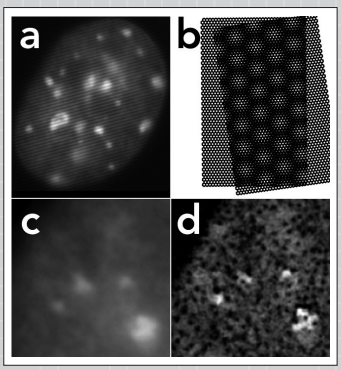
Superresolution 3D-SIM microscopy shows the structure of the synaptonemal complex, a protein polymer that holds paired chromosomes together, in meiotic prophase nuclei of C. elegans.



5hmC is actively enriched at DNA damage sites by the TET enzymes. Cells lacking TET enzymes display a significantly higher level of mitotic abnormalities, indicative of persistent damage. This type of chromosome loss or breakage is strongly associated with cancer.



The covalent DNA modification 5-hydroxymethylcytosine (red) accumulates at sites of DNA damage, marked with antibody staining against the 53BP1 protein (green) in HeLa cells.



3D Structured Illumination Microscopy (3D-SIM) doubles the resolution limit of optical microscopy. A striped illumination pattern (a) interacts with the fluorescent molecules, allowing the reconstruction of details too small to be detected with a normal microscope, in a manner similar to the magnification induced by the moiré effect (b). Two views of mouse myoblast interphase chromatin at the nuclear periphery demonstrate the increased resolution: (c), a conventional image before 3D-SIM reconstruction, and (d), the same region after reconstruction. The exclusion of chromatin from the nuclear pore complexes is visible as holes in the fluorescence signal less than 150nm in diameter. (See Schermelleh, Carlton, *et al.* 2008)

Shuhei Furukawa Lab

Coordination Chemistry,
Supramolecular Chemistry,
Materials Science, Chemical Biology

Faculty Members
Shuhei Furukawa (Associate Professor / PI)

Research Overview

The Furukawa group focuses on the development of new synthetic protocols of molecular assemblies at the mesoscale (5-1000 nm) by the power of coordination chemistry and supramolecular chemistry and the understanding of their unique properties. The resulting materials are further considered for microenvironmental applications such as sensor devices and cell biology.

1. **Mesoscopic Chemistry**: Chemists have been modifying molecules to induce a new property therein. Our chemistry enables to change a property by controlling the number of assembled molecules, in particular at the mesoscale, which is within the range between the molecular scale and the bulk material scale. In the last decade, our research group focused on framework materials with inherent porosity (known to be metal-organic frameworks or porous coordination polymers) and developed several synthetic protocols at the mesoscale to regulate the number of building units of frameworks, which leads to the controlled crystal size and morphology of resulting materials and the discovery of new phenomenon, so-called shape-memory effect. Currently, we are developing a new protocol for soft and amorphous coordination polymers by supramolecular chemistry approach.

2. **Materials Biology**: Living cells are recognized as an ultimate assembly of molecules. As its active matter, a living cell regulates its function by intracellular signalling molecules and communicates to each other by extracellular signalling molecules. We develop porous materials that accommodate important signalling molecules (**nitric oxide**, **carbon monoxide**, or **glutamic acid**) and give materials a chemical trick to release these signalling molecules by external trigger. We are currently developing these materials for therapeutic applications.

3. **Synthetic Ion Channels**: Ion channels expressed in cell membrane regulate the biological activity by transporting ions through lipid membranes. Our synthetic porous molecule known as metal-organic polyhedra is embedded into lipid bilayers and demonstrates ion transport property under applied electric field. We challenge to incorporate it to cell membrane to regulate biological function by controlled ion transport.

Selected Papers

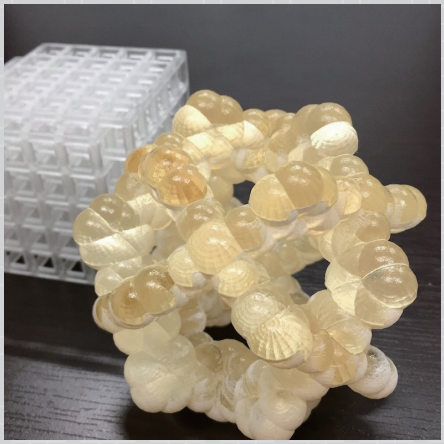
R. Kawano, N. Horike, Y. Hijikata, M. Kondo, A. Carné-Sánchez, P. Larpent, S. Ikemura, T. Osaki, K. Kamiya, S. Kitagawa, S. Takeuchi, S. Furukawa, Metal–organic cuboctahedra for synthetic ion channels with multiple conductance states. *Chem.* **2**, 393-403 (2017).

S. Furukawa, J. Reboul, S. Diring, K. Sumida, S. Kitagawa, Structuring of metal–organic frameworks at the mesoscopic/macroscopic scale. *Chem. Soc. Rev.* **43**, 5700-5734 (2014).

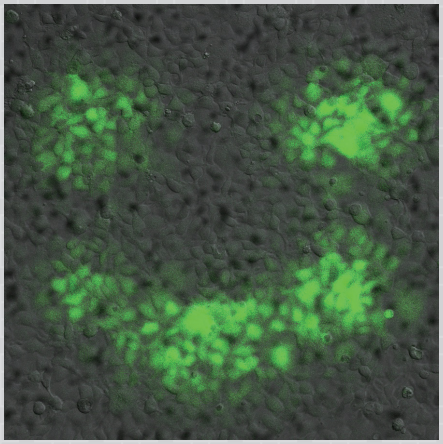
S. Diring, D. O. Wang, C. Kim, M. Kondo, Y. Chen, S. Kitagawa, K. Kamei, S. Furukawa, Localized cell stimulation by nitric oxide using a photoactive porous coordination polymer platform. *Nat. Commun.* **4**, 2684 (2013).

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).

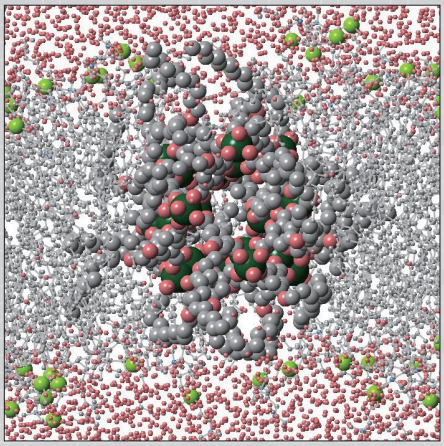
J. Reboul, S. Furukawa, N. Horike, M. Tsotsalas, K. Hirai, H. Uehara, M. Kondo, N. Louvain, O. Sakata, S. Kitagawa, Mesoscopic architectures of porous coordination polymers fabricated by pseudomorphic replication. *Nat. Mater.* **11**, 717-723 (2012).



3D printed models of porous materials. Metal-organic cuboctahedron (front) and entangled metal-organic frameworks (back)



Spatiotemporal cell stimulation by nitric oxide released from porous materials (green color indicating the incorporation of nitric oxide in cells).



Simulated image of synthetic ion channels embedded in lipid bilayers.

Itaru Hamachi Lab

Chemical Biology, Supramolecular Biomaterials

Faculty Members

Itaru Hamachi (Adjunct PI)

Research Overview

Protein is one of the most crucial biomolecules, which exhibits myriad functions in living systems. My group is studying proteins in molecular/atomic details, using approaches on the basis of organic chemistry, supramolecular chemistry, molecular engineering, biochemistry and **chemical biology**. For instance, chemical probes for selective imaging of a protein of interest in live cells or live tissues, chemistry-based strategies for specific labeling of proteins, chemical biology-based methods for controlling the function of protein of interest are being developed in my group. A final goal of our research project is to establish **live-cell organic chemistry** as a new research area, which allows selective chemical reactions, manipulation and visualization of target biomolecules under crude and miscellaneous conditions like live cell habitat. We are also making efforts to construct **complex but well-organized semi-wet soft-materials** mimicking live cells, consisting of multiple components of synthetic molecules as the building block. Such unprecedented challenge may help us to deeply understand live cell systems from the viewpoint of chemistry.

Selected Papers

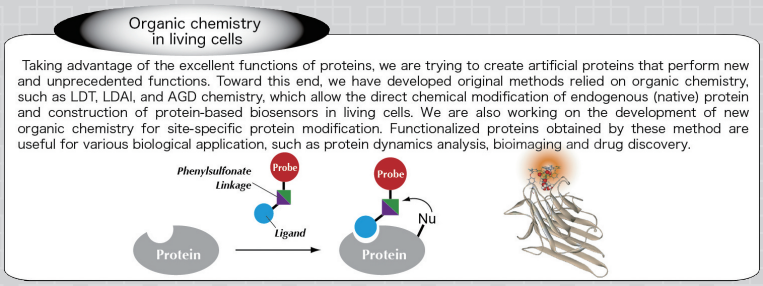
T. Miki, M. Awa, Y. Nishikawa, S. Kiyonaka, M. Wakabayashi, Y. Ishihama, I. Hamachi, A conditional proteomics approach to identify proteins involved in zinc homeostasis. *Nat. Methods* **13**, 931-937 (2016).

S. Kiyonaka, R. Kubota, Y. Michibata, M. Sakakura, H. Takahashi, T. Numata, R. Inoue, M. Yuzaki, I. Hamachi, Allosteric activation of membrane-bound glutamate receptors using coordination chemistry within living cells. *Nat. Chem.* **8**, 958-967 (2016).

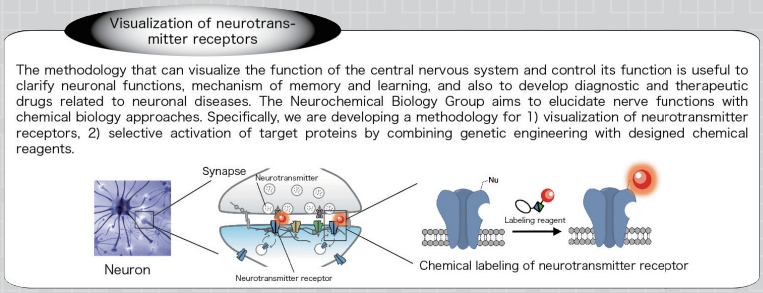
S. Onogi, H. Shigemitsu, T. Yoshii, T. Tanida, M. Ikeda, R. Kubota, I. Hamachi, In situ real-time imaging of self-sorted supramolecular nanofibers. *Nat. Chem.* **8**, 743-752 (2016).

M. Ikeda, T. Tanida, T. Yoshii, K. Kurotani, S. Onogi, K. Urayama, I. Hamachi, Installing Logic-gate Responses to a Variety of Biological Substances in Supramolecular Hydrogel–enzyme Hybrids. *Nat. Chem.* **6**, 511-518 (2014).

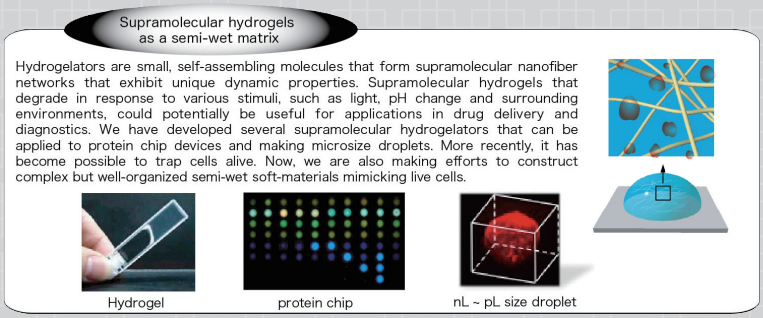
S. Tsukiji, M. Miyagawa, Y. Takaoka, T. Tamura, I. Hamachi, Ligand-directed Tosyl Chemistry for Protein Labeling in Vivo. *Nat. Chem. Biol.* **5**, 341-343 (2009).



Selective chemical modification of natural proteins by ligand-directed chemistry



Chemical approaches for visualization of neurotransmitter receptors



Supramolecular hydrogels as soft materials mimicking live cells

Kouichi Hasegawa Lab

Stem Cell Biology,
Stem Cell Engineering

Faculty Members
Kouichi Hasegawa
(Program-Specific Research Center Junior Associate Professor / PI)

Research Overview

Our group is studying **how stem cells can maintain their potency and differentiate into various cell types**. In our body, stem cells can glow, called self-renew, and differentiate into necessary cell types. Cues of the self-renewal and differentiation are extrinsic signaling molecules. The signaling molecules transmit signals into cell nuclear through intra-cellular signaling pathways, and changes cell status through turning on/of necessary genes in the nuclear. How the intracellular signaling control the gene expression is still not well known to date. Using human pluripotent stem cells, such as embryonic stem cells (ES cells) and induced pluripotent stem cells (iPS cells), and mouse pre-implantation embryos, we are focusing on understanding the signaling pathways involved in self-renewal and differentiation. Through this study, we want to develop platforms for stable and sustainable controlling of stem cell self-renewal and differentiation, and **contribute to regenerative medicine and drug development using stem cells**.

Through an institutional relationship between iCeMS and National Centre for Biological Sciences (NCBS) and Institute for Stem Cell Biology and Regenerative Medicine (inStem), Bangalore, India, our group is also developing **disease models with iPS cells** and studying disease mechanisms. One of the models is malaria *P. vivax* liver stage model with hepatocyte differentiated from patients' iPSCs. Using this model, we are studying infection, development, dormancy and relapse mechanisms of the malaria *P. vivax*. Other disease models including cardiomyopathy unique in South India and gallbladder cancer. We are hoping to **develop new regents for diagnosis and treatment of the diseases** through our models and studies.

Selected Papers

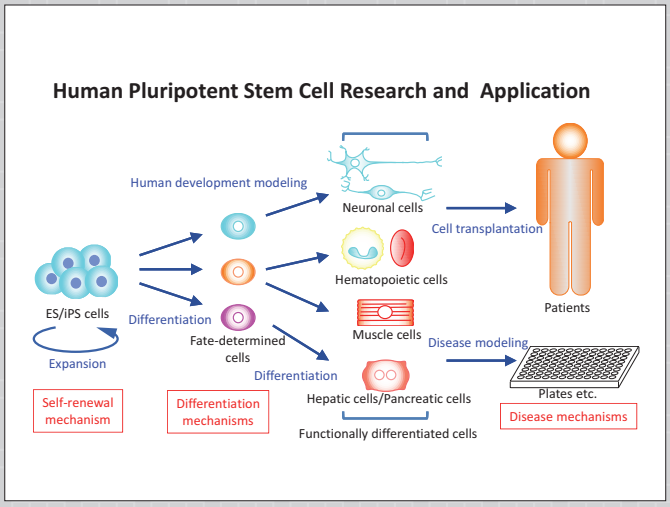
Y. Higuchi, C. Nguyen, S. Yasuda, M. McMillan, K. Hasegawa, M. Kahn, Specific Direct Small Molecule p300/β-Catenin Antagonists Maintain Stem Cell Potency. *Curr. Mol. Pharmacol.* **9** (3), 272-279 (2016).

M. Denham, K. Hasegawa, T. Menheniott, B. Rollo, D. Zhang, S. Hough, A. Alshawaf, F. Febbraro, S. Ighaniyan, J. Leung, D. Elliott, D. F. Newgreen, M. F. Pera, M. Dottori, Multipotent caudal neural progenitors derived from human pluripotent stem cells that give rise to lineages of the central and peripheral nervous system. *Stem Cells* **33** (6), 1759-1770 (2015).

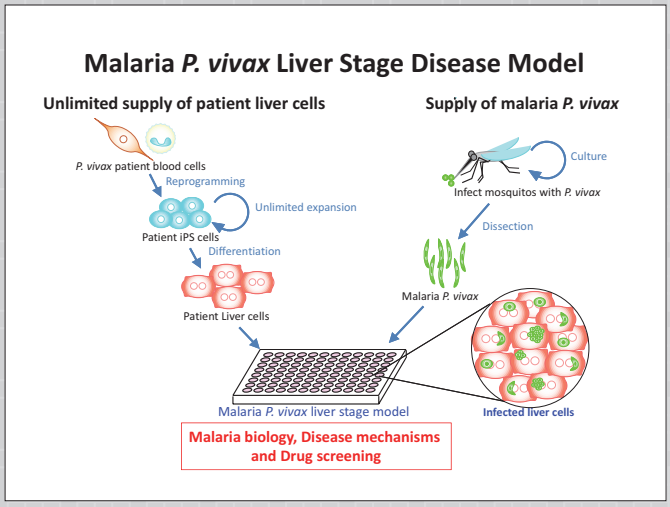
T. G. Otsuji, J. Bin, A. Yoshimura, M. Tomura, D. Tateyama, I. Minami, Y. Yoshikawa, K. Aiba, J. E. Heuser, T. Nishino, K. Hasegawa, N. Nakatsuji, A Novel 3D Sphere Culture System Containing Functional Polymers for Large-scale Human Pluripotent Stem Cell Production. *Stem Cell Rep.* **2** (5) 734-745 (2014).

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

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



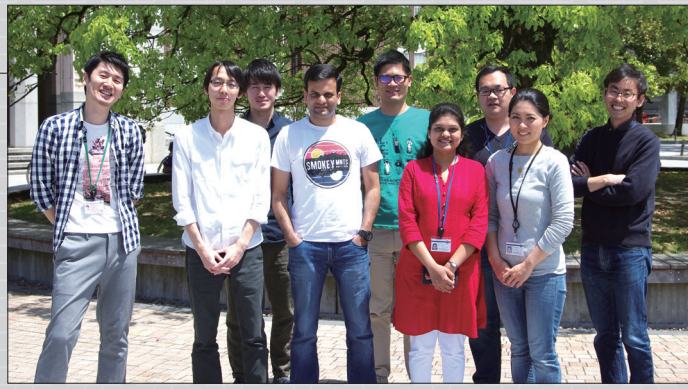
Human pluripotent stem cell research and application



Development of sustainable malaria P. vivax liver stage model with patients' iPS cells

Satoshi Horike Lab

Coordination Chemistry,
Solid State Chemistry,
Material Science



Faculty Members
Satoshi Horike (Associate Professor / PI)

Research Overview

Our research focuses on the synthesis and development of new solid materials for energy/environment issues involving fuel cell/battery and functional glass technologies. Among a various families of solid materials, we study the extended network structures from metal and molecules – namely **coordination polymer**. They are synthesized by the techniques of coordination chemistry and solid state chemistry.

For example, fuel cell is a clean energy device for a next-generation automobile from hydrogen and oxygen gases, and it requires high performance **proton (H^+) conducting solids**. Our H^+ conductive materials work well under the water-free condition with materials' softness. The property is also beneficial to reduce the amount of noble metal catalyst such as platinum in the fuel cell system. We further design optimized metal-molecular structures to have better property of proton and other ion conductivities for energy devices.

The materials composed of metal and molecule also serve as a new type of **glass** material. Silicate glass is an example of classical glass, and their transparency and thermal stability are widely used in our life. On the other hand, glasses do not have a periodic structure and it has been a big scientific challenge how to construct the glass network structure in atomic scale. We synthesize a new glass materials built by metal and molecules with rational design, and to elucidate the unique properties such as transparent electrical conductivity and **phase-change switching** for memory device.

Selected Papers

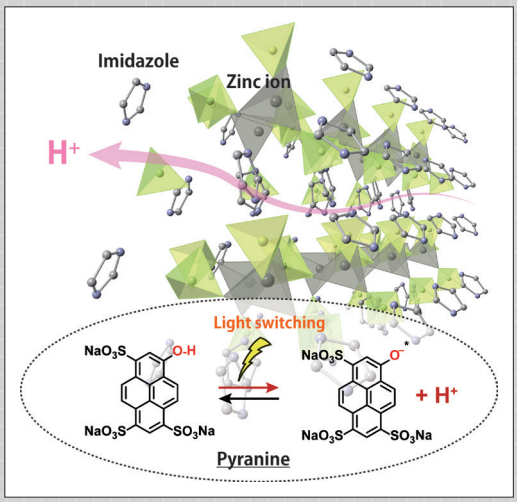
S. S. Nagarkar, S. Horike, T. Itakura, B. Le Ouay, A. Demessence, M. Tsujimoto, S. Kitagawa, Enhanced and Optically Switchable Proton Conductivity in Melting Coordination Polymer Crystal. *Angew. Chem. Int. Ed.,* in press (2017).

T. Panda, S. Horike, K. Hagi, N. Ogiwara, K. Kadota, T. Itakura, M. Tsujimoto, S. Kitagawa, Mechanical Alloying of Metal-Organic Frameworks. *Angew. Chem. Int. Ed.* **56**, 2413 (2017).

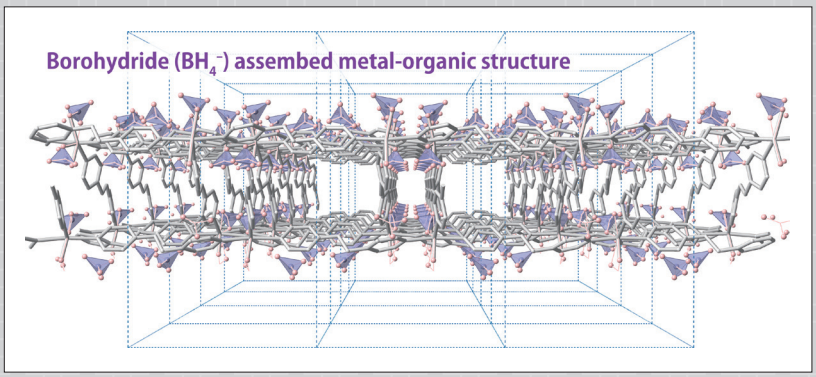
M. Inukai, S. Horike, T. Itakura, R. Shinozaki, N. Ogiwara, D. Umeyama, S. Nagarkar, Y. Nishiyama, M. Malon, A. Hayashi, T. Ohhara, R. Kiyanagi, S. Kitagawa, Encapsulating Mobile Proton Carriers into Structural Defects in Coordination Polymer Crystals: High Anhydrous Proton Conduction and Fuel Cell Application. *J. Am. Chem. Soc.* **138**, 8505 (2016).

W. Chen, S. Horike, D. Umeyama, N. Ogiwara, T. Itakura, C. Tassel, Y. Goto, H. Kageyama, S. Kitagawa, Glass Formation of a Coordination Polymer Crystal for Enhanced Proton Conductivity and Material Flexibility. *Angew. Chem. Int. Ed.* **55**, 5195 (2016).

D. Umeyama, S. Horike, M. Inukai, T. Itakura, S. Kitagawa, Reversible solid-to-liquid phase transition of coordination polymer crystals. *J. Am. Chem. Soc.* **137**, 864 (2015).



Crystal structure of proton (H^+) conductive coordination polymer made by zinc ion and imidazole molecules. Switching of H^+ conductivity is also conducted by use of doping of pyranine molecules in the crystals.



Crystal structure of two-dimensional layer coordination polymer having reactive borohydride (BH_4^-) ions. It promotes the reductive conversion of CO_2 gas to useful molecules such as formic acid.

Hiroshi Imahori Lab

Organic Chemistry, Photochemistry, Drug Delivery Systems

Faculty Members

Hiroshi Imahori (Adjunct PI)

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
2) **Light-emitting meso-scale materials** for cell imaging
3) **Photoinduced charge separation meso-scale materials** for controlling cellular functions (Mori, Kengaku labs)

Selected Papers

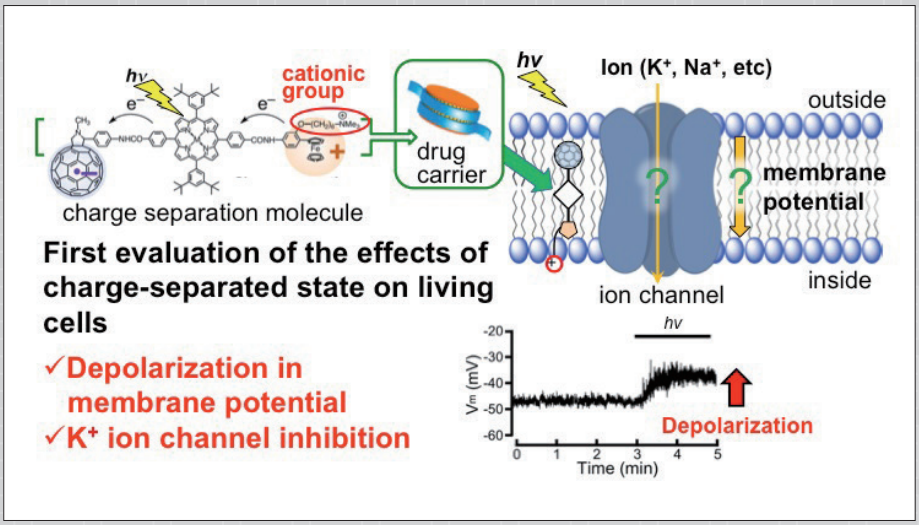
Y. Takano, T. Numata, K. Fujishima, K. Miyake, K. Nakao, W. D. Grove, R. Inoue, M. Kengaku, S. Sakaki, Y. Mori, T. Murakami, H. Imahori, Optical control of neuronal firing via photoinduced electron transfer in donor-acceptor conjugates. *Chem. Sci.* **7**, 3331-3337 (2016).

S. Zhou, M. Yamamoto, G. Briggs, H. Imahori, K. Porfyrakis, Probing the dipolar coupling in a hetero-spin endohedral fullerene–phthalocyanine dyad. *J. Am. Chem. Soc.* **138**, 1313-1319 (2016).

T. Higashino, T. Yamada, M. Yamamoto, A. Furube, N. V. Tkachenko, T. Miura, Y. Kobori, R. Jono, K. Yamashita, H. Imahori, Remarkable dependence of the final charge separation efficiency on the donor–acceptor interaction in photoinduced electron transfer. *Angew. Chem. Int. Ed.* **55**, 629-633 (2016).

H. Nakatsuji, T. Numata, N. Morone, J. E. Heuser, Y. Takano, Y. Mori, H. Imahori, T. Murakami, Thermosensitive ion channel activation in single neuronal cells by using surface-engineered plasmonic nanoparticles. *Angew. Chem. Int. Ed.* **54**, 11725-11729 (2015).

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.* **6**, 7732 (2015).



Hiroshi Kageyama Lab

Solid State Chemistry

Faculty Members

Hiroshi Kageyama (Adjunct PI)

Research Overview

Since the beginning of history, inorganic materials such as oxides have been indispensable for the development of technology. The discovery of new materials has often led to the development of new fields in chemistry and physics. Materials syn t hesis in **solid state chemistry** far focused on the combination of metals (usually in cationic form) with solid state reactions, but this approach is inherently limited in design flexibility when compared to organic synthesis, polymer chemistry, or the synthesis of inorganic complexes in solution.

The Kageyama group entails a comprehensive thrust to change the focus of inorganic synthesis to anions. Expanding the scope of **anion-based materials chemistry** will lead to new materials, which will impact both academia and industry by the creation of new academic fields and interesting applications. Anions are distinctly amenable to chemical manipulation, and our group will use this to design and synthesize new materials. To accomplish this, synthesis will primarily focus on three distinct techniques; low temperature topochemical reactions, where anions are manipulated while leaving the cationic framework intact, high pressure synthesis, which permits synthesis with gaseous elements, and the deposition of alternating layers of anions via thin film techniques. These techniques will lead to the efficient discovery of game-changing materials. The anions in **mixed anion compounds** have differing reactivities, sizes, polarizabilities, redox potentials, and orbital energy levels, thus offering a previously underutilized route to control various chemical and physical properties, such as photocatalysis, multiferroics, quantum topological phases, etc. We especially anticipate a high potential for highly active hydrogenation catalysis using oxyhydrides, efficient photocatalysis with anion-based band gap control, and interesting physical phenomena with two-dimensional ordered mixed anion systems. The MEXT “mixed-anion project” (2016-2022), led by Prof. Kageyama, targets emerging functions from mixed anion compounds.

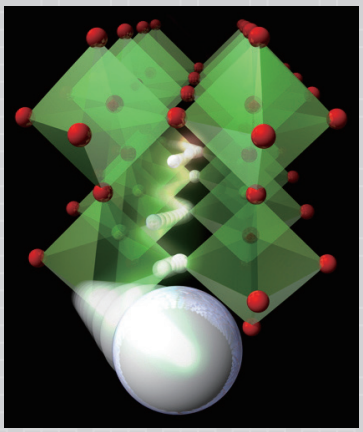
Selected Papers

T. Yajima, M. Koshiko, Y. Zhang, T. Oguchi, W. Yu, D. Kato, Y. Kobayashi, Y. Orikasa, T. Yamamoto, Y. Uchimoto, M. A. Green, H. Kageyama, Selective and Low Temperature Transition Metal Intercalation in the Layered Tellurides. *Nat. Commun.* **7**, 13809 (2016).

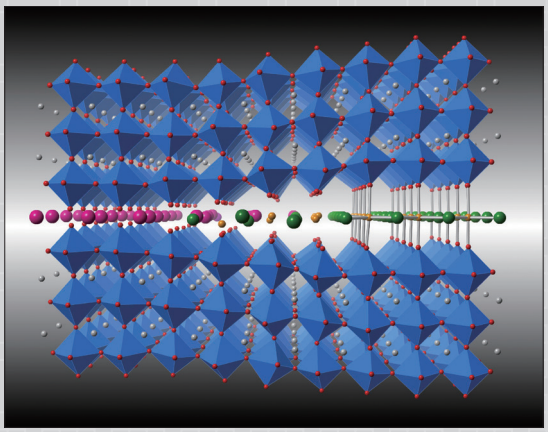
T. Yajima, F. Takeiri, K. Aidzu, H. Akamatsu, K. Fujita, M. Ohkura, W. Yoshimune, S. Lei, V. Gopalan, K. Tanaka, C. M. Brown, M. A. Green, T. Yamamoto, Y. Kobayashi, H. Kageyama, A Labile Hydride Strategy for the Synthesis of Heavily Nitridized $BaTiO_3$. *Nat. Chem.* **7**, 1017-1023 (2015).

Y. Kobayashi, O. J. Hernandez, T. Sakaguchi, T. Yajima, T. Roisnel, Y. Tsujimoto, M. Morita, Y. Noda, Y. Mogami, A. Kitada, M. Ohkura, S. Hosokawa, Z. Li, K. Hayashi, Y. Kusano, J. E. Kim, N. Tsuji, A. Fujiwara, Y. Matsushita, K. Takegoshi, K. Yoshimura, M. Inoue, M. Takano, H. Kageyama, An Oxyhydride of $BaTiO_3$ Exhibiting Hydride Exchange and Electronic Conductivity. *Nat. Mater.* **11**, 507-511 (2012).

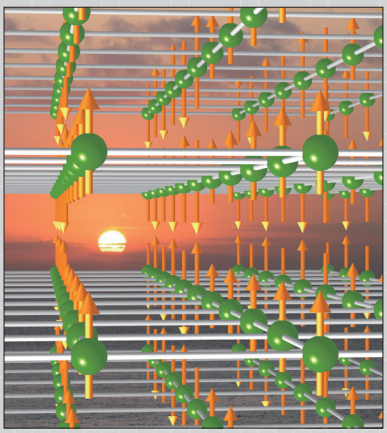
Y. Tsujimoto, C. Tassel, N. Hayashi, T. Watanabe, H. Kageyama, K. Yoshimura, M. Takano, M. Ceretti, C. Ritter, W. Paulus, Infinite-Layer Iron Oxide with a Square-Planar Coordination. *Nature* **450**, 1062-1065 (2007).



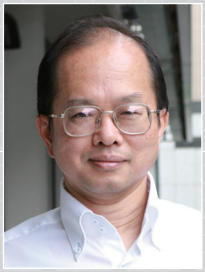
Hydride diffusion in oxyhydride



Ion-exchange reaction



Pressure-induced spin transition in $SrFeO_2$



Ryoichiro Kageyama Lab

Developmental Biology, Neural Stem Cell Biology

Faculty Members

Ryoichiro Kageyama (Adjunct PI / Deputy Director)

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 the 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. We also found that the Notch ligand **Delta-like1** (Dll1) expression, which is controlled by Hes1 and Ascl1, oscillates in neural stem cells, and that Dll1 oscillation is important for maintenance and proliferation of these cells.

Selected Papers

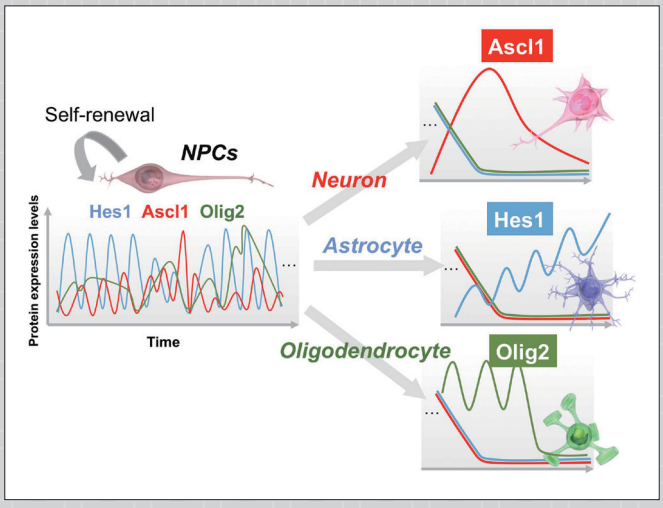
A. Isomura, F. Ogushi, H. Kori, R. Kageyama, Optogenetic perturbation and bioluminescence imaging to analyze cell-to-cell transfer of oscillatory information. *Genes Dev.* **31**, 524-535 (2017).

K. Kawaguchi, R. Kageyama, M. Sano, Topological defects control collective dynamics in neural progenitor cell cultures. *Nature* **545**, 327-331 (2017).

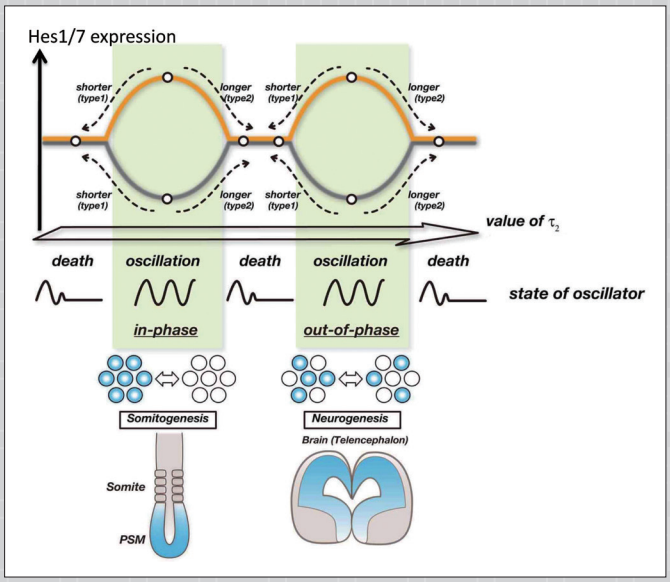
H. Shimojo, A. Isomura, T. Ohtsuka, H. Kori, H. Miyachi, R. Kageyama, Oscillatory control of Delta-like1 in cell interactions regulates dynamic gene expression and tissue morphogenesis. *Genes Dev.* **30**, 102-116 (2016).

I. Imayoshi, 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, R. Kageyama, Oscillatory control of factors determining multipotency and fate in mouse neural progenitors. *Science* **342**, 1203-1208 (2013).



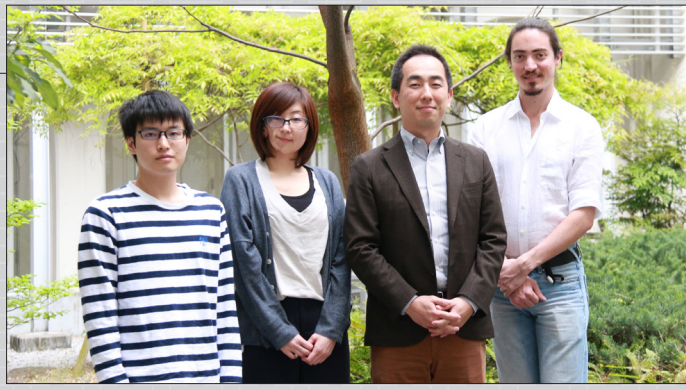
Expression dynamics of bHLH factors in multipotency and cell fate choice.
The expression of multiple bHLH factors oscillates in multipotent neural stem cells, whereas that of a selected factor becomes up-regulated and sustained during cell fate choice.



Amplitude/oscillation death of coupled oscillators.
Depending on the timing of Dll1 expression (τ2), Hes1/7 expression oscillates in phase, as in PSM cells (left green-shaded area), or out of phase, as in neural stem cells (right green-shaded area). When Dll1 expression is accelerated or delayed, both in-phase and out-of-phase oscillations would be dampened (broken arrows) or quenched (non-shaded area), a phenomenon known as “amplitude death” or “oscillation death” of coupled oscillators.

Ken-ichiro Kamei Lab

Micro/Nanoengineering, Stem Cell Engineering



Faculty Members
Ken-ichiro Kamei
(Program-Specific Research Center Associate Professor / PI)

Research Overview

The on-going research aim of Kamei Group is to recreate a living system within a single device, named "**Body on a Chip**" platform. This will allow the physiological and pathological conditions of the living system to be rebuilt in vitro and could be a powerful tool not only for studying fundamental biological systems but also in preclinical trials for drug development/screening as an alternative to animal tests. To achieve this goal, multiple micro-tissues need to be created and interconnected by fluidic channels to mimic vascular systems. For engineering mutiple micro-tissues, **induced pluripotent stem (iPS) cells** is a strong contender. Various types of human cells with the same genomic information can be derived from cells obtained from a single source. Because iPS cells have unlimited self-renewal and differentiation ability, sufficient numbers of human tissue cells can be obtained for tissue collection and drug screening. As such, iPS cells may be suitable for use in the BoC as well. However, the current macroscopic settings have limited access to cellular microenvironments, which are the major players to cellular regulation and tissue functions and organization. Therefore, our group has proposed interdisciplinary approaches for integrating **micro/nanotechnology** with **materials science** to create artificial cellular microenvironments in order to obtain cells or their functions of interest.

Here, we propose three research directions of BoC for contribution to global healthcare.

1. Personalized medicine
2. Saving animals on the earth
3. Next generation of drug screening

The ultimate goal of this project is to understand the mechanisms of a body construction by mimicking life processes in a microfluidic device. Furthermore, to facilitate progress in developing the BoC, we propose an interdisciplinary approach that integrates stem cell biology, chemical biology, physics, micro/nanotechnology, and materials science.

Selected Papers

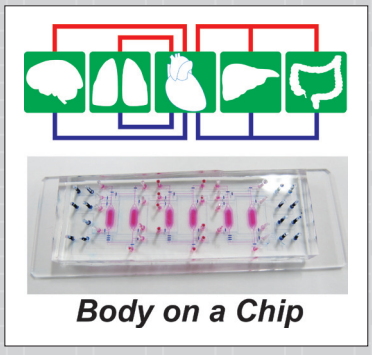
K. Kamei, Y. Mashimo, M. Yoshioka, Y. Tokunaga, C. Fockenberg, S. Terada, M. Nakajima, T. Shibata-Seki, L. Liu, T. Akaike, E. Kobatake, E. S. How, M. Uesugi, Y. Chen, Microfluidic-nanofiber hybrid array for screening of cellular microenvironments. *Small,* in press (2017).

L. Liu, K. Kamei, M. Yoshioka, M. Nakajima, J.J. Li, N. Fujimoto, S. Terada, Y. Tokunaga, Y. Koyama, H. Sato, K. Hasegawa, N. Nakatsuji, Y. Chen, Nano-on-micro fibrous extracellular matrices for scalable expansion of human ES/iPS cells. *Biomaterials* **124**, 47-54 (2017).

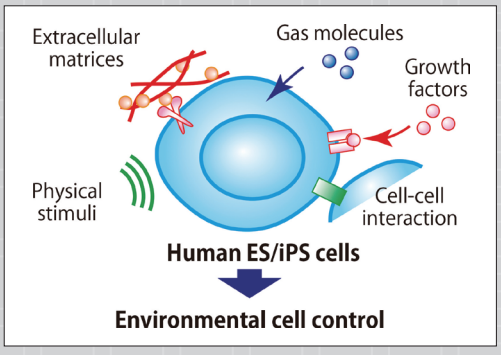
K. Kamei, Y. Koyama, Y. Mashimo, M. Yoshioka, C. Fockenberg, M. Nakashima, R. Mosbergen, O. Korn, J. Li, C. Wells and Y. Chen, Characterization of phenotypic and transcriptional differences in human pluripotent stem cells under two- and three-dimensional culture conditions. *Adv. Healthcare Mater.* **5** (22), 2951-2958 (2016).

K. Kamei, Y. Mashimo, Y. Koyama, C. Fockenberg, M. Nakashima, M. Nakajima, J.J. Li and 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).

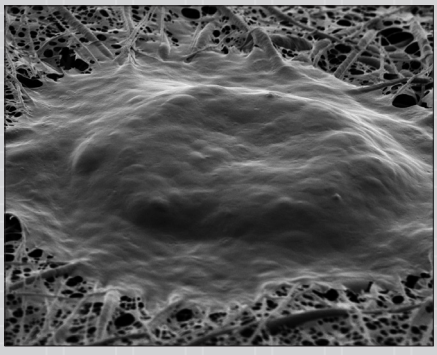
S. Diring, D. O. Wang, C. Kim, M. Kondo, Y. Chen, S. Kitagawa, K. Kamei, S. Furukawa, Localized cell stimulation by nitric oxide using a photoactive porous coordination polymer platform. *Nat. Commun.* **4**, 2684 (2013).



Tissues with a circulatory system into Body on a Chip



Cellular microenvironments for regulating human ES/iPS cells



Human ES cell colony on Fiber-on-Fiber matrix

Mineko Kengaku Lab

Developmental Neurobiology, Cell Biology

Faculty Members
Mineko Kengaku (Professor / PI)
Kazuto Fujishima (Program-Specific Assistant Professor)
Naotaka Nakazawa (Program-Specific 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

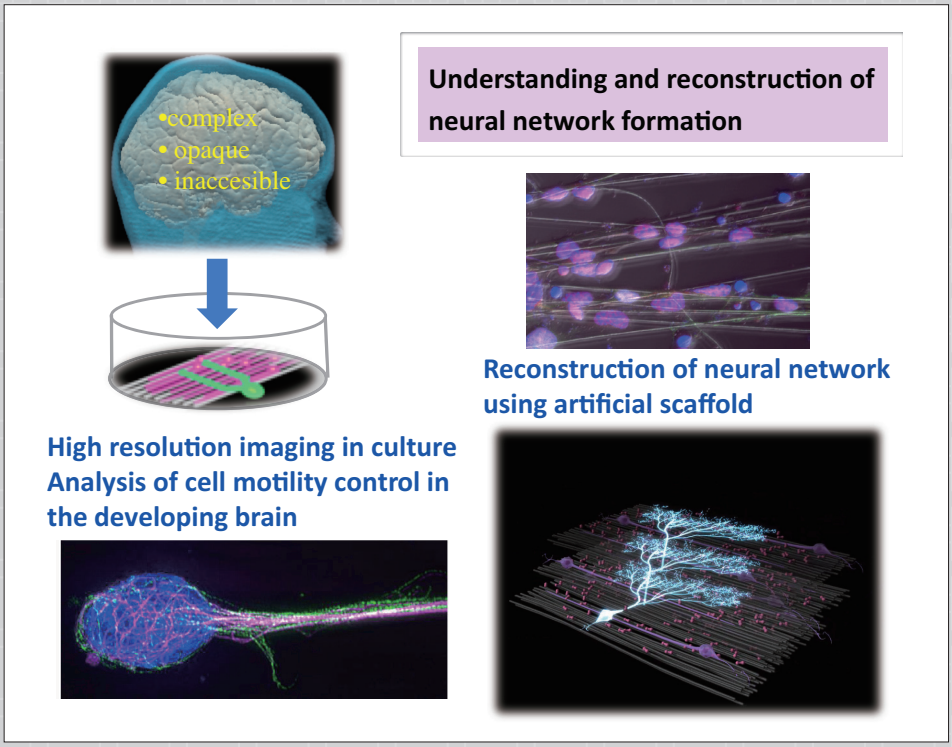
T. Hatsukano, J. Kurisu, K. Fukumitsu, K. Fujishima, M. Kengaku, Thyroid hormone induces PGC-1α during dendritic outgrowth in mouse cerebellar Purkinje cells. *Front. Cell. Neurosci.* doi: 10.3389/fncel.2017.00133 (2017).

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).

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).



Hiroshi Kitagawa Lab

Solid-State Chemistry,
Coordination Chemistry,
Inorganic Chemistry, Nano Science

Faculty Members

Hiroshi Kitagawa (Adjunct PI)

Research Overview

In this century, the emergence of new **molecular devices** which have the diversity and flexibility of biological systems is increasingly expected to occur. Although research of the basic concepts of these systems is still underway, we believe that innovative exploration into the fusion of electrons and protons (**protoelectronics**) may lead to novel breakthroughs. In our laboratory we are studying both quantum mechanical electronic phases (superconducting, magnetic, ferroelectric, metallic and insulating phases) and ionic phases (superionic and quantum paraelectric phases, and tunneling phenomena). In order to establish a foundation for the design of novel devices, we seek to utilize the diversity of electronic and ionic states. We seek to create a diverse range of new materials with unique crystal structures and electronic states in order to discover interesting functionalities based on phenomena such as the quantum-size effect, non-linear electrical conductivity, dielectric response or a variety of fluctuation effects. Our central focus is mainly on inorganic compounds which have interesting features. We investigate materials such as: low-dimensional strongly correlated electron systems; mixed valence compounds with a strong negative-U interaction; charge transfer compounds; metal-organic frameworks; nanoparticles; organic conductors; hydrogen storage materials; super-ionic conducting materials; etc.

Selected Papers

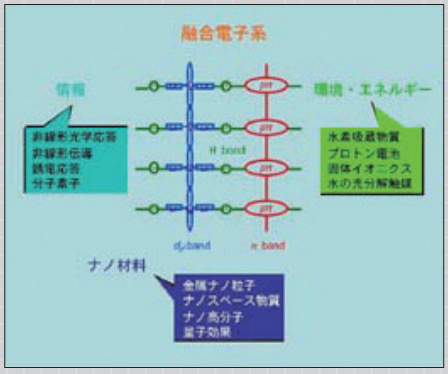
S. Sakaida, K. Otsubo, O. Sakata, C. Song, A. Fujiwara, M. Takata, H. Kitagawa, Crystalline Coordination Framework Endowed with Dynamic Gate-Opening Behaviour by Being Downsized to a Thin Film. *Nat. Chem.* **8**, 377-383 (2016).

H. Kobayashi, K. Kusada, H. Kitagawa, Creation of Novel Solid-Solution Alloy Nanoparticles on the Basis of Density-of-States Engineering by Interelement Fusion. *Acc. Chem. Res.* **48**, 1551-1559 (2015).

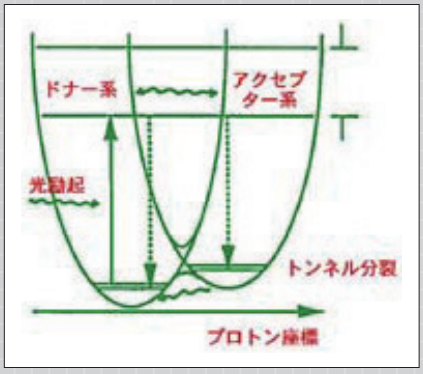
G. Li, H. Kobayashi, J. M. Taylor, R. Ikeda, Y. Kubota, K. Kato, M. Takata, T. Yamamoto, S. Toh, S. Matsumura, H. Kitagawa, Remarkably Enhanced Hydrogen-Storage Capacity and Speed in Pd Nano Crystals Covered with a Metal-Organic Framework. *Nat. Mater.* **13**, 802-806 (2014).

T. Yamada, K. Otsubo, R. Makiura, H. Kitagawa, Designer Co-ordination Polymers: Dimensional Crossover Architectures and Proton Conduction. *Chem. Soc. Rev.* **42**, 6655-6669 (2013).

K. Otsubo, Y. Wakabayashi, J. Ohara, S. Yamamoto, H. Matsuzaki, H. Okamoto, K. Nitta, T. Uruga, H. Kitagawa, Bottom-up Realization of A Porous Metal-organic Nanotubular Assembly. *Nat. Mater.* **10**, 291-295 (2011).



Organic-inorganic hybrid materials



Proton transfer system

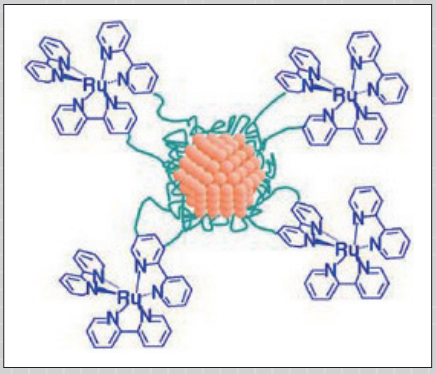
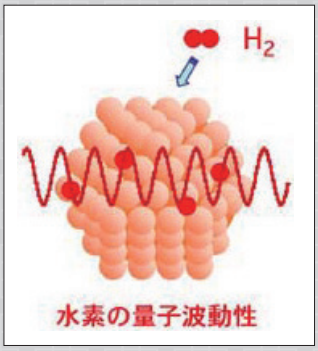


Photo-induced charge separration



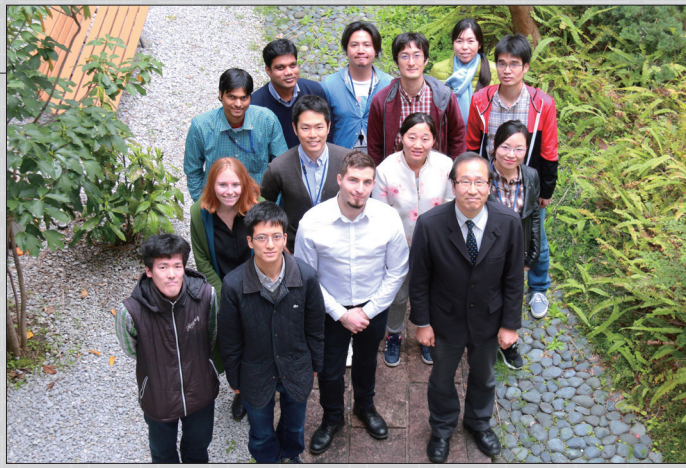
Metal nanoparticles

Superionic conductor

Susumu Kitagawa Lab

Coordination Chemistry

Faculty Members
Susumu Kitagawa (PI)
Koji Tanaka (Specially Appointed Professor)
Masakazu Higuchi (Program-Specific Assistant Professor)
Nobuhiko Hosono (Program-Specific Assistant Professor)
Shinpei Kusaka (Program-Specific Assistant Professor)
Reiko Sakaguchi (Program-Specific Assistant Professor)



Research Overview

1. Porous Material Chemistry for Gas Science and Technology

Porous materials have been used as indispensable tools to human life for over 3500 years from ancient Egyptian era (activated charcoal) to modern age (zeolite etc.). The main research themes of our group are **gas science and technology** using new porous materials known as porous coordination polymers/metal-organic frameworks (**PCPs/MOFs**) that have high surface area and structural diversity for potential industrial applications. We aim to address environmental 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.

2. Hierarchical Coordination Chemistry

Structural hierarchy is a vital feature of natural materials, in which the structure has more than one length scale. For instance, in the living organisms, a skeletal tissue (e.g. centimeter scale) itself consists of some smaller structures like cells (e.g. micro-to-nanometer scale). This hierarchical arrangement of structures beyond the scale plays an important role for material functions and properties. We focus on the design of such hierarchical structures on PCPs/MOFs over nanometers to macroscopic orders. Our research is directed towards developing methodology for creating the **hierarchical coordination structures** and functionalizing these materials in different size scales. This technology will not only enhance the above gas separation and storage properties for PCPs/MOFs but also impart the new synergistic functions over the different size ranges.

Selected Papers

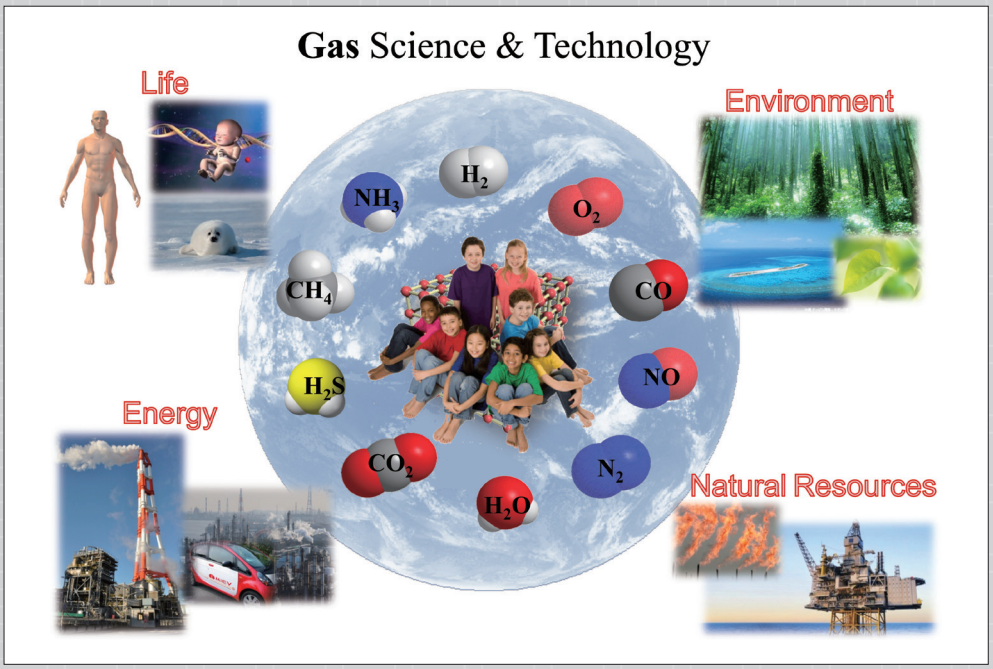
S. Kitagawa, Future Porous Materials. *Acc. Chem. Res.* **50**, 514-516 (2017).

N. Hosono, M. Gochomori, R. Matsuda, H. Sato, S. Kitagawa, Metal–Organic Polyhedral Core as a Versatile Scaffold for Divergent and Convergent Star Polymer Synthesis. *J. Am. Chem. Soc.* **138**, 6525-6531 (2016).

T. Kajiwara, M. Fujii, M. Tsujimoto, K. Kobayashi, M. Higuchi, K. Tanaka, S. Kitagawa, Photochemical Reduction of Low Concentrations of CO_2 in a Porous Coordination Polymer with a Ruthenium(II)-CO Complex. *Angew. Chem. Int. Ed.* **55**, 2697-2700 (2016).

S. Kitagawa, Porous Materials and the Age of Gas. *Angew. Chem. Int. Ed.* **54**, 10686-10687 (2015).

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).



Michiyuki Matsuda Lab

Bioimaging, Cell Biology, Pathology

Faculty Members

Michiyuki Matsuda (Adjunct PI)

Research Overview

Of course we know, although sometimes pretend not to know, that cells on the plastic dishes are totally different from those in living organisms. In the era of biochemistry and molecular biology, however, we needed a mass of homogenous cells for the detailed analysis of the molecule of interest and had to use cells on the dishes. Cell lysis, which is the first step of most biochemical and molecular-biological techniques, inevitably discards intracellular spatio-temporal information of the molecule of interest. To challenge this problem, we are developing biosensors to monitor the activity of intracellular signaling molecules. Because our biosensors are based on **Förster resonance energy transfer (FRET)**, these biosensors are collectively called the FRET biosensor. To date, we have developed FRET biosensors for **small GTPases, protein kinases**, and lipids and visualized how extracellular signals are perceived and transmitted within a cell. Timelapse imaging of cells expressing the FRET biosensor for up to several days has revealed that the activities of signaling molecules are fluctuating with various time scales and that growth factor signaling can be propagated by cell-to-cell communication. More recently, we succeeded in establishing a protocol to generate transgenic "FRET" mice that express FRET biosensors brightly enough for imaging under **two-photon excitation microscopes**. With such FRET mice for protein kinases, we discovered that activation of epidermal cells by epidermal growth factors can be propagated to neighboring epidermal cells in a firework-like manner, which phenomenon was named spatial propagation of radial ERK activity distribution, SPREAD. More FRET mice are coming to our laboratory. With such FRET mice, we are anticipating to see something that people never dreamed of.

Selected Papers

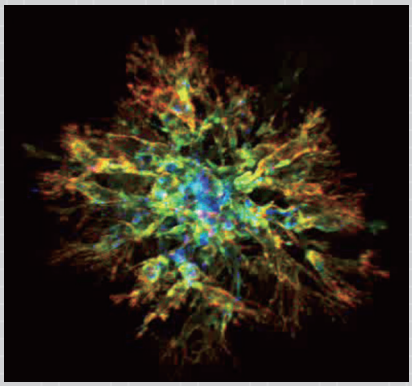
F. Yamauchi, Y. Kamioka, T. Yano, M. Matsuda, In vivo FRET imaging of tumor endothelial cells highlights a role of low PKA activity in vascular hyperpermeability. *Cancer Res.* **76**, 5266-5276 (2016).

T. Hiratsuka, Y. Fujita, H. Naoki, K. Aoki, Y. Kamioka, M. Matsuda, Intercellular propagation of extracellular signal-regulated kinase activation revealed by in vivo imaging of mouse skin. *eLife* **4**, e05178, (2015).

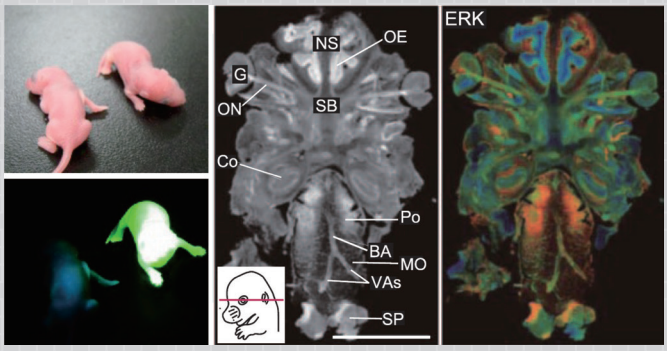
R. Mizuno, Y. Kamioka, K. Kabashima, M. Imajo, K. Sumiyama, E. Nakasho, T. Ito, Y. Hamazaki, Y. Okuchi, Y. Sakai, E. Kiyokawa, M. Matsuda, In vivo imagin g reveals PKA regulation of ERK activity during neutrophil recruitment to inflamed intestines. *J. Exp. Med.* **211**, 1123-1136 (2014).

K. Aoki, Y. Kumagai, A. Sakurai, N. Komatsu, Y. Fujita, C. Shionyu, M. Matsuda, Stochastic ERK activation induced by noise and cell-to-cell propagation regulates cell density-dependent proliferation. *Mol. Cell* **52**, 529-540, (2013).

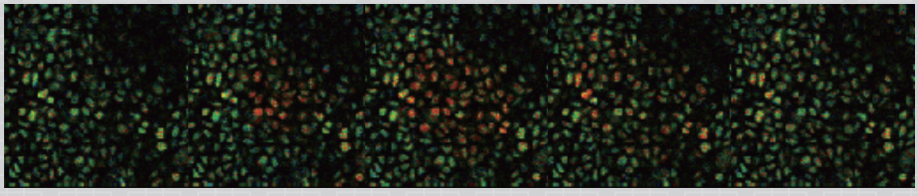
M. Kitano, M. Nakaya, T. Nakamura, S. Nagata, M. Matsuda, Imaging of Rab5 activity identifies essential regulators for phagosome maturation. *Nature* **453**, 241-245, (2008).



Spheroid invasion assay of C6 glioblastoma cells. C6 glioma cells expressing the Raichu–Rac1 FRET biosensor were imaged under a confocal laser scanning microscope after being embedded in 3D Matrigel. Rac1 activity as visualized by FRET biosensor is depicted by pseudocolor. Rac1 activity is high in the lamellipodial protrusion of leading glioma cells, but low in the glioma cells remaining in the center of tissues.



Transgenic mice expressing a FRET biosensor for the ERK serine/threonine protein kinase. A newborn transgenic mouse expressing the FRET biosensor and a control mouse were inspected under white light (upper) or blue light with an emission filiter (bottom). (Right panels) A transverse section of E14.5 embryo expressing the FRET biosensor was observed under a confocal fluorescence microscope. The right panel shows FRET activity in pseudocolor.



Spatial propagation of radial ERK activity distribution, SPREAD in mouse ear epidermis. ERK activity in the FRET mouse expressing FRET biosensor was visualized under a two-photon excitation microscope. Shown here are representative time-lapse images of SPREAD in the basal layer of ear epidermis. ERK activity is shown in pseudocolor.

Yasuo Mori Lab

Molecular Biology, Physiology

Faculty Members
Yasuo Mori (Adjunct PI)

Research Overview

My research was started in the field of organic chemistry, and went into the **biochemistry** and **molecular biophysics of ion channels**. Therefore, I was initially interested in resolving molecular entities of ion channels, which mediate Ca^{2+} influx to evoke release of neurotransmitters from the presynapse of neurons through molecular/functional characterization techniques. Now, my interest has been turned into understanding **physiological systems** controlled by ion channels with unique functions via interactions with molecules of different categories. By disclosing new physiological aspects of ion channels (what they sense, which ionic species they conduct into a cell?), we are trying to find out unprecedented or elusive functional aspects of cells and organs (or assemblies of cell). In particular, we are interested in how our body senses availability of O_2 and senses energy production, and thereby changes itself to adapt to the given O_2 environment. I also work on the subcellular structure pre-synaptic active zone, which provides Ca^{2+} influx ion channels with **molecular niche** via dynamic interactions with multiple presynaptic proteins. I enjoy researches by taking a comprehensive approach to ion channels, ranging from basic science including evolutionary biology to application science such as elucidation of channelpathies and invention of **ion channel-based drugs** and nano-devices.

Selected Papers

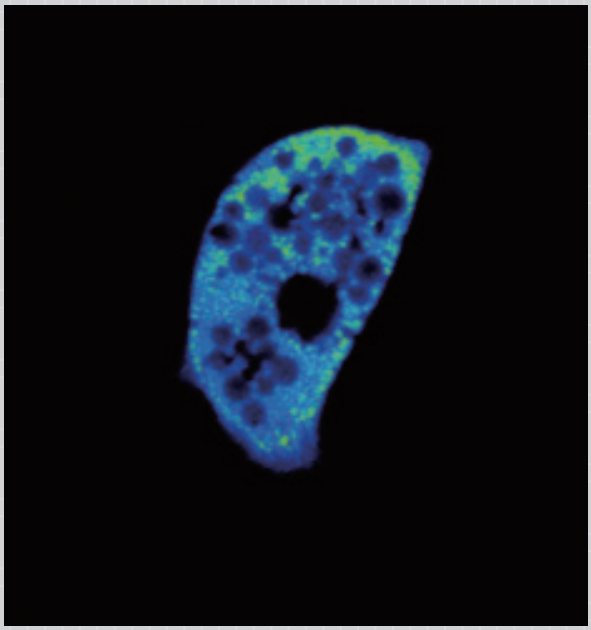
S. Kiyonaka, M. Wakamori, T. Miki, Y. Uriu, M. Nonaka, H. Bito, A. M. Beedle, E. Mori, Y. Hara, M. De Waard, M. Kanagawa, M. Itakura, M. Takahashi, K. P. Campbell, Y. Mori, RIM1 confers sustained activity and neurotransmitter vesicle anchoring to presynaptic Ca^{2+} channels. *Nature Neurosci.* **10**, 691-701 (2007).

S. Yamamoto, S. Shimizu, S. Kiyonaka, N. Takahashi, T. Wajima, Y. Hara, T. Negoro, T. Hiroi, Y. Kiuchi, T. Okada, S. Kaneko, I. Lange, A. Fleig, R. Penner, M. Nishi, H. Takeshima, Y. Mori, TRPM2-mediated Ca^{2+} influx induces chemokine production in monocytes that aggravates inflammatory neutrophil infiltration. *Nature Med.* **14**, 738-747 (2008).

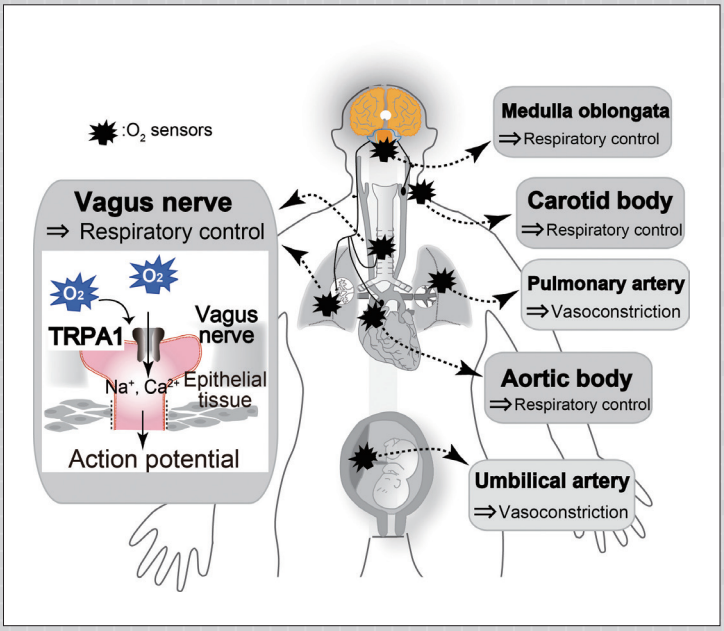
N. Takahashi, T. Kuwaki, S. Kiyonaka, T. Numata, D. Kozai, Y. Mizuno, S. Yamamoto, S. Naito, E. Knevels, P. Carmeliet, T. Oga, S. Kaneko, S. Suga, T. Nokami, J. Yoshida, Y. Mori, TRPA1 underlies a sensing mechanism for O_2. *Nature Chem. Biol.* **7**, 701-711 (2011).

S. Kiyonaka, T. Kajimoto, R. Sakaguchi, D. Shinmi, M. Omatsu-Kanbe, H. Matsuura, H. Imamura, T. Yoshizaki, I. Hamachi, T. Morii, Y. Mori, Genetically encoded fluorescent thermo-sensors for visualizing subcellular thermoregulation in living cells. *Nat Methods* **10**, 1232-1238 (2013).

S. Sawamura, M. Hatano, Y. Takada, K. Hino, T. Kawamura, J. Tanikawa, H. Nakagawa, H. Hase, A. Nakao, M. Hirano, R. Rotrattanadumrong, S. Kiyonaka, M. X. Mori, M. Nishida, Y. Hu, R. Inoue, R. Nagata, Y. Mori, Screening of transient receptor potential canonical channel activators identifies novel neurotrophic piperazine compounds. *Mol Pharmacol.* **89**, 348-63 (2016).



Looking at thermal distribution in a single heat-generating brown adipocyte using our probe tsGFP1-mito, a genetically encoded thermosensor.



Elucidating oxygen-watching systems in our body on the basis of oxygen sensor ion channel TRPA1.

Eisuke Nishida Lab

Aging / Longevity Biology,
Developmental Biology,
Stem Cell Biology

Faculty Members

Eisuke Nishida (Adjunct PI)

Research Overview

Aging is not just a passive process but can be regulated by many genes. Although the rate of aging varies from one organism to another, organisms share common mechanisms of aging. We work on the molecular mechanisms that regulate aging at tissue and organismal levels. We are particularly interested in understanding how environmental factors affect organismal lifespan and why an organism loses proper tissue homeostasis as it ages.

We use *Caenorhabditis elegans,* which is a well-established model organism in aging research. We have found that an intermittent fasting regimen, one of dietary restriction regimens, effectively extends lifespan. Using several approaches, we have identified a number of genes that control lifespan in response to fasting. We have recently found that environmental stresses induce transgenerationally inheritable survival advantages via germline-to-soma communication. We are interested in understanding the inter-organ communications that cope with environmental changes and regulate lifespan/aging.

Furthermore, our research aims to understand the mechanisms of aging at the tissue level in mammals. During aging, many tissues show a progressive decline in hemostasis and regenerative potential. We are now investigating age-related changes in phenotypes, functions, and global gene expression patterns of tissue stem cells, progenitor cells and stem-cell niches. Recent studies have shown the advantages of organoids (mini-organs) to understand the function of stem cells. Moreover, we have recently developed the gene transfer technology in specific tissue. Using these *in vitro* and *in vivo* approaches, we aim to elucidate the key molecules and signaling pathways involved in tissue stem cell aging.

Selected Papers

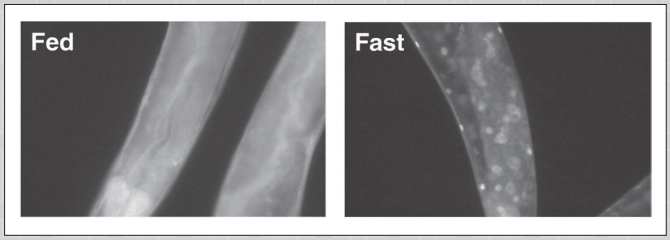
S. Kishimoto, M. Uno, E. Okabe, M. Nono, E. Nishida, Environmental stresses induce transgenerationally inheritable survival advantages via germline-to-soma communication in Caenorhabditis elegans. *Nat. Commun.* **8**, 14031 (2017).

M. Imajo, M. Ebisuya, E. Nishida, Dual role of YAP and TAZ in renewal of the intestinal epithelium. *Nat. Cell Biol.* **17**, 7-19 (2015).

K. Sunadome, T. Suzuki, M. Usui, Y. Ashida, E. Nishida, Antagonism between the master regulators of differentiation ensures the discreteness and robustness of cell fates. *Mol. Cell* **54**, 526-535 (2014).

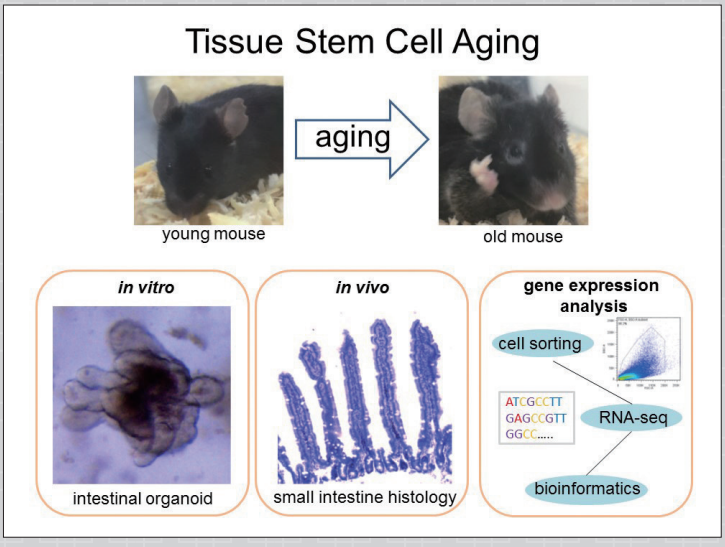
S. Honjoh, T. Yamamoto, M. Uno, E. Nishida, Signaling through RHEB-1 mediates intermittent fasting-induced longevity in C. elegans. *Nature* **457**, 726-730 (2009).

M. Ebisuya, T. Yamamoto, M. Nakajima, E. Nishida, Ripples from neighbouring transcription. *Nat. Cell Biol.* **10**, 1106-1113 (2008).



Tissue stem cell aging

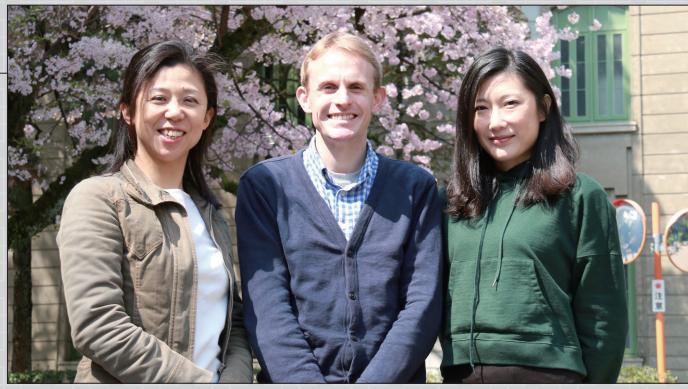
Young and old worms (C. elegans)



Nuclear accumulation of DAF-16

Daniel Packwood Lab

Theoretical Chemistry,
Applied Mathematics



Faculty Members

Daniel Packwood (Junior Associate Professor / PI)

Research Overview

Nanomaterials engineering involves manipulation of molecular-scale processes *via* careful design of molecular structure. Our research seeks **design principles for nanomaterials** by characterizing the relevant molecular processes with **mathematical models**. We employ tools from **theoretical chemistry**, **statistical mechanics**, **stochastic simulation**, and **statistics**, and are actively developing these tools further *en route* to our goals. Our approach compliments experimental research by clarifying hypotheses, identifying new research directions, and uncovering common concepts between different areas of nanoscience.

By turning our approach to a variety of problems in nanoscience, we have proposed methods for tuning diffusion rates inside of porous metals, controlling the degree of coagulation between metal nanoparticles with surface-adsorbed peptides, and controlling the composition of thin films formed by pulsed laser deposition. The latter research led to improved fabrication of transparent superconductors by experimental colleagues. In order to contribute to the synthesis of bio-functional materials, we are putting much effort into modeling **molecular self-assembly processes** that occur on inorganic surfaces and within cells. These studies demand cleverly designed models and efficient simulation techniques that can handle the enormous time-scales over which the self-assembly process takes place. Through the course of these kinds of studies, we ultimately aim to compile a 'periodic table' which connects molecular properties with nanomaterial structure, in contrast to the usual periodic table which connects atom properties with molecular structure.

Selected Papers

D. M. Packwood, T. Hitosugi, Rapid prediction of molecule arrangements on metal surfaces via Bayesian optimization. *Appl. Phys. Express* **10**, 065502 (2017).

D. M. Packwood, P. Han, T. Hitosugi, Chemical and Entropic Control of the Molecular Self-Assembly Process. *Nat .Commun.* **8**, 14463 (2017).

D. M. Packwood, P. Han, T. Hitosugi, State Space Reduction and Equivalence Class Sampling of a Molecular Self-Assembly Model. *R. Soc. Open Sci.* **3**, 150681 (2016).

D. M. Packwood, T. Jin, T. Fujita, M. Chen, N. Asao, Mixing time of Molecules Inside of Nanoporous Gold. *SIAM J. Appl. Math.* **74**, 1298 (2014).

D. M. Packwood, S. Shiraki, T. Hitosugi, Effects of collisions on the stoichiometry of thin films prepared by pulsed laser deposition. *Phys. Rev. Lett.* **111**, 036101 (2013).

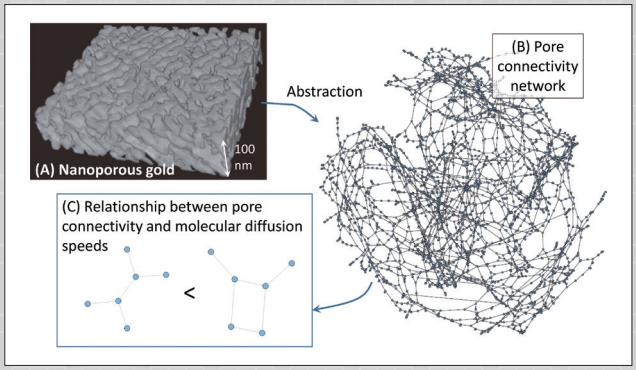


Figure 1. Application of network theory to nanoporous gold identifies how pore connectivity patterns affect molecular diffusion rates. The electron tomography image in (A) was collected by T. Fujita and M. W. Chen of Tohoku University.

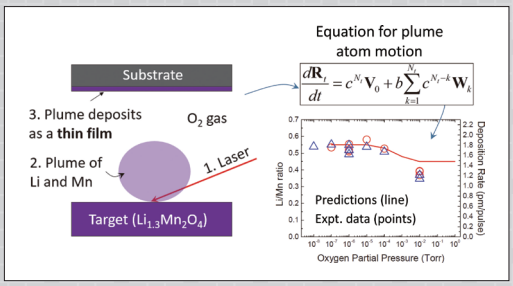


Figure 2. Modeling the composition of thin films formed by pulsed laser deposition using stochastic differential equations. The left-hand diagram outlines the pulsed laser deposition technique.

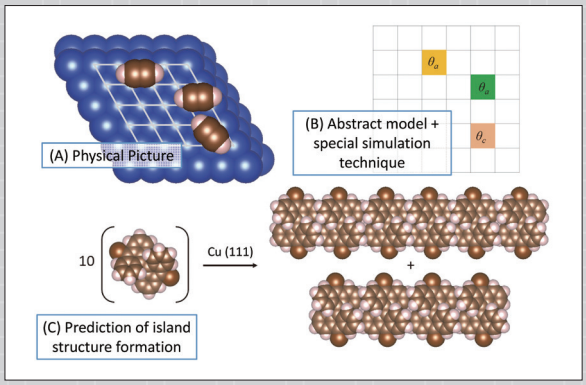


Figure 3. Modeling molecular island formation from self-assembly of organic molecules adsorbed to metal surfaces using special Monte Carlo simulation techniques.

Mitinori Saitou Lab

Germ Cell Biology, Stem Cell Biology

Faculty Members

Mitinori Saitou (Adjunct PI)

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 development, and have shown that **mouse embryonic stem cells (ESCs) / induced pluripotent stem cells (iPSCs)** are induced into epiblast-like cells (EpiLCs), which are in turn induced into **primordial germ cell-like cells (PGCLCs)** with characteristics of migrating PGCs. Importantly, PGCLCs bear a robust capacity both for **spermatogenesis** and **oogenesis**, upon transplantation or aggregation with gonadal somatic cells followed by appropriate culture. Based on this system, we have shown that **human induced pluripotent stem cells (hiPSCs)** with a primed pluripotency differentiate into incipient mesoderm-like cells (iMeLCs), which robustly generates human primordial germ cell-like cells (hPGCLCs) with a transcriptome similar to those in human PGCs. Furthermore, we have investigated the mechanism for the pre- and post-implantation development of a non-human primate, **cynomolgus monkeys**, and have defined a developmental coordinate of the spectrum of pluripotency among mice, monkeys, and humans. We have made an unexpected finding that the germ cell lineage in primates is specified in the nascent amnion segregated from early post-implantation epiblast, providing a critical insight into the biological relevance of the hPGCLC induction pathway. We hope that these lines of research will lead to a better understanding of the mechanism for the transmission/diversification of genetic information, for the regulation of epigenetic information, and for the acquisition of totipotency, among mice, monkeys, and humans.

Selected Papers

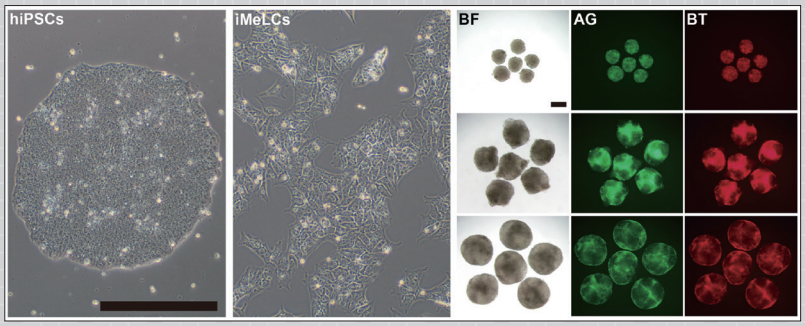
Y. Ishikura, Y. Yabuta, H. Ohta, K. Hayashi, T. Nakamura, I. Okamoto, T. Yamamoto, K. Kurimoto, K. Shirane, H. Sasaki, M. Saitou, In Vitro Derivation and Propagation of Spermatogonial Stem Cell Activity from Mouse Pluripotent Stem Cells. *Cell Rep.* **17**, 2789-2804 (2016).

K. Sasaki, T. Nakamura, I. Okamoto, Y. Yabuta, C. Iwatani, H. Tsuchiya, Y. Seita, S. Nakamura, N. Shiraki, T. Takakuwa, T. Yamamoto, M. Saitou, The Germ Cell Fate of Cynomolgus Monkeys is Specified in the Nascent Amnion. *Dev. Cell* **39**, 169-185 (2016).

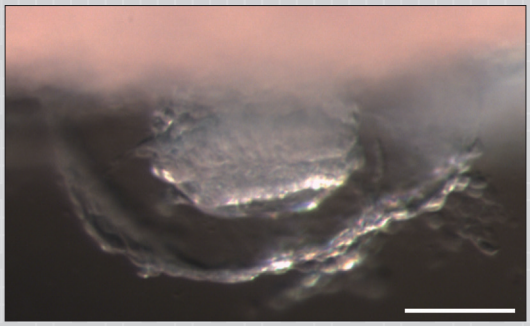
T. Nakamura, I. Okamoto, K. Sasaki, Y. Yabuta, C. Iwatani, H. Tsuchiya, Y. Seita, S. Nakamura, T. Yamamoto, M. Saitou, A developmental coordinate of pluripotency among mice, monkeys, and humans. *Nature* **537**, 57-62 (2016).

M. Saitou, H. Miyauchi, Gametogenesis from Pluripotent Stem Cells. *Cell Stem Cell* **18**, 721-735 (2016).

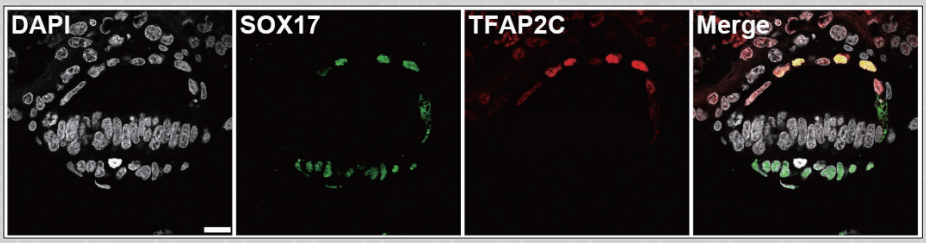
K. Sasaki, S. Yokobayashi, T. Nakamura, I. Okamoto, Y. Yabuta, K. Kurimoto, H. Ohta, Y. Moritoki, C. Iwatani, H. Tsuchiya, S. Nakamura, K. Sekiguchi, T. Sakuma, T. Yamamoto, T. Mori, K. Woltjen, M. Nakagawa, T. Yamamoto, K. Takahashi, S. Yamanaka, M. Saitou, Robust In Vitro Induction of Human Germ Cell Fate from Pluripotent Stem Cells. *Cell Stem Cell* **17**, 178-194 (2015).



Photomicrographs of hiPSCs (left), iMeLCs (middle), and the iMeLC aggregates induced for hPGCLC specification at day 2, 4, and 6 (right top, middle, bottom). BF: bright field; AG: *TFAP2C-2A-EGFP;* BT: *BLIMP1-2A-tdTomato*. Bars: (left) 200 μm; (right, top) 200 μm.



A photomicrograph of a post-implantation cynomolgus monkey embryo at embryonic day 14. Bar: 100 μm.



Immunofluorescence analysis of the expression of SOX17 (green) and TFAP2C (red) in a cynomolgus monkey embryo at E11, showing the emergence of SOX17/TFAP2C-positive PGCs in the amnion. Bar: 20 μm.

Easan Sivaniah Lab

Materials Science, Separation Technology

Faculty Members

Easan Sivaniah (Professor / PI)
Daisuke Yamaguchi (Program-Specific Associate Professor)
Behnam Ghalei (Program-Specific Assistant 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.

With such materials we are able to solve important issues in **tissue engineering**, in **kidney disease management**, in **facilitating respiratory function**. From another view point, the same materials can be applied to the **key challenges of global water scarcity and global warming**. For example, using materials that can separate and capture carbon dioxide in a cost-efficient way, is the only answer to resolving increasing CO_2 content in the air. Equally the materials that can be used as artificial lungs can also be used to improve the air inlet to combustion engines, leading to cars with better emissions and higher fuel efficiencies.

Selected Papers

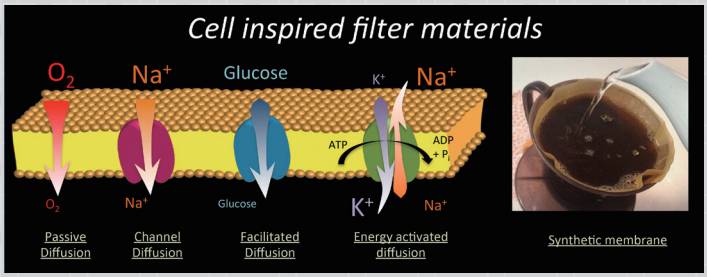
B. Ghalei, K. Sakurai, Y. Kinoshita, K. Wakimoto, A.P. Isfahani, Q. Song, K. Doitomi, S. Furukawa, H. Hirao, H. Kusuda, S. Kitagawa, E. Sivaniah, Enhanced selectivity in mixed matrix membranes for CO_2 capture through efficient dispersion of amine-functionalised MOF nanoparticles. *Nature Energy,* ASAP (2017).

Q. Song, S. Jiang, T. Hasell, M. Liu, S. Sun, A. K. Cheetham, E. Sivaniah, A. I. Cooper, Porous Organic Cage Thin Films and Molecular-Sieving Membranes. *Advanced Materials* **28** (13), 2629-2637 (2016).

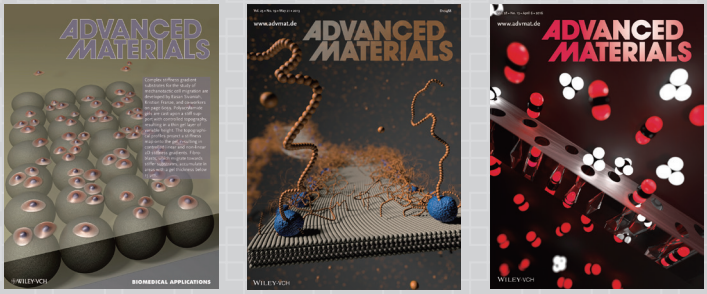
Q. Song, S. Cao, R. Pritchard, B. Ghalei, E. Terentjev, S. A. Al-Muhtaseb, A. K. Cheetham, E. Sivaniah, Controlled thermal oxidative crosslinking of polymers of intrinsic microporsity for tunable molecular sieve memrbanes. *Nature Communications* **5**, 4813 (2014).

Q. Song, C. Cao, L. Lu, P. Zavala-Rivera, W. Li, Z. Shuai, A. K. Cheetham, S. A. Al-Muhtaseb, E. Sivaniah, Photo-oxidative enhancement of polymeric molecular sieve membranes. *Nature Communications.* **4**, 1918 (2013).

S. Sangiambut, K. Channon, N. M. Thomson, S. Sato, T. Tsuge, Y. Doi, E. Sivaniah, A robust route to enzymatically functional, hierarchically self-assembled peptide frameworks. *Advanced Materials*, **25** (19), 2661-2665 (2013).



Membranes are everywhere. From our cells to coffee filters. And they have all kinds of mechanism by which molecules can be efficiently separated.



Cover image (L to R):
1. Use of topology to alter the effective stress that cells detect in materials.
2. Creating enzymatic scaffolds using self-assembling biomolecules.
3. Gas separation membranes with unique cage-like architectures.

Kaoru Sugimura Lab

Biophysics, Developmental Biology

Faculty Members
Kaoru Sugimura
(Program-Specific Research Center Associate Professor / PI)

Research Overview

How do cells push and pull each other to trigger precise deformations of a tissue when shaping the body? The answer to this central question is essential for understanding the development of animal forms including our body. Our group aims at deciphering the mechanisms by which tissue **mechanics** and biochemical signaling are orchestrated, to control epithelial **tissue morphogenesis** in *Drosophila*. By using knowledge, methods, and imaging data from non-biological cellular materials, we develop a new force measurement method (Bayesian force inference) and a new continuous model for use in biological tissues, and clarify novel physical mechanisms involved in cell packing and rearrangement. Moreover, we recently identify the F-actin regulation responsible for the tensile tissue stress-driven cellular rearrangements.

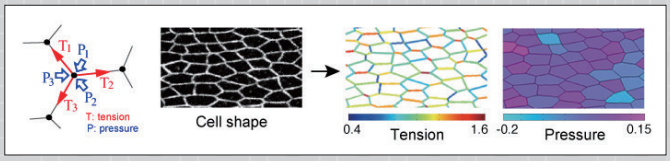
Selected Papers

K. Sugimura, P. F. Lenne, F. Graner, Measuring forces and stresses in situ in living tissues. *Development* **143**, 186-196 (2016).

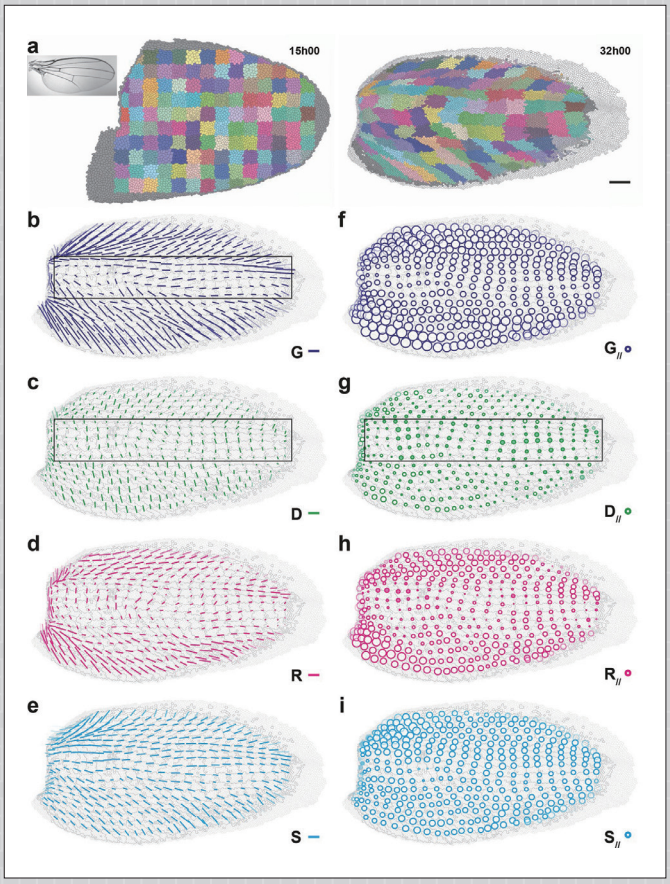
M. Kajita, K. Sugimura, A. Ohoka, J. Burden, H. Suganuma, M. Ikegawa, T. Shimada, T. Kitamura, M. Shindoh, S. Ishikawa, S. Yamamoto, S. Saitoh, Y. Yako, R. Takahashi, T. Okajima, J. Kikuta, Y. Maijima, M. Ishii, M. Tada, Y. Fujita, Filamin acts as a key regulator in epithelial defence against transformed cells. *Nat. Commun.* **5**, 4428 (2014).

K. Sugimura, S. Ishihara, The mechanical anisotropy of a tissue promotes ordering in hexagonal cell packing. *Development* **140**, 4091-4101 (2013).

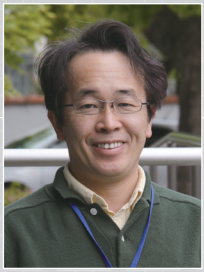
S. Ishihara, K. Sugimura, Bayesian inference of force dynamics during morphogenesis. *J. Theor. Biol.* **313C**, 201-211 (2012).



Bayesian force inference: By solving force-balance equations, the difference of cell pressure and cell junction tension are inferred up to unknown scale factor and basal level of cell pressure. Input image of epithelial cell shapes was taken in Drosophila pupal wing. (*J. Theor. Biol.* **313C**: 201-211 (2012))



Quantitative characterization of Drosophila pupal wing morphogenesis: Maps of total deformation (blue), cell division (green), cell rearrangement (magenta), and cell shape change (light blue) during the pupal morphogenesis of Drosophila wing. (*eLife* **4**: e08519 (2016))



Hiroshi Sugiyama Lab

Chemical Biology

Faculty Members
Hiroshi Sugiyama (Adjunct PI)
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, single molecule imaging of biomolecules and biomaterials and development of nanodevices based on **DNA nanotechnology**, and development of a general method probing DNA local conformation in vivo. The long-range goal are analysis of molecular behaviors involved in epigenetic regulation, and creation of **artificial genetic switches** for iPS cell production and targeted cell differentiation, and treatment of various diseases.

1. Sequence-specific DNA binder pyrrole-imidazole polyamides are developed and applied 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 eight 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) Visualization and biophysical analysis of the biomolecules in the designed nanostructure; (5) Development of novel delivery system for cellular applications; (6) Development of single-molecule devices; (7) Applications for photonic nanomaterials; (8) Applications for molecular robotics.

Selected Papers

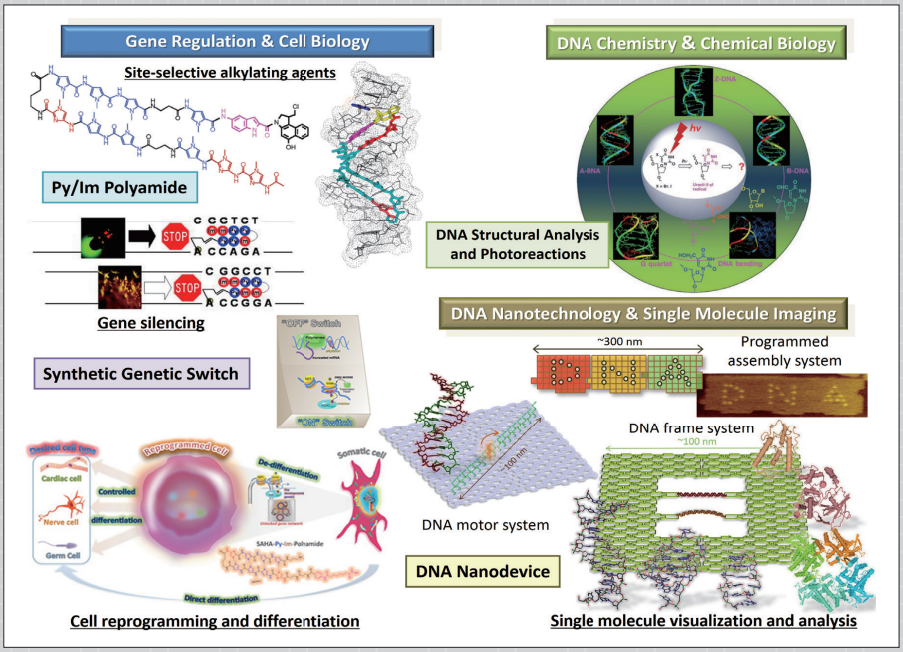
P. Shrestha, S. Jonchhe, T. Emura, K. Hidaka, M. Endo, H. Sugiyama, H. Mao, Confined Space Facilitates G-quadruplex Formation. *Nat. Nanotechnol.* **12**, in press (2017).

A. Kuzyk, Y. Yang, X. Duan, S. Stoll, A. O. Govorov, H. Sugiyama, M. Endo, N. Liu, A light-driven 3D plasmonic nanosystem that translates molecular motion into reversible chiroptical function. *Nat. Commun.* **7**, 10591 (2016).

M. H. Räz, K. Hidaka, S. J. Sturla, H. Sugiyama, M. Endo, Torsional Constraints of DNA Substrates Impact Cas9 Cleavage. *J. Am. Chem. Soc.* **138**, 13842-13845 (2016).

Y. Suzuki, M. Endo, H. Sugiyama, Lipid bilayer-supported two-dimensional self-assembly of DNA origami nanostructures. *Nat. Commun.* **6**, 8052 (2015).

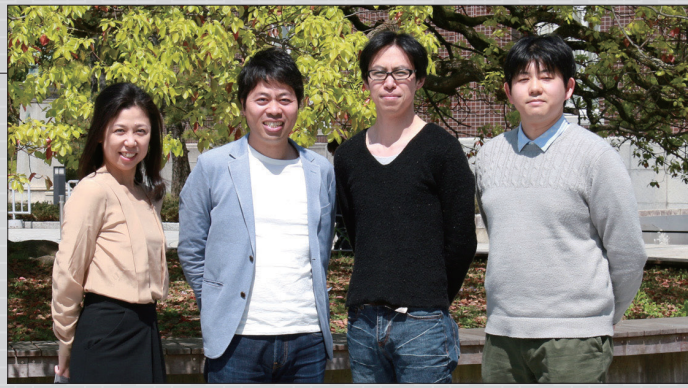
K. Hiraoka, T. Inoue, R. D. Taylor, T. Watanabe, N. Koshikawa, H. Yoda, K. Shinohara, A. Takatori, K. Sugimoto, Y. Maru, T. Denda, K. Fujiwara, A. Balmain, T. Ozaki, T. Bando, H. Sugiyama, H. Nagase, Inhibition of KRAS Codon 12 Mutants Using a Novel DNA-alkylating Pyrrole-imidazole Polyamide Conjugate. *Nat. Commun.* **6**, 6706 (2015).



Jun Suzuki Lab

Medical Biochemistry, Cell Membrane Biology

Faculty Members
Jun Suzuki (Professor / PI)
Masahiro Maruoka (Program-Specific Assistant Professor)



Research Overview

Plasma membranes of cells function not only as a barrier between other cells, but also as a scaffold to **communicate with other cells** such as recognition of **dead cells** and cell fusion, and to perform **chemical reaction** such as **blood coagulation**. Mutations in cell membrane-regulating proteins cause variety of human diseases. We have focused on phospholipids, constituents of plasma membranes, and their-regulating proteins. Among several phospholipids, phosphatidylserine (PS) locates mainly at the inner side of the membranes, but is exposed on the cell surface in several biological phenomenon to function as a signaling molecule for the cellular communications and chemical reaction. To identify PS-exposing proteins (called scramblases), we performed functional **screening** and identified the long sought proteins. During this process, we established several assay systems to investigate on membrane proteins. In my laboratory, we will keep studying the identified membrane proteins, and also start new project to identify novel proteins regulating plasma membranes and analyze their function in cells and in mice. As a basic research, we try to deeply understand how biological phenomenon related to plasma membranes is regulated and how **human diseases** occur, and think of how diseases can be cured.

Selected Papers

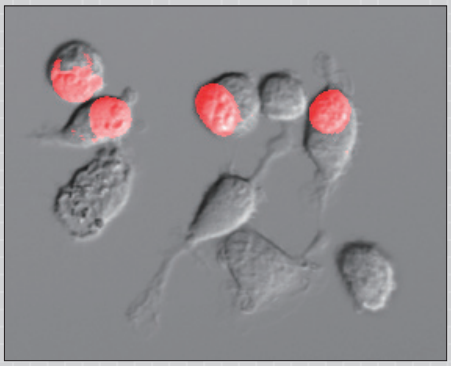
J. Suzuki, E. Imanishi, S. Nagata, The Xkr8 phospholipid scrambling complex in apoptotic phosphatidylserine exposure. *Proc. Natnl. Acad. Sci. USA* **113**, 9509-9514 (2016).

J. Suzuki, E. Imanishi, S. Nagata, Exposure of phosphatidylserine by Xk-related protein family members. *J. Biol. Chem.* **289**, 30257-30267 (2014).

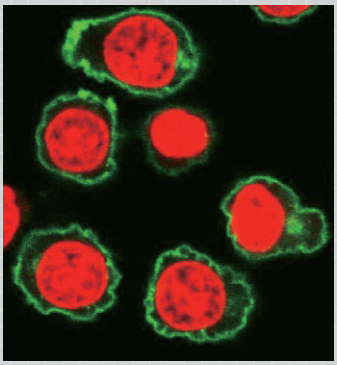
J. Suzuki, D. P. Denning, E. Imanishi, H. R. Horvitz, S. Nagata, Xk-related protein 8 and CED-8 promote phosphatidylserine exposure in apoptotic cells. *Science* **341**, 403-406 (2013).

J. Suzuki, T. Fujii, T. Imao, K. Ishihara, H. Kuba, S. Nagata, Calcium-dependent phospholipid scramblase activity of TMEM16 protein family members. *J. Biol. Chem.* **288**, 13305-13316 (2013).

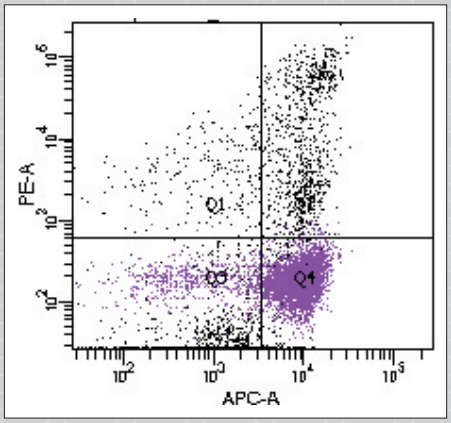
J. Suzuki, P. J. Sims, M. Umeda, S. Nagata, Calcium-dependent phospholipid scrambling by TMEM16F. *Nature* **468**, 834-838 (2010).



Phagocytosis of apoptotic cells by macrophages. The engulfed apoptotic cells show red fluorescence.



Localization of a scramblase on plasma membrane. The scramblase is fused with the green fluorescent protein EGFP and nucleus is stained with red dye.



Display of "Eat-me signal" on the cellular surface. Analysis of phosphatidylserine exposure after apoptotic stimuli by flow cytometry.

Fuyuhiko Tamanoi Lab

Cancer Research, Nanoparticle-Based Therapy

Faculty Members

Fuyuhiko Tamanoi (Program-Specific Professor / PI)

Research Overview

Nanoparticles provide valuable reagents for cancer therapy. These nano-sized materials accumulate in the tumor due to leaky vasculature at the tumor site. In addition, surface modification of nanoparticles enables their preferential uptake into cancer cells. We use nanoparticles called **mesoporous silica nanoparticles** (MSNs) that contain thousands of pores that provide storage space for anticancer drugs. At the opening of the pores, we place **nanovalves** that provide open and close function. Opening of the nanovalve can be controlled in a variety of ways. For example, we developed a nanovalve that opens when exposed to low pH conditions. By taking advantage of conformational changes of azobenzene upon light exposure, we have developed light responsive nanovalves and **nanoimpellers**. In addition, we have developed nanovalves that open upon exposure to **oscillating magnetic field** by using MSNs with **iron oxide core**. The heat generated in the nanoparticles opens the nanovalve. These and other types of mechanized nanoparticles are developed and tested in cancer cells and in animal model systems. Finally, we are initiating a new type of research on **boron neutron capture therapy** (BNCT). BNCT is based on the idea that the exposure of boron-10 to neutron beam results in the splitting of boron to lithium and helium thus generating alpha-beam that kills cancer cells. The key for the success of this therapy rests on the ability to accumulate boron-10 in the tumor. We plan to evaluate whether our nanoparticles can be used for this therapy.

Selected Papers

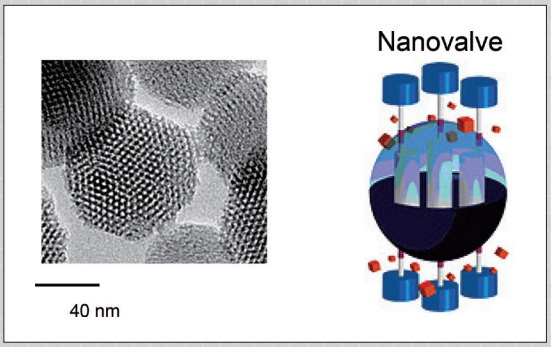
J. Lu, M. Liong, Z. Li, J. Zink, F. Tamanoi, Biocompatibility, biodistribution, and drug-delivery efficiency of mesoporous silica nanoparticles for cancer therapy in animals. *Small* **16**, 1794 (2010).

R.E. Yanes, D. Tarn, A.A. Hwang, D.P. Ferris, S.P. Sherman, C.R. Thomas, J. Lu, A.D. Pyle, J.I. Zink, F. Tamanoi, Involvement of lysosomal exocytosis in the excretion of mesoporous silica nanoparticles and enhancement of the drug delivery effect by exocytosis inhibition. *Small* **9**, 697 (2013).

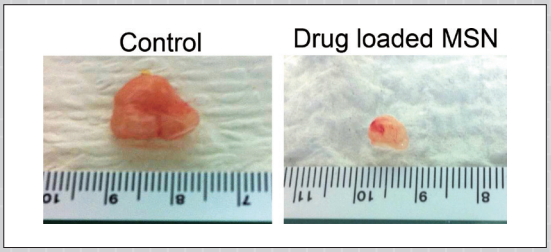
A.A. Hwang, J. Lu, F. Tamanoi, J. Zink. Functional nanovalves on protein-coated nanoparticles for in vitro and in vivo controlled drug delivery. *Small* **11**, 319 (2014).

J. Finlay, C.M. Roberts, J. Dong, J.I. Zink, F. Tamanoi, C.A. Glackin. Mesoporous silica nanoparticle delivery of chemically modified siRNA against TWIST1 leads to reduced tumor burden. *Nanomedicine* **11**, 1657 (2015).

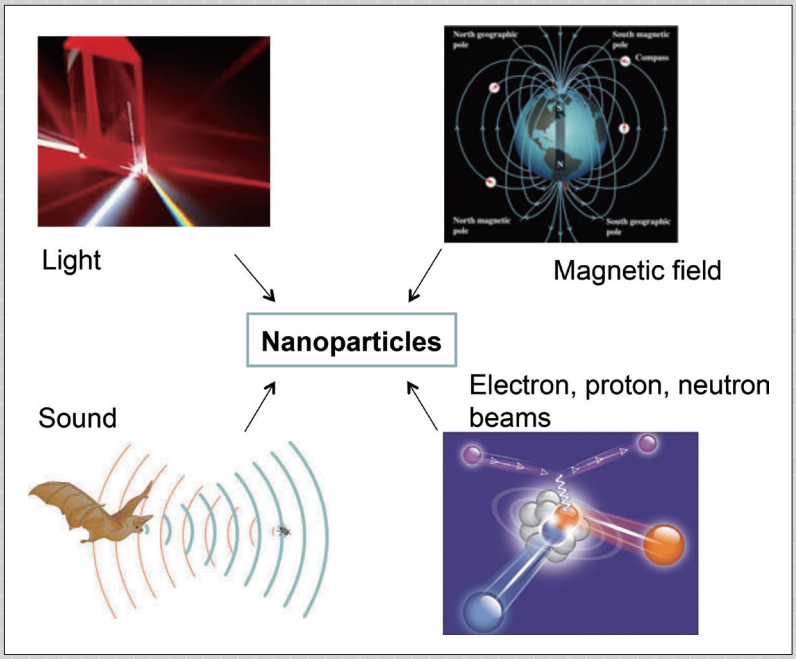
H. Mekaru, J. Lu, F. Tamanoi, Development of mesoporous silica-based nanoparticles with controlled release capability for cancer therapy. *Adv. Drug Deliv. Rev.* **95**, 40 (2015).



Mesoporous silica nanoparticles and nanovalves.



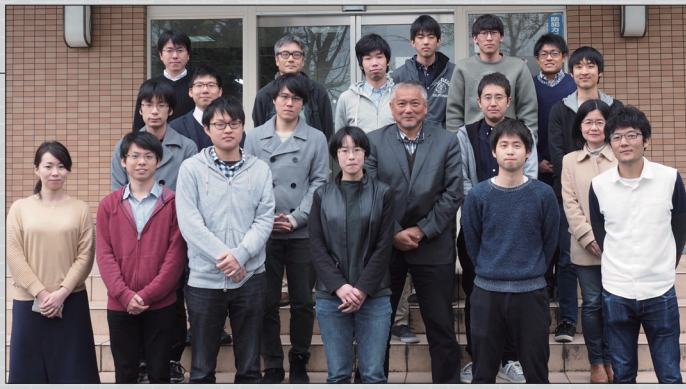
Tumor growth inhibition by MSN-mediated anticancer drug delivery.



Nanoparticles that respond to external cues.

Koichiro Tanaka Lab

Teraherz Optical Science



Faculty Members

Koichiro Tanaka (Adjunct PI)

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 groups in Faculty of Agriculture.
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

T. Arikawa, K. Hyodo, Y. Kadoya, K. Tanaka, Light-induced electron localization in a quantum Hall system. *Nature Phys.* doi:10.1038/nphys 4078 (2017).

K. Uchida, T. Otobe, T. Mochizuki, C. Kim, M. Yoshita, H. Akiyama, L. N. Pfeiffer, K. W. West, K. Tanaka, H. Hirori, Subcycle Optical Response Caused by a Terahertz Dressed State with Phase-Locked Wave Functions. *Phys. Rev. Lett.* **117**, 277402 (2016).

T. Tamaya, A. Ishikawa, T. Ogawa, K. Tanaka, Diabatic Mechanisms of Higher-Order Harmonic Generation in Solid-State Materials under High-Intensity Electric Fields. *Phys. Rev. Lett.* **116**, 016601 (2016).

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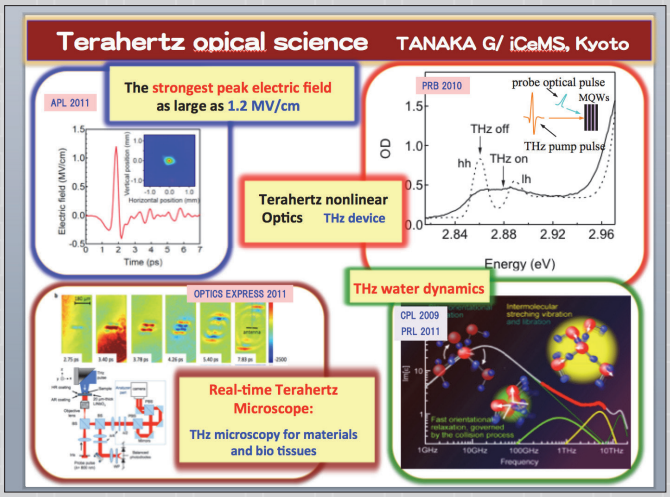

Kazumitsu Ueda Lab

Cellular Biochemistry

Faculty Members

Kazumitsu Ueda (Adjunct PI)

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

S. L. Liu, R. Sheng, J. H. Jung, L. Wang, E. Stec, M. J. O'Connor, S. Song, R. K. Bikkavilli, R. A. Winn, D. Lee, K. Baek, K. Ueda, I. Levitan, K. P. Kim, W. Cho. Orthogonal lipid sensors identify transbilayer asymmetry of plasma membrane cholesterol. *Nat. Chem. Biol.* **13**, 268-274 (2017).

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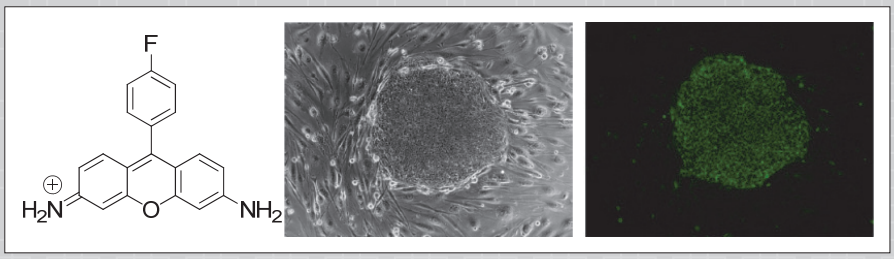
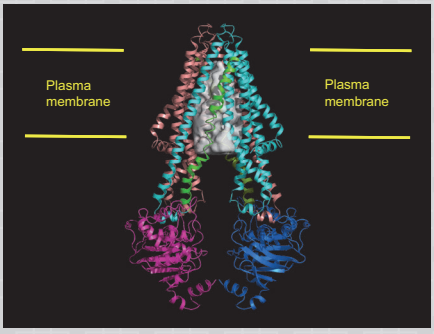
A. Kodan, T. Yamaguchi, T. Nakatsu, K. Sakiyama, C. J. Hipolito, A. Fujioka, R. Hirokane, K. Ikeguchi, B. Watanabe, J. Hiratake, Y. Kimura, H. Suga, K. Ueda, H. Kato, Structural Basis for Gating Mechanisms of a Eukaryotic P-glycoprotein Homolog. *Proc. Natl. Acad. Sci. U. S. A.* **111**, 4049-4054 (2014).

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



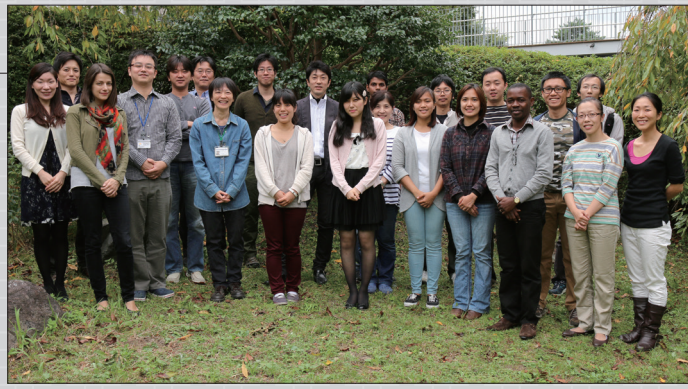
2. Multi-drug recognition mechanism by MDR1

Motonari Uesugi Lab

Chemical Biology

Faculty Members

Motonari Uesugi (Adjunct PI)



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

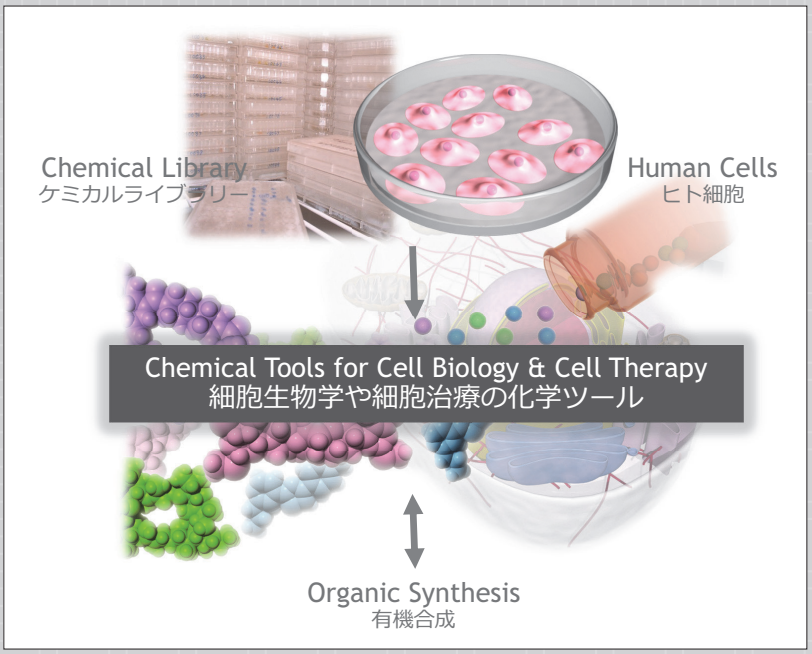
L. Asano, M. Watanabe, Y. Ryoden, K. Usuda, T. Yamaguchi, B. Khambu, M. Takashima, S. Sato, J. Sakai, K. Nagasawa, M. Uesugi, Vitamin D metabolite, 25-Hydroxyvitamin D, regulates lipid metabolism by inducing degradation of SREBP/SCAP. *Cell Chem. Biol.* **24**, 207-217 (2017).

D. Mao, S. Ando, S. Sato, Y. Qin, N. Hirata, Y. Katsuda, E. Kawase, T. F. Kuo, I. Minami, Y. Shiba, K. Ueda, N. Nakatsuji, M. Uesugi, A synthetic hybrid molecule for the selective removal of human pluripotent stem cells from cell mixtures. *Angew. Chem. Int. Ed.* **56**, 1765-1770 (2017).

Y. Katsuda, S. Sato, L. Asano, Y. Morimura, T. Furuta, H. Sugiyama, M. Hagihara, M. Uesugi, A small molecule that represses translation of G-quadruplex-containing mRNA. *J. Am. Chem. Soc.* **138**, 9037-9040 (2016).

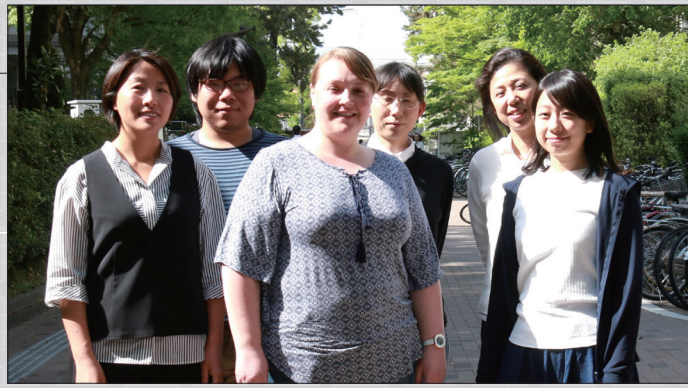
J. Takaya, K. Mio, T. Shiraishi, T. Kurokawa, S. Otsuka, Y. Mori, M. Uesugi, A potent and site-selective agonist of TRPA1. *J. Am. Chem. Soc.* **137**, 15859-15864 (2015).

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).



Dan Ohtan Wang Lab

Neurosciences, RNA Biology



Faculty Members

Dan Ohtan Wang

(Program-Specific Research Center Associate Professor / PI)

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 can be **activity-dependent and mediated by highly orchestrated gene networks**.

We are particularly interested in understanding how gene expression is spatially and temporally regulated in neural circuits, and how such dynamics may underlie long-term neuronal plasticity, a critical molecular aspect of the formation and storage of lasting memories. This level of gene expression regulation involves versatile but poorly understood post-transcriptional regulatory mechanisms such as alternative splicing,chemical modification, trafficking, translation repression, and degradation. Such cell biological mechanisms constitute a highly interactive and flexible gene expression network that can **rapidly respond to the changing neuronal environment and activities**.

To detect learning-related changes in gene expression in situ, we are developing live-cell fluorescence imaging methods using gene-specific hybridization-sensitive probes with high spatiotemporal resolution. The nature of our research requires the use of **novel bioactive materials** and **innovative technical approaches**, which drives us to conduct cross-disciplinary research projects both inside and outside iCeMS.

Selected Papers

I. Oomoto, A. Hirano-Suzuki, H. Umeshima, 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 Nuclera RNA Foci in Living Tissues. *Nucl. Acids. Res.* **43** (19), e126 (2015).

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E. Meer, D. O. Wang, S. M. Kim, I. Barr, F. Guo, K. C. Martin, Identification of a cis-element that localizes mRNA to synapses. *Proc. Natl. Acad. Sci.* **109** (12), 4639-44 (2012).

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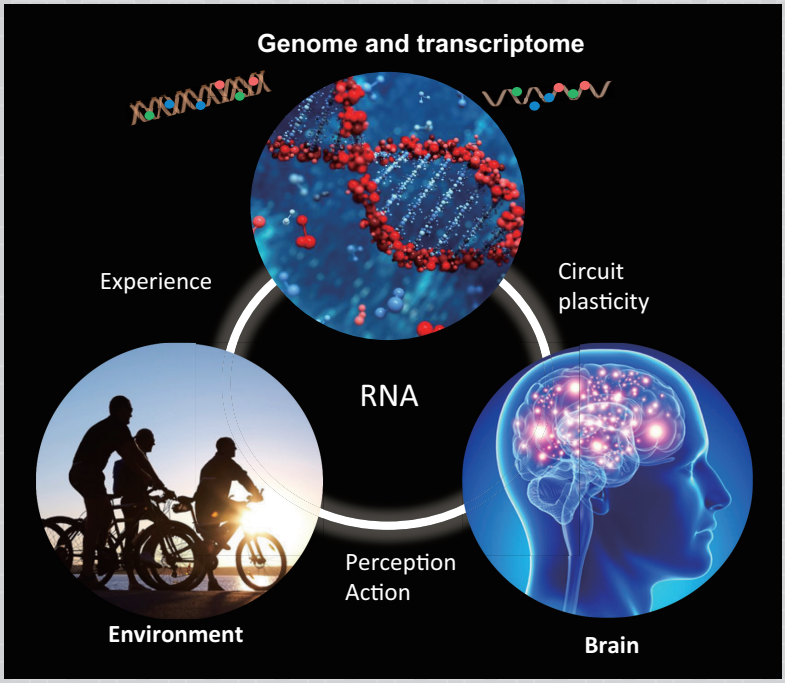
D. O. Wang, S. M. Kim, Y. Zhao, H. Hwang, S. K. Miura, W. S. Sossin, K. C. Martin, Synapse- and stimulus-specific local translation during long-term neuronal plasticity. *Science* **324**, 1536-1540 (2009).



A continuous loop of genes, brain, and environment.
Memory is created through complex interactions of complex genetic and environmental influences in the brain

What is a mouse thinking and remembering?
Visualization of RNA in learning neural circuits.

iCeMS Analysis Center

Director Mineko Kengaku (Professor)

Since its inception, iCeMS has focused on developing technologies for the observation, mechanistic understanding, transformation, and manipulation of cell-material interfaces. Establishment of our Analysis Center was a milestone of the 10-year history of iCeMS, allowing access of its cutting-edge technologies and equipment to researchers for further advancement and deepening of cell-material science studies.
The Center consists of the Materials Analysis Unit, with atomic/molecular characterization equipment, and the Bioanalysis Unit, which has facilities for the observation and analysis of biological molecules and cells. The Center also provides workshops and hands-on training to cultivate and educate the scientific community worldwide, from young scientists in the making to full-fledged specialists stepping into a new field of study.

Bioanalysis Unit

Leader Takahiro Fujiwara (Program-Specific Associate Professor)

Microscopes — The Bioanalysis Unit has in operation six confocal microscopes for long-term observation of live cells at 37°C and 5% CO_2 atmosphere, one of which is equipped with a multiphoton excitation unit. Three of these microscopes are also equipped with super-resolution capabilities: stimulated emission depletion (STED), detector array-based, and frequency domain processing-based microscopies. These advanced microscopes support the observation and analysis of a broad spectrum of cell dynamics and functions, ranging from subcellular molecular complexes to multicellular organization.

Molecular/Cellular Analysis — The Bioanalysis Unit also offers a flow cytometer and cell sorter for optical characterization and selective isolation of dispersed cells, as well as a capillary DNA sequencer. The cell sorter is equipped with four lasers, and is capable of single-cell sorting using multi-well plates, thus allowing research activities that require high-throughput identification and sampling of cells with various cytological properties.

Materials Analysis Unit

Leader Masakazu Higuchi (Program-Specific Assistant Professor)

Analysis — The Materials Analysis Unit provides support for the measurement and analysis of various physical properties, including nanoscopic morphology/state analysis (TEM, SEM), the analysis of electronic states and local structures around the specific element in a substance (XAS), and precision quantitative measurement of specific elements in the materials (ICP).

Evaluation — The Unit also provides measurement and analysis support necessary for the quantitative determination of materials contained in reaction systems (GC-MS), partial structural analysis for organic molecules (FT-IR), absorption tests for porous materials (e.g. BET specific surface area analysis and pore size distribution analysis), and characterization of chemical response properties.

Preparation — The sample preparation for electron microscopy and ICP, and handling of hazardous substances using a fume hood are also available.

Facilities

Yoshida Campus, Kyoto University

- **KUIAS Main Building**
- **KUIAS West Building**

Approx. 5,000 m^2 of floor space

The Main Building serves as the KUIAS' 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.

- **KUIAS iCeMS Research Building**
- Research Building No.1 / Project Lab
- Research Building No.1 Annex

Approx. 6,000 m^2 of floor space

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

Katsura Campus, Kyoto University

- **KUIAS iCeMS Katsura Laboratory**
  (in Funai Center)

Approx. 220 m^2 of floor space

A shared-use laboratory on Kyoto University's Katsura campus. Research includes work on synthesis of functional polymeric materials and porous coordination polymers (PCPs). Such materials can be combined together, for example, to enhance their functionality and compatibility with living cells.

Access

Yoshida Campus, Kyoto University

- **KUIAS Main Building**
- **KUIAS West Building**

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

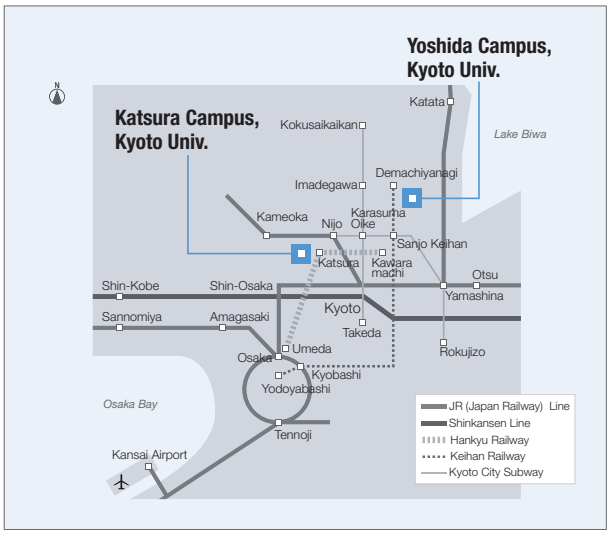
- **KUIAS iCeMS Research Building**
- Research Building No.1 / Project Lab
- Research Building No.1 Annex

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

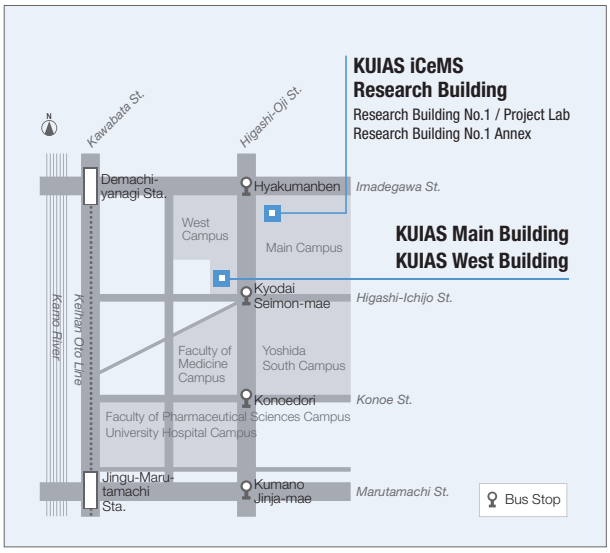
Katsura Campus, Kyoto University

- **KUIAS iCeMS Katsura Laboratory**
  (in Funai Center)

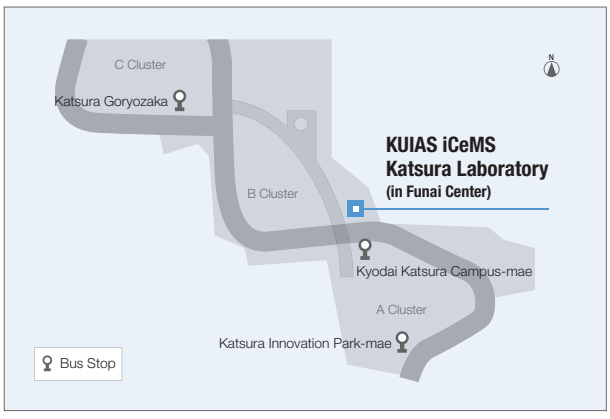
Kyoto University Katsura, Nishikyo-ku, Kyoto
Three-minute walk from“Kyodai Katsura
Campus-mae” Stop
(Kyoto City Bus / Keihan Kyoto Kotsu Bus)



Wide Area Map



Yoshida Campus, Kyoto University



Katsura Campus, Kyoto University

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iCeMS
KYOTO UNIVERSITY
WPI Research Center