Institute for Integrated Cell-Material Sciences

iCeMS

Our World, Your Future

Kyoto University

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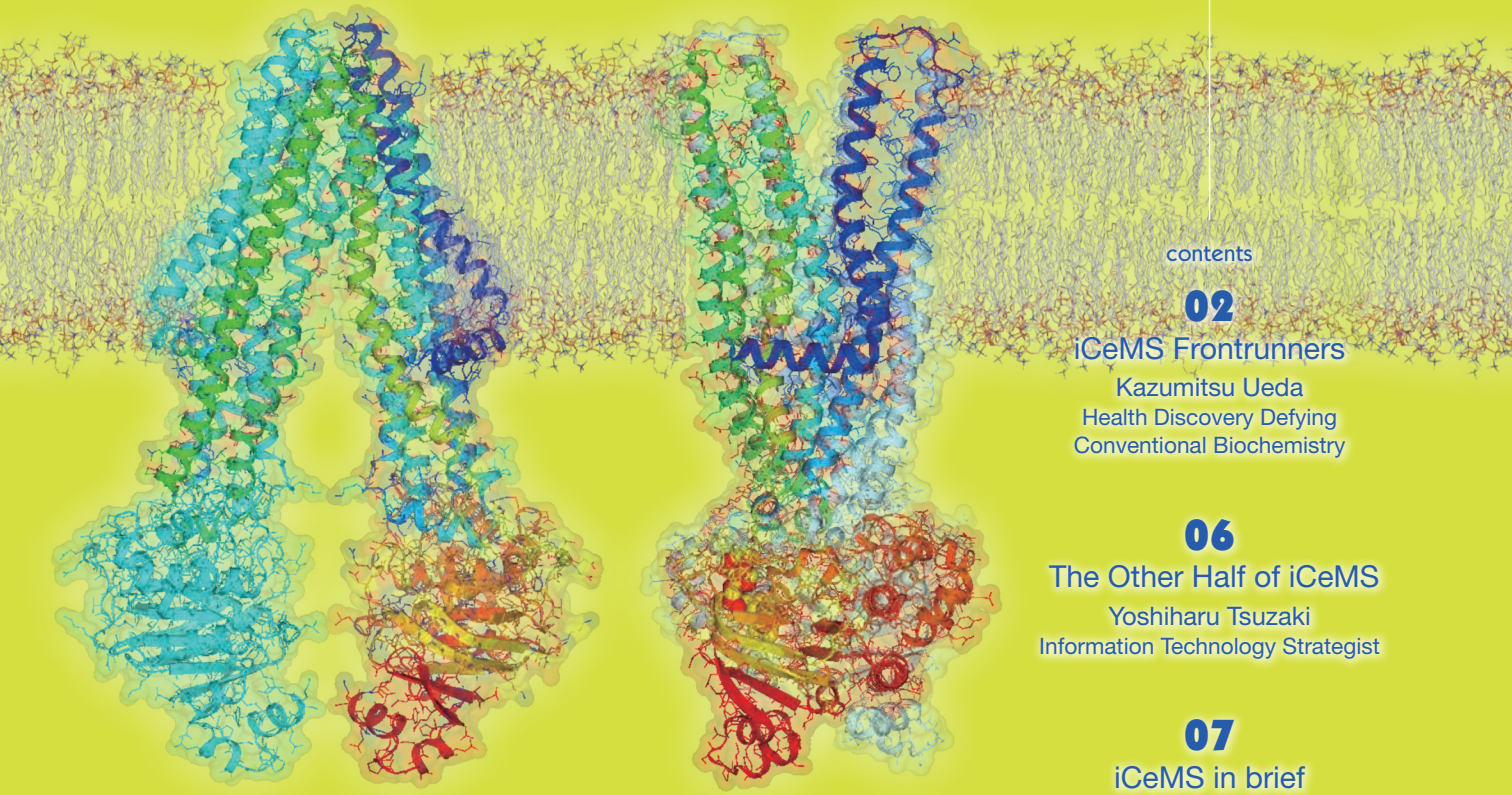


contents

MDR1 uses the energy of ATP hydrolysis to export lipid-soluble drug and harmful substances out of the cell, and plays an important role of human physiology and health. Turn to page 2 to read the full story.

In the world of science, a single discovery sometimes overturns many established notions. One such example is ABC proteins, including MDR1 protein. Professor Kazumitsu Ueda is the world's first person to isolate the MDR1 gene. ABC proteins are important players in human physiology and health. The workings of ABC proteins have many times defied the norms of understanding shared by scientists in the field of biochemistry. Before the discovery, people around Professor Ueda criticized him for "pursuing irrelevant research". Living by the motto "refrain from believing common notions", he unswervingly continued his research and opened the way to uncharted territory.

Kazumitsu Ueda
Born 1954 in Himeji. Received a PhD in agriculture from the Graduate School of Agriculture, Kyoto University in 1984. After working as Assistant and then Assistant Professor at the graduate school, in 2003, he took the post of Professor at the graduate school. He also worked as Professor at the Institute for Integrated Cell-Material Sciences, Kyoto University between 2007 and 2017. In 2019, he retired from the graduate school under the age limit and took his current post.

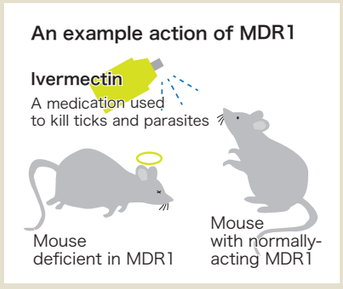
Health Discovery Defying Conventional Biochemistry

Kazumitsu Ueda Program-Specific Professor

"ABC proteins" are a family of proteins in cell membranes, which transport various substances. Forty-eight genes are expressed in human ABC proteins, of which MDR1 was the first in the world to be identified. Professor Ueda discovered it some 35 years ago.

Protection from Foreign Substance Entry at Cell Membranes

"Medication absorption greatly depends on the action of MDR1. For instance, you might have been advised not to take a certain medicine with grapefruit juice. The reason is that furanocoumarin, a compound contained in grapefruit, inhibits the medication pumping function of MDR1, which results in the small intestine's overabsorption of the drug. If a blood pressure-lowering drug effect becomes excessively strong, for instance, it is life-threatening." Professor Ueda's speaks gently in a low voice, invoking a medical doctor's sense of security.

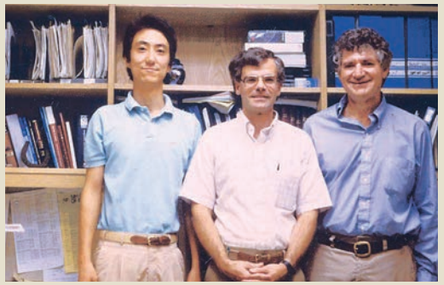


In 1994, a Dutch researcher sprayed ivermectin on a mouse deficient in MDR1. This resulted in the death of the mouse. Compared with the normal mouse, the mouse deficient in MDR1 had about a 100 times higher accumulation of ivermectin in their brain. This experiment revealed that MDR1 functions to prevent harmful substances from entering the brain via blood flow.

MDR1 acts not only on medications, but also on the absorption of nutrients from everyday food. Nutrients are absorbed by the small intestine, carried to the liver, and transported to cells via blood flow throughout the body. The risk of absorbing lipid-soluble toxic compounds, such as alkaloids produced by plants and microorganisms, is present during this process.

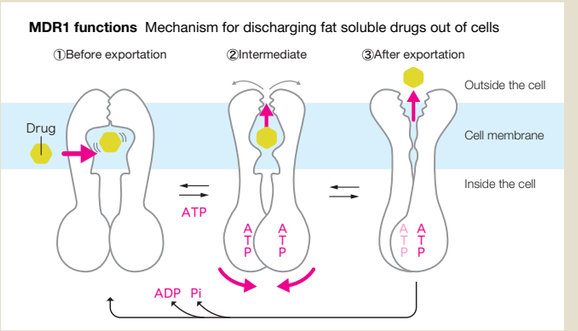
Using energy, MDR1 exports hazardous substances that have entered cells. For example, MDR1 wards off disease by preventing the small intestine's absorption of various lipid-soluble harmful substances from food. MDR1 is also active in brains and testes, preventing harmful substances from entering these important organs.

"Before the discovery of MDR1, the conventional notion was that harmful substances were detoxified by the liver.



Professor Ueda was a postdoctorial fellow at the U.S. National Cancer Institute; with Dr Ira Pastan (lab chief, right) and Dr Michael Gottesman (section chief, center).

However, its discovery revealed that we maintain good health largely due to the function of MDR1, alongside the liver's detoxication action. All living things, from microorganisms to plants and to animals, possess ABC proteins, including MDR1. Upon emerging as single cells, it is thought that living organisms acquired MDR1 to prevent lipid-soluble harmful substances present in their environment from entering the cell. Since MDR1's discovery, many other structurally similar proteins have been found, also grouped into the ABC protein family.



MDR1 takes a lipid-soluble drug from within the cell membrane into the molecule and directly exports the drug out of the cell like a pump, a result of a structural change powered by ATP binding.

MDR1 Against Common Notions

Professor Ueda discovered the MDR1 gene when he studied in the United States for two years from 1985. Before then, he had worked at the Graduate School of Agriculture, Kyoto University, researching the actions of anti-cancer drugs on DNA. He was specifically interested in the multidrug resistance of cancer. At the time, the loss of the efficacy of anti-cancer drugs with the recurrence of cancer several years post-surgery posed a problem. In these instances, anti-cancer drugs that had not been used during prior treatment also lost their efficacy. Multidrug resistance was implicated in more than 90% of deaths caused by cancer. Clarification of the mechanisms of multidrug resistance was urgently necessary.

"After I earned my Ph.D., I heard that the U.S. National Cancer Institute was looking for postdoctoral fellows. In the 1980s, the technique of cultivating human cells in petri dishes was established in the United States, enabling researchers to cultivate multidrug-resistant cancer cells. I thought this presented a chance for me to discover something new." Ueda grabbed this chance and left for America.

While working on team research tasks, he one day noticed that a certain gene was overexpressed in multidrug-resistant cells. It was a membrane protein gene. On the chance of encountering

something important, he promoted the gene's expression and observed that by using energy, the expressed protein pumped a lipid-soluble anti-cancer drug out of the cell. All institute members were wide-eyed. No one had thought that energy would be expended to remove membrane-permeating lipid-soluble compounds from the cell.

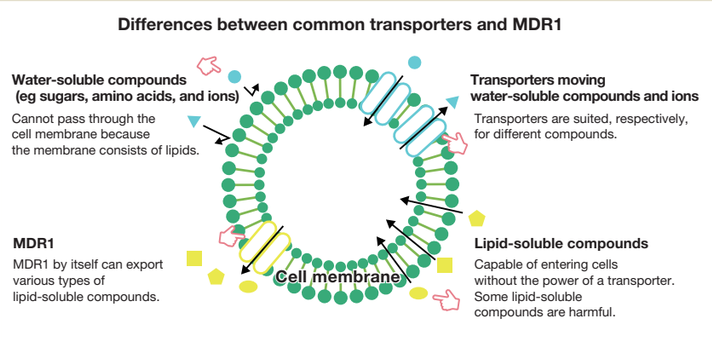
Before this discovery, many people doubted the research direction pursued by Professor Ueda. They thought that anti-cancer drug resistance was caused by too many genes and mechanisms, which would remain unsolved unless a vast number of genes were studied. Their views were quite understandable in light of the basic idea that biochemical reactions show high substrate specificity. For example, metabolic enzymes recognize specific sugars and amino acids. A one-on-one recognition mechanism was thought to exist in biochemical reactions. Notwithstanding this, Professor Ueda and other researchers witnessed a single transporter pumping various types of compounds out of cells. The transporter used the common characteristic of lipid solubility to recognize the compounds. "No one imagined the existence of a transporter like this. I was extremely lucky." The expressed gene was named MDR1, using an acronym for multidrug resistance.

His Research Mindset Originated on the Silk Road

"Believe not blindly in common notions" is Professor Ueda's motto. He cultivated this research mindset when he studied at the Faculty of Agriculture, Kyoto University. "At the time, it was popular to travel with a backpack. Many young Japanese people set out across the sea. Driven by this trend, and with an admiration for the Silk Road, I visited Turkey via the USSR and then traveled to Iran, Afghanistan, Pakistan, and India." He made a three-month penniless travel, overland by bus and train.

He saw directly that different countries, areas, and ethnic groups had quite different ways of thinking and customs. More than a few times, he experienced that norms in Japan went against the common notions of other ethnic groups. Departing from the norm, he quickly acquired a clearer view. "Being skeptical about common notions is an essential attitude for scientists. At a press conference when he won a Nobel Prize, Professor Tasuku Honjo said, 'Do not always believe what textbooks say'. Common scientific notions can dramatically change after one discovery. I was criticized by many forerunners. However, I came across the unknown after a steady, continuous research effort."

Since the discovery of the MDR1 gene, Professor Ueda has spent nearly 30 years working on elucidating MDR1 structure by thoroughly rejecting unproven assumptions and examining every conceivable hypothesis. Gradually he is shifting his research focus to other ABC proteins, based on his work with MDR1.



Membrane proteins known as "transporters" enable low-molecular compounds to pass through cell membranes. Water-soluble nutrients such as sugars and amino acids by themselves cannot pass through a cell membrane because the membrane consists of lipids. To enter cells through a barrier, therefore, transporters acting as pumps are essential. In contrast, lipid-soluble compounds readily enter and exit the cell membrane. Some lipid-soluble compounds are toxic to the human body. Using the energy of ATP hydrolysis, MDR1 transports harmful lipid-soluble compounds out of cells.

One example is ABCA1 protein, essential in forming high-density lipoprotein (HDL) cholesterol (good cholesterol). People with high HDL cholesterol levels are less prone to arteriosclerosis, and he believes that tracking down the mechanism of ABCA1 formation of HDL cholesterol will lead to the prevention of myocardial infarction and other heart failures, as well as cerebral strokes.

A Quest for the Most Interesting

In March 2019, after many years of service, Professor Ueda hit retirement age for the Graduate of School of Agriculture at Kyoto University. As a student, he affiliated with several schools, enrolling in the engineering faculty of another university and then the Department of Forest Science, the Faculty of Agriculture at Kyoto University. Finally, he selected the Department of Agricultural Chemistry, the Faculty of Agriculture.

He took a roundabout path because he wanted to know "what I would be good at and what fascinated me". At the engineering faculty, he was not interested in manufacturing; and at the Department of Forest Science, he could not memorize tree names, so he gave up. While still undecided, he by chance read *Chance and Necessity* published by Jacques Monod, a French molecular biologist. Ueda instantly became captured by the study of DNA. "DNA research required only remembering names for four nucleic acids and 20 amino acids. The subject was best suited to an individual like me who was not confident in memory retention (laugh)." After he enrolled in the Department of Agricultural Chemistry, every day became exciting and 40 years passed like an arrow.

At a carpet shop in Afghanistan; "The salesclerks were very kind, although they were tough-looking."

Subsequently in April 2019, Professor Ueda was invited to become a Program-Specific Professor at iCeMS, where he had long worked as a Principal Investigator while concurrently serving for the Faculty/Graduate School of Agriculture. He was even involved in setting up the institute as a founding member. Because he knows of the confusion during a hectic budding period, he is happy with the institute's current environment that fosters young researchers. "This is my restart, as I turn over a new leaf. Although I am not sure how long I can continue research, my curiosity for wanting to know what it is to be living is inexhaustible. The mechanisms of living organisms are profoundly complex and diverse. Humans, monkeys, and mice appear similar to each other in some respects, but they are actually different. They have evolved bodies best suited for their respective environments. As such, studying mice, however much insight it provides, can never be enough to understand humans. Even seemingly familiar things may reveal completely different aspects from a different angle. Discoveries may be gained by coincidence. You may pick up a stone at your feet and discover a valuable fossil. Research is like that. It excites me, so I cannot retire from it. At iCeMS, young talented researchers find many new challenges, and their activities flourish in various ways. I also continue to meet the challenge of overturning what is taken for granted."

He became a student at an aikido school at the age of 60. He was fascinated by techniques used to defeat the opponent without relying on force or placing importance on winning or losing. "I began practicing Aikido, as I really wanted to do something that I could continue to improve at, even when I am 70. Wearing a *hakama* is not allowed before a certain rank. My progress is slow, but I'd like to wear it someday."

The Other Half of iCeMS

Yoshiharu Tsuzaki
Information Technology Strategist
Specially Appointed Research Associate

People take for granted a reliable information environment. However, it is an essential part of research. For example, if your research results are on a virus-infected computer, your data and other confidential information can be leaked, allowing others to take credit for your hard work and innovation. Even worse, an unreliable information environment may result in discrediting or tarnishing the university and its reputation. Fortunately, Yoshiharu Tsuzaki, who is in charge of information security at the Institute, strives to maintain a secure, convenient, and safe information environment.

Network connectivity to services

- Provides connections to Kyoto University's email system and shared storage servers
- Establishes the IT environment for new laboratories (Internet connections, etc.)

Information security investigation

- Investigates iCeMS' information environment in cooperation with Kyoto University's Institute for Information Management and Communication

Information security awareness

- Encourages researchers to install anti-virus software
- Educates staff about information security

Inquiry support

- Provides remote and on-site support to resolve challenging computer issues
- Physically assists staff to provide the most appropriate solution to individual issues

Customized IT support

Tsuzaki•I love working at iCeMS due to the amazing people and supportive environment where researchers and staff respect each other. My primary responsibility is to oversee the Institute's information environment. Not only do I prepare the information environment from the perspective of ease of use each time the room use changes or new equipment is introduced, but I also take pride in clear and timely communication. Because each person has a different degree of comfort with information equipment, I tailor my response to the intent of the inquiry. Due to my continuous effort and ingenuity, I have gradually earned the trust of the people at this institute. It is a great honor to be treated as a specialist and a valuable part of the team.

Keeping information safe

Tsuzaki•Carelessness often results in security issues. For example, simple passwords make you vulnerable to third-party hacking and downloading malicious software (malware) might infect your computer with a virus. Those who think, "It won't happen to me" tend to be the most vulnerable.
My goal is to increase information security awareness, but I cannot achieve this alone. Unfortunately, universities, businesses, and researchers do not like to spend money or think about information security until it is too late. However, if each person on the network is conscious about their behavior, information can be protected. Thus, I will continue to help everyone implement best practices, allowing all researchers to focus on his or her own projects.

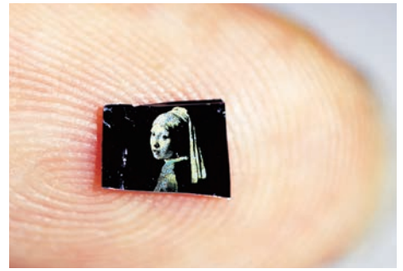
iCeMS in brief

• Research Highlights •

OM technology allows an inkless, large-scale color printing process

Easan Sivaniah and colleagues use a technology called OM (Organized Microfibrillation) that adjusts crazing and precisely form fibrils to develop a material that reflects light of a specific frequency that we recognize as a color through our eyes.

When polymers are under stress crazing occurs, producing fine fibers called "fibrils". Normally, crazing occurs randomly, such as when plastic products deteriorate. OM technology made it possible to control the crazing and print on flexible and transparent materials with a resolution of up to 14,000 dpi. This is expected to have various applications, such as the development of inkless color printing technology and the prevention of banknote counterfeiting.



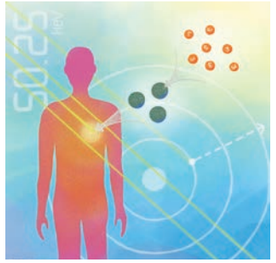
A very high resolution painting of approximately 1 mm width can be created without ink.

Masateru M. Ito, Andrew H. Gibbons, Detao Qin, Daisuke Yamamoto, Handong Jiang, Daisuke Yamaguchi, Koichiro Tanaka & Easan Sivaniah (2019). Structural colour using organized microfibrillation in glassy polymer films. *Nature,* 570(7761), 363-367

Towards safer, more effective cancer radiation therapy using monochromatic X-rays and nanoparticles

Fuyuhiko Tamanoi and colleagues revealed that cancer mass containing gadolinium were completely destroyed when hit by monochromatic X-rays.

Currently, radiation therapy is widely employed as a primary method of cancer treatment, but problems exist with the X-rays used to date, which cause unwanted side effect and have difficulty reaching the cancer tissue. The research group sent gadolinium into cancer spheroids using specially-designed silica nanoparticles. They then irradiated cancer spheroids with a monochromatic X-ray using the beam BL14B1 at the large synchrotron facility (SPring-8). The results demonstrate that cancer spheroids can be effectively attacked by irradiating with 50.25keV X-rays, which are most suited to release Auger electrons from gadolinium. These findings are expected to lead to the development of a new cancer radiation therapy.



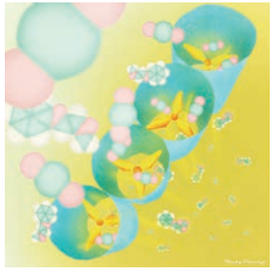
Precisely tuned X-rays can more effectively hit cancer mass without harming other parts of body by using gadolinium-loaded mesoporous silica particles. (Illustration by Mindy Takamiya)

Kotaro Matsumoto, Hiroyuki Saitoh, Tan Le Hoang Doan, Ayumi Shiro, Keigo Nakai, Aoi Komatsu, Masahiko Tsujimoto, Ryo Yasuda, Tetsuya Kawachi, Toshiki Tajima, Fuyuhiko Tamanoi (2019). Destruction of tumor mass by gadolinium-loaded nanoparticles irradiated with monochromatic X-rays: Implications for the Auger therapy, *Scientific Reports* 9, 13275

New material captures carbon dioxide

Susumu Kitagawa and colleagues successfully developed a new porous material that can selectively capture carbon dioxide (CO_2) and convert it into useful organic materials.

The porous material developed through this research has a jungle-gym-like network structure consisting of organic molecules and metal ions, which contain countless nano-sized pores. These pores have a high affinity towards CO_2 molecules and can selectively incorporate CO_2.



This new porous coordination polymer has propeller-shaped molecular structures that enable selective CO_2 capture and efficient conversion of CO_2 into useful carbon materials. (Illustration by Mindy Takamiya)

The newly developed porous material not only captures CO_2, but also increases the reactivity of CO_2 to enable its conversion into useful materials. This material will likely be utilized by technology that emits CO_2, a major cause of global warming, as a low-cost resource.

Pengyan Wu, Yang Li, Jia-Jia Zheng, Nobuhiko Hosono, Ken-ichi Otake, Jian Wang, Yanhong Liu, Lingling Xia, Min Jiang, Shigeyoshi Sakaki & Susumu Kitagawa, (2019). Carbon dioxide capture and efficient fixation in a dynamic porous coordination polymer, *Nature Communication* 10, 4362

• What's new? •

iCeMS to establish two on-site labs in UCLA and Taiwan

Kyoto University has approved iCeMS' plans to establish two on-site laboratories, the "Quantum Nano Medicine Research Center (iCeMS and the University of California Los Angeles)" and the "Center for Integrated Biosystems (iCeMS and Taiwanese Academia Sinica)". Last year, "The Smart Materials Research Center" was jointly established in Thailand by iCeMS and the Vidyasirimedhi Institute of Science and Technology (VISTEC). All together, iCeMS will have three on-site laboratories once UCLA and Taiwan are launched.

Sixty-two Japanese and British high school students visit iCeMS

On August 1st, 62 high school students from Japan and the UK visited iCeMS. High school students visited eleven booths that introduced iCeMS research, where the students learned about the fun and depth of science by touching research equipment and participating in experiments. Many comments were received from high school students such as, "I found it important not only to find answers but also to think together", and "I thought it would be easier to get better answers if different professionals work together".

Awards

- **Susumu Kitagawa receives Emanuel Merck Lectureship 2019**(May 13)
- **Ryoichiro Kageyama receives Takeda Medical Prize**(Sept 20)
- **Aiko Fukazawa receives Brilliant Female Researchers Award (The JST President Award)**(Oct 17)

Activities

- **iCeMS holds Shanghai-Kyoto Chemistry Forum**(Mar 23)
- **iCeMS holds "iCeMS Future Day" and "iCeMS Fund Thanks Gathering"**(Mar 25)
- **iCeMS holds SPIRITS International Symposium "Shaping Self-Assembled Mesoscale (Bio)Materials with Microengineering"**(Mar 28)
- **Stem cell culture medium developed by the Hasegawa group was commercialized**(Mar 29)
- **iCeMS holds joint symposium, marking the planned opening of the Taiwan office**(June 24-25)
- **iCeMS exhibits a booth at E-MRS 2019 Spring**(June 27-30)

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.

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Editorial note

Prof Ueda joined iCeMS at its establishment in 2007, and for many years has been supporting iCeMS with his outstanding research and gentle smiles. He always thinks outside the box, follows his curiosity, and enjoys everything. Listening to his story this time, I felt that this mindset lies in both his life and research. Personally, I have been a fan of him for a long time. We can finally introduce his genial and curious personality to readers, which makes me happy and excited.

Izumi Mindy Takamiya

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