RIKEN RESEARCH

WINTER 2021

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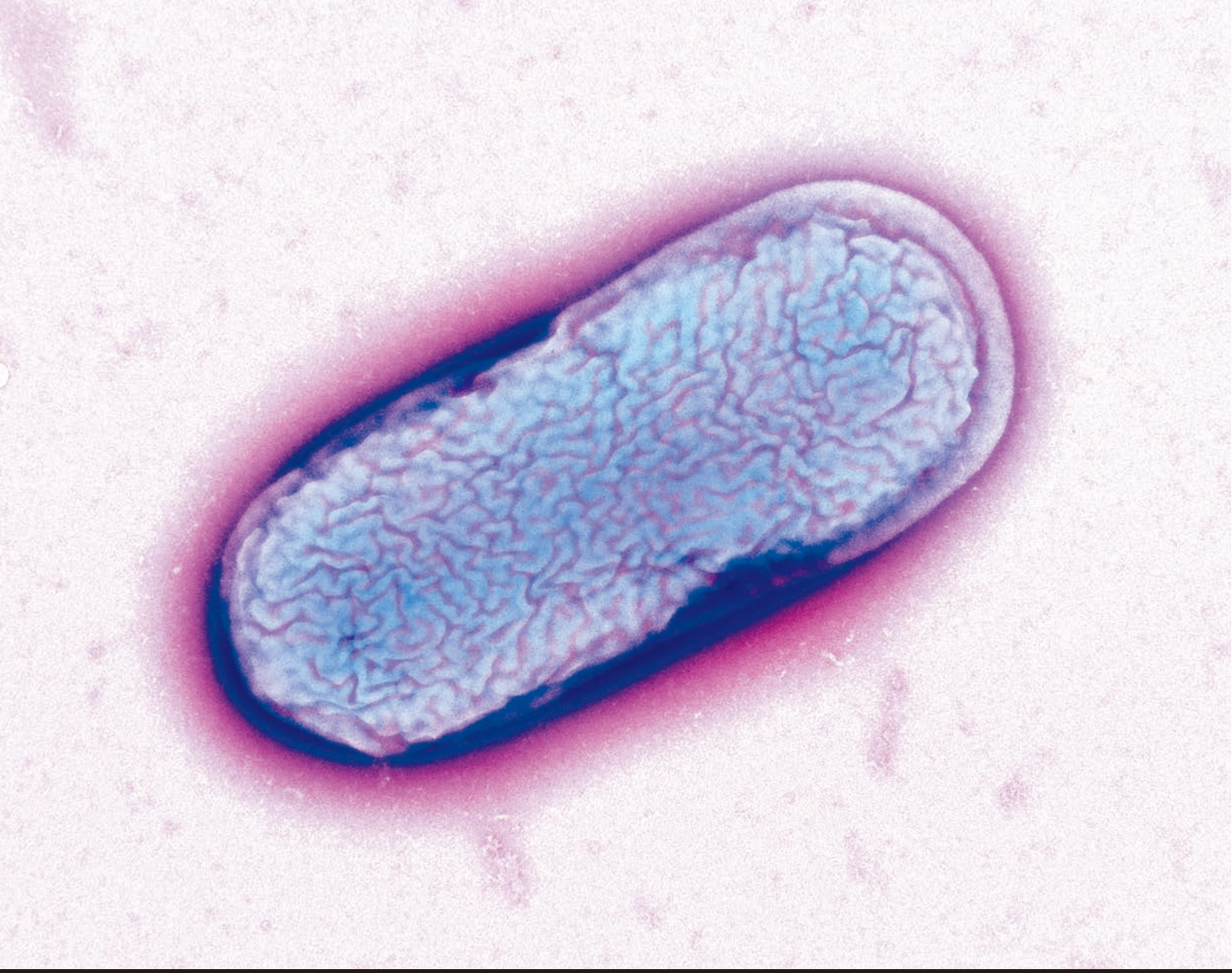
CODING CAUTION

How zebrafish predict danger

TREADING LIGHTLY
Testing microbes for sustainable tires

DNA DONORS
Our ancient virus ancestors

NEURAL CONNECTIONS
Building the basis for better brain studies



▲ **Microbe manufacturing**
Escherichia coli (pictured) and glucose have been used to produce 1,3-butadiene, one of the building blocks for a synthetic polymer used in vehicle tires. In collaboration with industry partners, RIKEN researchers are scaling up production (see page 26).

RIKEN RESEARCH

RIKEN, Japan's flagship research institute, conducts basic and applied research in a wide range of 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: https://www.riken.jp/en/news_pubs/research_news/ Please visit the website for recent updates and related articles. Articles showcase RIKEN's groundbreaking results and are written for a non-specialist audience.

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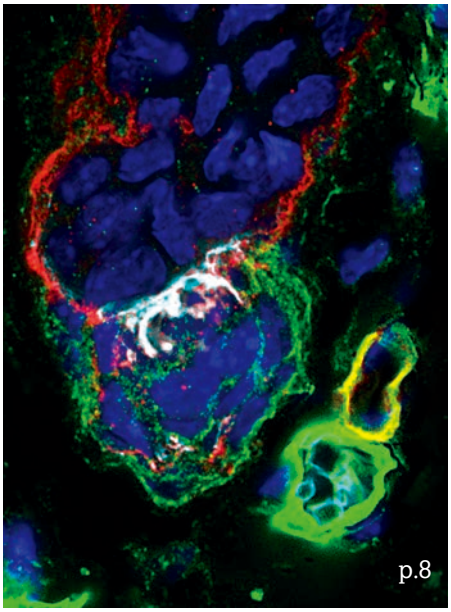
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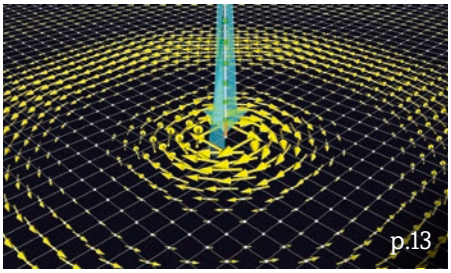
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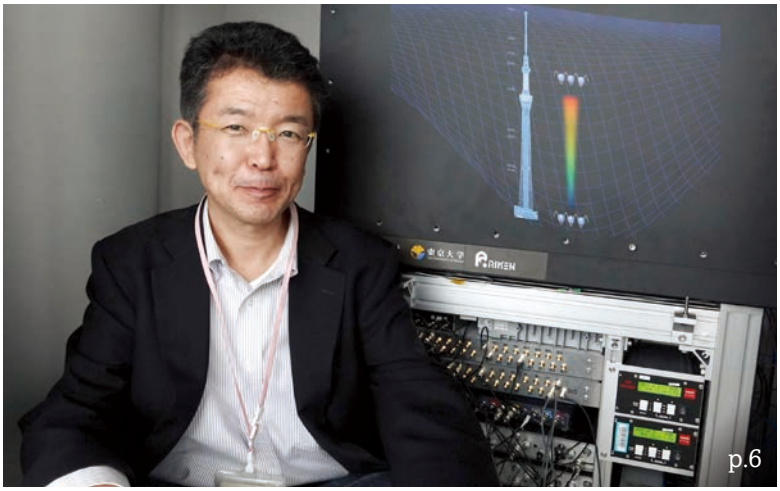
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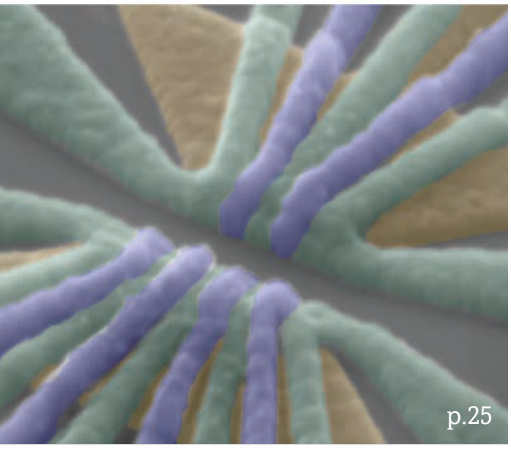
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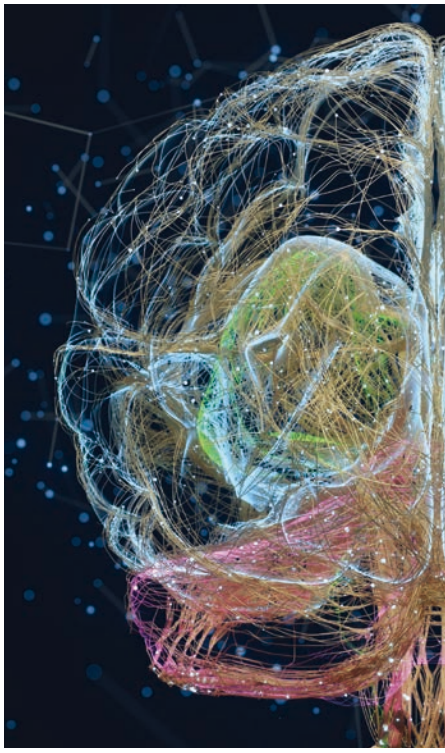
26 Feature COVER STORY

To make tire rubber, add bacteria and sugar: A chance change of pH resulted in a more sustainable means of producing a compound key to the manufacture of car tires using glucose and genetically modified bacteria.

29 COVER STORY Perspectives

Building a better future for the brain: Ryoichiro Kageyama from the RIKEN Center for Brain Science says their work developing optogenetic, gene editing and bioinformatic technologies, as well as cutting-edge animal models, is accelerating the real-world impact of brain research. For instance, new marmoset and mouse Alzheimer's disease models are addressing longstanding challenges in the study of therapies that break down plaques and generate fresh neurons.



Keep in touch with our alumni network

Yuko Harayama
Executive Director, RIKEN

I realize that many of our readers are RIKEN alumni. So I would like to share some information about the network we maintain for our alumni and our other outreach activities for researchers outside Japan who might wish to collaborate with us.

We make an effort to keep in touch with our alumni, as they are an important part of RIKEN's global community. On our website, in the section on careers, you can find information on how to register as an alumnus. We provide members of our network with a regular newsletter that includes information on RIKEN's latest work, upcoming events and other information that might be of value.

Also, as many of you know, we have a physical means of remaining in contact—three overseas offices that we have established in Beijing, Singapore and Brussels. While a large part of the mission of those offices is to promote ties with other institutes and universities in their regions, another important role is to help us maintain ties with alumni. Each office occasionally organizes events, so we would encourage you to get in contact with them if you are nearby.

Interactions with alumni form part of an important 'virtuous cycle' and help to birth new collaborative relationships that will flourish into successful projects. We encourage our networks to remain engaged.

I also want to briefly mention that we are active on several social media platforms—Twitter, Facebook and LinkedIn—and that we also share information through those channels. The account names are listed below.

Needless to say, if you have any suggestions or requests about what type of information you would like to receive from us, we are always happy to hear your feedback.

原 洋 子

COVER STORY:
RIKEN researchers have observed zebrafish neurons that are coding behavioral rules around danger and are also assessing the prediction error of the rule.
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Sparking sustainable catalysts

Laurean Ilies
Team Leader, Advanced Organic Synthesis Research Team
RIKEN Center for Sustainable Resource Science

Please describe your role at RIKEN.
I am the leader of the Advanced Organic Synthesis Team, a small team (nine people at the moment) of ambitious researchers who are inventing new synthetic methods that create molecules of interest for medicinal chemistry, materials science, etc.

We develop new ways to directly react Earth-abundant molecules, such as hydrocarbons, and rapidly build molecular complexity. This is important because we can streamline the synthesis of target molecules, and thus save resources and energy, while minimizing waste.

We also research the late-stage functionalization of complex molecules used in drugs; this is important because it builds molecular libraries focused on bioactivity, etc.

Finally, we are trying to find Earth-abundant metal catalysts and reagents, rather than often-used precious metals, which will help create more sustainable synthetic chemistry products.

Has being at RIKEN helped your research?
RIKEN gives (relatively) young researchers a rather unique chance to start an independent career, backed by generous funding and strong infrastructure. I started working at RIKEN in 2018, and I was quite worried about the process of building a lab and a research team, but I was fortunate to receive tremendous help, and after three years things are going smoothly.

What are the techniques and technologies you use to conduct your research?
The equipment we use the most is the nuclear magnetic resonance (NMR) machine and elemental analysis for characterization of molecules, x-ray for crystallographic analysis, and the RIKEN supercomputer for molecular calculations.

What is the best thing about working at RIKEN?
I think that the support from various offices is great, and we have time to focus on research, rather than doing tons of administrative work. I would add that funding is generous, there is a lot of technical support (for molecular characterization, for example), and there are also ample opportunities for collaboration. The Wako campus also has excellent facilities for relaxing after work. I am a user of the tennis courts and swimming pool.

> *We can streamline the synthesis of target molecules, and thus save resources and energy.*

What has been your most memorable experience at RIKEN?
It took some time to build the laboratory because we require special settings to do organic reactions safely. The first wet lab was finished at the end of August 2021, and entering the brand-new lab was a very emotional experience for me.

How do you balance family life with your work at RIKEN?
I have three children, and they are still small and my wife also works full time. Because I do less experimental work and more desk work nowadays, it is easier to plan my time, and I also work from home sometimes. ■

Accelerators accelerate many fields

Tomoko Abe
Deputy Director, RIKEN Nishina Center for Accelerator-Based Science
Group Director, Beam Mutagenesis Group/Team Leader, Ion Beam Breeding Team

Please briefly describe your current research.
My group, the Beam Mutagenesis Group, has developed a unique technology to induce mutations using energetic heavy ions at RIKEN's Radioactive Isotope Beam Factory (RIBF). At relatively low doses, ion beams induce mutations at a high rate without severely inhibiting growth. The heavy-ion beam is an excellent and highly efficient tool for mutation breeding of crops and microorganisms. Focusing the beam on scions, *in vitro* cultured tissue and plant seeds for a short time, just seconds to a few minutes, is enough to induce mutation. Using this method, we have already put 37 new cultivars onto the market in Japan.

How did you become interested in your current field of research?
Most large accelerator facilities are used purely for experiments in nuclear physics and particle physics. However, RIKEN has a tradition of giving machine time to researchers in other fields. And we have kind but tough physicists who patiently teach biologists who dislike physics about the physics of heavy-ion beams.

My own proposal for experiments in the life sciences passed the Program Advisory Committee and I was able to get machine time. During our first breeding experiments, we were able to obtain many albino mutants from tobacco plants.

Please describe your role at RIKEN.
I am not a physicist, but as the deputy director of the Nishina Center I have learned the importance and fun of physics from leading physicists. Thus, I am working to make RIBF the most user-friendly accelerator facility globally for non-physics researchers, and to promote research in applied areas, including plant breeding. China and South Korea plan to start operating their large accelerator facilities in the next few years, with a view to applied research. There are as many types of radiation in heavy-ion beam as there are ion species and energies. I would like to cooperate with researchers in each country to develop ion-beam breeding technologies tailored to each accelerator facility's characteristics.

"My research is important for sustainable development or society because..."
Some variants can be more sustainably farmed, including salt-resistant rice, high-yield rice, high-yield seaweeds, high oil-content algae and larger zooplankton.

What excites you the most about your current research?
It has been exciting to find many unexpected mutants using our method. For example, the S1200 line of Satsuma mandarin in Shizuoka prefecture is a late coloring one that is harvested about a month later than the original variety, but the fruits are sour when harvested. As the harvest time of the Satsuma mandarin has tended to come earlier due to global warming, it is desirable to breed new varieties suitable for long-term storage. 'Harushizuk', which was recently bred from the S1200 line, is suitable for long-term storage and the fruits turn into good quality sweet oranges during storage. They sell at a high price in March and April when oranges are in short supply, and this makes farmers happy. ■

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For further information, visit our Careers page:
Website: www.riken.jp/en/careers
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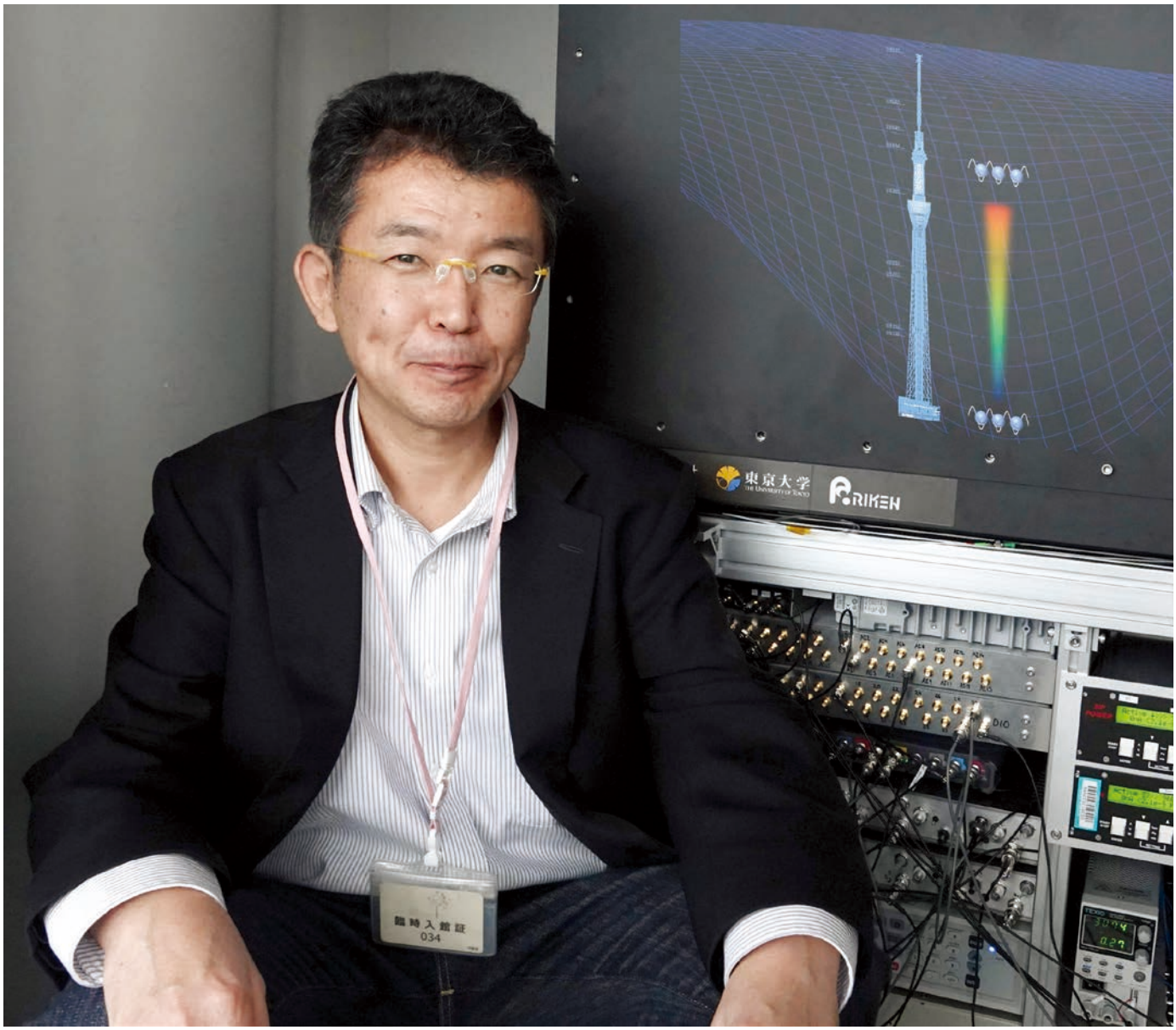


Optical lattice clock pioneer Hidetoshi Katori is the team leader of the Space-Time Engineering Research Team at the RIKEN Center for Advanced Photonics.

Hidetoshi Katori, Breakthrough Prize winner

Hidetoshi Katori, team leader of the Space-Time Engineering Research Team at the RIKEN Center for Advanced Photonics, has been awarded the prestigious Breakthrough Prize in Fundamental Physics for his work in developing the optical lattice clock, a phenomenally precise type of atomic clock. He won the award alongside Jun Ye from the National Institute of Standards and Technology and the University of Colorado. The clocks, which were developed independently by Katori's and Ye's teams, are so accurate that they will not go out of sync by even a second even after a period of time that reflects the amount of time the Universe has existed. In addition to measuring time, these clocks can be used to perform 'relativistic geodesy', meaning the measurement of heights using Einstein's theory of relativity. The Breakthrough Prize is a prestigious set of international awards presented by the Breakthrough Prize Foundation and its founding sponsors—Sergey Brin, Priscilla Chan and Mark Zuckerberg, Yuri and Julia Milner, and Anne Wojcicki. *Katori is also the Chief Scientist of the Quantum Metrology Laboratory in the RIKEN Cluster for Pioneering Research and a professor at the University of Tokyo.*

https://breakthroughprize.org/News/65

The Tenth Global Summit of Research Institute Leaders

In October 2021, an international cohort consisting of the heads of 25 national research institutes attended the Tenth Global Summit of Research Institute Leaders, which was themed 'Contributing to Resilient Societies through Science and Technology'. This event was held in conjunction with the 18th Annual Meeting of the STS *forum*. The group talked about managing science and technology and the challenges of multilateral collaboration during the COVID-19 pandemic. In closing, the participants resolved to explore new ways to coordinate research and share data across disciplines and national boundaries so that research can continue under trying conditions and contribute to global resilience. The meeting was co-hosted by RIKEN and the National Institute of Advanced Industrial Science and Technology.

www.riken.jp/en/news_pubs/news/2021/20211020_1/index.html

2021: Two OIST-RIKEN Joint Symposiums

In April 2021, the Okinawa Institute of Science and Technology Graduate University (OIST) hosted the first OIST–RIKEN Joint Symposium, which was focused on ecological research at the two institutes. Speakers covered everything from shark biology and jellyfish genomics to the biodegradable potential of plastics. This event followed an agreement, signed by the two institutes in March 2020, to work together to promote academic, scientific and technological advancements and the development of human resources globally and in Japan.
In October, a second OIST–RIKEN Joint Symposium was held online. The October event focused on the topic of 'What is thinking?' and the fields of neuroscience, data science and artificial intelligence. Fourteen speakers spoke on everything from manipulating information in the brain to neurorobotics.

Kengo Suzuki (left), team leader of the Microalgae Production Control Technology Laboratory in the RIKEN Baton Zone program, and Chihana Toyokawa of Euglena Co., Ltd. gave a live lecture on *Euglena*.

RIKEN Yokohama Open Day online

RIKEN Yokohama Campus and the Yokohama City University Tsurumi Campus hold a joint open day every year. But to prevent the spread of the new coronavirus, 2021's October open day was held online. Participants were able to join a live lecture on a project that aims to create a carbon-neutral society with the help of eukaryotes from the *Euglena* genus, as well as live experiments using green fluorescent proteins. On the event's website, visitors enjoyed interviews with RIKEN researchers, virtual-reality lab tours, and content on coronavirus studies using nuclear magnetic resonance. The special website for the open day was open to the public until the end of October and was accessed roughly 3,500 time by visitors from 35 prefectures. More than 3,600 views were recorded on the open day's YouTube Live.

RIKEN joins the Wellcome Leap Global Network

In September 2021, RIKEN become a member of the Leap Health Breakthrough Network, a global group of academic institutions whose goal is to build and execute bold, unconventional programs that aim to deliver breakthroughs in human health in five to ten years.

Wellcome Leap was founded in 2020 by the Wellcome Trust as a US nonprofit with US$300 million in start-up funds. RIKEN is the first Japanese institute to join this network, which also includes Harvard University, MIT, and the Francis Crick Institute. RIKEN researchers are now eligible to apply for funding as part of the network. These projects are to be started rapidly, without going through a long process of negotiation over intellectual property and the publication of research results.

BASEMENT MEMBRANE

‘Intelligent glue’ underpins tissue interactions in skin

The skin’s basement membrane is highly specialized to enable molecular crosstalk between different tissue types

In a discovery that could pave the way for therapies that promote wound healing and alleviate skin diseases, RIKEN researchers have found that the network of molecules under the outermost layer of mouse skin, the skin epithelium, is a highly specialized zone of biological activity that facilitates distinct sets of interactions between different types of tissues[1].

The extracellular matrix is a complex scaffold composed of hundreds of regionally specialized proteins that performs multiple roles, including supporting and organizing cells in organs and conveying biochemical signals that control their growth and differentiation.

Sandwiched between the outer epithelium and inner dermis, the basement membrane is a thin sheet of extracellular matrix. “This critical interface in the skin is like an optimally formulated, intelligent glue,” explains Hironobu Fujiwara of the RIKEN Center for Biosystems Dynamics Research. But how it operates in interactions between tissues is not well understood.

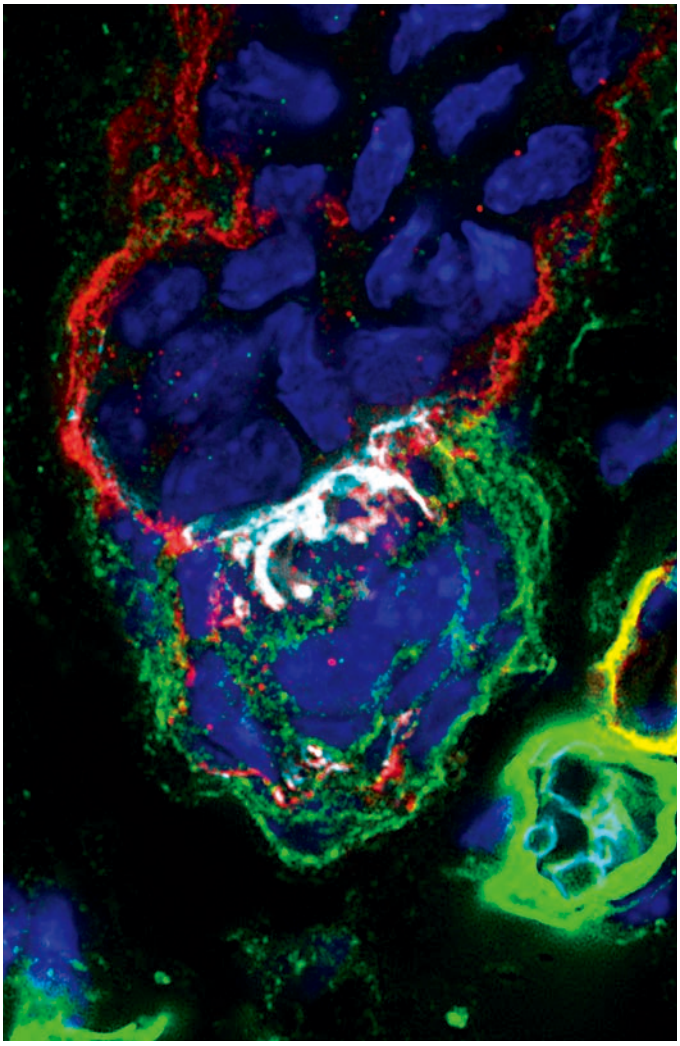
Now, by using gene-expression analyses and imaging techniques, Fujiwara and his colleagues have systematically characterized the cellular origins, molecular identities and distribution patterns of molecules in the basement membrane of mouse skin. They discovered that, within this tissue interface, there were a diverse series of regionally specialized niches, each impacted by the identity of nearby cells.

Around hair follicles, for instance, the identity of abutting cells in the dermis determined the nature of matrix proteins. Fibroblasts and their associated epithelial cells produced their own sets of proteins to facilitate molecular crosstalk between the two cell types, while epithelial cells facing sensory nerve cells or arrector pili muscles secreted a special concoction of proteins that allowed for unique interactions with those tissues as well.

In particular, the researchers found that the interface between the hair germ, a rudimentary epithelial structure from which a hair develops, and a specialized fibroblast population called the dermal papilla, essential for the development and regeneration of hair follicles, were tangled together in a never-before-described arrangement of basement membrane composition and architecture (see image).

These ‘hook and mesh’ basement membranes—so named because of their hooked shape and mesh-like deposition of secreted proteins—could help underpin the exquisite regenerative capacity of hair follicles, the researchers note. A better understanding of these structures could also inform the development of tissue engineering strategies for treating hair loss and other skin conditions.

Beyond the skin, Fujiwara expects to find similar patterns of basement membrane organization in other parts of the body as well. “Although this has not yet been investigated well, if confirmed the spatial patterns we have documented could represent a new paradigm of basement membrane composition and design,” he says.



A hook (white) and mesh (green) basement membrane forms at the interface of the hair germ (surrounded by red-colored basement membrane) and dermal papilla (surrounded by green-colored mesh basement membrane).

Reference

1. Tsutsui, K., Machida, H., Nakagawa, A., Ahn, K., Morita, R., Sekiguchi, K., Miner, J. H. & Fujiwara, H. Mapping the molecular and structural specialization of the skin basement membrane for inter-tissue interactions. *Nature Communications* **12,** 2577 (2021).

SECONDARY METABOLITES

Plants recycle metabolites

Plants break down complex metabolic products to recover and reuse the nutrients

Thale cress (*Arabidopsis thaliana*) is able to recycle specialized metabolic products to extract nutrients needed for basic metabolic activities.

Plants are able to reuse specialized metabolic products and break them down to recover nutrients needed for basic metabolic activities, RIKEN plant scientists have discovered[1]. Deactivating the enzyme responsible for this mechanism could improve the production of health-promoting chemicals in crops in the future.

In addition to producing sugars and other molecules directly involved in their growth and development, plants make a range of secondary metabolites—specialized molecules that help them adapt to their environment and interact with their ecosystem, by providing defence against planting-eating animals, for example. Scientists have long wondered whether the nutrients used to synthesize secondary metabolites can be released and reused in primary metabolism.

Now, a team led by Masami Hirai at the RIKEN Center for Sustainable Resource Science has explored this question by investigating whether Thale cress can use the secondary metabolite glucosinolate as a source of sulfur. Glucosinolates are partially responsible for the pungency of vegetables such as mustard and horseradish, as well as the nutritional value and health benefits of broccoli and Brussels sprouts.

The team grew the plants in cultures with no sulfur, varying amounts of sulfur, or a glucosinolate. Plants grown without sulfur had severe growth defects, whereas those grown with glucosinolate exhibited normal growth. This suggests that the plants were using sulfate in the supplied glucosinolate as an alternative source of sulfur.

"Our findings show that an important secondary metabolite is recycled by plants"

In fact, sulfur-concentration measurements revealed that the seedlings had accumulated more sulfur than plants grown with a similar amount of sulfate. This led the team to suspect that the plants were also using other sulfur atoms (that is, non-sulfate sulfur atoms) from the glucosinolate.

To investigate this, they prepared glucosinolates in which the sulfur atom making up a key bond in the molecule was a heavier isotope, so they could track it through later metabolic processes. The team found that the labeled sulfur accounted for 28–42% of different sulfur-containing amino acids in the seedlings, clearly demonstrating the breakdown of the supplied glucosinolate and its reincorporation into primary metabolism.

"I was very excited to see this," says Ryosuke Sugiyama, the lead author of the study. "Since the potential role of glucosinolate as a sulfur reservoir has been discussed based on the sulfate group, we were surprised that the other common sulfur atom is also available as a source. This supported the presence of a systematic breakdown pathway in plants."

"Although the potential recycling of secondary metabolites has been discussed for decades, there had been no direct evidence showing its physiological advantage," adds Sugiyama. "Our findings show that an important secondary metabolite is recycled by plants and can thus serve as a reservoir of nutrients for primary metabolism." ●

Reference

1. Sugiyama, R., Li, R., Kuwahara, A., Nakabayashi, R., Sotta, N., Mori, T., Ito, T., Ohkama-Ohtsu, N., Fujiwara, T., Saito, K. *et al.* Retrograde sulfur flow from glucosinolates to cysteine in *Arabidopsis thaliana*. *Proceedings of the National Academy of Sciences USA* **118,** e2017890118 (2021).

MOTT INSULATORS

A sharp response to electron injection

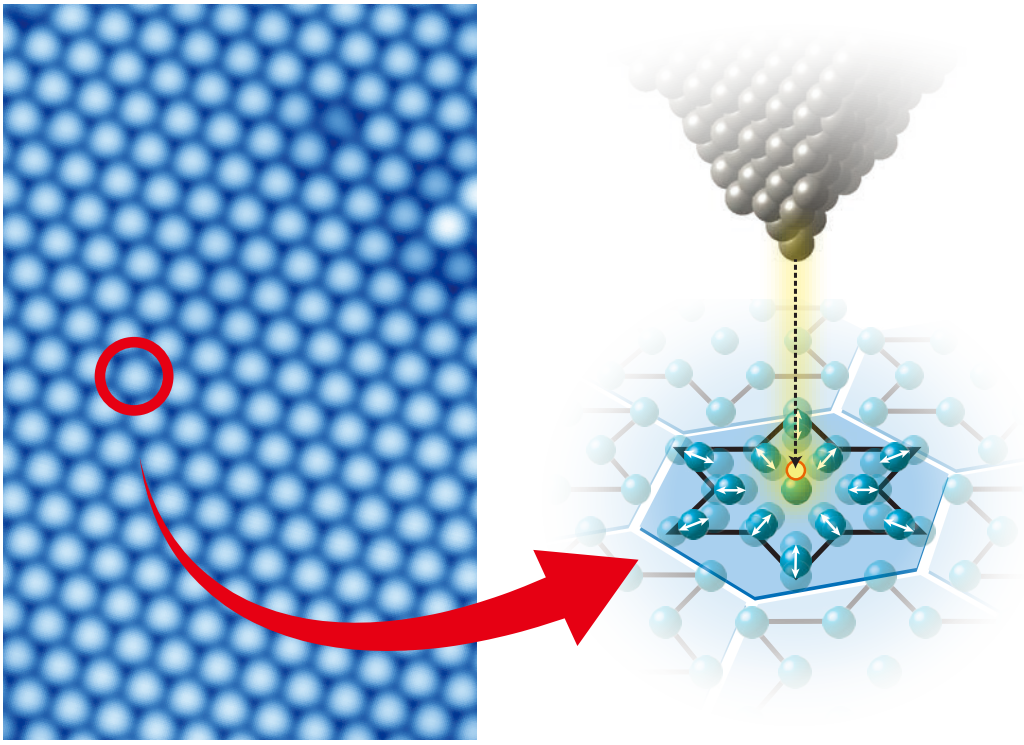
Unexpected peaks in a spectrum upset conventional models of an exotic quantum material

In a finding that will give theorists plenty to ponder, an all-RIKEN team has observed an unexpected response in an exotic material known as a Mott insulator when they injected electrons into it[1]. This observation promises to give physicists new insights into such materials, which are closely related to high-temperature superconductors.

Neither a chunk of silicon nor a Mott insulator conduct electricity—but for very different reasons. In silicon, electrons are tightly bound to atoms and require a lot of energy to become mobile conduction electrons. In contrast, in a Mott insulator, electrons may not be strongly bound to the atoms, but their movement is instead curbed by their mutual repulsion.

The Mott state's emergence from interactions between electrons leads to unusual properties. "A small excess or deficit of electrons in a Mott insulator can lead to high-temperature superconductivity, which could be of enormous practical value in the future," says Christopher Butler of the RIKEN Center for Emergent Matter Science (CEMS). "In Mott-insulating tantalum disulfide, electrons are localized not at each atom, but instead on the crests of a pre-existing 'charge density wave'. Because the charge density wave is rather delicate, the Mott state can easily be tweaked."

But to harness the potential of this Mott-insulating state and the charge density wave that hosts it, scientists need to better understand the physics



RIKEN physicists used the tip of a scanning tunneling microscope (gray inverted pyramid) to inject single electrons (gold sphere) into the surface of a Mott insulator).

"They may indicate that something is going on that is outside the bounds of the usual theory"

connecting them.

Now, Butler and three colleagues, all at CEMS, have added excess electrons to a Mott insulator using the tip of a scanning tunneling microscope (see image) and observed a surprising response—tunneling spectra showed a sharp feature, a distinct state that set off vibrations in the ionic lattice.

The conventional theoretical model for Mott insulators predicts that the spectrum should be smooth and non-descript. "It was most surprising that we saw such sharp features in our tunneling spectroscopy measurements," says Butler. "They may indicate that something is going on that is outside the bounds of the usual theory."

Butler notes that some theoretical calculations do predict sharp features similar to those his team saw, but they involve particle-like entities known as quasiparticles, which are controversial since they are not thought to exist in true Mott insulators. "There are competing explanations for the observation that are less controversial," says Butler. "But if it eventually turns out that the calculation results indicating the existence of quasiparticles are right, it might shake up the theoretical understanding of Mott insulators." ●

Reference

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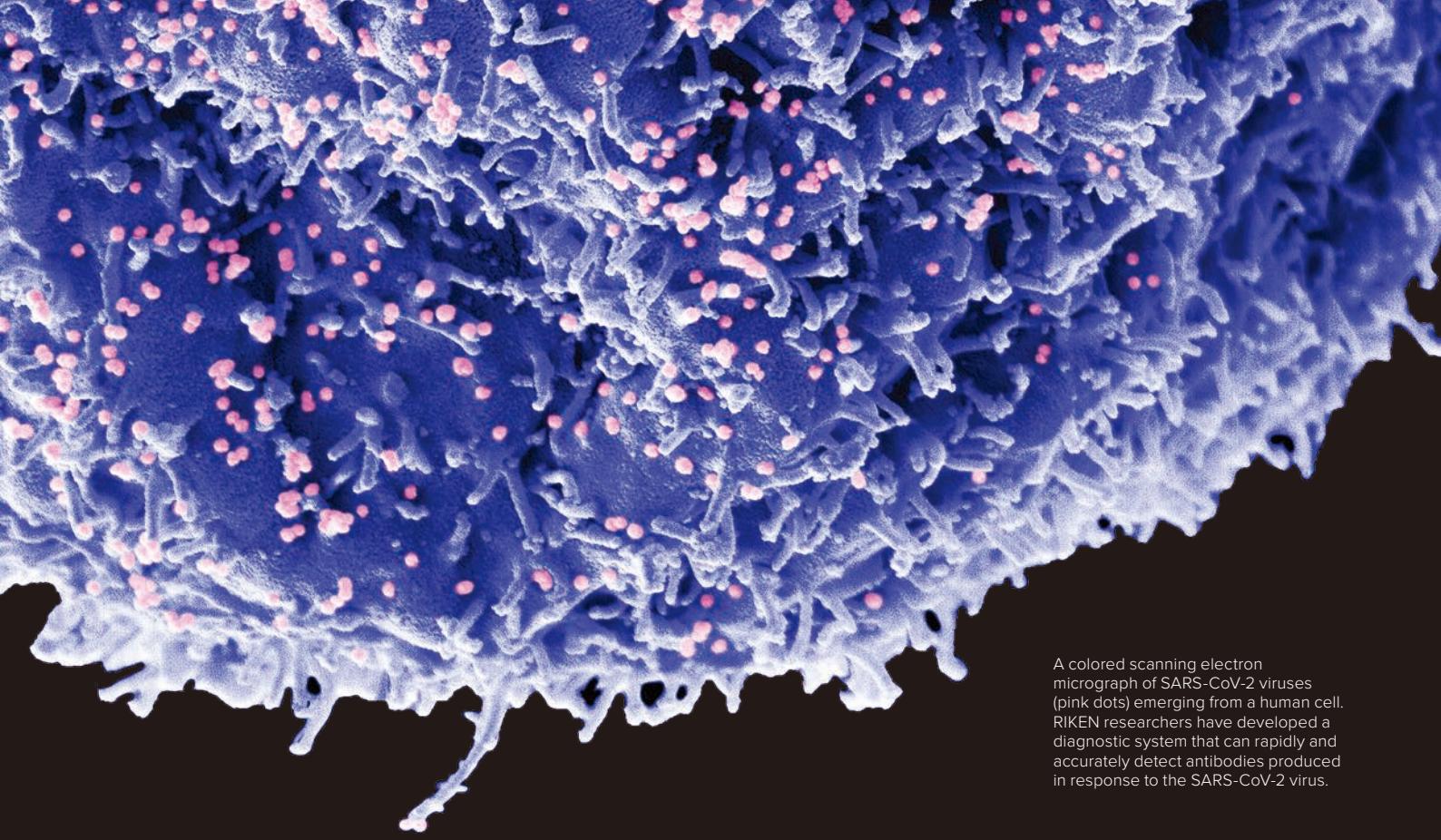


A colored scanning electron micrograph of SARS-CoV-2 viruses (pink dots) emerging from a human cell. RIKEN researchers have developed a diagnostic system that can rapidly and accurately detect antibodies produced in response to the SARS-CoV-2 virus.

ANTIBODY TESTING

Fast and sensitive on-site COVID-19 antibody tests

A new diagnostic system promises to enable rapid and sensitive on-site measurement of antibodies against the virus that causes COVID-19

Efficient and precise testing of SARS-CoV-2 vaccine efficacy at clinics will become possible thanks to a diagnostic system developed by a RIKEN team that can rapidly and sensitively measure antibody levels in the blood[1].

Several vaccines have been developed against SARS-CoV-2, the virus that causes COVID-19, and vaccination is being conducted worldwide. Antibody tests are performed at clinics to determine whether antibodies have been produced as a result of viral infection or vaccination, but their results are not very precise or sensitive. For more precise results, blood samples must be sent to a testing center, with a turnaround of several days to a week.

Previously, a team led by Yoshihiro Ito of the RIKEN Center for Emergent Matter Science had developed a technology that immobilizes any organic compound, including substances of biological origin. Now, they have extended the system so that it immobilizes several key SARS-CoV-2 proteins, allowing the automatic detection of antibodies against the virus.

In the light-based technique, a substance that reacts to light is coated on a plastic microchip. A drop of a liquid containing the protein of interest is dropped onto the microchip and ultraviolet light is used to immobilize the proteins.

Using this method, the researchers developed a chip called a microarray upon which key SARS-CoV-2 proteins are fixed. When antibodies in blood serum bind to the viral proteins on the chip, they emit light, and the amount of light emitted can be precisely measured with a CCD camera. This value can be used to quantify the number of antibodies.

"Standard quantitative analysis of antibodies usually requires a half milliliter of blood drawn from one of your arms, which is a lot," says Ito. "But in our system, all that is needed is a small drop of blood from the fingertip, and the sensitivity of the system is 500 times higher than that of conventional immunochromatography, meaning that detection is possible even when the number of antibodies is very low."

Furthermore, operation is simple—just drop human blood serum onto the chip, press the start button, and wait. The reaction process, washing and antibody detection are performed automatically in about 30 minutes.

"This system is practical to use and will enable precision testing at any medical facility, making it easier to quickly determine onsite whether or not vaccination is necessary," says Ito. "It can also be used to conduct epidemiological surveys in preparation for future pandemics."

Reference

1. Kashiwagi, H., Morishima, N., Obuse, S., Isoshima, T., Akimoto, J. & Ito, Y. SARS-CoV-2 proteins microarray by photoimmobilization for serodiagnosis of the antibodies. *Bulletin of the Chemical Society of Japan* **94,** 2435–2443 (2021).

VIRAL GENOMICS

Diversity among DNA derived from viruses

Powerful genetic analysis tools reveal that people exhibit a surprising level of variation in virus-derived genetic sequences

Three RIKEN geneticists have discovered previously undetected snippets of genetic material from viruses lurking in our DNA[1]. The methods they developed for this discovery will be valuable for determining when this viral genetic material entered the human genome and also whether it can give rise to differences between individuals.

Roughly 8% of the human genome can be traced backed to retroviruses—viruses that reverse the normal order of genetic transcription, having an RNA genome that is reverse-transcribed into DNA and then inserted into the genome of the host cell. The most infamous retrovirus is the human immunodeficiency virus (HIV).

Roughly 8% of the human genome can be traced backed to retroviruses

While retroviruses can have devastating effects on human health, the viral genetic material inserted in our genomes can provide useful functions. For example, retroviral proteins expressed in the placenta enable humans and other mammals to give birth to live offspring rather than eggs.

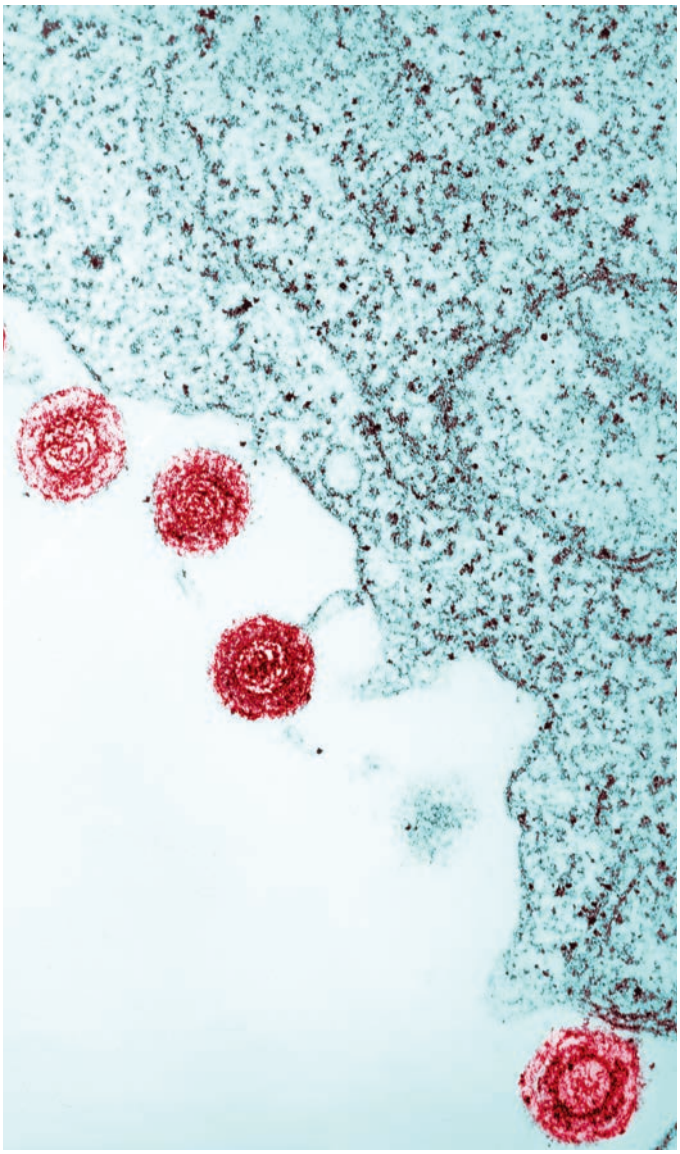
"During the course of human evolution our ancestors acquired many virus-derived sequences, some of which impart useful functions," says Shohei Kojima of the RIKEN Center for Integrative Medical Sciences (IMS). "I used to think that viruses were menaces, but some of their genetic sequences are essential for human development."

Over the last two decades, researchers have discovered much about the retroviral genetic sequences in the human genome, as well as viral-origin sequences derived from non-retroviruses. But it is unclear how much these sequences vary between people and whether variants could give rise to different human characteristics.

Now, Kojima, Anselmo Kamada and Nicholas Parrish, all at RIKEN IMS, have investigated virus-derived variations in 3,332 people from diverse populations using bioinformatic tools specially designed for the task.

They discovered that viruses are responsible for unexpected structural variations in the human genome. They also found rare variants in the germline that can be traced back to human herpesvirus 6.

Not all the viral genetic material they found had ancient origins, however. The trio discovered that some commonly used cell lines had been infected by viruses. "We think these sequences are likely caused by infection of the subject who donated their blood for human genetics research," says Parrish. "Strangely, the viruses don't usually infect B cells, which were used to make the cell lines we used, and so we don't fully understand how those viruses infected the cells."



A false-colored electron micrograph showing human herpesviruses 6 (HHV6; red circles) infecting a cell. RIKEN researchers have discovered new heritable structural variants derived from HHV6 in human genomes.

The team intends to explore the possible functions of the sequences they have identified. Some studies have suggested associations between viral genetic sequences and a higher risk of certain diseases, Parrish notes. "If that's true, how and why are they maintained in the human population?" he asks. "We want to see if they provide some benefit in addition to the cost." ●

Reference

1. Kojima, S., Kamada, A. J. & Parrish, N. F. Virus-derived variation in diverse human genomes. *PLoS Genetics* **17,** e1009324 (2021).

SPINTRONICS

Electric currents whirl by electron spins

Low-power information processing could be possible using a new method for converting between spin and charge currents

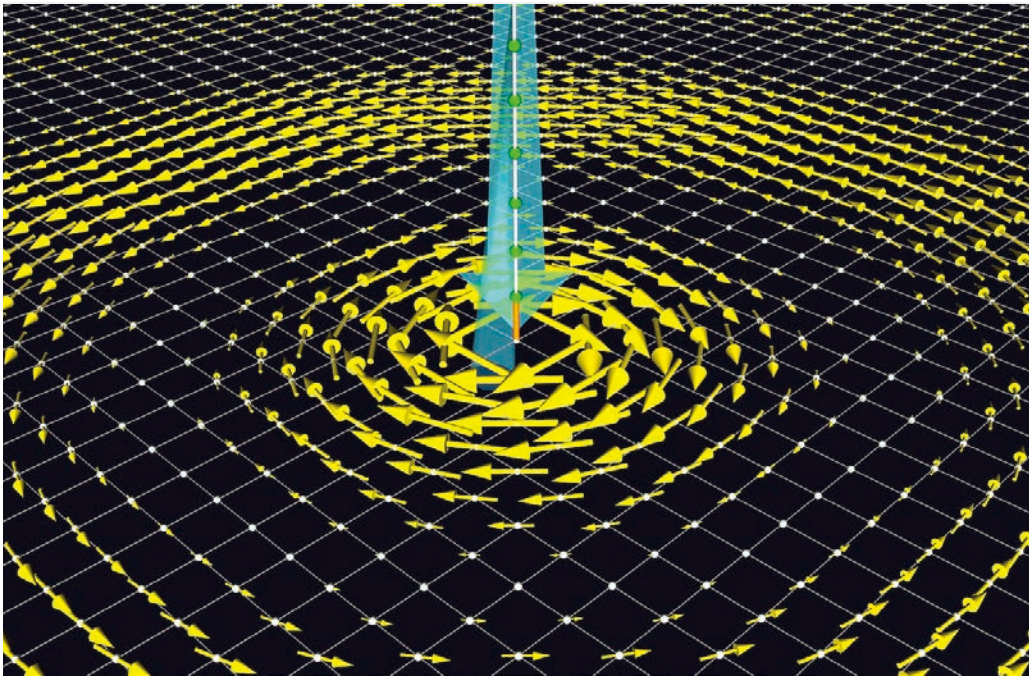
Energy-efficient spintronic devices are closer to being realized thanks to a new mechanism predicted by RIKEN physicists for converting between electrical current vortices and a spin current[1].

In addition to its negative electrical charge, an electron has a property known as spin, which can take one of two values: up or down. Just as an electron's charge is harnessed for information processing in electronics, so the flow of spin could be used in the emerging field of spintronics. Spintronics has the advantage of being more energy efficient than conventional electronics since, unlike an electrical current, a spin current does not generate Joule heat.

An efficient mechanism for converting an electronic current into a spin current and vice versa is crucial for developing spintronic devices.

Now, by using numerical simulations, Sadamichi Maekawa and Seiji Yunoki, both from the RIKEN Center for Emergent Matter Science, together with their co-workers have demonstrated the conversion of a spin current into a rotating vortex of charge current (see image).

The team hit on the idea of exploiting the Rashba effect—an unusual phenomenon discovered in 1959. It occurs at some surfaces or the interfaces between two materials, where the atomic structure is no longer symmetrical. The Rashba effect causes an electron's spin and orbital motion to interact.



The Rashba effect can convert a spin current (cyan arrow) into a charge current vortex (yellow arrows).

"Spin–orbit coupling is a relativistic effect that mixes the spin and orbital motion of electrons," explains Maekawa.

Our work shows the possibility of hydrodynamic spintronics

"Rashba coupling is important in oxide interface structures and in some two-dimensional materials, where it produces various novel topological phenomena that are useful for spintronics."

Maekawa and his co-workers used large-scale computer simulations to model what would happen when a spin current is injected into a Rashba material via a point-sized electrical contact. The team considered an arrangement in which the direction of the spins is perpendicular to the Rashba material, and their simulations indicated that this created a rotating flow of charge current. This is a result of a fundamental law that angular momentum must always be conserved, and thus the junction converts the injected spin angular momentum mostly into the orbital angular momentum of the current vortex.

"In electronics, the dynamics of electrons is everything: both diffusive flow and hydrodynamic, or turbulent, motion," says Maekawa. However, in spintronics only the diffusive flow of electrons has been considered so far. "With the generation of charge-current vortices, our work shows the possibility of hydrodynamic spintronics, which extends spintronics to include the hydrodynamic regime of electrons." ●

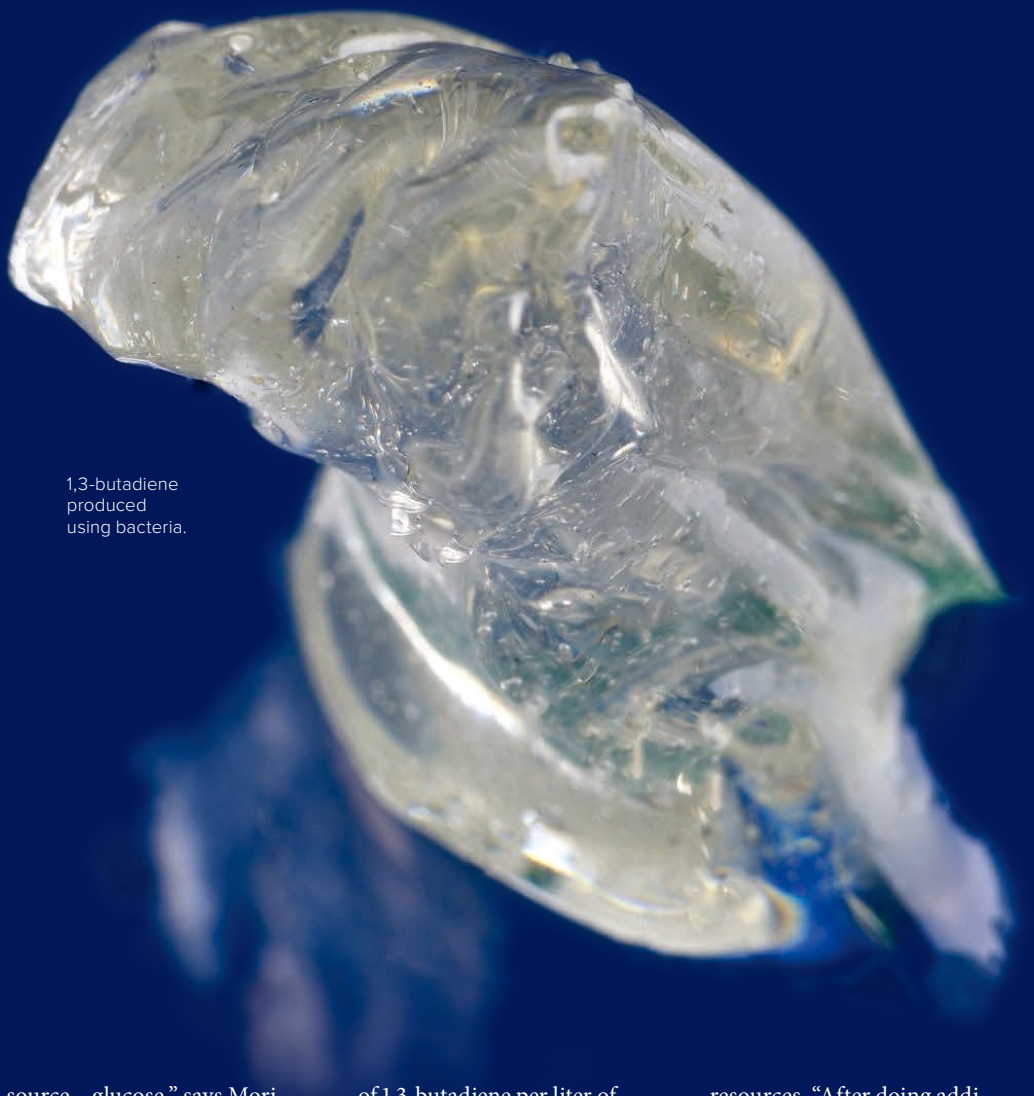
Reference

1. Lange, F., Ejima, S., Fujimoto, J., Shirakawa, T., Fehske, H., Yunoki, S. & Maekawa, S. Generation of current vortex by spin current in Rashba systems. *Physical Review Letters* **126,** 157202 (2021).

MICROBIAL ENGINEERING

Making rubber from microbes

Microbes are engineered to convert sugar into a chemical found in tires



1,3-butadiene produced using bacteria.

The future environmental footprint of the tire industry could substantially shrink thanks to a new ecofriendly way to harness bacteria to make a chemical used in synthetic rubber, found by four RIKEN researchers[1].

Each year, factories around the world churn out more than 12 million metric tons of the organic chemical 1,3-butadiene, which is used in tires, adhesives, sealants and other plastic and rubber products. They produce it by an energy-intensive process that relies on petroleum, which contributes to climate change.

Scientists have tried for many years to create 1,3-butadiene from more environmentally friendly starting materials by using specially designed microbes. But no one had previously succeeded in transforming a simple sugar such as glucose into the chemical in one easy step.

Now, by engineering bacteria to convert glucose into 1,3-butadiene, Yutaro Mori and his three co-workers, all at the RIKEN Center for Sustainable Resource Science, have devised a sustainable approach to rubber and plastic production.

"We constructed a novel artificial metabolic pathway and produced 1,3-butadiene directly from a renewable source—glucose," says Mori.

The RIKEN team succeeded in this long-sought goal by focusing on two parts of the biomanufacturing process. They first engineered a bacterial enzyme that could convert a biological compound that can be developed from glucose into 1,3-butadiene (see image). The researchers then modified a strain of the bacterium *Escherichia coli* to use this enzyme and produce the chemical. Since 1,3-butadiene is a gas at room temperature, it can be easily captured as the bacteria continue to divide and grow.

The technique still has a little way to go before it is ready for industrial application. The RIKEN team managed to synthesize only about 2 grams of 1,3-butadiene per liter of microbial brew. Much larger amounts will be needed for the method to be cost competitive with petroleum-based production.

But with some additional engineering and optimization, Mori believes his team will get there. They are now further tweaking the bacterium's metabolic pathways and enhancing the enzyme's efficiency. In collaboration with the companies Yokohama Rubber and Zeon Corporation, the RIKEN team is also scaling up the protocol to work with larger volumes of microbes.

The researchers are also exploring ways of harnessing the power of microbes to produce other chemicals from renewable resources. "After doing additional research into enzyme engineering and metabolic engineering, I hope we will be able to make a substantial contribution to realizing a low-carbon society and a sustainable bioeconomy in the not-so-distant future," says Mori.

For more on this study, see page 26.

Reference

1. Mori, Y., Noda, S., Shirai, T. & Kondo, A. Direct 1,3-butadiene biosynthesis in *Escherichia coli* via a tailored ferulic acid decarboxylase mutant. *Nature Communications* **12,** 2195 (2021).

SPINTRONICS

The battle for control of the electron

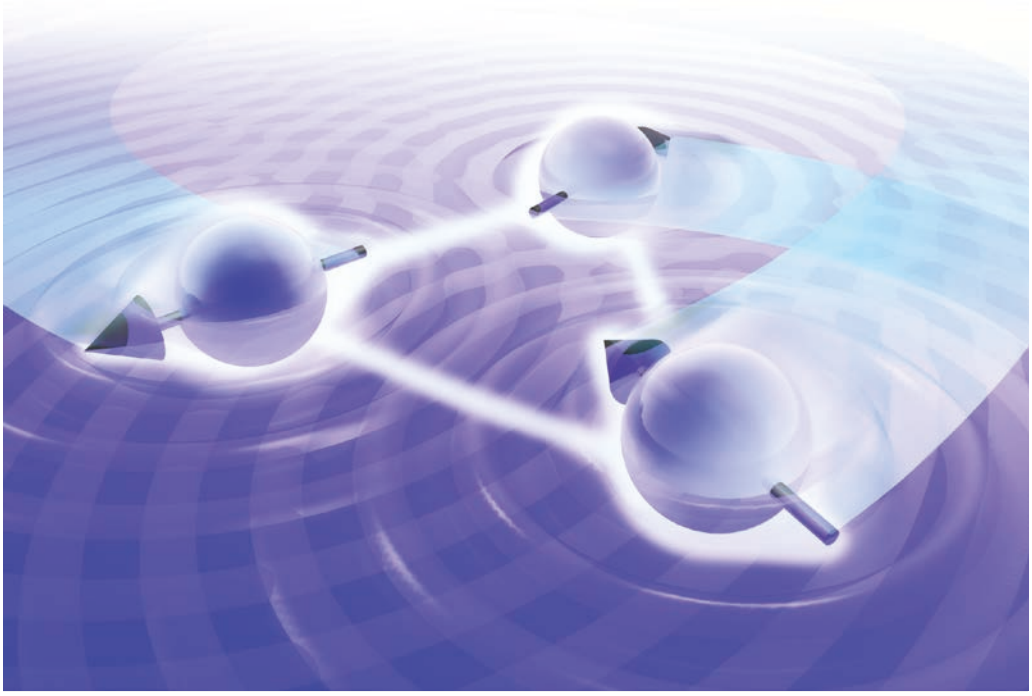
Competing interactions can spawn novel electronic states useful for future quantum technologies

In a finding that will help to identify exotic quantum states, RIKEN physicists have observed strongly competing factors that affect an electron's behavior in a high-quality quantum material[1].

Electrons have a property called spin, which can be crudely thought of as the rotation of an electron about an axis. As an electron moves, its motion and spin can become linked through an effect known as spin–orbit coupling. This effect is useful because it offers a way to externally control the motion of an electron depending on its spin—a vital ability for an emerging technology called spintronics, which is seeking to use electron spin to realize low-power-consumption information processing.

Spin–orbit coupling is a complex mix of quantum physics and relativity, but it becomes a little easier to understand by envisioning a round soccer ball. "If a soccer player kicks the ball, it flies on a straight trajectory," explains Denis Maryenko of the RIKEN Center for Emergent Matter Science. "But if the player gives the ball some rotation, or spin, its path bends." The ball's trajectory and its spinning motion are connected. If its spinning direction is reversed, the ball's path will bend in the opposite direction.

Unlike soccer balls, electrons also interact with each other: two negatively charged particles will repel each other, for example. This mutual repulsion and the spin–orbit interaction compete with each other: the former can act to align an electron's spin with that of other electrons, whereas the latter tries to align an electron's spin with its motion.



Electron spin is influenced by both the electron's motion, via spin–orbit coupling, and interactions with other electrons, through the Coulomb effect. (Image prepared by Ms. Mari Ishida of RIKEN.)

"This interplay has recently attracted a lot of interest, since it could lead to the emergence of novel electronic and spin phases, which may be used in future quantum technologies," says Maryenko. "It is thus important to understand the fundamentals of the interplay." But it is incredibly difficult to identify both effects at the same time.

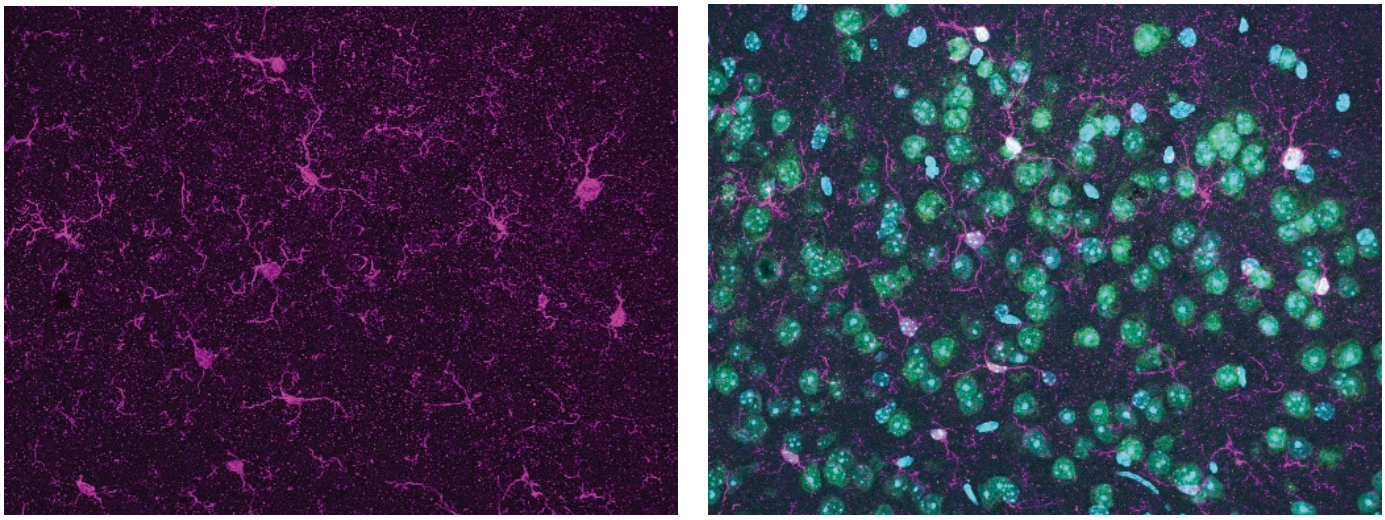
Now, Maryenko and his colleagues have succeeded in disentangling the two effects.

They looked at electrons trapped between two semiconductors, magnesium zinc oxide and zinc oxide. Since the system had very few atomic impurities, there was a strong interaction between electrons. And the researchers could control the strength of the spin–orbit coupling by varying the magnesium content. "We looked carefully at how the sample resistance changed when we applied a magnetic field," says Maryenko. In this way, they were able to identify signatures of both spin–orbit and the mutual repulsion due to the electrons' charges.

This high-quality material system thus represents a great resource for testing theoretical predictions and it opens a path to develop spintronic phenomena in strong-electron-correlation regimes. ●

Reference

1. Maryenko, D., Kawamura, M., Ernst, A., Dugaev, V. K., Sherman, E. Ya., Kriener, M., Bahramy, M. S., Kozuka, Y. & Kawasaki, M. Interplay of spin–orbit coupling and Coulomb interaction in ZnO-based electron system. *Nature Communications* **12,** 3180 (2021).



The G9a-like protein (GLP) controls histone and DNA (cyan) led translation of proteins related to brain development in neural cells (green). Increasing GLP in the brains of juvenile mice with an autistic-like neural disorder can eliminate symptoms. Researchers hypothesize that less-activated microglial cells (left magenta) lowers inflammation.

NEURODEVELOPMENTAL DISORDERS

A genetic brain disorder reversed after birth in mice

Boosting levels of a protein in the brains of juvenile mice with an autistic-like neural disorder can eliminate symptoms

Kleefstra syndrome, a genetic disorder that leads to intellectual disability, can be reversed after birth in a mouse model of the disease, RIKEN researchers have found[1]. This raises the possibility that the condition may be treatable in humans.

A person usually receives two good copies of most genes, one from each parent. In Kleefstra syndrome, one copy of the *EHMT1* gene is mutated or missing. This results in the person having half the usual amount of G9a-like protein (GLP)—a protein that controls genes related to brain development via a process called H3K9 methylation. Insufficient GLP leads to reduced H3K9 methylation, and neural connections do not develop normally, resulting in intellectual disability and autistic-like symptoms.

"We still don't know if Kleefstra syndrome is a curable disease after birth or how this epigenetic dysregulation leads to the neurological disorder," says Yoichi Shinkai of the RIKEN Cluster for Pioneering Research.

Reasoning that extra GLP might be an effective treatment, Shinkai and his co-workers investigated mice that were engineered to have only one good copy of the *EHMT1* gene. The brains of these mice exhibited characteristics of the human condition, including 40% less GLP and 30% less H3K9 methylation. The mice also displayed several behaviors seen in humans with Kleefstra syndrome, such as reduced movement and greater anxiety.

The team artificially induced GLP production throughout the whole brains of some mice and only to adult neurons in the brains of other mice. In both cases, treatment in juvenile mice quickly restored GLP and H3K9 methylation levels in the brain. Behavior improved several weeks later, but only when GLP was increased throughout the whole brain.

The researchers investigated why this treatment only fully worked when GLP was increased throughout the brain. They conjectured that the disorder might abnormally activate microglia cells in the brain, which control immune responses such as inflammation. The team found a well-known inflammatory response in the model mice brains, along with larger numbers of activated microglial cells. Knocking out a key protein involved in the inflammatory response reversed some of the brain abnormalities caused by inflammation but did not alter the behavior.

"This means that brain inflammation is only part of the story," explains first author Ayumi Yamada. "To have a complete understanding of the disease, we need to find out what happens in other non-neural cells when we increase GLP."

The next step is to determine if it also occurs in the human condition. Shinkai believes the chances are high. "Although we don't yet know if our findings will be applicable to patients with Kleefstra syndrome, we have shown that a cure after birth is possible," he says. ●

Reference

1. Yamada, A., Hirasawa, T., Nishimura, K., Shimura, C., Kogo, N., Fukuda, K., Kato, M., Yokomori, M., Hayashi, T., Umeda, M. *et al.* Derepression of inflammation-related genes link to microglia activation and neural maturation defect in a mouse model of Kleefstra syndrome. *iScience* **24,** 102741 (2021).

CHROMOSOME DYNAMICS

Untangling the details of chromatid assembly

An assay that replicates early mitosis reveals how one enzyme first untangles and then winds up chromosomal DNA into compactly organized structures

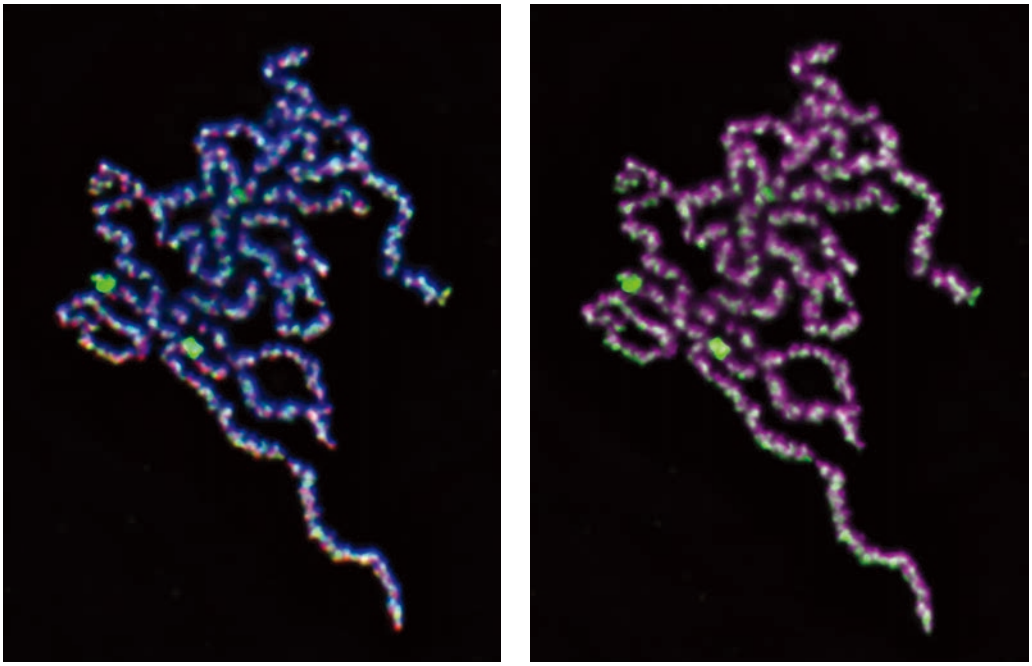
Two RIKEN researchers have discovered how, during cell division, one enzyme helps facilitate the tightly coordinated reorganization of chromosomal DNA into compact structures that can be evenly divided amongst the two resulting daughter cells[1].

Ever since the dynamics of chromosomes undergoing mitosis—the process by which a cell splits into two identical daughter cells—were first described about 140 years ago, scientists have been trying to better understand the intricacies of this process.

In the run-up to mitosis, each chromosome undergoes replication to form a pair of identical chromatids, with one chromatid slated for each daughter cell. By the time division begins, these two long chains of DNA have assembled into a pair of distinct, highly condensed structures, which are temporarily tethered to each other at their centers.

In 2015, Keishi Shintomi and Tatsuya Hirano, both of the RIKEN Chromosome Dynamics Laboratory, developed an assay that allowed them to induce chromatid assembly by combining isolated sperm nuclei with a mixture of six proteins. "Reconstituting a cellular process in a test tube using purified components is one of the most powerful approaches for dissecting and comprehending that process," explains Hirano.

While this technique has given valuable insights into the early stages of mitosis, critical elements of the chromatid assembly process remained poorly understood. In particular, Shintomi and Hirano sought to discover the role of topoisomerase IIα—one of the six proteins required for this assay—and set about optimizing their method in order to better characterize the function of this enzyme.



A cluster of mitotic chromatids made by combining chromosomal DNA with six purified proteins. The chromatids are bound with many topoisomerase IIα molecules (labeled green in both images); DNA is labeled blue (left) and magenta (right); a chromatid-binding protein complex called condensin is labeled red (left).

Their experiments revealed that topoisomerase IIα plays two roles in chromatid assembly. "The first is to dissolve entanglements between chromatids," says Shintomi. "While the second is to generate intra-chromatid entanglements that support condensation."

The disentangling function of topoisomerase IIα has been reported before, but the latter activity was unexpected. It appears to occur only when the enzyme is in a highly crowded environment with closely packed DNA strands. The two researchers were also able to identify a critical domain in topoisomerase IIα that directly coordinates the 'knotting up' of DNA during the chromatid condensation process.

Shintomi and Hirano are now keen to characterize other molecules that interact with topoisomerase IIα as part of the condensation process, including a class of DNA-binding proteins called linker histones. These proteins were absent in the researchers' original chromatid assembly assay, but the present study indicates that they interact with the same chromosomal regions that ultimately get targeted for proper actions of topoisomerase IIα.

"Such efforts will shed new light on the previously unrecognized action of linker histones and fierce competition among chromosomal proteins in the crowded environments of mitotic chromosome assembly," says Hirano. ●

Reference

1. Shintomi, K. & Hirano, T. Guiding functions of the C-terminal domain of topoisomerase IIα advance mitotic chromosome assembly. *Nature Communications* **12,** 2917 (2021).

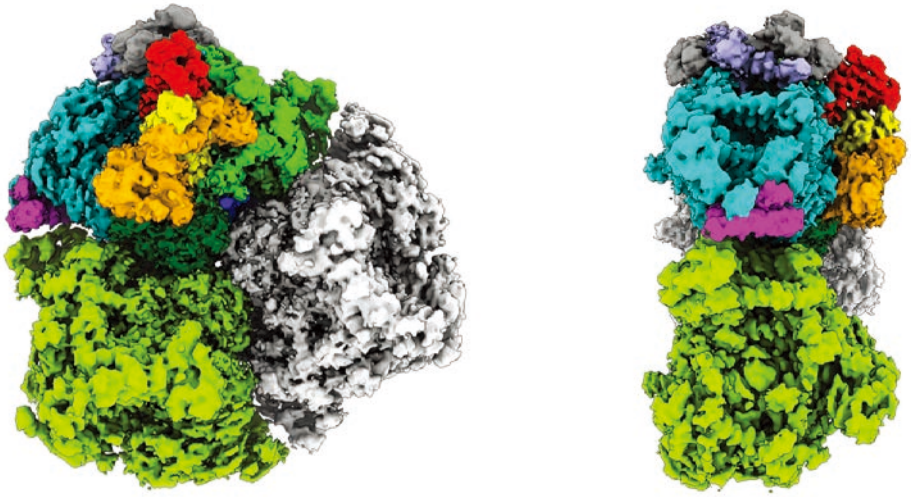
PHOTOSYNTHESIS

How a blue–green bacterium thrives on far-red light

High-resolution images of a form of unique pigments found in a photosynthetic membrane protein complex of a marine bacterium reveal how it can live in low-light conditions

A high-resolution structural analysis by RIKEN biochemists of photosystem I, which contains chlorophyll *d* and pheophytin *a*, the light-absorbing pigments found in a marine bacterium, could help scientists discover how the microbe survives in the low-energy light conditions of the deep sea[1].

In photosynthesis, plants, algae and some bacteria harness energy from sunlight to create oxygen and carbohydrates from carbon dioxide and water. Chlorophyll, the pigment responsible for giving plants their green color, plays a major role in absorbing sunlight and converting it into a useful form of chemical energy.



A cryo-electron microscopy density map of *Acaryochloris marina* photosystem I reveals structural elements that allow it to convert low-energy light into chemical energy.

It's possible that life beyond Earth could exist in similar low-light environments

Scientists used to believe that photosystem I, the membrane protein complex present in all aerobic organisms, utilized a form of chlorophyll called chlorophyll *a* for photosynthesis. But that changed when a marine cyanobacterium was discovered in the 1990s that employs a different form of chlorophyll; *Acaryochloris marina* uses chlorophyll *d* to harness far-red wavelengths of light, whose energy was previously considered to be too low to be useful for typical organisms.

"How *A. marina* uses low-energy light for photosynthesis has been a long-standing question," notes Koji Yonekura, who leads the Biostructural Mechanism Group at the RIKEN SPring-8 Center.

Now, Tasuku Hamaguchi, Keisuke Kawakami, Yonekura and their colleagues have shed light on this question by analyzing the structure of the photosystem I reaction center—the part of chlorophyll that converts sunlight into a form of chemical energy that can be used by the rest of the photosynthetic machinery—of chlorophyll *d* in *A. marina* (see image). They realized this by using cryo-electron microscopy at a higher resolution than has been applied to look at these protein complexes before.

The researchers' analysis revealed that one of the light-harvesting pigments is pheophytin *a*, a metal-free chlorin that differs from other type I reaction centers. This exquisite combination of pheophytin *a* and chlorophyll *d* helps to explain some ways that the cyanobacterium can efficiently harness the low energy of far-red light for photosynthesis.

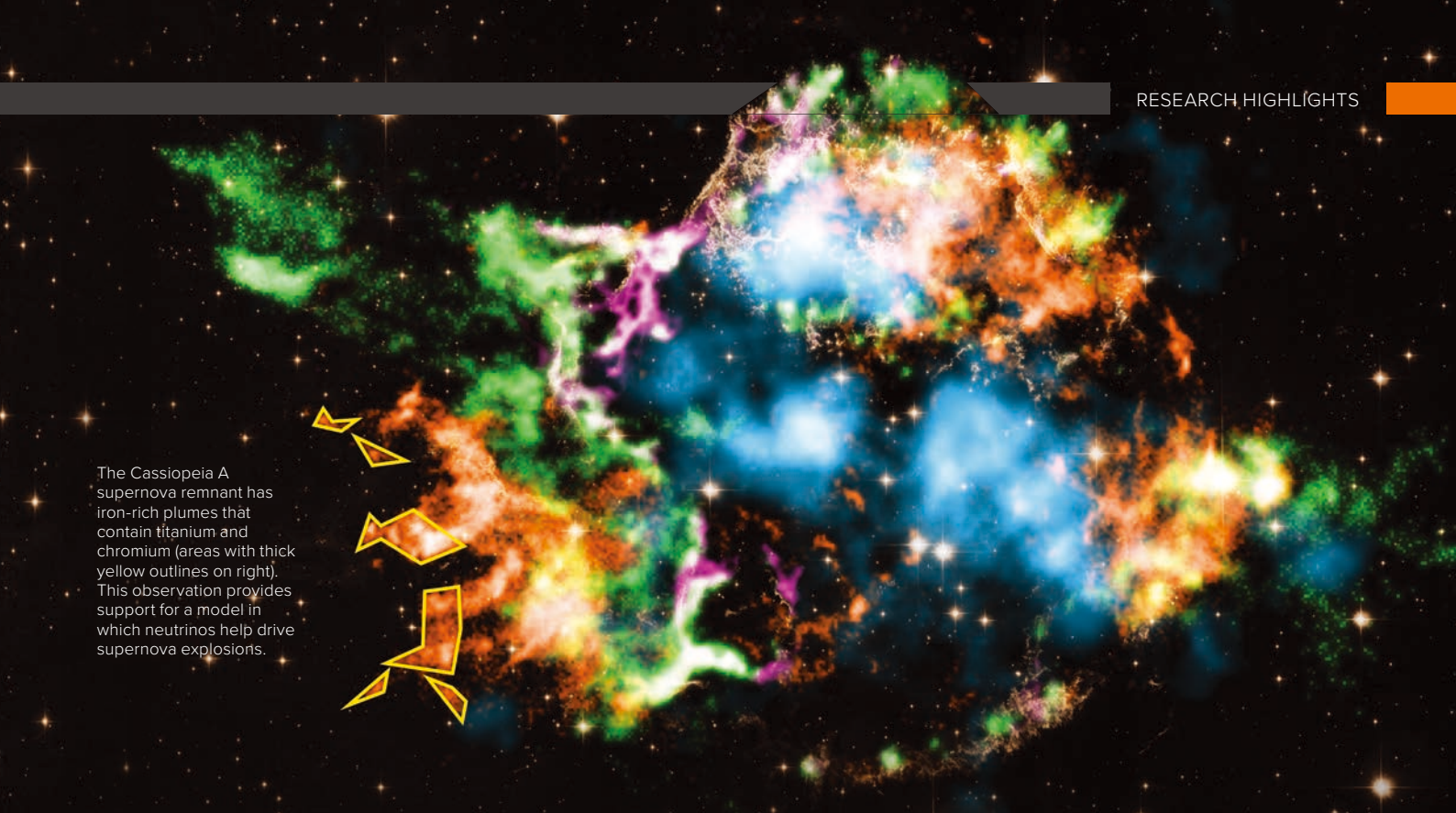
The team's findings could help us better understand how photosynthetic organisms are able to survive in extremely low-light environments, both here on Earth and potentially beyond. *A. marina* is found in extremely low-light regions of the ocean, and it's possible that life beyond Earth could exist in similar low-light environments.

The researchers realized the unprecedented resolution in this study by using a cryogenic electron microscopy producing superior high-resolution images with a highly coherent electron beam.

The team intends to continue their research of this mysterious organism and its method of converting light into chemical energy. They are also applying the same technique to investigate other biological macromolecules. "We're performing high-resolution single-particle cryogenic electron microscopy of other biologically important targets," says Yonekura. ●

Reference

1. Hamaguchi, T., Kawakami, K., Shinzawa-Itoh, K., Inoue-Kashino, N., Itoh, S., Ifuku, K., Yamashita, E., Maeda, K., Yonekura, K. & Kashino, Y. Structure of the far-red light utilizing photosystem I of *Acaryochloris marina*. *Nature Communications* **12,** 2333 (2021).



The Cassiopeia A supernova remnant has iron-rich plumes that contain titanium and chromium (areas with thick yellow outlines on right). This observation provides support for a model in which neutrinos help drive supernova explosions.

SUPERNOVAE

Cataclysmic explosions sustained by ghost-like particles

Supernova explosions are sustained by neutrinos from neutron stars, a new observation suggests

A model for supernova explosions first proposed in the 1980s has received strong support from the observation by RIKEN astrophysicists of titanium-rich plumes emanating from a remnant of such an explosion[1].

Some supernova explosions are the death throes of stars that are at least eight times more massive than our Sun. They are one of the most cataclysmic events in the Universe, unleashing as much energy in a few seconds as the Sun will generate in 10 billion years.

In contrast, neutrinos are among the most ethereal of members of the elementary-particle zoo—they are at least 5 million times lighter than an electron and about 10 quadrillion of them flit through your body every second without interacting with it.

It's hard to conceive that there could be any connection between supernovas and neutrinos, but a model advanced in the 1980s proposed that supernovas would not occur if it were not for the heating provided by neutrinos.

This type of supernova starts when the core of a massive star collapses into a neutron star—an incredibly dense star that is roughly 20 kilometers in diameter. The remainder of the star collapses under gravity, hits the neutron star, and rebounds off it, creating a shockwave.

However, many supernova models predict that this shockwave will fade before it can escape the star's gravity. Factoring in heating generated by neutrinos ejected from the neutron star could provide the energy needed to sustain shockwaves and hence the supernova explosion.

Now, Shigehiro Nagataki at the RIKEN Astrophysical Big Bang Laboratory, Toshiki Sato, who was at the RIKEN Nishina Center for Accelerator-Based Science at the time of the study, and co-workers have found strong evidence supporting this model by detecting titanium and chromium in iron-rich plumes of a supernova remnant.

The neutrino-driven supernova model predicts that trapped neutrinos will generate plumes of high-entropy material, leading to bubbles in supernova remnants rich in metals such as titanium and chromium. That is exactly what Nagataki and his team saw in their spectral analysis based on observational data from the Chandra X-ray Observatory on Cassiopeia A (see image), a supernova remnant from about 350 years ago. This observation is strong confirmation that neutrinos play a role in driving supernova explosions.

"The chemical compositions we measured strongly suggest that these materials were driven by neutrino-driven winds from the surface of the neutron star," says Nagataki. "Thus, the bubbles we found had been conveyed from the heart of the supernova to the outer rim of the supernova remnant."

Nagataki's team now intends to perform numerical simulations using supercomputers to model the process in more detail. "Our finding provides a strong impetus for revisiting the theory of supernova explosions," Nagataki adds.

Reference

1. Sato, T., Maeda, K., Nagataki, S., Yoshida, T., Grefenstette, B., Williams, B. J., Umeda, H., Ono, M. & Hughes, J. P. High-entropy ejecta plumes in Cassiopeia A from neutrino-driven convection. *Nature* **592,** 537–540 (2021).

Underwater photographs appear blue because orange/red light is preferentially absorbed over blue light. One consequence of this is that algae have more blue-light-detecting photoreceptors than orange/red-detecting ones. RIKEN researchers have found a single photoreceptor in a green picoplankton that detects light in both ranges.

PHOTORECEPTORS

Picoplankton sees light on both sides of the spectrum

A photoreceptor that can sense a wide range of the light spectrum may help oceanic picoplankton live at different depths

The discovery by a RIKEN-led team of a single photoreceptor that can detect orange, far-red, and blue light will provide new insights into the evolutionary history of plant photoreceptors[1].

Photoreceptors play important roles in many aspects of plant biology, from photosynthesis to the timing of developmental stages. In the oceans, since blue light penetrates deeper than red light, most marine algae and chlorophytes have a preponderance of blue-light-detecting photoreceptors called cryptochromes rather than phytochromes, which respond to mainly red and far-red light.

Now, a team led by Minami Matsui of the RIKEN Center for Sustainable Resource Science (CSRS) has discovered a single photoreceptor in a green picoplankton that responds to light in both ranges.

The team stumbled upon a chimeric gene—a gene that forms through the merger of two protein-encoding genes—that encodes a two-domain fusion of cryptochrome and phytochrome while investigating the effect of the Great East Japan Earthquake in 2011 on ocean life along the eastern coast of Japan. They were so surprised that they thought it was an error in the data. "We initially thought this fusion gene was an artefact, but it turned out to be real," explains Matsui.

The researchers dubbed the photoreceptor dualchrome1 due to its ability to detect both orange/far-red and blue light. They found that *Pycnococcus*, a widely distributed green picoplankton, and its relatives possess dualchrome1. *Pycnococcus* belongs to a large group of mainly marine green algae that are thought to represent the last common ancestor of all green plants.

In the model land plant *Arabidopsis*, phytochromes and cryptochromes are encoded by different genes, but interact under certain conditions. For reasons as yet unclear, instead of having two separate photoreceptors, *Pycnococcus* retains dualchrome1 as a chimeric protein.

It is unclear how dualchrome1 benefits *Pycnococcus*, but Matsui suggests a couple of possibilities: "In the ocean, light conditions change with depth, diurnally and seasonally; accordingly, dualchrome1 might sense ocean depth, or time and/or season." The team intends to make knock-out strains so that they can better understand the function of dualchromes and how they contribute to the ecological success of these tiny oceanic organisms. "This is important because green picoplankton sequester atmospheric carbon dioxide, thereby helping mitigate global warming," Matsui adds.

"The ability of dualchrome1 to sense orange, far-red and blue light could help us understand how three wavelengths of light are transduced in this microalga to respond to environmental changes," says Yuko Makita, also of CSRS and the first author of the study. ●

Reference

1. Makita, Y., Suzuki, S., Fushimi, K., Shimada, S., Suehisa, A., Hirata, M., Kuriyama, T., Kurihara, Y., Hamasaki, H., Okubo-Kurihara, E. *et al.* Identification of a dual orange/far-red and blue light photoreceptor from an oceanic green picoplankton. *Nature Communications* **12,** 3593 (2021).

DEVELOPMENTAL BIOLOGY

A 'gatekeeper' that regulates bone formation

An investigation of a rare developmental disorder helps clarify how signals that regulate bone formation enter the cellular nucleus

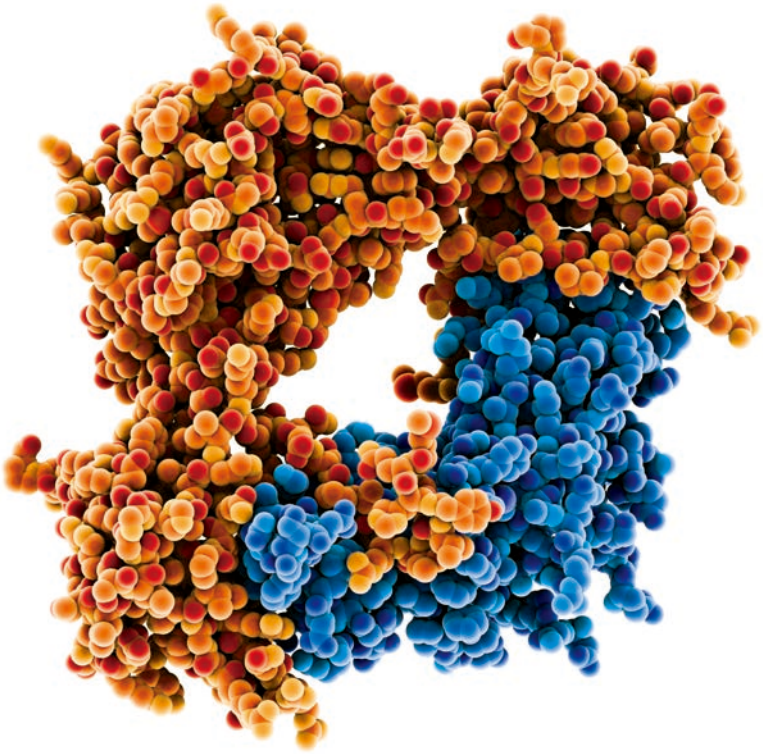
Important insights into the cellular processes underlying healthy bone formation and development have been gleaned by a RIKEN-led study into a previously unknown bone disorder[1].

Many bone disorders have genetic origins. Advances in genetics are helping scientists track down the mutations responsible for them.

Shiro Ikegawa of the RIKEN Center for Integrative Medical Sciences has been working on the genetic cause of bone disorders. In 2000, he co-founded the Japanese Skeletal Dysplasia Consortium to identify biological factors that contribute to bone malformation. "It's become a global network," says Ikegawa, "and has so far contributed to the discovery of more than 30 disease genes for bone disorders."

The consortium recently came into contact with four families in India with children who exhibited similar bone malformations, including unusually short limbs and skull deformities. These manifestations differed from those of other bone disorders identified to date, and the condition was named Ikegawa-type craniotubular dysplasia.

Ikegawa's team investigated the underlying genetic cause for it and found that all affected individuals had loss-of-function mutations affecting both copies of a gene called *TMEM53* (for transmembrane protein 53). Little was known about the protein encoded by this gene, except that it is embedded within the membrane that separates the contents of the nucleus from the cytosol, and so the researchers probed its cellular function.



A bone morphogenetic protein (BMP; orange) in complex with the secreted antagonist Noggin (blue). RIKEN researchers have found that loss of the gene *TMEM53* leads to excessive BMP signaling, resulting in poorly controlled bone formation.

"Finding a new skeletal phenotype in humans caused by mutations in a gene with unknown function was a golden opportunity to uncover a new biological mechanism of bone development and metabolism," says Long Guo, a senior researcher in Ikegawa's lab.

Initial experiments in mice confirmed that disrupting the *TMEM53* gene produces bone abnormalities similar to those seen in human patients. The researchers attributed this to increased formation of osteoblasts, the cells responsible for bone production. Osteoblast development depends on molecules belonging to the bone morphogenetic protein (BMP) family. BMP-induced signaling leads to activation of another set of proteins known as SMADs, which reside in the cytosol but enter the nucleus to switch on osteoblast-specific genes.

It has long been unclear precisely how SMADs enter the nucleus, but Ikegawa's team was able to show that TMEM53 appears to be an important gatekeeper, limiting this entry. The loss of TMEM53 thus results in excessive BMP signaling activity, leading to poorly controlled bone formation.

"This suggests a hitherto ignored but probably broad relationship between nuclear membrane proteins and bone density," says Guo, adding that their group is now looking for other proteins that collaborate with TMEM53 to control SMAD access to the nucleus. ●

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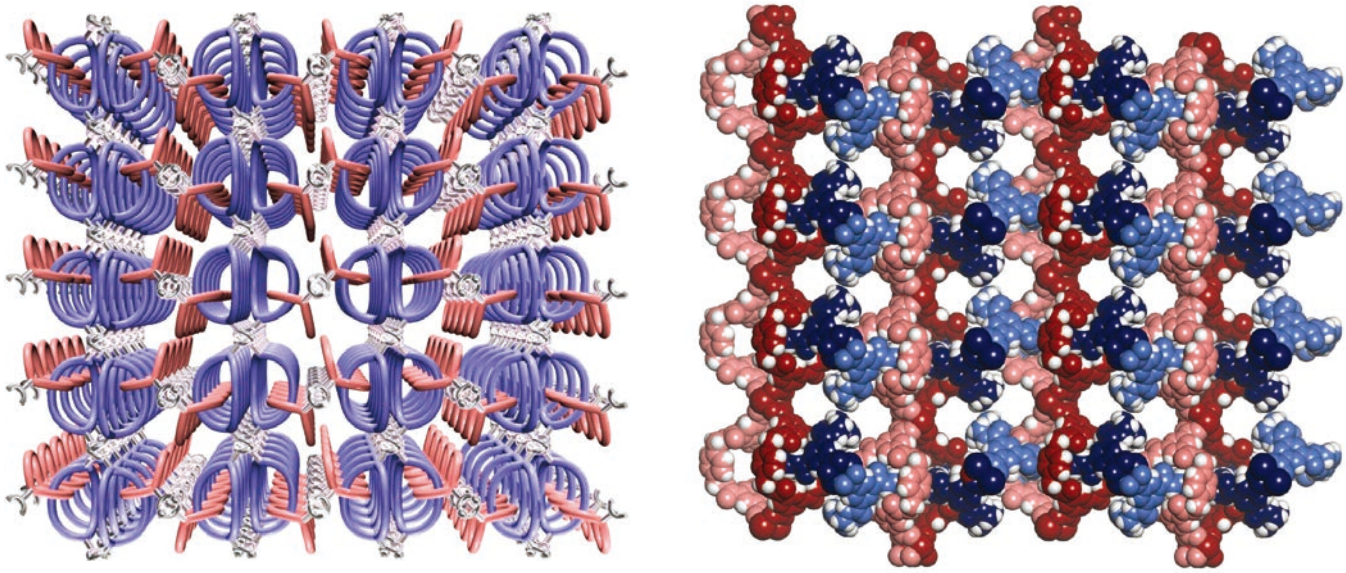

The crystal structure of a metal–organic crystal consisting almost entirely of catenanes. The backbones made of interlocking catenane molecules are shown side on.

CATENANES

Rings impart springiness to crystal

A crystal made up of interlocking rings exhibits surprising springiness

A soft, sponge-like crystal that could be used in materials that trap and release carbon dioxide and other gases has been created by a RIKEN-led team[1]. Many of the unusual properties of the material, including its squishiness, stem from its backbones of interlocking molecular rings known as catenanes.

A catenane is a molecule consisting of two or more mechanically interlocking rings. Resembling rings that magicians use, these rings can slide along each other, altering the shape of the molecule and giving rise to interesting material properties. Catenanes are found in nature, where they often function as molecular machines.

Two-dimensional chains of catenanes have been created previously, but three-dimensional crystals made up of these molecules have not been realized before.

Now, by carefully controlling the mechanical bonds between catenanes, a team led by Hiroshi Sato of the RIKEN Center for Emergent Matter Science has created a metal–organic crystal consisting almost entirely of catenanes.

The shape of the structure changed as the guest molecules entered or exited it.

The researchers examined the crystal's structure using single-crystal x-ray diffraction. As they had anticipated, catenanes accounted for more than 90% of the crystal by weight and the catenanes formed the backbones of the structure. The material was porous, containing holes that could adsorb a liquid or gas. The shape of the structure changed as the guest molecules entered or exited it.

The team also studied the material's mechanical properties using a nano-indenter, which measures how a material responds when a nanoscale diamond rod is pressed into it. The material deformed very easily—in the two dimensions at right angles to the catenane backbones, it had a softness comparable to that of polypropylene, a plastic used for packaging. When the force was removed, it sprung back to its original shape, without any damage, which differs from the response of typical crystalline materials.

When the researchers compressed the material, they were surprised to find that it compressed most in the third dimension, parallel to the catenane backbones. It could contract by up to 5% on compression without any structural damage. The team was able to explain this squishiness by showing that the rings of the catenane molecules were slipping, allowing the material to compress.

The team considers their material is promising for various practical applications such as adsorbing gases. "We believe these results could lead to the creation of innovative porous materials that can adsorb and desorb gas molecules such as carbon dioxide simply by pinching and releasing them with our fingers," says Sato. ●

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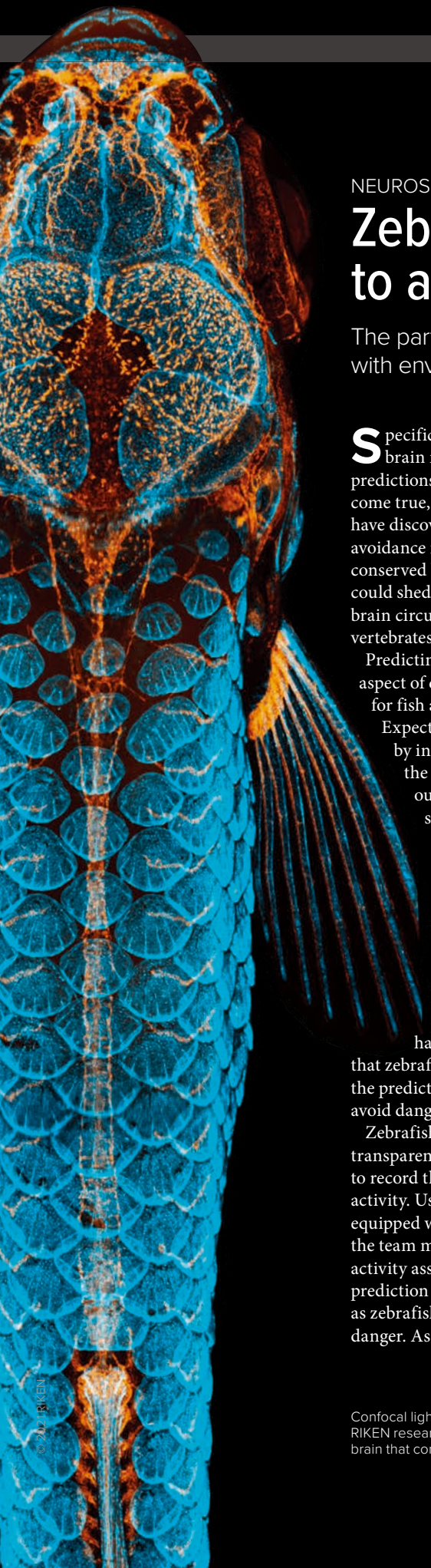

NEUROSCIENCE

Zebrafish predict the future to avoid virtual danger

The part of the zebrafish brain that compares present reality with envisioned expectations has been identified.

Specific neurons in the brain monitor whether predictions made by zebrafish come true, RIKEN researchers have discovered[1]. Because risk avoidance is an evolutionarily conserved behavior, this finding could shed light on important brain circuits shared across all vertebrates, including humans.

Predicting the future is a key aspect of decision making for fish and humans alike. Expectations are formed by internal models of the environment in our brains. When real situations differ from our expectations, the brain lets us know by generating prediction errors.

Now, researchers at the RIKEN Center for Brain Science and collaborators have discovered that zebrafish try to keep the prediction error low to avoid danger.

Zebrafish are small and transparent, making it easy to record their whole-brain activity. Using an aquarium equipped with virtual reality, the team monitored brain activity associated with prediction error in real time as zebrafish learned to avoid danger. As the fish swam virtually, they were presented with a choice between red or blue virtual-reality zones, and they learned to associate the colors with danger or safety.

Zebrafish try to keep the prediction error low to avoid danger

As zebrafish learned to avoid danger in virtual reality, the time-lapse change in their brain activity was recorded, leading to the discovery of the neurons responsible for representing the prediction error. Distinct active populations of neurons emerged as fish started to learn that choosing the virtual route through blue surroundings led to danger and choosing the red route meant safety. Subsequent reversal of this association (with red signifying danger rather than blue) caused these neurons to become inactivated. This indicated that the neurons were probably coding a behavioral rule, not simply the color the fish were seeing.

In another experiment, the scenery remained unchanged even when a fish moved its tail. For example, when a fish tried to swim forward by flipping its tail, its view did not recede as expected. This revealed a group of neurons that was activated only when actions the fish thought would allow them to reach safety failed to have the expected result.

"We think this population of neurons is encoding a prediction error in the brain, comparing the actual view of their surroundings with the predicted view that they have learned would get them to safety if they behaved in a certain way," explains lead author Makio Torigoe.

"Every animal has to make predictions for its future based on what it has learned before," adds team leader Hitoshi Okamoto. "Now we know how these predictions are compared to what animals actually encounter in the world, and which parts of the zebrafish brain drive the subsequent decision making." ●

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Confocal light micrograph showing the top view of a zebrafish. RIKEN researchers have identified the region of the zebrafish brain that compares present reality with expectations.

Stefan Ulmer working on the BASE experiment at CERN. His team has developed a new method for cooling fundamental particles at a distance.

ANTIMATTER

Cooling at a distance

A new method for cooling trapped fundamental particles could find wide application in particle physics

Efforts to solve the enigma of why the Universe contains almost no antimatter have received a boost by a new method developed by a RIKEN-led team for cooling protons and their antimatter counterparts, antiprotons[1].

The standard model of particle physics has been wildly successful in describing the zoo of fundamental particles, but it predicts there should be equal amounts of matter and antimatter in the Universe, whereas observations indicate that matter far outweighs antimatter. Scientists are trying to determine whether this gross imbalance can be linked to miniscule differences in certain properties of matter and antimatter.

A promising avenue is exploring whether protons and antiprotons have different magnetic moments, something that the BASE experiment at CERN is investigating. Using a Penning trap—a sophisticated device that can capture and detect a single particle—the BASE team had previously found that the magnetic moments of the proton and the antiproton are the same to nine significant figures.

For precise magnetic moment measurements, the particles need to be cooled to close to absolute zero. In previous experiments, such temperatures were realized using a time-consuming technique that involved a lot of hit and miss.

Now, the BASE team has cooled a single proton in a Penning trap by coupling the particle to a cloud of laser-cooled beryllium ions that were located 9 centimeters away in another Penning trap. This cooling at a distance was realized by connecting the two traps using a circuit called a resonator. When the natural oscillation frequency of the proton matches that of the beryllium ions, the ions cool the resonator, which in turn cools the proton.

This demonstration is an important first step. "Further development of this method will ultimately lead to an ideal spin-flip experiment, in which a single low-temperature proton will be prepared within just a few seconds," says Christian Smorra of the RIKEN Fundamental Symmetries Laboratory (FSL). "This will allow us to determine the particle's spin state in just one measurement that takes about a minute."

"This is considerably faster than our previous magnetic moment measurements, and will improve both sampling statistics and the resolution of our systematic studies," adds Matthew Bohman, who is also at the FSL.

"The reported achievement has applications not only in proton/antiproton magnetic moment measurements," says Stefan Ulmer of the FSL. "It adds general new technology to the toolbox of precision Penning-trap physics and also has potential applications in other nuclear magnetic moment measurements, ultraprecise comparisons of charge-to-mass ratios in Penning traps, or even in enhancing the production of antihydrogen."

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QUANTUM COMPUTING

Silicon-based spin qubits form a triad

A three-qubit entangled state has been realized in a fully controllable array of spin qubits in silicon

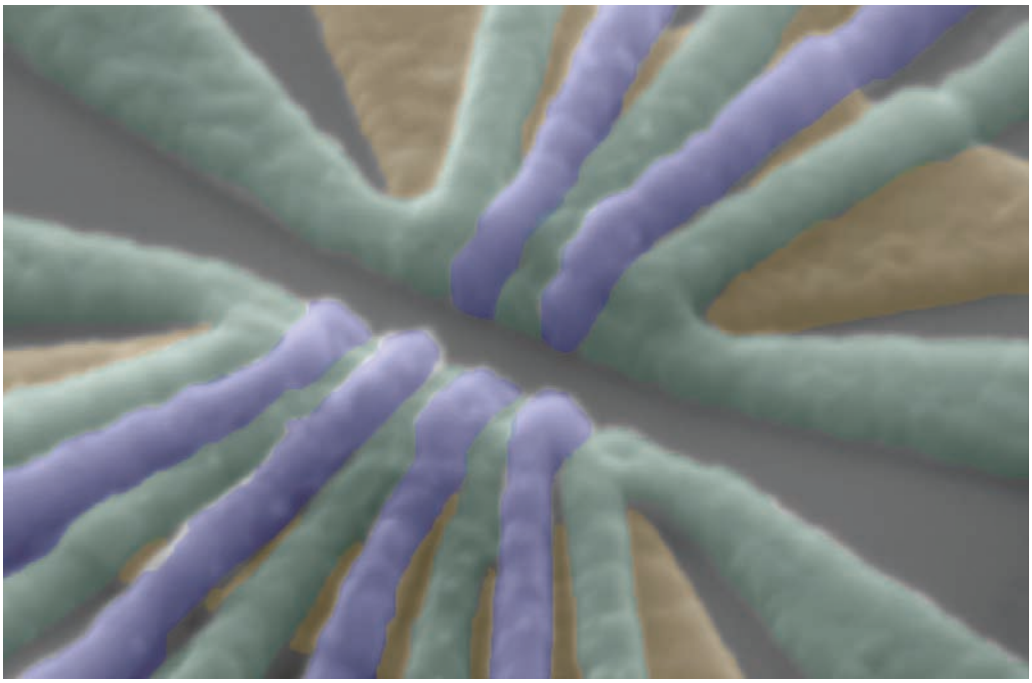
An all-RIKEN team has increased the number of silicon-based spin qubits that can be entangled from two to three, highlighting the potential of spin qubits for realizing multi-qubit quantum algorithms[1].

Quantum computers have the potential to leave conventional computers in the dust when performing certain types of calculations. They are based on quantum bits, or qubits, the quantum equivalent of the bits that conventional computers use.

Although less mature than some other qubit technologies, tiny blobs of silicon known as silicon quantum dots have several properties that make them highly attractive for realizing qubits. These include long coherence times, high-fidelity electrical control, high-temperature operation and great potential for scalability. However, to usefully connect several silicon-based spin qubits, it is crucial to be able to entangle more than two qubits, an achievement that had evaded physicists until now.

Seigo Tarucha and five colleagues, all at the RIKEN Center for Emergent Matter Science, have now initialized and measured a three-qubit array in silicon with high fidelity (the probability that a qubit is in the expected state). They also combined the three entangled qubits in a single device (see image).

This demonstration is a first step toward extending the capabilities of quantum systems based on spin qubits. "Two-qubit operation is good enough to perform fundamental logical calculations," explains Tarucha. "But a three-qubit system is the minimum unit for scaling up and implementing error correction."



False-colored scanning electron micrograph of a silicon/silicon–germanium heterostructure. The purple and green structures represent the aluminium gates. RIKEN physicists succeeded in entangling three silicon-based spin qubits using the device.

The resulting three-qubit state had a remarkably high state fidelity of 88%

The team's device consisted of a triple quantum dot on a silicon/silicon–germanium heterostructure and is controlled through aluminum gates. Each quantum dot can host one electron, whose spin-up and spin-down states encode a qubit. An on-chip magnet generates a magnetic-field gradient that separates the resonance frequencies of the three qubits, so that they can be individually addressed.

The researchers first entangled two of the qubits by implementing a two-qubit gate—a small quantum circuit that constitutes the building block of quantum-computing devices. They then realized three-qubit entanglement by combining the third qubit and the gate. The resulting three-qubit state had a remarkably high state fidelity of 88%, and was in an entangled state that could be used for error correction.

This demonstration is just the beginning of an ambitious course of research leading to a large-scale quantum computer. "We plan to demonstrate primitive error correction using the three-qubit device and to fabricate devices with ten or more qubits," says Tarucha. "We then plan to develop 50 to 100 qubits and implement more sophisticated error-correction protocols, paving the way to a large-scale quantum computer within a decade." ●

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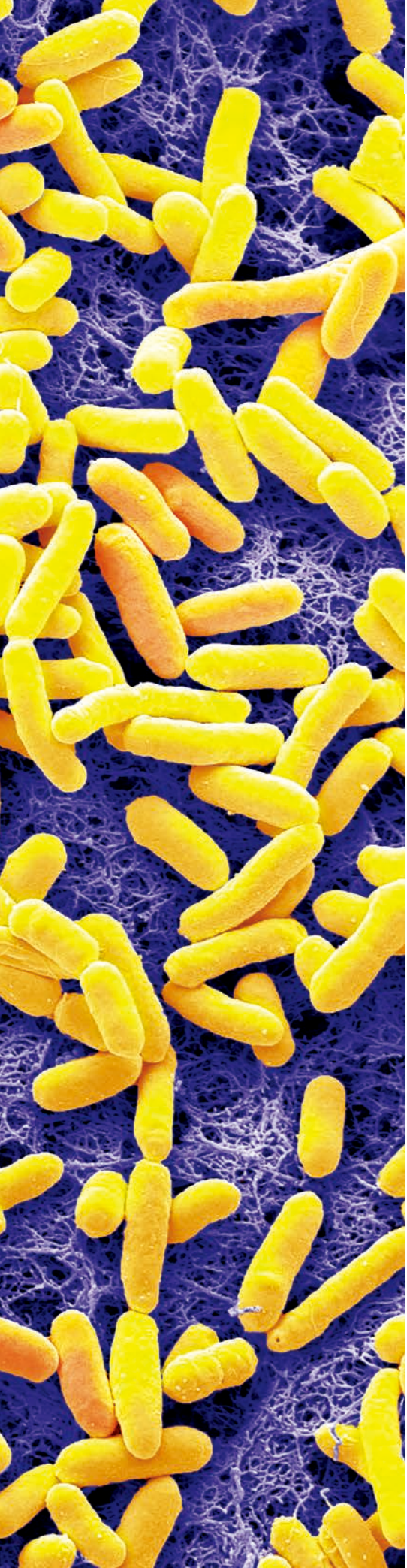
TO MAKE TIRE RUBBER, ADD **BACTERIA AND SUGAR**

A chance change of pH resulted in a more sustainable means of manufacturing car tires using glucose and genetically modified bacteria.



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Four RIKEN researchers have succeeded in using genetically engineered bacteria, *Escherichia coli*, to convert glucose into a key synthetic compound used to make tires[1].

The chemical in question, 1,3-butadiene, doesn't seem very impressive at first sight, consisting of just four carbon atoms and six hydrogen atoms, but its global market was worth US$19 billion in 2019. One of the main reasons is because it is the building block for a synthetic polymer used in vehicle tires.

Prior to the development of synthetic rubber in 1931, car tires used to be made almost entirely from natural rubber, a natural compound derived from the sap of rubber trees.

These days, car tires contain more synthetic polymer than natural rubber. But Yutaro Mori of the RIKEN Center for Sustainable Resource Science (CSRS) envisages a day when all the polymer component of tires will once again come from natural sources. "A long-term goal of our research is to produce various manufactured goods including tires that can be made using natural materials and processes," he explains.

The researchers have been collaborating with two companies since 2013: tire manufacturer Yokohama Rubber and Zeon Corporation. "Yokohama Rubber wants to make eco-friendly tires with a view to addressing the Sustainable Development Goals," says Mori. "And so they approached us to see if we would be interested in collaborating." Yokohama Rubber and Zeon jointly established a laboratory at RIKEN and started to scale up the researchers' work from 2020.

SWAPPING FOSSIL FUELS FOR BACTERIA

In their study, Mori and three CSRS co-workers have taken the first step toward that goal by producing 1,3-butadiene from glucose by using genetically modified *E. coli*—a species of bacteria found in the intestines of people and some animals, and the most extensively researched prokaryotic model organism.

Like many synthetic polymers, 1,3-butadiene is usually made from crude oil, a resource that is being rapidly depleted and that unlocks carbon from the Earth's reservoirs of fossil fuels. The ability to produce it from biomass with *E. coli* promises to make its production much more sustainable, says Mori. And his team's demonstration also opens up the possibility of using microbes to produce other industrially important chemicals.

"The production of industrial chemicals without using fossil fuels is attracting attention as key to realizing the Sustainable Development Goals," says Mori. "Bioproduction using microorganisms makes it possible to switch the raw material from fossil fuels to biomass, thus creating a sustainable carbon cycle."

Mori notes that as a result this is a highly

This feature looks at the work of **YUTARO MORI**

Yutaro Mori is a researcher in the Cell Factory Research Team at the RIKEN Center for Sustainable Resource Science (CSRS). He received his PhD in protein engineering from Kyushu University in 2015. His thesis focused on the fabrication of high-order functional protein assemblies via site-specific linkage reactions. After graduating he moved to RIKEN and joined Akihiko Kondo's lab at CSRS, where he researches bioproduction using enzyme engineering technology. He is trying to come up with a versatile strategy for the rational design of enzymes in order to improve the production of valuable compounds and to produce unnatural/nonbiological target compounds by modifying enzyme core regions. He also belongs to the Bio-monomer Production Laboratory jointly established with RIKEN, Yokohama Rubber and the Zeon Corporation in 2020. In 2021, he received the Incentive Award from the Japanese Society of Enzyme Engineering.

competitive area of research globally. "This kind of research is being done all over the world," he says. "In particular, other groups are conducting computer simulations for the rational design of high-performance microbes and enzymes to produce target compounds. We're competitive with each other, but for the greater good."

The four researchers employed a combination strategy of a rational enzyme engineering and a metabolic pathway modification in *E. coli*. To do this, they first engineered a bacterial enzyme that takes a biological precursor compound that *E. coli* produce from glucose and converts it into 1,3-butadiene. The team then genetically modified a strain of the *E. coli* to produce the precursor more efficiently. The engineered strain could then use this tailor-made enzyme to produce 1,3-butadiene. A gas at room temperature, 1,3-butadiene can easily be siphoned off from a glucose fermenter while *E. coli* continues to grow.

Yokohama Rubber and Zeon Corporation have been working with Yutaro Mori since 2013. They have set up a laboratory at RIKEN to look at upscaling the production of 1,3-butadiene using bacteria with an eye to eventually producing sustainable tire rubber.

SERENDIPITY AND SCALE

An element of serendipity was involved in a change of pH during fermentation. "We were trying to increase the production of 1,3-butadiene, but we weren't making much progress," recalls Mori. The received wisdom was that optimal production happens at a neutral pH, and so the researchers added alkali to offset the acidity being produced by bacteria in one of their experiments.

But, unknown to Mori, the pH monitors on one of the jar fermenters wasn't functioning properly. When Mori checked the production of 1,3-butadiene, he found that it was nearly four times that of the other jar fermenters. It was only then that he discovered that the pH monitor was broken, and so pH adjustment has not worked. That led to the discovery that using a low pH can boost the production of 1,3-butadiene from their microbes.

The researchers propose two possible explanations. One, that the cell growth rate of their *E. coli* was slower at a pH of 6.0 than at a pH of 7.0, and proliferation of its growth continued after the conditions were shifted to microaerobic conditions so that the tailored enzyme maintained the ability to produce of 1,3-butadiene. Or, the proportion of intracellular precursor compounds of 1,3-butadiene increases under low pH conditions. The extracellular precursors, or the *E. coli* strain produced and released into the medium, can re-enter cells at a low pH which may promote the conversion to butadiene, says Mori.

In the current study, the researchers produced 2 grams of 1,3-butadiene per liter. The next challenge will be to scale the process up so that it can be used to make 1,3-butadiene in industrial quantities. Yokohama Rubber and Zeon are setting up a laboratory at RIKEN that will seek to produce the chemical in 5-liter fermenters—five times larger than the those used in the initial study and to improve the productivity of 1,3-butadiene.

The team is confident that the same strategy could also be used to utilize microbes to produce other industrially important chemicals that are currently produced from petroleum, such as styrene and isoprene.

The hope is to contribute to a more 'circular bioeconomy' in which things such as biomass and organic waste are used to produce chemicals. "The research to create such compounds is challenging, but it is very meaningful and important to the realization of the United Nations' Sustainable Development Goals," says Mori.

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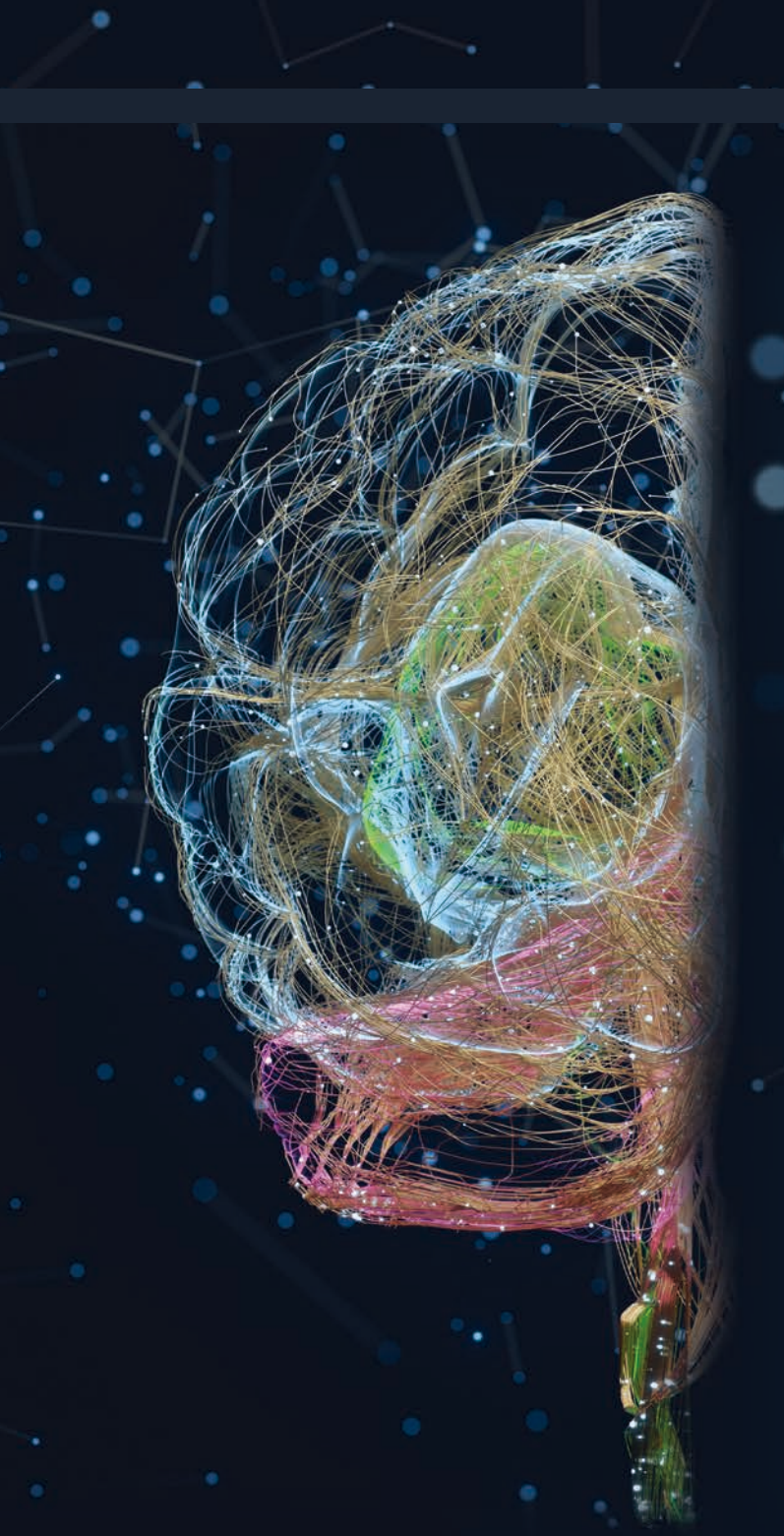

BUILDING A BETTER FUTURE FOR THE BRAIN

Ryoichiro Kageyama from the RIKEN Center for Brain Science says their work developing optogenetic, gene editing and bioinformatic technologies, as well as cutting-edge animal models, is accelerating the real-world impact of brain research. For instance, new marmoset and mouse Alzheimer's disease models are addressing long-standing challenges in the study of therapies that break down plaques and generate fresh neurons.

Eric Kandel won the Nobel Prize in Physiology or Medicine in 2000 for discovering the central role that synapses play in memory and learning. He made his seminal discoveries using a simple animal model, a sea slug called the California sea hare (*Aplysia californica*).

There has been a huge acceleration in neuroscience since then. Faster cell culture methods, the means to insert or knock out individual genes in mice, flies and other model animals, light technologies that can activate specific neurons in living models and the use of functional magnetic resonance imaging (fMRI) to study the link between activity and blood flow in different regions of the brain, have all meant that researchers can now better study the link between neuron activation patterns and behavior.

These tools, all of which are used by the RIKEN Center for Brain Science (CBS), have led to recent breakthroughs at RIKEN on the brain regions associated with protective parenting behaviors, new social

4 PILLARS: RIKEN CENTER FOR BRAIN SCIENCE

The RIKEN CBS investigates the mechanisms of the brain that create the mind using these four approaches.

HUMAN BRAINS

Better understanding how the mind emerges from the brain, and how people reflect on their thoughts, perform actions and build relationships and societies.

STUDY OTHER SPECIES

Better understanding cellular interactions, neural networks, and functional, universal and higher brain features via the study of different brains.

BIG BRAIN DATA

Compiling and processing big data on the brain to generate fresh insights. The center is also using the brain as inspiration for AI-efficiency advances.

BRAIN HEALTH

Understanding neurodevelopmental issues and neurological diseases, with the aim of finding diagnostic and therapeutic tools to support brain health.

interactions and epileptic seizures, as well as on biomarkers for autism and schizophrenia, and research on formation of long-term memory, among others.

BIG DATA ON BRAINS

RIKEN CBS has long been at the forefront of memory-tracking engram tagging and light-activated optogenetic technologies, as well as developing key animal models, including a recent breakthrough Alzheimer's model, a topic to which we will return.

However, the brain has 86 billion neurons able to adapt and fire an almost infinite number of patterns, so the next generation of insights, revealing the source of higher cognitive functions—such as the ability to evaluate and reach goals, and adapt behavior—will likely require the help of artificial intelligence.

Over the next few years, neuroinformatics in Japan will be hugely boosted by the multi-institutional Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS) project, which is being coordinated by RIKEN CBS. The project provides one of the world's largest three-dimensional digital brain atlases using a unique experimental model, the marmoset.

Launched in 2014, it has been granted 40 billion yen (US$350 million) in funding for ten years to digitize brain data. Currently, the Brain/MINDS project is linking detailed data on brain physiology with macro-scale functional analysis, performing intermediate-scale mapping of the marmoset prefrontal cortex, and detailing 3D images of brain connections that can be hundreds of gigabytes in size.

To support this project, CBS's Brain Image Analysis Unit is developing algorithms that process marmoset brain images and the Connectome Analysis Unit is creating 3D models, allowing the exploration of very high-resolution image data to reveal real connectivity patterns between brain regions.

Tomomi Shimogori at the Laboratory for Molecular Mechanisms of Brain Development at RIKEN CBS is also using *in situ* hybridization analysis to show changes in messenger RNA expression in marmosets over their lifetime. Her team is aiming to perform this analysis on developing marmoset brains for 5,000 genes. In June 2021, her team published on an unbiased, automated, large-scale, cellular-resolution *in situ* hybridization-based gene-expression profiling system to reveal gene-expression patterns in marmoset brains that are distinct from those in mice. This technology should help reveal the molecular mechanisms underlying primate neurobiology, and developmental psychiatric and neurological disorders.

DEMYSTIFYING DEMENTIA

RIKEN CBS is also doing work to combat the most serious neurological diseases we face. Alzheimer's disease is the world's most common form of dementia, and if we live into very old age, there is a good chance that we will develop it. Japan has the world's most rapidly aging population, and so any insights from RIKEN CBS that could lead to the development of therapies are a prime example of how we can meaningfully contribute to solving real-world problems.

Using studies on mice, my own lab has discovered a pathway for the activation of dormant stem cells that could generate new neurons to replace those lost due to the disease. However, as writer Anthony King pointed out in *Nature* in 2018; "Although researchers have conducted more than 400 trials in people of potential treatments for Alzheimer's disease, almost no drugs have been brought to the market. And despite the blame being placed on a variety of factors, one of the main sources of researchers' concern is the

animal models that are used in the initial stages of drug development."

Mouse models of amyloidosis don't develop neurofibrillary tangles or neurodegeneration, nor can they reflect most of the cognitive and behavioral changes that affect people with Alzheimer's disease. Alzheimer's is also generally considered to be a disease of old age. The mouse models, which are short lived, might therefore reflect only the early stages of the disease. If that is the case, clinical trials of drugs could be failing because people are treated too late to halt brain cell attrition. Could monkeys model the disease more fully? Many think so. Unlike mice, both macaques and marmosets typically develop hyperphosphorylated tau and amyloid plaques as they age. And their amyloid beta sequence is identical to the human protein.

So in the last few years, researchers led by Takaomi Saido at RIKEN CBS and Erika Sasaki at the Central Institute for Experimental Animals, Japan, have created the first nonhuman primate genetic model of Alzheimer's disease using marmosets.

> **"Already fibroblasts from the marmosets make an increased amount of one of the two major forms for amyloid beta, Aβ42.**

FIRST MARMOSET ALZHEIMER'S MODEL

However, marmosets, which are smaller than macaques, can develop both amyloid beta plaques and hyperphosphorylated tau deposition within seven years, rather than about 25 years for macaques.

Kenya Sato and Hiroki Sasaguri at RIKEN CBS used transcription activator-like effector nucleases (TALEN) to genetically alter the ova of the common marmoset, *Callithrix jacchus*, deleting a part of a gene found in some people with familial Alzheimer's disease, exon 9 in the presenilin 1 gene. The ova were then fertilized with sperm from wild marmosets. Of the six babies that survived until birth, three carried the presenilin 1 mutation. The researchers are hopeful these will develop into a useful model population, as already fibroblasts from the model animals make an increased amount of one of the two major forms for amyloid beta, Aβ42, compared with cells from control animals, which is similar to human presenilin 1 mutation carriers. RIKEN CBS is also making other brain-disease marmoset models, for Parkinson's disease and autism, for example.

POWERING A PIPELINE

In Alzheimer's disease, two key things happen: neurons die more rapidly and stem cells do not produce new neurons as quickly.

Neural stem cells in embryos are very active, but stem cells in adult brains are only occasionally activated and start proliferating, eventually making a small number of new neurons. Formation of new neurons decreases with age, and in Alzheimer's disease this decrease happens more rapidly and severely.

With my collaborators, I have found that oscillatory expression of the *Ascl1* gene plays a critical role in the activation of quiescent neural stem cells and production of new neurons in the adult brain.

We have been studying how gene manipulation and optogenetics can activate aged stem cells for a longer period in model mice and would also like to replicate these studies in marmosets.

But despite the development of primate models, mouse models continue to make important contributions. In 2005, Saido's group found that the neuropeptide, somatostatin, can increase the neuronal production of the enzyme neprilysin, which can degrade one type of accumulated amyloid beta. Neprilysin production decreases with age, and so activation of the somatostatin pathway may lead to an Alzheimer's disease therapy.

While there are already many drugs that stimulate the somatostatin pathway, studies of these have been hampered by current Alzheimer's animal models.

In September 2021, Saido's group published on a promising new Alzheimer's disease mouse model.

His group had previously developed two mouse models harboring what are known as the Swedish and Beyreuther/Iberian mutations, with or without the Arctic mutation.

The first model, with the Arctic mutation, exhibited extensive plaque formation in tissue as early as six months, but is unsuitable for investigating amyloid beta metabolism and clearance because the Arctic mutation also renders the amyloid beta resistant to proteolytic degradation. The second model may take as long as 18 months for the pathology to become prominent, which only leaves a short window for study before the end of the mouse's life.

Saido's team generated their new model by cross-breeding a model based on a presenilin 1 mutation and their previous model without the Arctic mutation. This new model exhibits early and strong signs of amyloid beta accumulation that isn't resistant to enzymatic degradation, and the authors say it should be useful for the study of agonists for somatostatin receptor subtypes. The team also has high hopes for studying potential therapies on their new marmoset models.

REFERENCE

For a full list of references, please see the online version of this article: https://www.riken.jp/en/news_pubs/research_news/

RYOICHIRO KAGEYAMA
Director, RIKEN Center for Brain Science

Ryoichiro Kageyama received his PhD in 1986 from Kyoto University. He then spent a few years as a postdoctoral fellow at the National Cancer Institute in the United States, after which he returned to Japan and was appointed an assistant professor at Kyoto University in 1989. He became an associate professor in 1991. While there, he began describing genes, such as *Hes1* and *Math1*, and their role in neural development. He then moved to Kyoto University's Institute for Virus Research in 1997, becoming a professor. In April 2006, he was appointed director of the same institute. He moved to RIKEN and became the director of the RIKEN Center for Brain Science in 2021.

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PROGRAMS FOR YOUNG RESEARCHERS

INTERNATIONAL PROGRAM ASSOCIATE

International Program Associates (IPAs) are graduate students that are jointly guided, for up to three years, by RIKEN researchers, alongside researchers from a partner graduate school or research institution. The latter are located in either Japan or overseas. To apply, you must be a non-Japanese doctoral student enrolled (or to be enrolled) at a university that has (or is expected to have) a Joint Graduate Program agreement with RIKEN.

FIELDS: Mathematical science, physics, chemistry, biology, medical science and engineering
SUPPORT: Living allowance of ¥5,200/day; free on-campus housing or housing allowance of up to ¥70,000/month for off-campus housing; and one round-trip travel fare to and from RIKEN.
APPLICATIONS: RIKEN researcher can apply to host a student in spring and autumn. Students should start by contacting the RIKEN researcher they would like to work with.
LEARN MORE: riken.jp/en/careers/programs/ipa

RIKEN HAKUBI FELLOWS PROGRAM

RIKEN Hakubi Fellows are junior principal investigator (PI) positions for up to seven years of independent research by exceptionally talented individuals who are able to manage their laboratories as Principal Investigators.

SUPPORT: Research budget of ¥10 to 40 million per year; salary of ¥910,000/month; commuting and housing allowances.
LEARN MORE: riken.jp/en/careers/hakubi

SPECIAL POSTDOCTORAL RESEARCHERS PROGRAM

The Special Postdoctoral Researchers (SPDRs) program provides roughly 60 creative young scientists with the opportunity to conduct independent research on a topic of their own choosing, for up to three years. Applicants must have been awarded a PhD within five years of application or expect to be awarded a PhD by the date of hire.

FIELDS: Mathematical science, physics, chemistry, biology, medical science and engineering
ANNUAL RESEARCH BUDGET: ¥1,000,000
MONTHLY SALARY: ¥487,000 and commuting and housing allowances
APPLICATIONS: February to April
LEARN MORE: riken.jp/en/careers/programs/spdr

JUNIOR RESEARCH ASSOCIATES

Junior Research Associates are given part-time research positions for up to three years (or four years in some cases). These roles are aimed at young researchers enrolled in PhD programs in Japanese universities that have collaborative agreements with RIKEN or are involved in joint research with RIKEN scientists.

FIELDS: Mathematical science, physics, chemistry, biology, medical science and engineering
SUPPORT: ¥164,000/month with a commuting allowance
APPLICATIONS: October–November
PROGRAM START: 1 April or 1 October
LEARN MORE: riken.jp/en/careers/programs/jra

RIKEN'S CENTERS AND FACILITIES

across Japan and around the world

WAKO (RIKEN's Headquarters)

- ● Center for Emergent Matter Science (CEMS)
- ● RIKEN Center for Quantum Computing (RQC)
- ● Center for Sustainable Resource Science (CSRS)
- ● Center for Brain Science (CBS)
- ● Interdisciplinary Theoretical and Mathematical Sciences Program (iTHEMS)
- ● RIKEN Nishina Center for Accelerator-Based Science (RNC)
- ● RIKEN Center for Advanced Photonics (RAP)
- ▲ RIKEN Cluster for Science, Technology, and Innovation Hub (RCSTI)
- ▲ Cluster for Pioneering Research (CPR)
- ◆ Radio Isotope Beam Factory (RIBF)
- ▼ RIKEN Information R&D and Strategy Headquarters (R-IH)

LEGEND

- ● Strategic Research Center
- ■ Research Infrastructure Center
- ◆ Large Research Infrastructure
- ▲ Research Cluster
- ▼ Information Research and Infrastructure

SENDAI

- ● Center for Advanced Photonics (RAP)

TSUKUBA

- ■ BioResource Research Center (BRC)
- ◆ BioResource

YOKOHAMA

- ● Center for Sustainable Resource Science (CSRS)
- ● Center for Integrated Medical Sciences (IMS)
- ● Center for Biosystems Dynamics Research (BDR)
- ■ RIKEN Center for Computational Science (R-CCS)
- ▲ RIKEN Cluster for Science, Technology, and Innovation Hub (RCSTI)
- ◆ Genome Sequencing
- ◆ Nuclear Magnetic Resonance (NMR)
- ▼ RIKEN Information R&D and Strategy Headquarters (R-IH)

TOKYO

- ● Center for Advanced Intelligence Project (AIP)
- ▼ Innovation Design Office
- ▼ RIKEN Information R&D and Strategy Headquarters (R-IH)

HARIMA

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

NAGOYA

KEIHANNA

- ■ BioResource Research Center (BRC)
- ● Center for Advanced Intelligence Project (AIP)
- ▼ Guardian Robot Project (R-IH)

KOBE

- ● Center for Biosystems Dynamics Research (BDR)
- ■ RIKEN Center for Computational Science (R-CCS)
- ◆ Molecular Imaging
- ◆ Supercomputer Fugaku

OSAKA

- ● Center for Biosystems Dynamics Research (BDR)

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, Malaysia, Singapore and other countries. 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, Beijing and Brussels.

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