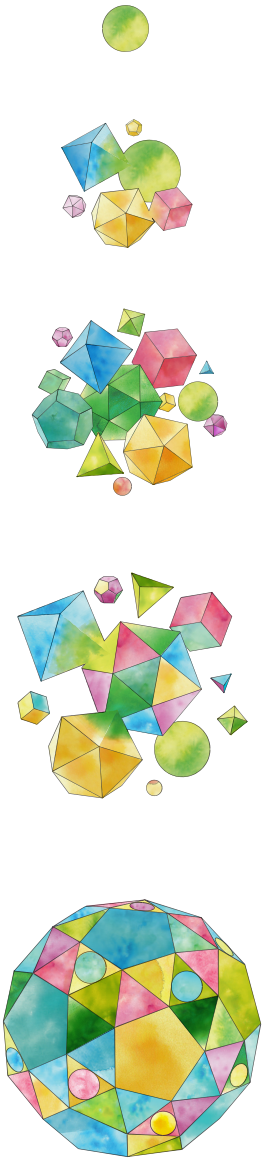
iCeMS



Inspiring Creativity

Institute for Integrated Cell-Material Sciences


Integrated Cell-Material Sciences
京都大学 物質-細胞統合システム拠点
iCeMS
KYOTO UNIVERSITY
WPI Research Center

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 ulti-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

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

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.

Organization Chart

Kyoto University Institute for Advanced Study

- Director-General
- Executive Board
- Deputy Director-General
- Planning and Co-ordination Office
- Center for Advanced Study

Research Centers

Institute for Integrated Cell-Material Sciences

Executive Board


Susumu Kitagawa
Director


Ryoichiro Kageyama
Deputy Director


Motonari Uesugi
Deputy Director


Jun Suzuki
Deputy Director


Shuhei Furukawa
PI Board Chair


Mitsuru Hashida
Research
Administrative Director

Academic Advisory Committee

iCeMS
KYOTO UNIVERSITY
WPI Research Center

- Research Groups (15 PIs / 14 Adjunct PIs)
- Research Administrative Office
  - Innovation Unit
  - Public Engagement Unit
  - iCeMS Analysis Center

- Institute for the Advanced Study of Human Biology (ASHBi)

Collaborative Research Centers

- AIST-Kyoto University Chemical Energy Materials Open Innovation Laboratory (ChEM-OIL)
- RIKEN-Kyoto University Science, Technology and Innovation Hub (RIKEN-Kyoto U Hub)

Endowed Research Section / Industry-University Joint Research Section

- Center for Integrative Medicine and Physics (iCeMS-CiMPhy)

- Administrative Office

Management

Internationalization

- English used as the official Language, and strong support for non-Japanese researchers provided to meet the international standards

Interdisciplinary Resaerch

- Open offices and common labs designed to encourage interaction

International Brain Circulation

- Hosting international symposia and iCeMS Seminars regularly conducted by noted international researchers
- Strengthening the network with industry and partnership with overseas institutions

Research Administration

- Building closer ties with the Kyoto University URA office (KURA)

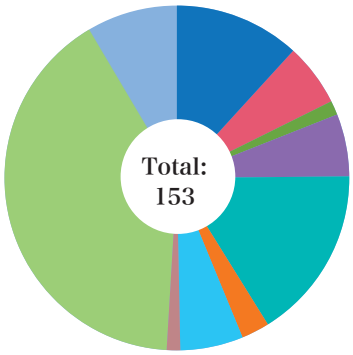
Outreach

- Communicating to the public
  (Providing Internet videos of research presentations for non-scientists, and holding events for high school students)

Fact and Figures

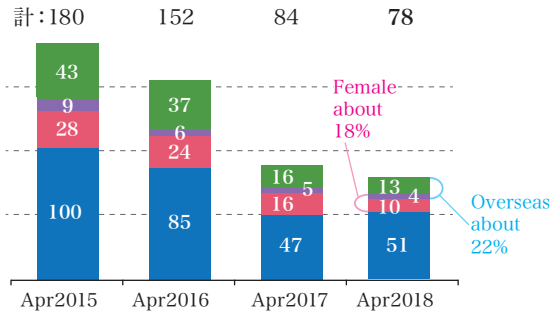
(As of April 2018)

All Staff



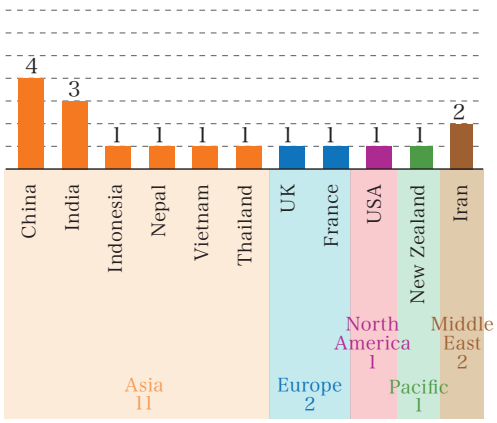
Professor	18	Adjunct Professo	4
Associate Professo	9	Visiting Professo	9
Senior Lecturer	2	Specially Appointed Professor	2
Assistant Professo	9	Research Support Staf	62
Research Associate	25	Administrative Staf	13

Researchers

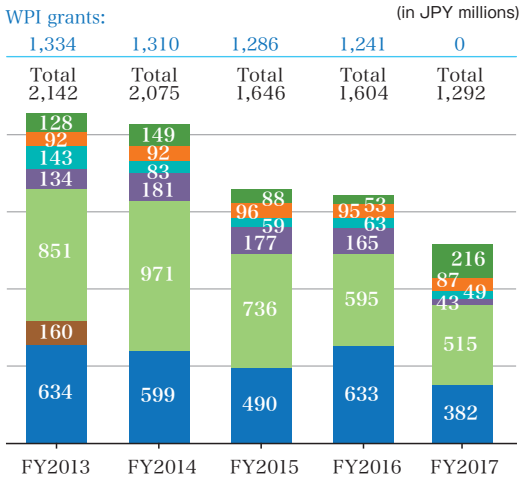


Overseas male / Overseas female
Japanese female / Japanese male

Researchers from Overseas



Finance



- Budget from KU (excl. indirect costs)
- Collaborative personnel support from other KU departments
- Donations
- Collaborative research funding
- Sponsored research funding (incl. NEDO)
- Funding Program for Next-Gen World-Leading Researchers
- Grants-in-Aid for Scientific Research

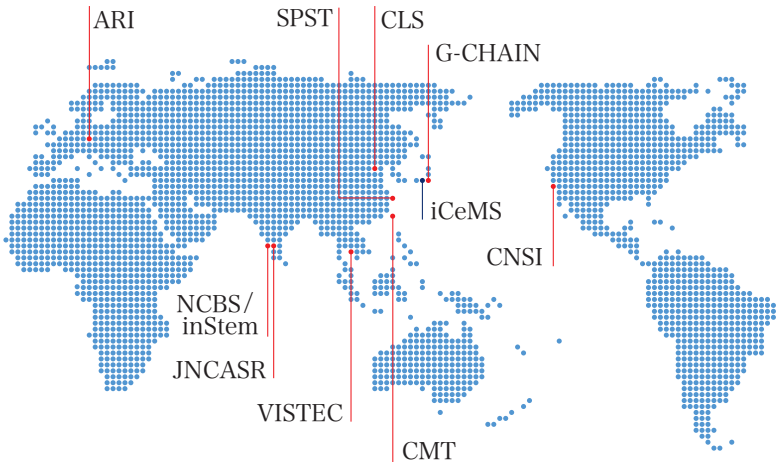
Honors and Awards

Year / Month		Award / Prize	Awardees
2018	Nov	Clarivate Analytics Highly Cited Researcher	Susumu Kitagawa
	Nov	Nishina Memorial Prize	Koichiro Tanaka
	Nov	Medal with Purple Ribbon	Ryoichiro Kageyama
	Apr	Naito Foundation Merit Award	Ryoichiro Kageyama
	Jan	Stem Cell and Regenerative Medicine Action Award	Norio Nakatsuji
2017	Nov	Medal with Purple Ribbon	Mitsuru Hashida
	Sep	2017 Chemistry for the Future Solvay Prize	Susumu Kitagawa
	Sep	The International Pharmaceutical Federation Høst Madsen Medal	Mitsuru Hashida
	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
- Research and Development Center for Membrane Technology (CMT), Chung Yuan Christian University, Taiwan
- School of Physical Science and Technology (SPST), ShanghaiTech University, China
- AO Research Institute Davos (ARI), Switzerland
- 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.

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

Chemical Biology

Motonari Uesugi (p36)

Dan Ohtan Wang (p37)

Materials Science

Shuhei Furukawa (p13)

Daishi Fujita (p11)

Easan Sivaniah (p28)

Susumu Kitagawa (p23)

Cell Biology

Jun Suzuki (p31)

Ryoichiro Kageyama (p19)

Ganesh Pandian Namasivayam (p26)

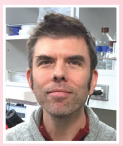
Itaru Hamachi (p14)

Fuyuhiko Tamanoi (p32)

Hiroshi Imahori (p17)

Satoshi Horike (p16)

Hiroshi Kageyama (p18)



Peter Carlton (p10)

Mineko Kengaku (p21)

Kazumitsu Ueda (p35)

Aiko Fukazawa (p12)

Ryu Abe (p9)

Hiroshi Kitagawa (p22)

Michiyuki Matsuda (p24)

Kouichi Hasegawa (p15)

Hiroshi Sugiyama (p30)

Yasuo Mori (p25)

Daniel Packwood (p27)

Koichiro Tanaka (p33)

Motomu Tanaka (p34)

Ken-ichiro Kamei (p20)

Kaoru Sugimura (p29)

Tissue Engineering

Biophysics

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

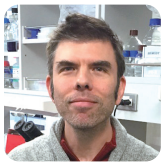
H Fujito, H Kunioku, D Kato, H Suzuki, M Higashi, H Kageyama, R Abe, Layered Perovskite Oxychloride Bi4NbO8Cl: A Stable Visible Light Responsive Photocatalyst for Water Splitting. *J Am Chem Soc* **138**, 2082-2085 (2016)

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 CoOx/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 BaTaO2N 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

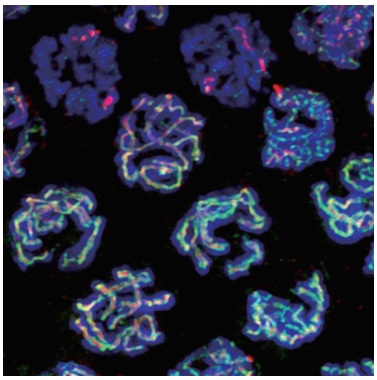
Meiosis, Chromosome Segregation, Superresolution Microscopy

Faculty Members Peter Carlton (Adjunct PI)

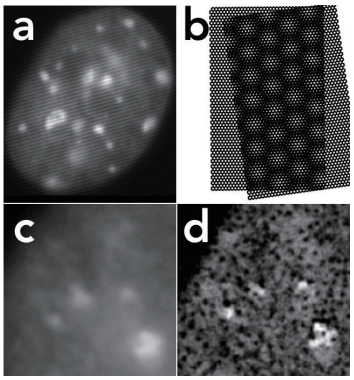
Research Overview

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.**

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.



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.



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)

Selected Papers

A Sato-Carlton, C Nakamura-Tabuchi, S K Chartrand, T Uchino, P M Carlton, Phosphorylation of the synaptonemal complex protein SYP-1 promotes meiotic chromosome segregation. *J Cell Biol* **217**, 555–570 (2018)

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)

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)

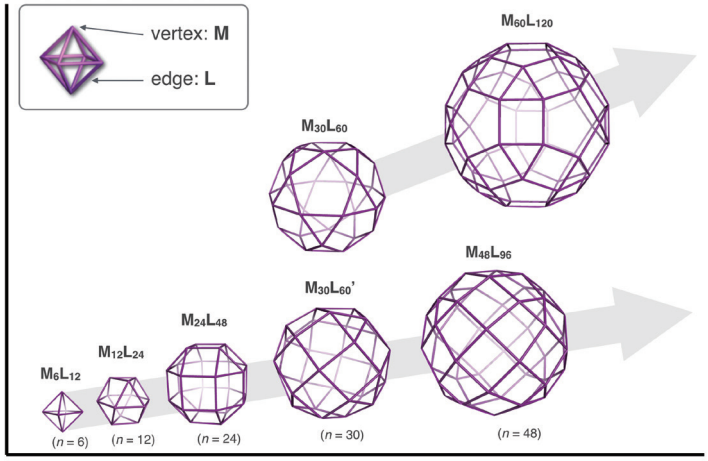
Daishi Fujita Lab

Supramolecular Chemistry, Chemical Biology

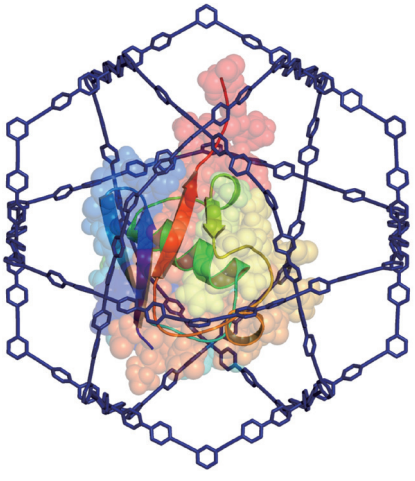
Faculty Members Daishi Fujita (Associate Professor / PI)

Research Overview

Molecular self-assembly is a phenomenon in which multiple molecular subunits autonomously assemble into an ordered structural piece or pattern without any external direction. Self-assembled monolayer (SAM) films and mesoporous materials etc. are the well-established examples that harness the mechanism of molecular self-assembly. Many people are more likely to recognize the word "self-assembly" as a topic of chemistry accordingly. However, the concept of self-assembly is never limited to chemistry. Rather than that, many aspects of biological activity inside the cell can be appreciated as the ultimate form of molecular self-assembly. We have really a lot to learn from such biological system to make our technology advanced. Unfortunately, it is not yet common to discuss the two systems linked: chemical and biological self-assembly. This is mainly because the size or number of subcomponents participates in self-assembly substantially differs between the one of chemistry and the one in biology. We own a self-assembly technology to synthesize the largest known artificial self-assembled objects, which are even capable of encapsulating whole protein molecules. Having such molecular materials in our hand, we will pioneer this new space and explore the applications exploiting the chemical-protein composites.



Molecular design of self-assembly based on polyhedral shape



Spatial modification of protein

Selected Papers

D Fujita, Y Ueda, S Sato, N Mizuno, T Kumasaka, M Fujita, Self-assembly of tetravalent Goldberg polyhedra from 144 small components. *Nature* **540**, 563–566 (2016)

D Fujita, Y Ueda, S Sato, H Yokoyama, N Mizuno, T Kumasaka, M Fujita, Self-Assembly of M30L60 Icosidodecahedron. *Chem* **1**, 91-101 (2016)

D Fujita, H Yokoyama, Y Ueda, S Sato, M Fujita, Geometrically Restricted Intermediates in the Self-Assembly of an M12L24 Cuboctahedral Complex. *Angew Chem Int Ed* **54**, 155-158 (2015)

D Fujita, K Suzuki, S Sato, M Yagi-Utsumi, Y Yamaguchi, N Mizuno, T Kumasaka, M Takata, M Noda, S Uchiyama, K Kato, M Fujita, Protein encapsulation within synthetic molecular hosts *Nature Commun* **3**, 1093 (2012)

Aiko Fukazawa Lab

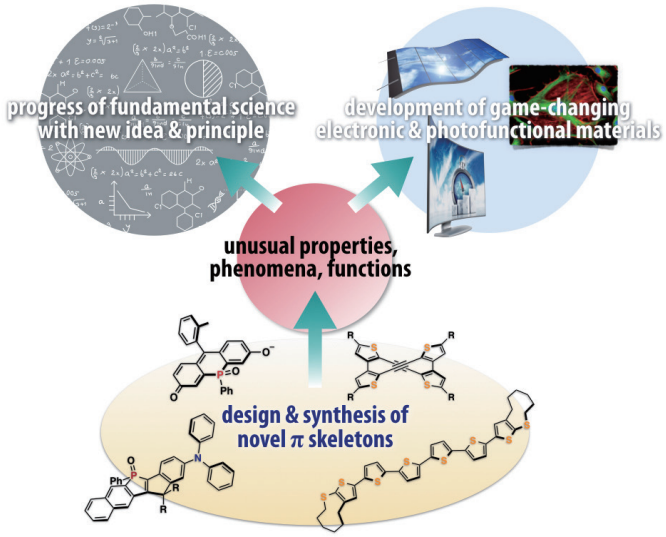
Organic Synthesis, Physical Organic Chemistry

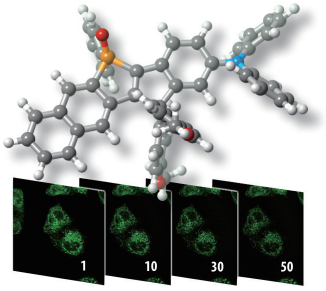
Faculty Members Aiko Fukazawa (Professor / PI)

Research Overview

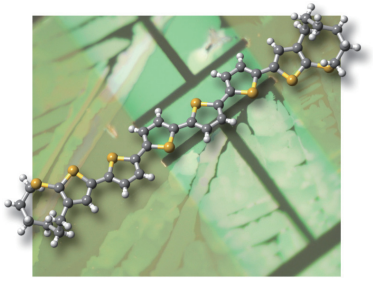
The one of the biggest excitement and mission of chemistry is the manufacturing of novel substances, which have a potential for solving several underlying issues for human beings. From this viewpoint, The Fukazawa group focuses on the development of **organic photo- and/or electro-functional materials** based on the design of the **novel π-conjugated systems.** By pursuing on the physical properties and functions of these compounds, we are also trying to gain rational molecular design of the functional π-electron systems in order to contribute the progress of fundamental science as well as materials science.

This group has just started in November 2018 - we are also going to work on the development of photo- and/or electro-functional molecular materials for the understanding and modulation of the function of living cells with the strong collaboration with the other research groups in iCeMS.





Molecular structure of our phosphorus-containing fluorescent dye and the repeated STED images of cells stained with it. This dye retains the emission intensity even under consecutive STED imaging because of the superior photostability.



Molecular structure of an end-capped oligothiophene with sulfur-containing medium rings and the microscope image of a OFET device using this material. This compound exhibits sufficient solubility as well as crystallinity owing to the structural feature of a medium ring.

Selected Papers

C Wang, M Taki, Y Sato, A Fukazawa, T Higashiyama, S Yamaguchi, A Super-Photostable Phosphole-Based Dye for Multiple-Acquisition STED Imaging. *J Am Chem Soc* **139**, 10374-10381 (2017)

H Oshima, A Fukazawa, S Yamaguchi, Facile Synthesis of Polycyclic Pentalenes with Enhanced Hückel Antiaromaticity. *Angew Chem Int Ed* **56**, 3270-3274 (2017)

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Shuhei Furukawa Lab

Coordination Chemistry, Supramolecular Chemistry, Materials Science, Chemical Biology

Faculty Members Shuhei Furukawa (Associate Professor / PI)
Reiko Sakaguchi (Program-Specific Assistant Professor)
Gavin Craig (Program-Specific Assistnt Professor)

Research Overview

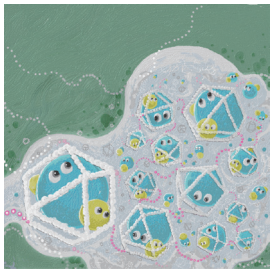
The Furukawa group focuses on the development of new synthetic protocols of molecular assemblies at the mesoscale (5-1000 nm) by the power of coordination chemistry and supramolecular chemistry and the understanding of their unique properties. The resulting materials are further considered for microenvironmental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

1. **Chemistry at the mesoscale:** 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.

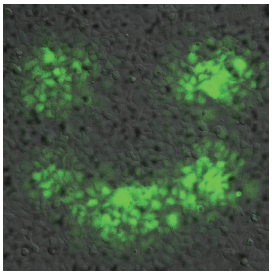
2. **Porous Soft Matters:** Introducing a porosity into materials, in particular, microporosity which ranges the size of pores from a few angstroms to a few nanometers, requires materials rigidity to maintain its “vacuum” therein. We are currently developing microporous materials with softness like gels. We chemically synthesize molecules with rigid backbone to maintain a porosity so-called metal-organic polyhedra (MOP) and assemble these porous molecules into soft matters like colloidal particles or gels. These novel porous materials will be used for unconventional applications including sensing, battery, electronics and cell biology.

3. **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.

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



Cartoon of porous gels made of metal-organic polyhedral (MOP).



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

Selected Papers

A Carné-Sánchez, G A Craig, P Larpent, T Hirose, M Higuchi, S Kitagawa, K Matsuda, K Urayama, S Furukawa, Self-assembly of metal–organic polyhedra into supramolecular polymers with intrinsic microporosity. *Nat Commun* **9**, 2506 (2018)

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)

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Itaru Hamachi Lab

Chemical Biology, Supramolecular Biomaterials

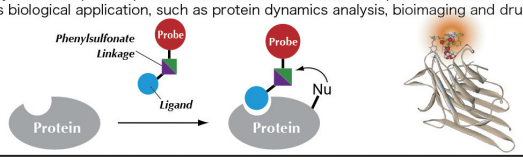
Faculty Members Itaru Hamachi (Adjunct PI)

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 multi-molecular 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.

Organic chemistry in living cells

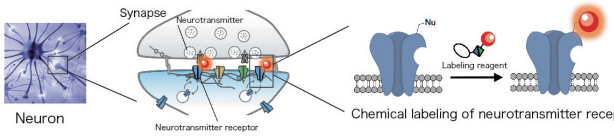
Taking advantage of the excellent functions of proteins, we are trying to create artificial proteins that perform new and unprecedented functions. Toward this end, we have developed original methods relied on organic chemistry, such as LDT, LDAI, and AGD chemistry, which allow the direct chemical modification of endogenous (native) protein and construction of protein-based biosensors in living cells. We are also working on the development of new organic chemistry for site-specific protein modification. Functionalized proteins obtained by these method are useful for various biological application, such as protein dynamics analysis, bioimaging and drug discovery.



Selective chemical modification of natural proteins by ligand-directed chemistry

Visualization of neurotransmitter receptors

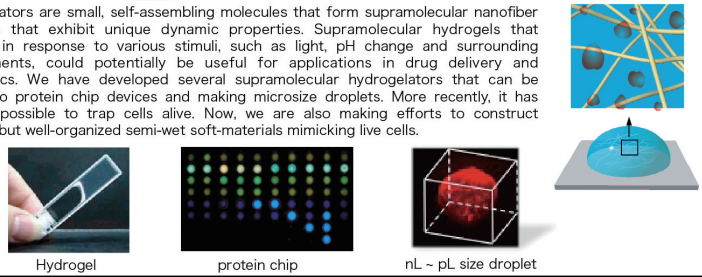
The methodology that can visualize the function of the central nervous system and control its function is useful to clarify neuronal functions, mechanism of memory and learning, and also to develop diagnostic and therapeutic drugs related to neuronal diseases. The Neurochemical Biology Group aims to elucidate nerve functions with chemical biology approaches. Specifically, we are developing a methodology for 1) visualization of neurotransmitter receptors, 2) selective activation of target proteins by combining genetic engineering with designed chemical reagents.



Chemical approaches for visualization of neurotransmitter receptors

Supramolecular hydrogels as a semi-wet matrix

Hydrogelators are small, self-assembling molecules that form supramolecular nanofiber networks that exhibit unique dynamic properties. Supramolecular hydrogels that degrade in response to various stimuli, such as light, pH change and surrounding environments, could potentially be useful for applications in drug delivery and diagnostics. We have developed several supramolecular hydrogelators that can be applied to protein chip devices and making microsize droplets. More recently, it has become possible to trap cells alive. Now, we are also making efforts to construct complex but well-organized semi-wet soft-materials mimicking live cells.



Supramolecular hydrogels as soft materials mimicking live cells

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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)

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Kouichi Hasegawa Lab

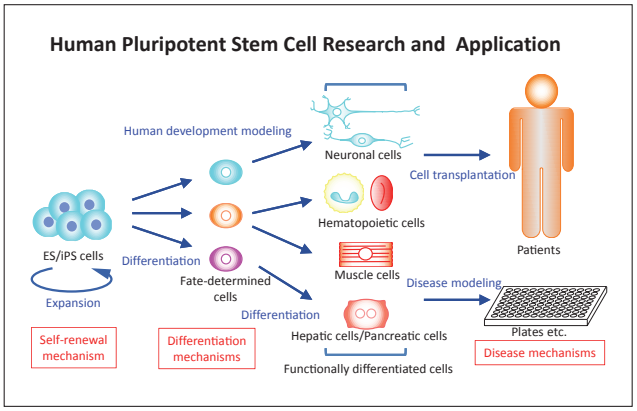
Stem Cell Biology, Stem Cell Engineering

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

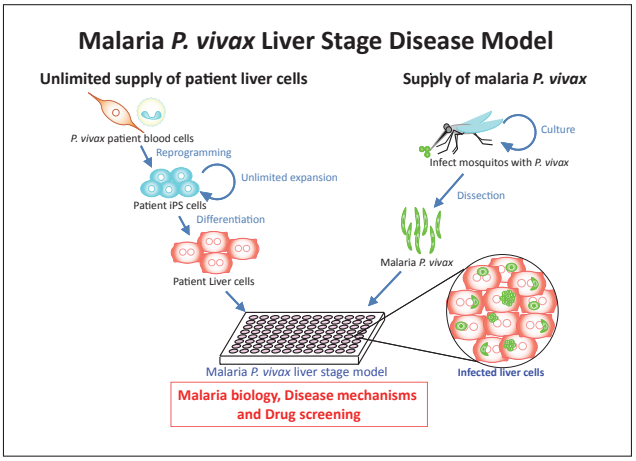
Research Overview

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. We are also identifying chemical compounds and polymers to regulate the self-renewal and differentiation to develop platforms for stable and sustainable controlling of stem cell. Through this study, **we want to contribute to regenerative medicine and drug development.**

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** and studying disease mechanisms. One of the models is malaria *P.vivax* liver stage model with hepatocyte differentiated from patients' iPS cells. 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.



Human pluripotent stem cell research and application



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

Selected Papers

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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)

Satoshi Horike Lab

Coordination Chemistry, Solid State Chemistry, Material Science

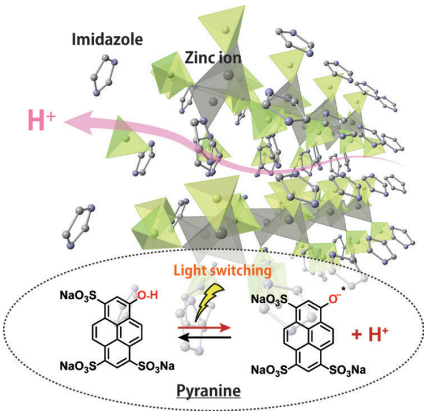
Faculty Members Satoshi Horike (Associate Professor / PI)

Research Overview

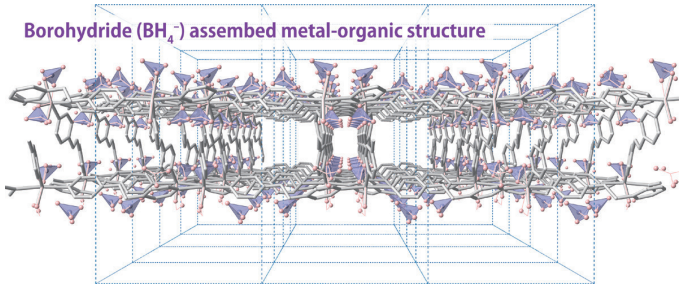
Our research focuses on the synthesis and development of new solid materials for energy/environment issues involving fuel cell/battery and functional glass technologies. Among a various families of solid materials, we study the extended network structures from metal and molecules – namely **coordination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



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. twitter.

Selected Papers

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Hiroshi Imahori Lab

Organic Chemistry, Photochemistry, Drug Delivery Systems

Faculty Members Hiroshi Imahori (Adjunct PI)

Research Overview

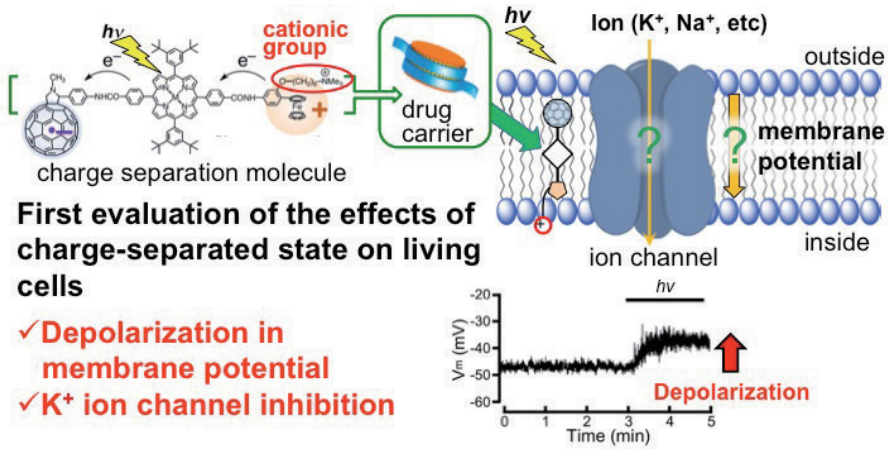
Our laboratory has been working on **artificial photosynthesis** and **solar energy conversion**. In particular, we have demonstrated small reorganization energies of fullerenes, which is favorable for efficient solar energy conversion. Namely, they have made it possible to produce a long-lived charge-separated 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

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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

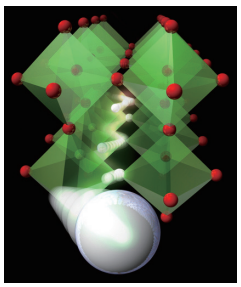
Solid State Chemistry

Faculty Members Hiroshi Kageyama (Adjunct PI)

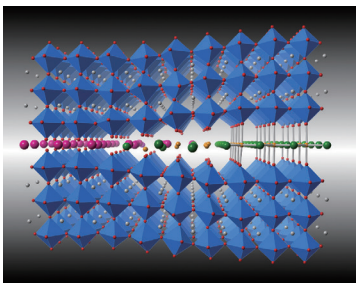
Research Overview

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.

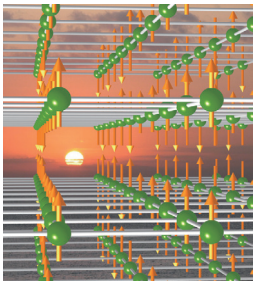
The Kageyama group entails a comprehensive thrust to change the focus of inorganic synthesis to anions. Expanding the scope of **anion-based materials chemistry** will lead to new materials, which will impact both academia and industry by the creation of new academic fields and interesting applications. 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.



Hydride diffusion in oxyhydride



Ion-exchange reaction



Pressure-induced spin transition in SrFeO2

Selected Papers

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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 BaTiO3. *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 BaTiO3 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)

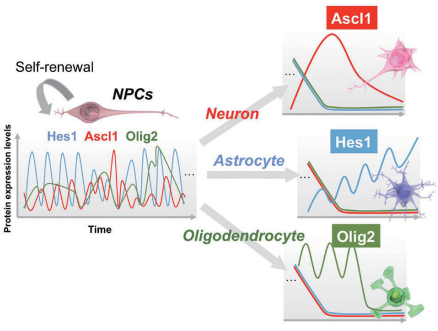
Ryoichiro Kageyama Lab

Developmental Biology, Neural Stem Cell Biology

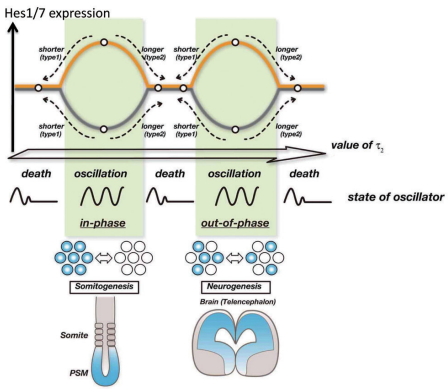
Faculty Members Ryoichiro Kageyama (Adjunct PI)

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.



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, 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.

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)

Ken-ichiro Kamei Lab

Micro/Nanoengineering, Stem Cell Engineering

Faculty Members Ken-ichiro Kamei (Associate Professor / PI)
Rodi Abdalkader (Program-Specific Assistant Professor)

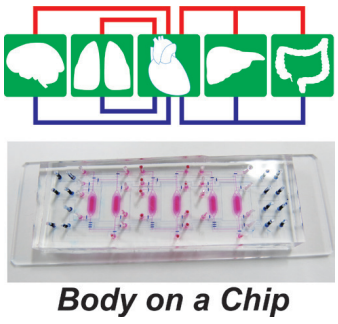
Research Overview

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.

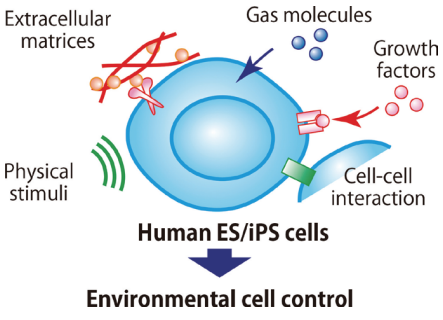
Here, we propose three research directions of BoC for contribution to global healthcare.

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

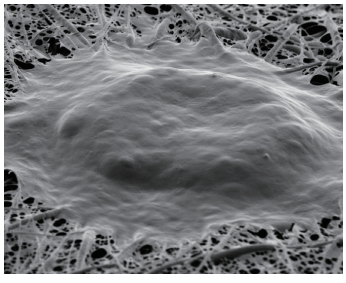
The ultimate goal of this project is to understand the mechanisms of a body construction by mimicking life processes in a microfluidic device. Furthermore, to facilitate progress in developing the BoC, we propose an interdisciplinary approach that integrates stem cell biology, chemical biology, physics,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



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

Selected Papers

K Kamei, Y Kato, Y Hirai, S Ito, J Satoh, A Oka, T Tsuchiya, Y Chen and O Tabata, Integrated Heart/Cancer on a chip to reproduce the side effects of anti-cancer drug in vitro. *RSC Advances* **7**, 36777-36786 (2017)

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, icrofluidic-nanofiber hybrid array for screening of cellular microenvironments. *Small* **13** (18), 1603104 (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)

Mineko Kengaku Lab

Developmental Neurobiology, Cell Biology

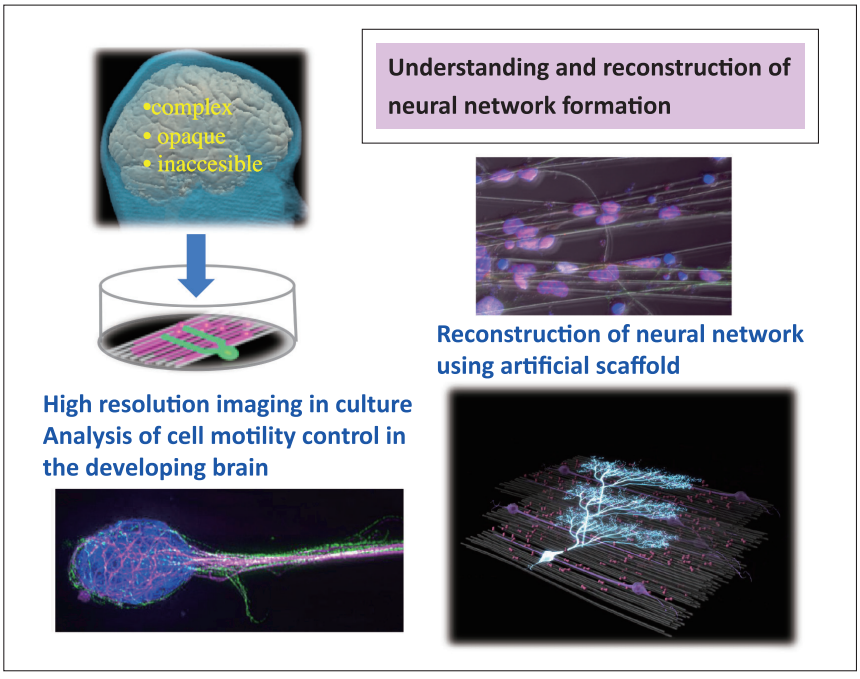
Faculty Members Mineko Kengaku (Professor / PI) Kazuto Fujishima (Program-Specific Assistant Professor)
Naotaka Nakazawa (Program-Specific Assistant Professor)

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 their birth places 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 regulating the shape and motility of the cellular structures** during **neuronal migration** and **dendrite branching.** We also aim to develop imaging techniques for real-time observation of molecular and cellular dynamics of neurons in the developing brain.

Three main research directions are as follows:

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



Selected Papers

K Kawabata-Galbraith, K Fujishima, H Mizuno, S J Lee, T Uemura, K Sakimura, M Mishina, N Watanabe, M Kengaku, MTSS1 regulation of actin-nucleating formin DAAM1 in dendritic filopodia determines final dendritic configuration of Purkinje cells. *Cell Rep* **24**, 95-106 (2018)

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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)

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

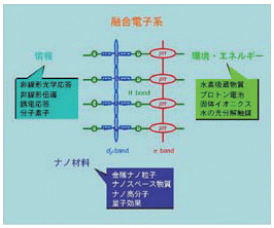
Solid-State Chemistry, Coordination Chemistry, Inorganic Chemistry, Nano Science

Faculty Members Hiroshi Kitagawa (Adjunct PI)

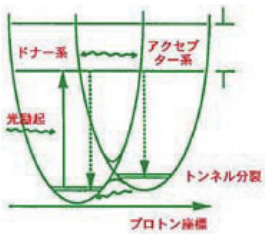
Research Overview

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.



Organic-inorganic hybrid materials



Proton transfer system

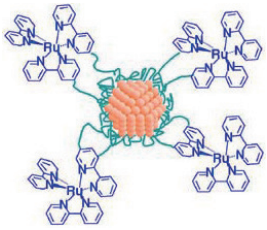
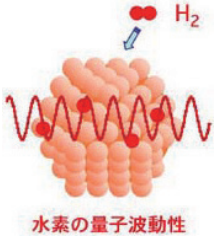


Photo-induced charge separration



Metal nanoparticles

Superionic conductor

Selected Papers

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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)

Susumu Kitagawa Lab

Coordination Chemistry

Faculty Members Susumu Kitagawa (PI) Koji Tanaka (Specially Appointed Professor)
Ken-ichi Otake (Program-Specific Assistant Professor)

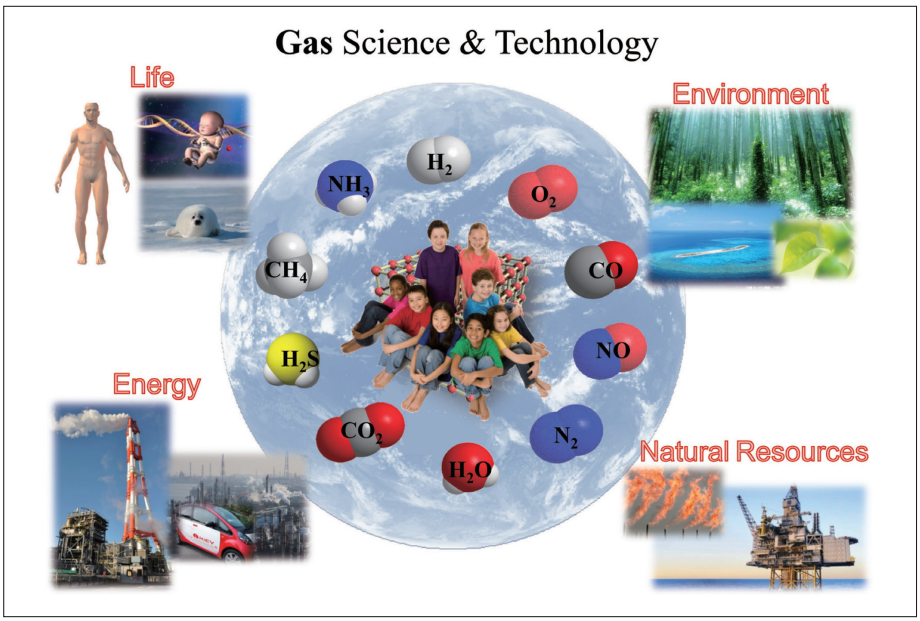
Research Overview

1. Porous Material Chemistry for Gas Science and Technology

Porous materials have been used as indispensable tools to human life for over 3,500 years from ancient Egyptian era (activated carbon (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

occurs widely in nature. For instance, in the living organisms, an organ is composed of small tissues and a tissue consists of even smaller cells. 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

M Shivanna, Q-Y Yang, S Sen, A Bajpai, N Hosono, S Kusaka, T Pham, K A Forrest, B Space, S Kitagawa, M Zaworotko, Readily Accessible Shape-Memory Effect in a Porous Interpenetrated Coordination Network. *Sci Adv* **4**, eaaq1636 (2018)

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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)

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

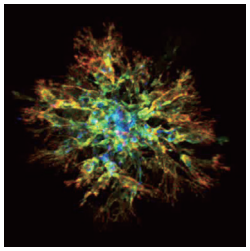
Bioimaging, Cell Biology, Pathology

Faculty Members Michiyuki Matsuda (Adjunct PI)

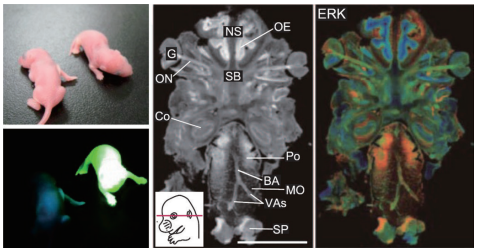
Research Overview

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.

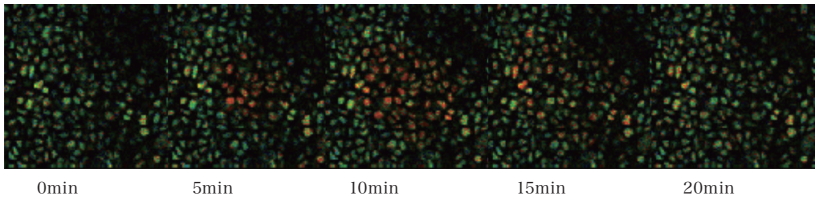
Timelapse imaging of cells expressing the FRET biosensor for up to several days has revealed that the activities of signaling molecules are fluctuating with various time scales and that growth factor signaling can be propagated by cell-to-cell communication. More recently, we succeeded in establishing 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.



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.

Selected Papers

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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)

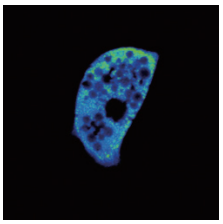
Yasuo Mori Lab

Molecular Biology, Physiology

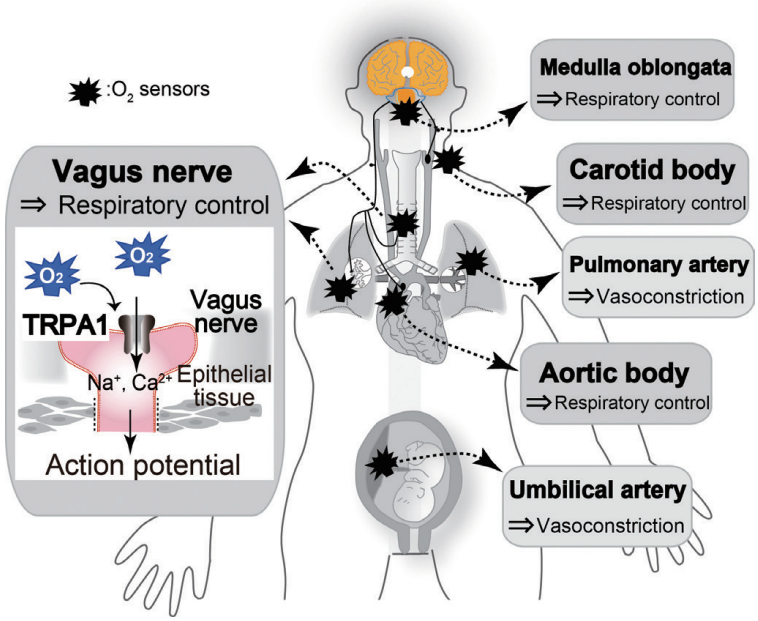
Faculty Members Yasuo Mori (Adjunct PI)

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.



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.

Selected Papers

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)

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)

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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)

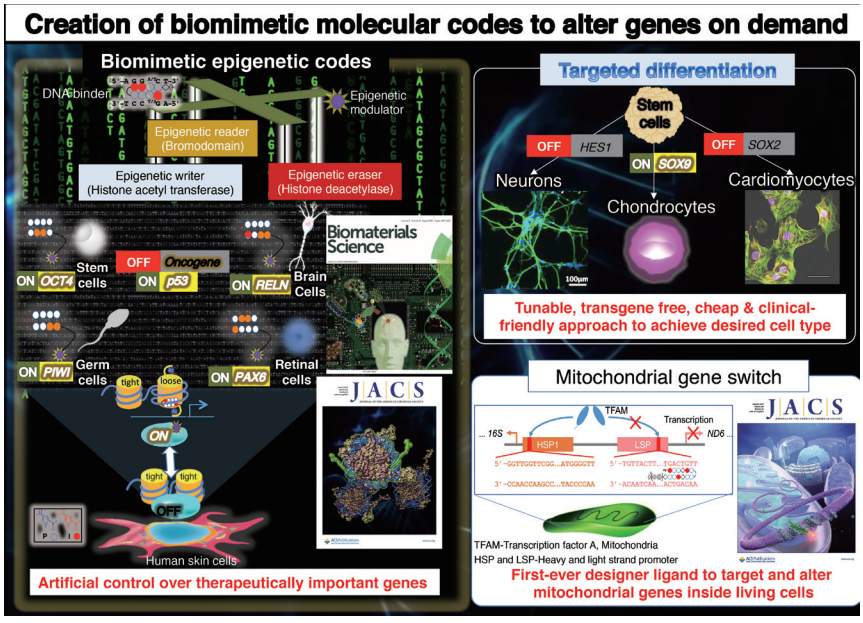
Ganesh Pandian Namasivayam Lab

Biomimetic Epigenetic Codes, Therapeutic Gene Modulation

Faculty Members Ganesh Pandian Namasivayam (Junior Associate Professor / PI)

Research Overview

The modern sequencing techniques and 'Omics' tools aid us to unlock the cell's secret codes associated with cell fate control and complex diseases. Still, there is a considerable gap between the accumulated knowledge database and the available tools to modulate them at the right place and time. **Our lab harnesses key biological information and creates biomimetic synthetic molecular codes to switch ON and OFF the therapeutically important genes in a spatial-temporal manner.** We integrate synthetic modulators of epigenetic enzymes with programmable DNA-binding small molecules and design biomimetic epigenetic codes capable of scripting **artificial control over genes and non-coding RNAs associated with germ cells, stem cells, retinal cells, cancer cells, Alzheimer's, autism** and obesity. Likewise, we design synthetic molecular codes to **alter the gene transcription program inside the stem cells and coax them into desired cell types** like functional cardiomyocytes, chondrocytes and neurons. Encouraged with the success of our first-ever mitochondrial gene switch called MITO-PIP, we are advancing our molecular codes to **script chemical control over the mitochondrial genes** associated with rare diseases. Because the patients and clinicians favor the use of small molecules over biological drugs, our synthetic molecular codes have potential applications in therapeutic gene modulation and regenerative medicine.



Creation of smart biomaterias to control cell fate

Selected Papers

J Taniguchi, Ganesh N Pandian, Y Feng, F Hashiya, T Hidaka, K Hashiya, S Park, T Bando, S Ito and H Sugiyama, Biomimetic artificial epigenetic code for targeted acetylation of histones. *J Am Chem Soc* **140**, 7108-7115 (2018)

T Hidaka, Ganesh N Pandian, J Taniguchi, T Nobeyama, K Hashiya, T Bando, H Sugiyama, Creation of a synthetic ligand for mitochondrial DNA sequence recognition and promoter-specific transcription suppression. *J Am Chem Soc* **139**, 8444-8447 (2017)

J Taniguchi, Ganesh N Pandian, T Hidaka, K Hashiya, T Bando, K Kim, H Sugiyama, A synthetic DNA-binding inhibitor of SOX2 guides human induced pluripotent stem cells to differentiate into cardiac mesoderm. *Nucleic Acids Res* **45**, 9219-9228 (2017)

Ganesh N Pandian, H Sugiyama, Nature-inspired design of smart biomaterials using the chemical biology of nucleic acids. *Bull Chem Soc J* **89**, 843868 (2016)

Ganesh N Pandian, J Taniguchi, S Junetha, S Sato, C Anandhakumar, A Saha, T Bando, H Nagase, H Sugiyama. Distinct DNA-based epigenetic switches trigger transcriptional activation of silent genes in human dermal fibroblasts. *Sci Rep* **4**, e3843 (2014)

Daniel Packwood Lab

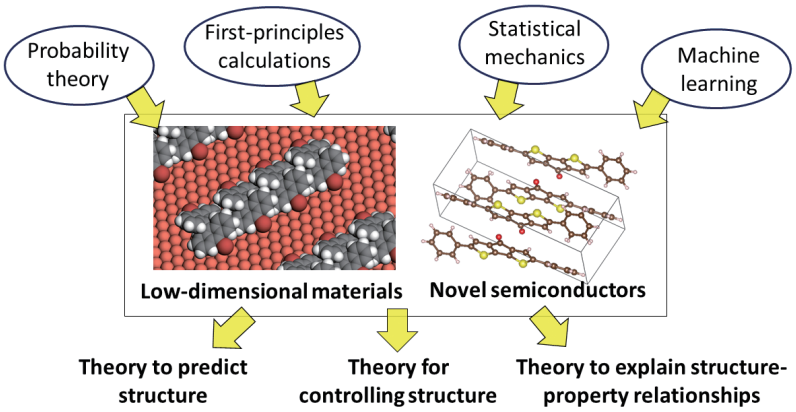
Theoretical Chemistry, Applied Mathematics

Faculty Members Daniel Packwood (Junior Associate Professor / PI)

Research Overview

Creating novel functions by careful design of a material's nano-scale structure is the essence of materials science. By devising novel theories and computational techniques, our group aims to elucidate design principles for next-generation thin film materials, semiconductors, and others. In order to elucidate such design principles, we utilize a mixture of computational physics, mathematical modeling, and information science, and focus our efforts on predicting the nano-scale structure of materials and elucidation of structure-property relationships in materials (Figure 1). By collaboration with experimental groups at iCeMS and elsewhere, we seek to test our theoretical predictions in the laboratory while creating a paradigm of 'theory-driven materials science'.

By turning our approach to a variety of materials, we have succeeded to create theories for predicting the structure of two-dimensional molecular assemblies, predicting the composition of thin film oxide materials, and explaining charge transport properties in organic semiconductors. Our work on two-dimensional molecular assemblies has also allowed us to deduce new rules for controlling the molecular self-assembly process on metal surfaces. Moving forward, we aim to deduce material design principles by rigorous analysis of these theories, while simultaneously expanding these theories to broader classes of materials. Moreover, we try as much as possible to interact with iCeMS cell biology researchers, and hope to obtain hints for materials design by considering the assembly of functional objects in the cell.



Selected Papers

D M Packwood, T Hitosugi, Material informatics for self-assembly of functionalized organic precursors on metal surfaces. *Nat Commu* **9**, 2469 (2018)

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

D M Packwood, *Bayesian Optimization for Materials Science*. SpringerBriefs in the Mathematics of Materials (volume 3). Springer, Singapore (2017)

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

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.

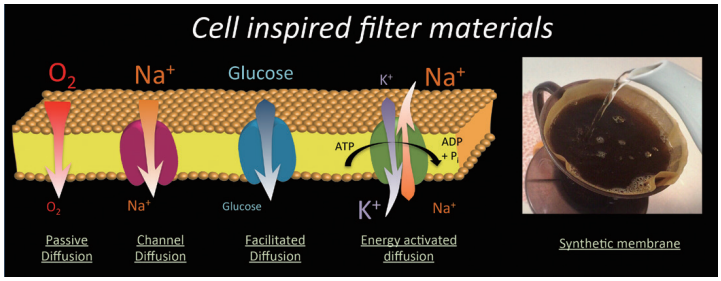
In recent years we have delivered notable biomaterials research papers on intelligent scaffolds to interrogate the factors that influence cell migration. One example is well-defined scaffolds to determine the role of 3-D architectures on cell migration (Biomaterials **31**, 2201-2208, 2010).

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.

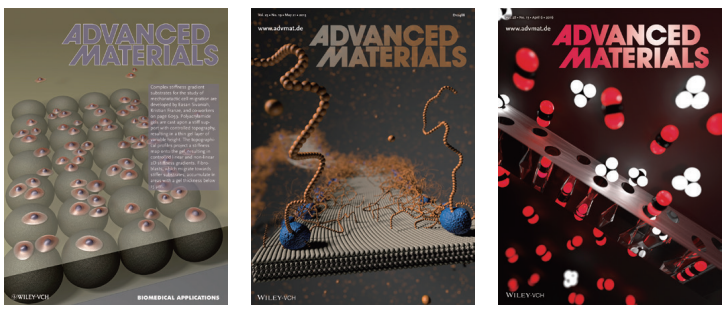
Although soft-matter bionanotechnology forms one key part of our research, our approach is to mix both synthetic and biosynthetic methods of materials development (with a current primary focus in **achieving energy efficiency and environmental targets in separation technology).**

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.



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.

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. *Nat Energy* **2**, 17086 (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. *Adv Mater* **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. *Nat Commun* **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. *Nat Commun* **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. *Adv Mater* **25** (19), 2661-2665 (2013)

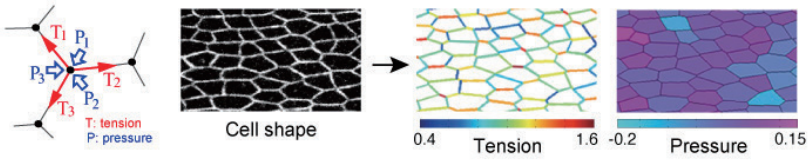
Kaoru Sugimura Lab

Biophysics, Developmental Biology

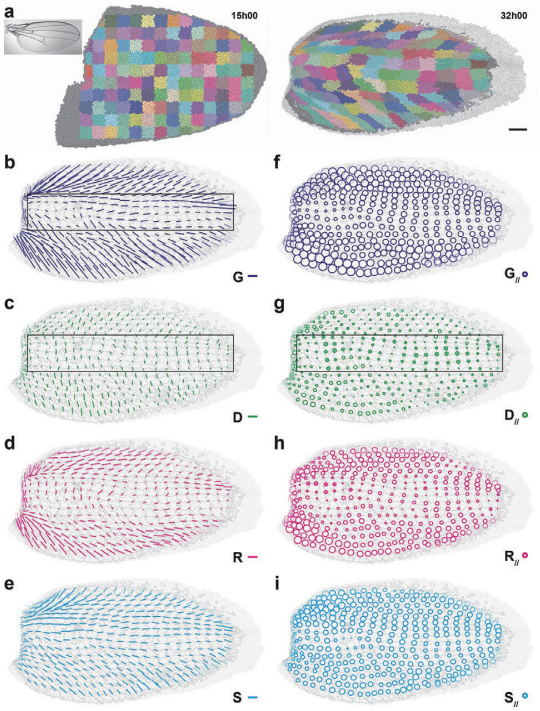
Faculty Members Kaoru Sugimura (Program-Specific Research Center Associate Professor / PI)

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.



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) .(eLife **4**: e08519 (2016))

Selected Papers

K Ikawa, K Sugimura, AIP1 and cofilin ensure a resistance to tissue tension and promote directional cell rearrangement. *Nat Commun* **9**, 3295 (2018)

M Arata, K Sugimursa, T Uemura, The difference in Dachsous amounts between migrating cells coordinates the direction of collective cell migration. *Dev Cell* **42**, 479-497 (2017)

S Ishiahra, P Marcq, K Sugimura, From cells to tissue: A continuum model of epithelial mechanics. *Phys Rev E* **96**, 022418 (2017)

Ishimoto Y, Sugimura K A mechanical model for diversified insect wing margin shapes. *J Theor Biol* **427**, 17-27 (2017)

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

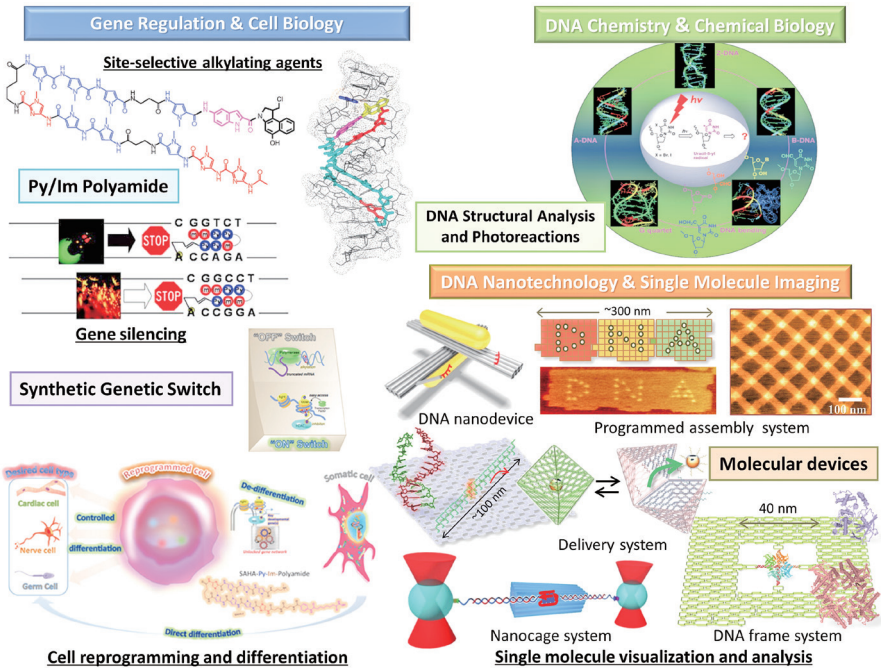
Hiroshi Sugiyama Lab

Chemical Biology

Faculty Members Hiroshi Sugiyama (Adjunct PI)

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 various diseases.



Selected Papers

S Jonchhe, S Pandey, T Emura, K Hidaka, M A Hossain, P Shrestha, H Sugiyama, M Endo, H Mao, Decreased water activity in nanoconfinement contributes to the folding of G-quadruplex and i-motif structures. *Proc Natl Acad Sci USA* 115, 9539-9544 (2018)

T Masubuchi, M Endo, R Iizuka, A Iguchi, D H Yoon, T Sekiguchi, H Qi, R Iinuma, Y Miyazono, S Shoji, T Funatsu, H Sugiyama, Y Harada, T Ueda, H Tadakuma, Construction of integrated gene logic-chip. *Nat Nanotechnol* 13, 933-940 (2018)

J Taniguchi, Y Feng, G Pandian, F Hashiya, T Hidaka, K Hashiya, S Park, T Bando, S Ito, H Sugiyama, Biomimetic Artificial Epigenetic Code for Targeted Acetylation of Histones. *J Am Chem Soc* **140**, 7108-7115 (2018)

P Shrestha, S Jonchhe, T Emura, K Hidaka, M Endo, H Sugiyama, H Mao, Confined Space Facilitates G-quadruplex Formation. *Nat Nanotechnol* **12**, 582-588 (2017)

T Hidaka, G Pandian, J Taniguchi, T Nobeyama, K Hashiya, T Bando, H Sugiyama, Creation of a Synthetic Ligand for Mitochondrial DNA Sequence Recognition and Promoter-Specific Transcription Suppression. *J Am Chem Soc* **139**, 8444-8447 (2017)

Jun Suzuki Lab

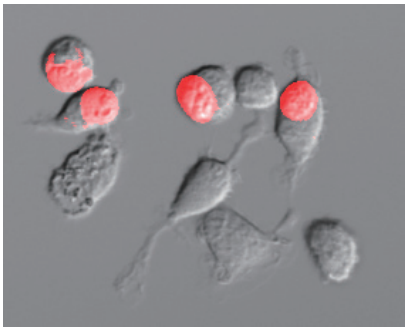
Medical Biochemistry, Cell Membrane Biology

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

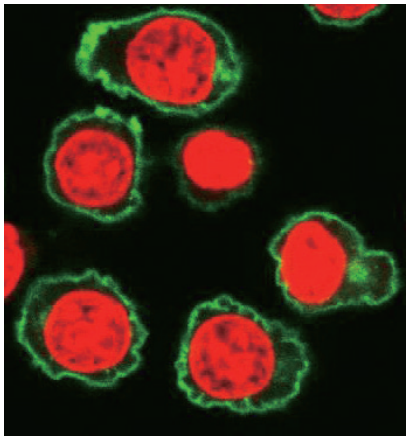
Research Overview

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.

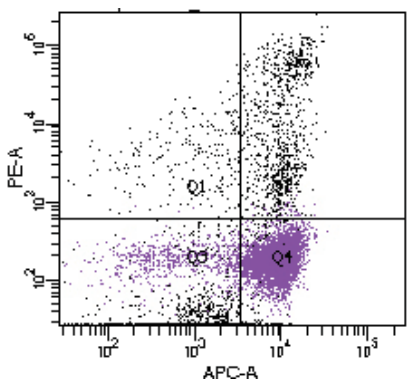
To identify PS-exposing proteins (called scramblases), we performed functional **screening** and identified the long sought proteins. During this process, we established several assay systems to investigate on membrane proteins. In my laboratory, we will keep studying the identified membrane proteins, 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.



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.

Selected Papers

S Gyobu S, K Ishihara, J Suzuki, K Segawa, S Nagata, Characterization of the scrambling domain of the TMEM16 family. *Proc Natl Acad Sci USA* **114**, 6274-6279 (2017)

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)

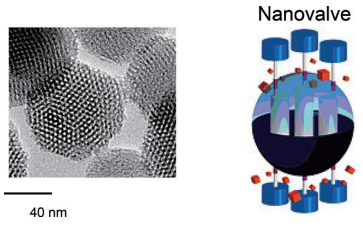
Fuyuhiko Tamanoi Lab

Cancer Research, Nanoparticle-Based Therapy

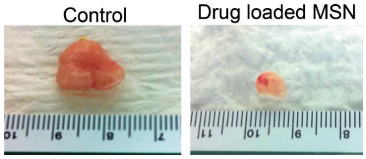
Faculty Members Fuyuhiko Tamanoi (Program-Specific Professor / PI)

Research Overview

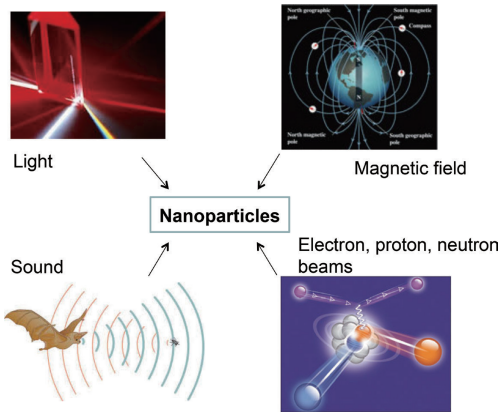
Nanoparticles provide valuable reagents for cancer therapy. These nano-sized materials accumulate in the tumor due to leaky vasculature at the tumor site. In addition, surface modification of nanoparticles enables their preferential uptake into cancer cells. We use nanoparticles called **mesoporous silica 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.



Mesoporous silica nanoparticles and nanovalves.



Tumor growth inhibition by MSN-mediated anticancer drug delivery.



Nanoparticles that respond to external cues.

Selected Papers

V Binh, S Shahin, J Croissant, Y Fatieiev, K Matsumoto, T Le-Hoang Doan, T Yik, S Simargi, A Conteras, L Ratliff, C Mauriello Jimenez, L Raehm, N Khashab, J-O Durand, C Glackin, F Tamanoi, Chick chorioallantoic membrane assay as an in vivo model to study the effect of nanoparticle-based anticancer drugs in ovarian cancer. *Scientific Reports* **8**, 8524 (2018)

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)

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)

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)

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 LiNbO3 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 wavesand related THz science and technologies including:

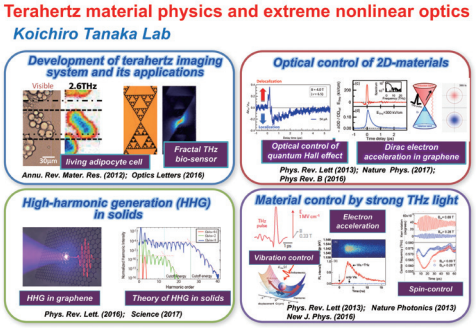
1. Biological applications of **THz near-field microscopy.** We hav developed a special sensing crystal that enables us to convert the THz near-field image to a visible image using a non-linear optical process inside the sample mount. The current target for special resolution is below 5 micrometers. 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)

Y Onishi, Z Ren, K Segawa, W Kaszub, M Lorenc, Y Ando, K Tanaka, Ultrafast carrier relaxation through Auger recombination in the topological insulator Bi1.5Sb0.5Te1.7Se1.3. *Phys Rev B* **91**, 085306 (2015)

T Kampfrath, K Tanaka, K A Nelson, Resonant and nonresonant control over matter and light by intense terahertz transients. *Nat Photon* **7**, 680-690 (2013)

Motomu Tanaka Lab

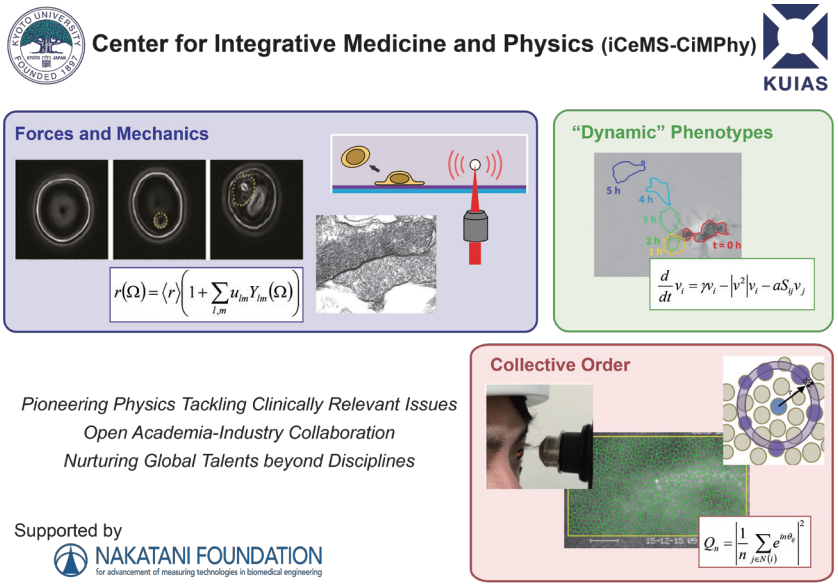
Medical Physics, Soft Matter Physics

Faculty Members Motomu Tanaka (Adjunct PI)

Research Overview

The PI of our Lab, Prof Motomu Tanaka, has developed his academic career over 20 years and holds a chair in Heidelberg University, which is the most historical university in Germany (established in 1386). In April 2018, we launched "Center for Integrative Medicine and Physics" as a newly established, endowed department in Kyoto University Institute for Advanced Study, supported by the Nakatani Foundation. Since our Lab in Japan started in 2013 in iCeMS, we sustain our scientific cooperation with iCeMS.
One of our core scientific missions is to open up a new scientific field through the integration of medicine and physics.

We strongly believe it's time for physicists to graduate from oversimplified toy models and tackle clinically relevant issues by dealing with human samples. This requires not only a paradigm shift in research, but also a cross-institutional network of scientists who are willing to jump into cold water. Therefore, one of the obvious contributions to the society is to nurture younger talents who can perform top-level research in a global scene. In addition to the activities in academia, this Center opens up collaboration with various industry partners, so that our scientific findings can be used for the society.



Cimphy: Concept of our department

Selected Papers

C Monzel, AS Becker, R Saffrich, P Wuchter, V Eckstein, A D Ho, M Tanaka, Dynamic cellular phenotyping defines specific mobilization mechanisms of human hematopoietic stem and progenitor cells induced by SDF1α versus synthetic agents. *Sci Rep* **8**, 1841 (2018)

T Ohta, C Monzel, AS Becker, AD Ho, and M Tanaka, Simple physical model unravels influences of chemokine on shape deformation and migration of human hematopoietic stem cells. *Sci Rep* 8,10630 (2018)

H Rieger, H Y Yoshikawa, K Quadt, M A Nielsen, C P Sanchez, A Salanti, M Tanaka, M Lanzer, Cytoadhesion of P. falciparum-infected erythrocytes to chondroitin-4-sulfate is cooperative and shear-enhanced. *Blood* **125**, 383 (2015)

E Schneck, T Schubert, O V Konovalov, B E Quinn, T Gutsmann, K Brandenburg, R G Oliveira, DA Pink, M Tanaka, Quantitative determination of ion distributions in bacterial lipopolysaccharide membranes by grazing-incidence X-ray fluorescence. *Proc Natl Acad Sci USA* **107**, 9147 (2010)

M Tanaka, E Sackmann, Polymer-supported membranes as the model of cell surfaces. *Nature* **437**, 656 (2005)

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:

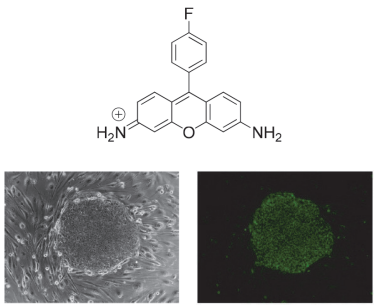
1. We are revealing the physiological roles of **ABC proteins** in pluripotent **ES and iPS cells**, and developing small-molecule fluorescent probes specific for **ES and iPS cells**. These compounds can be used to identify pluripotent **ES and iPS cells** and will be a useful tool for basic cell biology 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.**

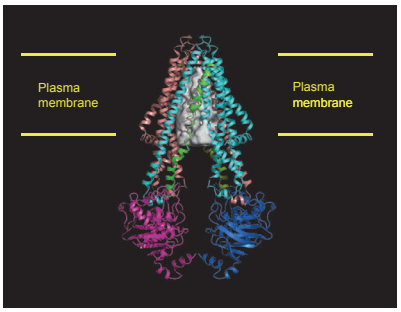
3. ABCA1 and ABCG1 are key molecules for generating plasma **meso-particle** high-density lipoprotein (HDL), which is so-called "good cholesterol" and critical for cholesterol homeostasis. Furthermore, it is suggested that they reorganize some **meso-domains** on the plasma membrane and modulate immune 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.



1. Fluorescent probe for human ES/iPS cells



2. Multi-drug recognition mechanism by MDR1

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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)

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Motonari Uesugi Lab

Chemical Biology

Faculty Members Motonari Uesugi (Adjunct PI)

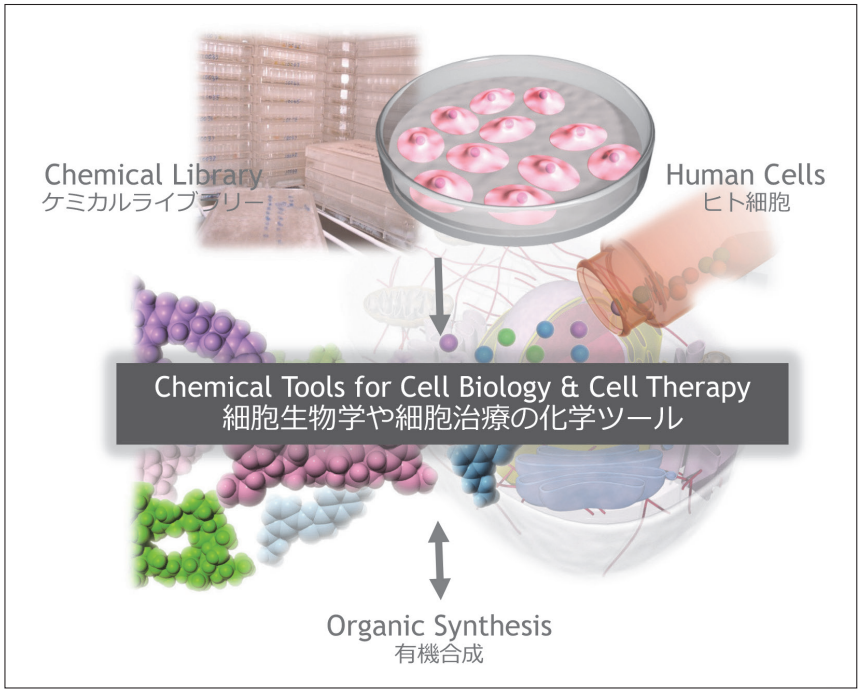
Research Overview

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 a 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.



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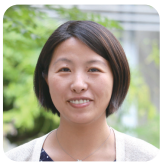


Dan Ohtan Wang Lab

Neurosciences, RNA Biology

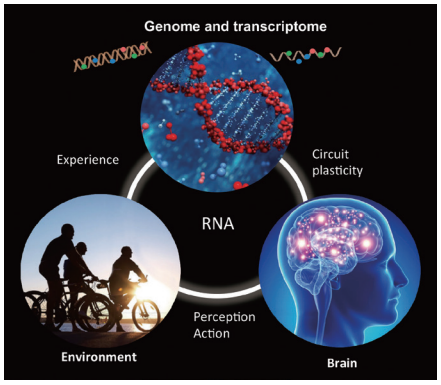
Faculty Members Dan Ohtan Wang (Program-Specific Research Center Associate Professor / PI)

Research Overview

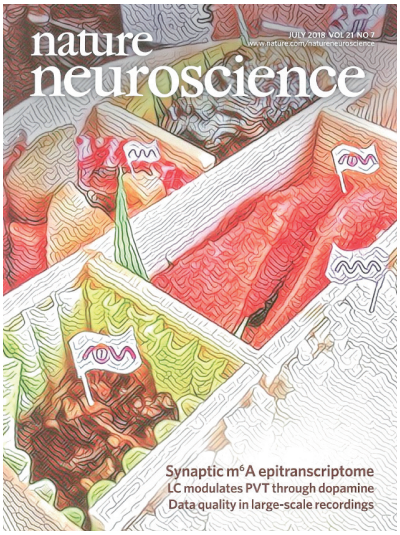
Our group studies the molecular and cell biological mechanisms of learning-related neuronal plasticity, a process in which the strength and the number of synaptic connections between neurons are altered by experience. Such structural and functional changes in our brain can be activity-dependent and mediated 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.



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



Our work on “RNA methylation at synapses” featured on the cover of Nature Neuroscience (2018)

Selected Papers

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Research Administration Office

Mitsuru Hashida (Program-Specific Professor / Research Administrative Director)

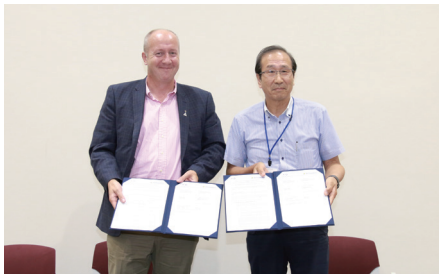
The Research Administration Office was founded to 1) promote brain circulation between iCeMS and domestic and international universities and institutes, 2) enhance international research networks, and 3) apply the research outcomes of iCeMS to society. In April 2017, the Analysis Center was founded in the Research Administration Office. The Innovation Unit and the Public Engagement Unit began operating in December 2017 and April 2018, respectively.
In 2007, iCeMS was designated as a World Premier International (WPI) Research Center by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and was supported by MEXT for 10 years. Since 2017, iCeMS has been a member of the WPI Academy. Within the WPI Academy, the iCeMS Research Administration Office will strive to establish a world-class research environment by employing cutting-edge approaches and measures, sharing good practices across the entire university, and enhancing collaboration with other WPI Research Centers.

Innovation Unit

Hiroyuki Takigawa (Program-Specific Associate Professor / Unit Leader)
Eiji Fujii (Program-Specific Junior Associate Professor)

To strengthen the research base of iCeMS, the Innovation Unit plans, performs, and provides support for diverse measures to promote financial support (external funding, donation, and other resources) and human exchange (academic exchange, industry-academia collaboration, technology transfer, etc.).

- **iCeMS fund-establishing project**
  Planning for fund sourcing
  Fundraising activities
- **External funds-sourcing project**
  Development of strategies to acquire intellectual properties
- **Collaboration with external institutes**
  Agreement on academic exchange
  Industry-academia collaboration



MoU with AO Research Institute Davos of Switzerland

Smart Materials Research Center, a locally operated laboratory

Public Engagement Unit

Mari Toyama (Program-Specific Associate Professor / Unit Leader)
Izumi Mindy Takamiya (Program-Specific Assistant Professor)
Takayuki Homma (Program-Specific Assistant Professor)

The Public Engagement Unit focuses on outreach activities as well as domestic and international public relations to share iCeMS research outcomes. With these activities, this Unit aims to eventually promote international brain circulation.

- **Public relations**
  Development of public relation (PR) strategies
  Planning and production of PR brochures, websites, videos, and merchandise
- **Outreach activities**
  Planning for public events, seminars, etc
- **Spreading research outcomes**
  Press releases and other means of distribution
- **Planning for exchange of researchers**
  Researcher internationalization program
  Planning and organizing international research conferences

iCeMS Newsletter

Science Festival for high school students from Japan and Singapore

iCeMS Analysis Center

Mineko Kengaku (Professor / Center Director)
Takayuki Homma (Program-Specific Assistant 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 handson 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

Takahiro Fujiwara
(Program-Specific Associate Professor / Unit Leader)

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 superresolution 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

Masakazu Higuchi
(Program-Specific Assistant Professor / Unit Leader)

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).

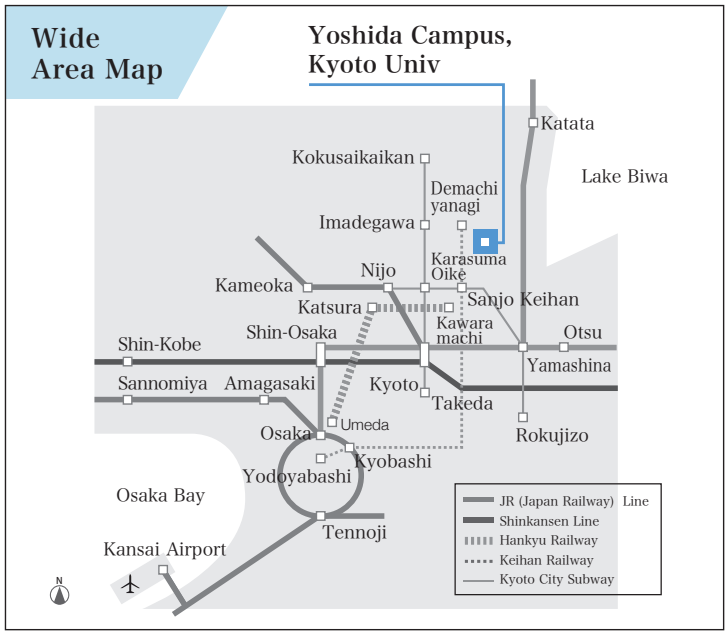
Evaluation — The Unit also provides measurement and analysis support necessary for the quantitative determination of materials contained in reaction systems (GC-MS), partial structural analysis for organic molecules (FT-IR), absorption tests for porous materials (e.g. BET specific surface area analysis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

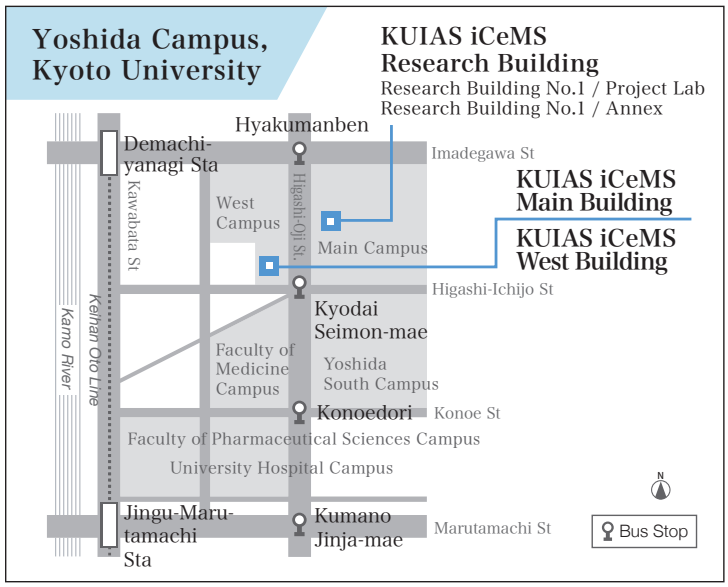
Preparation — The sample preparation for electron microscopy and ICP, and handling of hazardous substances using a fume hood are also available.

Access

KUIAS iCeMS Main Building
KUIAS iCeMS 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)





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