RIKEN
RESEARCH
SUMMER 2018
SHOWCASING THE BEST OF JAPAN'S PREMIER RESEARCH ORGANIZATION • www.riken.jp/en/research/rikenresearch

GETTING A GRIP
Keeping cancer cells corralled

A LIGHT TOUCH
Nanoparticles to delve deeper into the brain

CLOUD COMPUTING
Aerosols' role in climate explained

POLLUTION REVOLUTION
Moss that cleans lead from water

RIKEN insect toxicologist Takashi Abe's fascination with Asian giant hornets (*Vespa mandarinia*) led to insights into the amino acid composition of its larvae saliva. This saliva fuels the adult hornets' 100 kilometer daily journeys for food, and was found to improve energy metabolism. See page 32.

RIKEN, Japan's flagship research institute, conducts basic and applied experimental research in a wide range of science and technology fields including physics, chemistry, medical science, biology and engineering.

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

RIKEN Research is an online and print publication that highlights the best research published by RIKEN. This publication is a selection of the articles published by RIKEN at: www.riken.jp/en/research/rikenresearch Please visit the website for recent updates and related articles. Articles showcase RIKEN's groundbreaking results and are written for a non-specialist audience.

For further information on the research presented in this publication or to arrange an interview with a researcher, please contact:

RIKEN International Affairs Division
2-1, Hirosawa, Wako, Saitama, 351-0198, Japan
Tel: +81 48 462 1225
Fax: +81 48 463 3687
E-mail: rikenresearch@riken.jp

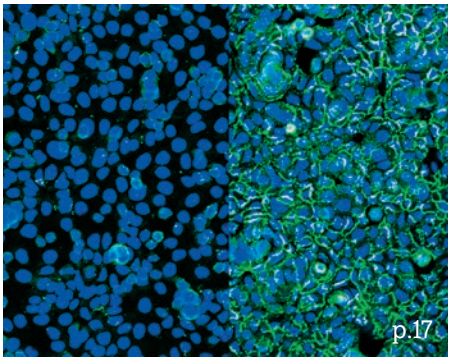
ISSN 1883-3519

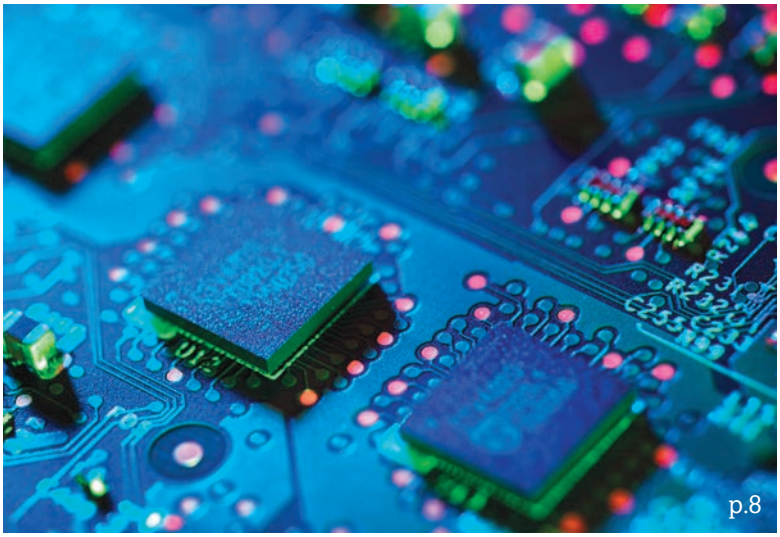
RIKEN Research is published by RIKEN in collaboration with the Partnership and Custom Media unit of Nature Research, a division of Springer Nature.

www.riken.jp/en

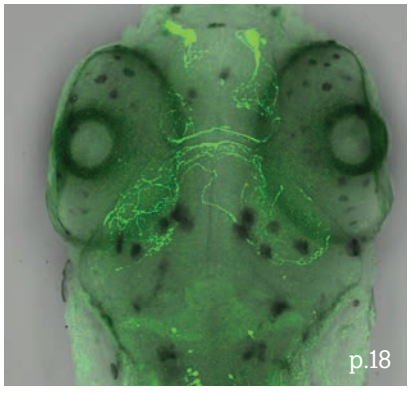
RIKEN RESEARCH

RIKEN





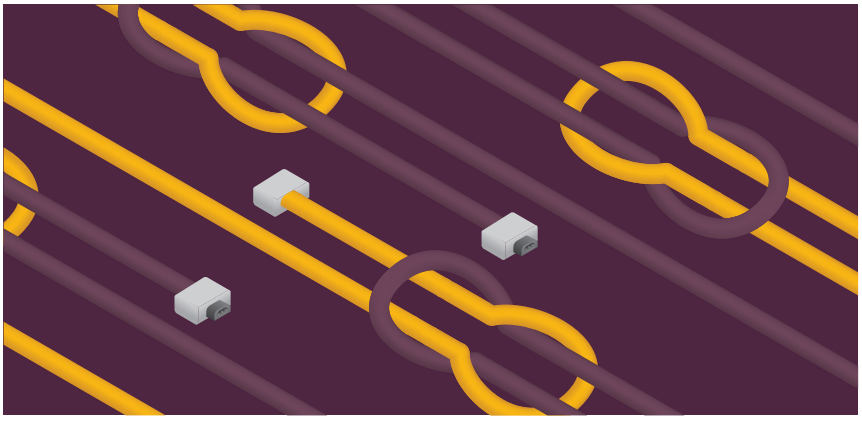
18 Research highlights


p.18


p.25

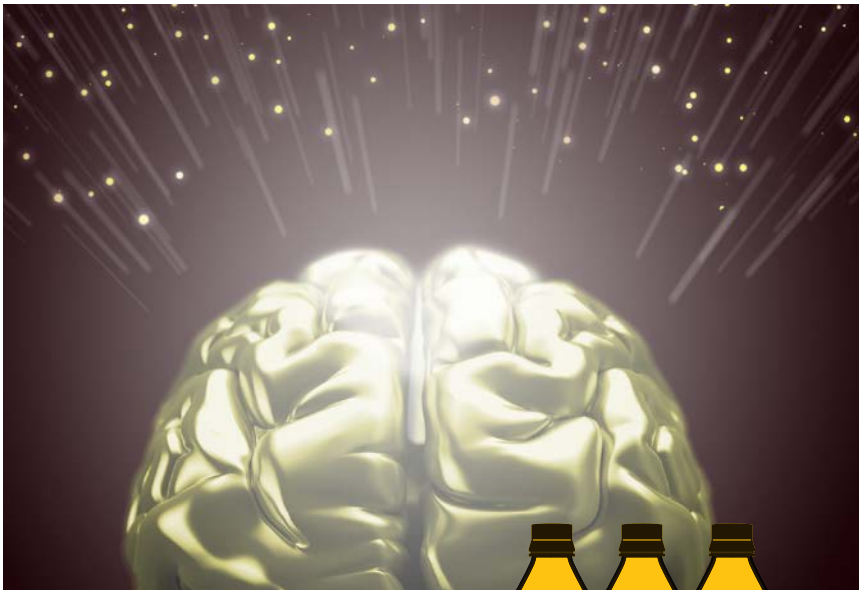
26 Perspectives

Engaging society, changing society



29 Feature COVER STORY

Lighting up the depths of the brain



32 Infographic

Patent powerhouse

Meeting social needs by maximizing on basic research

Hiroshi Matsumoto
President, RIKEN

This is the first issue of *RIKEN Research* published after the institute has embarked on a fourth mid- to long-term plan, in effect from April 2018 to March 2025. Under this new plan, we have reorganized our life-science centers to encourage further interdisciplinary collaboration. We have also set up a number of new systems to ensure that our research output is maximized and that the results are returned to society in line with the industrious RIKEN spirit first articulated by Masatoshi Okochi, the third president of RIKEN (for details, see my Perspectives article on page 26).

One of the major objectives of the new plan is to continue to maintain the high quality of RIKEN's basic research, a characteristic reflected in the number of top-quality articles RIKEN consistently publishes in prestigious journals. This will enable us to remain a top-tier global research institute and to carry on increasing our international standing.

However, another vital goal is to ensure that our science connects with society. To this end, we have established a new organization, the Innovation Design Office. 'Innovation designers' at this new office will help forge and foster long-term visions for research outcomes to ensure that the basic research we do contributes to the wider world.

Furthermore, to promote innovation, we aim to become an essential science and technology hub for Japan's academic community and its industry partners. To help achieve this, we plan to establish a subsidiary company that will take RIKEN's research breakthroughs and transform them into social innovation. In the coming year, Perspectives articles in *RIKEN Research* will introduce some of these new systems and research centers as well as the exciting work they are doing in new research fields.

COVER STORY:
The moss *Funaria hygrometrica* has been found by RIKEN scientists to absorb lead from water. *Page 16*

Keep up to date

Online
www.riken.jp/en

Facebook
facebook.com/RIKEN.english

Twitter
twitter.com/RIKEN_en

LinkedIn
linkedin.com/company/riken

Seeing the sweet side to everything

Chengcheng Huang
Postdoctoral Researcher, Glycometabolic Biochemistry Laboratory
RIKEN Cluster for Pioneering Research

Why do you study sugars?
Our lab studies the metabolic processes of an important group of proteins—those modified with sugar or sugar chains, which we call glycoproteins. In particular, we look at the degradation process of glycoproteins within the cytosol—the water-based fluid in which all the other components of a cell are suspended. These processes are part of the cell's quality-control system that degrades misfolded proteins, which are always non-functional and can often be toxic to a cell.

What are you looking into at the moment? Why is your current research important?
Until recently, I'd been focusing on an enzyme called Ngly1, which cuts up glycans in misfolded glycoproteins so that they can efficiently degradate. This enzyme is so critical that patients born with a single small change to it suffer from a wide range of symptoms. My colleagues and I discovered the detrimental effect of an enzyme produced when Ngly1 is missing, and we looked for inhibitors, which could be used to treat patients who lack Ngly1. More recently, I've been exploring the release of free glycans into the bloodstream. We hope to find the origin of the sugar molecules in the bloodstream, known as complex glycans, as we believe they are released from liver cells and that they may indicate whether the liver is healthy or diseased and so could potentially be used in diagnostic tests.

What made you decide to become a scientist?
I grew up in the countryside in China and have always been interested in living creatures. I became extremely interested in genetics in middle school, when I learned about Mendel's experiment on peas and the genetic code inside each of us that makes who we are. That opened a door for me into the huge field of life science. I wanted to discover as much as I could.

How did you become interested in your current field of research?
I was initially curious about the regulatory events in cell organelles that cause cells to work so perfectly. I became interested in glycobiology when I learned that even a tiny change to the structure of a glycan molecule can radically alter its biological functions in cells.

What excites you the most about your current research?
I'm fascinated by the miniature world of the cell. While the main focus of our research is basic science, I was really thrilled when I found out that our findings could help patients.

> *This enzyme is so critical that patients born with a single small change to it suffer from a wide range of symptoms*

What is the best thing about working at RIKEN?
I love it when the cherry trees blossom in spring and when the leaves on the ginkgo trees turn yellow in fall. It's great fun just walking around campus.

What has been your most memorable experience at RIKEN?
In my first year at RIKEN, I attended a summer school at Izumo in Shimane prefecture. In addition to poster sessions where we could talk with students from different fields, we students also had the chance to talk to the then RIKEN president Ryoji Noyori about science and scientific careers. We also watched traditional Japanese dance and learned about the fascinating history of Izumo. It was a wonderful experience.

Scoping out cosmic rays

Marco Casolino
Research Scientist, Computational Astrophysics Laboratory
RIKEN Cluster for Pioneering Research

Please describe your role at RIKEN
From 2011 to 2017, I led the international Extreme Universe Space Observatory (EUSO) team developing a next-generation Fresnel-lens telescope to study ultrahigh-energy cosmic rays. Since 2018, I have been a part of Toshikazu Ebisuzaki's Computational Astrophysics Laboratory. The plan is for the Fresnel-lens telescope to be installed on the Japanese Experiment Module of the International Space Station (ISS), where it will help us investigate ultrahigh-energy cosmic rays, which travel through the Universe at the highest energies known to man. The findings will likely allow us to test our knowledge of physics at energies much higher than those we can achieve with particle accelerators on Earth. This year, a prototype observatory we developed, the MINI-EUSO, will be installed on the ISS, and it will search for strange quark matter and measure the ultraviolet emissions of terrestrial, atmospheric and meteoric sources.

Why is your current research important?
Currently, the origin and basic nature of ultrahigh-energy cosmic rays are still a mystery. It is not known, for example, whether these particles are protons or heavier nuclei such as iron. Nor is it clear what produces them. Are they accelerated near black holes? Are they related to some new physics still unknown to us?

How did you become interested in your current field of research?
I began studying charged cosmic rays after finishing my Masters degree when I began working on superconducting magnetic spectrometers on balloon payloads and satellite-borne detectors. By helping to adapt several detectors, I've since investigated the effect of radiation on the bodies of astronauts on the ISS, and on Russia's Mir space station before it was deorbited in 2001. Between 2006 and 2016, I worked on the PAMELA space mission, a 500-kilogram space instrument designed to study cosmic rays. Its precision measurements of cosmic-ray matter and antimatter (in the range between 100 mega electron volts and 1 tera electron volts) completely changed how astrophysicists understand cosmic rays and has helped tighten constraints on the nature of dark matter. After the launch of the PAMELA mission, my group was invited to join the Japanese Experiment Module–EUSO space telescope collaboration. In 2005, our group also began collaborating with a group led by RIKEN Chief Scientist Ebisuzaki to develop detectors for this project.

What unique techniques do you use to conduct your research?
The capability to manufacture large-area Fresnel lenses for space observatories with high precision and clarity is, to my knowledge, unique to RIKEN. The techniques were developed by RIKEN's Ohmori Laboratory and are used today by Yoshiyuki Takizawa, who is currently part of the Ultrahigh Precision Optics Technology Team at the RIKEN Center for Advanced Photonics.

How and when did you join RIKEN?
I started working at RIKEN in April 2011, just after the nuclear accident at Fukushima, and so the situation at the time was peculiar. I worked on the recovery of the region and helped monitor the radiation. I also became the principal investigator of the LANFOS Project (2012–2015), which developed a detector for assessing radiation in food affected by the Fukushima accident. For this, we applied our knowledge of space technology to construct a detector capable of assessing the amount of radioactive cesium-137 in food and other materials. Private companies are now commercializing this technology.

Careers at RIKEN
For further information, visit our Careers page:
Website: www.riken.jp/en/careers
E-mail: pr@riken.jp

MEETINGS

Joint workshop on aging research

On 1–2 February 2018, RIKEN and the Universiti Sains Malaysia (USM) held a joint workshop on their ongoing collaborative research into aging. RIKEN has enjoyed a long relationship with USM that started with an exchange of researchers in 1993. Collaborations have continued since then, and, in February 2015, the USM–RIKEN International Center for Aging Science (URICAS) was opened on the USM campus in Penang, Malaysia. The workshop provided an opportunity for researchers involved in the project to present their findings and to discuss future directions in collaborative research.

www.riken.jp/en/pr/topics/2018/20180208_1/

Scientific Director Mark Lathrop of McGill University giving an overview of the insitution at the RIKEN–McGill Symposium on Immunology, Cancer, RNA and Genetics.

The RIKEN–McGill symposium on genetics, immunology and cancer

The second RIKEN–McGill Symposium on Immunology, Cancer, RNA and Genetics was held on 19–20 February 2018 at RIKEN's Yokohama campus. After forging a comprehensive cooperative agreement in 2010, RIKEN and McGill University held their first joint symposium on these topics in May 2017 at McGill University in Montreal, Canada. There, the institutes decided to hold regular joint activities and agreed to advance the use of combined immunological and genetic approaches to address emerging questions in biology and medicine. The symposium began with welcoming addresses by Ichiro Taniuchi from the RIKEN Center for Integrative Medical Sciences (IMS), RIKEN Executive Director Shigeo Koyasu, and Delegate General of Quebec in Tokyo, Luci Tremblay. IMS Director Tadashi Yamamoto and McGill's Scientific Director Mark Lathrop also presented overviews of their respective organizations. Researchers from both institutes gave talks on infection, immunity, and cancer, and held sessions on RNA biology and human genomics. A third symposium will be held soon.

http://www.ims.riken.jp/?p=3128

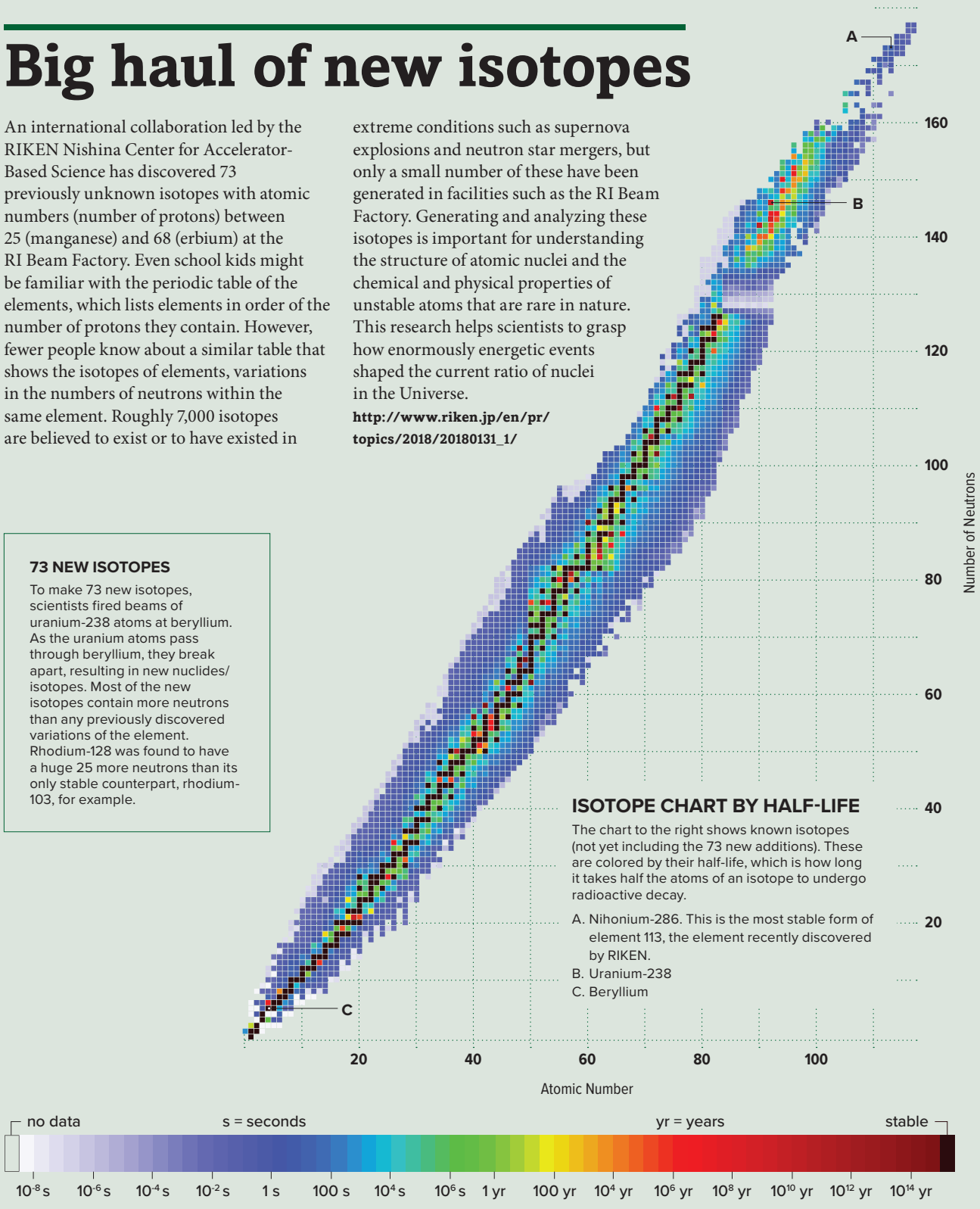
Big haul of new isotopes

An international collaboration led by the RIKEN Nishina Center for Accelerator-Based Science has discovered 73 previously unknown isotopes with atomic numbers (number of protons) between 25 (manganese) and 68 (erbium) at the RI Beam Factory. Even school kids might be familiar with the periodic table of the elements, which lists elements in order of the number of protons they contain. However, fewer people know about a similar table that shows the isotopes of elements, variations in the numbers of neutrons within the same element. Roughly 7,000 isotopes are believed to exist or to have existed in extreme conditions such as supernova explosions and neutron star mergers, but only a small number of these have been generated in facilities such as the RI Beam Factory. Generating and analyzing these isotopes is important for understanding the structure of atomic nuclei and the chemical and physical properties of unstable atoms that are rare in nature. This research helps scientists to grasp how enormously energetic events shaped the current ratio of nuclei in the Universe.

http://www.riken.jp/en/pr/topics/2018/20180131_1/

73 NEW ISOTOPES

To make 73 new isotopes, scientists fired beams of uranium-238 atoms at beryllium. As the uranium atoms pass through beryllium, they break apart, resulting in new nuclides/isotopes. Most of the new isotopes contain more neutrons than any previously discovered variations of the element. Rhodium-128 was found to have a huge 25 more neutrons than its only stable counterpart, rhodium-103, for example.



ISOTOPE CHART BY HALF-LIFE

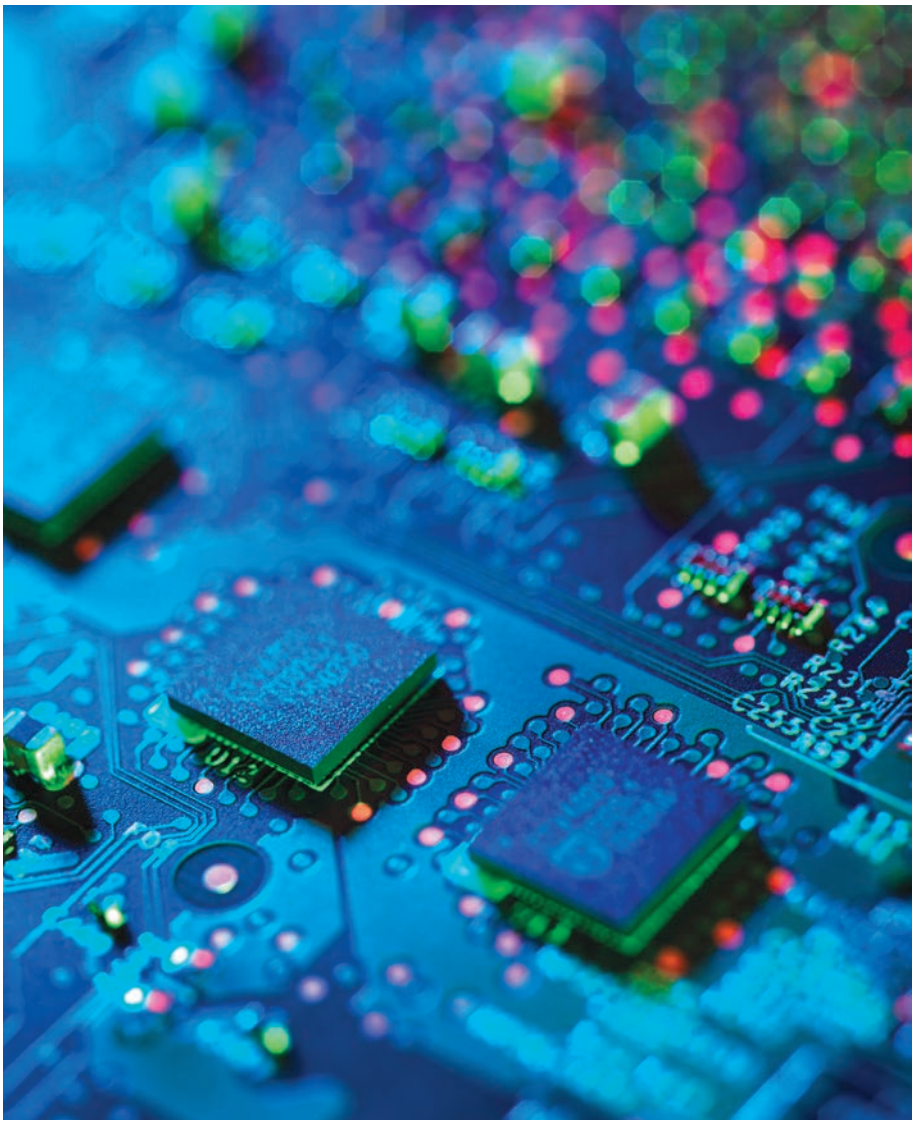
The chart to the right shows known isotopes (not yet including the 73 new additions). These are colored by their half-life, which is how long it takes half the atoms of an isotope to undergo radioactive decay.

A. Nihonium-286. This is the most stable form of element 113, the element recently discovered by RIKEN.
B. Uranium-238
C. Beryllium

BenRG/Wikipedia/Public Domain

Many-core processors make light work

The International Symposium on New Horizons of Computational Science with Heterogeneous Many-Core Processors was held at RIKEN's Wako campus on 27–28 February 2018. Heterogeneous many-core processors are an emerging technology promising increased performance in computing for science, technology and for industrial applications. Sixty-two researchers from seven countries discussed the scientific applications of this technology, ranging from biology, neuroscience and disaster prevention to astronomy and fluid dynamics. At the conference, Jack Dongarra from the University of Tennessee, USA, also talked about the history of the popular TOP500 supercomputer ranking, which he helped develop and launch in 1993. Zhao Liu of the National Supercomputing Center in Wuxi, China, spoke about the system and applications for the Chinese supercomputer, Sunway TaihuLight. Ryutaro Himeno, the director of RIKEN's Advanced Center for Computing and Communication, introduced a new project to develop application software for heterogeneous many-core processors, such as PEZY SC2 and SW26010.



RIKEN's Advanced Center for Computing and Communication is pushing boundaries, currently collaborating on a successor to the K computer, the 'post-K', with Fujitsu and MEXT.

RIKEN co-hosts the 2018 Human Genome Meeting

The RIKEN Center for Life Science Technologies (CLST) co-hosted the 22nd Human Genome Meeting (HGM) on 12–15 March 2018 at RIKEN's Yokohama campus and the convention center, Pacifico Yokohama. The meeting, once dedicated to the project of mapping the human genome, is now a major annual scientific conference on human genetics and genomics, genomic medicine and genome biology and is organized by the Human Genome Organisation. Piero Carninci, former deputy director of CLST (now deputy director of the Center for Integrative Medical Sciences), chaired the local organizing committee. The theme of this year's meeting was genome data and health. Topics discussed included genome editing, single-cell biology and cancer genomics. RIKEN has played a vital role in the international efforts to sequence the human genome, and continues to be a major contributor to developing next-generation genome sequencing technologies, international genome-wide association studies and the International HapMap Project, a project to develop a haplotype map of the human genome that will describe the common patterns of human genetic variation. RIKEN also leads the FANTOM project to identify the fundamental roles of the non-coding regions of the genome, including non-coding RNAs.

NEUTRON STARS

Tightening the noose on neutron star radii

The observation of gravitational waves and light from a merging neutron-star binary system has allowed scientists to get closer to determining the radius of a neutron star

By using data collected by gravitational-wave detectors, a RIKEN researcher and his collaborators have established a new lower limit for the radius of a neutron star, a vital parameter for understanding these intriguing astronomical bodies[1].

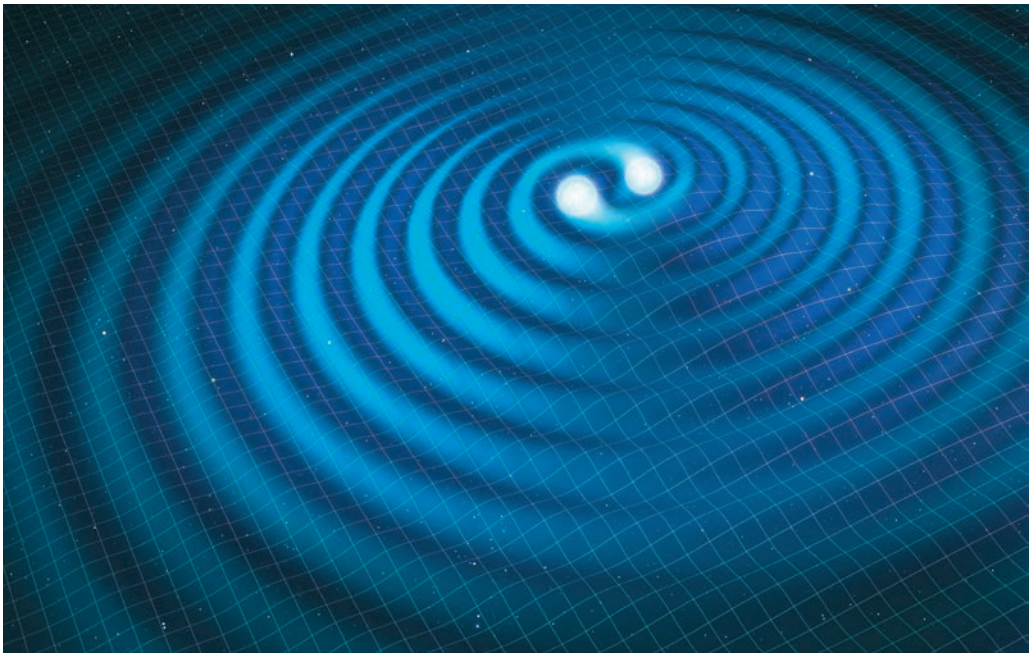
Neutron stars are the carcasses of stars that have collapsed under their own gravity. Typically, they are roughly 1.4 times more massive than the Sun, but a mere 20 kilometers in diameter. They are thus incredibly dense: one teaspoon of neutron-star material would weigh roughly 10 million metric tonnes.

"Neutron stars have insane densities," says Oliver Just of the RIKEN Astrophysical Big Bang Laboratory. "Only the nuclei inside atoms have similar densities on Earth."

Just says that there is still a lot we do not know about neutron stars. The microphysics of a neutron star—which is composed mainly of neutrons that are also found in atomic nuclei—is "still a mystery," he comments.

The study by Just and collaborators in Germany and Greece has added much needed clarity to limiting the neutron star radius, a parameter that provides vital clues about the microphysics of neutron stars and hence also about the microphysics of nuclei on Earth. "Before our study, the radius of a neutron star was only weakly constrained from below," Just says.

The group devised a way to get closer to determining the radii of neutron stars. The method is based on so-called multi-messenger astronomy, in which astronomers detect gravitational waves while simultaneously observing electromagnetic waves in the form of radio, visible and x-ray light.



A conceptual image showing gravitational waves radiating from a pair of merging neutron stars.

"Before our study, the radius of a neutron star was only weakly constrained from below"

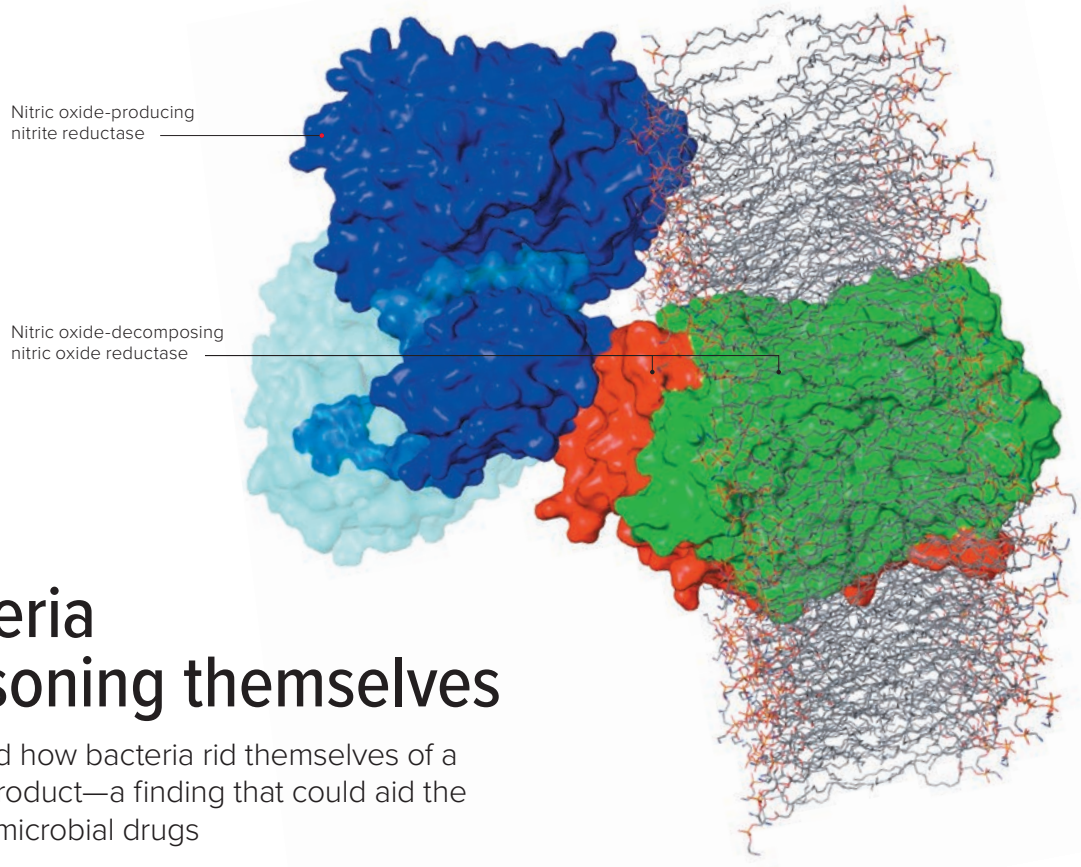
On 17 August 2017, gravitational waves from a neutron-star merger were observed for the first time by Advanced LIGO and Advanced Virgo gravitational-wave detectors. Equally exciting, astronomers also measured the light emitted by this event.

The gravitational-wave signal revealed the masses of the two merging neutron stars, while the light signal suggested that the merged neutron stars did not immediately collapse to form a black hole, implying that the neutron-star material had a sufficiently large pressure to withstand collapse. From this, the scientists could infer that a typical neutron star must have a radius greater than about 10.7 kilometers, which nicely complements the finding by other researchers based on the same merger event that the radius cannot exceed 13.5 kilometers.

The method can be applied to future observations and will help further tighten the constraints on the neutron star radius. "As more gravitational wave detectors and light telescopes go online around the world, this will allow more accurate measurements and observations of neutron radii," says Just. "It's a very exciting time to be working in the field."

Reference

1. Bauswein, A., Just, O., Janka, H.-T. & Stergioulas, N. Neutron-star radius constraints from GW170817 and future detections. *The Astrophysical Journal Letters* **850,** L34 (2017).



Nitrite reductase (dark blue) and nitric oxide reductase (red and green) form a complex that prevents the pathogenic bacteria *Pseudomonas aeruginosa* from poisoning itself with nitric oxide.

DENITRIFICATION

How bacteria avoid poisoning themselves

Scientists have found how bacteria rid themselves of a toxic metabolic by-product—a finding that could aid the development of antimicrobial drugs

RIKEN researchers have discovered how bacteria that produce the toxic gas nitric oxide avoid poisoning themselves[1]. They found that proteins that generate and degrade nitric oxide form a single complex, allowing bacteria to neutralize it immediately after it is produced.

In low-oxygen environments, some bacteria can produce energy using nitrate instead of oxygen. These include some pathogenic bacteria, such as *Pseudomonas aeruginosa*, a notorious cause of opportunistic infections in hospital patients.

The process by which these bacteria generate energy from nitrate, known as denitrification, produces nitric oxide as a toxic by-product. Although researchers knew that denitrifying bacteria need to tightly control nitric oxide production, they did not know how this was controlled.

In *P. aeruginosa*, nitric oxide is produced by the enzyme nitrite reductase (NiR) and decomposed by the enzyme nitric oxide reductase (NOR). Takehiko Tosha at the RIKEN SPring-8 Center and his colleagues conjectured that these two proteins might combine to form a single structure. To test this idea, they isolated the two enzymes and examined their structures using x-ray diffraction. They found that the proteins did indeed fit together like puzzle pieces.

They found that the proteins did indeed fit together like puzzle pieces.

"Nitric oxide-producing NiR and nitric oxide-decomposing NOR form a complex to prevent cytotoxic nitric oxide diffusing into the cellular environment," says Tosha. Locating nitric oxide production and disposal in a single unit effectively prevents leakage of the toxic by-product (see image).

The researchers next investigated how the complex is bound together as well as the consequences of breaking it apart. Using computer simulations, they determined which parts of the protein form the key chemical associations that bind NiR and NOR. They then created mutant strains of *P. aeruginosa* in which these key interactions were disrupted, impeding complex formation. The mutant strains showed up to a 30 per cent reduction in growth. Inhibiting complex formation hampered the bacteria's ability to neutralize nitric oxide, causing them to poison themselves.

These results could have potent medical applications. "Denitrification is crucial for some pathogenic bacteria including *P. aeruginosa* to survive under low-oxygen conditions, such as inside biofilms, during infection," explains Tosha. "Since we found that the interaction between NiR and NOR contributes to denitrification-dependent anaerobic growth of *P. aeruginosa*, compounds that inhibit this interaction might work as antimicrobial drugs."

Tosha and his colleagues next plan to investigate whether the proteins responsible for processing nitrite, another toxic intermediate in this pathway, also form a complex that could be disrupted. ●

Reference

1. Terasaka, E., Yamada, K., Wang, P.-H., Hosokawa, K., Yamagiwa, R., Matsumoto, K., Ishii, S., Mori, T., Yagi, K., Sawai, H. *et al.* Dynamics of nitric oxide controlled by protein complex in bacterial system. *Proceedings of the National Academy of Sciences USA* **114,** 9888–9893 (2017).

BIOLUMINESCENCE IMAGING

Seeing cells from outside the body

A brighter source of bioluminescent light enables scientists to image cells from outside the body

A bioluminescent compound has been supercharged by RIKEN researchers, making it up to a 1,000 times brighter in deep tissues[1]. This bioengineered light source enabled them to image cells from outside the body and to monitor cancer cells in mice and brain-cell activity in monkeys.

Glowing creatures like fireflies and jellyfish are a boon for science as their bioluminescent molecules can be used to visualize a host of biological processes. Bioluminescence is the result of a partnership between an enzyme and a substrate. In particular, a yellow-green glow is created by using luciferase, an enzyme derived from fireflies, to catalyze the substrate D-luciferin.

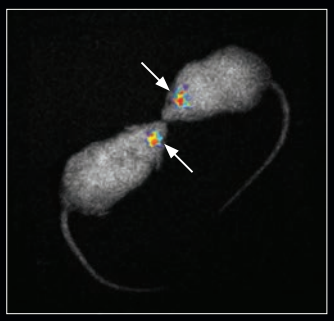
Considerable research has gone into enhancing the efficiency of this reaction. For example, synthetic analogs have been used instead of luciferin and the rate of catalysis has been improved.

Now, Atsushi Miyawaki of the RIKEN Center for Brain Science and colleagues have gone further and refined both components to create a completely bioengineered bioluminescence system that can be used inside animal bodies.

A synthetic luciferin called AkaLumine-HCl can penetrate the blood–brain barrier and produce a reddish light that is more visible in body tissues than the yellow-green glow of luciferin. But AkaLumine-HCl is not very compatible with natural luciferase. To improve the enzyme's pairing with AkaLumine-HCl, the researchers successively mutated luciferase. The resulting Akaluc protein was a more efficient catalyst for the substrate and was expressed more abundantly by cells.

In the mouse brain, the combination of Akaluc catalyzing AkaLumine-HCl, dubbed AkaBLI, produced a bioluminescence signal that was 1,000 times stronger than that from the natural luciferase–luciferin reaction. Furthermore, just one or two glowing cells were clearly visible from within the mouse lung, which could be useful for monitoring transplanted cells.

Bioluminescence could be introduced easily and voluntarily by adding AkaBLI to animals' drinking water. While this gave the most persistent glow, injecting the molecules yielded greater intensity.



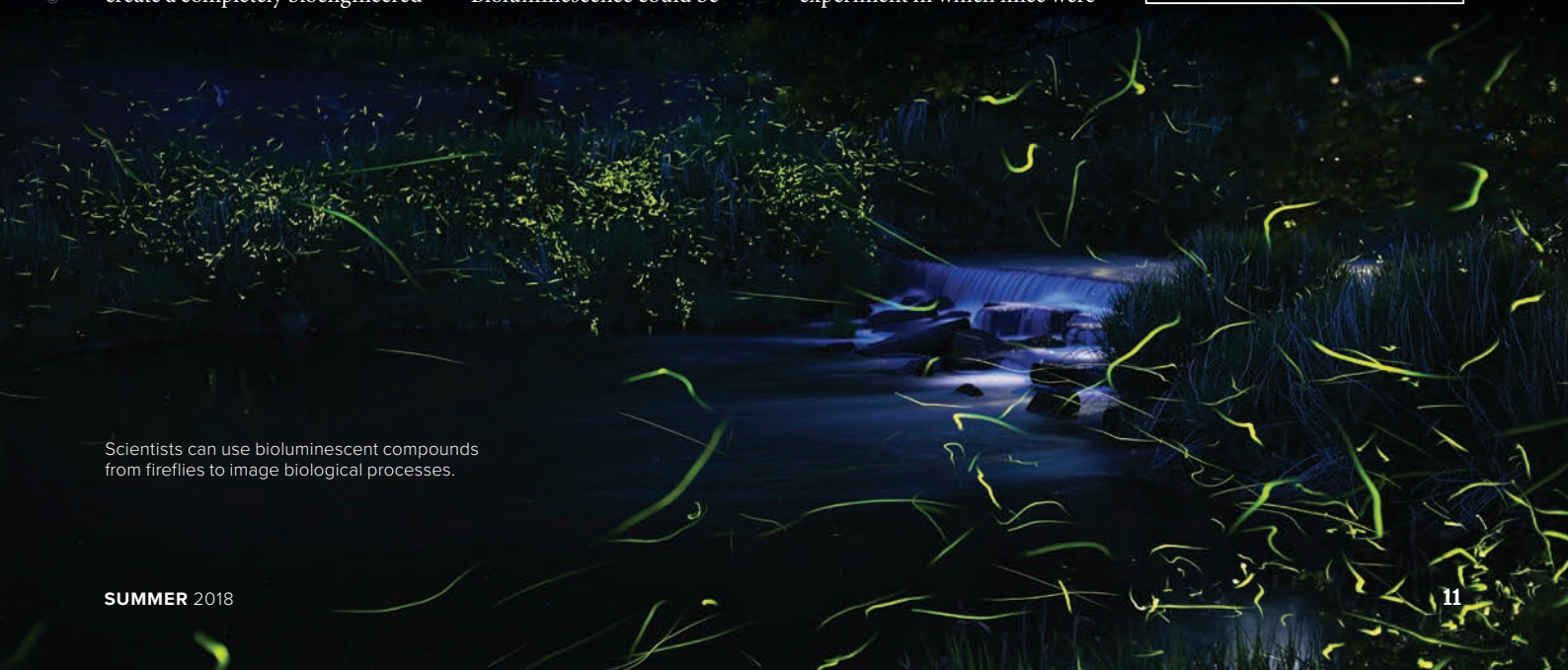
A brighter bioluminescent compound allowed scientists to non-invasively monitor the activity of neurons in the hippocampus (patches of color) of mice while simultaneously observing their behavior.

"The fundamental improvement is the practical applicability for *in vivo* physiological studies," explains Miyawaki. By using AkaBLI, changes in brain activity and structures with behavior can be directly observed over time. In an experiment in which mice were exposed to familiar and new cage environments, the same neurons in the hippocampus could be recorded over multiple days (see top image). "This is the first time that such a small ensemble of a few dozen deep neurons related to a specific learning behavior could be visualized non-invasively," notes Miyawaki.

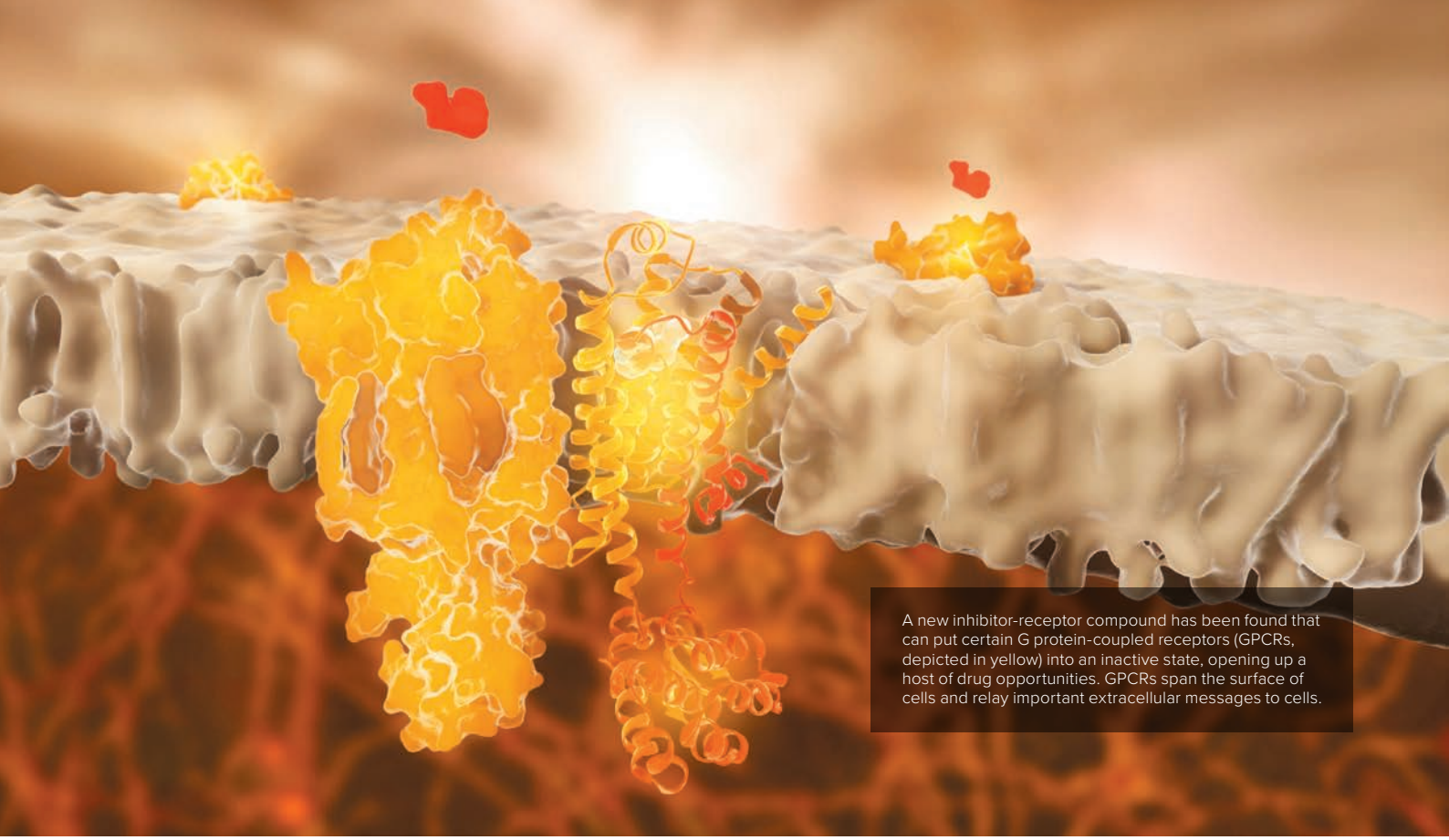
And in a marmoset monkey, the researchers were able to track deep-brain neurons for more than a year using AkaBLI. The potential for using this kind of stable and long-lasting bioluminescence to explore neural circuitry during natural behaviors is huge, observes Miyawaki.

Reference

1. Iwano, S., Sugiyama, M., Hama, H., Watakabe, A., Hasegawa, N., Kuchimaru, T., Tanaka, K. Z., Takahashi, M., Ishida, Y., Hata, J. *et al.* Single-cell bioluminescence imaging of deep tissue in freely moving animals. *Science* **359,** 935–939 (2018).



Scientists can use bioluminescent compounds from fireflies to image biological processes.



A new inhibitor-receptor compound has been found that can put certain G protein-coupled receptors (GPCRs, depicted in yellow) into an inactive state, opening up a host of drug opportunities. GPCRs span the surface of cells and relay important extracellular messages to cells.

SIGNALING PROTEINS

Signaling off-switch for cells

A surprisingly powerful inhibitory mechanism could lead to potent new drugs aimed at almost an entire class of essential signaling proteins

G protein-coupled receptors (GPCRs) are cellular signaling molecules that control some of the most important biological functions in the body, ranging from hormone secretion to blood clotting. Accordingly, many of them are drug targets: between 30 and 50 per cent of medicines work by modifying the behavior of one of more than 800 GPCRs. Researchers led by Shigeyuki Yokoyama at the RIKEN Baton Zone Program have now identified a new mechanism for switching GPCRs off, which could lead to the development of a plethora of new drugs[1].

The proteins the researchers are studying are lodged in the membranes of cells, with additional domains jutting into the cellular exterior and interior. Recently, GPCRs were found to be maintained in an inactive state in the presence of individual sodium ions. The ions block activation agents by tethering together a cluster of water molecules within the membrane-spanning portion of the receptor.

Yokoyama speculated that other chemical inhibitors may act as similar 'off-switches'. He and his colleagues have confirmed this hypothesis with a structural analysis of a complex made of the leukotriene B4 receptor (BLT1), which plays a role in various inflammatory disorders, and a chemical inhibitor known as BIIL260. They chose the BIIL260 inhibitor as it was reported to exhibit a high affinity to the BLT1 receptor, which is important for effective crystallographic analysis, explains Yokoyama. When the researchers analyzed the receptor–inhibitor complex, they learned that the inhibitor had indeed locked the GPCRs in an inactive state, essentially taking the same place as the sodium ion and water molecule complex within the membrane-spanning segment of the receptor.

The BLT1 receptor is normally activated by a compound called leukotriene B_4 (LTB_4), but was shown to be inactivated when the new complex was present. "It was beyond our wildest imaginings to find that this structure mimicked the sodium ion and water molecule complex and even functions more strongly than the complex," Yokoyama says. He was also taken aback because the inhibitor was found to bind to the receptor via a structure known as a benzamidine group, which has dramatically different chemical properties from the water and sodium ion complex that triggered the research.

The receptor they studied shares structural similarities with many other GPCRs, and so Yokoyama's team is now trying to identify additional inhibitors that act in the same way. "Other benzamidine derivatives may also negatively modulate the activity of GPCRs," he explains. "There are about 300 promising GPCRs drug targets, and we would like to find the most effective derivative for each of them."

Reference

1. Hori, T., Okuno, T., Hirata, K., Yamashita, K., Kawano, Y., Yamamoto, M., Hato, M., Nakamura, M., Shimizu, T., Yokomizo, T. *et al.* Na^+-mimicking ligands stabilize the inactive state of leukotriene B_4 receptor BLT1. *Nature Chemical Biology* **14,** 262–269 (2018).

ORGANOMETALLIC CHEMISTRY

Removing noxious nitrogen from crude oil

A multimetallic framework makes an essential step in petroleum refining much easier

Stripping nitrogen-containing impurities from crude oil could become easier thanks to a low-energy chemical procedure developed by RIKEN researchers[1]. The innovation should also help to open up more-sustainable sources of hydrocarbons such as biomass and shale, which contain higher levels of impurities.

The hydrocarbons in crude oil are used to power most vehicles and much of industry, in addition to providing the raw materials for plastics, fibers and pharmaceuticals. Crude oil is a messy mix of molecules, however, and has to be subjected to various processing steps before its chemical components can be used.

As well as separating desirable components, processing also removes unwanted contaminants from crude oil. Some of the most troublesome contaminants are nitrogen-containing (nitrogenous) molecules that can produce toxic nitrogen oxides when fuels derived from crude oil are burned. These contaminants also interfere with the processing of crude oil.

Currently, complicated catalysts as well as high temperatures (300–500 degrees Celsius) and pressures (up to 200 atmospheres) are needed to break apart the strong bonds between carbon and nitrogen in nitrogenous molecules in order to remove the nitrogen.

Now, Zhaomin Hou at the RIKEN Center for Sustainable Resource Science and his colleagues have found an easier way to remove nitrogen from nitrogenous molecules called pyridines and quinolines, which are both ring-shaped molecules. They used a framework of the inorganic compound titanium hydride in a cooperative way to break two carbon–nitrogen bonds in each pyridine or quinoline molecule, without breaking the ring.

Some of the complex chemistry in oil refining could become simpler and cheaper thanks to new catalysts.

Their experimental and computational work revealed that this approach is easier than alternative options that involve splitting open pyridine and quinoline rings.

"Our work is the first example of removing nitrogen from pyridines and quinolines under mild conditions," comments Hou.

The researchers were inspired to investigate this approach due to previous work with similar compounds that had revealed that they could break some very stable chemical bonds. They were also guided by computational chemistry techniques that shed light on the chemical mechanisms at the molecular level.

"Our work is the first example of removing nitrogen from pyridines and quinolines under mild conditions"

The fact that a multimetallic hydride compound works at atmospheric pressure and at much lower temperatures than existing ones should help develop more cost-effective processing methods for the petrochemical industry. "This work may lead to the design of a range of new catalysts that can work under milder and simpler conditions," says Hou. This innovation that addresses a specific problem in oil refining may eventually have widespread significance for the chemical industry. ●

Reference

1. Hu, S., Luo, G., Shima, T., Luo, Y. & Hou, Z. Hydrodenitrogenation of pyridines and quinolines at a multinuclear titanium hydride framework. *Nature Communications* **8,** 1866 (2017).

INFLAMMATION

Dousing fires fueled by food

Inhibitors that block a key component of the inflammatory response could put a damper on dietary allergies

Food allergies have become increasingly prevalent over the last few decades. Patients with severe food allergies may require an emergency dose of adrenaline to stave off a potentially deadly anaphylactic reaction. Insights into the allergic inflammatory response gained by researchers at RIKEN could open up other, less drastic, treatments for food allergy[1].

"It may be possible to develop an oral medicine for food allergy"

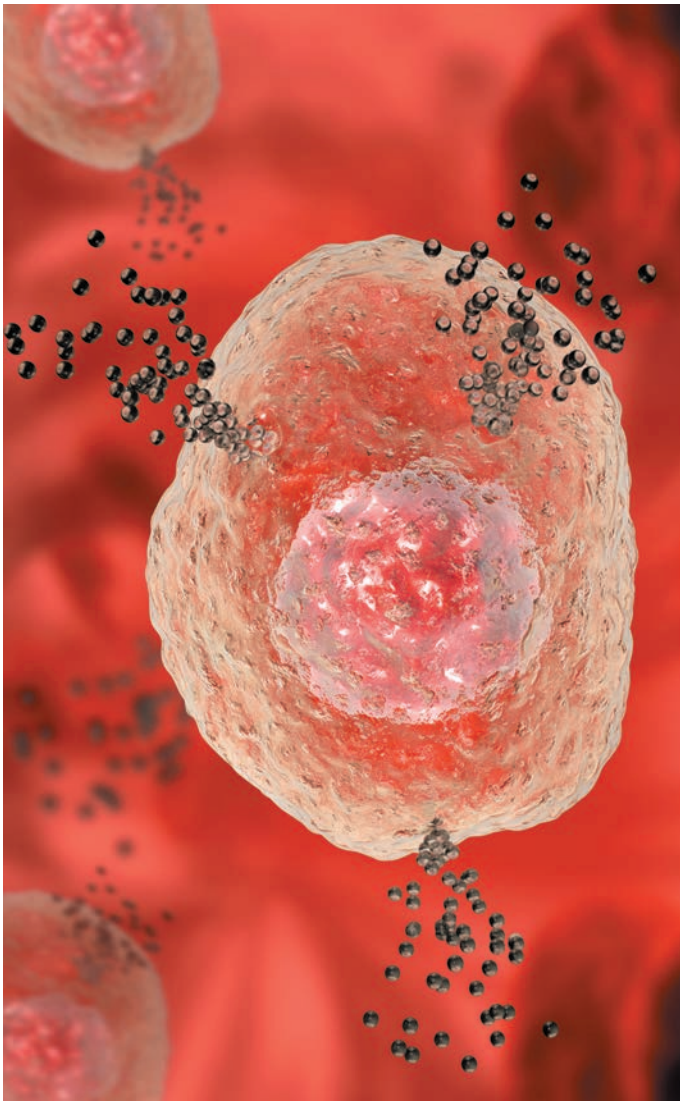
Allergic reactions to food are fueled partly by mast cells in the intestine, which release various inflammatory molecules including histamine (see image). Tomoaki Ando at the RIKEN Center for Integrative Medical Sciences and his co-workers suspected that the histamine-releasing factor (HRF) protein may play an important role in this process. HRF stimulates the release of inflammatory molecules by mast cells. But it also has many other functions, which makes it challenging to study. The team overcame this problem by developing a molecule that selectively prevents HRF from activating mast cells.

Working with a mouse model, the researchers showed that food allergies result in the production of high levels of IgE antibodies that can bind to HRF. These IgE antibodies are captured by mast cells, enabling them to respond to HRF, and HRF is in turn responsible for switching on mast cells and driving inflammation.

The HRF inhibitor developed by Ando and his colleagues interferes with antibody binding. Mice models that were pretreated with the inhibitor exhibited reduced allergy-induced inflammation and diarrhea.

Importantly, this compound also mitigated allergic responses that were already underway. "Orally applied HRF inhibitors can prevent food allergy in mice," says Ando. "This means it may be possible to develop an oral medicine for food allergy."

The same mechanism also appears to contribute to egg allergy in humans, and the researchers observed elevated HRF-reactive antibody levels in a cohort of patients. Several studies have suggested that controlled dosing with food allergens reduces allergic responses in some patients. Ando and the team demonstrated that patients who exhibited a sustained response to this treatment had high HRF-reactive IgE levels prior to the treatment. Thus, measurements of these antibodies could offer a valuable indicator for clinicians to predict patients' responses.



An illustration depicting a mast cell releasing histamine during an allergic response. Inhibitors that prevent mast cells from releasing inflammatory histamines could help bring food allergies under control.

This correlation also suggests that food allergies in humans could be staved off by using interventions that block the interaction between antibodies and HRF—or the production of HRF-reactive antibodies.

With proof of concept established, Ando hopes to develop superior compounds for clinical testing. "It is still not clear which type of inhibitors, such as peptides or recombinant HRF, will be best for this application," he explains. "We are now focusing on developing the most potent HRF inhibitors." ●

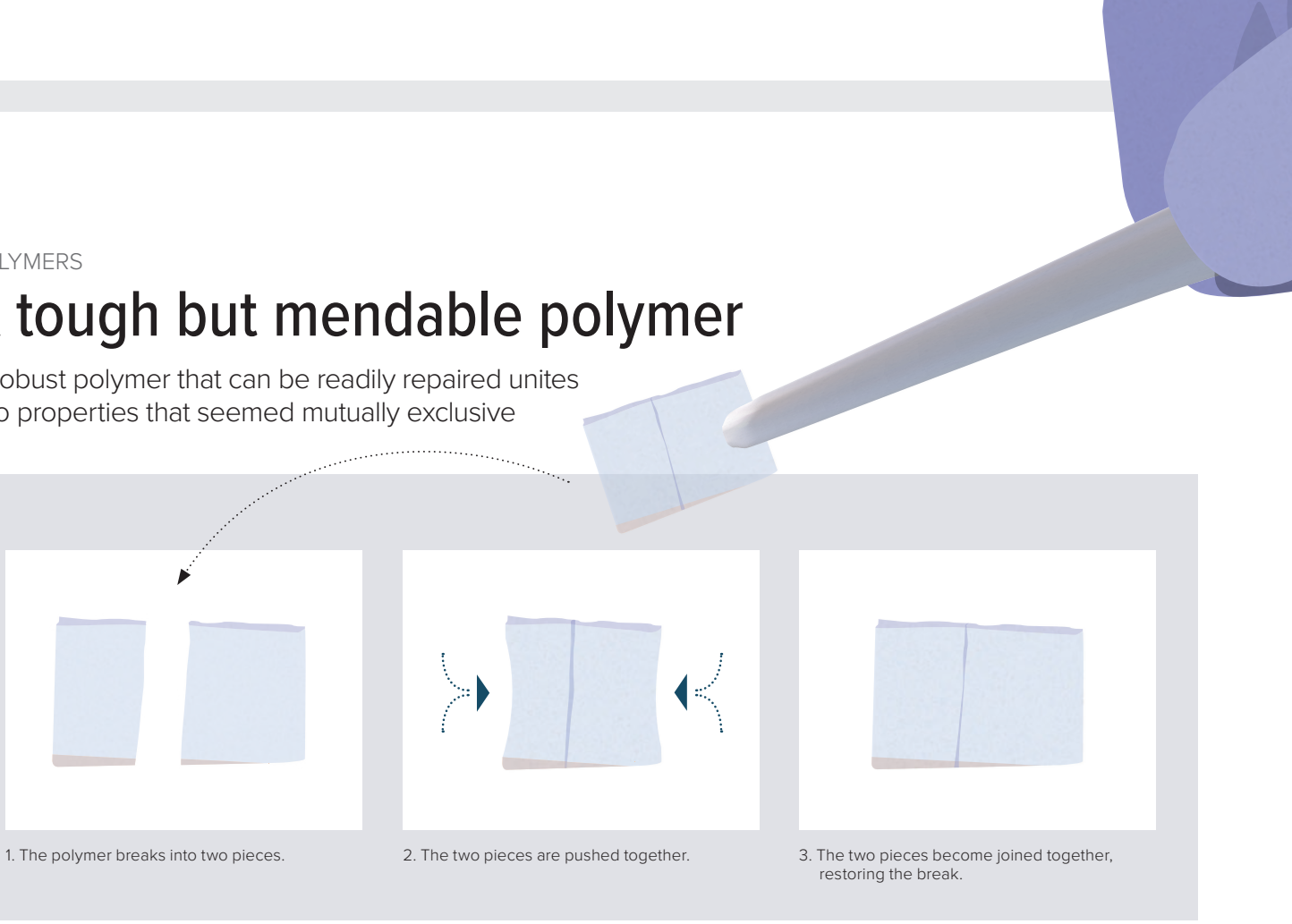
Reference

1. Ando, T., Kashiwakura, J., Itoh-Nagato, N., Yamashita, H., Baba, M., Kawakami, Y., Tsai, S. H., Inagaki, N., Takeda, K., Iwata, T. *et al.* Histamine-releasing factor enhances food allergy. *The Journal of Clinical Investigation* **127,** 4541–4553 (2017).

POLYMERS

A tough but mendable polymer

A robust polymer that can be readily repaired unites two properties that seemed mutually exclusive



1. The polymer breaks into two pieces.

2. The two pieces are pushed together.

3. The two pieces become joined together, restoring the break.

A mechanically robust polymer that can be repaired simply by manually pressing damaged portions together (see image) has been developed by researchers at RIKEN and the University of Tokyo[1]. This finding demonstrates that healing is not limited just to soft materials, and it may lead to display materials that can be fixed rather than replaced.

Using durable polymers is important for realizing a sustainable society, but it is typically difficult to repair such mechanically robust polymers when they sustain damage. That is because they are usually made of long, entangled polymer chains, which do not readily diffuse to repair fractures unless the polymer is heated or even melted.

Shorter chains that are held together by many hydrogen bonds have been devised, but hydrogen-bonded structures tend to organize into ordered arrays, promoting crystallization and rendering the material brittle.

Now, Takuzo Aida from the RIKEN Center for Emergent Matter Science and his PhD student Yu Yanagisawa at the University of Tokyo, together with their co-workers, have hit on a way to circumvent crystallization by using a polymer made of thiourea units (–NH(C)SNH–), which engage in hydrogen bonding, and ether linkers.

The researchers stumbled on the concept serendipitously while studying another system. "We were synthesizing poly(ether thiourea) as a precursor for a biomolecular glue that is water soluble and adheres tightly to biomacromolecules such as proteins and nucleic acids," explains Aida.

The team noticed that, in the presence of a solvent, this precursor strongly adhered to lab gloves and other surfaces. "After removing the solvent, we found that fractured surfaces of the dried polymer merged on manual compression, even though it was rigid and not tacky," says Aida.

The polymer is mechanically robust and yet can be mended in hours simply by compressing

The polymer is mechanically robust and yet can be mended in hours simply by compressing fractured fragments together at room temperature.

The team attributes this unusual combination of properties to the presence of both thiourea and ether moieties. Unlike most hydrogen-bond-forming units, which form linear arrays that lead to problematic crystallization, the thioureas are arranged in less ordered arrays. At the same time, the ether groups are mixable with the thioureas, so that gentle compression at fractured sites allows hydrogen-bonded polymer chains to slip and interpenetrate, generating the cross-links necessary for repair.

"We hope this study will alter the preconception that only soft materials such as rubber and elastomeric gels are capable of healing," says Aida.

The team next intends to work on enhancing the physical properties of their polymer. ●

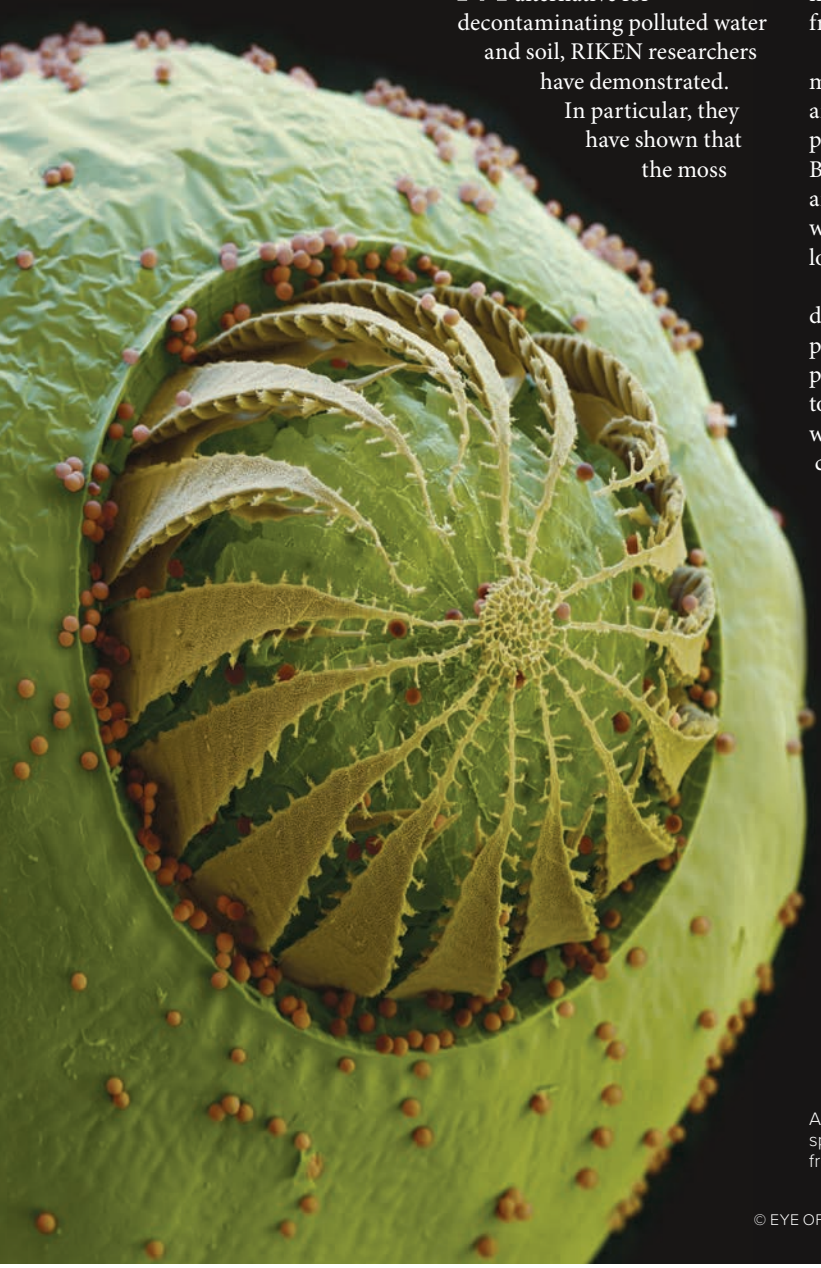
Reference

1. Yanagisawa, Y., Nan, Y., Okuro, K. & Aida, T. Mechanically robust, readily repairable polymers via tailored noncovalent cross-linking. *Science* **359,** 72–76 (2018).

ENVIRONMENTAL REMEDIATION

Moss strips lead from contaminated water

A moss species that thrives in metal-contaminated sites shows promise in adsorbing lead from polluted water



Moss can be a green alternative for decontaminating polluted water and soil, RIKEN researchers have demonstrated. In particular, they have shown that the moss *Funaria hygrometrica* adsorbs an impressive amount of lead from contaminated water[1].

Lead-contaminated water is a major environmental concern and can cause serious health problems, especially in children. But the usual way to remove lead and other heavy metals from water involves fossil fuels and a lot of energy.

An alternative decontamination method is phytoremediation, which uses photosynthesizing organisms to clean up contaminated water and soil. The researchers considered that *F. hygrometrica* might be promising for phytoremediation because the moss is known to grow well in sites contaminated with metals like copper, zinc and lead.

"We found that the moss can function as an excellent lead adsorbent when in the protonema stage of development," says Misao Itouga of the RIKEN Center for Sustainable Resource Science, referring to the first stage in the life cycle of mosses, which produces thread-like chains of cells. "This valuable ability means that moss protonema will likely make exceptional wastewater cleaners in the mining and chemical industries."

The team characterized the metal-adsorbing ability of the moss by exposing *F. hygrometrica* protonema to solutions with varying concentrations of 15 metals. After 22 hours of exposure, mass spectrometry analysis showed that the moss cells had adsorbed up to 74 per cent of their dry weight of lead.

"Moss protonema will likely make exceptional waste-water cleaners in the mining and chemical industries"

Knowing where the lead accumulates is important for understanding how adsorption occurs and for optimizing phytoremediation. The researchers found that within the moss protonema cells, more than 85 per cent of the lead had accumulated in the cell walls. The team found that the cell walls adsorbed lead even after being removed from living moss,

A spore capsule of the moss *Funaria hygrometrica*. The spores (small pink spheres) produce protonema, long strings of cells that are good adsorbers of lead from contaminated water, RIKEN researchers have shown.

indicating that the cell walls of this moss species have a special characteristic that allows the moss to thrive in environments that are toxic to other plants.

Nuclear magnetic resonance indicated that polygalacturonic acid in the cell walls was responsible for adsorbing the lead. "We compared *F. hygrometrica* data with those from land plants and seaweeds and found that the presence of polygalacturonic acid in the cell wall is one of the characteristics that separated this type of moss from other plants," explains Itouga.

"Our findings show that *F. hygrometrica* is a useful biomaterial for recovering lead from aqueous solutions and will contribute to the Sustainable Development Goals set by the United Nations, specifically the Life on Land goal," says group leader Hitoshi Sakakibara. "We're currently exploring opportunities to work with recycling-oriented companies."

Reference

1. Itouga, M., Hayatsu, M., Sato, M., Tsuboi, Y., Kato, Y., Toyooka, K., Suzuki, S., Nakatsuka, S., Kawakami, S., Kikuchi, J. *et al.* Protonema of the moss *Funaria hygrometrica* can function as a lead (Pb) adsorbent. *PLOS One* **12,** e0189726 (2017).

CANCER

Getting a grip on tumor cells

Creating stronger seals between tissue surface cells could prevent cancers from spreading

Metastatic cancer cells have a weak grip on each other, which creates the opportunity for them to spread to other parts of the body. By understanding how to strengthen the bonds between these cells, a team led by Masatoshi Takeichi at the RIKEN Center for Biosystems Dynamics Research has uncovered a potential way to help stop cancers from spreading[1].

Many organ surfaces are composed of sheets of epithelial cells, knitted together by tightly sealed junctions made up of multi-protein complexes, including 'apical-junctional complexes'. In cancerous tissue, these structures often fail to assemble properly, which can result in cancerous cells detaching, travelling and stimulating secondary cancers, a process known as metastatic growth.

Many cancerous cells still produce the correct junction building blocks but are unable to form normal junctions "even though they express key cell–cell adhesion molecules," Takeichi says. "We suspected that junction formation is physiologically blocked and that their junctions could be restored by proper pharmacological treatments of the cells."

His group at RIKEN tested this hypothesis by exposing human colon cancer cells with junction-forming defects to more than 150,000 different compounds. A tiny fraction of these proved capable of restoring normal epithelial cell organization—remarkably, many of them belonged to a particular class of compounds known as microtubule polymerization inhibitors, or MTIs (see image). MTIs directly interfere with the formation of microtubules, protein-based cellular structures important to a number of processes.

Takeichi and his colleagues then explored the interaction between microtubules, epithelial cells and MTI and discovered that the key to normal epithelial binding is a signaling cascade set in motion by MTI's disassembly of microtubules. MTI treatment stimulated a sharp increase in levels of a protein called RhoA, which promotes apical-junctional complex formation by triggering extensive reorganization of other structural proteins, including myosin-IIA.

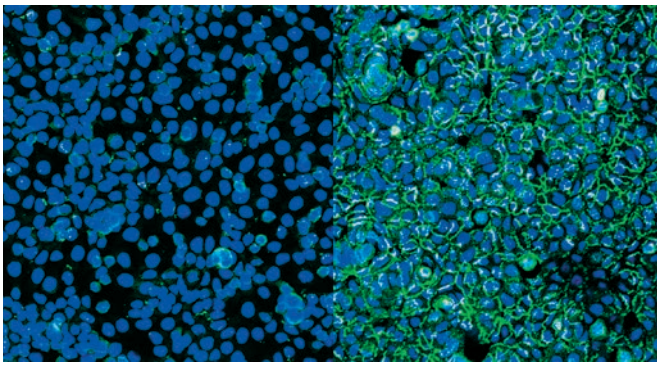
"It seems that colon carcinoma cells are defective in that they require more RhoA activity to organize epithelial-specific cell–cell junctions," says Takeichi

The takeaway is that it is hypothetically feasible to strengthen cancerous cell junctions with drugs that stimulate RhoA. However, mechanisms other than using MTIs would have to be found, given that microtubules perform many important functions in healthy cells and so inhibiting them could be highly toxic to the body.

Takeichi adds that there a still several steps before the RhoA mechanism could be tested in clinical trials. "We need to test whether artificially induced junction formation indeed affects invasion and metastasis of cancer cells in the body," he says.

Reference

1. Ito, S., Okuda, S., Abe, M., Fujimoto, M., Onuki, T., Nishimura, T. & Takeichi, M. Induced cortical tension restores functional junctions in adhesion-defective carcinoma cells. *Nature Communications* **8,** 1834 (2017).



Human colon cells HT29 that have been treated (right) with the microtubule polymerization inhibitor nocodazole show many more green junction proteins holding the tissue together than those that were not treated (left). Bolstering these proteins could help stop cancerous cells from breaking off and travelling to other parts of the body to form secondary cancers.

NEUROBIOLOGY

The nose knows how to avoid carbon dioxide

Chemical sensors in the nose that play no part in smelling are involved in the zebrafish's avoidance of high carbon dioxide levels

A neuronal pathway that enables fish to avoid high carbon dioxide concentrations has been discovered by RIKEN researchers[1].

Many animals have built-in behaviors to avoid dangerously high levels of carbon dioxide. To investigate the neurobiology behind this response, the researchers turned to zebrafish.

When touched on the head, larval zebrafish flee within 10 milliseconds. "In contrast, we showed that their avoidance response to carbon dioxide happened after around 4–5 seconds, which is about 400 to 500 times slower," notes Tetsuya Koide of the RIKEN Center for Brain Science. Additionally, the escape routes the fish took to avoid carbon dioxide were much more variable than those after being touched, and they swam away much more slowly. These differences pointed to an unknown sensation-response pathway in the brain.

To identify this pathway, the researchers used transgenic zebrafish made for calcium imaging. Their technique visualizes brain activity by genetically expressing a fluorescent protein sensitive to calcium, a key molecule involved in the transmission of neuronal signals.

The team saw a series of neural responses to carbon dioxide (see top image). The first occurred in the olfactory bulb—the brain region that processes smell in mammals. A few seconds later, the researchers saw responses in trigeminal sensory neurons, which carry touch and pain sensations from the face. The final response was from the habenula, which is involved in learning associations with unpleasant experiences.

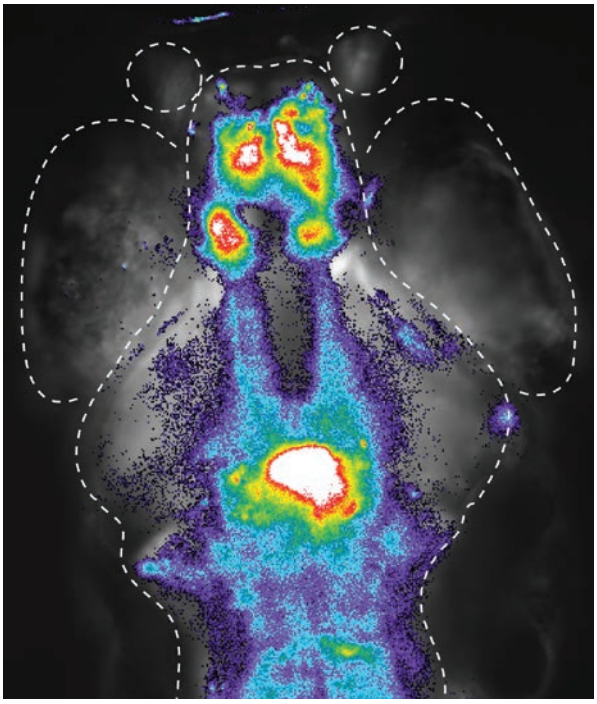
To determine which of these three systems was necessary for the carbon dioxide response, the team removed each one separately using a laser. Only damage to the trigeminal pathway and the nose affected the carbon dioxide response, which was surprising because damaging the olfactory pathway itself did not affect it. "This meant that a non-olfactory component in the nose is critical for avoiding carbon dioxide," explains Koide.

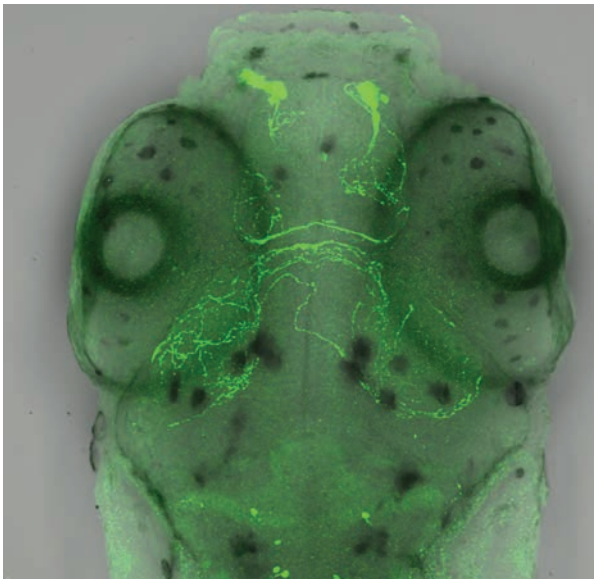
The team next determined how the nose senses carbon dioxide. Calcium imaging of the zebrafish nose revealed a cluster of cells that respond to carbon dioxide. Tests indicated that these cells were part of the terminal nerve (see bottom image), and their removal blocked the avoidance response to carbon dioxide. Thus, the zebrafish nose contains terminal-nerve chemosensors unrelated to smell that control behavioral responses to noxious chemicals.

"We were surprised to find that the terminal nerve acts as a carbon dioxide sensor in zebrafish. Although it was identified as an additional cranial nerve in humans and other vertebrates more than a century ago, we are the first to report its function in chemosensation," says Koide. "As humans and other vertebrates also possess the terminal nerve system, we next hope to further characterize its chemosensory functions across different species, including humans."

Reference

1. Koide, T., Yabuki, Y. & Yoshihara, Y. Terminal nerve GnRH3 neurons mediate slow avoidance of carbon dioxide in larval zebrafish. *Cell Reports* **22,** 1115–1123 (2018).





Carbon dioxide activates ensembles of neurons in multiple brain regions (top image). Chemical sensors in the nose (the two bright patches at the top) help zebrafish avoid high carbon dioxide levels (bottom image).

Researchers at RIKEN used the SACLA X-ray free-electron laser at RIKEN's SPring-8 facility (photo) to confirm a prediction made over 60 years ago about the quantum-mechanical behavior of special resonant systems. The inset depicts an analogy of such a system with bells resounding in unison.

QUANTUM OPTICS

Quantum physics prediction confirmed at last

The world's strongest x-ray source confirms a prediction made in the 1950s about superradiant systems

A prediction made more than 60 years ago about the quantum-mechanical behavior of resonant systems has been verified by an international team of scientists from Japan, Europe and the United States[1].

The quantum behavior of isolated particles is generally well understood. However, things become much more complex when considering an ensemble of such particles.

In 1954, the physicist Robert Dicke predicted that when many photons, or quanta, interact with a system consisting of many atoms, the atoms can respond much faster than an isolated atom. He calculated that the response will be fastest, 'super-radiant', when there are twice as many atoms as quanta.

It can be helpful to think of an analogy with bells: Dicke's prediction is similar to saying that the sound from many bells excited at the same time will both be much louder and fade away much more quickly than the sound of a single bell in isolation.

While this prediction has since been verified and is commonly accepted, Dicke also predicted that the decay rate will change greatly even when atoms far outnumber quanta in the system. This is what the researchers investigated in the current study. They did this by replacing the low-energy quanta envisioned by Dicke with high-energy x-rays, which allowed them to follow the decay of the system one quantum—one x-ray—at a time.

Generating appropriate intense x-ray pulses requires state-of-the-art x-ray sources known as x-ray free-electron lasers. Of the few operating in the world, only SACLA at the RIKEN SPring-8 Center (see image) had strong enough pulses at the high energies necessary for such experiments.

The scientists used pulses of x-rays to excite the nuclei of atoms in a perfect crystal (see inset in image) and then monitored their subsequent decay, with up to 68 x-ray photons counted after a single pulse. They found that the time to emit the first x-ray dropped dramatically with increasing number of x-rays, in good agreement with the prediction made by Dicke.

"We were able to demonstrate that Dicke's work was correct and were also able to offer an alternative picture of the decay properties, based on a statistical approach," says Alfred Baron of the RIKEN SPring-8 Center. "This both varifies the prediction and will be valuable for understanding future work." ●

Reference

1. Chumakov, A. I., Baron, A. Q. R., Sergueev, I., Strohm, C., Leupold, O., Shvyd'ko, Y., Smirnov, G. V., Rüffer, R., Inubushi, Y., Yabashi, M. *et al.* Superradiance of an ensemble of nuclei excited by a free electron laser. *Nature Physics* **14,** 261–264 (2018).

QUANTUM MATERIALS

Bouncing electrons along a magnetic wall

Chiral edge states could offer a way to store and manipulate information in low-power electronic devices

By controlling magnetized patches within thin films of material, RIKEN researchers have created electronic channels that can carry a current without any loss of energy[1]. This principle could eventually lead to extremely low-power electronic devices for storing and processing information.

The researchers' work relies on a phenomenon called the quantum anomalous Hall effect (QAHE). This is related to the Hall effect, in which a magnetic field applied at right angles to an electrical current causes electrons in the current to drift to one side of the conductor, creating a voltage across the material.

"Since these electrons are never scattered by disorders or defects, they can flow without loss of energy"

The QAHE typically occurs in thin films at very low temperatures. Magnetic atoms within the material, rather than an external magnetic field, cause the same sort of electron drift.

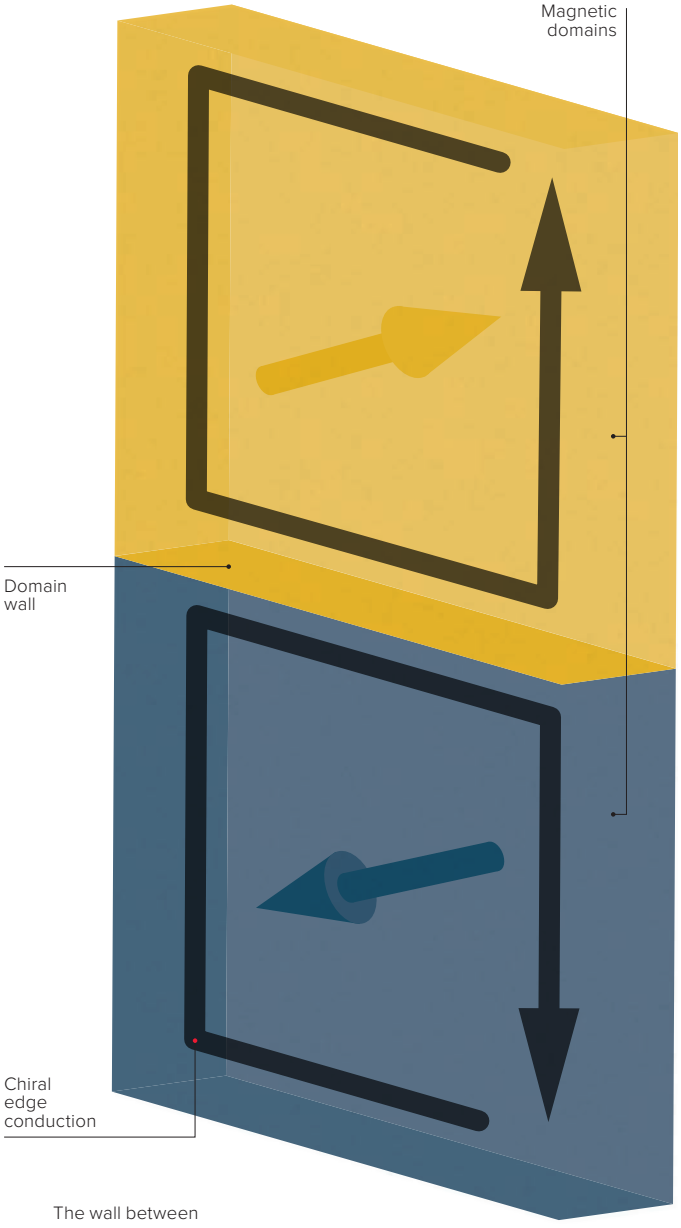
Now, Kenji Yasuda of the University of Tokyo, along with colleagues at the RIKEN Center for Emergent Matter Science, has created a device that demonstrates how the QAHE could be exploited in computer chips.

Their device contained layers of bismuth antimony telluride, each a few nanometers thick, with alternating layers seeded with magnetic chromium atoms. Working at just half a degree Celsius above absolute zero, the researchers used a magnetic force microscope to apply a small magnetic field to it. They scanned the microscope over the device to create a magnetic patch, or domain, a few tens of micrometers wide. The edges of this area, known as domain walls, acted as magnetic boundaries: the magnetic orientation of the material pointed upward on one side of the wall and downward on the other side (see image).

The researchers found that electrons, drifting due to the QAHE, could bounce along the domain wall in a process called chiral edge conduction. This happened because each domain wall had two 'chiral edge states', one on either side of the wall, which acted as channels to carry electrons in the same direction (see image). "Since these electrons are never scattered by disorders or defects, they can flow without loss of energy," says Yasuda.

The team built more of these devices and used the magnetic force microscope to create a range of different domain wall patterns that controlled how current flowed through the devices. By using the microscope to move the domain wall patterns around, they could also modify the performance of the devices.

The team now hopes to create chiral edge states at higher temperatures and control their position using an electric current. "These developments will be important steps for realizing electronic devices based on chiral edge states," Yasuda comments.



The wall between two magnetic domains (yellow and blue) creates chiral edge states that act as channels to carry electrons with no loss of energy.

Reference

1. Yasuda, K., Mogi, M., Yoshimi, R., Tsukazaki, A., Takahashi, K. S., Kawasaki, M., Kagawa, F. & Tokura, Y. Quantized chiral edge conduction on domain walls of a magnetic topological insulator. *Science* **358,** 1311–1314 (2017).

PLANT SIGNALING

Hormone helps plants avoid dehydration

A newly discovered hormone causes leaves to close their pores when water is in short supply

A hormone that helps plants retain water when none is available in the soil has been discovered by RIKEN researchers[1]. They have shown how the peptide CLE25 moves from the roots to the leaves when water is scarce and helps prevent water loss by closing pores in the leaf surface.

Like animals, plants have hormones. The researchers wanted to discover whether any plant hormones respond to physical stress.

"Although we know that some peptide hormones in plants mediate cellular development, until now nobody had identified any that regulate responses to physical stresses such as dehydration," explains Fuminori Takahashi of the RIKEN Center for Sustainable Resource Science.

The team began by looking at ABA—a hormone that accumulates in leaves and helps close pores in response to drought stress—and CLE peptides that are synthesized in the roots. Applying many different CLE peptides to plant roots revealed that CLE25 led to increased ABA in the leaves and pore closure. The researchers determined that the link between these two events was the increase in an enzyme necessary for making ABA. The scientists showed that CLE25 levels increase in the roots of plants that are subjected to dehydration stress, leading to the same results.

The team next investigated whether CLE25 moved through the plant circulatory system. Detecting functional peptide hormones is very difficult in living cells because the amounts are so small. "We resolved this problem by using a highly sensitive mass spectrometry system and developing a screening system that can identify the mobile peptides moving from root to shoot," says Takahashi. With this technology, the researchers were able to tag CLE25 molecules and visualize their movement from the roots to the leaves, indicating that it was indeed mobile and that it likely interacted with other molecules in leaves to produce ABA.

The team created mutant plants that lacked CLE25 or ABA and performed several control experiments to confirm their findings. In particular, after only 3 hours of dehydration, plants without CLE25 already showed 7 times less leaf ABA and had lost more water than control plants (see image).

Plants with mutations to the *cle25* gene (center and right columns) are more sensitive to dehydration than a non-mutant plant (left column). This demonstrates that the protein CLE25 is important for imparting resistance to dehydration.

"Our research absolutely has applications in the real world"

"Our research absolutely has applications in the real world and should contribute to the development of abiotic stress-resistant crops that take advantage of the mobile peptide system in plants," Takahashi notes. "We are working on modified peptides that are more effective for stress resistance than the natural ones and on ways to mix functional peptides into fertilizer to enhance drought resistance of crops in the field." ●

Reference

1. Takahashi, F., Suzuki, T., Osakabe, Y., Betsuyaku, S., Kondo, Y., Dohmae, N., Fukuda, H., Yamaguchi-Shinozaki, K. & Shinozaki, K. A small peptide modulates stomatal control via abscisic acid in long-distance signalling. *Nature* **556,** 235–238 (2018).

CATALYSIS

Probing a car exhaust catalyst in high resolution

A laser-like x-ray beam has been used to look under the hood of a catalyst employed in car exhaust systems

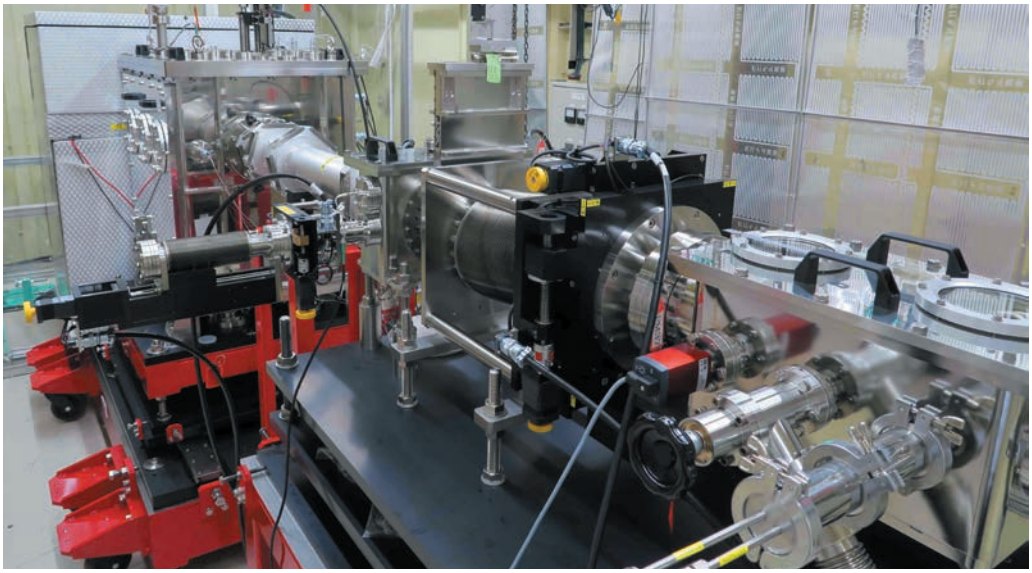
An x-ray technique developed at RIKEN has revealed new insights into the oxidation capabilities of catalysts used in car exhaust systems[1]. This improved understanding of catalyst behavior could help to develop higher performing, next-generation catalysts, and one day, cleaner cars.

Multi-component catalysts oxidize toxic carbon monoxide in car exhaust fumes into non-toxic carbon dioxide. To understand more about this reaction, scientists measure the oxidation states of the solid catalysts. They typically use an analytical technique known as x-ray absorption fine structure spectroscopy, but its spatial resolution is not very high.

Now, Yukio Takahashi of the RIKEN SPring-8 Center and colleagues have used a newly developed technique called hard x-ray spectro-ptychography (see image) to observe the oxidation process at the nanoscale, achieving a level of detail never realized before.

"Hard x-ray spectro-ptychography enables us to image the valence states in a solid material with a high spatial resolution," explains Takahashi. "This is the first time it has been used to image real samples."

The technique involves scanning a very precise, laser-like x-ray beam across a solid sample. This scan is repeated at various x-ray energies, and the resulting diffraction patterns are collected using a highly sensitive two-dimensional detector. The data is then processed to obtain spatially resolved x-ray absorption spectra.



The x-ray spectro-ptychography system developed by RIKEN researchers to study the fundamental behavior of materials at high resolution.

The researchers used the technique to examine particles of cerium zirconium oxide supported on a platinum substrate ($Pt/Ce_2Zr_2O_x$, where x is between 7 and 8). Cerium-based mixed oxides such as these are widely used as co-catalysts in car catalytic converters. The team was able to map the precise location and oxidation state of the cerium ions in this catalyst.

"We discovered several oxygen diffusion modes in the particles for the first time"

"Oxygen diffusion is a key process in the oxygen storage and release property of $Ce_2Zr_2O_x$, but there has never been direct imaging of this process inside these solid particles," explains Takahashi. "We applied this technique to visualize the spatial variation of the cerium oxidation state in the $Ce_2Zr_2O_x$ particles."

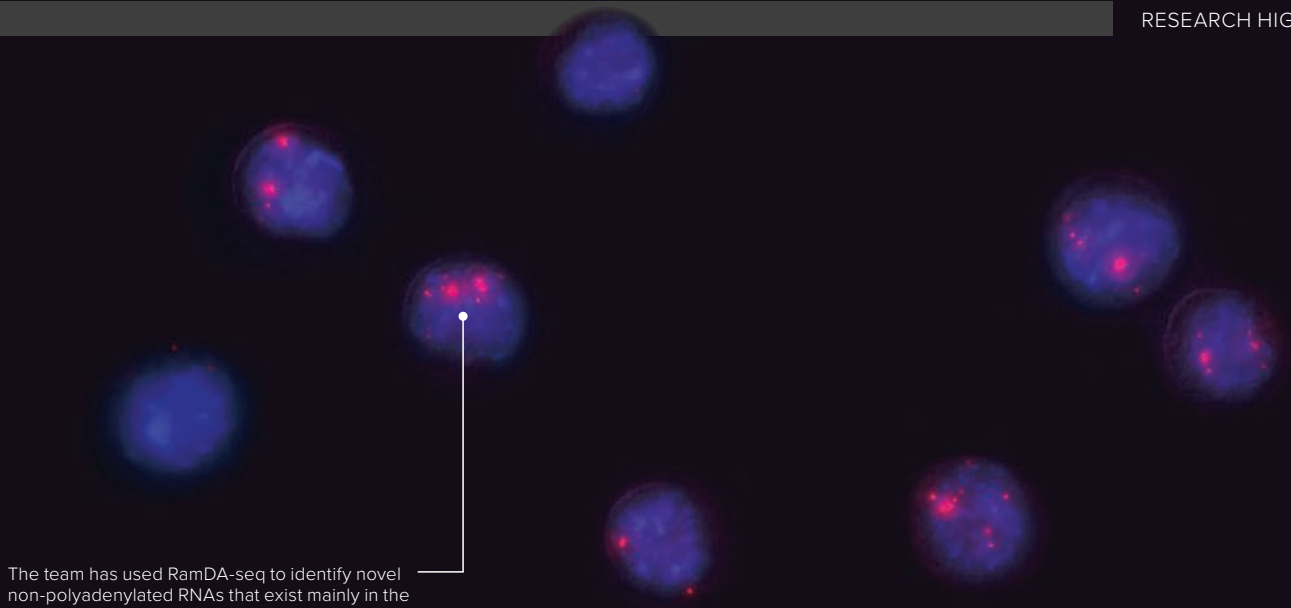
Statistical analysis revealed four distinct oxygenation processes occurred as oxygen diffused through this catalyst. "We discovered several oxygen diffusion modes in the particles for the first time," says Takahashi. These multiple oxidation pathways are thought to originate from the multifaceted, diverse structure of this material.

To probe this process further, the team will combine hard x-ray spectro-ptychography with computed tomography. "This will elucidate more detailed intrinsic heterogeneous reaction behaviors of the material," Takahashi explains.

The team also intends to use hard x-ray spectro-ptychography to enhance the understanding of functionality in other synthetic materials, such as energy transducers, and in biological materials, such as cells. ●

Reference

1. Hirose, M., Ishiguro, N., Shimomura, K., Burdet, N., Matsui, H., Tada, M. & Takahashi, Y. Visualization of heterogeneous oxygen storage behavior in platinum-supported cerium-zirconium oxide three-way catalyst particles by hard X-ray spectro-ptychography. *Angewandte Chemie International Edition* **57,** 1474–1479 (2018).



The team has used RamDA-seq to identify novel non-polyadenylated RNAs that exist mainly in the nucleus of mouse embryonic stem cells. Single red dots indicate one such RNA molecule, while larger red blobs show accumulations of them.

GENETICS

Sequencing all the RNA in a single cell

A new technique allows geneticists to decode all the RNA in single cells

By combining several methods, RIKEN researchers have developed a technique that can perform full-length sequencing of the total RNA of a single cell[1]. Such full-length sequencing is important for understanding how single cells develop and function in biological systems.

Geneticists have made great progress in decoding the complete sets of DNA and RNA in various species and organisms, but much work remains to be done to understand what occurs on the level of single cells.

One key challenge in decoding, or sequencing, all the RNA of a single cell has been the difficulty in determining sequences of RNAs that are not polyadenylated—a characteristic found in half of RNAs, excluding ribosomal RNAs. Compared with polyadenylated RNAs, non-polyadenylated RNAs have lower expression and slightly different structures. Recent studies have implicated them in diverse cell functions and diseases. Despite the importance of non-polyadenylated RNAs, methods have been unable to detect them or only able to detect them with very low sensitivity.

To overcome this limitation, the RIKEN scientists have combined a variety of methods to develop a system, which they call random displacement amplification sequencing (RamDA-seq), that is highly sensitive to both polyadenylated and non-polyadenylated RNAs and strongly immune to biases that often occur during preparation of sequencing library.

By performing several tests, the researchers determined that RamDA-seq is very sensitive and has good reproducibility. They found that it can provide full-length sequences of extremely long transcripts, and, unlike previous methods, is very sensitive to non-polyadenylated RNAs. The team applied RamDA-seq to mouse embryonic stem cells and properly detected the sequence of known RNAs, as well as additional, previously unknown sequences (see images).

Using RamDA-seq, the scientists showed that non-polyadenylated RNAs are dynamically regulated in a manner that depends on the differentiation state of the cell, so that a single cell in a different stage might express them differently.

In certain genes, they found a phenomenon called recursive splicing, which has been generating much interest in recent years, and were able to analyze it at the single-cell level. Finally, the team found that RamDA-seq is useful for understanding the activity of enhancer RNAs—RNAs that reflect the functions of regulatory genomic regions.

"We're very excited at the positive results we got from this new system and very much hope that researchers around the world will be able to use it to give us new insights into gene expression in individual cells, allowing us to better understand the complexity of biological systems," says Itoshi Nikaido of the RIKEN Center for Biosystems Dynamics Research.

Reference

1. Hayashi, T., Ozaki, H., Sasagawa, Y., Umeda, M., Danno, H. & Nikaido, I. Single-cell full-length total RNA sequencing uncovers dynamics of recursive splicing and enhancer RNAs. *Nature Communications* **9,** 619 (2018).

GENETICS

Not dead, just desiccated

An insect that can withstand extreme dehydration co-opts a ubiquitous gene to achieve this

Sleeping chironomid larvae survive desiccation by co-opting a gene present in some form in nearly all living organisms, RIKEN researchers have discovered[1].

The larva of the sleeping chironomid—a mosquito-like insect that inhabits semi-arid areas of Africa—can resuscitate after losing up to 97 per cent of its body's water content (see image). The genetic mechanisms that allow the insect to achieve this have remained largely elusive.

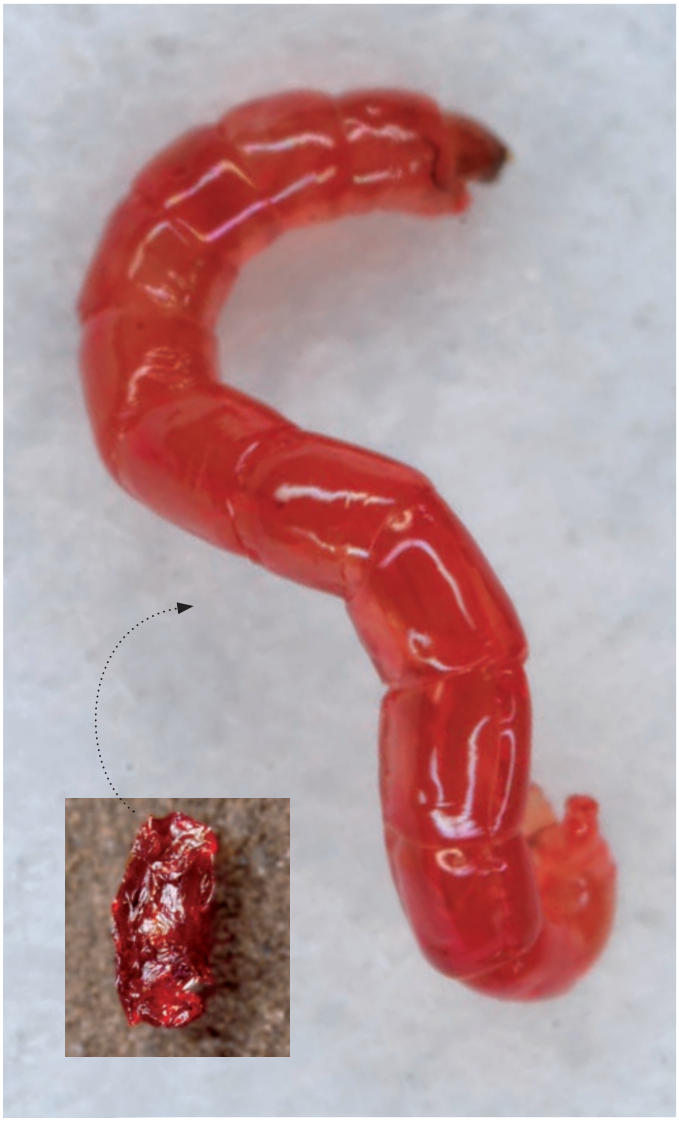
The gene heat shock factor (HSF) plays an important role in allowing cells to withstand stressful conditions such as cold, heat and radiation. The researchers found that, under certain conditions, HSF can upregulate itself in desert insects. This leads to several downstream processes, including the synthesis of heat shock proteins, which protect proteins in the cell from misfolding.

"One potential application will be preserving cells outside the body in a dry state"

The scientists compared data on RNA expression in the sleeping chironomid with that of a closely related species that cannot survive desiccation. They found that in the sleeping chironomid, hundreds of genes, including genes known to be involved in forming a molecular shield against dehydration-induced damage, were expressed during the early stages of desiccation. They also discovered that the DNA motif TCTAGAA, the binding site for HSF, was highly enriched around the transcription start site of the genes activated by desiccation in the sleeping chironomid, but not in the other species. Intriguingly, the genes responsible for synthesizing trehalose—a sugar that stabilizes cells in a dry state—contained the TCTAGAA motif in the desiccation-tolerant species but not in the other species.

To explore the role of trehalose, the researchers treated a cultured cell line from the sleeping chironomid with trehalose and found that many of the genes activated by desiccation were also activated, including the HSF gene. This effect of trehalose was prevented by knocking down the HSF gene, showing HSF was clearly involved in the response.

"The discovery that HSF is an important regulator of gene expression in response to desiccation was very interesting for us," says Oleg Gusev of the RIKEN Baton Zone Program. "Our data suggests that HSF is activated during dehydration, and then HSF actually self-activates by binding to the upstream region of its own gene.



Co-opting the heat shock factor gene gives a desiccated larva (inset) of the sleeping chironomid the ability to resuscitate.

This leads to the activation of the downstream genes that allow the insects to survive desiccation. What was very surprising to us was the finding that trehalose itself can activate HSF."

"One potential application will be preserving cells outside the body in a dry state, if we can activate the HSF gene," Gusev adds. "We now have a good understanding of how it works in this insect, so we will want to investigate if this is true for other organisms as well." ●

Reference

1. Mazin, P. V., Shagimardanova, E., Kozlova, O., Cherkasov, A., Sutormin, R., Stepanova, V. V., Stupnikov, A., Logacheva, M., Penin, A., Sogame, Y. *et al.* Cooption of heat shock regulatory system for anhydrobiosis in the sleeping chironomid *Polypedilum vanderplanki*. *Proceedings of the National Academy of Sciences USA* **115,** E2477–E2486 (2018).

CLIMATE MODELING

Modeling the influence of tiny particles on clouds

Increasing the density of aerosols in the air does not necessarily increase cloud cover, a high-resolution model has shown

By harnessing the impressive computing power of the K computer, an international group led by RIKEN researchers has calculated the effect dust particles have on cloud formation and development in a climate model, resulting in better agreement with satellite observations[1]. This advance will enhance the precision of models of global climate change.

Global climate is a tremendously complex phenomenon, and researchers are making painstaking progress in developing ever more accurate models. The action of tiny particles in the air known as aerosols is an important factor to consider when researching climate change, as they partially counteract the heating effect of greenhouse gases.

In particular, aerosols play a key role in cloud formation and development, as they both provide the seeds that allow clouds to form and affect the subsequent life cycle of clouds. Droplets form through water in the air condensing onto the tiny aerosol particles and when these droplets reach a certain size they precipitate as raindrops.

It was previously believed that a higher aerosol density would always result in more clouds forming, but recent satellite observations have shown that this is not necessarily the case. It is now understood that temperature differences between the top and bottom layers of clouds give rise to a delicate balance between evaporation and condensation of moisture. Consequently, aerosols in the lower parts of clouds promote cloud formation, whereas those in the upper parts allow water to evaporate.

A view of the Aegean Sea from the International Space Station. An improved climate model of the effect dust particles have on cloud formation and development provides better agreement with satellite observations of cloud cover.

This advance will enhance the precision of models of global climate change

Earlier climate models were unable to model the response of these microprocesses within the clouds to aerosol variation. Now, by using the K computer, the RIKEN-led group combined a model that simulates the entire global climate over a year, at a horizontal resolution of just 14 kilometers, with a simulation of how the aerosols behave within clouds.

Unlike conventional models, which showed a uniform increase in clouds over the Earth when there was an increase in aerosols, the high-resolution model, which accounts for vertical processes inside clouds, accurately depicted how large areas experience a drop in cloud cover.

"It was very gratifying to see that we could use a powerful supercomputer to accurately model the microphysics of clouds, giving a more accurate picture of how clouds and aerosols behave in the real world," says Yousuke Sato of the RIKEN Center for Computational Science. "In the future, we hope to use even more powerful computers to allow climate models to have more certainty in climate prediction." ●

Reference

1. Sato, Y., Goto, D., Michibata, T., Suzuki, K., Takemura, T., Tomita, H. & Nakajima, T. Aerosol effects on cloud water amounts were successfully simulated by a global cloud-system resolving model. *Nature Communications* **9,** 985 (2018).

Engaging Society, Changing Society

As RIKEN embarks on its new seven-year plan, President Hiroshi Matsumoto discusses his vision for ensuring that research engages society and contributes to sustainable development.

When Prime Minister Shinzo Abe introduced the Japanese Government's Fifth Science and Technology Basic Plan early in 2017, he outlined his thoughts on what he calls Society 5.0, or the 'super-smart society'. He predicted that Society 5.0 will be a fifth step in an evolution away from the industrial and information societies, at the culmination of which "all things are connected and all technologies fuse". We will address the rapidly changing landscape of science and technology as RIKEN enters its next seven-year phase, which was outlined in April 2018 as part of our fourth mid- to long-term plan.

RIKEN's reforms under the new plan address three specific agendas: to help raise the overall standard of science and technology in Japan; to act as a catalyst for innovation through research; and to provide greater stability to RIKEN's personnel by offering more indefinite-term employment contracts. These changes also tie into adjustments linked to RIKEN's move from an Independent Administrative Institution to a Designated National Research and Development Institute in 2016, which came with the promise of more flexibility in funding and an increased responsibility to initiate new high-level research systems.

STAYING AT THE CUTTING EDGE

As part of the new plan, I have called for the introduction of three innovation designers — appointees who will specialize in identifying real-world problems and communicating those needs to researchers, not only from a scientific perspective but also from the viewpoints of the social sciences and humanities. One of these designers is a team leader from RIKEN who has a keen interest in development of artificial intelligence and its impact on society, while the other two have been brought in from outside of RIKEN, moving from private consultancies into positions where they can influence the long-term vision of the organization. This shift toward more contact with the social sciences is particularly important to us: RIKEN researchers are not permitted to purely pursue social science research, but this does not preclude research related to the intersection between the natural and social sciences.

> Exploring the 'missing area' between the two is important to help engage with society and to drive future breakthroughs, and so I wish to encourage young scientists to tackle issues from many angles.

As part of the drive to ensure that the basic research we carry out is at the science's forefront, we have also established a new organization—the Cluster for Pioneering Research—which is tasked with encouraging scientists to become pioneers in new scientific fields and to build upon RIKEN's unique capabilities for interdisciplinary research.

Another new aspect of our strategy to strengthen RIKEN's basic research and to promote interdisciplinary collaboration has been the reorganization of our bioscience-related centers. From April 2018, RIKEN's six bioscience centers have been reorganized into four: the BioResource Research Center, the Center for Brain Science, the Center for Biosystems Dynamics Research, and the Center for Integrative Medical Sciences.

RIKEN recently launched a new engineering network. Early on, RIKEN was focused on engineering, and Japan's postwar recovery was underpinned by this emphasis in many of the country's leading universities and institutes. However, I think that the engineering mindset has been lost in subsequent years, and researchers have forgotten the importance of 'daily science'—science with real-world impact. I have thus called for a new framework that will identify the seeds for innovation and foster new engineering network initiatives. This will include interdepartmental collaborations as well as partnerships with industry.

JAPAN'S HUB FOR SCIENCE AND TECHNOLOGY

These reforms complement ongoing, Japan-wide measures to build a stronger research ecosystem, within which RIKEN will act as one of the country's premier research hubs.

RIKEN has earned this role, remaining Japan's top institution for highly cited research. Of the approximately 2,400 papers produced by our scientists each year, 5.6 per cent are in the top 1 per cent of papers cited in their field, a number head-and-shoulders above figures at other Japanese research institutions.

As a result of our efforts to strengthen global collaborations, the use of RIKEN's large-scale technical research facilities has also been increasing in recent years, including the RI Beam Factory, SPring-8 and the K computer, which are all available for shared use by researchers from around the world.

The intent is to parlay these research strengths to position RIKEN as a hub for the most innovative research and academia–industry collaborations with a global outlook and strong input from other

HIROSHI MATSUMOTO
RIKEN President

Hiroshi Matsumoto has been president of RIKEN since 2015. He has a doctorate in engineering. Much of his work centered on plasma in the geomagnetosphere and cosmosphere. He is an Honorary Officer of the Most Excellent Order of the British Empire (OBE) and a Chevalier in the French Legion of Honor and has twice been part of group efforts recognized with NASA Group Achievement Awards.

international bodies. To facilitate this, we have established a new organization, the Cluster for Science, Technology, and Innovation Hub, which will expedite collaborative research with both academia and industry.

Progressing in parallel are plans to form a subsidiary company that will be responsible for managing all of RIKEN's intellectual property. Preparations are now underway to develop a platform for discussing new directions in scientific research, the best use of existing resources and support for new ventures. The aim is for this company to yield a return of US$100 million in 10 years, based on $80 million in joint-research funding and $20 million in patent income.

GIVING RESEARCHERS THE CHANCE TO TAKE A LONG-TERM VIEW

Starting in April, a new, longer-term vision for projects has been extended to staffing. By 2025, we plan to increase the proportion of indefinite-term employees to 40 per cent, a huge jump from the current 10 per cent. This change has been much discussed, since the previous system, in which the vast majority of researchers were on fixed-term contracts (renewed every three to five years), may have prevented researchers from exploring a particular subject in-depth or seeing projects through to fruition. It may also have created instability and deterred applications from international researchers.

> **We plan to increase the proportion of indefinite-term employees to 40 per cent, a huge jump from the current 10 per cent**

THE HAKUBI PROGRAM

Finally, the new Hakubi program is an initiative that brings together many of the ideas I have mentioned. It will give young researchers the chance to pursue their own projects in their own labs. This program is also designed to encourage original thinking and bridge the divide between the sciences and humanities in order to tackle society's future challenges: for example, artificial intelligence researchers are developing robotics and computer-based intelligence, so there is a need to integrate ethical and philosophical viewpoints into research so that it is meaningful to society. This emphasis ties in with our focus on interdisciplinary collaboration elsewhere.

Prime Minister Shinzo Abe (front left) visited the former RIKEN Center for Developmental Biology (CDB) in 2017. Masayo Takahashi (front right) of the Laboratory for Retinal Regeneration, whose work led to a world first clinical trial that used induced pluripotent stem (iPS) cells in humans, explains developments in her recent research.

BUILDING ON OUR UNIQUE STRENGTHS

Although there is, of course, a need for reform to move foward, there has been much to be proud of in the three years since I assumed my post. Not the least of which was the naming of a new element after RIKEN scientists were the first to successfully synthesize element 113, the first addition to the periodic table in many years. This achievement, which was brought about through research projects with long-term perspectives and goals, saw the element named nihonium (after Japan) in November 2016. We are continuing our search for new elements, starting with 119 and moving on from there.

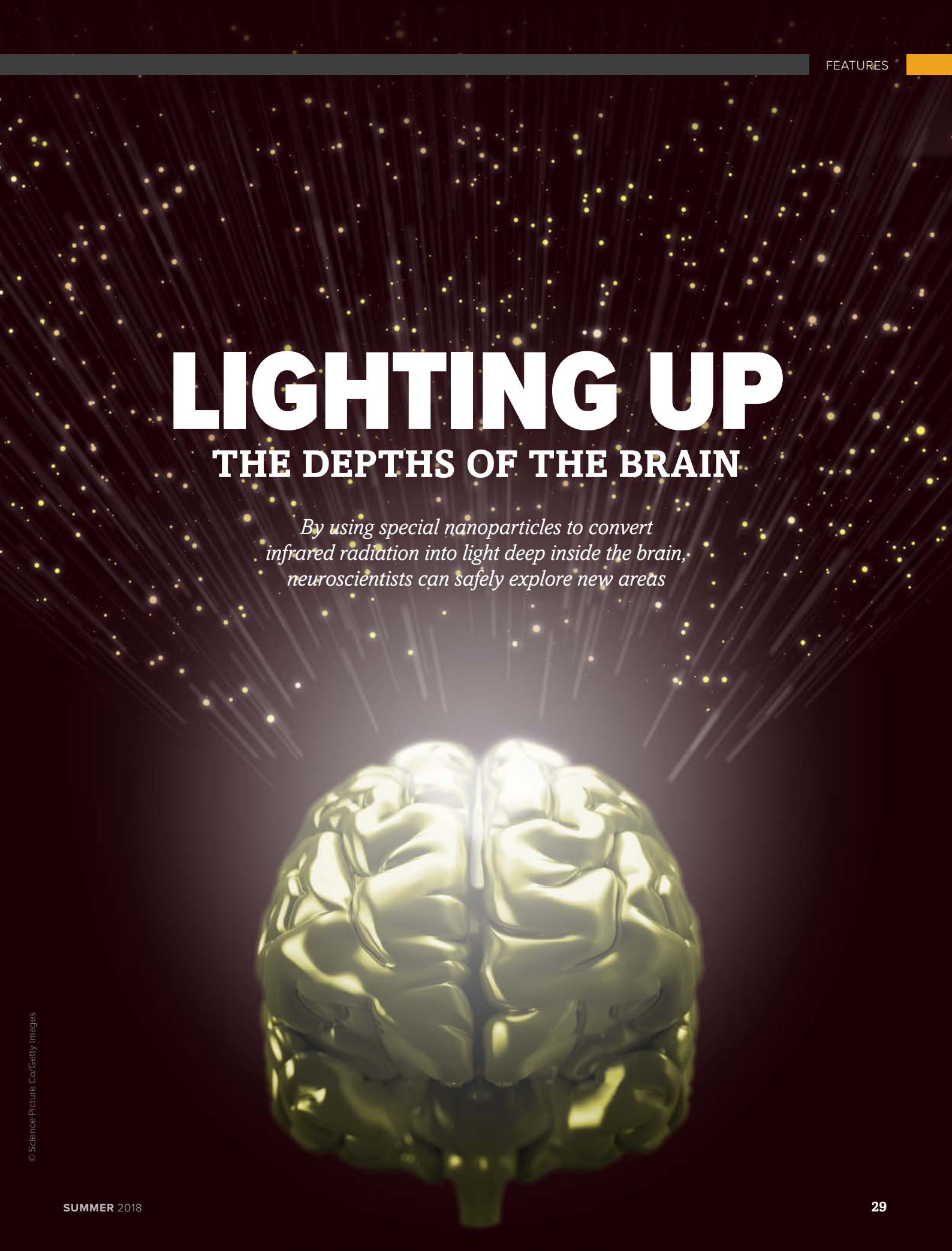
But as Prime Minister Abe suggested last year, it is also critical to recognize the trends that will shape Society 5.0, including the rise of artificial intelligence, big data, the Internet of Things and sustainability science. While the name for this set of changes differs from country to country—in Germany and in other places it is sometimes called Industry 4.0—when people talk of a post-digital society, there are universal themes that impact all sectors, including government, industry, academia and average citizens.

Fortunately, as a Designated National Research and Development Institute, RIKEN has some unique strengths upon which it can build to do this. Our research units tend to be much larger than those of counterparts at Japanese universities. The research environment also promotes interdisciplinary exchange and a free flow of opinions. Academic scientists and those from industry are treated on equal terms. Moreover, owing to our independent status, the institute has been able to launch large-scale national projects such as the SPring-8 and the BioResource Research Center, enabling researchers to engage in 'big science'—high-investment, large-scale projects with equally big implications for research outcomes.

Ever since joining RIKEN in 2015, I have felt that RIKEN's long-term standing internationally and its importance to Japan's research environment could not be underestimated, and my goal has been to continue to strengthen it, so that we can truly lead the world. It is vital to our shared futures that we remain at the forefront and be the drivers of social change. ●

LIGHTING UP
THE DEPTHS OF THE BRAIN

By using special nanoparticles to convert infrared radiation into light deep inside the brain, neuroscientists can safely explore new areas



Neuroscience is in the grips of transformation. In the quest to understand the brain's messenger systems, researchers no longer have to rely on crude electrodes to prod and probe. Instead, they study the brain using highly focused laser beams of visible light that stimulate neural circuits in living, even moving, animals. This technique, known as optogenetics, was developed about a decade ago and has resulted in a huge growth in neuroscience's output.

However, there is a fundamental problem with using light on brain matter—it cannot travel far before it is absorbed or scattered, which has limited the reach of optogenetics to about half a millimeter into the brain. To overcome this restriction, neuroscientists insert optical fibers (see image below), but these fibers sometimes damage surrounding brain tissue. Now, in a study published in *Science*, Thomas McHugh of the RIKEN Center for Brain Science and his co-workers have found a way around this problem: they are using a near-infrared beam and 'upconverting' it to visible light in the relevant brain region by injecting sophisticated nanoparticles[1].

DEEPER WITH NEAR-INFRARED LIGHT

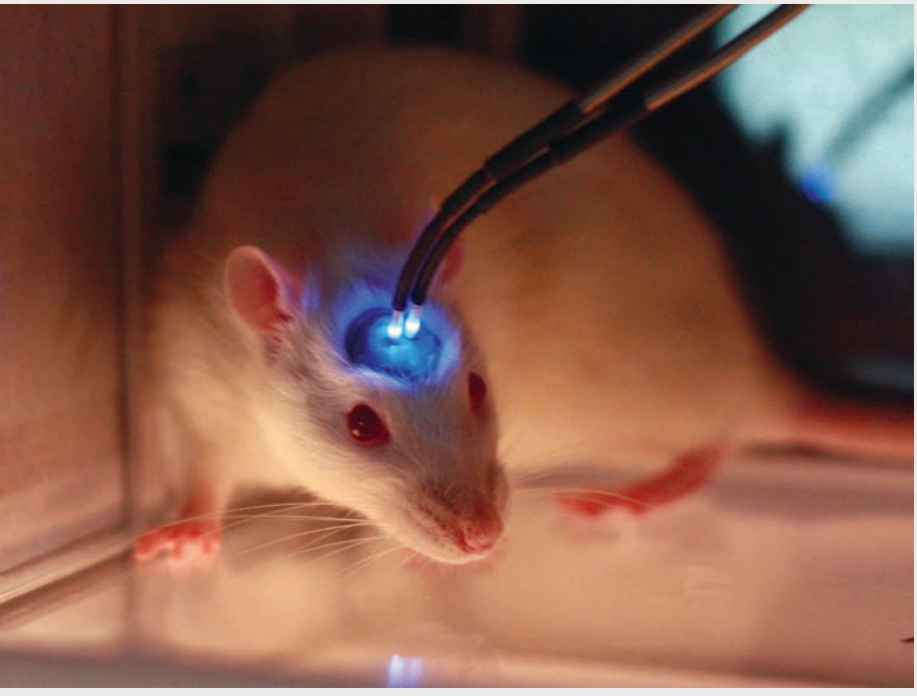
Near-infrared light can travel considerably further into the brain than visible light. But near-infrared light cannot stimulate neurons, so McHugh's team had to devise a means to convert it into visible light within the brain.

Converting high-energy ultraviolet light into lower energy visible light is fairly simple—scientists have a plethora of fluorescent dyes at their disposal that do this. But going in the opposite direction and changing low-energy infrared light into more energetic visible light is more of a challenge. Two or more particles, or photons, of infrared light need to pool their energies to produce a single photon of visible light. The process requires special particles known as upconversion nanoparticles, so-named because they can convert low-energy photons into higher energy ones.

It was at this point that the expertise and connections of Shuo Chen, a postdoctoral researcher in McHugh's lab, proved invaluable. "Chen did a PhD in chemistry, and he knew people working on particle synthesis," says McHugh. "He came to my lab to do optogenetics and said 'I think there are ways we can improve this tool if we talk to the right chemists.'"

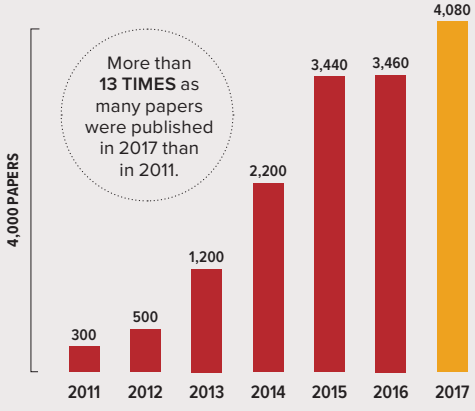
TEAMING UP ON UPCONVERSION

Chen connected McHugh with chemists at the National University of Singapore who specialize in making upconversion nanoparticles. When McHugh's team injected these nanoparticles close



GROWING NUMBER OF PAPERS

The graph below shows the steady increase in papers published in the field of optogenetics according to Google Scholar. Conventional optogenetics requires optical fibers to be inserted into the brain to investigate depths greater than 0.5 millimeters (left). A RIKEN team has developed a far less invasive technique that uses near-infrared light and nanoparticles, opening up new potential for the field.



to a brain region of interest, they were able to convert the near-infrared light into visible light, which in turn stimulated neurons. This process has extended the reach of optogenetics to about 4.5 millimeters—roughly a tenfold improvement on the conventional method and about the same depth as that of a mouse brain.

Using this method, the team has already been able to stimulate the release of dopamine, trigger the recall of memories and modify mouse fear responses.

Wolfgang Parak, who co-authored an accompanying article on the paper's findings in *Science*, is confident of the importance of overcoming the visible light "dilemma". Parak, who is from the Center of Hybrid Nanostructures at the University of Hamburg, Germany, and his two co-authors, chose to focus their article on the possible future applications of the method to control neurological issues in human patients, such as those with Parkinson's disease. Without it, they note that altering brain activity in a "substantial and targeted way" requires a complex tangle of electrodes. Due to this and the size of conventional electrode arrays, they point out that up until now optogenetics has had "severely limited clinical applications".

MAKING THE METHOD SAFE

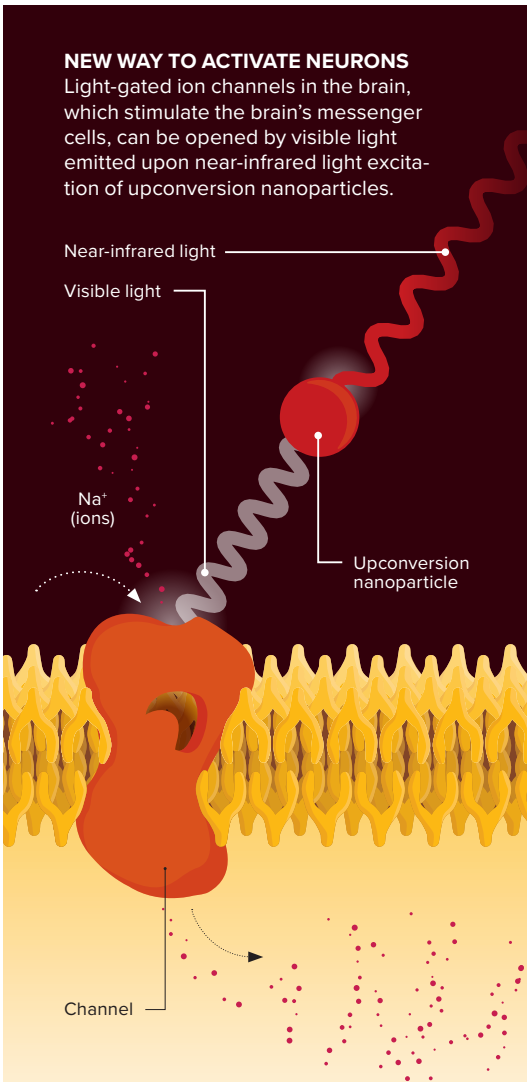
However, there is still much testing to be done. McHugh's team has already had to address a number of challenges to get their technique to work. "As a biologist, there were two things that raised red flags," he says. "One was that these nanoparticles use heavy metals to work the magic of upconversion. And when I think of heavy metals, I think of poison!" To get around this problem, the team made the particles biocompatible by encasing them with a silica coating.

The second challenge was ensuring that the near-infrared light did not cook the rodents' brains. Since infrared radiation is essentially heat, even low levels of absorption can heat a material. Fortunately, simulations performed by the team revealed that blood absorbs a lot of the infrared light, and so a lot of the heat is quickly circulated away.

NEW CLINICAL AND RESEARCH POSSIBILITIES

In the next phase, McHugh points to two areas of research that could benefit. The first is the study of the brain stem. Because the brain stem is very deep and contains many highly sensitive nuclei, any damage can severely affect an animal's health and behavior.

The other area is studying how the brain develops in infant mice. "Researchers who study development have been behind on this optogenetics bandwagon because they can't use it—they can't put a fiber in something so small," McHugh says. "But I think this will work. I'm pretty optimistic: we're going to try to use it to do pattern simulation in the brains of one- to two-day-old mice."



As for use in human patients, Parak and his colleagues suggest that the method might eventually be used to "optically control neuronal dysfunctions, such as Parkinson's disease or even paralysis."

McHugh is also optimistic, and says that in the near future it might also find application in treating peripheral nerves for chronic pain.

REFERENCE

Chen, S., Weitemier, A. Z., Zeng, X., He, L., Wang, X., Tao, Y., Huang, A. J. Y., Hashimotodani, Y., Kano, M., Iwasaki, H. *et al.* Near-infrared deep brain stimulation via upconversion nanoparticle-mediated optogenetics. *Science* **359,** 679–684 (2018).

This feature looks at the work of THOMAS MCHUGH

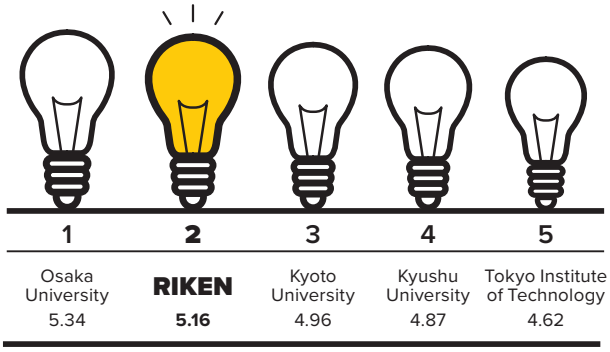
Thomas McHugh majored in molecular and cellular biology at the University of California, Berkeley, before moving to the Massachusetts Institute of Technology (MIT) where he finished a PhD in biology. At MIT, he studied genetics and the physiology of spatial memory with Matt Wilson and Susumu Tonegawa, and continued to study the circuits of hippocampal memory as part of his postdoctoral studies. In 2009, he moved to what is now known as the RIKEN Center for Brain Science to start his own laboratory. His Laboratory for Circuit and Behavioral Physiology at RIKEN takes a multidisciplinary approach to understanding how memories are formed, stored and recalled in the mammalian brain, and how damage from factors such as stress and disease impair these functions.

PATENT POWERHOUSE

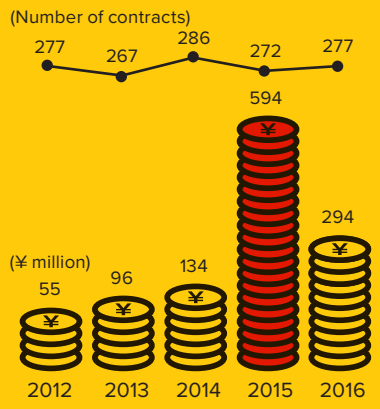
Japan is an innovation powerhouse. The World Intellectual Property Organisation analyzed the addresses of inventors named in all international patent applications published under the Patent Cooperation Treaty between 2011 and 2015 and found that Tokyo–Yokohama is the world's leading patent and innovation cluster. RIKEN's influence on patents is equally impressive say the creators of a new scoring system published by The Lens, a major global patent information platform containing over 100 million applications. The Lens ranks RIKEN as second in Japan (right) and 39th globally for its influence on patents. The Lens score is based on an analysis of an institution's input into papers cited in patent applications between 1980 and 2015.

LENS SCORE

(MEASURING INFLUENCE ON PATENTS)



RIKEN'S INCOME FROM LICENSE CONTRACTS



The huge ¥460 million (US$4.3 million) spike in revenue in 2015 came from just one product. The fact that a single product can make such a difference to RIKEN's revenue highlights the potential of patents to generate huge income streams for science.

PATENT CITATIONS 1980–2015

(EXCLUDING SELF-CITATIONS)

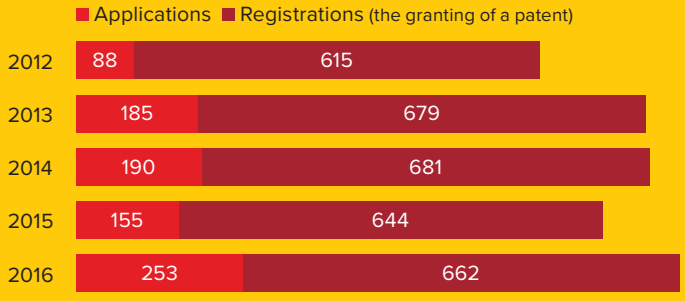
123,762 papers

INFLUENTIAL PAPERS 1980–2015

(FROM THE WEB OF SCIENCE)

42,847 papers

INCREASING INTERNATIONAL APPLICATIONS FOR RIKEN PATENTS



POTENT PATENTS

The sports drink *VAAM* has been endorsed by Olympic marathon gold-medal-list Naoko Takahashi. It contains a synthetic amino-acid mix patented by RIKEN that mimics the saliva of Asian giant hornet larvae, which was found to help metabolize energy better. More online and in *RIKEN Research* Winter 2015.

RIKEN'S CENTERS AND FACILITIES

across Japan and around the world

WAKO
(RIKEN's Headquarters)
- ● Center for Emergent Matter Science (CEMS)
- ● Center for Advanced Photonics (RAP)
- ● Center for Sustainable Resource Science (CSRS)
- ● Center for Brain Science (CBS)
- ● Interdisciplinary Theoretical and Mathematical Sciences Program (iTHEMS)
- ● Nishina Center for Accelerator-Based Science (RNC)
- ▲ Cluster for Science, Technology, and Innovation Hub (CSTIH)
- ▲ Cluster for Pioneering Research (CPR)
- ◆ Radio Isotope Beam Factory (RIBF)

Head Office for Information Systems and Cybersecurity

LEGEND
- ● Strategic Research Center
- ■ Research Infrastructure Center
- ◆ Large Research Infrastructure
- ▲ Research Cluster

SENDAI
- ● Center for Advanced Photonics (RAP)

YOKOHAMA
- ● Center for Sustainable Resource Science (CSRS)
- ● Center for Integrated Medical Sciences (IMS)
- ◆ Genome Sequencing
- ◆ Nuclear Magnetic Resonance (NMR)

TSUKUBA
- ■ BioResource Research Center (BRC)
- ◆ BioResource

HARIMA
- ■ SPring-8 Center (RSC)
- ◆ SPring-8
- ◆ SACLA

TOKYO
- ● Center for Advanced Intelligence Project (AIP)

OSAKA
- ● Center for Biosystems Dynamics Research (BDR)

KOBE
- ● Center for Biosystems Dynamics Research (BDR)
- ■ Center for Computational Science (R-CCS)
- ◆ Molecular Imaging
- ◆ K computer

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 to 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.

For more information, please visit:
www.riken.jp/en/research/labs/
www.riken.jp/en/outreach/research/

RIKEN RESEARCH

www.riken.jp/en/research/rikenresearch

Science Blog
itaintmagic.riken.jp

Find us on Facebook
www.facebook.com/RIKEN.english

RIKEN
www.riken.jp/en

@riken_en
www.twitter.com/riken_en

LinkedIn
www.linkedin.com/company/riken

RIKEN 2018-029