Institute for Integrated Cell-Material Sciences

iCeMS

Our World, Your Future

Kyoto University
Institute for Advanced Study

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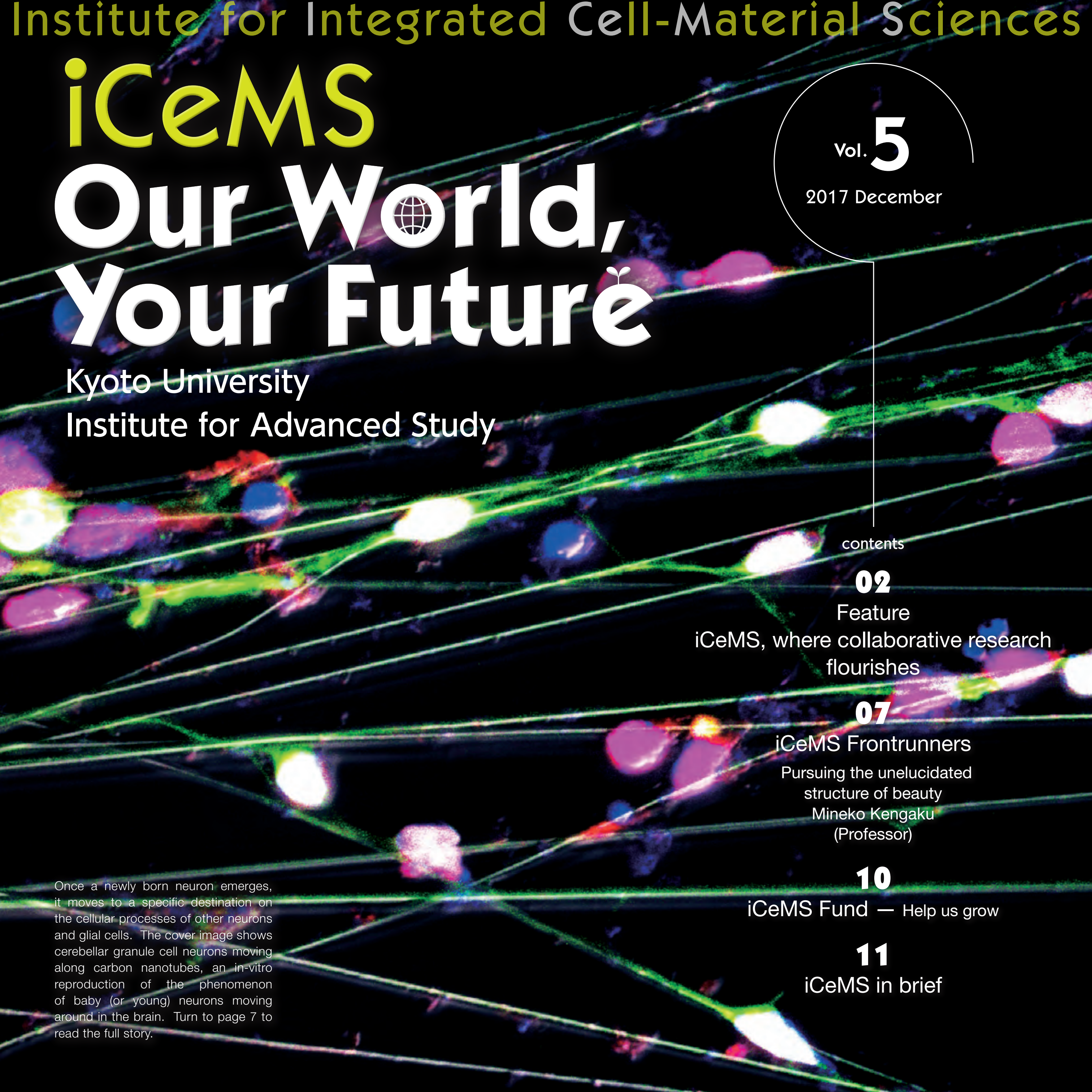


contents

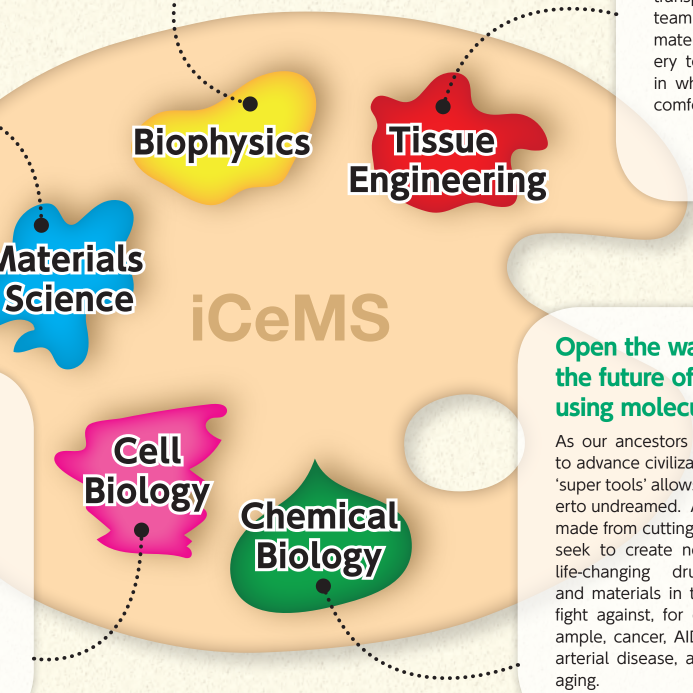
Once a newly born neuron emerges, it moves to a specific destination on the cellular processes of other neurons and glial cells. The cover image shows cerebellar granule cell neurons moving along carbon nanotubes, an in-vitro reproduction of the phenomenon of baby (or young) neurons moving around in the brain. Turn to page 7 to read the full story.

Feature

iCeMS, where collaborative research flourishes

Many researchers in different areas, such as cell biology, chemistry, and physics, work together at iCeMS. By sharing their individual perspectives and discussing issues again and again, they devise new approaches. We asked two of these researchers, who are conducting a joint research project at iCeMS, about the attractiveness of this method.

iCeMS's disciplines

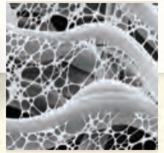


Understand the principle of life in physics approach

Everything obeys physical and chemical laws, and living things are no exception. iCeMS has lead the world in imaging and measurement methods. Using our own unique set of tools, we seek to unlock life's physical laws, such as how molecules transform chemical reactions into life, and how cells build the structure of living creatures.

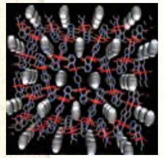
Build the "environment" for cell tissue

Twenty-two people in America die every day due to a shortage of donated organs. There is an urgent need for a safe, cost-effective alternative to transplantation. At iCeMS, our team develops cell-inspired materials and nano-machinery to build an "environment" in which cell tissue can grow comfortably.



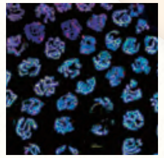
Create new materials to change the world

All materials, such as glass, plastic and bronze, have the utility to create something of use. Today, various materials are artificially created: for example, materials that are easy for molding or ones that can accommodate gas molecules. At iCeMS, collaborating with knowledge from chemistry and biology, we create novel materials for something that has not yet been invented.



To understand cell – the starting point of biology

All living creatures are made up of cells whose characters and roles are highly differentiated and specialized, yet which work collectively. All biology begins with understanding the function of the cell, the minimum unit of life. We probe how stem cells give rise to specialized cells with unique shapes and functions, and how germ cells magically transmit the genome to the next generation.



Open the way for the future of medicine using molecular tools

As our ancestors used rocks as tools to advance civilization, the invention of 'super tools' allows us to do things hitherto undreamed. At iCeMS, using tools made from cutting edge molecules, we seek to create new life-changing drugs and materials in the fight against, for example, cancer, AIDS, arterial disease, and aging.

Mathematical model shows the mechanisms of a molecular phenomenon

Daniel Packwood
Junior Associate Professor

Works on the molecular self-assembly process, using mathematical theories and computers. The molecular self-assembly process is a phenomenon by which molecules spontaneously gather to form a structured or functional assembly. Snow crystal growth and double-helical DNA are examples of molecular self-assembly. To develop, among other outcomes, molecular-sized fine electronic circuits by applying this phenomenon to nanotechnology, Packwood conducts computer analyses of the complex movement of molecules and their environment.

Dan Ohtan Wang
Program-Specific Research Center Associate Professor

Works on the development of live-imaging methods used to observe individual cells in living brains. This research observes the actions that occur, and where they take place in the brain, in learning or memory processes. Associate Professor Wang is interested in the RNA molecules that direct the synthesis of proteins to build the body of a living organism according to the genetic information in DNA. She intends to explore the mechanisms of forming neural network structures in the brain, starting with understanding how RNA works.

Q1 How did your joint research project begin?

During a 2014 symposium, I talked with Ohtan about both of our respective projects. At that time, I was working for AIMR,*1 Tohoku University, and Ohtan for iCeMS.

Daniel studies self-assembly processes,*2 which overlap with my research themes in many aspects. In a cell under stress, ribonucleic acid (RNA) molecules gather in a self-assembly process. When the stress is removed, they return to their original positions, which I then observed by the live-imaging method.*3 I wondered why such a phenomenon occurred. My biological knowledge was not enough to infer the necessary conditions for the phenomenon. I was a bit frustrated at that time.

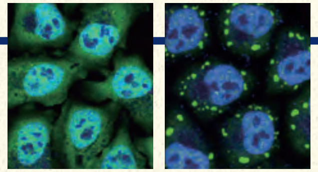
While I was discussing the topic with Ohtan, some ideas about mathematical models came to my mind. These models could potentially reproduce the movement of RNA molecules. I thought the idea would be worth giving a try.

*1 AIMR : Advanced Institute for Materials Research, Tohoku University. Founded in 2007.
*2 Self-assembly : A phenomenon by which molecules spontaneously gather to form a structured or functional assembly
*3 Live-imaging method : A technique designed to visualize and observe tissues and cells in a living body

Daniel Packwood
Born in 1985 in Christchurch, New Zealand. Completed his PhD in chemistry at the College of Science of the University of Canterbury in 2010 and came to Japan as a chemistry postdoc of the Kyoto University Graduate School of Science. Has been at his present position since 2016, after working for the Advanced Institute for Materials Research (AIMR) at Tohoku University.

Dan Ohtan Wang
Born in Shenyang City of Liaoning Province, China. After graduating high school in 1994, she entered the school of Bioscience and Biotechnology at the Tokyo Institute of Technology in Japan. In 2004, she received her PhD at USC. She worked as a postdoc at UCLA, as a JSPS Postdoctoral Fellowship for Overseas Researcher at RIKEN, and as an Associate Professor at iCeMS. Has been at her position since 2017.

Q2 What results have you seen from your joint research?

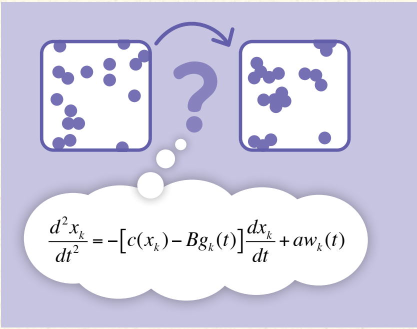


The photo on the left shows cells before pressure is applied and on the right after pressure is applied. The blue parts of the image are DNA, and the green, RNA

These are live-imaging data (photo). Under stress, intra-cellular RNA molecules have gathered. Daniel reproduced the phenomenon using a computer model.

I developed a computer simulation method and explained the mechanisms behind the phenomenon using an equation. The equation contains parameters (numerical values) that represent, among other factors, liquid viscosity and molecule radius. Varying each parameter causes the phenomenon to change. By examining how the phenomenon changes, it is possible to find out what factors are required for the self-assembly process. Simulations are more convenient than observing cells in practice. In an experiment, it is difficult to thoroughly track and control the environment in which cells are placed. Simulations enable us to set up an ideal environment by means of mathematical expressions.

The imaging technique is useful for examining what is taking place in the cells. However, to infer what parameters are important among factors that are not readily visible, such as those that occur in environmental changes, Daniel's equation played a key role.

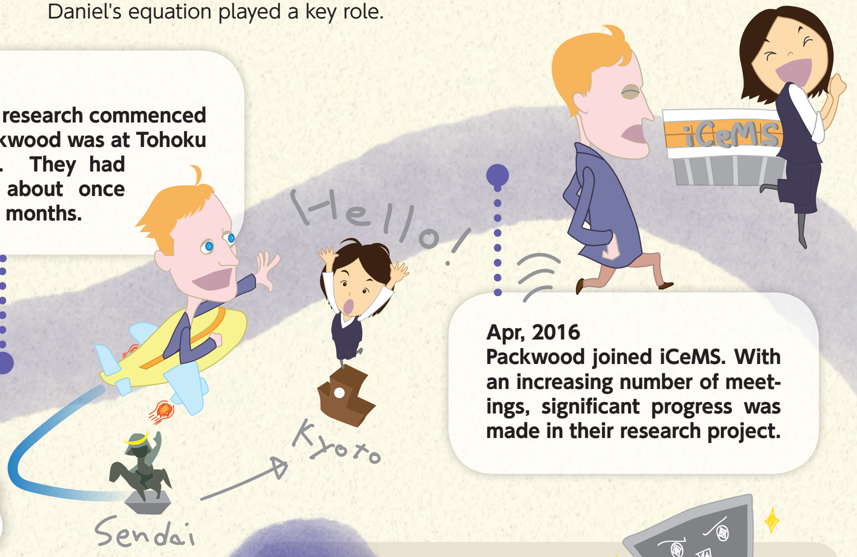


$$\frac{d^2x_k}{dt^2} = -[c(x_k) - Bg_k(t)]\frac{dx_k}{dt} + aw_k(t)$$

During the 10 to 20 minutes that the RNA molecules gathered, Packwood clarified a mathematical formula to describe the influences on the molecules and their movement.

Dec, 2014
The two researchers met with each other for the first time and discussed their research topics.

Feb, 2015
Full-scale research commenced when Packwood was at Tohoku University. They had meetings about once every two months.



Apr, 2016
Packwood joined iCeMS. With an increasing number of meetings, significant progress was made in their research project.

Some mathematical models can be used for understanding phenomenon....

What is the mechanism behind the gathering of RNA molecules?

What is indispensable in your research?

I am the only member on the mathematical end. If anything, computers are also powerful members. They are wonderful. Even going without eating and drinking, they are reliable and never cry or worry [laughs].

Q3 What is the benefit of working together?

Verifications using varied parameters revealed that inter-molecular friction retarding molecular movements had a significant effect on the self-assembly process. This finding enables us to draft further research plans, which take this into consideration.

New research themes emerge based on the solutions derived by equations. This is a major role played by mathematics.

Experimenting with all kinds of conditions is a demanding task. Simulations of various conditions enable us to infer, before the experiment, which conditions are promising. Simulation is beneficial in that it saves us from conducting experiments.

They discussed again and again, and after trial and error many times......

What is indispensable in your research?

There are three things essential for cellular imaging: a powerful imaging system with fluorescent molecular probes, the creative mind and inquisitive eye of a researcher, and the co-operation of the cells.

"This is it!" Finally, they had the result!

Q4 What was the most rewarding moment?

When viewing the two sets of results side by side and seeing Daniel's simulation results present a motion similar to my imaging data, I was very excited.

We followed different paths of thought, but arrived at the same point. Computation alone did not reveal whether the results would be useful or not. I was uncertain. I was reassured to see Ohtan wearing a broad smile.

Additionally, Daniel reported that the substances on the surface of the assembly seemed important. Previously, it was thought that surface proteins were important for self-assembly processes. However, in actual observation, I found RNA molecules on the surface. Contrary to the traditional hypothesis, he showed me a new way to conduct research.

Mathematical models are like a compass pointing to a destination. They suggest the whereabouts of key points.

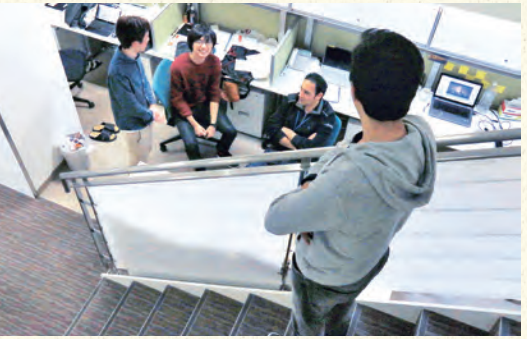
Q5

What do you think are the good points about conducting joint research at iCeMS?

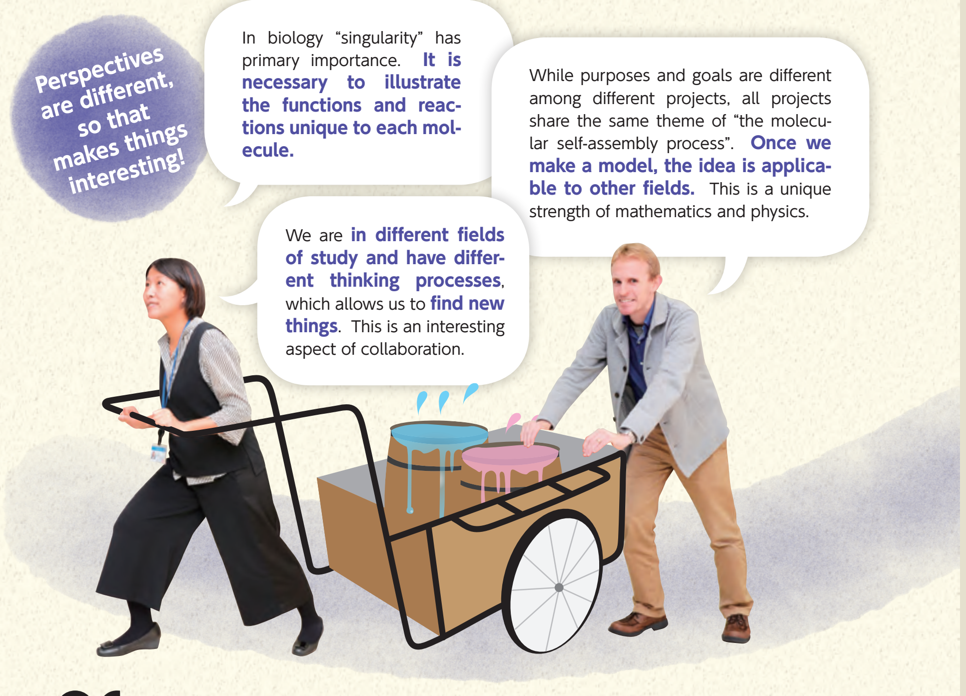
Because the work space on each floor is unpartitioned, researchers often see each other. We frequently have casual meetings; for instance, when we pass each other, we say hi and start discussing research topics.

It is a cultural characteristic of iCeMS.

At iCeMS, it is easy to learn across disciplines. All you need is the interest. Members here are strongly motivated by curiosity.



There are no wall partitions between laboratories in the iCeMS work space. The central open stairwell creates an atmosphere for interaction among different floors.



Q6 Is joint research attractive or interesting？

The most attractive point is that I can use mathematical and physical ways of thinking to contribute to other researchers' projects, even if indirectly. I am by nature a science nerd [laughs]. It is sheer joy for me to learn in areas that are new to me.

In the research conducted with Daniel, I have realized the beautiful simplicity of mathematically-derived answers. People I meet in joint research are specialists in their respective fields, so they are good teachers for me.

I have come to understand cells to some degree, though below Dan's level.

Through the joint research project, I have become aware that learning in areas other than my own enables me to have a deeper understanding of my field as well. In my field, I must grasp almost all the available information to be a leader on the frontlines of research. While it is fun and important to go as far as possible in one field, through joint research, I have additionally enjoyed growing my curiosity.

I feel it very human to pursue cross-disciplinary joint research. With research in my field, in which I am familiar with the methodology, I follow, for better or worse, a logical or mechanical sequence. However, conducting research with researchers from other fields is fun because I need to start thinking from scratch beyond the framework or processes to which I am accustomed.

Interview **iCeMS Frontrunners** 6

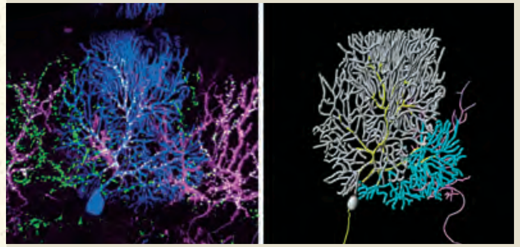
Our brain contains about 86 billion neurons and more than tenfold this number of glial cells, which create a complicated neural circuit. In recent years, by developing cell visualization methods, the process and mechanisms of neural circuit formation have been gradually clarified. Professor Kengaku seeks to understand the mechanism behind how the brain is constructed by studying the dynamic movement of developing neurons.

Pursuing the unelucidated structure of beauty

Mineko Kengaku Professor

"This is a deep world, like a universe. I think it is so beautiful." Kengaku refers to neither a glittering jewel nor the works of famous artists. She speaks of a Purkinje cell, orderly located in the cerebellum. "As when people walk through a crowd without hitting others, neurons stretch to make way for others. In the end, they create a tissue that looks like a peacock with open feathers. Each cell acts with consideration and propriety, like a human. When I see the world through a fluorescent microscope, I find new things." She cannot keep cool when talking about her research.

Kengaku joined iCeMS in October 2008 as a project leader. She works with young researchers and throws herself into it every day. "I always cooperate with students and other researchers. By arguing with one another, we advance only with struggle. Sometimes I am surprised by what my colleagues find, and it motivates me. By respecting each other's ideas and personalities, we make new discoveries. This is my job." With this gentle attitude, Kengaku shows a feeling of pride. She has achieved many results, but as a youth,



Left: Multiplex fluorescent staining of an inferior olivary nucleus neuron axon (magenta) coming into a Purkinje cell (blue) and a synapse molecule (green) .
Right: Graphic of a neural circuit made by tracing 3D images

Mineko Kengaku
Born in Tokyo. Received a PhD in 1995 from the University of Tokyo Graduate School of Medicine. Held the positions of Postdoctoral Research Fellow with the Department of Genetics at Harvard Medical School, Assistant Professor and Junior Associate Professor of Neurobiology with the Department of Biophysics at Kyoto University, a Team Leader at RIKEN Brain Science Institute, and of Associate Professor with iCeMS. Has been at her current position since 2012.

she did not aim to become a researcher.

Connecting with nature as a young person

When young, Kengaku lived in Higashikurume, a suburb of Tokyo. There, she developed a fondness for nature. She ran in nearby mountains, chased insects or frogs until dark, caught and observed wild creatures, and read encyclopedia of animals at night. Their behaviors and shapes attracted her, and she gradually began to admire jobs related to animals. "Should I be a veterinarian? Or have a job protecting wildlife?" She imagined her own future, but couldn't decide on an occupation.

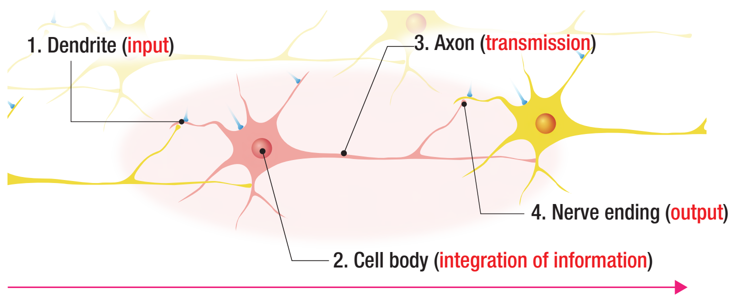
Kengaku decided to explore various fields, so she chose the University of Tokyo, where students don't have to commit to their faculty upon entering. "I noticed that I was more interested in pursuing undiscovered truths than something already known. I wanted to know the workings of life and the structure of living things more fully, so I chose the department of Biological Sciences, Faculty of Science." She was especially curious about the functions of nerves. In physiology class, extracting the giant axons of squid and measuring the organ potential of electric rays absorbed her. "I thought that if I knew the mechanisms of nerves, I could unravel the mystery of creatures' action patterns."

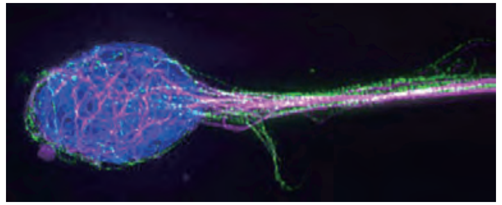
The joy of discovery led to becoming a researcher

At graduate school, she conducted experiments until the last train every night. In those days she researched neural differentiation. The nervous system is an organ that stretches from a creature's head to tail. In the nervous system, neural tubes divide into sections, and each section organizes into the spinal cord, cerebrum, cerebellum and other parts. While humans have a large number of genes, about 22,000, this number cannot clarify the mechanism of complex neural tube differentiation. During her graduate school, this mechanism was not yet unraveled. The only thing already clarified was that neural tubes gradually become nerves through exposure to certain protein molecules. Knowing this, she put protein molecules called FGF on the undifferentiated embryonic cells of a clawed frog, changing the concentration gradually. She noticed that embryonic cells turned into different parts of the brain with different concentrations. "The parts exposed to strong FGF concentrations became spinal cord, and those exposed to weaker FGF concentrations became the frontal brain. When I found this pattern, I got so excited that my leg trembled."

Science is competitive. As a project leader, Kengaku bears the responsibility of success. Even with new findings, she feels more relieved than happy. "Graduate school was a treasure for me. Finding something big with a pure mind becomes a moment you'll never forget." This experience led her to decide to be a researcher.

Work of a neuron in a neural circuit





Novel neuron in the developing brain, moving with a long cellular process. A cell nucleus (blue) moves forward by the force that actin (green) and microtubules (magenta) create.

The reality and the ideal that women researchers face

While her passion for research grew, her path was full of setbacks. In those days, women researchers in Japan faced barriers too high to overcome. "Now, many people say that women should work like men, but it was a male-dominated society at that time. There were many laboratories that didn't hire women at all." Intrusive thoughts always assailed her, such as "I have to give up my research before long", but she couldn't give up easily. Kengaku followed her interest, and she decided on a post-doctorate at Harvard University.

Surprisingly, half of the laboratory members were women. "I found myself shut in a small world. They considered science as the one thing they lived for. By them, I felt pushed to continue researching what interested me."

After returning to Japan, Kengaku was invited to Kyoto University by Tomoo Hirano, one of her seniors in graduate school. "I think Kyoto University is a research mecca. Many unique and famous researchers come here. After Kyoto University, I moved other places, but I wanted to return because my husband was still in Kyoto. Fortunately, iCeMS prepared the position of project leader, allowing Kyoto to challenge me again."

Treasuring the curiosity to know

This is her ninth year at iCeMS. While Kengaku is still crazy about research, she also values life balance.

A picture taken when Kengaku was at Harvard Medical School. With the members of the lab, she visited Chicago, where her boss (second from the left) was born.

Kengaku took a tour of the factory in Haneda Airport with her son. According to her, he likes airplanes, but is not very interested in biology.

"It is hard to be successful at both research and private life. Cooking for and eating with my son is the most enjoyable time for me to think about this nutritive balance." These days, she cannot research from morning to night. However, with a family she can return to her roots and focus on the unsolved questions she wants to research.

"Many young researchers tend to focus on a fast way to help people, researching drug discoveries or a cause of disease. Of course, this is very important. However, if you pay attention to social needs too much, you'll lose what really interests you. I hope young researchers follow what they want to know and value the ambition to find new things. Creating new knowledge is helpful for the future of humanity."

iCeMS Fund — Help us grow

At iCeMS, we develop new insights into the principles of life that distinguish living things from non-living things, and harness these ideas to create bio-inspired super materials and devices that will revolutionize health-care, medicine, industry and the Environment to create a sustainable world for us all.

Whilst much of the work we do here is Pure Science, we are absolutely certain that our research combining high-level chemistry, cell biology and physics, at the border between materials and life, will meaningfully impact the world in which we live.

The research we carry out at iCeMS will help doctors to fight such perennial problems as heart disease, cancer, and degenerative brain conditions, as well as develop invaluable new medicines and therapies. Our revolutionary work also addresses key issues such as global warming, pollution, over-dependency on fossil fuels, and the availability of clean drinking water.

Generous gifts from donors like you provide the financial and moral support needed to continue and develop this research at the cutting edge of modern science. We are not merely content to improve existing technologies, but seek to affect paradigm shifts in the way science may benefit humanity.

Help us to help the world. Together we can make a difference because we care.

Donors

iCeMS would like to sincerely thank all those who have given their support.

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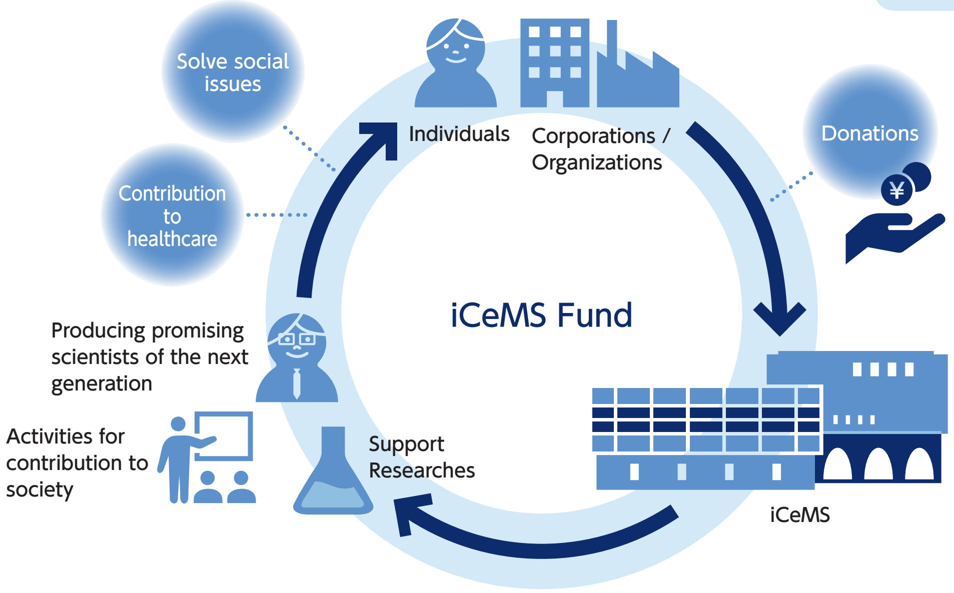


Kyoto University Fund webpage

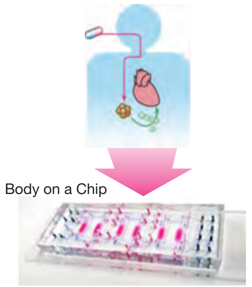
http://www.kikin.kyoto-u.ac.jp/contribution/icems/

iCeMS in brief

Research Highlights

Next-generation drug testing on Chips

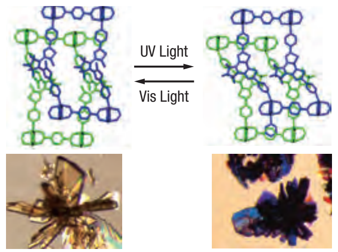
Researchers, led by Ken-ichiro Kamei, have designed a small 'body-on-a-chip' device that can test the side effects of drugs on human cells. The device solves some issues with current, similar microfluidic devices and offers promise for the next generation of pre-clinical drug tests.



The 'body-on-a-chip' device is a novel in-vitro human model that doesn't use people or animals for drug discovery.

Getting closer to porous, light-responsive materials

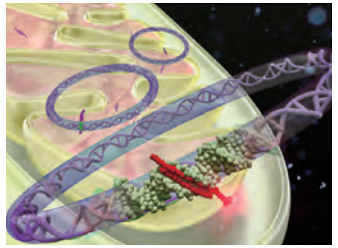
Susumu Kitagawa and his colleagues succeeded in developing a light-responsive crystalline material that can control CO_2 sorption by light. Combining the rigid crystals of porous materials like 'wire-and-string puzzles' enabled them to make a dynamic scaffold. Based on this new idea, it became possible to coordinate the shapes and sizes of pores by manipulating light. This made it easier to collect and eject CO_2 at any time.



By combining crystals of porous materials like 'wire-and-string puzzles', it became possible to make a dynamic scaffold and coordinate the shape and size of pores.

Accessing DNA in the cell's powerhouse to treat disease

A team led by Ganesh Pandian Namasivayam succeeded in re-directing molecules of Pyrrole-imidazole polyamides (PIPs) to cross the mitochondrial membrane. This enables it to access mitochondrial DNA to treat some genetic nerve and muscle diseases.



Schematic illustration of MITO-PIPs that selectively read a target DNA sequence

What's new?

iCeMS invites high school students from Singapore and Kyoto to its Science Festival

On November 10th, 2017, iCeMS held the "iCeMS Science Festival", and about eighty high school students from Singapore and Kyoto visited iCeMS. The students experienced science activities, such as experimentation and observation, and had a fun time talking with the scientists. At the end of the day, a quiz session was held based on what the students learned on the day.

iCeMS holds international symposium

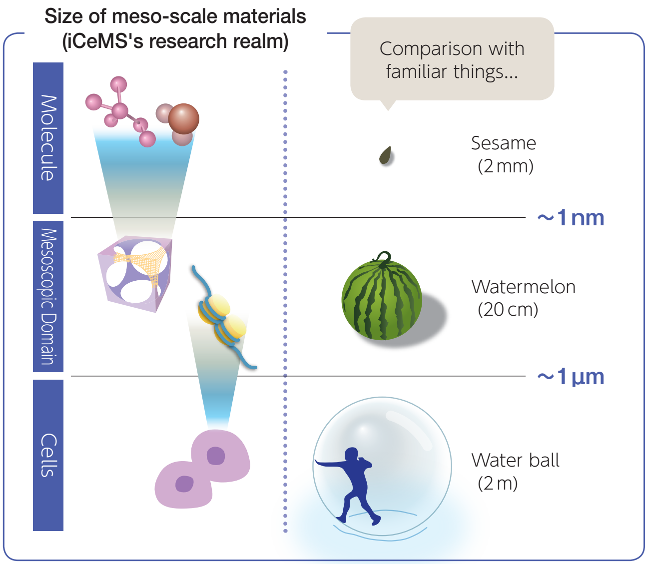
On May 30th and 31st of 2017, iCeMS held its 23rd International Symposium, "Emerging Science for Unlocking the Cell's Secrets", at the KUIAS Main Building. Sixteen up-and-coming young scientists from Japan and overseas delivered research talks, each leading to a lively discussion. About 160 researchers attended from Kyoto University and elsewhere.

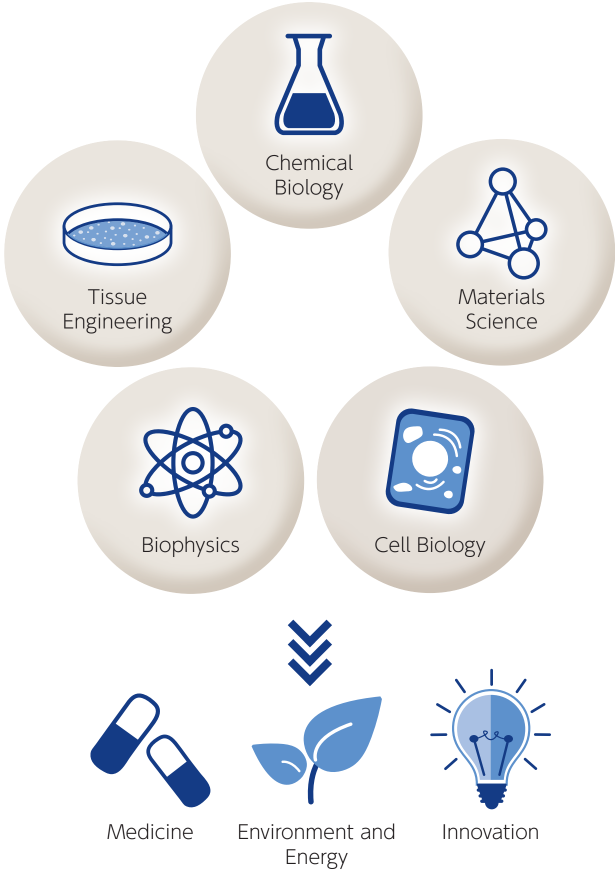
Explore the secrets of life and innovate for the good of society

iCeMS's Mission

- Explore the secrets of life by creating compounds to control cells
- Create life-inspired new materials for the future

Global warming. Pollution. Disease. Aging. These major concerns can no longer be countered by traditional single discipline-based research. 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. We find inspiration through collaboration. We leverage our critical mass of scientific and technological knowledge into purposeful, transformative innovations for the practical benefit of society.





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