Institute for Integrated Cell-Material Sciences

iCeMS

Our World, Your Future

Kyoto University

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contents

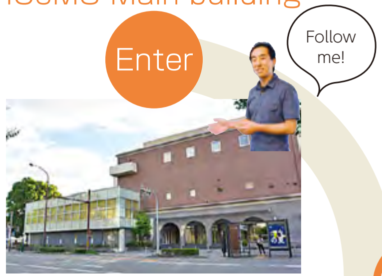
A spherically-grown nerve cell. Behavior of the target gene can be observed from synapses protruding from the sphere's outer surface. Axons are labelled in green and synapses in red.
Turn to page 6 to find out more about the research. (Photo credit: Ohtan group)

Feature iCeMS tour with researchers

The facilities of iCeMS embody the goal of the institute, which is an amalgamation of cell biology,chemistry and physics. In this issue, Associate Professors Ken-ichiro Kamei, Shuhei Furukawa and Hideki Hirori guide your tour of iCeMS with their knowledge of the institute.

Dr. Kamei Dr. Furukawa Dr. Hirori

iCeMS Main building



The main building of iCeMS is located right in front of the Kyodai Seimon-mae bus stop (at the main gate of Kyoto University).

▼ 1st floor Courtyard

The shrubbery at the center, planted to depict a cell, symbolizes iCeMS. The wisteria and cherry tees blossom in the spring.

1st floor

▲ 1st floor Researchers room

There are no partitions separating the laboratories, which facilitates discussion and information exchange. Extensive use of glass in the building design creates an expansive feel.

▼ 2nd floor Exchange Lounge

iCeMS members can enjoy their lunches here, viewing the street lined with gingko trees. The lounge is used to hold meetings, concentrate on individual projects, or, sometimes, have a party.

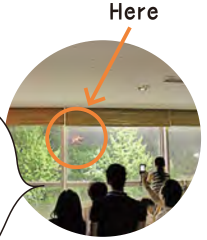
2nd floor

Sliding *shoji* doors and *sudare* blinds add a tint of the traditional Japanese style.

▼ 2nd floor Seminar room

This room is used to hold symposiums and other events. It is equipped for communications with Kyoto University's Uji Campus and a satellite office at Gifu University.

You might hear the piano played by a staff member now and then.



A party is held on August 16 each year to view the Daimonji bonfire.

Paintings are located throughout the facility.

I can construct testing apparatuses myself, even if they are large. Three-dimensional printers are very useful for building testing devices because they can materialize ideas quickly, such as in the case of this cell cultivation instrument.

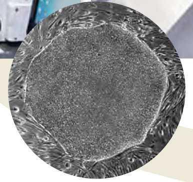
◀ 2nd floor Shared laboratory / common equipment room

The institute encourages the shared use of equipment, an economical measure that helps create new ideas through casual conversations between neighboring groups. This is an example of efforts made by iCeMS to create a setting for cross-disciplinary amalgamation.

3rd floor

▶ 3rd floor Cell culture room

Researchers handle ES and iPS cells in the shoe-free incubation room. The incubator is maintained at 37°C to approximate the environment in the human body. Researchers conduct experiments in a biological safety cabinet, only putting their hands in the test cabinet.



Dr. Kamei is observing iPS cells produced by Prof. Yamanaka.

To research building

iCeMS Research Building

Enter

Welcome !

Drs. Hideki Hirori (laser spectroscopy and optical science) and Shuhei Furukawa (coordination chemistry) guide you through the iCeMS research building. They share humorous exchanges, even though they study in different fields.

1st floor 2nd floor

◀ 1st floor-2nd floor Researchers room

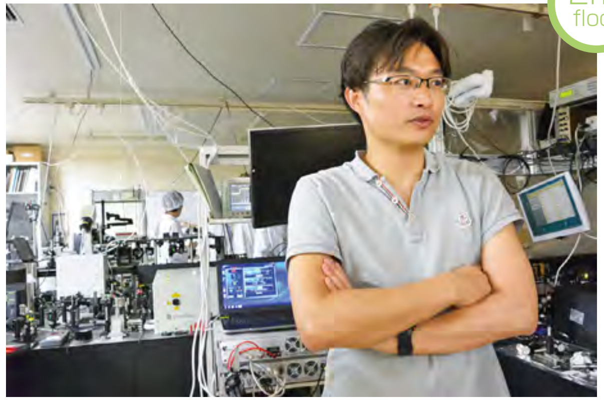
The stairs at the center of the room give an expansive feel and are intended to facilitate casual exchange of information between floors.

The meeting room is set up to allow you to have discussions whenever you want. The clear-glazed doors facilitate transparency.

Researchers arrange and decorate their designated workspace to inspire their creativity.

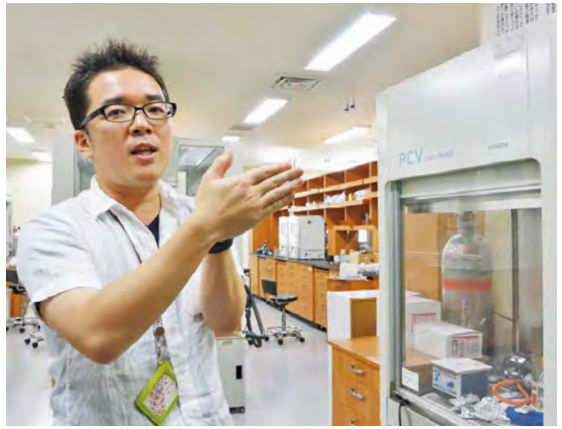
One of our favorite places is between the research building and the project lab. We often have lunch at the western-style table and chairs placed here.

2nd floor



◀ 2nd floor Project Lab

Terahertz radiation consists of electromagnetic waves with a frequency between radio waves and light (infrared) waves. The intensity of terahertz waves developed by Dr. Hirori is the highest in the world. His laboratory betters its record each day and accepts tour applicants from across the globe. Advances in terahertz wave generation technology are expected to lead to the discovery of new phenomena that will enable faster and more energy-efficient computers. Moreover, novel products can make use of the new phenomena, and this technology can assist technical innovation in security systems to, for instance, detect hazardous substances and illegal drugs at airports. He is also meeting the unprecedented challenge of finding out what will happen when cells meet this range of electromagnetic radiation.

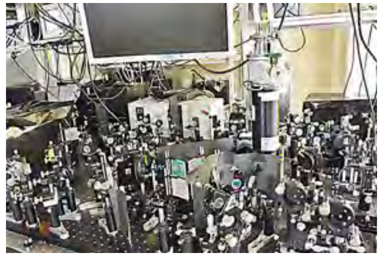


▼ 2nd floor Chemistry lab

Dr. Furukawa pursues gas compression technology by chemistry of porous materials. When vaporized, one milliliter of liquid expands to a volume greater than one liter. A safe gas compression technology can improve fuel tanks of natural gas-fueled vehicles and pharmaceutical development. Among other technologies, he is working on controlling vaporization of encapsulated chemicals in porous materials by providing a signal from outside.

This apparatus is commonly known as a “glove box.” The user places their arms into the box via the black gloves to work while ensuring that the interior is isolated from the surrounding air. The box is filled with nitrogen or another inert gas.

This apparatus, popular in the laboratory, is commonly called a “microwave oven.” It operates on the same principles as market-available ones. In several minutes it heats liquids, which via other heat sources would take hours. Different from common microwave ovens, it is built to be explosion-proof, which means it is robust enough to prevent the container from scattering away in postulated explosions.



The rows of magnifying glass-like tools create a device that generates terahertz waves.

The official language used in iCeMS is English. Foreign researchers account for about 30% of all researchers working at the institute.

3rd floor

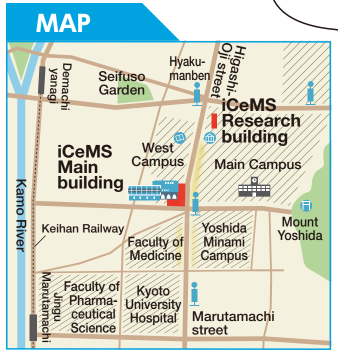
▶ 3rd floor Biochemical system laboratory

Biochemical science laboratories are far quieter than chemical science laboratories, which create considerable ventilation noise from the release of vaporized chemicals.

Exit

Thank you!

MAP



As Wang talks about the inner working of the brain, her eyes light up. "The human memory is a big mystery. The experiences and knowledge we accumulate as we age eventually shape us as individuals distinct from one another." Her passion, or more like obsession, for the brain's ability to memorize information and experience began in her late teens. Wang continues to push the limits in the study of life sciences because she sees vast potential for new methods of treatment that can help this generation and those to come.

"Reversing the brain damage" to treat mental diseases

Dan Ohtan Wang

iCeMS Kyoto Fellow, Assistant Professor

The human brain is made up of several thousand-billion brain cells, each nerve cell with an average of a few thousand synapses that form an intricate network responsible for learning and memory. Wang's research explores how these synapses function on a molecular scale in memory formation and preservation.

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 2000, she studied Cellular Molecular Biology at the Univ. of Alabama. In 2002, she transferred to USC and received her PhD in 2004. From 2005, she worked as a postdoc at UCLA, as a JSPS Postdoctoral Fellowship for Overseas Researcher at RIKEN, and as an Assist. Prof. at iCeMS since 2011. In 2015, her research project was selected by the Hirose International Scholarship Foundation as the first project to be funded in neuroscience.

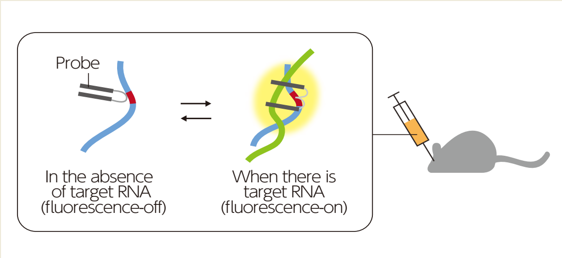
Dreaming of becoming a doctor

"My mother comes from a lineage of doctors. I heard that my grandfather was famous in his village for his expertise in both Western medicine and Chinese traditional and herbal medicine." She was inspired by her family to pursue a profession where she could help people. "I enjoyed learning about biology and health in school. I thought, maybe this is the direction I should be headed…" Wang was about to enter middle school when she had the idea of studying abroad in Japan. Back then, her hometown, Liaoning Province, had close to zero foreigners. One day a gift of paper cranes was sent to her from a Japanese elementary school. "They were breathtakingly beautiful. I began to take an interest in Japan and had to find out more about the country." Around the same time, watching Japanese movies on TV became her new obsession. "'Izu no Odoriko (The Dancing Girl of Izu)' was my favorite. I was a huge fan of the lead actor." Soon she longed to visit Mt. Fuji, which appeared as a landmark in TV shows.

Six years of classes, experiments, and working part-time jobs

Wang's first college choice was one in Japan. She attended a language school for three years to prepare for exams but still dreamt of becoming a doctor. "Back then, only Japanese nationals were eligible to attend Japanese medical schools. I had to choose between becoming a doctor in China or studying abroad, and I chose the latter." She ultimately picked a university program that was close to medicine, the Interdisciplinary Graduate School of Science and Engineering at the Tokyo Institute of Technology. An emotional teenager traveling overseas for the first time, "everything was so different from China," says Wang. "Tokyo is a city full of exciting information and commercial goods. It's still a special place for me."

In her undergraduate degree, Wang studied immunology to explore the world of genomes under Prof. Akira Kudo. The theme of her graduation thesis was genomic rearrangement and the somatic hyper mutation in immune cells. The human body produces antibodies for all antigens that invade it, and this process, on a molecular level, is a rearrangement and facilitated mutationing process of the genome.



RNA labeling technique in live brain tissue of mice, as developed by Ikumi Omoto of the Ohtan group. Fluorescent probes are introduced into the cell through injection and the application of electric current pulses to label target RNA in live tissue. This new labeling technique allows us to observe localized RNA in the cells of live tissue.

Dr. Belinda Goldie studies specific RNA regulators in human nerve cells.

"The genome has this incredible ability to deliberately mutate to increase variation. If we can discover how this works, we can understand how to treat particular illnesses."

However, learning experimental techniques and conducting research was an arduous experience for her. Rent and monthly bills ate away most of her scholarship money. Lab work and part-time jobs occupied most of her free time. After finishing her master's degree, Dr. Kudo suggested studying in the United States so she could focus more on research. "Dr. Kudo was extremely supportive in many aspects, not just my research but also the practical side of life."

Visiting multiple labs in America

At age 24, Wang joined Prof. Peter

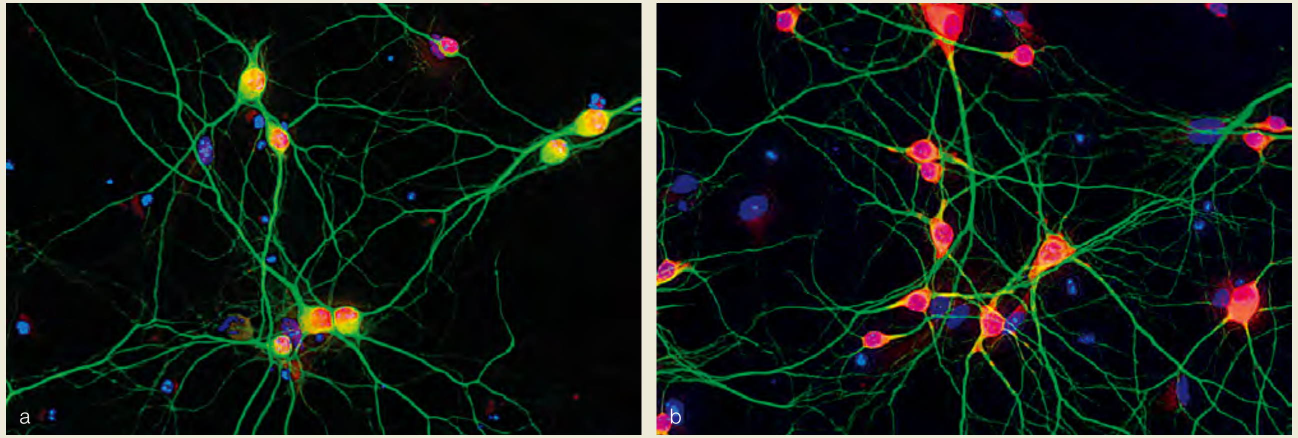
Barrows' lab to make a fresh start at the University of Alabama, where she studied genome reorganization and mutation mechanisms. However, soon after her move, major discoveries in her field were published in the journal, *Cell*. "I felt a sense of despair, that there was nothing left for me to do. Looking back, those two papers only revealed a small part of the immune functions. But back then, I couldn't help but feel depressed."

She picked herself up by building her confidence in the field of research. "In America, where people of many cultures and races coexist, there are no given standards of how a person should be. I felt free to be who I was. I was treated the same as everyone else." What followed numerous lab visits was her newfound curiosity toward neuroscience. "The world we see and the world projected in the brain, are they identical? And how can two different people recognize the same color? I was intrigued by lectures that addressed simple but fundamental questions like this."

Rewiring the brain's neural circuit subconsciously through experience

Wang transferred from the University of Alabama to USC to study psychiatry, after learning that a person's emotions or wakefulness-sleep conditions are controlled by the chemical balance in the brain. "I have been studying transporter molecules, or neurotransmitters (brain hormones) like serotonin and dopamine, since I was in graduate school. I wanted to understand the molecular mechanism of how we feel 'happiness' is influenced by memory."

Wang looked at the brain's memory storage process, or "episodic memory", a subconscious rewriting that occurs in the brain's neuronal circuit every time a person experiences something new. This inspired her current research, which may lead to better treatments for mental diseases. "Molecular biology is my expertise… I was certain that this was the field I could shine in." According to Wang, by seeing and analyzing genomic activity in a living brain's neural pathway, researchers can begin questioning where and how memory is being stored. Discovering the function of RNA (ribonucleic acid) and unveiling memory function seem like two dots that simply do not connect. "My job is to 'bridge' the divide. Understanding RNA is not a cure-all, but it can certainly help develop a hypothesis. We needed a hook, and this was it."



Primary cultures of neurons taken from mice hippocampus. Activity in the cell can be observed by dyeing the neurons. Dendrites are colored in green, and RNA regulatory proteins are colored in red. You can see that RNA regulatory proteins are localized in the nucleus in a, and in the cell body in b.

iCeMS Researcher Q&A

1. Your favorite spot at iCeMS?
   The iCeMS research building in the fourth floor joint laboratory. From the window the north-facing Kitayama and Hiei look great.
2. Please tell me what you are fussy about at work?
   I want as much as possible to empty what is in my head. I try not to accumulate work. I immediately reply after reading an e-mail. I do not open the same e-mail twice.
3. How do you spend lunchtime?
   In communication with lab members or research discussions with colleagues.
4. What are your moments of relief?
   Looking at the sleeping face of my daughter.
5. What is your creed? Do you have a desk motto?
   You must do the thing you think you cannot do. —Eleanor Roosevelt
6. What surprised you, coming to Japan?
   On my first visit to Japan in 1994, I was surprised at the convenience store and the phone box.

The first working day at iCeMS. That day was also my daughter's entrance ceremony at a kindergarten.

Seeing the world through different colored glasses

Wang returned to Japan in 2010 to join Riken at Wako, Saitama prefecture. She resided for a year at the Organic Synthetic Chemistry Lab to make probes, or "illumination markers", that help visualize RNA activity in a living brain. When seen from a chemist's point of view, RNA looked completely different. It was almost like seeing a magic trick for the first time. "The special probes instantly make the RNA shine when injected into the cell." After practicing with various tools since her days in UCLA, seeds started to bear fruit in Kyoto. Approached by Dr. Nakatsuji, founding director of iCeMS, at an iCeMS seminar, she soon became in charge of a research group. Japan's strength in chemistry helped produce many groundbreaking discoveries and consequently Nobel Prize winners, and Kyoto University is one of the best universities in Japan. "I felt that my research could only be achieved in Japan. I am experiencing a life that I could never have imagined before arriving here."

Using the mechanism of learning and memory

The truth is, many people suffer from mental illnesses in the modern age, and plenty of previous studies prove that these illnesses are related to patients' gene abnormalities. Surprisingly, the only effective treatments that exist are medication and electric shock, despite treatments for mental diseases being around for some time. Eliminating side effects of drugs have proven difficult since it leaves the entire body vulnerable to the drug's effect. There are ways to directly control the chemical balance of the brain and modify the genome, but Wang suggests we tap into our innate functions, such as memory and learning. The brain's neural network is being constantly overwritten by external signals. By taking advantage of the brain's "reversibility" we can fine-tune the expression pattern of the genome just by changing the surrounding environment. "If the neural network is rewritten by gene expression, behavior can be altered," says Ohtan. Antidepressants promote the production of serotonin and help deliver them to the body. "The human brain is not a flask. To treat the target

area, it is far more effective to use the brain's delicate import system. Why? Because the brain has the inherent ability to restore itself."

She is experimenting on mice for her project on targeted RNA illumination. "One day I want to develop probes that can be used in hospitals and clinics," says Wang. "My teenage dream of becoming a doctor is connected to where I am now." She says iCeMS has provided a perfect environment where researchers across disciplines can engage in discussions that lead to innovation. Wang's research happens to be a concoction of life sciences and technology. "I discovered that there are no limits to fusing disciplines at iCeMS."

Challenges of leading a team

Wang is the head of her team of ten staff, all working toward one goal: finding links between genes and brain plasticity. However, the process is a constant tug-of-war, and multiple experiments collide. Research background and interests vary from person to person, and the ideas and interpretations of results largely influence the overall direction of the project. Small differences can lead to interesting developments or digress from the original plan. "I struggle to find a balance between exercising the right amount of leadership and respecting the space of each staff. Needless to say, leadership is essential in order to produce maximum results from projects that are limited in time and resources. I need to communicate and manage staff effectively. Staff members that are actually doing the experiments are one step ahead in the future by coming into contact with the latest data, and I am in the past waiting for them to report to me. I want to minimize this time lag. Until now, I was fine with having one hard drive, but I am learning to compartmentalize according to the role that I play."

Family time is just as important

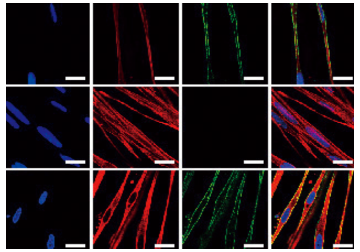
Wang steps into the office before nine a.m. She begins her morning routine with a cup of coffee and flipping through science magazines such as Nature, Science, Cell, and Neuron. "I enjoy this time a lot," says Wang. After the lab members arrive, she attends meeting, checks e-mails, and finishes other administrative tasks until noon. During lunch she takes the time to interact with her lab members. "Research funding applications, writing papers, updating the group homepage… I am always writing. Around six p.m. I take off to pick up my daughter. I eat dinner with my family. We even play games together. My daughter turned nine. I want her to grow up so she can be my scientist buddy [laughs]." Wang's husband is also a researcher. Same age, and at similar stages in their careers, the couple often turn to each other for support. "My little girl seems to have taken on some of our traits. One day I came into work and opened my bag. There was a note with a message that read 'good luck with your paper.' Around the time of the Nobel Prize Announcement, she asked how many Nobel Prizes I've gotten so far. In a way, she has helped a lot; she gives me energy."

iCeMS in brief

Research Highlights

iPS cells used to correct genetic mutations that cause muscular dystrophy

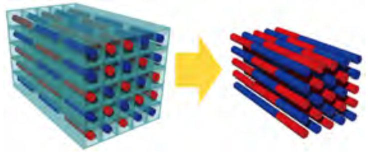
Assistant Professor Akitsu Hotta's team revealed that induced pluripotent stem (iPS) cells can be used to correct genetic mutations that cause Duchenne muscular dystrophy (DMD). The research, published in *Stem Cell Reports*, demonstrates how engineered nucleases can be used to edit the genome of iPS cells generated from the skin cells of DMD patients.



Expression of dystrophin in skeletal muscle cells by iPS cells derived from patients

Original technique to successfully blend polymers

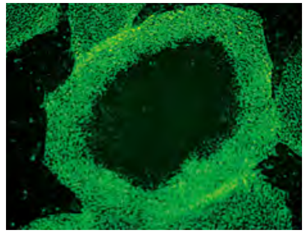
A team of researchers led by Dr. Susumu Kitagawa has developed a new technique to successfully blend different types of polymers for the first time. This finding, published on July 1st in *Nature Communications*, will significantly contribute to the development of novel smart materials.



By using porous materials as a mold, this technique completely mixes the polymer at the molecular level which has not been done before

KP-1 probes to identify Human iPS cells on sale from June 1

A chemical probe that becomes selectively embedded in human embryonic stem (hES) and induced pluripotent stem cells, discovered by Professors at iCeMS, are manufactured and sold by Goryo Chemicals. The probe could be used to help scientists and doctors select cultivated cells for use in efficient and safe regenerative medicine treatments.



Collection of shiny iPS cells

What's new?

Princess Maha Chakri Sirindhorn of Thailand visits iCeMS

On April 20, Her Royal Highness Princess Maha Chakri Sirindhorn of Thailand and a Thai delegation visited iCeMS. Princess Sirindhorn discussed with core members the future of iCeMS' role as a global hub for research collaboration. After presentations, the Princess was given a lab tour to introduce research using state-of-the-art equipment.

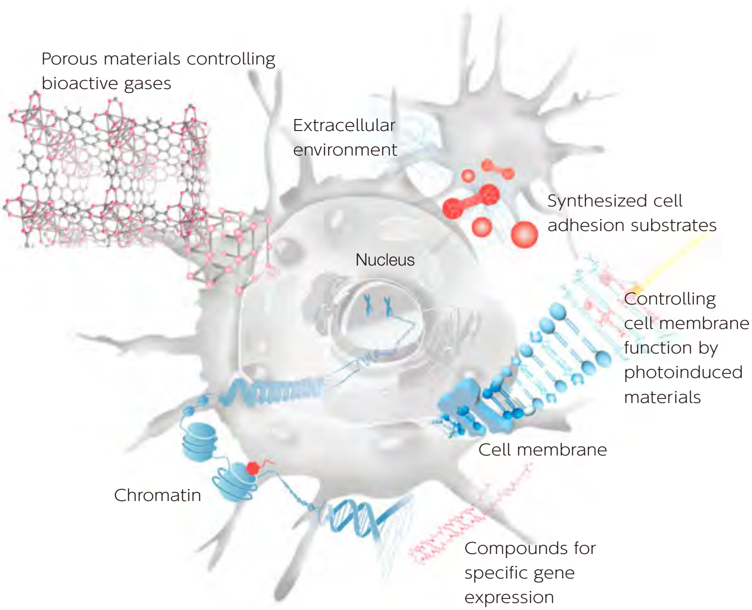
"Learning Lounge" series available online

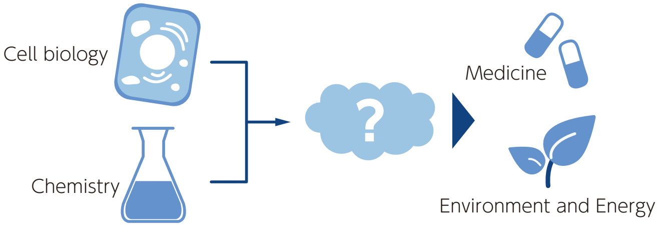
The "Learning Lounge" features young scientists who, in 20 minutes, deliver a presentation to persuade any listener, even those without a scientific background, why their research area is important to the world. The series can be viewed on the iCeMS YouTube channel and from the iCeMS website.
http://www.icems.kyoto-u.ac.jp/e/rsch/ll/

Groundbreaking research at the border between Materials and Life

At iCeMS, we develop new insights into the principles of life that distinguish living things from non-living things. We 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.

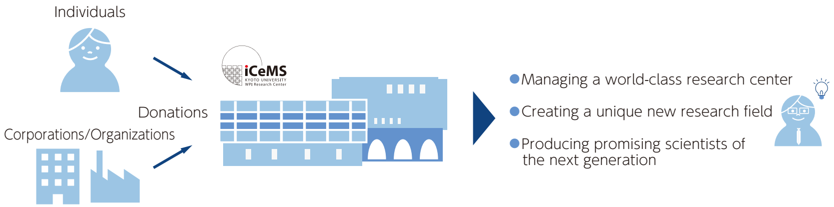
Whilst much of the work we do here at the Institute is pure science, we are absolutely certain that our research, combining high-level chemistry, cell biology and physics at the border between materials and life, will meaningfully impact the world in which we live.





Help us grow

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



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