Institute for Integrated Cell-Material Sciences

A Research Institute to Expand Knowledge by Integrating Cell and Material Science

The mission of iCeMS is to create new chemicals for the elucidation and control of cellular functions. We are also committed to developing sophisticated cell-inspired materials, which can contribute solutions to problems such as disease diagnosis/treatment and environmental pollutant cleanup. iCeMS' research horizons extend far beyond the borders of any single existing field. We therefore conduct our research by crossing different perspectives from multiple fields of study (interdisciplinary research) such as biology, chemistry, physics, engineering and mathematics. Researchers at iCeMS share ideas and inspire each other as they work together to pursue their research objectives.

Research Center's Information (FY 2015)

Center Director: Susumu Kitagawa (up to 2012:Norio Nakatsuji)
Principal Investigators (PI): 25 (including 6 overseas researchers and 3 female researchers)
Other Researchers: 149 (including 44 overseas researchers and 34 female researchers)
Research Support Staff: 124
Administrative Division:
  Administrative Director: Shinji Tomita
  Administrative Staff: 27 (percentage of bilingual staff: 50%)
Satellites and Cooperative Organizations: Gifu University, Japan; National Centre for Biological Sciences (NCBS), India; Institute for Stem Cell Biology and Regenerative Medicine (inStem), India; UCLA California NanoSystems Institute (CNSI), USA; Heidelberg University, Germany; Vidyasirimedhi Institute of Science and Technology (VISTEC), Thailand; and others
URL: http://www.icems.kyoto-u.ac.jp/en/

iCeMS
KYOTO UNIVERSITY
WPI Research Center

Major Research Achievements

1 Successful regulation of the fate of neural stem cells by light technology

The oscillatory expression of the transcription factor Mash1 leads to maintenance and proliferation of neural stem cells, while steady Mash1 expression induces neuronal differentiation. We control such Mash1 expression dynamics by light technology to enable regulation of the proliferation and differentiation of neural stem cells.

2 Epigenetics drive cancer development

Cancer cells harbor changes in epigenetic modifications. However, the contributions of altered epigenetic modifications to cancer development remains to be fully understood. Taking advantage of properties of iPS cell technology, we demonstrate that epigenetic regulation can drive particular types of cancer.

3 Cell-inspired porous materials

The simultaneous implementation of "selection" and "storage" of matter is a basic aspect of compartmentalization within cells. We create artificial materials called porous coordination polymers (PCPs) that efficiently and inherently store and select small molecules. However, we seek to mimic cellular systems that do this in massively sequential ways and have developed several strategies to control sequential storage and selection in such cell-inspired compartments.

4 Mechanisms of ABC proteins involved in optimal health maintenance

ABC proteins maintain optimal health in several ways, including eliminating various toxic compounds from cells and generating HDL-cholesterol. We reveal the functional mechanisms of ABC proteins by determining 3D-structures and visualizing them at the single molecule level.

5 Generation of functional oocytes from mouse pluripotent stem cells

We succeeded in inducing mouse embryonic stem cells (ESCs)/induced pluripotent stem cells (iPSCs) into primordial germ cell-like cells (PGCLCs). When aggregated with embryonic ovarian somatic cells and transplanted in mice, the PGCLCs differentiated into oocytes that contributed to fertile offspring.

6 Chemical tools for programming stem cells

Realization of regeneration therapy requires new technologies that coax stem cells to differentiate or behave as we desire. We have developed several such cell-controlling technologies by combining chemistry and cell biology.

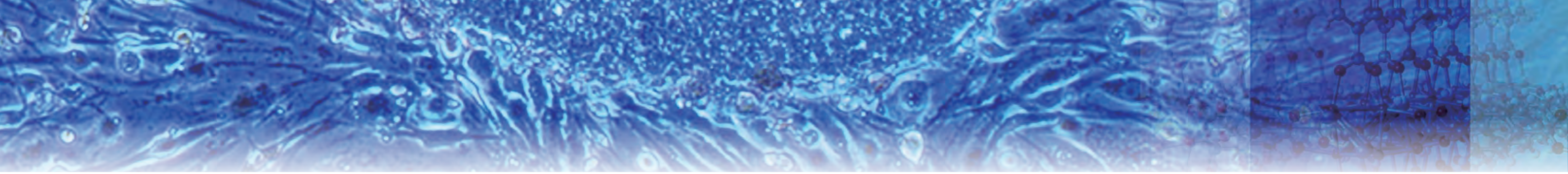
Research Paper's Information

Number of Research Papers:	1,477
Top 10% Papers:	25.4%
Top 1% Papers:	4.3%
Internationally Collaborative Research Papers:	22.2%

(Database: WoS between 2007-2015)

The background images are human iPS cells and porous coordination polymers (PCPs) with a jungle gym-like molecular structure.

Yoshida Ushinomiya-cho, Sakyoku, Kyoto Japan 606-8501, Japan
Phone: +81-75-753-9753
Email: info@icems.kyoto-u.ac.jp



Research Background

Biological phenomena are explainable as an integration of chemical reactions. If we can precisely explain these phenomena by the principles of chemistry, it should be possible to imitate and reproduce cellular functions using chemical substances.

The idea to explain cellular functions by chemistry per se is not necessary a new concept. In the classic research discipline of biochemistry, cellular functions are illuminated at the molecular level starting with proteins; whereas, in molecular biology, cellular functions are approached by studying DNA.

In contrast, cell biology developed to understand the entire living organism starting with cells. This field has bloomed into embryonic stem (ES) cell and induced pluripotent stem (iPS) cell research. The attempt to unveil the secrets of cellular functions by beginning from proteins and DNA, and the effort to explain living organisms starting from cells, have both contributed to the development of pharmaceutical and biotechnology industries.

Taking the next step in the history of cellular function study, iCeMS now focuses on the "mesoscopic" point of view. This is neither "macroscopic", like observing cells in the field of cell biology, nor "microscopic", like investigating proteins and DNA in the fields of biochemistry and molecular biology, but somewhere in the middle of these two. This region, which ranges from a few tens to a few hundreds of nano meters (1 nano meter is one billionth of a meter) is the border that separates life and material. We believe that by studying this boundary region, we can understand the vital activity of cells as the chemical reactions of materials and ultimately mimic the functions of living organisms using materials. In this way, we can contribute to treating diseases and promoting a healthy society.

Research Purpose

The purpose of iCeMS is to expand current knowledge by approaching this unexamined border between life and materials. To be more precise, we try to design and utilize novel materials to better understand and control cellular functions. Our future goal is to develop unique, cell-inspired materials to apply to problems, such as the diagnosis and treatment of diseases or the purification of environmental pollutants.

To approach this challenge, iCeMS researchers of various specialties, such as biology, chemistry, physics, mathematics, and engineering, collaborate to integrate their knowledge. Cells produce various chemical substances and utilize them to maintain vital activity. The behaviors of these materials change dynamically both temporally and spatially inside cells. Therefore, development of various visualization techniques and modeling approaches, along with analysis systems to understand complicated cellular activities using physical and chemical approaches, are required to create novel materials to regulate cellular functions. The representative research areas in our institute can be divided into 3 areas: A: Nucleus information, B: Membrane compartments, and C: Cell communication. (Fig1,2)

Achievements

A: Nucleus information

The nucleus of a cell regulates the storage and utilization of cellular information. Our challenge at iCeMS is to unveil the mechanisms of the dynamic remodeling of the nucleus structure, which is accompanied by proliferation, initialization, reorganization, and the readout of genetic information. To do this, we aim to develop techniques to visualize

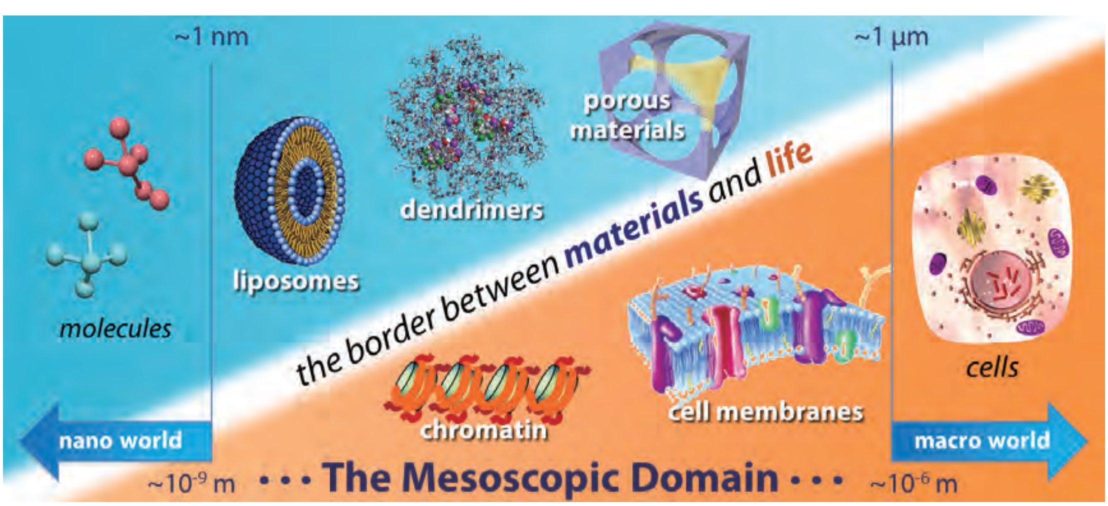


Fig. 1 Mesoscale region: The border between materials and life (from 10^{-9} m ~10^{-6} m)

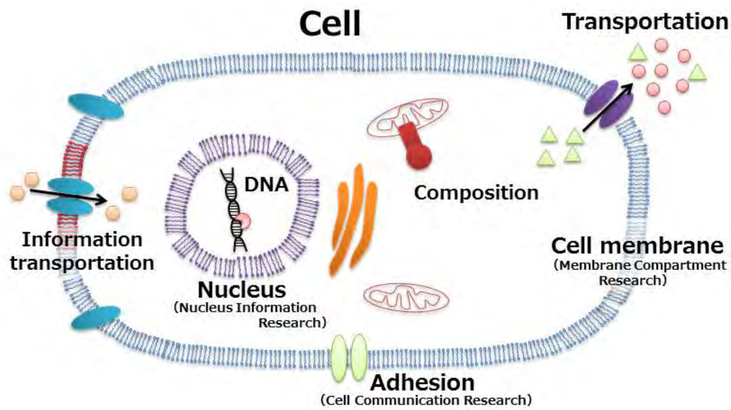


Fig. 2. A model of cells and cell functions as they related to the research areas of iCeMS

and control information transformation inside the nucleus using light-responsive materials and functional molecules.

1 Successful regulation of the fate of neural stem cells by light technology

Ryoichiro Kageyama (PI)

Neural stem cells have the ability to give rise to various types of neurons while proliferating. However, the technology to control this capability has not been established. Time-lapse imaging of gene expression at the single-cell resolution revealed that the expression of the transcription factor Mash1 is oscillatory in neural stem cells but steady in differentiating neurons. Furthermore, control of Mash1 expression dynamics by light technology showed that this oscillatory expression leads to the proliferation of neural stem cells, while steady expression induces neuronal differentiation. This light technology now enables us to control the fate of neural stem cells at will. This opens the way to regulate endogenous neural stem cells, a feat which has been difficult until now. Even in the adult brain there are neural stem cells, although they are mostly dormant. If we can induce such endogenous neural stem cells to proliferate and differentiate into neurons using our light technology, we can apply this method to developing therapies for various neural disorders.(Fig.3)

Kageyama, R et al., Science 342, 1203 (2013)

2 Epigenetics drive cancer development

Yasuhiro Yamada (Professor)

Cancer is believed to arise primarily through the accumulation of genetic mutations. Research shows that cancer cells also harbor changes in epigenetic modifications. However, the contribution of altered epigenetic modifications to cancer development remains to be fully understood.

Induced pluripotent stem cell (iPSC) technology can actively modify epigenetic regulation without affecting the genomic information. We developed a murine system in which iPS cells can be established through the forced expression of reprogramming factors in vivo. We demonstrated that transient expression of reprogramming factors in vivo results in the development of kidney cancers that exhibit global changes in epigenetic modifications. We next established iPS cells from kidney cancer cells. Notably, kidney cancer-derived iPS cells gave rise to non-

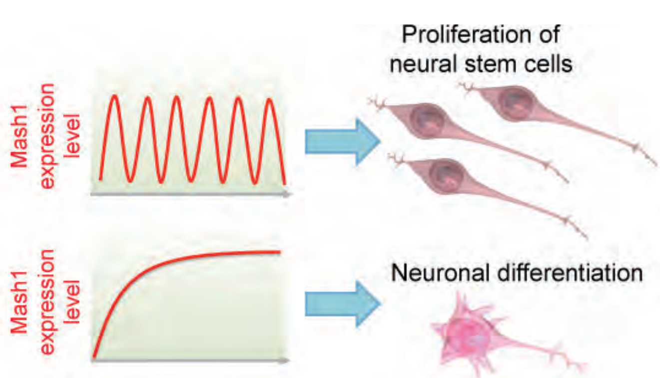


Fig.3. By using the light-responsive protein GAVPO, we can switch on and off the Mash1 expression with blue light and dark conditions. With this method, we can induce oscillatory and steady expression of Mash1, which activates proliferation of neural stem cells and neuronal differentiation, respectively.

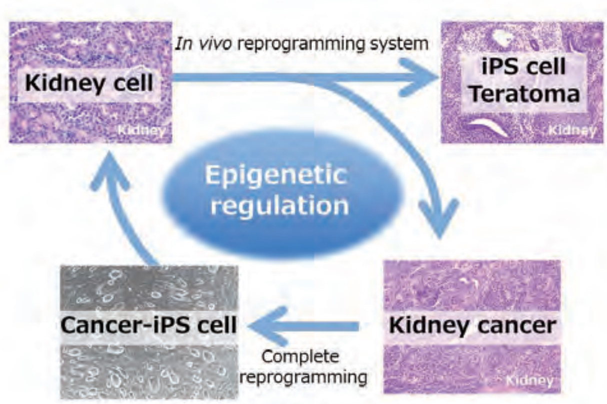


Fig.4. Epigenetic regulation controls the fate of cancer cells

neoplastic kidney cells in mice, proving that they did not undergo irreversible genetic transformation. These findings suggest that epigenetic regulation associated with iPSC derivation may drive the development of particular types of cancer and could be a potential target for cancer treatment. (Fig.4.)

Yamada, Y et al. , Cell 156, 663 (2014)

B: Membrane compartment

Cellular membranes coordinate the selection and concentration of materials and information inside and outside of cells. In other words, membranes regulate signal conversion, energy conversion and material exchange flowing from the inside to the outside of cells and vice versa. At iCeMS, we aim to clarify the principles of these membrane-region reactions and are developing environmentally-sensitive molecules and molecular assemblies to regulate the above-mentioned conversion reactions by light, heat, or magnetic stimuli.

3 Cell-inspired porous materials

Susumu Kitagawa (PI),
Shuhei Furukawa (Associate Professor)

The simultaneous implementation of "selection" and "storage" of molecules and ions is a basic aspect of compartmentalization within cells, which regulates the balance of substances inside cells. We create artificial materials called porous coordination polymers (PCPs), which possess a structure of billions of nanosized pores that efficiently and inherently store and select small molecules. Our group's key achievement is to realize the synthesis of transformable pores in a fashion similar to proteins. Our new PCPs transform their structure when incorporating target molecules, giving rise to high molecular selectivity. One of the important industrial applications of this type of transformable pore structure is to selectively trap carbon monoxide molecules.

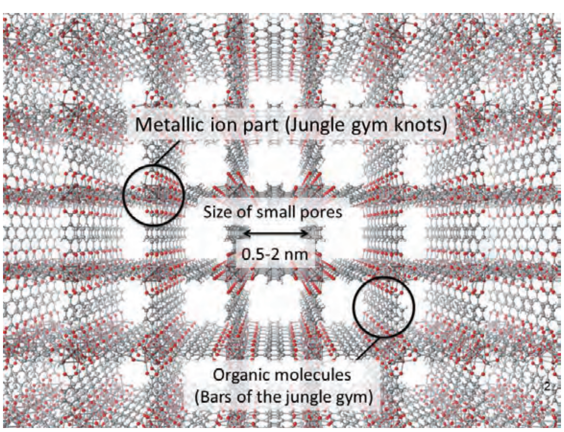


Fig.5: Crystal structure of one example of a porous coordination polymer (PCP). It possesses a jungle gym-like molecular structure and inherent voids as nanosized pores.

Generally, these PCP materials are fabricated as micrometer-sized crystalline powders; however, with new mesoscale chemistry, we can shape materials into a variety of morphologies. For instance, shaping PCPs into a hollow box structure, like a cell membrane, allows for controlling internal molecular balance to improve the selection efficiency for target organic molecules. (Fig.5)

Furukawa, S et al. , Science 339, 193 (2013)

4 Mechanisms of ABC proteins involved in optimal health maintenance

Kazumitsu Ueda (PI)

Membranes define the boundaries of all cells of the body and separate the intra- from the extra-environment. ABC proteins function on cellular membranes as transporters, which eliminate various toxic or nonessential compounds from cells and maintain optimal health. Collaboration among iCeMS research groups have revealed several functional mechanisms of human ABC proteins that contribute to improving health.

The mechanism of the multidrug exporter MDR1, an ABC protein that eliminates various structurally unrelated toxic compounds from cells, has been unclear for a long time. By determining the 3D-structure of MDR1 at the highest resolution we have revealed its mechanism.

Cholesterol is an indispensable component of our bodies, whose concentration is elaborately regulated. Furthermore, 'good' cholesterol (HDL) is invaluable in preventing heart disease. We have also established the mechanism of ABCA1, a key protein for HDL generation, by observing its movement on membranes at the single molecule level.

In humans 48 ABC proteins play important physiological roles. Functional defects are related to

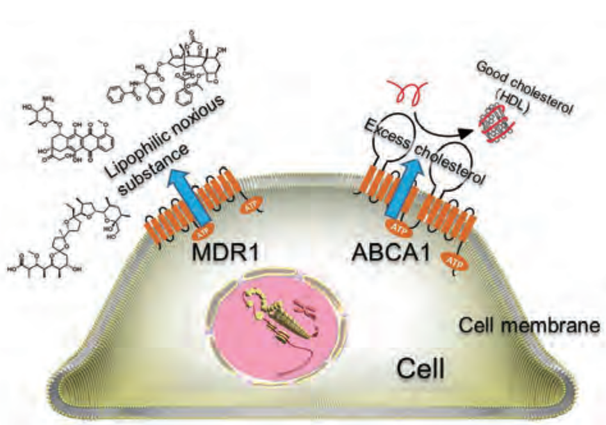


Fig.6 ABC proteins help maintain optimal health by eliminating toxic compounds from cells and generating HDL-cholesterol.

various diseases, such as atherosclerosis, diabetes, gout and Alzheimer's disease. Improving the understanding of ABC protein structures and mechanisms through this work at iCeMS will help the prevention and cure of these diseases.(Fig.6)

Ueda, K et al., Proc. Natl. Acad. Sci. U. S. A. 111, 4049 (2014)

C: Cell communication

The proliferation from stem cells to specific tissues in multi-cellular organism is a process that is strictly controlled by cell-cell and/or cell-material interactions. At iCeMS, we strive to decipher these mechanisms to design and create scaffolding materials at the molecular level. This allows us to regenerate the structure and functions of organs such as the brain, cardiac muscle, and the reproductive system.

5 Generation of functional oocytes from mouse pluripotent stem cells

Mitinori Saitou (PI)

The germ cell lineage differentiates into spermatozoa and oocytes and contributes to new individuals, thereby transmitting genetic information to new generations. Understanding the mechanism of germ cell development contributes to the development of reproductive medicine/technology, stem cell biology, and regenerative medicine.

iCeMS has been investigating germ cell development using the mouse as a model organism. Based on this achievement, iCeMS succeeded in inducing mouse embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) into primordial germ cell-like cells (PGCLCs). When transplanted into neonatal testes lacking endogenous germ cells, PGCLCs contributed to spermatogenesis and fertile offspring. Similarly, when PGCLCs were aggregated with embryonic ovarian somatic cells and transplanted in mice, the PGCLCs differentiated into oocytes that, upon fertilization and transfer to foster mothers, led to fertile offspring. These findings are the first to demonstrate the feasibility of generating germ cells in culture dishes. (Fig.7)

Saitou, M et al., Science 338, 971 (2012)

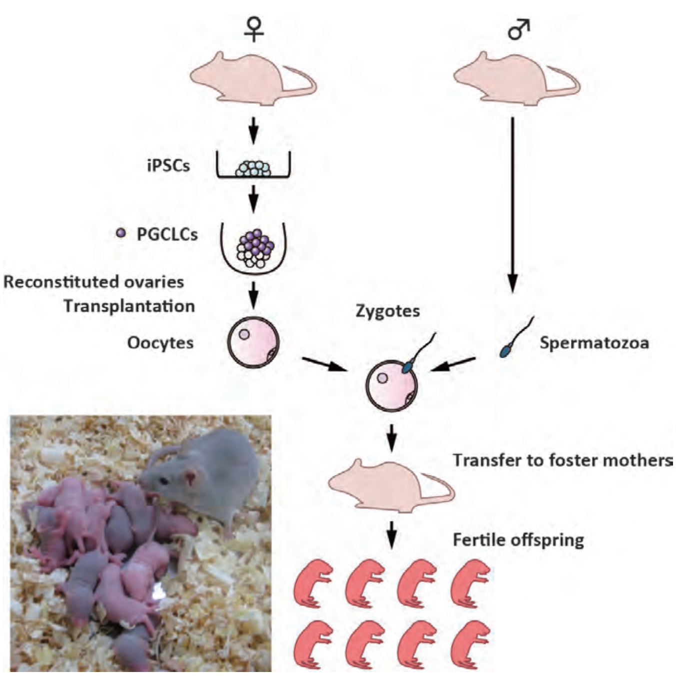


Fig.7. Offspring from oocytes generated from pluripotent stem cells.

6 Chemical tools for programming stem cells

Motonari Uesugi (PI)

Realization of regeneration therapy requires new technologies that coax stem cells to behave as we desire. iCeMS has developed many such cell-controlling technologies by combining chemistry and cell biology.

Regeneration therapy requires a large amount of iPS cells. iCeMS developed a material that permits mass production of iPS cells, and we initiated a collaboration with the industry sector to develop their automated culture. After production, the next step is to coax the resulting iPS cells to differentiate into clinically useful cells. From iCeMS's collection of 70,000 chemicals (chemical library), we discovered chemical compounds that coax iPS cells to become heart muscle cells and pancreatic βcells. These chemical tools have now been used by researchers all around the world.

One of the major problems encountered in regeneration therapy is the low survival of transplanted cells. iCeMS has developed a chemical compound that impairs detachment-induced cell death, known as anoikis, to improve cell engraftment. This promising chemical has now been licensed to industry. Another hurdle in stem cell therapy is the tumorigenic risk of residual, undifferentiated stem cells. The collaboration of chemists and biologists at iCeMS has enabled the development of several chemicals that eliminate residual iPS cells.

These fruits from multidisciplinary research activities in iCeMS result in chemical tools that serve both regeneration therapy and basic research.

Uesugi, M et al., Cell Reports 2, 1448-1460 (2012)

Unique Achievements by iCeMS as a WPI Center

(1) Interdisciplinary Research Environment

Problems of modern society, such as global warming, environmental pollution, disease and aging, are often too complex to be adequately tackled by a single academic discipline. An interdisciplinary approach, crossing different perspectives from multiple fields of study, is essential to generate breakthrough solutions (Fig. 8 & 9).

Since its inception, iCeMS has tailored its organization and facilities towards the goal of cell-material science integration. In conventional faculties and departments of Kyoto University, researchers from different laboratories seldom see each other or have friendly discussions about their studies. That is why iCeMS adopted an interdisciplinary architecture in its facility design. Having open offices with no private rooms and open laboratories with shared experimental equipment means that every researcher is surrounded by people from other research areas. This research climate has acquainted members across all laboratories and specialized domains, nurturing an atmosphere in which researchers feel free to consult with those in other specialties about a problem they cannot solve or to ask for measurements or other specialized tasks they need for their research. Even casual greetings and subsequent chats can sometimes offer a fresh perspective or inspiration for future research.

In addition to the environmental arrangements described above, iCeMS promotes further interdisciplinary collaboration with its annual overnight retreat for all members. Participating researchers discuss possible solutions to their common challenges, submitting ideas based on their respective expertise. The retreat also invites suggestions for interdisciplinary projects for young researchers. These activities help researchers understand each other's work, appreciate their differences, and stimulate each other intellectually to find new inspiration.

As fruits of these approaches, iCeMS has presented 537 interdisciplinary papers compiled by multiple laboratories, out of a total of 1,477 papers published to present. It has also fabricated over 2,000 synthetic compounds for use in various sectors, contributing to the further advancement of interdisciplinary research.

(2) Realizing a True International Setting

True internationalization does not progress until there is a critical mass of foreigners seen on a daily basis. Pointing to similar critical mass adoption, tools such as the telephone and the Internet flourish only when their users represent over 15% of the population. iCeMS currently has 44 international members, which account for 30% of the total. In contrast, the average ratio at Kyoto University is 7–8%. Meetings and seminars at iCeMS are all conducted in English, and most documents are written in English and Japanese, side by side. Half of iCeMS' administrative staff members are bilingual, and each laboratory has a bilingual secretary. iCeMS' researchers (and students) naturally improve their communication skills through everyday interaction with overseas colleagues. These interactions yield even greater cooperation as researchers are able to have deeper discussions and understanding. Moreover, iCeMS has an Overseas Researchers Support Office to assist international members in having a comfortable life in Japan. All these efforts have allowed iCeMS to successfully remove language and cultural barriers and to achieve an environment in which all members can pursue their research regardless of nationality—in other words "true internationalization."

(3) An Environment to Focus on Research

Most graduate schools and research institutes have small "non-research" budgets, which often forces faculty members, especially younger ones, to do less relevant jobs along with their own research. iCeMS, in contrast, has successfully established an environment that allows researchers to focus on research by utilizing WPI funds as described below.

a) Shared Equipment Support Office: Full-time technicians undertake time-consuming maintenance of much of the laboratory equipment owned by iCeMS.

b) Research Support Staff: Well-experienced support staff are indispensable for a research institute to

Fig. 8 A researcher running an experiment

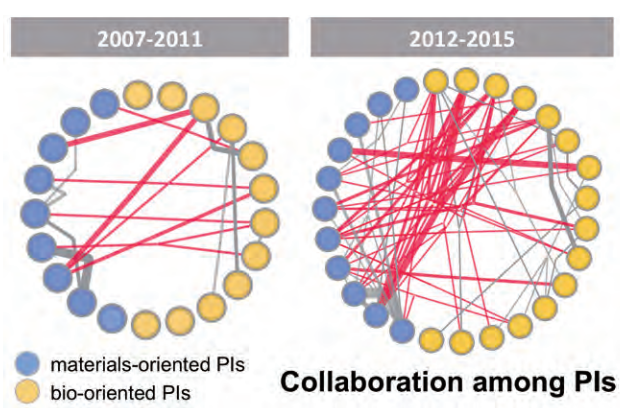


Fig. 9 Interdisciplinary collaboration among PIs

procure budgets of hundreds of million yen. iCeMS hires support staff who specialize in cell and material sciences as specially appointed Professors. Their paperwork assistance in budgetary requests contributes to the successful acquisition of large amounts of competitive research funds.

(4) Outreach Activities for Social Recognition

With the Social Communication Group (SCG) established upon its inception, iCeMS has constantly stressed that researchers should not only educate but also dialogue with the public to foster a view of "science in society." Towards this, the SCG has developed diverse programs to inform the public about the content and concepts of iCeMS's innovative research. Examples of these programs include the Science Café; "Hands on with Stem Cells!" classrooms for high school students/teachers (which received the Commendation for Science and Technology from the Minister of Education, Culture, Sports, Science and Technology in 2014); and "iCeMS Caravan" active learning classrooms on "the mechanism (karakuri) of study" for high school students (the iCeMS Caravan held at Nagasaki Prefectural Goto High School was broadcast by NHK). SCG also implements various projects to familiarize the public with science, including the "iCeMS Art Exhibition" (covered by the Kyoto Shimbun newspaper and other media), which exhibited fashion designs featuring synthetic compounds developed by iCeMS and cell micrographs. (Fig. 10)

Fig. 10 Juichi Yamagiwa, President of Kyoto University, delivering his lecture at the WPI joint symposium in December 2015

(5) Establishment as a "Globally Visible" Research Institute

iCeMS has an Overseas Affairs and Planning/Public Relations section for worldwide dissemination of its research accomplishments. This section engages in various public relations activities, including press release assistance, manuscript preparation, and utilization of EurekAlert! and other international news distribution services, to globally and effectively convey iCeMS research achievements. Furthermore, iCeMS is the first Japanese university to join the "edX" massive open online course run by a consortium of universities, including MIT, Harvard and over 20 world-leading universities. For this course, Prof. Motonari Uesugi, Deputy Director of iCeMS, gave a free lecture in English titled "The Chemistry of Life", which was delivered worldwide to about 26,000 registered students. Such global-scale dispatches of information about iCeMS' vision and interdisciplinary research achievements, establishes it as an attractive institute for researchers from around the world.

Future Outlook

The research theme of iCeMS has hitherto been, "can we chemically describe cellular processes and create materials to control them?" From now on, while continuing our present research, we will also work with the theme, "can we reproduce cellular structures with materials?"

Renowned Nobel 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. Replication of cellular functions with designed materials should be possible once a full understanding of such cellular processes has been achieved. We therefore simultaneously advance analysis and synthesis, applying the resulting higher level of knowledge to further research towards the creation of new materials and technologies, including the following:

a) Materials for Cell Membrane Functions: Development of catalytic materials mimicking the complex yet efficient mechanisms of the cell membrane (e.g. material transformation, production)

b) Gas biology: Creation of "gaseous medicine" for storage and as-needed retrieval of gas molecules such as carbon monoxide and nitric oxide. Once considered toxic, these gases have proven to be efficacious in cells and act on various diseases when used in small amounts

c) Artificial photosynthesis: Study of efficient methods to realize plant photosynthesis, a light-mediated chemical reaction that converts atmospheric carbon dioxide into carbohydrates, through utilization of porous or other materials as regulators

d) Energy Storage in Cells: Creation of materials that mimic a living systems' ability to sort and store energy-bearing ions and molecules and of materials that unlock the energy storage potential of carbon dioxide, carbon monoxide, methane and other gases

Shinji Tomita (iCeMS)