Institute for Integrated Cell-Material Sciences

iCeMS Our World, Your Future

Kyoto University

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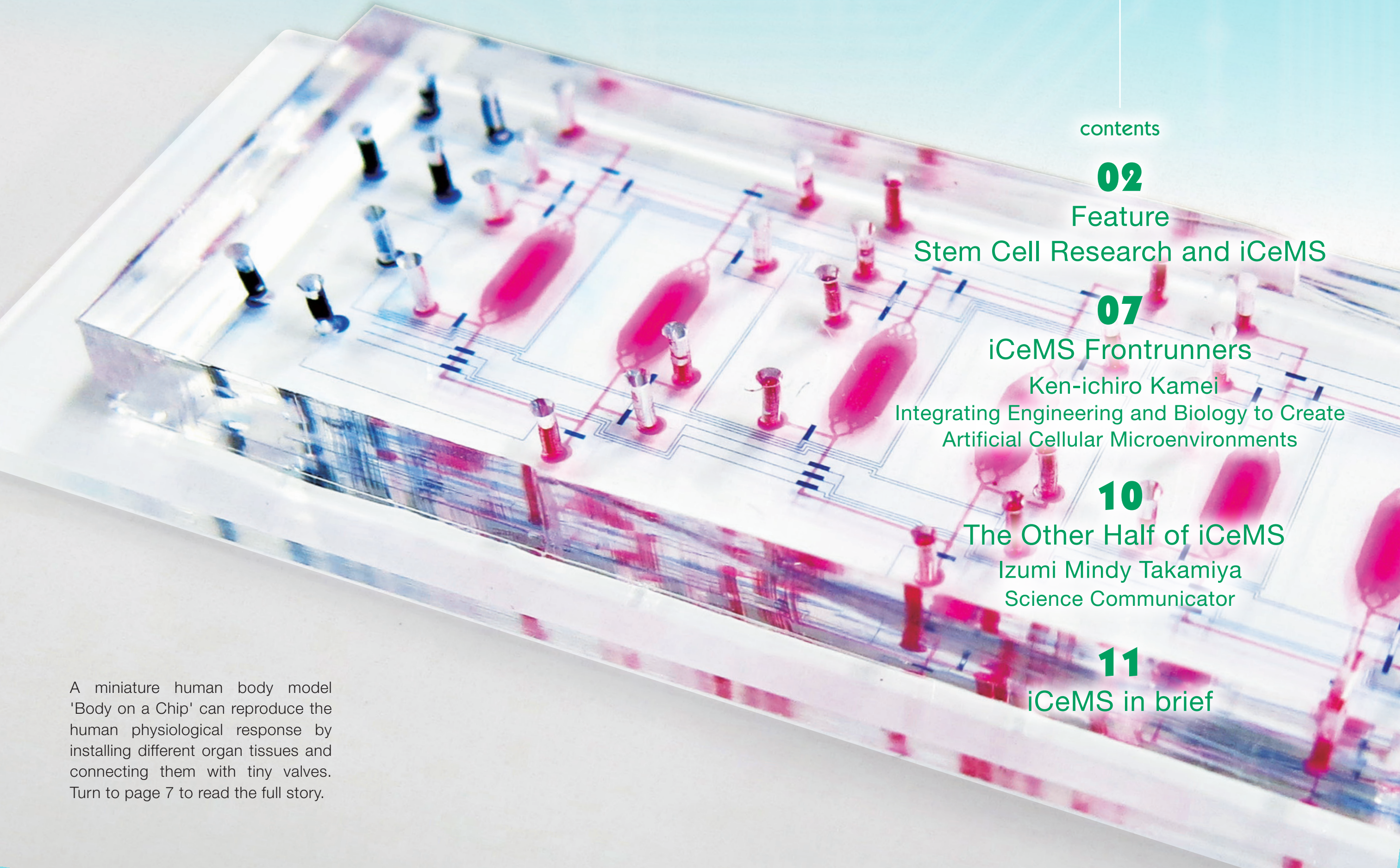


contents

A miniature human body model 'Body on a Chip' can reproduce the human physiological response by installing different organ tissues and connecting them with tiny valves. Turn to page 7 to read the full story.

Feature

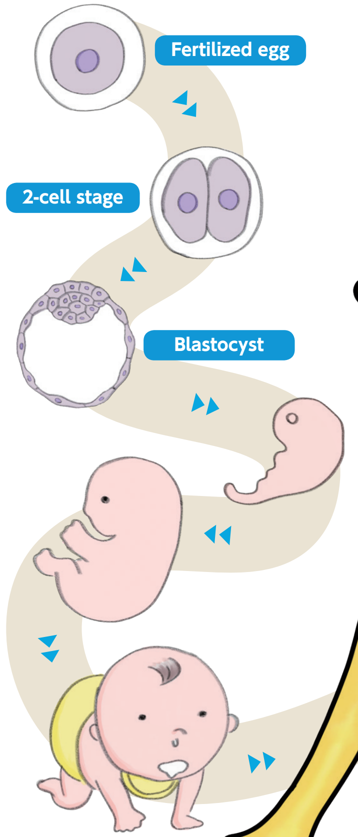
Stem Cell Research and iCeMS

Stem cells, found in almost all multicellular organisms, have the ability to turn into different types of cells in the body. Stem cells are believed to have played an important role in the evolution of multicellular organism from ancient single-cell organisms that date back roughly a billion years.
iCeMS has been researching basic stem cell biology from a wide variety of perspectives since its inception in 2007. Dr Kouichi Hasegawa tells us about iCeMS stem cell research.

The human body contains an estimated 37 trillion cells, categorized into more than 200 different types. These vast numbers of cells can be traced back to a single cell, the fertilized egg. In the mother's womb, the fertilized egg undergoes repeated cell division and produces stem cells, which are the source of all tissues and organs, each with their own specialized physiological functions. Let's have a look at the enigmatic nature of stem cells.

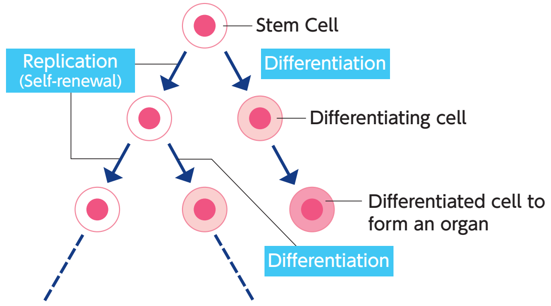
Kouichi Hasegawa
Born in Kumamoto, Japan, in 1972. In his current position since 2017. He received his PhD degree in 2000 from Kwansei Gakuin University Graduate School of Science. He served as an assistant professor at University of Southern California, US, an assistant investigator at the Institute for Stem Cell Biology and Regenerative Medicine, India, and as a senior fellow at the University of Melbourne, Australia. He also serves as a scientific advisor to several biotech startups.

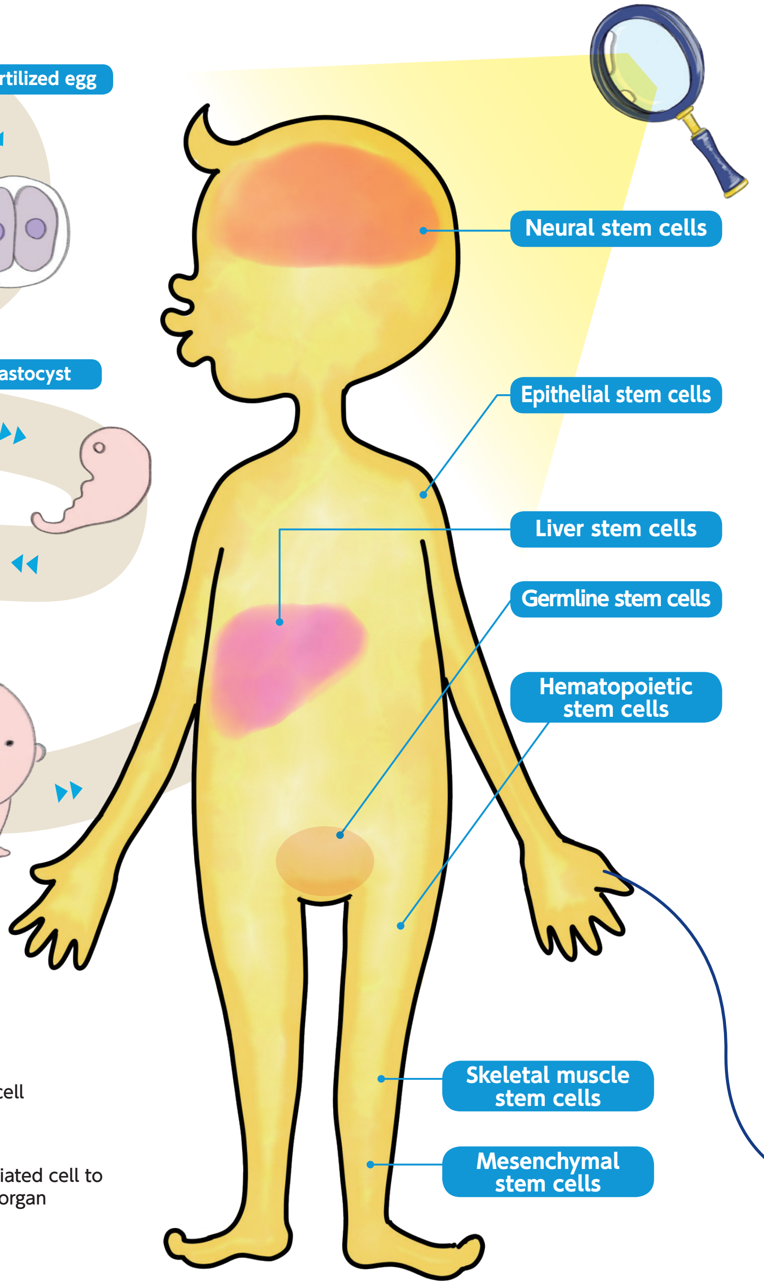
Kouichi Hasegawa
Program-Specific Research Center
Junior Associate Professor



Self-Renewal and Differentiation Potentials

The key features of the stem cell include its power to duplicate itself and its ability to produce other cell types. While the stem cell can make multiple copies of itself without losing its potential (self-renewal), it also has the potential to turn into a different type of cell (differentiation). For example, the fertilized egg produces skin, nerve, liver, and many other types of cells while undergoing repeated cell division.





Tissue (Adult) Stem Cells Are Present in and Supporting our Body

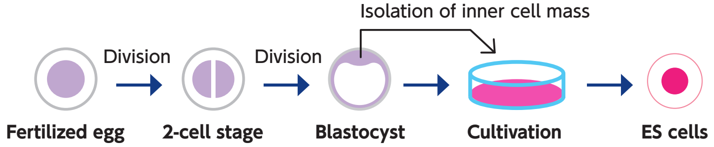
It is sometimes incorrectly thought that stem cells are a man-made tool for regenerative medicine and other cutting-edge science. The truth is that even after birth, the human body naturally contains tissue or adult stem cells (as opposed to embryonic stem cells).
There are various types of adult stem cells, including hematopoietic (blood-producing) and neural stem cells. The former are progenitors for red blood cells, white blood cells, platelets, and many other blood components, while the latter produce neurons. Adult stem cells are present in a population of differentiated cells for the purpose of maintenance and repair. When you fall and scratch the skin on your knee; epidermal stem cells there are able to heal the skin in a few weeks.

Pluripotency of Embryonic Stem and iPS Cells

The term "pluripotency" refers to the ability of a cell to generate all of an organism's somatic cells. Unlike adult stem cells, embryonic stem (ES) cells and induced pluripotent stem (iPS) cells are pluripotent because they can differentiate into all types of cells in our body.

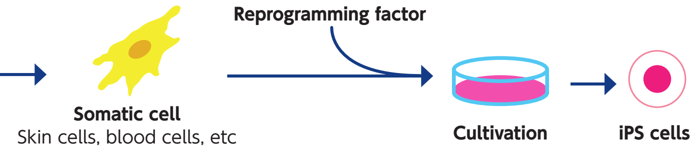
· ES cells

ES cells are derived from the inner cell mass of blastocyst-stage embryos. The harvested cells are cultured to establish ES cell lines. Following the 1981 establishment of the first mouse ES cell line, the first human ES cell line was developed in 1998. In Japan, the first human ES cell line was established by the Kyoto University team led by Prof Nakatsuji (iCeMS founding director). Subsequent technological developments have made it possible to stably cultivate this cell line, allowing for its wide application in medicine and biology. Many years of research on pluripotent ES cells gave rise to iPS cells.



· iPS cells

Prof Shinya Yamanaka of Kyoto University and his colleagues were the first to announce in 2006 the induction of iPS cells from mouse fibroblasts. Pluripotent iPS cells can be induced from somatic cells (eg, skin and blood cells) by introducing a key set of ES cell genes. The iPS cell technology can be applied to regenerate neural, myocardial, and other tissues damaged or lost because of an illness or accident. In addition, this technology can be applied to somatic cells taken from a patient with an intractable illness, and then used to reproduce the disease condition in culture dish. Comparison between diseased and healthy cells may help discover the pathology and its treatment. Prof Yamanaka was one of the founding members of iCeMS. After becoming the CiRA director in 2010, he continued to serve iCeMS as a Principal Investigator until March 2016.

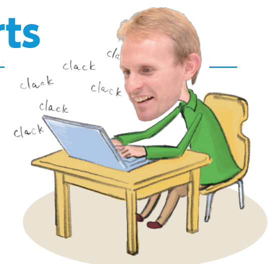


Transdisciplinary Collaboration

iCeMS encourages transdisciplinary research activities, and researchers with different backgrounds enjoy its vibrant and friendly research culture. Dr Hasegawa works with Dr Kamei and many other experts in his stem cell research projects. They actively support one another by exchanging input and experimental materials.

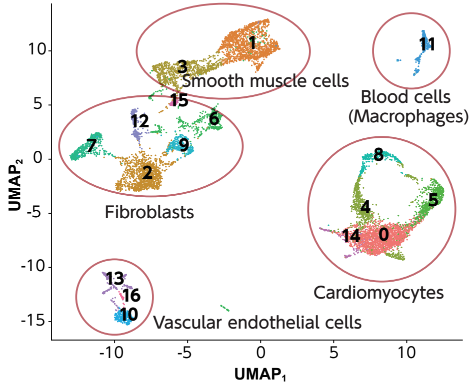
Ken-ichiro Kamei
Associate Professor

Collaboration with Computational Experts



Daniel Packwood
Junior Associate Professor

Visiting Prof Atsushi Nakano (cardiophysiology) and Dr Daniel Packwood (applied mathematics) from iCeMS are working together to understand how the heart develops from the cells in the embryo.
The figure below is like a 'map' of the different cells in the heart. Each point corresponds to one cell, and the points are placed according to their gene expression.
From this plot, we can identify different types of cells (indicated by the colors). By determining which of these cell types arise from which parts of the embryo, we can obtain useful insights into heart development.



This plot was created with a mathematical procedure called UMAP. The cells can clearly be categorized into 16 types.

COLUMN

iCeMS Was Founded by a Stem Cell Pioneer

Prof Norio Nakatsuji is the founding director of iCeMS. He was the first to create the simian and human ES cell lines in Japan, and established the standard human ES cell culture system. As a leading pioneer in this field, he advanced ES cell-based drug and cell therapy research and development.
When iCeMS was launched in 2007, Prof Nakatsuji focused on stem cell control using meso-scale (5–100 nm) materials. He was looking for ways to use novel substances and materials that have interesting biological properties.

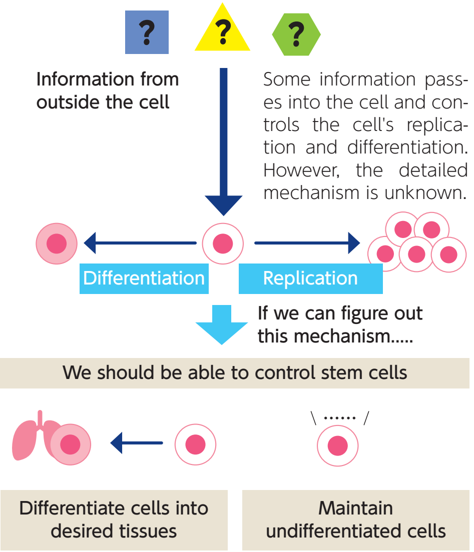
Norio Nakatsuji
iCeMS Founding Director

Stem Cell Researchers at iCeMS

Three iCeMS Principal Investigators engaged in stem cell science tell us about their research interests.

Unlocking the mystery of stem cells
How they remain undifferentiated

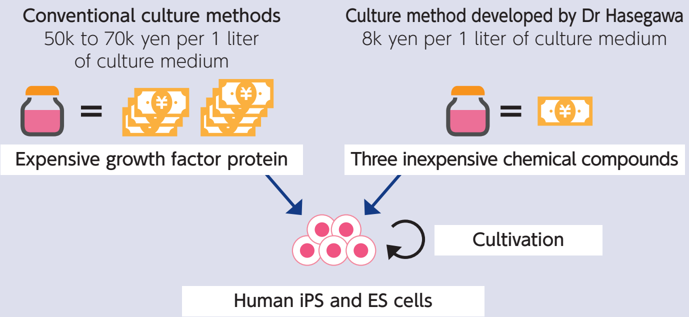
Undifferentiated stem cells undergo self-renewal and differentiation when triggered by external signals, but the mechanism of this signaling remains unknown.
Our lab is investigating what and how external information is transmitted to inside of the stem cell to regulate these processes. Information on this control mechanism will shed light on how to maintain stem cells undifferentiated, expand them efficiently and induce their differentiation to particular cell types of interest.
Basic stem cell research can open the door to new drugs and other therapeutics.



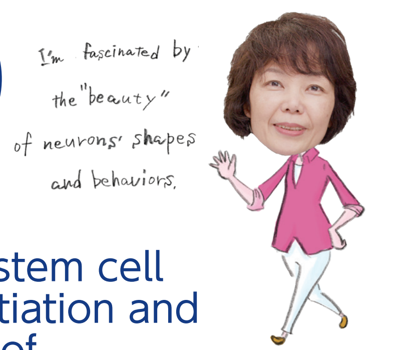
\ An example of applied research! /

Developing a low-cost culturing medium

Culturing iPS and ES cells requires a large amount of medium. The use of expensive medium is a bottleneck in the cost of iPS cell research. We have developed a novel synthetic medium at a five- to ten-fold lower cost for expanding iPS and ES cells.



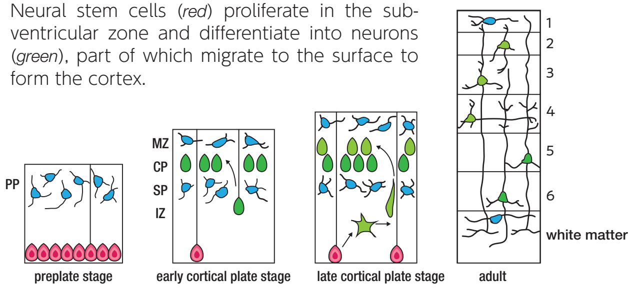
Mineko Kengaku
Professor

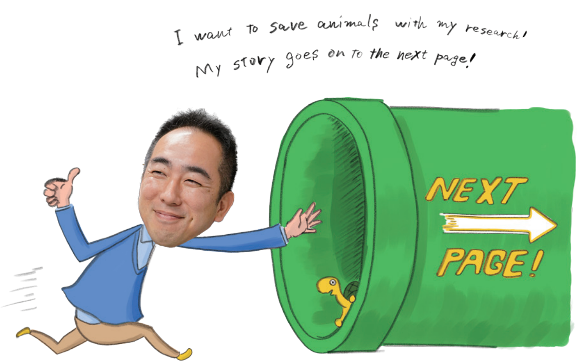


Neural stem cell differentiation and control of neuronal migration dynamics

The human brain is a network of billions of communicating neurons that regulate conscious and unconscious behaviors. Neurons are orderly arranged in the cortex, multilayered cell architecture, where they establish precise synaptic connections with their specific targets. At our lab we directly observe the brain development process to elucidate the principle underlying it. The fetal brain has a layer of proliferating stem cells. These stem cells repeat cell division and sometimes produce neurons. Neurons leave the germinal layer of proliferating stem cells and migrate through tissues and stack up to form the cortex.
Abnormal neuronal migration is associated with epilepsy, mental retardation, ataxia, and other neurological disorders. We reproduce the neuronal migration process on glass plates to analyze the underlying dynamics.

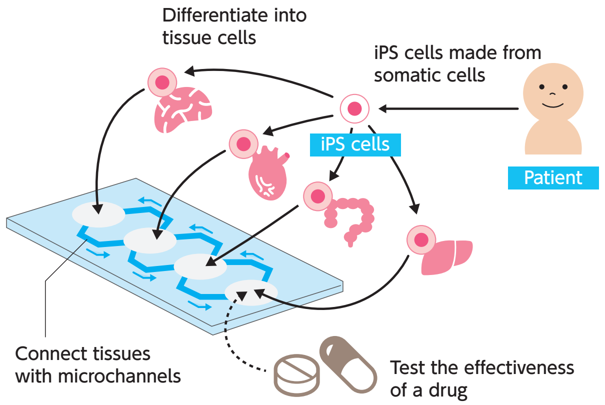
Neuronal migration and cerebral cortex formation
Neural stem cells *(red)* proliferate in the subventricular zone and differentiate into neurons *(green)*, part of which migrate to the surface to form the cortex.





Reproducing biological processes on a microchip
Another example of iPS cell technology

Our lab is working on a "Body-on-a-Chip (BoC)" device. This microchip device is designed to simulate biological reactions by encapsulating iPS cells and differentiating them to variety of tissues including liver, heart, and others, and these tissues are connected by vessels similar to human body. iPS cells derived from an individual will enable us to produce tissues in a BoC that possess his or her genetic traits.
This BoC, which miniaturizes living organisms' responses, can be useful for physiological, pathological, and therapeutic studies.



Interview **iCeMS Frontrunners** 10

Bringing drugs and other medical products to the market requires large capital R&D investments and many years of research. Before investigational products can be tested in humans, their efficacy and safety must be evaluated in mice and other lab animals. Since experimental animals often respond differently from humans, nonclinical data are often insufficient for predicting human responses. Moreover, experimental animal use is a matter of intense debate in terms of animal welfare. The "Body-on-a-Chip (BoC)" device, currently under development by Dr Ken-ichiro Kamei, is expected to result in a major breakthrough in this regard. This device is created using iPS cells and microfluidic technologies, paving the way for testing drugs in an ex vivo (outside the body) environment. The microfluidic chip is a promising tool for personalized medicine.

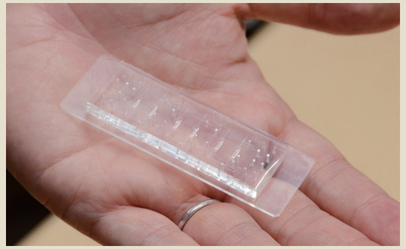
Integrating Engineering and Biology to Create Artificial Cellular Microenvironments

Ken-ichiro Kamei Associate Professor

Ken-ichiro Kamei
Born in 1975 in Tokyo. Received PhD degree in 2003 from the Tokyo Institute of Technology's Department of Biological Information. After serving as a post-doctoral researcher at the California NanoSystems Institute at UCLA, he became an assistant professor at iCeMS in 2010, and has held his current position since 2015.

"I recently spent three weeks at the San Diego Zoo, USA, involved in joint research on the northern white rhinoceros. The zoo has the last two surviving individuals in the world. Preserving endangered species is another important research area of mine," Kamei says with a gentle smile. Although his words may sound like those of zoological fieldworkers and ecologists, he is an engineer by training.

His BoC device contains iPS cell-derived heart and liver tissues that simulate human physiological responses and disease conditions. Possible applications include new drug development and animal preservation.



The size of the chip is 75 x 25 mm. Using a three-dimensional microfabrication technology developed from their original photolithography technique, Kamei has succeeded in integrating high-performance valves and micro-pumps in a chip.

The BoC technology can be used to create ex vivo models of endangered species to discover remedies for intractable diseases and other risks faced by 3,000 species that are threatened with extinction.

Born with a Passion for Crafting

"I love to create new things, at work and during my time off. I assembled on my own the laser cutter machine that was required for the trial production of a new version of the BoC device. I had the parts shipped from manufacturers, and I built the machine in my time off. It was a fantastic way to pass the time," he says with a chuckle.

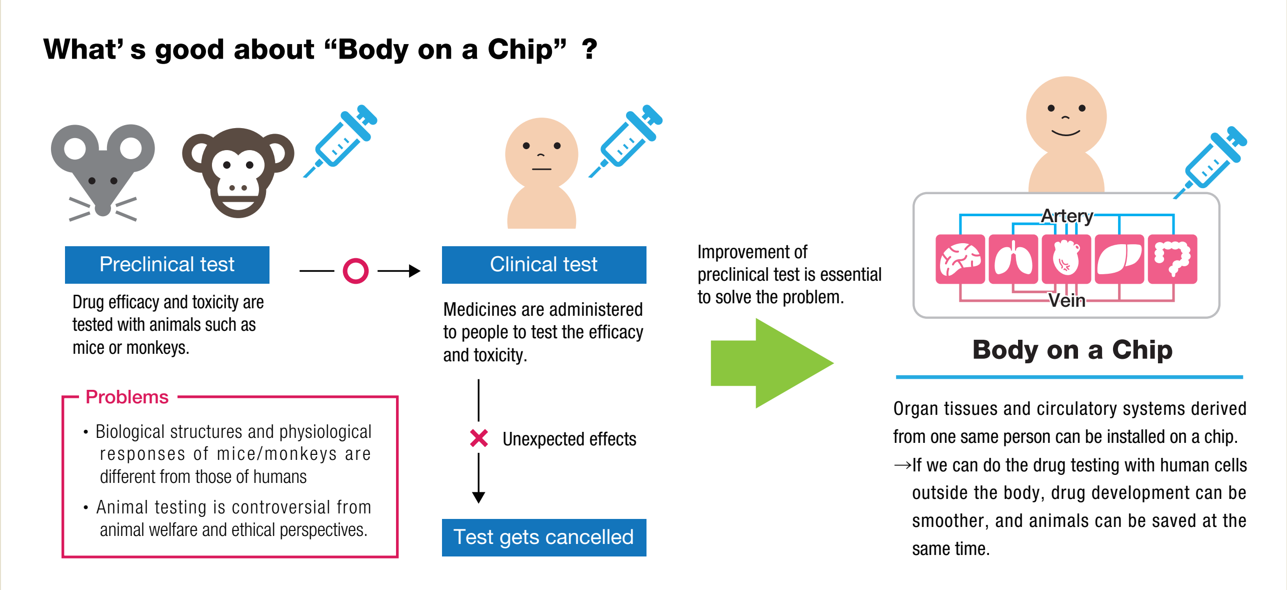
Kamei's craftsmanship was already visible as a first grader, when his father bought him a plastic Gundam model kit. He had a deep sense of accomplishment as he admired his completed handiwork. His interests spread to remodeling radio-controlled toy vehicles and disassembling clocks. During his teenage years, he contemplated creating new things on his own. At that time he dreamed of becoming an aerospace rocket engineer or Formula One car designer. He wanted to become one of the professionals who astonished the world with their products.

He chose to join the Department of Biotechnology, Tokyo Institute of Technology. "I studied both engineering and biology because I was interested in artificial and natural systems. As I became involved in research activities, I enjoyed the trial-and-error process of making and testing working hypotheses. I envisaged becoming an academic researcher because I valued the freedom of starting from scratch."

From Basic Biology to Applied Engineering

After completing his doctoral degree, Kamei was accepted as a postdoctoral fellow at the University of California, Los Angeles (UCLA). "It was a deliberate decision to join a laboratory focusing on basic biology. Although engineering is my strong suit, I thought that a skill set in basic biology research would enrich my perspective." He spent day after day manipulating genes and taking care of genetically engineered mice. He had much to learn. Hands-on practice handling embryonic stem cells for genetic modification is one example. Kamei acquired a significant amount of new knowledge and experience, which would not have been possible if he had not joined UCLA.

In his second postdoctoral year, Kamei had a chance to demonstrate his expertise and skills. He joined a project to develop a microfluidic system that generates the positron emission tomography (PET) reagent necessary for cancer diagnostic testing. "PET can accurately locate malignant cells using a glucose-like radioactive tracer. To avoid human radiation exposure, we tried to produce the tracer automatically using a microfluidic circuit." Substantial knowledge of engineering and biology is required to verify whether the synthesized tracer enters the target cells. "I did my best to produce positive results in my research. This project opened a new door in my research path. Since then, I have focused on microfluidic devices that encapsulate functional cells."



Harnessing Engineering to Serve the Community

After returning home in 2010, Kamei was accepted as an assistant professor at iCeMS. He started his work on the BoC device in 2012, and published his achievements in 2017.

Family time is as important as research is. Kamei sometimes goes on trips with his only daughter and restores his energy to do research work.

With a white rhinoceros at San Diego Zoo. Kamei also studies endangered species such as zebras or golden eagles, collaborating with Kyoto University's Wildlife Research Center.

He was the first to create a microchip device that simulates interactions between biological tissues connected by microfluidic circuits — a masterpiece resulting from trial and error using iPS cells and high-precision, nano-scale engineering technologies.

Although the device is capable of mimicking a complex vasculature, Kamei is working to create a model that more closely simulates human physiology. He is searching for ways to load the microchip with a large number of sensors and electrodes.

Kamei is convinced that engineering serves the world. "I do not pursue engineering for the sake of engineering. Engineers should seek opportunities to contribute to the various needs and well-being of their communities."

The Other Half of iCeMS

Izumi Mindy Takamiya

Science Communicator & Illustrator
Assistant Professor at Public Engagement Unit

To communicate the significance of nanoscale research at iCeMS, complex ideas need to be presented in an easy-to-understand and approachable manner. "Creativity is the key in our public relation (PR) activities," says Mindy Takamiya. Her job is to effectively disseminate information on scientific research at iCeMS. She writes and creates graphic illustrations to reach a wide audience.

Mindy creates illustration artworks to express scientific research, and communicates iCeMS' science domestically and internationally in many ways:

Production of advertisement media

PR publications and promotional goods

- Planning brochures and this newsletter series
- Designing clear folder and handkerchief based on scientific research

Press communication

- Preparing press releases (summaries of research results) for domestic and overseas media outlets
- Interacting with journalists

Website and social media

- Creating or planning visual contents (illustrations, photos, videos, etc.)
- Writing news and following up responses

Face-to-face interactions

- Conducting lab tours open to the general public
- Talking to international scientists for future recruitment

Reader-Friendly Writing and Intuitive Illustrations

As I come from a humanities background, it was challenging for me to understand the world of natural science in the early days of my job as a science communicator. Unfamiliar jargon. Realism-oriented three-dimensional graphics of cells. Expressions common for natural scientists were not only difficult to understand for me—in fact, they were even alienating.

The target recipients of our messages are not limited to science-savvy people. I wanted to publicize the significance of iCeMS' research and the enthusiasm of its researchers in a manner that effectively speaks to the general audience, including those who are unfamiliar with science. I thought I would be able to express science in a way wider range of people can feel close to it because I knew how it feels to think that "science is not my thing." That is why I started hand-drawing illustrations to make scientific news reader-friendly.

Art Goes On Mission as a "Translator"

My artworks for iCeMS press releases are receiving positive feedbacks, and now my efforts to make visuals to attract a wider audience are gaining momentum. A variety of activities have been started, such as exhibitions of science illustration works and the creation of promotional goods. Moreover, I receive requests to create illustration art for scientific journal cover pages, which is a visual tool to aid academic communication between researchers.

In the six years working at iCeMS, I have grown my understanding of natural science and widened my range of expression. Still, the passion that I had at the beginning remains the same. Now I understand scientists' words and feelings, and those of the general public too. It is like being bilingual in two different cultures. I have found my calling as a translator who connects science and the rest of society.

iCeMS in brief

Research Highlights

Proper delay in intercellular coupling

An essential molecular mechanism for regulating segmentation clock synchrony

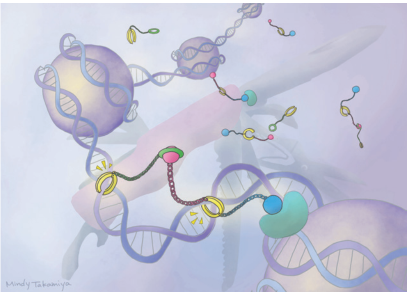
A group of researchers led by Prof Ryoichiro Kageyama discovered that a correctly timed delay in cell-cell coupling signal transmission is essential for synchronized expression of segmentation clock genes.

Using Achilles, a new florescent reporter in mouse presomitic mesoderm cells, this research group monitored synchronous oscillations of Hes7 expression at a single-cell resolution. They found that the Notch signaling modulator lunatic fringe (LFNG) delayed the intercellular signaling process and a correct delay was essential for synchronized oscillation. Their findings will help elucidate the synchronization mechanisms reported in humans and many other species.

Researchers established a way to observe embryonic development in single live cells, which enabled observing how clock genes work to control dynamics in cells. (Illustration by Mindy Takamiya)

Kumiko Yoshioka-Kobayashi, Marina Matsumiya, Yusuke Niino, Akihiro Isomura, Hiroshi Kori, Atsushi Miyawaki & Ryoichiro Kageyama (2020). Coupling delay controls synchronized oscillation in the segmentation clock. *Nature*

A new therapeutic molecule that will help manipulate the genetic switch



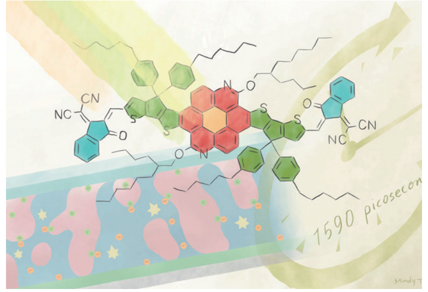
The novel DNA-binding molecule combines multiple tools into a single synthetic platform, like a chemical Swiss knife. (Illustration by Mindy Takamiya)

Dr Ganesh Pandian Namasivayam's research team synthesized a new, biologically active compound, ePIP-HoGu, which consists of the combination of an epigenetic modulator, DNA-binding pyrrole-imidazole polyamide (PIP), and a "host-guest" unit.

The HoGu moiety acts like a precise linker to the transcription factor, thereby allowing the PIP-HoGu system to successfully disrupt target gene transcription. The PIP-HoGu system also enables the delivery of the epigenetic drug component in a site-specific manner, suggesting that this novel compound will be useful in future biological and medical research.

Zutao Yu, Mengting Ai, Soumen K. Samanta, Fumitaka Hashiya, Junichi Taniguchi, Sefan Asamitsu, Shuji Ikeda, Kaori Hashiya, Toshikazu Bando, Ganesh N. Pandian, Lyle Isaacs, and Hiroshi Sugiyama (2020) A synthetic transcription factor pair mimic for precise recruitment of an epigenetic modifier to the targeted DNA locus. *Chemical Communications*

A promising building block for future high-performance organic photovoltaics



The new electron-accepting molecule TACIC can maintain its excited state 50 times longer than a conventional one. (Illustration by Mindy Takamiya)

Adjunct PI Prof Hiroshi Imahori and colleagues created a non-fullerene acceptor (TACIC) film that has an extremely long exciton lifetime. The TACIC-based photovoltaic device showed a 10% power conversion efficiency.

The newly developed electron-acceptor materials may help overcome the technical challenge of producing nano-scale bicontinuous donor-acceptor structures. This new discovery marks a step toward the commercialization of thin-film organic photovoltaics.

Tomokazu Umeyama, Kensho Igarashi, Daiki Sasada, Yasunari Tamai, Keiichi Ishida, Tomoyuki Koganezawa, Shunsuke Ohtani, Kazuo Tanaka, Hideo Ohkita and Hiroshi Imahori(2020) Efficient light-harvesting, energy migration, and charge transfer by nanographene-based nonfullerene small-molecule acceptor exhibiting unusually long excited-state lifetime in film state. *Chemical Science*

• What's new? •

ZEISS-iCeMS Innovation Core bioimaging center inaugurated

Carl Zeiss Microscopy GmbH and iCeMS signed a partnership agreement to establish the ZEISS-iCeMS Innovation Core, a bioimaging center focusing on the application and evaluation of high-resolution live-imaging fluorescent microscopy technologies. The inauguration ceremony and founding symposium were held on October 28, 2019.

iCeMS Caravan visits a high school in China

On January 9, 2020, iCeMS researchers visited Northeast Yucai School in Shenyang, China, to conduct interactive learning workshops. A total of 34 high school students attended the program, including several Japanese students from Okinawa and Kyoto. After iCeMS researchers gave scientific lectures, students came up with their own original research ideas, and gave presentations on them.

Awards

- **Dir Susumu Kitagawa selected as 2019 highly cited researcher** (Nov 20, 2019)
- **Dir Susumu Kitagawa named member of Japan Academy** (Dec 12)
- **Dr Kaoru Sugimura receives Kyoto University Tachibana Award** (Feb 4, 2020)

Activities

- **iCeMS holds a mixer with the press** (Sept 19, 2019)
- **iCeMS tied an MoU with King Abdullah University of Science and Technology** (Oct 23)
- **Delegation from the University of Vienna visits iCeMS** (Oct 24–25)
- **iCeMS Science Festival held** (Nov 8)
- **iCeMS Caravan visits a high school in Hokkaido** (Nov 30)
- **iCeMS holds a joint meeting with NCKU and ASHBi** (Dec 16)
- **iCeMS and Academia Sinica tie an MoU and hold a joint** (Dec 18)
- **iCeMS and Kanazawa WPI NanoLSI co-host their first joint symposium** (Jan 23–24, 2020)
- **Knowledge Capital Cho-Gakko Series "Print without ink, but with crack!"** (Feb 1)

iCeMS Fund — Help us grow

At iCeMS, researchers from Japan and abroad devote themselves to research both day and night. Research results may sometime lead to applications, such as saving the lives of those suffering from incurable diseases or improving the global environment 100 years in the future. On the other hand, pure science we do may not be readily understood by people in the early stage. No one can predict the landscape we will be standing in after our challenges, however, we believe that our research will steadily advance science.

In order for iCeMS researchers to continue moving forward, it is necessary to establish a stable fiscal foundation. We appreciate your understanding of the activities and spirit of iCeMS, and we thank you for your continued support through the iCeMS Fund.

Contact details
Kyoto University Institute for Integrated Cell-Material Sciences
Research Administration Office
Phone: +81-(0)75-753-9749 | E-mail: innovpe@mail2.adm.kyoto-u.ac.jp
Website: u.kyoto-u.jp/kuif

Editorial note

Stem cell research has been a field of major interest to iCeMS since its inception. In this issue, Dr Hasegawa explains how basic research on stem cells leads to applied science.
The iCeMS frontrunner interviewed this time is Dr Kamei. Please read how he contributes to the world with his cutting-edge Body-on-a-Chip technology.
Mindy featured in the Other Half of iCeMS creates eye and heart catching pictorial illustrations to express iCeMS' researches. I'm excited to see her future works.

Mari Toyama

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Production Institute for Integrated Cell-Material Sciences at Kyoto University
Research Administration Office Public Engagement Unit
Mari Toyama, Izumi Mindy Takamiya
Yoshida Ushinomiya-cho, Sakyo-ku, Kyoto 606-8501, Japan | Phone: +81-(0)75-753-9753
E-mail: info@icems.kyoto-u.ac.jp | Website: www.icems.kyoto-u.ac.jp
Facebook:@Kyoto.Univ.iCeMS | Twitter:@iCeMS_KU | Instagram:@iCeMS_KU
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