SUMMER 2017

RIKEN RESEARCH

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19,000 new keys to genetic traits

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Researchers at the CSRS (see more about the center on page 25) are using disciplines ranging from plant sciences to chemistry to help achieve a sustainable society that recycles both resources and energy.

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Initially established as a private research foundation in Tokyo in 1917, RIKEN became a national research and development institute in 2015.

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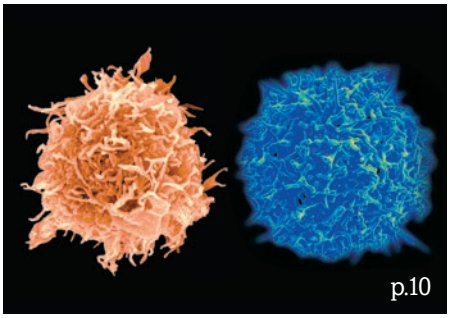

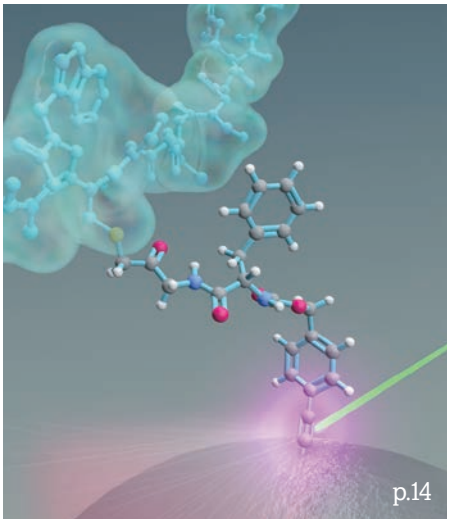

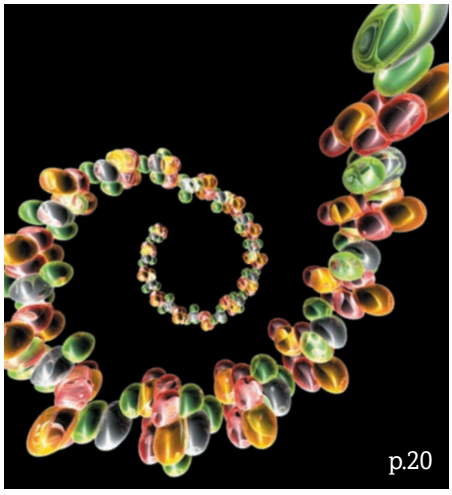

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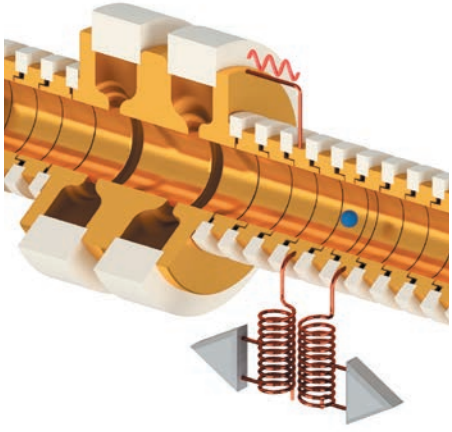

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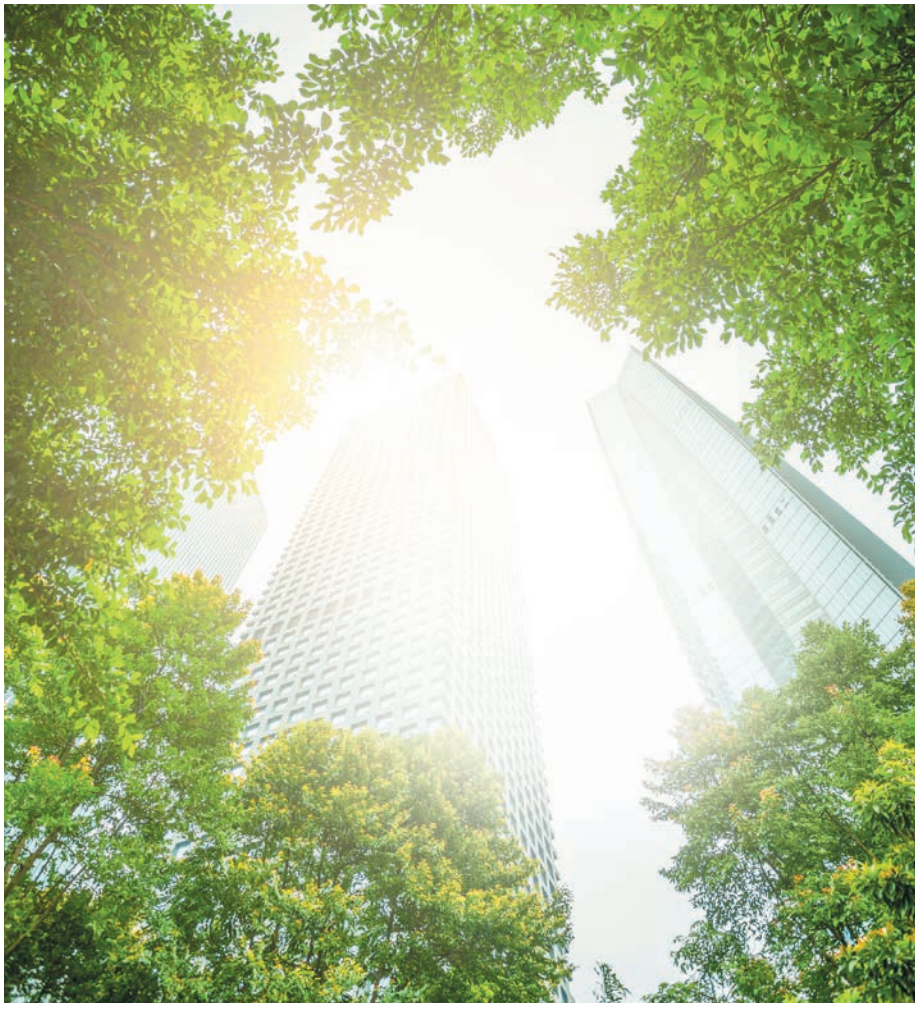

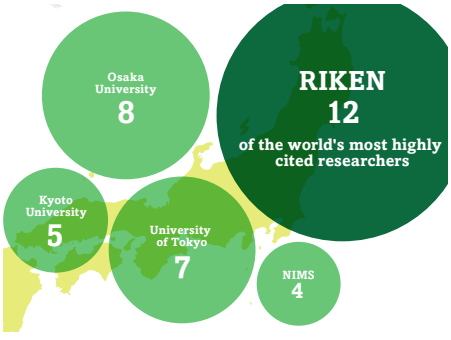

Fulfilling our responsibility to society

Motoko Kotani
Executive Director, RIKEN

As RIKEN's newest executive director, I am excited by the changes going on in the organization. Scientists have a mission to carry out fundamental research by bringing original viewpoints that help humanity go beyond our current limitations by pioneering new frontiers of science and to strive to create true prosperity. In today's world, where science and technology involve not only understanding physical and social phenomena, but also improving the lives of citizens, scientists need to think seriously about the future of society to ensure that science and technology develop in a healthy way. Scientists must always maintain humility and sincerity. In particular, they must never forget that scientific results are a public asset since science serves society and is supported by society.

I am thus happy to note that this issue of RIKEN Research has a new focus—examining the Sustainable Development Goals (SDGs) adopted by the United Nations in 2015 and looking at how our RIKEN can contribute to realizing them. Kazuo Shinozaki, head of the RIKEN Center for Sustainable Resource Science, outlines how his center is contributing to realizing these goals. Future issues of RIKEN Research will examine the efforts of other organizations in RIKEN.

One of RIKEN's important functions is to act as a hub for global brain circulation, and, as executive director in charge of international relations, I hope to focus on creating and strengthening ties with other research institutions and companies both in Japan and overseas.

As a mathematician, I am honored to join RIKEN, whose first president, Dairoku Kikuchi, was a mathematician. Until recently, RIKEN did not have laboratories involved in mathematical research. But this year, which is RIKEN's 100th anniversary, sees the establishment of the Center for Advanced Intelligence Project (AIP), whose mission is to promote research on artificial intelligence, and the Interdisciplinary Theoretical and Mathematical Sciences (iTHEMS) program, which brings together scientists in RIKEN. Both have the potential to contribute to opening up new fields in science.

I look forward to working with all our partners and readers to achieve RIKEN's missions to contribute to society, both in the present and in the future.

小谷元子

Cover story: Short-term memories do not become the enduring recollections that make us who we are. Long-term memories in fact form instantly and take about a week to mature. **Page 24**

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Revealing our clever immune system

Alexis Vogelzang

Special Postdoctoral Researcher

Laboratory for Mucosa Immunity
RIKEN Center for Integrative Medical Sciences

What do you do at RIKEN?
I was fortunate to receive funds from the Special Postdoctoral Researcher grant system through which RIKEN supports young scientists from Japan and abroad. I then developed an independent project on immunity at mucosal surfaces.

> *I'm currently examining the way antibodies interact with both disease-causing and health-promoting microbes in the gut.*

What are you researching, and why is it important?
I'm interested in how our immune cells affect the health and function of other parts of the body, especially the digestive system and its microbial inhabitants. At RIKEN, I'm working in Sidonia Fagarasan's laboratory, where we are using models of autoimmunity or immune deficiency to tease out the molecular interactions that help maintain a healthy immune system. Improving our basic understanding of this system promises to help refine a growing class of drugs known as immunotherapeutics, which improve the body's function by inducing, enhancing, or suppressing immune responses.

How did you become interested in this field of research?
I have always been fascinated by the immune system, but, like most scientists, my research focus constantly evolves. I began my career doing preclinical testing of genetically engineered antibodies in the cutting-edge field of immunotherapy. Antibodies are a class of immune molecule produced to fight infection, but they can be manipulated to modify immune responses. I chose to pursue a PhD in the basic biology of antibody production, and afterwards began to look more closely at how the immune system's antibodies fight bacterial infection at the surfaces of our lungs. My growing interest in mucosal immunity led me to RIKEN, where I'm currently examining the way antibodies interact with both disease-causing and health-promoting microbes in the gut.

What is the best thing about working at RIKEN?
The best thing is working with many immunologists who have made cutting-edge discoveries in mucosal immunity. I been lucky enough to have the opportunity to work in the laboratory of Fagarasan, whose work has helped us understand that antibodies not only defend us against viruses and other infections, but also nurture microbes that are beneficial for the health of the digestive tract. In addition, our associate Hilde Cheroutre discovered new immune cell subsets in the gut and showed how they have adapted to this uniquely complicated environment in an exquisite balance between tolerance of some foreign substances (harmless bacteria or nutrients from the diet) and protective responses against others (cancer cells or infectious microbes).

What has been your most memorable experience at RIKEN?
Shortly after arriving in Japan, I attended a ceremony at RIKEN where hundreds of staff, including directors and researchers, offered flowers in memory of the animals used for scientific research in the previous year. I was quite moved by the communal recognition of our responsibility as scientists to reflect on humane treatment of animals and to limit their use in research. While I have often thought about these issues, I have never experienced anything like it. ■

New energy ideas from the sea's dark depths

Ryuhei Nakamura

Team Leader

Biofunctional Catalyst Research Team
Center for Sustainable Resource Science

Please describe your role at RIKEN
I lead a group investigating how nature organizes robust and efficient energy cycles. We hope that understanding unique systems, such as those found in the dark depths of the oceans, will inspire advances in sustainable energy production.

How did you become interested in your current field of research?
I'm a physical chemist and have always been inspired by the elegance of photosynthesis. As a result, I've been researching this chemical reaction from the vantage of physical chemistry for the last 15 years. However, I came into contact with one of my other current areas of interest eight years ago, after talking to a microbiologist working on deep-sea hydrothermal fields. In these fields, life is nurtured in water heated by contact with the Earth's crust through fissures in the sea bed. I was surprised to learn that deep-sea microbes and animals organize very robust and efficient ecosystems in these fields without using any solar energy. In fact, deep-sea ecosystems have been around far longer than ecosystems sustained by photosynthesis. In parallel with researching the solar-powered ecosphere, my team is now trying to replicate deep-sea life's unique energy-harvesting systems, which we hope will prove useful models for new technologies—just as photosynthesis was a key to solar energy.

What excites you the most about your current research?
While microbiologists and geologists are aware of solar-independent ecosystems, few physical chemists or material scientists think much about them. Deep-sea ecosystems show that not only solar energy, but also geothermal and chemical energy can sustain life. Photosynthesis has always served as a blueprint for solar energy use, and I believe that the deep-sea ecosystems will tell us about how to utilize thermal and chemical energy in similar ways.

What do you think has been the most interesting discovery in your field in the last few years? How has it influenced your research?
More than a billion years ago, bacteria developed the mechanisms to harness electricity. These became inspirations for developments in modern technologies such as fuel cells, sensors, thermoelectric devices and voltage multipliers. The mechanisms in deep minerals that interconvert chemical, thermal and electric energy could also open up new technological possibilities. We are trying to understand how life utilizes abundant resources such as water, carbon dioxide and earth-crust minerals to synthesize chemical fuels. This knowledge could be used to design more environmentally friendly technology, such as by applying the voltage multiplying mechanism found in the deep-sea ecosphere to reduce atmospheric carbon dioxide. Moreover, a better understanding of how to keep the environment in 'biological redox homeostasis'—where the energy needed by living things is created through processes that maintain a balanced and stable ecosystem—will contribute to conservation efforts and environmental rehabilitation.

Tell us about your professional and personal goals.
My goal as a scientist is to reveal the elegance and beauty in biological and geological processes to help us create more sustainable ways of producing energy in harmony with nature. I want to understand how nature maintains its balance in different scenarios while creating energy for life, and how these ecosystems allow for sustainable evolution. ■

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For further information, visit our Careers page:
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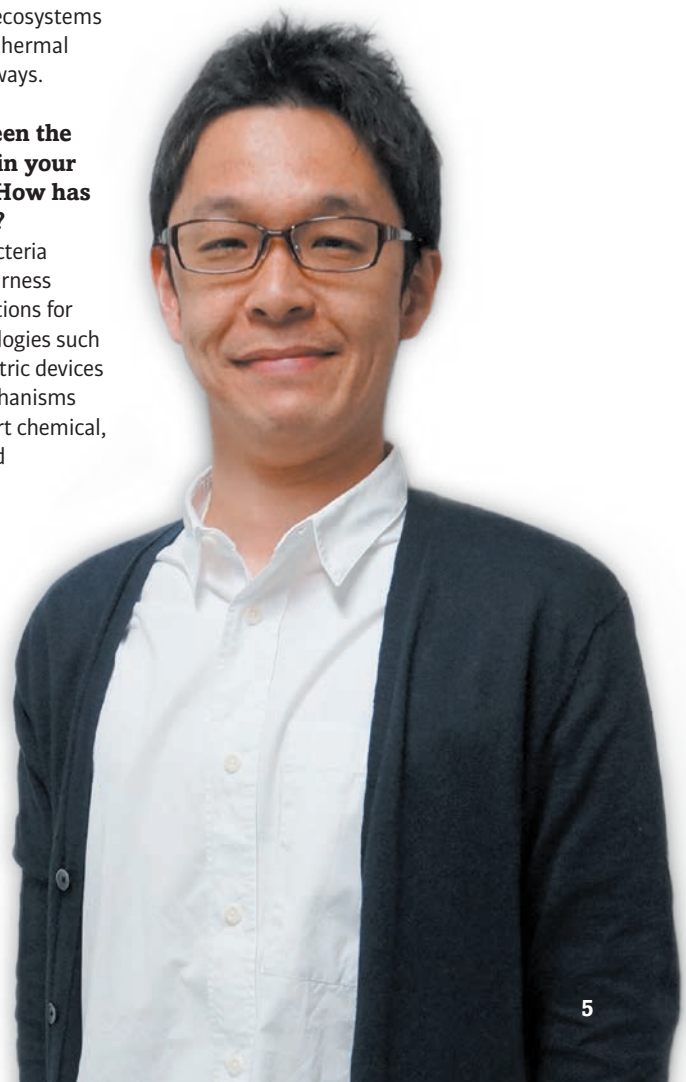


Fighting eye disease with stem cells

In March, a man in his 60s with a common degenerative eye-disease known as wet-type age-related macular degeneration became the first person to receive a transplant of retinal cells made from induced pluripotent stem cells (iPS cells) derived from an adult donor. The study was led by Kobe City Medical Center General Hospital in collaboration with RIKEN, Osaka University Hospital and Kyoto University. Age-related macular degeneration is one of the leading causes of significant vision impairment in Japan, affecting roughly one person in 100 over the age of 50, with wet-type being the most common form. The procedure is part of a clinical study looking at transplanting cells generated from adult donor iPS cells, significantly reducing the time and cost of the procedure compared to harvesting the patient's own cells. Masayo Takahashi, project leader of the Laboratory for Retinal Regeneration, RIKEN Center for Developmental Biology, reported that the surgery took about an hour and had no major complications. The group intends to look further into the safety and feasibility of these transplants by performing this surgery on at least five patients over the next two years.

www.cdb.riken.jp/en/news/2017/topics/0404_10343.html

RIKEN and Berlin Big Data Center work on machine learning

From front left: BBDC Co-Director Klaus-Robert Müller and RIKEN Center for AIP Director Masashi Sugiyama

On 15 March, a ceremony held at the German embassy in Tokyo celebrated a memorandum of understanding on machine learning between the RIKEN Center for Advanced Intelligence Project (AIP) and the Berlin Big Data Center (BBDC). The two institutions have agreed to encourage research, academic material and faculty exchanges, and to hold joint meetings on machine learning.

www.riken.jp/en/pr/topics/2017/20170315_1/

Ninth HOPE Meeting participants visit

HOPE meeting participants at Wako RI Beam Factory.

On 2 March, roughly 110 doctoral students and young researchers from 22 Asia–Pacific and African countries and regions came to RIKEN's Wako campus as part of a four-day exchange of ideas. The HOPE meetings have been organized by the Japan Society for the Promotion of Science since 2008, with the aim of exposing young researchers to a range of new ideas. This year, the group has heard from six lecturers, including five Nobel Laureates in the days preceding their Wako visit. On arriving at RIKEN, the visitors were given tours of some of the laboratories. It was drizzling during the visit but the participants braved the rain to dash between labs and ask questions of the researchers introducing their work.

www.riken.jp/en/pr/topics/2017/20170306_1/

RIKEN President Hiroshi Matsumoto (center) at the 600-strong ceremony.

RIKEN's 100th birthday party

On 26 April , in the presence of Their Majesties the Emperor and Empress, more than 600 guests celebrated RIKEN's centennial at a ceremony held at the Tokyo International Forum. RIKEN was established in 1917 to conduct scientific and applied research and contribute to the development of Japanese industry. It was funded by grants from the Imperial Family, private sector donations and a government subsidy. RIKEN President Hiroshi Matsumoto outlined his vision for the institution's future. Two Nobel Laureates—Takaaki Kajita, director of the Institute for Cosmic Ray Research at the University of Tokyo, and Shinya Yamanaka, director of the Center for iPS Cell Research and Application at Kyoto University—gave commemorative lectures.

www.riken.jp/en/pr/topics/2017/20170427_1/

New element first to be formally named by Asian researchers

The ceremony to formally declare the name of element 113 was attended by His Imperial Highness the Crown Prince and RIKEN President Hiroshi Matsumoto.

A ceremony to commemorate the naming of element 113 as 'nihonium' was held at the Japan Academy in Tokyo on 14 March 2017, with His Imperial Highness the Crown Prince in attendance. This was the culmination of a series of events leading to the naming. On 31 December 2015, IUPAC announced the verification of the discovery of element 113 and that a Japanese research group, headed by Kosuke Morita of the RIKEN Nishina Center for Accelerator-Based Science, was invited to suggest its name and symbol. This was the first time that the right to suggest a name for a new element was granted to a group in Asia.

Following a public review, on 30 November 2016, IUPAC officially announced the name nihonium and symbol, Nh, proposed by Morita's group for element 113.

www.riken.jp/en/pr/topics/2017/20170331_2/

Japanese–French agreement on scientific supercomputing

Both Japan and France are strengthening collaborations between national projects on cutting-edge supercomputers for use in scientific study, particularly for scientific simulations. RIKEN and the French Alternative Energies and Atomic Energy Commission (CEA) signed an agreement in Tokyo that will see the two organizations work closely together in a range of areas, including developing open software libraries and applications, and addressing issues that arise in supercomputing management. RIKEN President Hiroshi Matsumoto and CEA Chairman Daniel Verwaerde both attended the ceremony.

www.riken.jp/en/pr/topics/2017/20170117_2/

Israeli Minister of Science, Technology and Space visits Wako

Delegates viewing at the Shoubu supercomputer.

On 24 March, a delegation led by Ofir Akunis, Israel's minister of science, technology and space, visited the RIKEN Wako campus. A briefing on RIKEN was followed by a report by RIKEN Cluster for Industry Partnerships Director Akihiro Fujita on his visit to Israeli research institutes the previous week. The delegation then visited the RIKEN Brain Science Institute. At the Laboratory for Circuit and Behavioral Physiology, Team Leader Thomas McHugh introduced his group's research on animal behavior. The delegation was also given a tour of several supercomputers at RIKEN including Shobu, Satsuki and Hokusai.

www.riken.jp/en/pr/topics/2017/20170328_1/

RIKEN Advisory Council look toward a globalized future

The tenth meeting of the RIKEN Advisory Council (RAC) was convened in December 2016 to evaluate the institute's efforts to enhance its presence as an internationalized and world-class research institute. Established in 1993, the RAC consists of world-renowned scientists, both Japanese and international. The meeting was chaired by Professor Colin Blakemore at the University of London. RIKEN President Hiroshi Matsumoto introduced his vision for the institute as it prepares to enter its second century. The report can be found here:

www.riken.jp/en/about/reports/evaluation/rac/

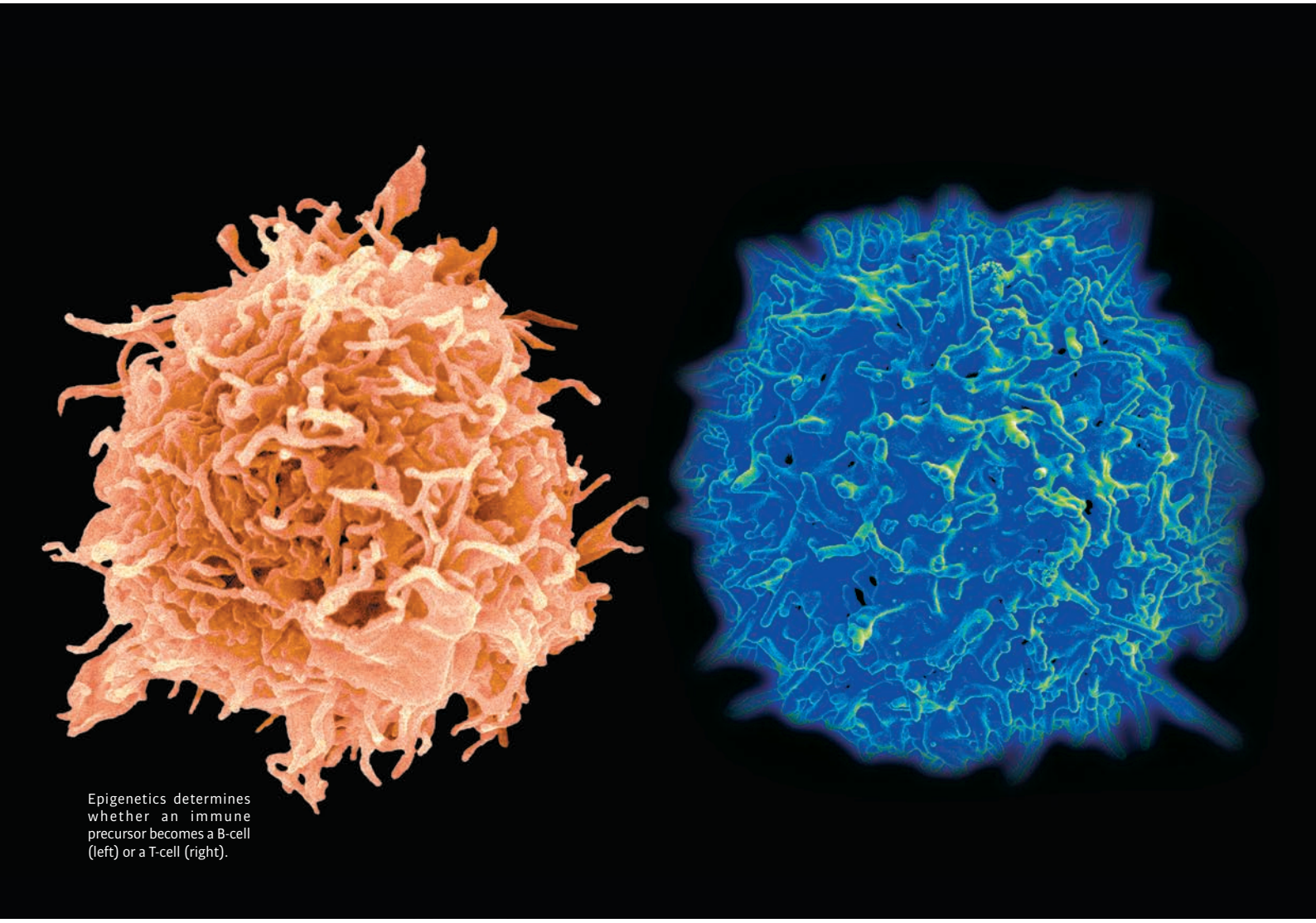
Conferences

Third RIKEN–Academia Sinica Joint Conference

During this year's RIKEN–Academia Sinica Joint Conference: Focus on Chemistry and Chemical Biology, about 100 attendees heard 11 Academia Sinica and 14 RIKEN researchers present their achievements at the Wako campus. The presentations covered topics ranging from new catalysts and cell-to-cell communication to immunity and new antibiotics. Since working out a research agreement in 2008, RIKEN and Academia Sinica, the national academy of Taiwan, have collaborated in several areas, including chemical, developmental and structural biology. Chemical biology has been particularly productive, with joint conferences held in Taipei during March 2013 and October 2015. The next joint conference will take place in Taipei in March 2019.

http://www.riken.jp/en/pr/topics/2017/20170411_1/

The 2017 RIKEN–Academia Sinica Joint Conference was held at RIKEN's Wako campus near Tokyo.



Epigenetics determines whether an immune precursor becomes a B-cell (left) or a T-cell (right).

BIOLOGY

To B or not to B

Epigenetic mechanisms help determine whether immune precursors become T-cells or B-cells

To defend against invading pathogens, the body's immune system creates two main types of white blood cells: T-cells, which recognize infected tissues, and B-cells, which help mount an antibody attack. Whether a blood stem cell turns into a T-cell or a B-cell depends partly on the activity of regulatory proteins known as transcription factors. A study led by RIKEN researchers indicates that epigenetic mechanisms—changes that affect gene activity and expression but leave the sequence of genes in DNA unaltered—play a critical role as well[1].

During development, cell progenitors have the potential to become various kinds of cells. Which kind they become was thought to depend primarily on transcription factors, with epigenetic processes later confirming that choice.

Now, a team led by Tomokatsu Ikawa of the RIKEN Center for Integrative Medical Sciences has uncovered an

> **"This is the first study showing that the inactivation of epigenetic machinery results in a cell fate conversion."**

exception. They engineered mice that lack the machinery needed to epigenetically activate or silence genes in their T-cells. This machinery works by modifying DNA-packaging proteins called histones. It involves what are known as polycomb proteins. Specifically, the T-cells of the mice lacked two particular polycomb proteins, Ring1A and Ring1B.

These mice, the researchers found, had T-cells that halted their development prematurely. However, these arrested T-cell precursors could be transferred to other mice where they would form functional B-cells. "This was unexpected since there had been no reports that showed the conversion of T-cells into B-cells in any knockout mouse models," says Ikawa, adding: "This is the first study showing that the inactivation of epigenetic machinery results in a cell fate conversion."

Ikawa's team dug deeper into what the Ring1A/B proteins normally do in T-cells and found that the proteins bind directly with genes involved in B-cell development. That hinted that some determinant of B-cell fate might still be active in the T-cell precursors in the absence of the epigenetic machinery. But what could that determinant be?

The researchers' prime suspect was a transcription factor called Pax5, which Ikawa describes as "a master regulator of B-cell differentiation." When he and his colleagues eliminated Pax5 activity along with the epigenetic equipment in the mice, normal T-cell differentiation was fully restored. "This indicates that Pax5 is one of the most important targets of Ring1A/B at this developmental stage," Ikawa explains.

Because Ring1A/B and related proteins are often deregulated in various types of cancer, including leukemia, the research could lead to new insights into the tumor-initiating process. ■

Reference

1. Ikawa, T., Masuda, K., Endo, T. A., Endo, M., Isono, K., Koseki, Y., Nakagawa, R., Kometani, K., Takano, J., Agata, Y. *et al.* Conversion of T cells to B cells by inactivation of polycomb-mediated epigenetic suppression of the B-lineage program. *Genes & Development* **30,** 2475–2485 (2016).

CHEMISTRY

Smaller is better for water-splitting catalyst

Experiments reveal how manganese oxide nanoparticles can mimic water-splitting biological complexes

Splitting water into oxygen and hydrogen is a very attractive way of converting renewable energy sources into the ultimate clean energy source—hydrogen. It is something that plants do very well in photosynthesis, but scientists have struggled to produce artificial systems that have efficiencies approaching those of plants.

Now, by using manganese oxide crystals smaller than 10 nanometers, researchers at RIKEN and Seoul National University in Korea have uncovered an unexpected catalytic pathway that promises to realize water-splitting reactions in the lab with efficiencies edging closer to those of photosynthesis[1].

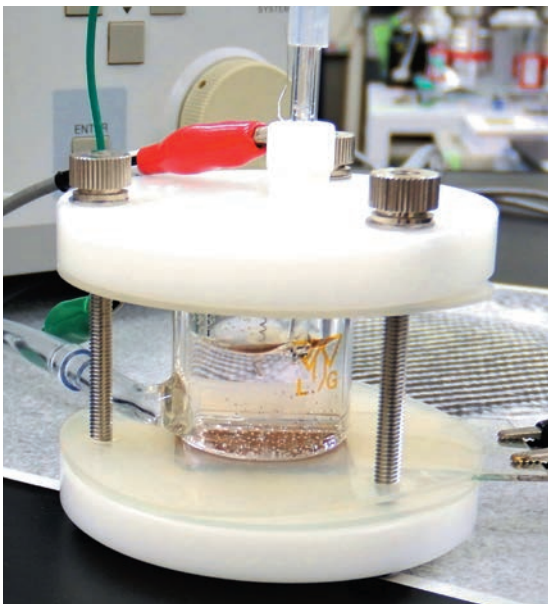
> **"This could support ideas about splitting water with abundant elements."**

Of the two reactions involved in water splitting, the problematic one is the oxygen evolution reaction, which plucks four protons and four electrons from two water molecules. Researchers have been searching for a catalyst that accelerates this reaction. One natural target is the protein complex photosystem II. This biomolecule allows the reaction to proceed under mild conditions with sunlight, thanks to its cluster of calcium and manganese ions.

Ryuhei Nakamura (see profile on page 5) from the RIKEN Center for Sustainable Resource Science has spearheaded efforts to replicate photosystem II's activity using inexpensive manganese oxide clusters. His team recently uncovered a critical bottleneck—a trivalent manganese ion (Mn^{3+}) with a far shorter lifespan than in photosynthetic proteins, which decreases the system's oxidation potential. By synthesizing manganese oxides with enough structural flexibility to stabilize this ion, they split water under mild, neutral-pH conditions.

Further exploration revealed a curious enhancement of activity when the manganese oxide nanoparticles were shrunk. The researchers saw that crystals smaller than 10 nanometers stabilized Mn^{3+} species on their surfaces during the demanding electrolysis process. To understand these effects, they sought to capture the chemical behavior of the nanoparticles in action.

"With four electrons and four protons being transferred, this reaction mechanism is really



The experimental setup the researchers used to split water. The bubbles in the beaker are oxygen gas.

complicated," concedes Nakamura. "We had to improve the sensitivity of our tools to detect the species present on the nanoparticle surfaces."

The researchers pinned down the differences between conventional manganese catalysts and their nanoscale counterparts using high-resolution structural measurements under the action of electrolysis. While bulky catalysts had trouble extracting an initial electron to set off the oxygen evolution reaction, the nanoparticles showed no such issues, and even snatched an additional proton. This new mechanism enhanced the catalytic output by making it easier to attract charges from water.

Nanoscale distortions of crystal lattices can induce electronic differences in materials; Nakamura suspects this may be occurring in the tiny manganese oxide catalysts. "This could support ideas about splitting water with abundant elements such as manganese, instead of the platinum or iridium catalysts widely used today."

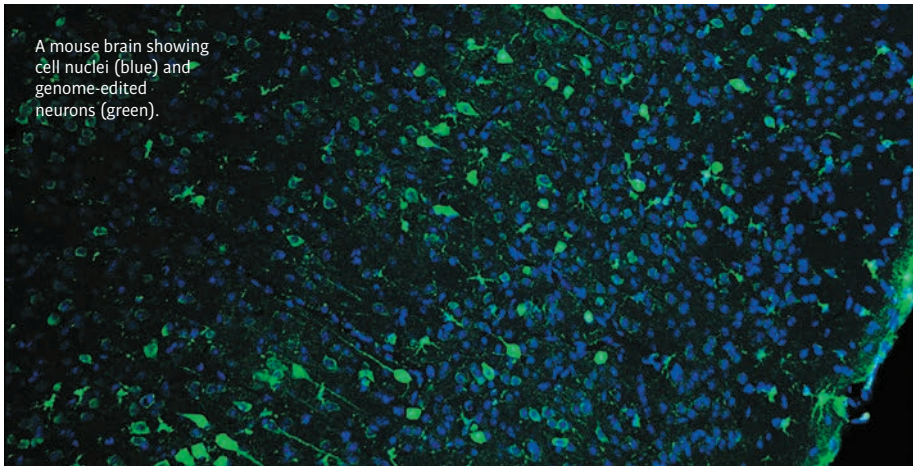
Reference

1. Jin, K., Seo, H., Hayashi, T., Balamurugan, M., Jeong, D., Go, Y. K., Hong, J. S., Cho, K. H., Kakizaki, H., Bonnet-Mercier, N. *et al.* Mechanistic investigation of water oxidation catalyzed by uniform, assembled MnO nanoparticles. *Journal of the American Chemical Society* **139,** 2277–2285 (2017).

BIOLOGY

Non-dividing and conquered

A method for targeted insertion of DNA into non-dividing cells helped partially restore vision to blind rats



A mouse brain showing cell nuclei (blue) and genome-edited neurons (green).

Faulty genes responsible for disease can now be replaced with healthy versions in any cell type in the body, thanks to a new gene-editing technique developed by a team that includes RIKEN researchers[1]. In the future, this development is expected to make many incurable diseases treatable by gene replacement therapy.

The CRISPR-Cas9 gene-editing system holds great therapeutic potential because it allows scientists to modify the genome at specific locations. However, the ability to modify the genome in this way has historically been most effective in dividing cells, such as those found in the liver and bone marrow. Unfortunately, the vast majority of the body's cells—including those in the eye, brain, pancreas and heart—are non-dividing.

To develop a more versatile gene-editing platform, an international team, which included Yuji Tsunekawa and Fumio Matsuzaki from the RIKEN Center for Developmental Biology, focused on a mechanism for repairing DNA known as non-homologous end joining. This molecular repair system normally fixes broken strands of the genome in both dividing and non-dividing cells by reconnecting the original strand ends.

The researchers adapted the cell's natural non-homologous end-joining machinery to work in tandem with introduced CRISPR-Cas9 tools to insert desired DNA into targeted positions. This strategy allowed them to deliver genetic instructions to human neurons in a laboratory dish and to the brains of adult mice (see image).

"We have developed the first method that can efficiently target the genome of non-dividing cells both in a culture dish and in the body," comments Tsunekawa.

To demonstrate the potential of this new application of CRISPR-Cas9 for gene-replacement therapy, the researchers tested the system in a rat model of retinitis pigmentosa—a major incurable cause of blindness that afflicts one person in every 3,000–4,000 people in Japan. They delivered a functional copy of one of the genes damaged in people with this vision disorder to the eyes of three-week-old rats. One month later, they documented gene expression in the rats' retinas. In addition, the animals showed improved responses on light-sensitive eye tests.

These are still early days since many improvements are needed to ensure the safety and efficacy of the method. "It will take a long time before this gets to clinical testing," Tsunekawa notes. But the researchers are very excited about the development. "In principle, most human diseases that are caused by a single gene defect could be treated by this method," says Tsunekawa.

Reference

1. Suzuki, K., Tsunekawa, Y., Hernandez-Benitez, R., Wu, J., Zhu, J., Kim, E. J., Hatanaka, F., Yamamoto, M., Araoka, T., Li, Z. *et al.* *In vivo* genome editing via CRISPR/Cas9 mediated homology-independent targeted integration. *Nature* **540,** 144–149 (2016).

PHYSICS

Sturdy skyrmions stack up

A new form of low-power computing that uses miniscule magnetic whirlpools to store and process data is a step closer to becoming a reality

Tiny swirling magnetic patterns called skyrmions (see image, left) can pack together to form neat lattices inside certain magnetic materials. These lattices are promising for spintronics—a new form of computing that exploits the magnetic characteristics of atoms to manage data. But their usefulness is limited because they typically exist only within a narrow window of temperatures and magnetic fields.

Now, Kosuke Karube of the RIKEN Center for Emergent Matter Science and colleagues have discovered that skyrmion lattices in a crystalline cobalt–zinc–manganese alloy can survive over a wide range of temperatures and magnetic fields, pointing the way to practical skyrmion-based spintronics[1].

Each of the three metals—cobalt, zinc and manganese—in the alloy has unique magnetic properties that influence the material's magnetism. Below 27 degrees Celsius, the alloy can assume several different magnetic states, which Karube's team mapped using techniques such as neutron scattering.

Between 11 and 27 degrees Celsius, a stable honeycomb lattice of skyrmions (see image, top right) formed when a small magnetic field was applied. But when the temperature dropped below 11 degrees Celsius, the skyrmion lattice was no longer in the most energetically stable state. Instead, very slow cooling caused each atom to orient its magnetism so that it was slightly out of alignment with its neighbors, which collectively formed spirals in the crystal's intrinsic magnetism. These spirals come in two forms, known as helical and conical magnetic states.

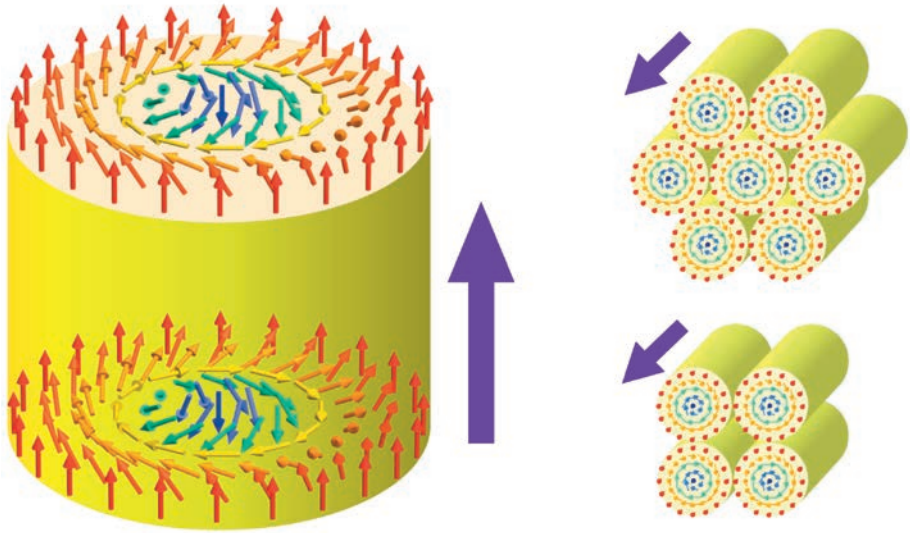
However, relatively rapid cooling prevented these states from occurring and preserved the honeycomb skyrmion lattice in a higher-energy 'metastable' state. This lattice was stable enough to last indefinitely below –13 degrees Celsius under a broad range of magnetic fields.

Below about –123 degrees Celsius, the lattice began to change shape to form a square lattice, which had never been seen before (see image, bottom right). Warming reinstated the honeycomb lattice, rather than degrading it to the lower-energy helical or conical states—the first time such a skyrmion lattice transition has been observed. "Once created, the metastable skyrmions are difficult to destroy," says Karube.

> **"Cobalt–zinc–manganese alloys are very exciting and promising materials, but their whole picture is still a mystery."**

Practical applications will require skyrmions that are stable at room temperature and zero magnetic field, he adds. Lowering the manganese concentration within the alloy could enable the team to achieve this.

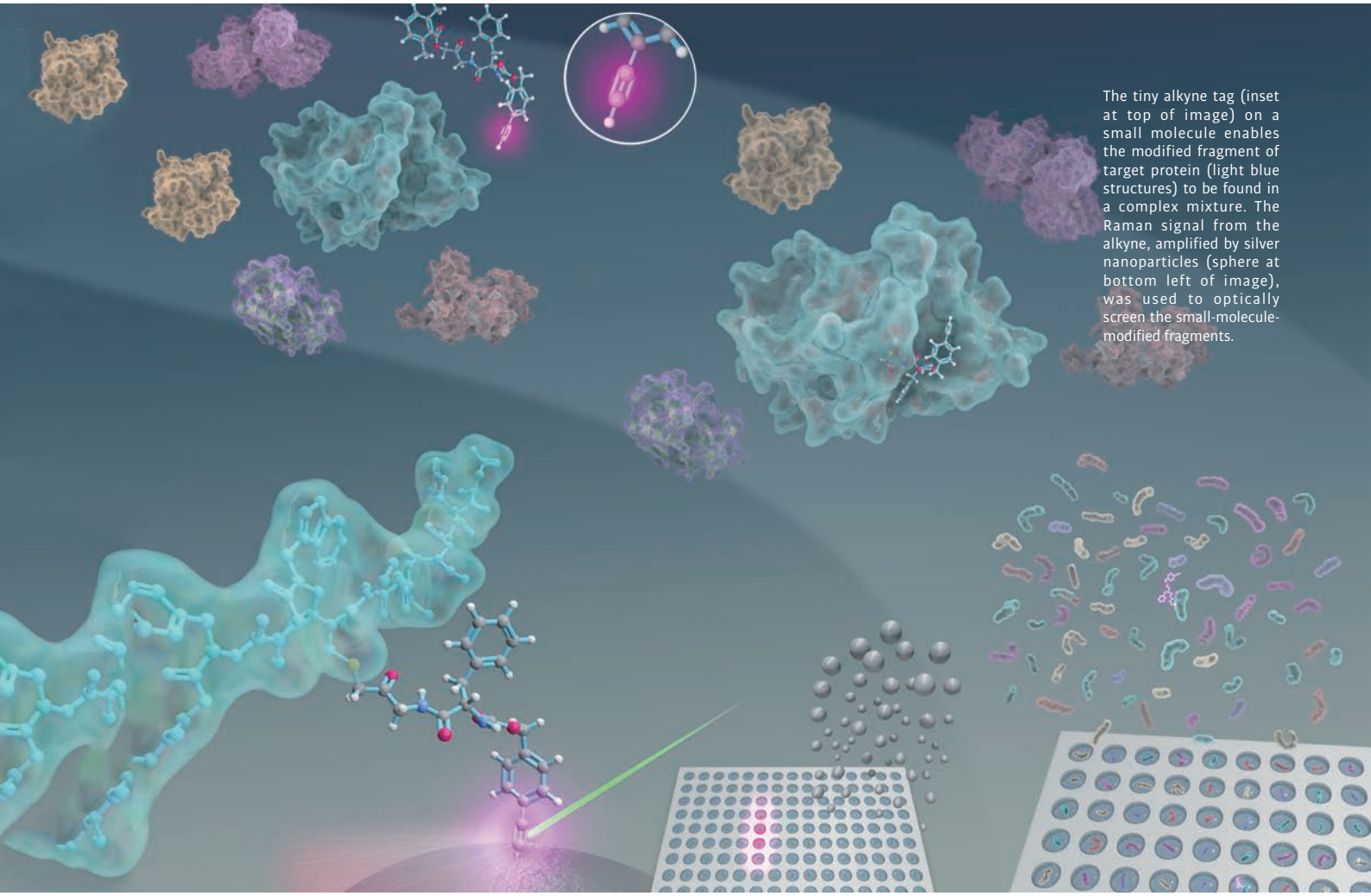
"Cobalt–zinc–manganese alloys are very exciting and promising materials, but their whole picture is still a mystery," says Karube. "By controlling their chemical composition, we aim to clarify the mechanism behind the observed novel skyrmion states, and further explore these new physical phenomena." ■



Left: Skyrmions are whirling patterns in the magnetic orientations of atoms. Under an external magnetic field (purple arrows), atoms on the outside of the skyrmion align their magnetic moments (red) with the field, while those at the core of the skyrmion point in the opposite direction (blue). Right: Skyrmions can stack up to form a triangular ('honeycomb') or square lattice.

Reference

1. Karube, K., White, J. S., Reynolds, N., Gavilano, J. L., Oike, H., Kikkawa, A., Kagawa, F., Tokunaga, Y., Rønnow, H. M., Tokura, Y. *et al*. Robust metastable skyrmions and their triangular–square lattice structural transition in a high-temperature chiral magnet. *Nature Materials* **15,** 1237–1242 (2016).



The tiny alkyne tag (inset at top of image) on a small molecule enables the modified fragment of target protein (light blue structures) to be found in a complex mixture. The Raman signal from the alkyne, amplified by silver nanoparticles (sphere at bottom left of image), was used to optically screen the small-molecule-modified fragments.

CHEMISTRY

Lighting up drug discovery

A simple molecular tag offers a new way to study potential drug targets

Some proteins can be most uncooperative. Some refuse to form nice crystals for analysis by x-ray crystallography, others are too insoluble for nuclear magnetic resonance (NMR), while still others—including some of great interest for their role in disease—can be isolated only in trace amounts.

Researchers at RIKEN have developed a new way to study these problematic proteins and their interactions with small molecules, a discovery that could greatly benefit drug discovery research[1].

When studying how a protein interacts with a potential drug, it is essential to find out where the drug binds on the protein. For proteins that cannot be analyzed by x-ray or NMR, researchers try to covalently bond a drug-like molecule to the protein, break up the protein and then use mass spectrometry to pick out the relevant protein fragment based on its predicted mass. But it can be difficult to identify the protein fragment of interest from such a complex cocktail of protein pieces.

Now, Mikiko Sodeoka from the RIKEN Synthetic Organic Chemistry Laboratory and her colleagues, in collaboration with Katsumasa Fujita at Osaka University, have found a way to overcome this problem. They tagged small molecules and then analyzed them using a technique called Raman spectroscopy, which is similar to infrared spectroscopy in that it involves using light to excite molecules and examining how they vibrate.

Molecules known as alkynes contain a triple bond between two carbon atoms; this bond produces a telltale signal in the Raman spectrum. Thus, by incorporating an alkyne into a small molecule that binds to a protein, the protein fragment of interest from a complex mixture can be quickly identified using Raman spectroscopy (see image). Since

alkynes are small, they rarely interfere with the interaction between the small molecule and the protein.

"All the equipment we used is commercially available," Sodeoka says, "But we made considerable effort to optimize and automate the analysis conditions." One of the team's most important optimizations was the addition of silver nanoparticles, since they powerfully amplify the alkyne's Raman signal.

The researchers demonstrated the potential of their technique by using it to identify the drug-binding site of a protein called cathepsin B, an anticancer drug target. They were able to pick out the protein from the highly complex protein mixture produced by rupturing a cell.

The method is not limited to the analysis of proteins, Sodeoka notes. "We expect it could contribute to various research fields such as proteomics, epigenetics and metabolomics."■

Reference
1. Ando, J., Asanuma, M., Dodo, K., Yamakoshi, H., Kawata, S., Fujita, K. & Sodeoka, M. Alkyne-tag SERS screening and identification of small-molecule-binding sites in protein. *Journal of the American Chemical Society* **138,** 13901–13910 (2016).

BIOLOGY

How DNA traffic jams cause cell differences

A study of identical bacterial cells reveals that congestion on the DNA molecule is responsible for differences between them

The underlying molecular process that causes genetically identical cells in the same environment to behave differently has been uncovered by three RIKEN scientists.

Cells manufacture proteins through a multistep process that begins with making copies of the relevant stretches of DNA. These copies, which are known as messenger RNA, are then 'translated' into proteins.

Two cells containing identical DNA and in the same environment might be expected to behave in the same way, but it turns out that they do not. The cause of this surprising variability lies in the gene copying process—rather than being smooth and continuous, it is jerky because it is subject to random fluctuations. This is known as transcriptional bursting, and it results in the erratic expression of genes.

"This variability contributes to the difference in individual cell behaviors, which in turn plays a critical role in various biological processes such as differentiation of mammalian cells and decision making of bacterial cells," explains Keisuke Fujita of the RIKEN Quantitative Biology Center.

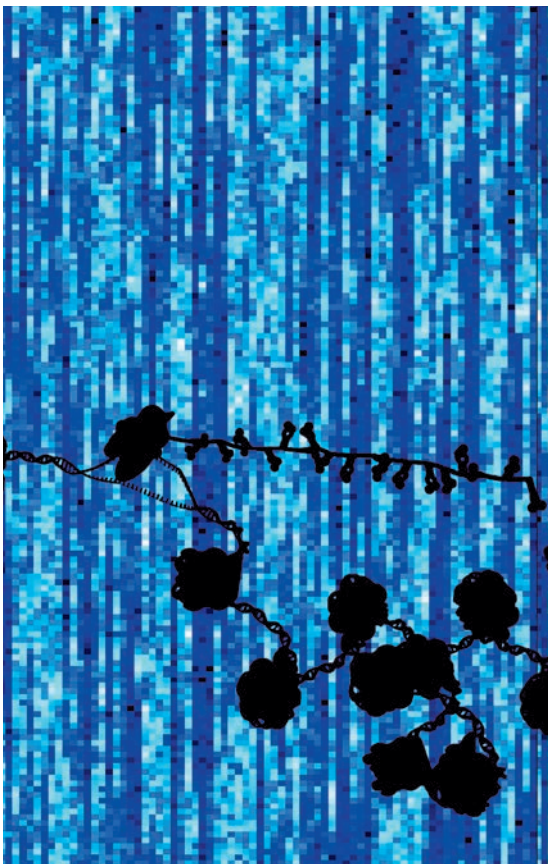
"Understanding the molecular mechanism of this variability may open the way for regulating cell-to-cell variability and could be useful for controlling the differentiation of stem cells into various kinds of cells, for example."

While there has been much speculation about the molecular origins of transcriptional bursting, there has been little consensus to date. In particular, there has been debate about whether transcriptional bursting is caused by transcription factors (proteins that bind to DNA and turn nearby genes on and off) or RNA polymerase (enzymes that bind to DNA and catalyze the copying of genetic information from the double helix).

> **"We found that 'traffic congestion' of RNA polymerases on the DNA road causes cell-to-cell variability."**

Now, Fujita, with colleagues Mitsuhiro Iwaki and Toshio Yanagida, has shed light on this problem by analyzing the kinetics of the process in reconstituted transcription[1]. The trio discovered that variability originates from the interplay between RNA polymerases. "We found that 'traffic congestion' of RNA polymerases on the DNA road causes cell-to-cell variability," comments Fujita.

"We were surprised because previous *in vivo* experiments had suggested that



Chromatin with an RNA polymerase transcribing some RNA.

transcriptional bursting results from interactions between various other molecules, whereas our *in vitro* experiment implies that it is intrinsically caused without such additional factors," says Fujita. "Although apparently contradictory, we conjecture that highly organized biological systems are maintained by a balance between intrinsic noise and extrinsic control caused by other factors."

The researchers intend to investigate this difference between single cells and whole biological systems by performing *in vivo* experiments. They also plan to explore how the molecular mechanism of DNA copying affects the behaviors and fates of cells. ■

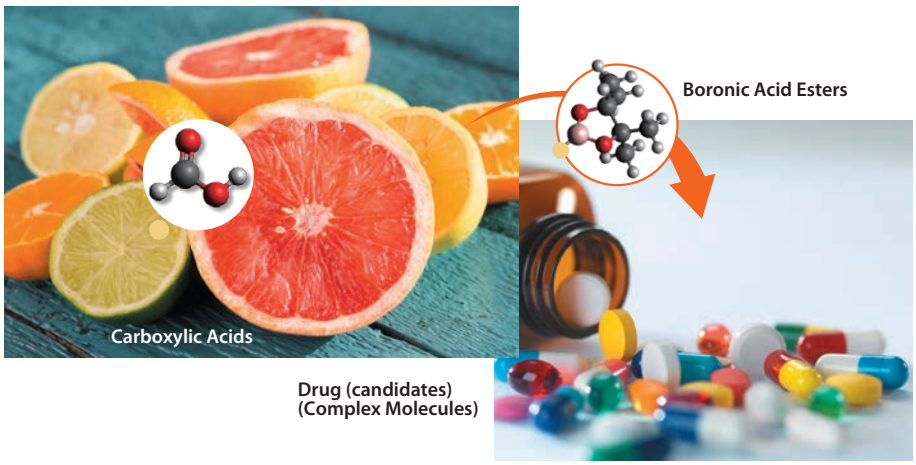
Reference

1. Fujita, K., Iwaki, M. & Yanagida, T. Transcriptional bursting is intrinsically caused by interplay between RNA polymerases on DNA. *Nature Communications* **7,** 13788 (2016).

CHEMISTRY

Making stepping stones to drugs

A mild method has been developed for converting common starting materials into highly useful intermediate compounds



Carboxylic acids—widely available starting materials, including from many natural sources—can now be converted into boronic esters under mild conditions.

One of the most powerful ways of forming complex organic molecules such as pharmaceuticals, agrochemicals and other functional materials is to use 'metal-catalyzed cross-coupling reactions'. Unfortunately, such reactions are very picky about their starting materials, requiring reagents that contain one of a select set of functional groups that cross-coupling catalysts can recognize.

Now, researchers at RIKEN have developed a method for forming a particular type of cross-coupling-ready molecules called boronic esters[1].

The team selected a large family of molecules called aromatic carboxylic acids as the starting materials for producing boronic esters (see image). "Carboxylic acids are found in a broad range of molecules and are thus easily available," says Takamitsu Hosoya from the RIKEN Center for Life Science Technologies, who led the work.

A mild method for converting carboxylic acids would thus open up a way to produce a diverse set of boronic esters for cross-coupling and a range of other transformations. But previously discovered methods typically require temperatures of 150 degrees Celsius or above, which can destroy sensitive starting materials.

Hosoya and his co-workers suspected that converting the carboxylic acid group into a more reactive derivative would make it easier to displace it with boron under mild conditions. They initially tried common carboxylic acid derivatives such as acid chlorides and acid anhydrides but found them to be too reactive and unstable.

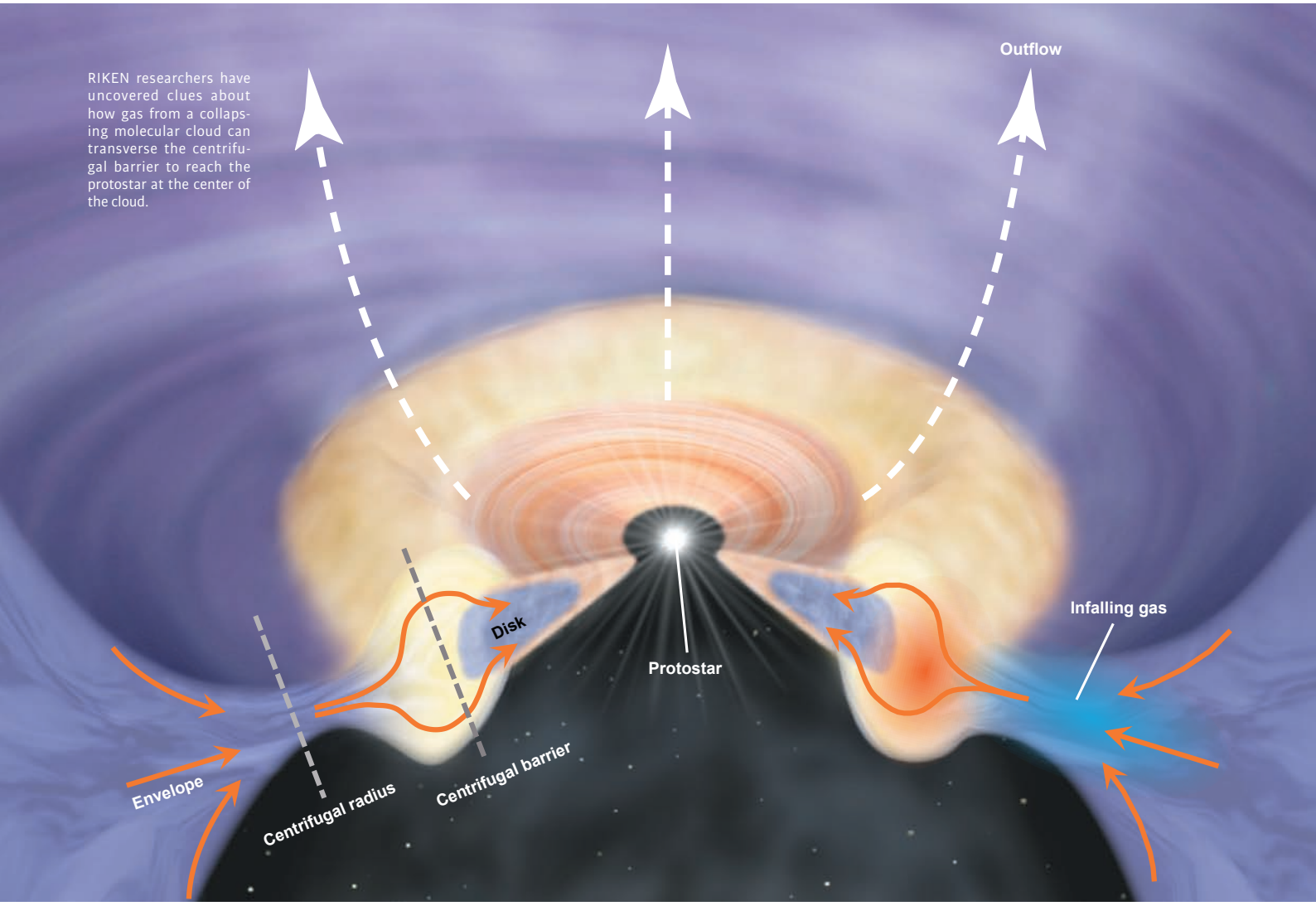
However, a sulfur-containing derivative called a thioester proved to have just the right level of reactivity. Using a rhodium catalyst, the researchers were able to convert thioester into the desired boronic ester at just 80 degrees Celsius.

"Testing the reactions on a wide range of carboxylic acids, we discovered that our method has a superb substrate scope, which includes densely functionalized compounds," Hosoya says. "These results convinced us that our method would be applicable to the late-stage derivatization of complex molecules, which is a useful method for drug discovery."

The method developed by Hosoya and co-workers is currently limited in that it works well only for carboxylic acids attached to aromatic substrates, such as benzene rings. "As 'aliphatic' acids are much more ubiquitous than aromatic ones, we believe that developing borylative transformation of aliphatic carboxylic acids is important and highly desirable," Hosoya says. The team showed one example of an aliphatic borylation in the current study, but its reaction efficiency was low. "We are now working to realize this transformation by refining our catalytic strategy," he says. ■

Reference

1. Ochiai, H., Uetake, Y., Niwa, T. & Hosoya, T. Rhodium-catalyzed decarbonylative borylation of aromatic thioesters for facile diversification of aromatic carboxylic acids. *Angewandte Chemie International Edition* **56,** 2482–2486 (2017).



RIKEN researchers have uncovered clues about how gas from a collapsing molecular cloud can transverse the centrifugal barrier to reach the protostar at the center of the cloud.

PHYSICS

Strange geometry a clue to how a star is born

Observations using a radio telescope in Chile reveal how gas in a molecular cloud can pass through a seemingly impenetrable barrier and form a new star

From observations of molecules in a protostar, RIKEN researchers have uncovered clues about how gas in a collapsing molecular cloud can shed angular momentum and find its way to the inner disk and eventually to the forming star[1].

A big puzzle in astrophysics is how stars like the Sun form from collapsing molecular clouds in star-forming regions of the Universe. The rotation of gas in the star-forming cloud gives it angular momentum. As the gas collapses inward under gravity, it reaches the point, called the centrifugal barrier. At this point, the gas will no longer collapse unless it can shed some of its angular momentum.

A team led by Nami Sakai of the RIKEN Star and Planet Formation Laboratory has found clues as to how the gas in the cloud finds its way to the surface of the forming star. They observed protostar L1527, which is about 450 light years away in a nearby star-forming region, using the ALMA observatory—a network of 66 radio dishes in northern Chile. The protostar has a spinning protoplanetary

disk embedded in a large envelope of molecules and dust.

Sakai had previously discovered from observations of molecules around the protostar that the transition from envelope to inner disk, which later forms into planets, was very complex.

"As we looked at the observational data, we realized that the region near the centrifugal barrier—where particles can no longer infall—is quite complex, and that analyzing the movements in this transition zone could be crucial for understanding how the envelope collapses," says Sakai. "Our observations showed that there is a broadening of the envelope at that place, indicating something like a 'traffic jam' in the region just outside the centrifugal barrier, where the gas heats up as the result of a shock wave. It became clear from the observations that a significant part of the angular momentum is lost by gas being cast in the vertical direction from the flattened protoplanetary disk that formed around the protostar."

> **"This work could also help us to better understand the evolution of our own solar system"**

This behavior accorded well with calculations the group had done using a purely ballistic model, where the particles behave like simple projectiles that are not influenced by magnetic or other forces.

"We plan to continue to use observations from the powerful ALMA array to further refine our understanding of the dynamics of stellar formation and fully explain how matter collapses onto the forming star," says Sakai. "This work could also help us to better understand the evolution of our own solar system."■

Reference

1. Sakai, N., Oya, Y., Higuchi, A. E., Aikawa, Y., Hanawa, T., Ceccarelli, C., Lefloch, B., López-Sepulcre, A., Watanabe, Y., Sakai, T. *et al.* Vertical structure of the transition zone from infalling rotating envelope to disk in the Class 0 protostar, IRAS04368+2557. *Monthly Notices of the Royal Astronomical Society* **467,** L76–L80 (2017).

BIOLOGY

Gene mutations play a hand in the body clock

Studying the effects of seventeen phosphorylation-site mutants in mice reveals that they control circadian rhythms and help the body keep time

RIKEN researchers have examined 17 phosphorylation-site mutations and found that they create different circadian rhythms in mammals.

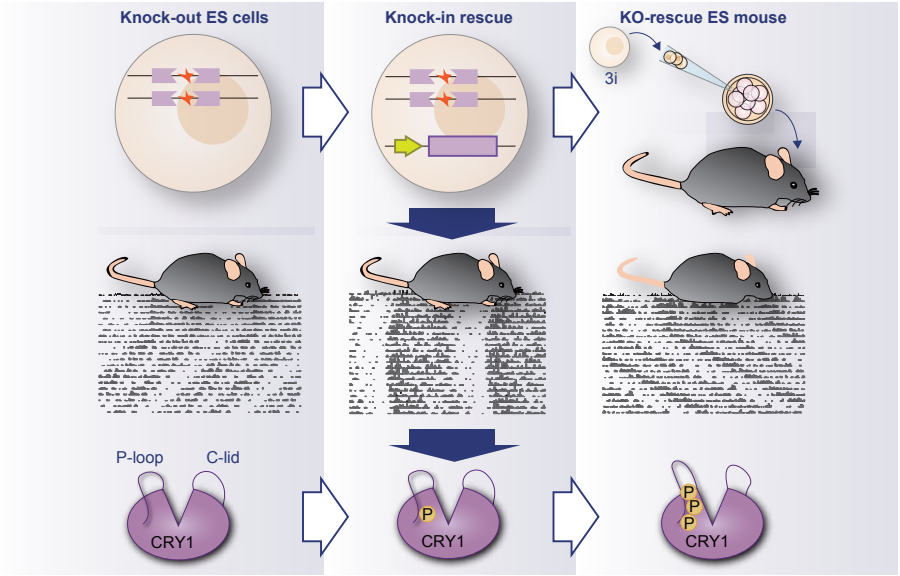
Almost all plants and animals have circadian rhythms, physiological changes at the cellular level that follow a 24-hour cycle. These are guided by internal biological clocks, affected by genetic factors, which in turn can influence behavior.

In mammals, the cryptochrome family gene *Cry1* is essential for a normal circadian rhythm, but its exact role in regulating the circadian rhythm, or 'circadian period', remains unclear.

Hiroki Ueda and his team at the RIKEN Quantitative Biology Center identified more than ten residues in the protein that affect the circadian period in cultured cells. They then selected 17 *Cry1* mutations and added each to the embryonic stem cells of mice specially bred to lack this gene, after which they examined the body clock patterns of the mature mice.

"Mice without these genes lack a circadian rhythm," explains Koji Ode, the paper's lead author. "By adding the *Cry1* gene back into these mice, we were able to rescue the circadian rhythm. Interestingly, the lengths of the restored circadian periods depended on the nature of the mutations."

The versions of the *Cry1* gene most effective at restoring normal day–night rhythms had a mutation near the 'p-loop'. This zone codes for a pocket-like area on the protein that can be



After inserting rescue genes into knockout embryonic stem cells (first row), researchers studied the behavior of the mouse when it matures—all within a single generation (second row). They discovered that phosphorylation around flexible loops can act as a cumulative timer in the circadian clock (third row).

modified by a process called phosphorylation—the attachment of phosphate groups. The mice with mutations that limited the amount of phosphorylation around the CRY1 p-loop had longer than normal circadian periods.

"This p-loop is critical for CRY1 to function as a circadian clock component," says Ueda. "We think that the accumulation of phosphorylation at this site serves as a time-keeping mechanism, and thus the quality of the p-loop is a fundamental element that regulates circadian rhythm. Our next challenge is to actually observe changes in phosphorylation level on the p-loop over the course of a day."

This study was only possible because the team developed a new method to create genetic 'knockout-rescue mice', which are created by adding back the *Cry1* gene, or a mutated version of it, into 'knockout' animals developed to lack functioning CRY1. Creating these mice is usually laborious and costly, involving several generations of mice, but the RIKEN team developed a more efficient 'three-inhibitor' treatment of mouse embryonic stem cells. This allowed them to begin with knockout embryonic stem cells, insert rescue genes and analyze the behavior of the mouse when it matures—all within a single generation. ■

Reference

1. Ode, K. L., Ukai, H., Susaki, E. A., Narumi, R., Matsumoto, K., Hara, J., Koide, N., Abe, T., Kanemaki, M. T., Kiyonari, H. & Ueda, H. R. Knockout-rescue embryonic stem cell-derived mouse reveals circadian-period control by quality and quantity of CRY1. *Molecular Cell* **65,** 176–190 (2017).

PHYSICS

Precision and hot nuclei

Exact solutions to a problem in highly-excited nuclei help determine crucial quantities for synthesis of elements in stars

A unified and consistent microscopic approach that can simultaneously describe two vital quantities for understanding the statistical properties of nuclei has been developed by a RIKEN researcher. These two quantities are essential for describing the synthesis of nuclei in stars.

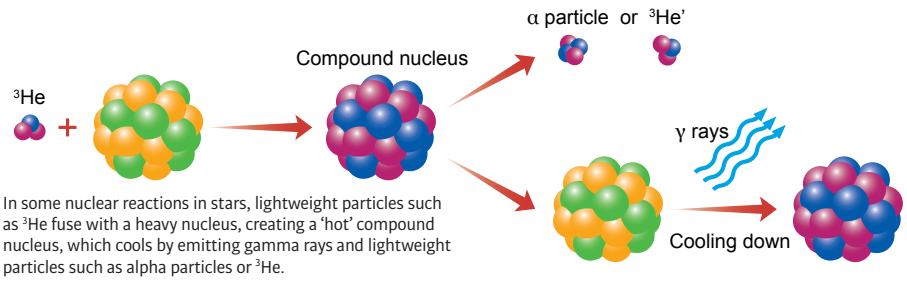
Atomic nuclei have discrete energy levels, whose spacing decreases rapidly as the excitation energy increases. At high excitation energies such as those found in stars and nuclear reactors, the nuclear energy levels are so bunched up that it is impractical to deal with individual levels. Instead, it is more efficient to consider the average properties of nuclear excitations in terms of two quantities: the nuclear level density (NLD)—the number of excited levels per unit of excitation—and the radiative strength function (RSF)—the probability that a nucleus will emit a gamma ray. These two quantities are crucial for understanding the synthesis of nuclei in astrophysical settings, as well as in nuclear power generation.

Experimentalists had previously proposed a method to simultaneously extract the two quantities from a single experiment, but the method suffers from uncertainties related to the normalization process. Given the importance of these two quantities, it is imperative to have a consistent theoretical basis for understanding them. Nonetheless, a unified theory capable of simultaneously and microscopically describing both parameters had been lacking until now.

By employing the mean fields of protons and neutrons interacting via the pairing force, the researchers have now solved the problem exactly. These exact solutions are employed to construct the partition function for calculating the NLD. To calculate the RSF, the exact neutron and proton pairing gaps as well as the related quantities obtained from the same partition function are put into a model previously proposed by one of the authors, Nguyen Dinh Dang of the RIKEN Nishina Center for Accelerator-Based Science.

"The good agreement between the predictions of the present approach and experimental data indicates that the use of exact solutions for pairing is indeed very important for the consistent description of both NLD and RSF at low and intermediate excitation and gamma-ray energies," says Nguyen Quang Hung of Duy Tan University in Vietnam.

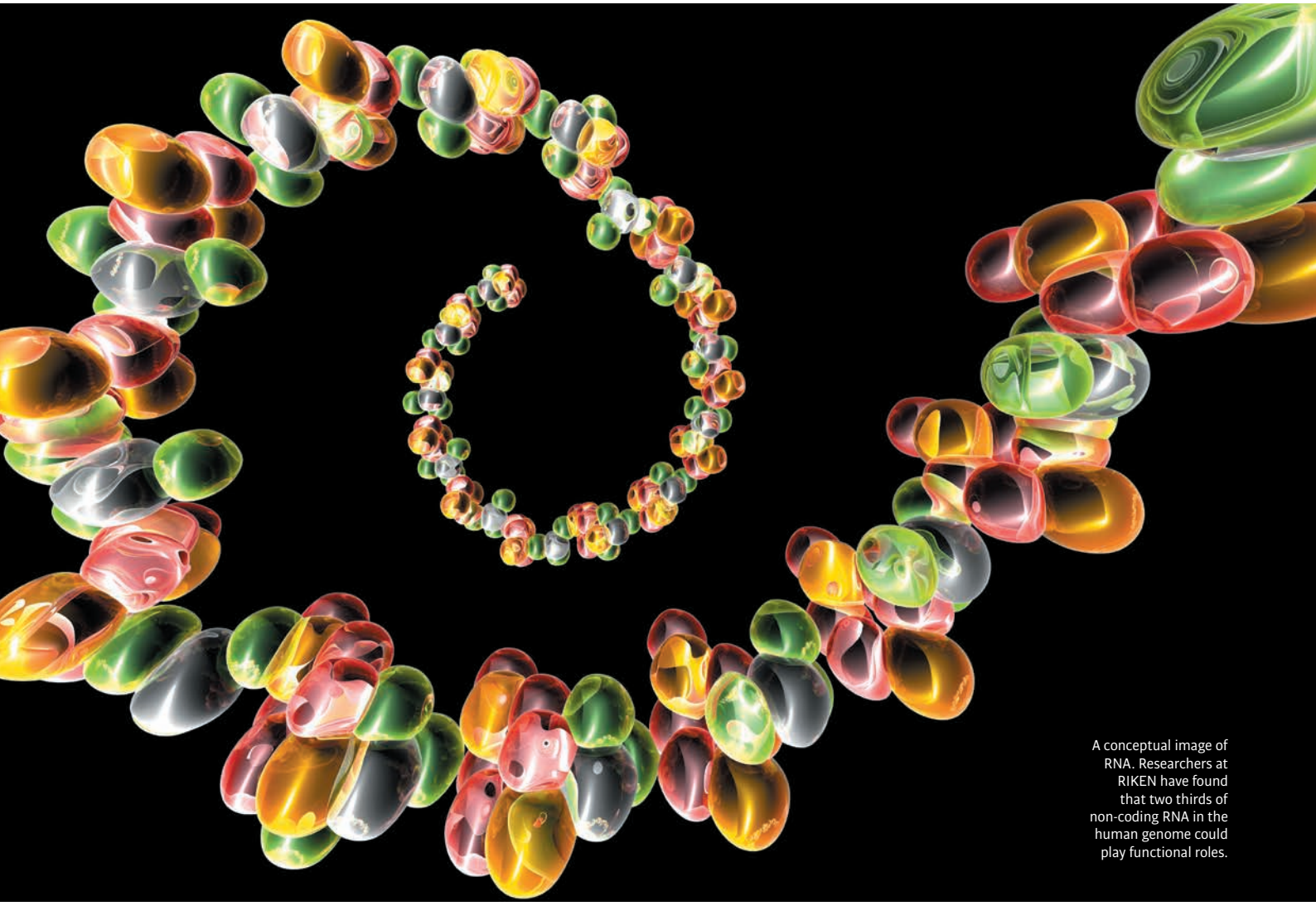
"Our approach shows that the temperature dependence of the giant dipole resonance shape in hot nuclei is crucial for the correct description of the gamma-ray emission probability at low gamma-ray energies, explains Dang. "Our next goal is to develop a fully self-consistent approach based on exact pairing and the microscopic structure of the vibrational states to study nuclear collective excitations." ■



In some nuclear reactions in stars, lightweight particles such as ^{3}He fuse with a heavy nucleus, creating a 'hot' compound nucleus, which cools by emitting gamma rays and lightweight particles such as alpha particles or ^{3}He.

Reference

1. Quang Hung, N., Dinh Dang, N. & Quynh Huong, L. T. Simultaneous microscopic description of nuclear level density and radiative strength function. *Physical Review Letters* **118,** 022502 (2017).



A conceptual image of RNA. Researchers at RIKEN have found that two thirds of non-coding RNA in the human genome could play functional roles.

BIOLOGY

Atlas could become 'Rosetta stone' of RNA

A highly accurate survey of long non-coding RNA in the human genome reveals that two thirds of them could play functional roles

By generating a comprehensive atlas of almost 28,000 human, long, non-coding RNAs and comparing it with genomic and genetic data, the RIKEN-led FANTOM consortium has found that more than 19,000 of these RNAs may be functional[1]. This hints that there could be as many—or even more—functional non-coding RNAs than the approximately 20,000 protein-coding genes in the human genome.

Genes were once thought to regulate biological functions almost exclusively by being transcribed to coding RNAs, which are then translated into proteins. But the actual picture is now known to be much more complex than that. Studies examining the association between genes and diseases have shown that most disease variants are found outside of protein-coding genes.

More than ten years ago, the RIKEN-led FANTOM consortium led the investigation of non-coding RNAs, revealing the complexity of the transcriptional landscape in mammalian genomes for the first time. Now, the team has

generated a comprehensive atlas of human, long, non-coding RNAs with substantially improved gene models, allowing them to better assess the diversity and functionality of these RNAs.

Most attempts to draw maps of RNA transcription rely on sequencing technologies that do not always accurately identify the beginnings, or 5' ends, of the RNA transcripts. To overcome this limitation, the team used a technology known as cap analysis of gene expression (CAGE), which was developed at RIKEN, to build an atlas of human long non-coding RNAs with accurate 5' ends, pinpointing where in the genome their transcription is initiated.

"There is strong debate in the scientific community on whether the thousands of long non-coding RNAs generated from our genomes are functional or simply byproducts of a noisy transcriptional machinery," says Alistair Forrest, a senior visiting scientist at the RIKEN Center for Life Science Technologies (CLST). "By integrating the improved gene models with data from gene expression, evolutionary conservation and genetic studies, we find compelling evidence that the majority of these long, non-coding RNAs appear to be functional, and for nearly 2,000 of them we reveal their potential involvement in diseases and other genetic traits."

"The improved gene models and the broad functional hints of human, long, non-coding RNAs derived from this atlas could serve as a Rosetta Stone for us to experimentally investigate their functional relevance as part of our ongoing work for the upcoming edition of the FANTOM consortium," says Piero Carninci of CLST. "These results could further push the boundary of our understanding of the functions of the non-coding portion of our genome." ■

Reference

1. Hon, C.-C. Ramilowski, J. A., Harshbarger, J., Bertin, N., Rackham, O. J. L., Gough, J., Denisenko, E., Schmeier, S., Poulsen, T. M., Severin, J. *et al.* An atlas of human long non-coding RNAs with accurate 5' ends. *Nature* **543,** 199–204 (2017).

PHYSICS

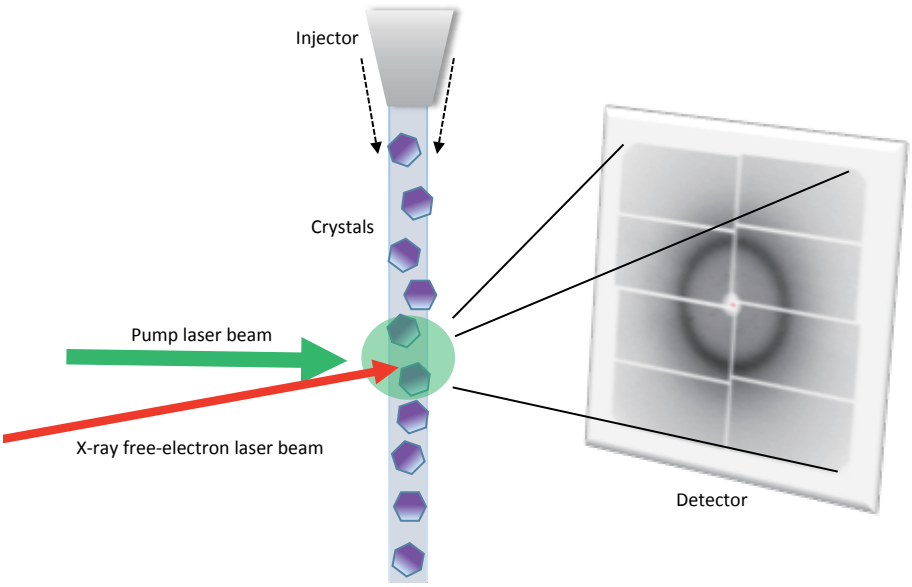
X-ray beam reveals archaeal protein's proton pump

Scientists use a powerful x-ray beam to prove how a archaeal protein harnesses light to pump protons across the cell membrane

Using a powerful x-ray beam, RIKEN researchers have demonstrated how a archaeal protein uses light to pump protons across the cell membrane to create a charge difference that can be used to power the cell's activities.

Bacteriorhodopsin is a protein found in salt-loving archaea that absorbs light and transports protons across cell membranes. Scientists have long tried to work out how it does this and how it can push protons in a single direction—from the inside to the outside of the cell.

To find out, the researchers turned to the SPring-8 Angstrom Compact free electron LAser (SACLA), a powerful free-electron laser that produces x-ray beams a million times brighter than conventional synchrotron facilities. SACLA's x-rays can be used to determine the structure of proteins and other molecules. But the beam is so intense that it vaporizes samples almost instantly, and so images need to be captured before samples are destroyed.



Using powerful x-ray beams generated at SACLA, RIKEN researchers were able to detect diffraction patterns that revealed the structural changes occurring in crystals of the proton-pumping protein bacteriorhodopsin.

The team took thousands of images of bacteriorhodopsin at various points in time after it had been irradiated by the x-ray beam. Combining the images enabled them to piece together the story of how the membrane protein is able to move protons against a gradient into the more positively charged environment outside the cell, creating a charge like a battery that could be used to power chemical reactions.

"With this work, we were able to shed light on the mechanism of proton transfer and bring closure to a long-standing debate regarding the mechanism," says Eriko Nango of the RIKEN SPring-8 Center. "Photoexcitation leads to a change of conformation in retinal, a key part of bacteriorhodopsin that absorbs light. This, in turn, leads to the displacement of amino acid residues above the retinal toward the cytoplasm, and transient water appears in that space to assist primary proton transfer. Following this, a delicate molecular cascade prevents the proton from moving backward, and it is pushed up and outside the cell."

Previous studies based on other methods had identified many of the steps, but an inkling that the radiation itself might be causing changes made it impossible to conclusively show the precise mechanism. With the new technique, the group finally pinned this down.

"New techniques using powerful x-ray lasers are giving us insights into precisely how processes such as proton pumping take place in actual biological systems," says So Iwata, who led the team. "This will give us much greater understanding of these actions and ultimately lead to insights that will allow us to manipulate them more effectively." ■

Reference

1. Nango, E., Royant, A., Kubo, M., Nakane, T., Wickstrand, C., Kimura, T., Tanaka, T., Tono, K., Song, C., Tanaka, R. *et al.* A three-dimensional movie of structural changes in bacteriorhodopsin. *Science* **354,** 1552–1557 (2016).

BIOLOGY

Long-range communication bridge within cells found

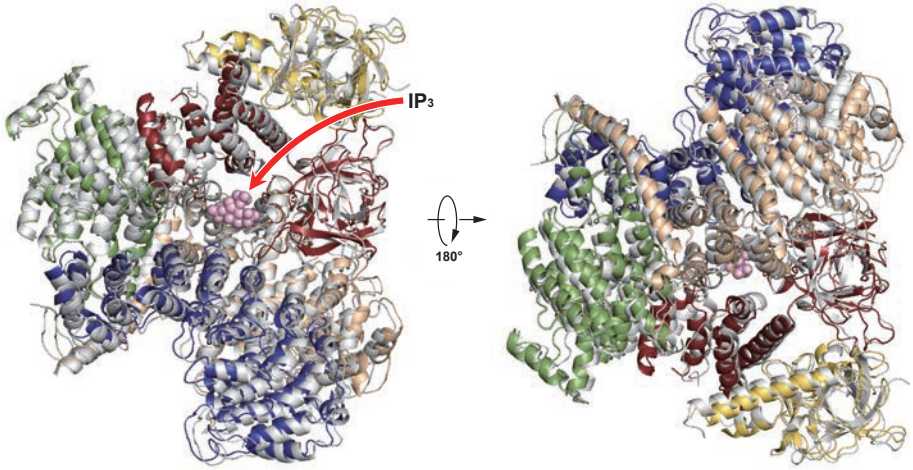
Figuring out how long-range chemical communication happens within a cell may help treat many diseases

A better understanding of the structure of a molecule that acts as a 'train station' for transferring signals that control many cell functions could open up new avenues for treating many diseases[1]. This finding on the inositol tris-phosphate receptor (IP_3R) molecule had long been a major goal in biomedical research.

All living cells use chemical signals to communicate between their various components. One such chemical is inositol 1,4,5-trisphosphate (IP_3), which binds to a receptor (IP_3R) to release calcium ions from stores within a cell. Calcium ions play pivotal roles in processes as diverse as neural communication, differentiation, plasticity and metabolism.

Katsuhiko Mikoshiba at the RIKEN Brain Science Institute and co-workers have taken a new look at the crystal structure of the key IP_3R within the brain. They discovered that the distance from the receptor-binding site to the channel pore that it needs to signal is the longest of its type.

By performing X-ray crystallography of a mouse brain's IP_3 receptor at the RIKEN SPring-8 synchrotron radiation facility, the researchers then pinpointed how the binding physically opens the channel from long range. This long-range communication was found to involve the movement of a part of the receptor called the curvature α-helical domain, which serves as a bridge between the proteins and metabolites inside a cell and the channel. Examining this bridge revealed the essential role of a leaflet structure that relays IP_3 signals to the channel and may help to explain how long-range coupling occurs between IP_3 binding and the channel that controls calcium ion storage.



Comparison of inositol trisphosphate receptor (IP_3R) cytosolic domain structures in the absence of IP_3 (colored) with one in the presence of IP_3 (gray).

Calcium ion stores are thought to be key to brain-related diseases, such as spinocerebellar ataxia, a genetic disease associated with progressive problems with movement, and Gillespie syndrome, a genetic disease that typically features eye abnormalities, problems with balance and movement, and mild to moderate intellectual disability. The IP_3 receptor also regulates cellular waste-disposal processes, which are linked to neurodegenerative diseases such as Alzheimer's.

The researchers hope that resolving the long-standing mystery of this long-range intracellular communication will aid future drug design. In addition, it may help clarify this processes' role in cellular aging and tumor suppression, to which is has been linked.

The study also identified an amino acid sequence in the leaflet that is retained in parasites such as *Trypanosoma cruzi*, which causes Chagas disease, and *brucei*, which causes African trypanosomiasis, or sleeping sickness.

The team suggest these structural insights may assist in drug discovery for these devastating conditions as well. ■

Reference

1. Hamada, K., Miyatake, H., Terauchi, A. & Mikoshiba, K. IP_3-mediated gating mechanism of the IP_3 receptor revealed by mutagenesis and X-ray crystallography. *Proceedings of the National Academy of Sciences USA* **114,** 4661–4666 (2017).

PHYSICS

Ultra-accurate antiproton measurements confirm standard model

The magnetic moment of the antiproton has been measured to greater accuracy than ever before, confirming predictions made by the standard model of particle physics

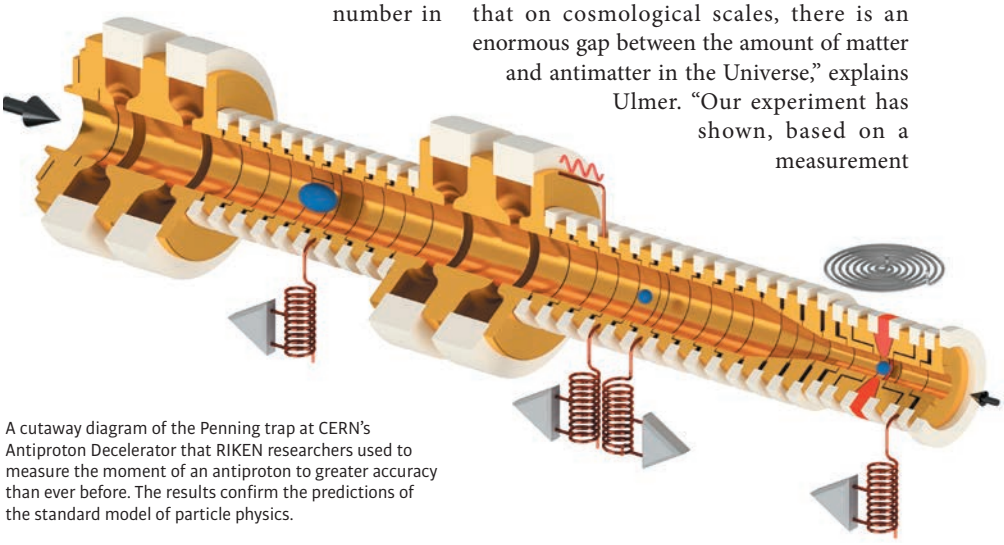
One of the deepest mysteries of physics today is why the Universe is composed almost entirely of normal matter when the Big Bang should have created equal amounts of matter and antimatter. Scientists around the world, including Stefan Ulmer's team at RIKEN, are performing high-precision measurements to try to discover any fundamental differences between matter and antimatter that could lead to the observed discrepancy.

Using a sophisticated technique that involves trapping individual particles in a magnetic device, Ulmer's team found that the magnetic moment of the antiproton is extremely close to that of the proton, with a six-fold higher accuracy than previous measurements[1].

The researchers trapped antiprotons generated by CERN's Antiproton Decelerator in a powerful magnetic device, called a Penning trap, where they can be stored for more than a year. They measured the magnetic moment of individual antiprotons by moving them from the containment trap into another trap, where they were cooled to about 1 degree Kelvin and subjected to a powerful and complex magnetic field.

The team found that the moment (g-factor) of the antiproton is 2.7928465(23), while that of the proton had previously been found to be 2.792847350(9) (the number in parentheses indicates the uncertainty in the final digits). This puts the two measurements to within 0.8 parts per million of one another.

"We see a deep contradiction between the standard model of particle physics, under which the proton and antiproton are identical mirror images of one another, and the fact that on cosmological scales, there is an enormous gap between the amount of matter and antimatter in the Universe," explains Ulmer. "Our experiment has shown, based on a measurement



A cutaway diagram of the Penning trap at CERN's Antiproton Decelerator that RIKEN researchers used to measure the moment of an antiproton to greater accuracy than ever before. The results confirm the predictions of the standard model of particle physics.

six times more precise than any done before, that the standard model holds up and that there seems in fact to be no difference in the proton/antiproton magnetic moments at the achieved measurement uncertainty. We didn't find any evidence for CPT violation."

The team plans to use an even more sophisticated double Penning trap technique, which promises a 1,000-fold improvement in accuracy. They have already applied this technique to measure the magnetic moment of a proton, and have the set of required methods to conduct this measurement with the antiproton as well. "However, the implementation of this experimental scheme is technically very challenging and will require several iterations", says Hiroki Nagahama, a PhD student in Ulmer's group, "we are planning to conduct this measurement in one of the next antiproton runs." ■

Reference

1. Nagahama, H., Smorra, C., Sellner, S., Harrington, J., Higuchi, T., Borchert, M. J., Tanaka, T., Besirli, M., Mooser, A. & Schneider, G. Six-fold improved single particle measurement of the magnetic moment of the antiproton. *Nature Communications* **8,** 14084 (2017).

BIOLOGY

Ingrained in the brain

Neurons in the front of the brain and their connections with other regions are implicated in the formation of long-term memories

RIKEN scientists have found evidence for how we recall experiences from long ago by demonstrating the existence of enduring engram cells in the frontal part of the brain and showing how connections with other brain regions allow these cells to mature[1].

A team led by Susumu Tonegawa, director of the RIKEN Brain Science Institute and the RIKEN–MIT Center for Neural Circuit Genetics, is studying memory formation in mice by combining associative learning with optogenetics and cell labeling. This allows them to tag neurons that represent the memory of an event as they are formed in the hippocampus. The activation of these neurons, called engram cells, is the basis for memory recall.

Episodic memories stored in hippocampal engram cells are short lived. Scientists had theorized that permanent memories form gradually as new engram cells and neuronal connections form in the cerebral cortex.

The team has now demonstrated that this is only partially correct. "We discovered the existence of cortical engram cells, but it turns out that they are not formed gradually over time," explains Takashi Kitamura. "They actually form at the same time as the initial memory in the hippocampus."

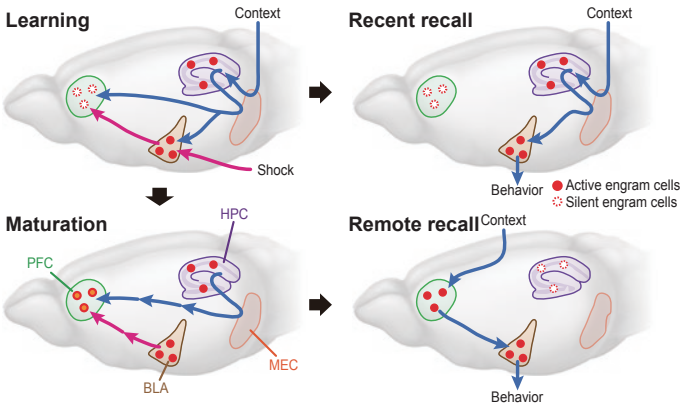
To determine the cortex areas important for forming long-term memories, the researchers blocked inputs to different brain areas during conditioning or memory recall over a period of 3 weeks. Long-term recall was affected only when information transfer to the frontal cortex of the brain was blocked during conditioning. "This was surprising," notes Tonegawa, "because it indicated that the cortical memory was likely created on the very first day, and not gradually as has been assumed."

The team inserted light-sensitive ion channels into prefrontal cells that were active during conditioning and then excited the cells with blue light when the animals were in an unconditioned context. The mice exhibited behavior indicative of their remembered experience—a hallmark of engram cells.

Animals should remember an event when engram cells respond naturally to a conditioned context and be unable to do so when the cells are silent. The team showed this was true for cortical engram cells, but only when tested more than a week after conditioning, when the hippocampal engram cells had lost their memories.

"Although the engram cells formed on the first day, they could only be activated naturally much later," says Kitamura. "This means that it took time for them to mature and change from silent engrams to active ones."

"These results will allow researchers to delve deeper into the neural circuit mechanisms and engrams needed for their formation in the neocortex," notes Kitamura. ■



RIKEN researchers have found that memories of past events are consolidated in the prefrontal cortex and circuitry through the amygdala shifts as hippocampal engram cells become silent and cortical engrams become active.

Reference

1. Kitamura, T., Ogawa, S. K., Roy, D. S., Okuyama, T., Morrissey, M. D., Smith, L. M., Redondo, R. L. & Tonegawa, S. Engrams and circuits crucial for systems consolidation of a memory. *Science* **356,** 73–78 (2017).

Environmental science

Nature's genius aids sustainability science

From bioplastics and stress-resistant rice to drugs and biofuels, the nature-inspired RIKEN Center for Sustainable Resource Science is one of the pivotal science hubs helping Japan reach its ambitious 2030 sustainability targets.

Kazuo Shinozaki
Since joining RIKEN as a chief scientist in 1989, Kazuo Shinozaki has conducted research into molecular biology and functional genomics, with specific emphasis on plant response and tolerance to environmental stresses. More recently, his interests have focused on the application of basic research to the sustainable production of food, biomass and energy as the CSRS director. He is one of the world's most highly cited researchers in plant sciences (see page 32).

SUSTAINABLE DEVELOPMENT GOALS

Life on Earth is driven by a myriad of fascinating processes, which are under greater environmental pressure than ever before. Scientists at the RIKEN Center for Sustainable Resource Science (CSRS) are seeking to contribute to Japan's sustainability efforts by better understanding nature's cycles and using the knowledge to create greener solutions to the world's environmental issues.

In 2015, two historic proposals—the Paris Agreement on global warming (COP21) and the United Nations 2030 Agenda for Sustainable Development—were supported by more than 190 countries. Japan promised to work on realizing the Agenda's 17 sustainable development goals (SDGs) and to move toward a 26 per cent reduction of greenhouse gases from 2013 levels by 2030.

Led by Director Kazuo Shinozaki, CSRS researchers are addressing these goals through exploring the potential of biological compounds, microorganisms and plants, and the processes at which nature excels. Its experts in plant science, chemical biology and catalytic chemistry are seeking innovative and biologically inspired technological solutions that have minimal impact on the environment. "The SDGs are vital for the well-being of future generations," says Shinozaki. "Scientists should think about their potential to contribute to achieving them."

Toward the United Nation's sustainable development goals

13 CLIMATE ACTION — Tackling greenhouse gases: Photosynthesis in the lab

Carbon dioxide (CO_2), the most significant greenhouse gas, is being generated at worrying levels. Plants and some microorganisms reduce the amount of CO_2 in the atmosphere through photosynthesis. Currently, CSRS researchers are investigating the possibility of enhancing plant uptake of CO_2 and ways to realize artificial photosynthesis as a means to reduce greenhouse gases and to harness its energy-creating potential.

One of the first steps of photosynthesis is splitting water into hydrogen and oxygen, a major hurdle in an artificial setting. Plants and microorganisms accomplish this with low energy input and a neutral pH, whereas artificial photosynthesis typically requires high energy input and pH, which is expensive. However, in 2016 a key CSRS finding by Ryuhei Nakamura's Biofunctional Catalyst Research Team revealed that splitting water in the presence of manganese oxide nanoparticles is more efficient than using bulk manganese oxide, moving scientists one step closer toward harnessing this process for green energy and using hydrogen as a low-carbon fuel (see research highlight on page 11).[1]

2 ZERO HUNGER — Zero hunger: Resilient crops

Global warming is causing droughts and environmental stresses that reduce crop yields. As a result, the CSRS is working on creating plants that can grow in tough conditions and with limited nutrients and fertilizers. "By studying plants' immunity, genes, and metabolic pathways, we can breed plants that are resistant to diseases and tolerant to environmental stresses such as drought, high salinity, soil erosion and pollutants," Shinozaki explains.

During drought, plants tend to accumulate molecules such as metabolite galactinol, which can protect their cells from the effects of a lack of water. Shinozaki's Gene Discovery Research Group has increased rice drought tolerance by introducing a gene responsible for synthesizing galactinol from Arabidopsis into rice, producing plants that accumulate more than 70 times the usual amount of the metabolite.[2] This rice was recently tested in Colombia in collaboration with the International Center for Tropical Agriculture (CIAT) and showed a higher yield under dry conditions. It will soon be trialed in Africa and other parts of South America.

CSRS researchers are also exploring ways to reduce the use of nitrogen fertilizers, which are applied to crop topsoil. Excess nitrogen fertilizers make their ways into waterways, causing algal blooms and unnatural plant growth, and stimulate soil microbes to convert nitrogen to nitrous oxide, another potent greenhouse gas. Common crop staples, such as rice and wheat, need a lot of fertilizer, but some soil bacteria have an enzyme that can convert the abundant nitrogen in the atmosphere into ammonia—a form of nitrogen that plants can use. These soil bacteria naturally have a symbiotic relationship with legumes, but Makoto Hayashi's Plant Symbiosis Research Team is looking at introducing nitrogen-fixing bacterium rhizobium into other staple crops, which would dramatically cut the use of nitrogen fertilizers.

3 GOOD HEALTH AND WELL-BEING — Good health and well-being: Aging, new drugs and the deep seas

To look into the aging aspect of health and well-being, the CSRS, in collaboration with other RIKEN centers, has launched an interdisciplinary project to study how immunity, brain, nervous system and metabolic functions change during aging. Minoru Yoshida's Chemical Genomics Research Group, Hiroyuki Osada's Chemical Biology Research Group and Mikiko Sodeoka's Catalysis and Integrated Research Group are screening libraries of chemical products synthesized or collected from microorganisms, plants and animals, in the hope of finding new drugs, antibiotics and other compounds essential for human health. Furthermore, Jun Kikuchi's Environmental Metabolic Analysis

Overexpression of an Arabidopsis galactinol synthase gene improved drought tolerance in transgenic upland rice and increased grain yield in dry fields in South America.

Research Team is collaborating with the Japan Agency for Marine-Earth Science and Technology (JAMSTEC) to search for deep-sea microorganisms that may reveal valuable new molecules. "Our genetic analysis of samples collected by JAMSTEC scientists could lead to the discovery of useful deep-sea dwelling microorganisms, whose diversity and properties have yet to be explored," notes Shinozaki.

Affordable and clean energy: Planes powered by algae

CSRS is also taking part in the race to find alternatives to fossil fuels. Cultured algae may help create the jet fuels of the future. In collaboration with biofuel and research company euglena Co., Ltd, CSRS is analyzing how the metabolic pathways of the microalgae *Euglena* could increase biofuel yields for the aviation industry. "Algae can grow faster than other plants and produce more oil than rapeseed. For this reason, Keiichi Mochida's Cellulose Production Research Team and Kikuchi's team are analyzing *Euglena*'s metabolites to boost the key metabolic pathways that will increase oil yield," explains Shinozaki.

Responsible consumption and production: More bioplastic, less ammonia

Keiji Numata's Enzyme Research Team is working on a biodegradable plastic known as polyhydroxyalkanoate (PHA), which is produced by bacteria that feed on lignin, a major component of wood. CSRS is also working with marine photosynthetic bacteria to synthesize PHA from CO_2 in seawater. The biodegradable plastic could be employed as plastic mulch, covering the soil around agricultural crops to help retain moisture and improve soil health as well as increase the soil temperature during seed germination. Their techniques are being developed with the Kaneka Corporation.

Another huge issue CSRS scientists are tackling is the fossil fuel–heavy production of ammonia, the main ingredient in crop fertilizers. Ammonia is currently manufactured at high temperatures and pressures, in a process estimated to account for more than 1 per cent of global energy consumption. CSRS researchers are investigating new means to help plants absorb nitrogen and reduce fertilizer use. Moreover, Zhaomin Hou's Advanced Catalysis Research Group has recently managed to partially bypass the need for ammonia by making important chemical compounds called nitriles directly from nitrogen.

Life below water: Healthy fishes in clean oceans

A CSRS project is looking at removing heavy-metal pollutants such as mercury from contaminated water via bioremediation—the use of naturally occurring organisms to neutralize pollutants at contaminated sites. Hitoshi Sakakibara's Plant Productivity Systems Research Group and Misao Itouga are exploring how contaminated sites can be treated using mosses and other plants that are able to live on pollutants. Kikuchi's team also began a project with the Fishery Research Agency to study how the metabolites and gut bacteria of farmed tunas and eels change depending on the fishes' diet and its health conditions.

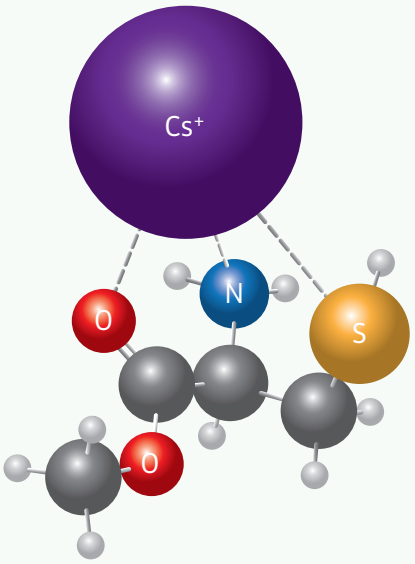
Life on land: Cleaning up radiation and getting the most from soils

Similar bioremediation technologies as above are also being applied to protect land-dwelling creatures. Recently, Ryoung Shin's Regulatory Network Research Unit found a chemical compound that promotes radioactive cesium accumulation in Arabidopsis plants. This may be useful for rehabilitating land contaminated after nuclear disasters such as Fukushima. Sakakibara's group and Itouga are also working in collaboration with recycling-oriented company DOWA HOLDINGS CO., LTD to promote the recovery of useful material sources from the soil using plants and microorganisms. In particular, CSRS researchers are studying methods to recover rare and heavy metals, like gold and platinum, using mosses. In addition, Ken Shirasu's Plant Immunity Research Group and Hayashi's team are working with farmers to better understand how soil bacteria, fix nitrogen and help plants fight diseases.

Looking ahead

The success of the Agenda depends on co-operation between governments, the private sector and civil society. CSRS is collaborating with more than 30 companies, over 20 research institutes and universities worldwide, and several Japanese government research institutes. It's a CSRS strength, says Shinozaki, who emphasizes that they "stress the importance of local and international collaborations to achieve real applications of basic knowledge."

Next year, the CSRS will begin its second phase and focus on employing all available technologies in chemistry, genomics and big data toward its ends. Furthermore, in collaboration with the recently established RIKEN Center for Advanced Intelligence Project, the CSRS will look into using big data science and artificial intelligence to enhance agricultural planning and the design of high-performance chemical reactions. ■



An amino acid derivative, L-methyl cysteinate, promotes cesium accumulation in plants, which could be harnessed to decontaminate agricultural land contaminated with cesium more efficiently.

References

1. Jin, K., Seo, H., Hayashi, T., Balamurugan, M., Jeong, D., Go, Y. K., Hong, J. S., Cho, K. H., Kakizaki, H., Bonnet-Mercier, N. *et al.* Mechanistic investigation of water oxidation catalyzed by uniform, assembled MnO nanoparticles. *Journal of the American Chemical Society* **139,** 2277–2285 (2017).

2. Selvaraj, M. G., Ishizaki, T., Valencia, M., Ogawa, S., Dedicova, B., Ogata, T., Yoshiwara, K., Maruyama, K., Kusano, M., Saito, K. *et al.* Overexpression of an *Arabidopsis thaliana* galactinol synthase gene improves drought tolerance in transgenic rice and increased grain yield in the field. *Plant Biotechnology Journal* advance online publication, May 2017 doi: 10.1111/pbi.12731

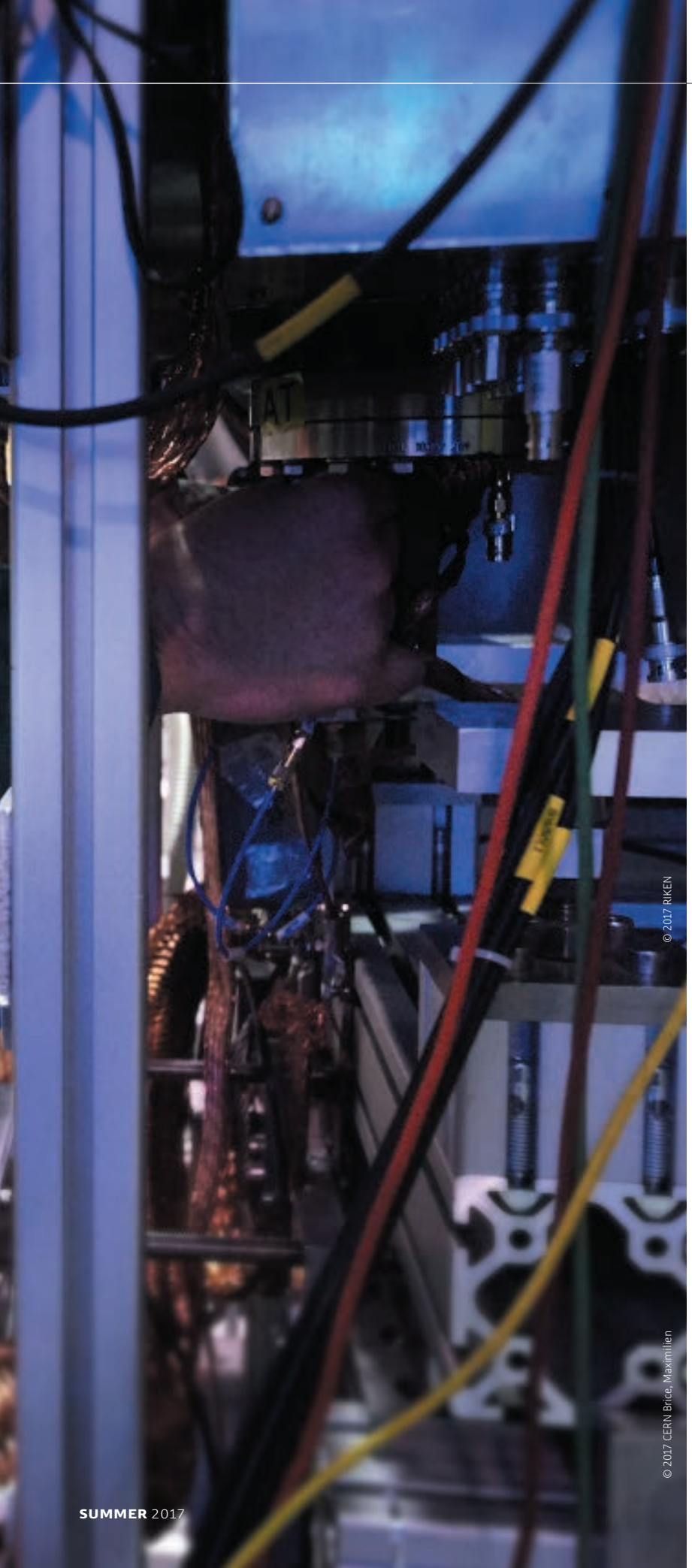
For additional references, visit the online version of this article at:
www.riken.jp/en/research/rikenresearch/perspectives/8283/

Stefan Ulmer working on the BASE radio-frequency system at CERN in Geneva, Switzerland. As part of the Initiative Research Unit program, Stefan set up a team to look into one of the hottest topics in modern physics—the difference between matter and antimatter.

Initiative Research Units

RIKEN's incubators for young research leaders

As RIKEN launches a new framework to nurture young principal investigators, the Hakubi Fellows Program, we look back at an earlier system, the Initiative Research Units, which fostered 18 gifted scientists



With the graduation of its last researcher, Stefan Ulmer, in March 2017, the Initiative Research Unit (IRU) program came to a close after more than 15 years in operation. In April this year, RIKEN has launched a new system for fostering young talented researchers—the RIKEN Hakubi Fellows Program. Like the IRU—whose graduates have done everything from explaining the regulation of cell function in the central nervous system to developing leading-edge terahertz imaging technology—the new program is designed to develop exceptional researchers. As the new program is launched, it's a good time to review the lessons that can be taken from the groundbreaking IRU.

Looking back at the Initiative Research Units

Launched in 2001, the IRU program was designed to give young researchers the chance to run an independent laboratory during the most productive time in their careers, which is generally their thirties. Each was given a five-year budget for equipment and researchers. Kohei Tamao, who played a key role in the IRU program after joining RIKEN in 2005, shares his thoughts and recollections. These are followed by the testimonies of three IRU alumni.

Kohei Tamao, Director of the RIKEN Global Research Cluster

In April 2005, I became head of the RIKEN Frontier Research System (FRS)—an innovative program designed to stimulate research in new fields of science and technology. While at FRS, I became aware of the IRU program. It offered its young appointees generous financial and administrative support, after which these researchers were expected to spread their wings in new laboratories outside of RIKEN. Each was given a rare level of independence as they were placed directly under the executive director in charge of research. I was initially concerned that this independence would prevent them from benefitting from one of RIKEN's most important merits—the low barriers between disciplines, which make it easy to exchange knowledge and build human networks across disciplines.

This was somewhat remedied in April 2006, when the IRUs were placed in the FRS, putting them in closer contact with the 200 other researchers working there at the time. Then, with the termination of the FRS program in April 2008, the IRU researchers were incorporated in the newly launched Advanced Science Institute, an organization that had approximately 700 researchers.

After that I served as head of the IRU program's nomination and evaluation committees. I am

Between 2011 and 2016 Hye Ryung Byon (far right) led an IRU looking into energy storage and conversion.

"We made leaps in… improving the energy densities of batteries"

very honored and appreciative that I could share the joys and tribulations of all 18, from the very first graduates—Kodo Kawase and Ichiro Masai, who broke new ground in terahertz imaging technology and neuromuscular connections.

Initially, IRU recruitment was done without regard for the field of study. But from 2007, we began recruiting based on the fields we wanted to build and adopted a system to encourage the researchers to remain at RIKEN after the end of their tenure.

In 2011, we began to actively recruit non-Japanese researchers to promote the further internationalization of RIKEN. In 2012, the Advanced Science Institute was dismantled, and, for various reasons, recruitment stopped for the IRU, with Stefan Ulmer being the 18th and last appointee. As the list of researchers below shows, all have done fantastic things following their tenure at RIKEN. However, there are always lessons to be learned, and I list some of them below.

Build independent funding capabilities: It's important that young researchers develop their capabilities freely. In the early years, IRU researchers were not permitted to apply for external funding. This prohibition was lifted when they were incorporated into the FRS, and they were encouraged to apply for funding under Kakenhi or the JST Sakigake researcher program.

Giving projects time to mature: I think researchers need at least five years to concentrate purely on their research and have long considered that seven years is a magic number for young researchers. Mid-term IRU reviews were conducted in the third year. Since these essentially looked at just over two years of work, there were many cases when laboratories had insufficient time to make outstanding achievements. However, final reviews were often glowing. If the projects ran for seven years, mid-term reviews could be held during the fifth year, making evaluations more accurate and giving young researchers more appropriate advice to help them advance their work.

I am happy to see that all the young researchers appointed under the program are now working as principal investigators and have their own labs. And I can see that the generous spirit of the program will be continued under the new RIKEN Hakubi program.

Stefan Ulmer, Ulmer Initiative Research Unit (2012–2017)

I set up a team to explore one of the hottest topics in modern physics—the difference between matter and antimatter. We began by doing experiments at the Antiproton Decelerator at CERN, Switzerland—the only place where such high-precision experiments can be done. We designed a state-of-the-art multi-Penning trap system and recently measured the magnetic moment of the antiproton with record precision and also were able to make the most accurate CPT test to date in the baryon sector, by comparing the proton-to-antiproton charge-to-mass ratio with a precision of better than ten significant figures. Although my work through the IRU program has ended, RIKEN has generously continued to support the project through the new Ulmer Fundamental Symmetries Laboratory. My colleagues and I want to acknowledge the strong

support provided by RIKEN as it enabled us to make good progress on our high-precision physics project.

Hye Ryung Byon, Byon Initiative Research Unit (2011–2016)

Under the IRU program, I led a lab that examined the storage and conversion of energy using nanotechnology. We made leaps in knowledge about improving the energy densities of batteries, which is fundamental to enhancing the efficacy of technologies like electric cars. The IRU program gave scientists such as me the opportunity to start careers as principal investigators without the stress of having to apply for research funding. That kind of support is hard to find anywhere else in the world, and it was key to significantly improving each principal investigator's abilities as an independent scientist. As a result, I and the members of my group became more serious about selecting fruitful research and felt a high level of investment in, and responsibility for, the results.

Akimitsu Okamoto, Okamoto Initiative Research Unit (2006–2011)

My focus at my IRU was analyzing and imaging nucleic acid functions at the atomic level, as well as designing new organic chemical systems for recognizing and transforming a single component or atom into biopolymers of interest. These open up the means to better detect and diagnose genetic diseases and predispositions, among other things. I sometimes hear about researchers whose funding windows ended without making significant progress on their projects. However, through the IRU program, I was given a large research budget, which allowed me to hire several researchers, as well as solid administrative and specialist support. As a result, the process of translating research results into patent applications, journal articles and press releases was very smooth and my five years in the IRU were very productive.

RIKEN Hakubi Fellows Program

The new Hakubi program offers an opportunity for promising young researchers to lead a group as the principal investigator of an ambitious research topic of their choosing for up to seven years. Proposals will be accepted each year in all natural and mathematical sciences, and in boundary areas involving the humanities and social sciences, with a focus on issues that are in urgent need of solutions.

For more information about the Hakubi scheme, see www.riken.jp/en/careers/hakubi/

Alumni of the IRU program

in order of appointment year

● Current position ● IRU project

Kodo Kawase
- Professor at Nagoya University
- Development of terahertz imaging technology

Ichiro Masai
- Associate Professor at Okinawa Institute of Science and Technology Graduate University
- Molecular mechanism underlying neuronal differentiation and neural circuit formation in the retina

Tatsuro Imakubo
- Associate Professor at Nagaoka University of Technology
- Development of novel supramolecular organic conductors with controlled crystal structure and multiple properties

Mitsunori Fukuda
- Professor at Tohoku University
- Roles of synaptotagmin-like proteins (Slps) in intracellular membrane trafficking

Tsutomu Kishi
- Associate Professor at Nihon University
- Cellular regulation by the SCF ubiquitin ligase

Ichiro Nishii
- Associate Professor at Nara Women's University
- Molecular and genome analysis on evolution of multicellularity in volvocine algae

Takao Iwawaki
- Professor at Kanazawa Medical University
- Physiological and pathological function of endoplasmic reticulum stress response *in vivo*

Shinichi Nakagawa
- Professor at Hokkaido University
- Deciphering the molecular mechanisms that regulate cell type specific behavior in the central nervous system

Takashi Manabe
- Professor at University of Shizuoka
- Development of novel catalytic systems for innovative organic synthesis

Akimitsu Okamoto
- Professor at the University of Tokyo
- Design of functional biopolymers on an atomic scale using organic synthesis

Shin-ya Miyagishima
- Professor at the National Institute of Genetics
- Characterization of the regulatory mechanisms of chloroplast and mitochondrial proliferation

Changyong Song
- Associate Professor at POSTECH, South Korea
- Atomic resolution coherent x-ray diffraction imaging by utilizing the Japan XFEL

Hsiao-Hua Yu
- Principal Investigator at Academia Sinica, Taiwan
- Conductive biomaterials: from tailored organic molecules to Nano-Assemblies

Kam Zhang
- Team Leader at RIKEN Center for Life Science Technologies
- Computational structural biology-protein folding prediction using x-ray diffraction data as constraints

Jonathan Heddle
- Professor at Jagiellonian University, Poland
- Self-assembled nano-bio building blocks for the construction of complex devices

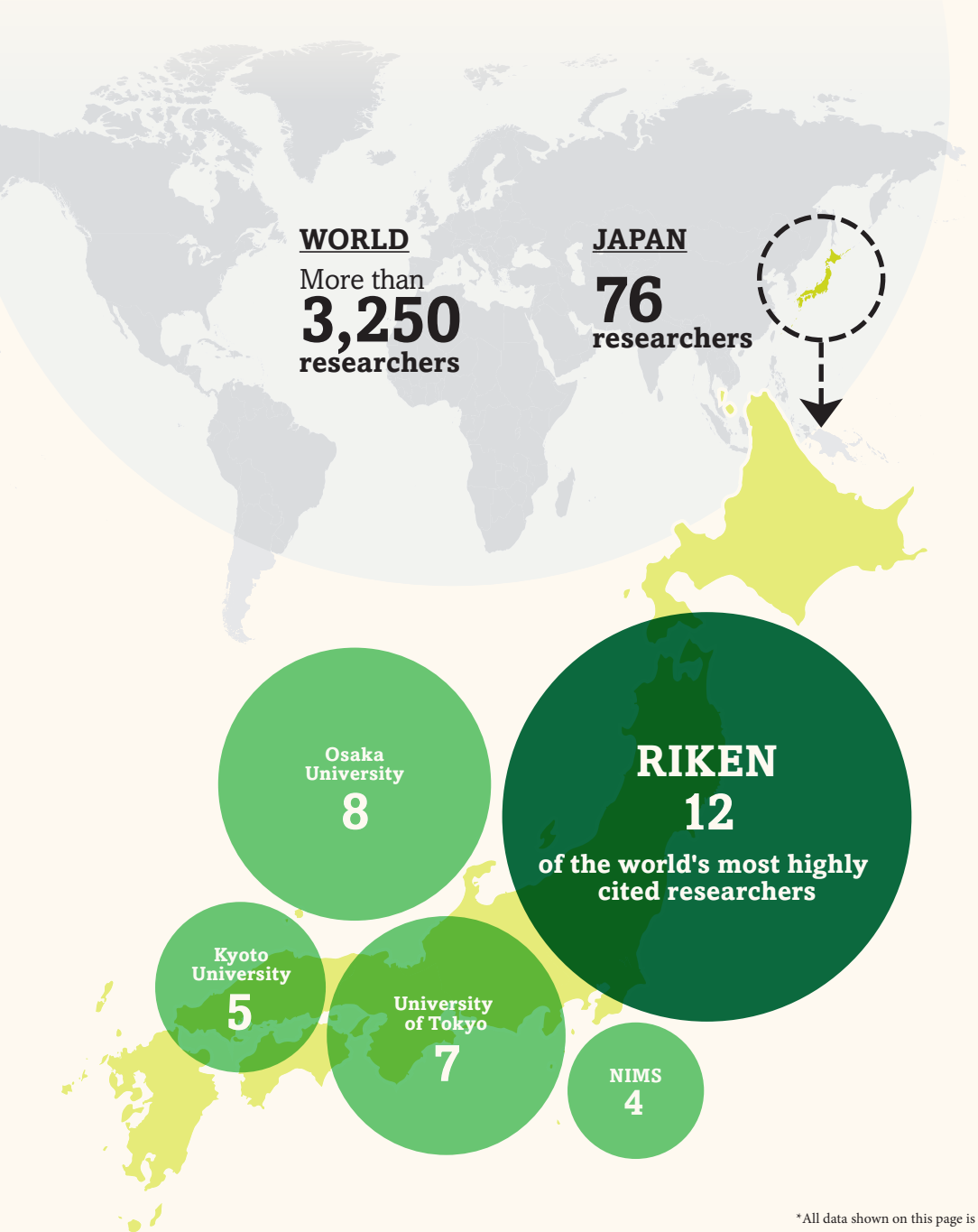
Hye Ryung Byon
- Assistant Professor at KAIST, South Korea
- Elucidating fundamentals of electro-chemical reactions in lithium–air battery systems for developing high-performance energy-storage devices

Urs Frey
- Group Leader at ETH Zurich, Switzerland
- Bioelectronics: CMOS-based biosensors for advanced measurements and perturbations for systems and synthetic biology

Stefan Ulmer
- Chief Scientist at RIKEN
- High-precision determination of the magnetic moment of the proton and the Antiproton – Quantum jump spectroscopy with antimatter

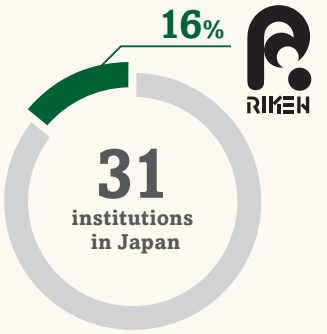
World-class performance in Highly Cited Researchers list

Clarivate Analytics published a list of highly cited researchers in November 2016, based on more than 128,000 papers between 2004 and 2014, ranked among the top 1 per cent in their year of publication. With 12 researchers listed, RIKEN outperformed every other institution in Japan, and many around the world.



#1 Institution

with the greatest number of highly cited researchers in Japan



Researcher spotlight

Kazuo Shinozaki

#1 Number of citations in plant sciences world-wide

Director of the RIKEN Center for Sustainable Resource Science

➡ Read about CSRS on page 25

Cited Total **58,452** times
2016 **5,500** times

Most highly cited paper

The complete nucleotide-sequence of the tobacco chloroplast genome – its gene organization and expression

*All data shown on this page is for the primary affiliation of researchers from November 2016 via Clarivate Analytics, formerly the Intellectual Property & Science business of Thomson Reuters

RIKEN centers and facilities
across Japan and around the world

1 Sendai
Center for Advanced Photonics

2 Tsukuba
BioResource Center

3 Wako
(RIKEN Headquarters)
Center for Emergent Matter Science
Center for Advanced Photonics
Center for Sustainable Resource Science
Brain Science Institute
Nishina Center for Accelerator-Based Science (RI Beam Factory)
Advanced Center for Computing and Communication
Cluster for Industry Partnerships
Cluster for Science and Technology Hub
Chief Scientist Laboratories*
Research Groups
Global Research Cluster
Interdisciplinary Theoretical and Mathematical Sciences Program
*Chief Scientist Laboratories are located throughout Japan

4 Tokyo
Tokyo Liaison Office
Center for Advanced Intelligence Project

5 Yokohama
Center for Sustainable Resource Science
Center for Integrative Medical Sciences
Center for Life Science Technologies
Distinguished Senior Scientist Laboratory

6 Nagoya

7 Osaka
Quantitative Biology Center

8 Kobe
Center for Developmental Biology
Center for Life Science Technologies
Advanced Institute for Computational Science (K computer)
Quantitative Biology Center

9 Harima
SPring-8 Center
(SPring-8 Synchrotron Radiation Facility)
(SACLA X-ray Free Electron Laser Facility)

Since relocating its original campus from central Tokyo to Wako on the city's outskirts in 1967, RIKEN has rapidly expanded its domestic and international network. RIKEN now supports five main research campuses in Japan and has set up a number of research facilities overseas. In addition its facilities in the United States and the United Kingdom, RIKEN has joint research centers or laboratories in Germany, Russia, China, South Korea, India, and Malaysia.

To expand our network, RIKEN works closely with researchers who have returned to their home countries or moved to another institute, with help from RIKEN's liaison offices in Singapore and Beijing.

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