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SUMMER 2019

RESEARCH

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## PLANETARY INCLINATIONS

How a solar system  
becomes tilted

## A QUICK FIX

Plastics that repair  
themselves

## FROM VIRTUAL TO REALITY

Fleeting particle  
trapped in exotic nucleus

# INHERITED STRESS

Evidence that parental  
angst affects children's DNA



▲ **Bound by physics**

Former MIT physicist Harry C. Kelly (far left) and former RIKEN director Yoshio Nishina (center) worked together to keep RIKEN afloat after two-thirds of its buildings were destroyed during World War II. Here they are in 1949 with Nobel Prize winning physicist Isidor Rabi (right), who was involved in the creation of the Brookhaven National Laboratory and CERN (both of which are now the sites of large RIKEN-led projects, see pages 29–30). Kelly is remembered as a vital advocate for Japanese science in the war's aftermath.

## 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.

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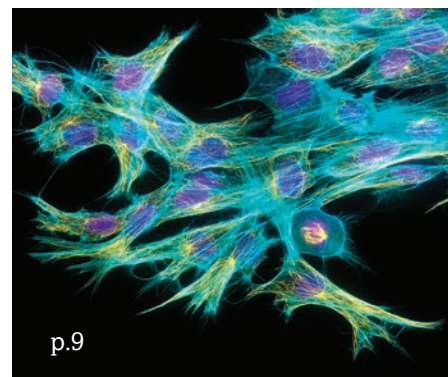


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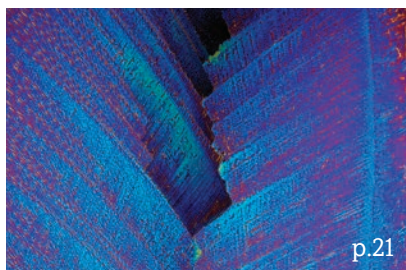
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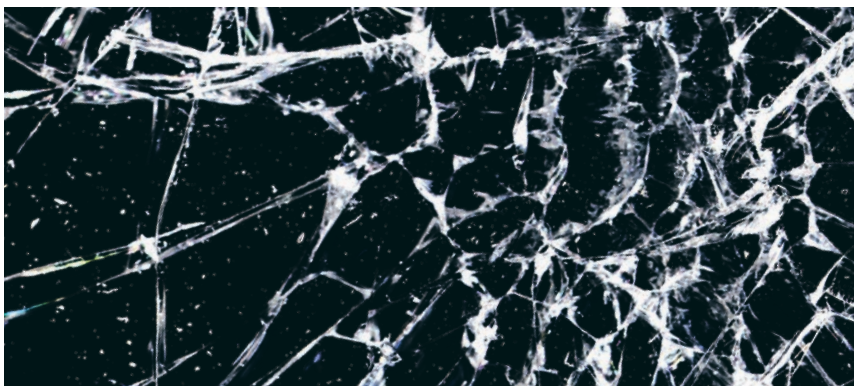
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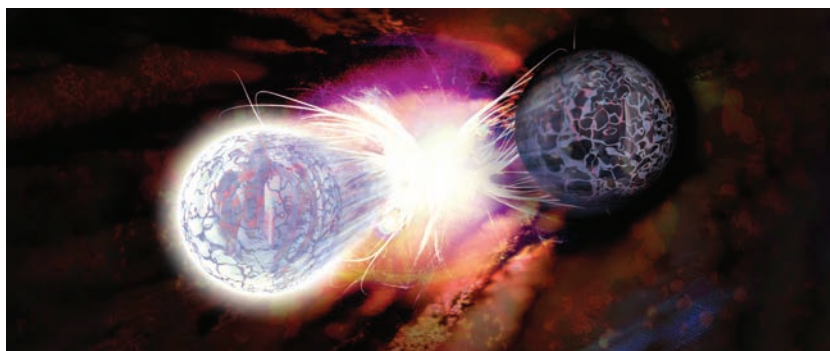
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**World wise:** RIKEN's international links span both time and space



# RIKEN to open a subsidiary company to commercialize its work



**Hidetoshi Kotera**  
Executive Director, RIKEN

I have some exciting news to report regarding RIKEN's future collaborations with industry—we are currently working toward the establishment of a private-sector subsidiary company that will take charge of innovation and the transfer the discoveries made at RIKEN into forms that can be put to the use of society. A law went into force early this year that allows RIKEN to invest in innovation companies, and we are taking the necessary steps now to take advantage of this opportunity.

The establishment of the new company is part of our efforts to achieve the goals set out under our current mid- to long-term plan, which began in April 2018. One of the major pillars of our new mission is to “maximize research and development achievements,” and several of the tasks listed under that mission focus on strengthening innovation. To promote collaboration within RIKEN, we have established an engineering network and finalized comprehensive joint research agreements with six national universities in Japan through our Science, Technology and Innovation hub, and are

now planning for the new company to strengthen ties with industry.

I want to stress that this new focus on innovation in our current seven-year (mid- to long-term) plan is, in essence, a return to RIKEN's roots, as we were established in 1917 primarily with the aim of contributing to the development of Japanese society and industry. In the pre-war period, a number of companies were established based on RIKEN technologies, and some of them remain international players today in their respective fields.

Also, I hope that some of the articles in this issue, in particular, the Feature Highlight focusing on Zhaomin Hou's work on self-healing materials (page 26), will give you some insight into the work that we do today that could benefit society. I encourage you to approach us if you have ideas on how we can work together on innovative technologies.

小寺秀俊



#### COVER STORY:

Male mice can inherit more problematic RNA if their parents experience a lot of stress. This discovery shows how stress can be passed down through genetics. Page 20

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# Leading the race to regenerate eyes

## **Michiko Mandai**

Deputy Project Leader, Laboratory for Retinal Regeneration  
Center for Biosystems Dynamics Research

### ▣ Please describe your role at RIKEN.

I explore the therapeutic possibilities for diseased eyes of using regenerative medicine (the treatment of degenerative eye disorders). Specifically, I'm involved in pre-clinical studies using retinal tissue and cells derived from stem cells.

### ▣ Please briefly describe your current research?

For the past few years, I've focused on using self-organized retinal tissue prepared using embryonic stem cells (ES) and/or induced pluripotent stem cells (iPS) in animal models to see if these tissues can contribute to functional retinal reconstruction after degeneration.

### ▣ What excites you the most about your current research?

I'll never forget the day that I saw what looked like a real mature retina, after an ES-derived retina was transplanted into the degenerated eye of a mouse. The question of if transplanted retinal cells or tissues really make connections with host neural retinal cells has long plagued

researchers. However, the fact that a dead neural network could be rebuilt in an adult is exciting. I see traces of neural regeneration in animal models, but I still wonder if they can be replicated in humans, and how I can help maximize the effects.

### ▣ How did you decide on what you wanted to study?

I started as a clinical ophthalmologist, but I became interested in disease pathology. Today, I try to interpret diseases through basic science as well as clinical ophthalmology.

### ▣ What have been the most interesting recent discoveries in your field?

Two great contributions have come from Japanese researchers. Mototsugu Eiraku has been working on producing three-dimensional retina from stem cells. Yoshiaki Sasai's lab has examined guiding human embryonic stem cells in tissue cultures into cells from the brain cortex, eyes and other organs. From these findings we can now obtain retinas from ES/iPS cells by reproducing the developmental process *in vitro*.

### ▣ How and when did you join RIKEN?

Previously, I had worked with Masayo Takahashi as a clinical ophthalmologist, but I was also interested in performing preclinical studies, and so it was ideal when she joined RIKEN to do more fundamental research and I was able to join her lab.

### ▣ What are some of the technologies that you use in your research?

We use volume imaging and analysis via immunohistochemistry, a type of immunostaining, and are also trying the serial block-face electron microscope to generate three-dimensional images from small samples. We are still struggling with three-dimensional reconstructions of large-volumes of data, but I would like to see if the characteristic ribbon synapse formation of photoreceptor bipolar and horizontal cells is reproducible between host retina and graft tissue. The multiple electrode array system is also an important tool used to record the retinal function through electrophysiology.

“*I'd like to see if we can restore substantial vision in humans through photoreceptor reconstruction and replacing or repairing other retinal cells*”

### ▣ Tell us about your goals.

I'd like to see if we can restore substantial vision in humans through photoreceptor reconstruction and replacing or repairing other retinal cells. This will also provide clues to how the visual system is organized. Clinically, we would like to move from seeing small effects, such as patients being able to see some light, to patients being able to see shapes or movement.

### ▣ “My research is important to society because....”

...it challenges us to understand the regenerative potential of the human neural network. ■



# Smashing results from nuclei

## Frank Browne

Special Postdoctoral Researcher, Radioactive Isotope Physics Laboratory  
RIKEN Nishina Center for Accelerator-Based Science

### ▣ Please briefly describe your current research

I study exotic isotopes. To quickly explain, perhaps the most successful description of atomic nuclei is that of the shell model; this dictates that protons and neutrons exist in well-defined spatial configurations called orbitals, which are associated with particular energies. My focus is on measuring how these orbitals change when we adjust the number of protons and/or neutrons in nuclei. I do this by examining the radiation they emit.

In particular, I study atomic nuclei that have many more neutrons than naturally occurring isotopes. The properties of such exotic isotopes challenge established concepts of nuclear structure. They are also responsible for the chemical composition of stellar environments, including our solar system. Thus, my findings could provide the means to test poorly understood fundamental nuclear forces, and ultimately could help improve nuclear technology.

*The capabilities of the RIBF are beyond those of any other facility, and will be for the next several years* ”

### ▣ What are some of the technologies used to conduct your research?

RIKEN hosts the Radioactive Isotope Beam Factory (RIBF), a facility capable of producing the most intense beams of radioactive nuclei in the world. It does this by accelerating a beam of stable uranium to 70 percent the speed of light

and smashing it against lighter nuclei. We probe the structure of the resultant nuclei, which have extreme imbalances of protons and neutrons.

### ▣ What excites you the most about your current research?

The capabilities of the RIBF are beyond those of any other facility, and will be for the next several years. This makes for a great atmosphere during an experimental run, when you are almost guaranteed to find something new and exciting in the preliminary data.

### ▣ What has been the most interesting discovery within your field of the last few years?

While atomic nuclei are notoriously difficult to explain in a theoretical manner, it has been predicted that the mass-54 calcium isotope might be particularly stable. This was confirmed in a landmark experiment performed at the RIBF. I'm presently investigating the same nucleus, but using different production pathways. My results provide firmer confirmation of this important result, and hint at a rare competition between nuclear decay modes.

### ▣ “My research is important to sustainable development because...”

The electric car marks a turn towards burgeoning electricity consumption. In order to match this consumption, reliable and high-density power generation methods must be pursued. Nuclear

technologies provide a low-carbon solution. Promising developments towards safer and more efficient power generation include; reactor-neutrino observation as a means of non-intrusive reactor monitoring, and the development of nuclear reaction mechanisms for transmutation of long-lived nuclear waste.

### ▣ What are your thoughts on science today?

With the increased emphasis being put on the “impact” of scientific results, I believe that there's a danger of overselling ourselves. Even more dangerous is the active seeking of phenomena in our data that we know will garner attention. Whilst combating this is difficult, indeed these are mostly subconscious behaviours, we should strive to admit our ignorance and treat expected results with the same reverence as those that are unexpected. ■

### Careers at RIKEN

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## Supercomputer Fugaku—A new name for Japan's soon-to-be top supercomputer

Japan's next exascale supercomputer is still just a plan on paper, but now it has a name, Fugaku, or, Supercomputer Fugaku.

The new supercomputer, which is scheduled to go into operation at RIKEN's Kobe campus in 2021, will be up to a hundred times more powerful than its predecessor, Japan's most powerful supercomputer, the K computer.

Fugaku is currently being developed by RIKEN in collaboration with Fujitsu, and its processing power will be used to examine social challenges in health and longevity, disaster prevention, weather forecasting, energy conservation, clean energy, material design, and manufacturing processes. It will also help researchers working in data intensive fields such as AI, data science and the elucidation of the fundamental laws of the universe.

Fugaku is another name for Mount Fuji, Japan's tallest mountain. It was chosen to symbolize the power of the K computer's successor and also the expansive research horizon the supercomputer will open up. The name was chosen after a call for suggestions, from which 5,181 submissions were received.

The hardware for Fugaku has now been created, including the A64FX™, a high-performance CPU, developed by Fujitsu, that uses ARM instruction set architecture. Fujitsu will work with open source communities to promote the ARM ecosystem and utilize open source software for Fugaku.



From left: Executive Director Michihiko Minoh, Executive Director Motoko Kotani, President Hiroshi Matsumoto, Deputy Executive Director Shigeo Okaya and Director of R-CCS Satoshi Matsuoka

## EVENTS



Physicists and institution representatives at the signing ceremony for the MPG-PTB-RIKEN Center.

## New physics force: The MPG-PTB-RIKEN Centre for Time, Constants and Fundamental Symmetries

*The world's best experimental physicists to align on precision*

At the new MPG-PTB-RIKEN Centre, which opened in January 2019, the world's leading experimental groups in atomic and nuclear physics, antimatter research, quantum optics and metrology will collaborate to measure time and its natural constants, using ultraprecise equipment.

This partnership brings together the Max Planck Institutes for Nuclear Physics (MPIK; Blaum and Pfeifer) and for Quantum Optics (MPQ; Hänsch and Udem), the National Metrology Institute of Germany, also known as the Physikalisch-Technische Bundesanstalt (PTB), The QUEST Institute (Peik and Schmidt) and RIKEN (Katori and Ulmer).

This collaboration will bring together a “unique combination of outstanding scientists,” says Klaus Blaum, MPIK director and one of the new center's spokespersons.

The goals of the center include finding the answers to questions such as:

- Whether natural constants really are constant, or if they change over time by tiny amounts;
- What the differences are in the properties of matter and antimatter (besides the reversed charge);

- And, if there are any new types of physics, beyond the standard model of particle physics.

To answer these questions, the researchers intend to develop:

- Novel clocks based on atoms, nuclei and highly charged ions;
- Improved measurements of fundamental constants, such as the Rydberg constant, the fine-structure constant and the proton charge radius;
- And, new experimental techniques, which will outperform state-of-the-art contemporary methods and enable measurements at shorter time scales with improved sensitivity.

“The combined expertise of the individual groups with their complementary approaches and different methods has the potential for substantial progress,” says RIKEN's Stefan Ulmer, who will be a key player at the new center.

The center's scientific activities will be coordinated at MPIK, while an exchange program for young scientists will support increased collaboration.

The three namesake partners agreed to contribute equally to roughly €7.5 million in funding over five years.

[http://www.riken.jp/en/pr/topics/2019/20190416\\_2/](http://www.riken.jp/en/pr/topics/2019/20190416_2/)





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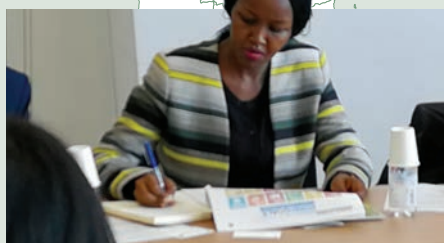
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for Biosystems  
Dynamics Research

**ZHEJIANG, CHINA**

**HANGZHOU, CHINA**  
Zhejiang Hangzhou Future  
Science and Technology City

**RWANDA**

## CSRS researchers establish joint lab in China's own Silicon Valley



### Visit by Rwandan officials

On January 7, Paula Ingabire, Minister for Information Communication Technology (ICT) and Innovation for the Republic of Rwanda, visited the Tokyo campus to discuss future collaborations.

Ingabire spoke about a project that has been launched to establish Rwanda as a hub for research and development in sub-Saharan Africa. Rwanda is seeking opportunities to collaborate, especially in the fields of ICT or digital health care, in the near future.

[http://www.riken.jp/en/pr/topics/2019/20190115\\_1/](http://www.riken.jp/en/pr/topics/2019/20190115_1/)

From April 2019, a joint laboratory run by RIKEN and Zhejiang Ivy Institute of Technology will research natural products and chemical biology at the Zhejiang Hangzhou Future Sci-Tech City, near Shanghai.

Hiroyuki Osada, Deputy Director of RIKEN Center for Sustainable Resource Science, one of the initiators of the project, says: "This project represents the first large-scale collaboration between RIKEN and a local government overseas, and represents a new milestone in the institute's internationalization. As such, it is very exciting for us."

The joint laboratory will identify useful substances from natural compounds collected from microorganisms and plants, with the hope that these will contribute to drug discovery. China is famous for its traditional medicine, and RIKEN aims to ensure this joint laboratory will be a hub for medicinal natural product chemistry research in China.

The Future Sci-Tech City, which has been described as China's Silicon Valley, is a huge science park with a total area of



Jiansheng Mai (center left), secretary for the Party Committee of Zhejiang Hangzhou Future Science and Technology City and Kazuo Shinozaki (center right), director of the RIKEN Center for Sustainable Resource Science, and delegates from Japan and China unveiled the new lab sign.

123 square kilometers and is home to some 9,000 IT companies, including Alibaba, the famous Chinese behemoth in the world of internet sales and IT finance, as well as many universities, including Zhejiang University, Zhejiang Institute of Technology and Hangzhou Normal University.

[http://www.riken.jp/en/pr/topics/2019/20190426\\_3/](http://www.riken.jp/en/pr/topics/2019/20190426_3/)

## Biosystems Dynamics Research Symposium: On control and design

In March, the first Biosystems Dynamics Research (BDR) Symposium 'Control and Design of Biosystems' examined the design and manipulation of biological functions at different scales, ranging from molecules and cells to tissues, organs and individuals. Twenty international speakers came to contribute

to the three-day event, which was held at RIKEN's Kobe campus, and was attended by 174 researchers from 15 different countries.

The first day of the conference focused on the creation of artificial cells and organoids, while the second and third days focused on how to combine engineering techniques and

theory, and how to enhance aging and reproduction research.

The BDR Symposium 2020, 'Emergence in Biosystems', will be held at the Kobe campus next year.

<https://www2.bdr.riken.jp/sympo/2019/index.html>

## NUCLEAR PHYSICS

# The super-heavy magnesium mystery

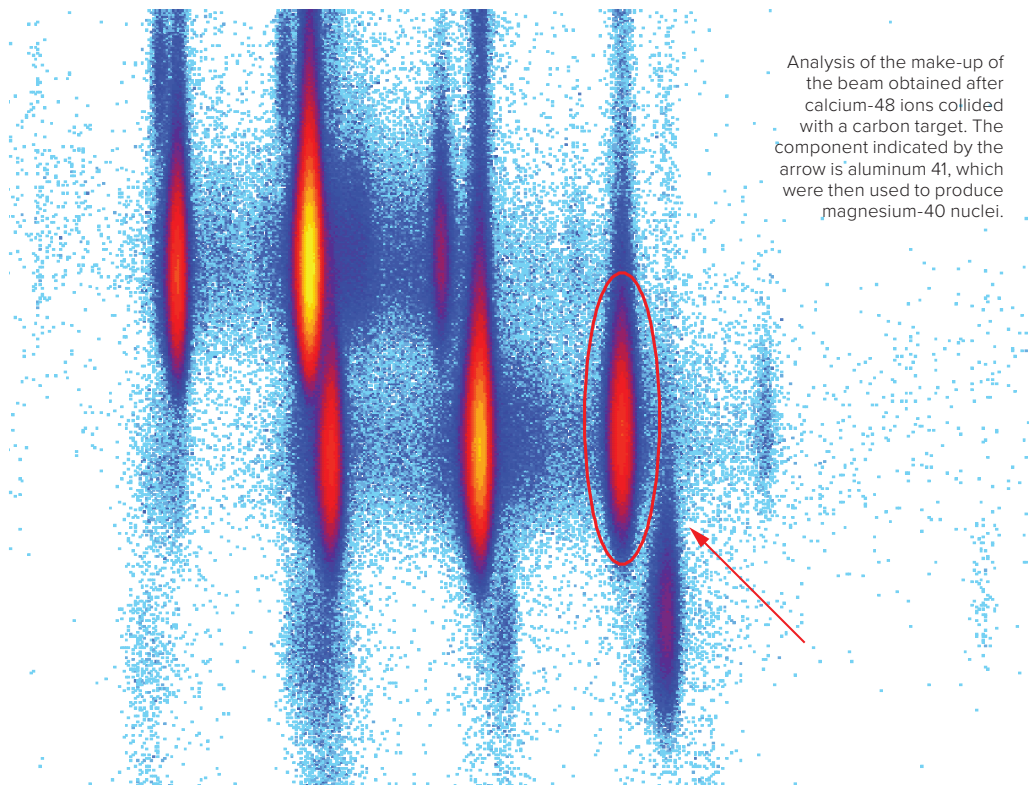
Measurements of neutron-rich magnesium nuclei leave theorists scratching their heads

For the first time, scientists have measured the energies of gamma rays emitted by super-heavy magnesium nuclei, but the results defy textbook expectations<sup>1</sup>.

Atomic nuclei appear deceptively simple, being made up of positively charged protons and electrically neutral neutrons held together by the nuclear strong force. But their underlying complexity is so great that scientists can perform exact calculations only for the lightest elements. For heavier nuclei that contain more than about ten subatomic particles, nuclear physicists rely on theoretical models. Consequently, any experimental measurements of these bigger nuclei are keenly sought so that these models can be better informed.

Now, Hiroyoshi Sakurai and Pieter Doornenbal of the RIKEN Nishina Center for Accelerator-Based Science and co-workers have packed 28 neutrons into a magnesium nucleus and measured the gamma rays emitted. This is almost twice the usual number of neutrons and is thought to be close to the maximum number that a magnesium nucleus can contain. Indeed, magnesium 40 (so-called because it has 12 protons and 28 neutrons) has so many neutrons that if it were possible to make a lump of it, it would be more than 1.5 times heavier than normal magnesium, despite having identical chemical properties.

Sakurai and Doornenbal measured the gamma-ray spectrum of magnesium 40, anticipating that the energies



Analysis of the make-up of the beam obtained after calcium-48 ions collided with a carbon target. The component indicated by the arrow is aluminum 41, which were then used to produce magnesium-40 nuclei.

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**“Nobody knows what is going on. It’s mysterious.”**

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would be similar to those for lighter magnesium isotopes. But to their surprise they turned out to be considerably lower. “This result was very surprising and unexpected,” comments Sakurai.

Furthermore, the measured energies were much lower than those predicted by theoretical models. “It’s almost like some kind of phase transition happens at magnesium 40,” says Sakurai. “Nobody knows what is

going on. It’s mysterious.”

To perform the measurement, the team used the RIKEN’s Radioactive Isotope Beam Factory (RIBF), which generates extremely intense ion beams using a particle accelerator. “This facility is better than any other in the world right now,” notes Doornenbal.

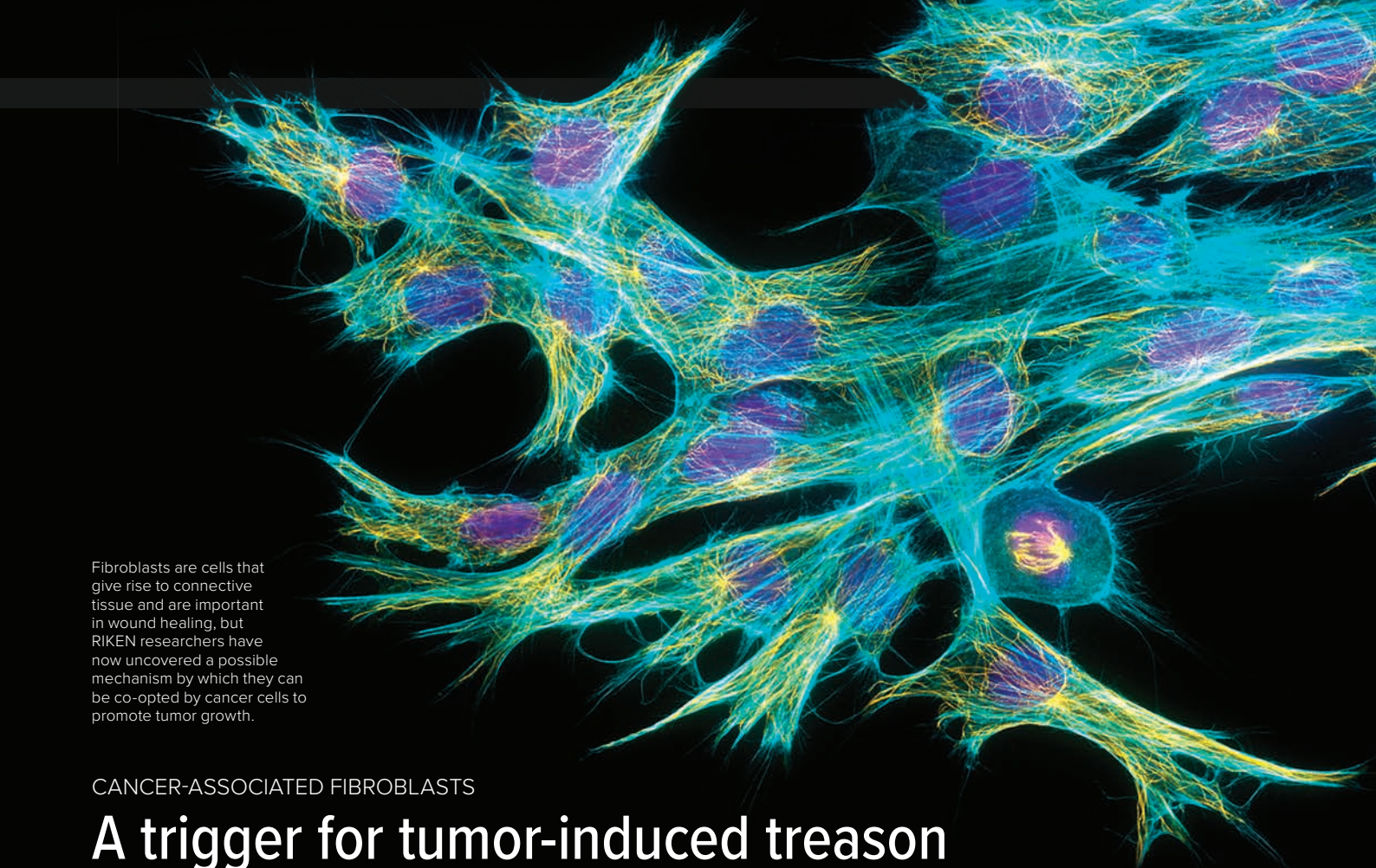
The scientists slammed a beam of calcium-48 ions, accelerated to about 70 percent of the speed of light, into a beryllium target, which produced a beam of aluminum-41 ions. These were then collided with a polyethylene target, which stripped off a proton to give magnesium 40. Over the course of about a week, the team produced just a few

hundred magnesium-40 nuclei from several quintillion ( $10^{18}$ ) calcium-48 ions.

Following upgrades to the RIBF, the team intends to perform follow-up measurements to obtain more clues about why magnesium 40 is so special. ●

## Reference

1. Crawford, H. L., Fallon, P., Macchiavelli, A. O., Doornenbal, P., Aoi, N., Browne, F., Campbell, C. M., Chen, S., Clark, R. M., Cortés, M. L. *et al.* First spectroscopy of the near drip-line nucleus  $^{40}\text{Mg}$ . *Physical Review Letters* **122**, 052501 (2019).



Fibroblasts are cells that give rise to connective tissue and are important in wound healing, but RIKEN researchers have now uncovered a possible mechanism by which they can be co-opted by cancer cells to promote tumor growth.

## CANCER-ASSOCIATED FIBROBLASTS

# A trigger for tumor-induced treason

Screening a massive chemical library has uncovered a potential mechanism by which cancer cells may recruit other cells to promote the growth of a tumor

**A** possible mechanism by which cancer cells may enlist other cells to facilitate tumor growth has been identified by researchers at RIKEN<sup>1</sup>. This finding may eventually lead to new strategies for combating cancer.

Most efforts to treat cancer focus on the tumor cells themselves, but these are located in a larger ‘microenvironment’ that can profoundly affect a patient’s prognosis.

A team led by Nobumoto Watanabe of the RIKEN Center for Sustainable Resource Science is especially interested in fibroblasts, which play a supportive structural role in many tissues and are important for wound healing. While not cancerous themselves, fibroblasts can actively support malignant growth.

“Cancer-associated fibroblasts occupy much of the tumor

microenvironment,” explains Kruthi Suvarna, a graduate student in Watanabe’s lab. “We were intrigued by how cancer cells activate them.” However, these cells are generally poorly characterized, and this process has proven difficult to study.

Activation of fibroblasts is generally associated with increased migration. So Watanabe’s team designed an assay that enabled them to screen roughly 16,000 chemical compounds to identify molecules that interfere with this cellular mobilization. They cultivated thin layers of fibroblasts in the presence of breast cancer cells, and then ‘wounded’ those layers with a scratch—a trigger that induces the activation of fibroblasts to heal the wound.

Out of their original chemical library, the team identified a handful of compounds that inhibited migration in

the presence of cancer cells. Importantly, no such inhibition occurred when fibroblasts were cultured on their own, indicating that the mechanism was specific to cancer.

The researchers identified a cellular target for one of these compounds, NPD8733. Valosin-containing protein (VCP) is associated with a wide range of important biological processes, including critical safeguards against cancerous growth. Although VCP has never before been tied to fibroblast activation, Suvarna and colleagues showed that inhibition of VCP markedly impairs activation and migration of fibroblasts, and they were even able to identify the specific domain of VCP bound by NPD8733.

However, it is unclear how NPD8733 modulates VCP function, and Suvarna—now a postdoc at the RIKEN Center for

Advanced Intelligence Project—sees this as an important follow-up goal. “It would be interesting to study genes upregulated or downregulated in activated fibroblasts upon treatment with NPD8733,” she says.

This screen also identified other potentially useful inhibitor molecules, but the researchers have not yet uncovered targets for these agents. That will be another future objective for Watanabe’s team. “We’re hoping to improve our methods for identifying target proteins,” says Suvarna. ●

### Reference

1. Suvarna, K., Honda, K., Muroi, M., Kondoh, Y., Osada, H. & Watanabe, N. A small-molecule ligand of valosin-containing protein/p97 inhibits cancer cell-accelerated fibroblast migration. *Journal of Biological Chemistry* **294**, 2988–2996 (2019).

## CIRCADIAN RHYTHM

# The shape of circadian rhythm

A model uncovers the mechanism that keeps circadian clocks stable when the temperature increases

The waveforms of circadian cycles in bacteria, flies and mammals become increasingly jagged as the temperature rises, two RIKEN researchers have predicted<sup>1</sup>. This finding is a step toward solving the mystery of how circadian rhythms remain consistent under changing conditions.

We become very aware of our circadian rhythm when jet lag keeps us wide awake at night after jetting across the world. In addition to governing sleep patterns, circadian rhythm regulates hormone secretion and body temperature in 24-hour cycles. In humans, insects and plants, this daily rhythm is driven by cyclical changes in the expression of ‘clock’ genes, whereas in cyanobacteria, it is generated by the phosphorylation of proteins.

**“It’s a paradox that has remained unsolved for more than 60 years,”**

Although higher temperatures tend to speed up biochemical reactions, circadian rhythms remain stable when the temperature varies. This phenomenon has been widely observed in many organisms, but its underlying mechanism is still unclear.

“It’s a paradox that has remained unsolved for more than 60 years,” comments Shingo Gibo at the RIKEN Interdisciplinary Theoretical and Mathematical Sciences. “We wanted to address how the circadian rhythm remains stable under temperature changes.”

While previous studies had used complex simulators to analyze these 24-hour cycles, Gibo and his colleague Gen Kurosawa adopted a more streamlined approach to uncover the mechanism. They constructed a simple biochemical model of the circadian rhythm and developed a mathematical index to express how much the waveforms deviated from a smooth, sinusoidal waveform.

Gibo and Kurosawa then used this approach to investigate how the dynamics of circadian rhythms in mammalian and cyanobacterial models changed when the temperature was increased. By analyzing the shape of the circadian time series, represented as a waveform, they were able to pinpoint how the rhythm remains constant when the temperature changes.

When the researchers modeled the mammalian circadian cycle, they found that the shape of the waveform shifted from being smooth to jagged as the temperature increased. The same held true when they analyzed the



A theoretical analysis has shown that for the circadian clock to be precise, the shape of the circadian waveform needs to change with temperature.

cyanobacterial circadian rhythm model, despite cyanobacteria having different molecular machinery. In both cases, the researchers found that the circadian rhythm lengthened and stabilized as the waveform shape distorted with increasing temperature.

“The architecture of the circadian rhythm for cyanobacteria differs from that of mammals,” says Gibo. “We were surprised that the stability of the circadian period in the cyanobacterial model also required more

non-sinusoidal waveforms at higher temperatures.”

The findings could pave the way for exploring how non-sinusoidal waveforms play a role in modifying circadian rhythms according to seasonal, climatic and environmental changes. ●

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## ENVIRONMENTAL SCIENCE

# Detecting traces of sulfur in ice cores

An advanced isotope-measuring system can reveal insights about past environments in shorter time

**A**n instrument for analyzing isotopes is sensitive enough to monitor environmental changes with a resolution of 1 year<sup>1</sup>. The instrument, which was developed by RIKEN researchers, can detect trace amounts of sulfates in Antarctic ice cores.

Scientists can obtain detailed insights into when past climatic changes occurred and how they affected the environment by analyzing sulfur isotopes in Antarctic ice cores. When present in high concentrations, these isotopes can also reveal how sulfur moves through the atmosphere after volcanic eruptions.

But the amount of sulfates in ice cores is often too low to obtain precise isotopic readings using existing analytical equipment. Consequently, previous analyses had to use thick samples, which limited their time resolution to 50–100 years. But environmental scientists would like to examine sulfur isotopes over much shorter time frames.

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**“We can use this advanced system to estimate the size of past volcanic eruptions.”**

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“In many cases, chemical effects resulting from climatic or environmental events appear within 1 year,” says Kazuya Takahashi of the Astro-Glaciology Research Group at



An ice core that has been drilled from near the Dome Fuji station in Antarctica.

the RIKEN Nishina Center for Accelerator-Based Science. “But we often miss these important events, as most analytical systems provide only a rough time resolution.”

Similar to standard sulfur isotopic measuring devices, Takahashi’s instrument consisted of an elemental analyzer, cryo-flow device and an isotope ratio mass spectrometer. But Takahashi and his team upgraded the system’s components to improve its sensitivity. In particular, they used thinner tubes in the cryo-flow device and replaced the conventional tin cup used in standard systems with a sulfur-free aluminum cup for heating and drying samples.

The team then tested their system on two sections of an

Antarctic ice core drilled at the Dome Fuji station in 2001 (see image). The top section included surface snow and the lower one contained a high concentration of volcanic sulfate, which was previously linked to the Krakatau volcanic eruption of 1883.

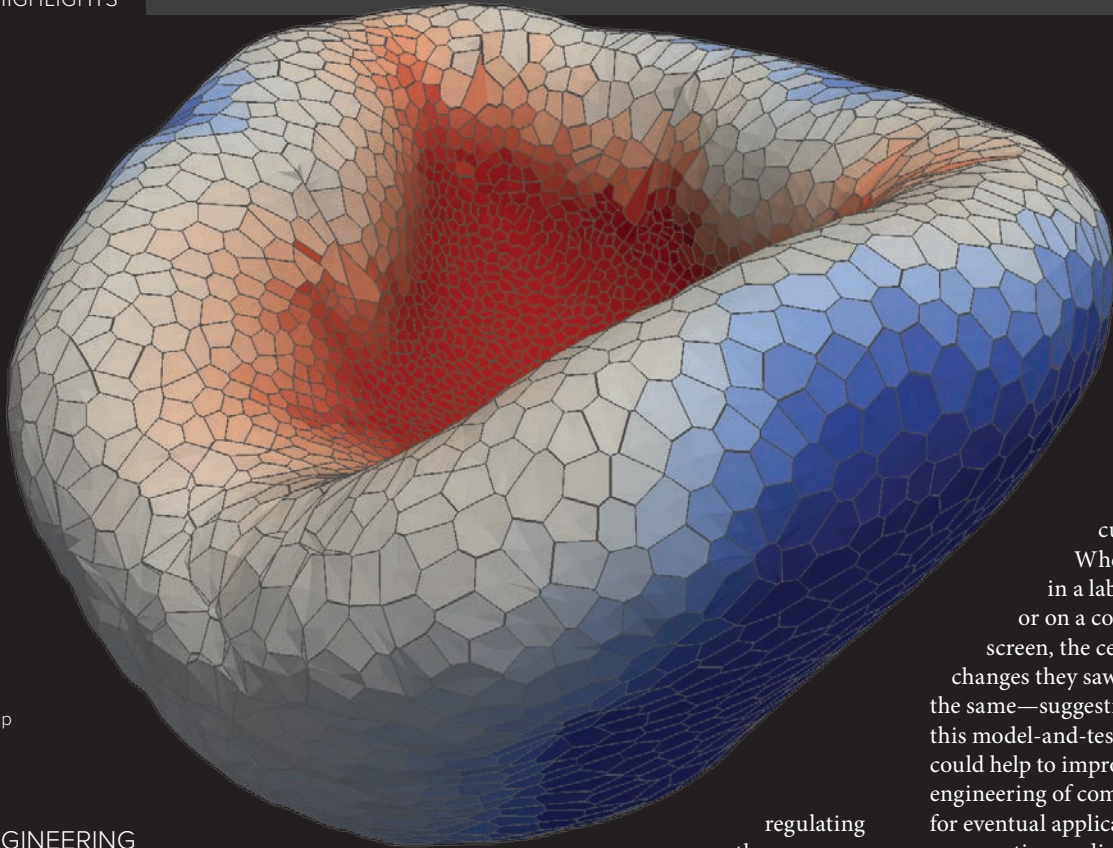
The team examined the instrument’s sensitivity at various sulfate concentrations and found it was able to obtain precise measurements of sulfur isotopes in samples containing minuscule amounts of sulfur. The results were consistent with previous analyses carried out with standard measurement systems without the need for large ice samples. Unlike conventional methods, the modified system provided sulfur isotopic measurements corresponding

to a time resolution of less than 1 year.

The device also detected a higher concentration of sulfate in one of the ice samples, indicating a large volcanic eruption. “We can use this advanced system to estimate the size of past volcanic eruptions and their impact on the environment,” notes Takahashi. ●

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Computer simulations have revealed the mechanics behind optic cup indentation.

## TISSUE ENGINEERING

# An eye on 3D tissue mechanics

A computer model could help to advance regenerative therapies for retinal disease

**A** new computer model that simulates how tissues bend and move to form complex structures is helping RIKEN scientists grow retinas in a dish more reliably<sup>1</sup>. The method could one day help doctors repair damaged eyes in the clinic. More immediately, it offers a way for researchers to study retinal development and what goes wrong in optic disease.

Previously, Satoru Okuda, a biophysicist who co-led the study with Mototsugu Eiraku at the RIKEN Center for Biosystems Dynamics Research (both are now based at Kyoto University but maintain affiliations at RIKEN) and their RIKEN colleagues had shown that embryonic stem cells

from both mice and humans could spontaneously fashion themselves into a primordial eye construct known as an optic cup (see image). In those initial experiments, they coaxed the stem cells to form retinal precursor cells. Over several days, those retinal cells then coalesced into a bubble-like ‘optic vesicle’ that folded in on itself, creating the optic cup with an outer layer of supporting cells and an inner layer of light-sensing retinal tissue.

However, it was unclear how exactly that complex biological structure took shape—and the researchers were left with a number of unanswered questions surrounding the role of mechanical forces in

regulating three-dimensional (3D) tissue formation.

Initially, says Okuda, the team assumed that it was the wedging of tissue at the boundary between cells fated to become either a supporting layer or the retina itself that drove the indentation behind the characteristic horseshoe shape of the optic cup.

But when, in the current study, the researchers inputted their experimental data into a quantitative simulation model, they realized that the physics pointed to a different explanation. According to the simulations, the caving in of the early retina was directly responsible for the dimpling of the optic cup, and it was the strain of that invagination that provoked the constriction of cells at the tissue boundary. Specifically, cells at the boundary modulated the shape of the whole optic cup through mechanosensing.

The team tested the model’s predictions by experimentally applying mechanical forces at various stages of mouse stem

cell-derived optic cup induction.

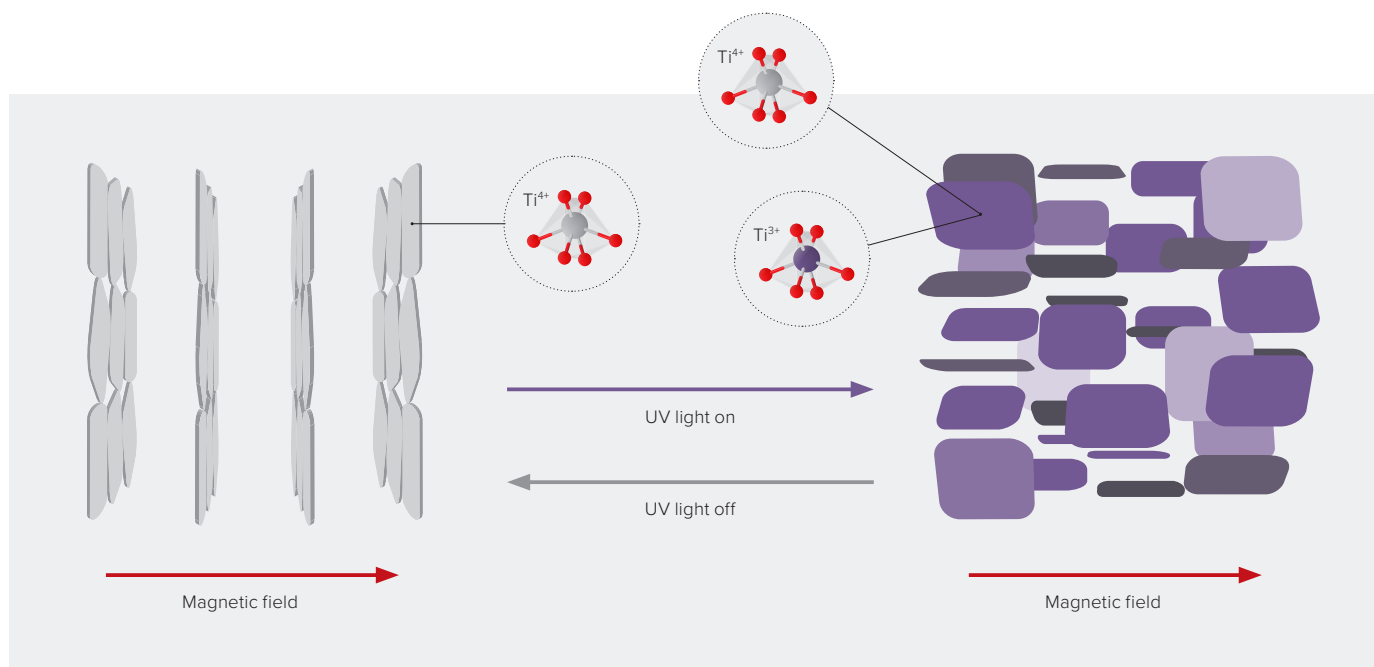
Whether in a lab dish or on a computer screen, the cell shape changes they saw were the same—suggesting that this model-and-test strategy could help to improve the engineering of complex tissues for eventual applications in regenerative medicine.

**“These findings highlight the usefulness of combining 3D modeling and culture systems.”**

“These findings highlight the usefulness of combining 3D modeling and culture systems,” says Okuda. “This approach not only contributes to our understanding of 3D morphogenesis, but also allows us to precisely control complex tissue structures derived from embryonic stem cells in culture.” ●

### Reference

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When titanate nanosheets dispersed in water are irradiated by ultraviolet light, the nanosheets are chemically reduced, the dispersion changes color to purple and the nanosheets line up parallel to the magnetic field. This change can be reversed by turning the ultraviolet light off.

## MAGNETIC MATERIALS

# Flipping the switch on magnetism

Light induces photoreactions that activate the switch of the magnetic orientation of 2D materials dispersed in water

The possibility of liquid crystal displays based on two-dimensional materials has been opened up by RIKEN researchers. They have found a way to use light to induce changes in the optic and magnetic properties of water-dispersed titanate nanosheets<sup>1</sup>.

The properties of liquid crystals lie somewhere between those of solids and liquids. For example, they can be fluid like a liquid and yet exhibit a molecular order similar to that of solid crystals. The properties of liquid crystals depend both on their composition and the orientations of the molecules that make up the crystals. The molecular orientation can be altered by varying the temperature or applying light or a

magnetic field—an ability that is exploited in several applications, including displays and sensors.

Dispersions of 2D materials such as nanosheets in water behave similarly to liquid crystals. In particular, external stimuli, including electric fields and mechanical forces, can be used to tune the orientation of the nanosheets. However, such stimuli can also damage the nanosheets.

Magnetic fields offer a gentler stimulus that preserves the material integrity. But it is not known what effect combining magnetic fields with other inputs will have.

Now, the team led by Yasuhiro Ishida and Takuzo Aida from the RIKEN Center for Emergent Matter Science have investigated

the combined effect of light and magnetic field on the orientations of titanate nanosheets dispersed in water.

When exposed to a magnetic field, the nanosheets oriented their planes perpendicular to the magnetic field. This behavior is a result of the intrinsic magnetic properties of the titanate nanosheets, which are often difficult to manipulate.

When the aqueous dispersion was irradiated with ultraviolet light, it changed color to purple and the nanosheets oriented their planes parallel to the magnetic field, becoming paramagnetic (see image). This color change indicated that the ultraviolet light had chemically reduced the titanate nanosheets. This and the consequent change in magnetic

properties were reversed when the light was switched off.

“We can easily control the position of the light stimulus, and we would like to use this to control the orientations of the nanosheets in a local fashion. We may then be able to use a combination of magnetic orientation and photoswitching to pattern the dispersion with applications in the production of smart optical devices,” explains Ishida. “We hope our present finding will inspire similar studies of other 2D materials and produce new innovations in related fields.” ●

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## PARTICLE PHYSICS

# Weird nucleus created

A fleeting particle has been used to make an exotic atomic nucleus

**A**n exotic atomic nucleus consisting of two protons and a ‘kaon’ has been created for the first time by an international team led by RIKEN researchers<sup>1</sup>. This discovery could provide new insights into the origin of mass in the Universe following the Big Bang.

Kaons are a type of meson—a group of subatomic particles that consist of a quark and an anti-quark. Japanese theoretical physicist Hideki Yukawa first proposed the existence of mesons in 1935, and 14 years later he became the first Japanese to receive a Nobel Prize after the existence of mesons had been confirmed experimentally.

Mesons usually exist as ‘virtual particles’ in nuclei that flit in and out of existence. But this does not exclude the possibility of a meson binding as a ‘real particle’ to an ordinary atomic nucleus made up of protons and neutrons. Understanding how this happens could provide insights into mysteries such as the origin of mass. However, such exotic nuclei have not been observed experimentally until now.

An international team of 75 scientists led by researchers from the RIKEN Meson Science Laboratory have now used a high-intensity proton accelerator in Japan called J-PARC to bombard a helium-3 target—a nucleus made up of two protons and one neutron—with a kaon.

By bombarding the nucleus with negatively charged kaons, they were able to eject a neutron. The knocked-out neutron was then replaced by a kaon, resulting

in a tightly bound nucleus consisting of two protons and one kaon. The nucleus had a large binding energy and proved to be bound more tightly than the researchers had anticipated.

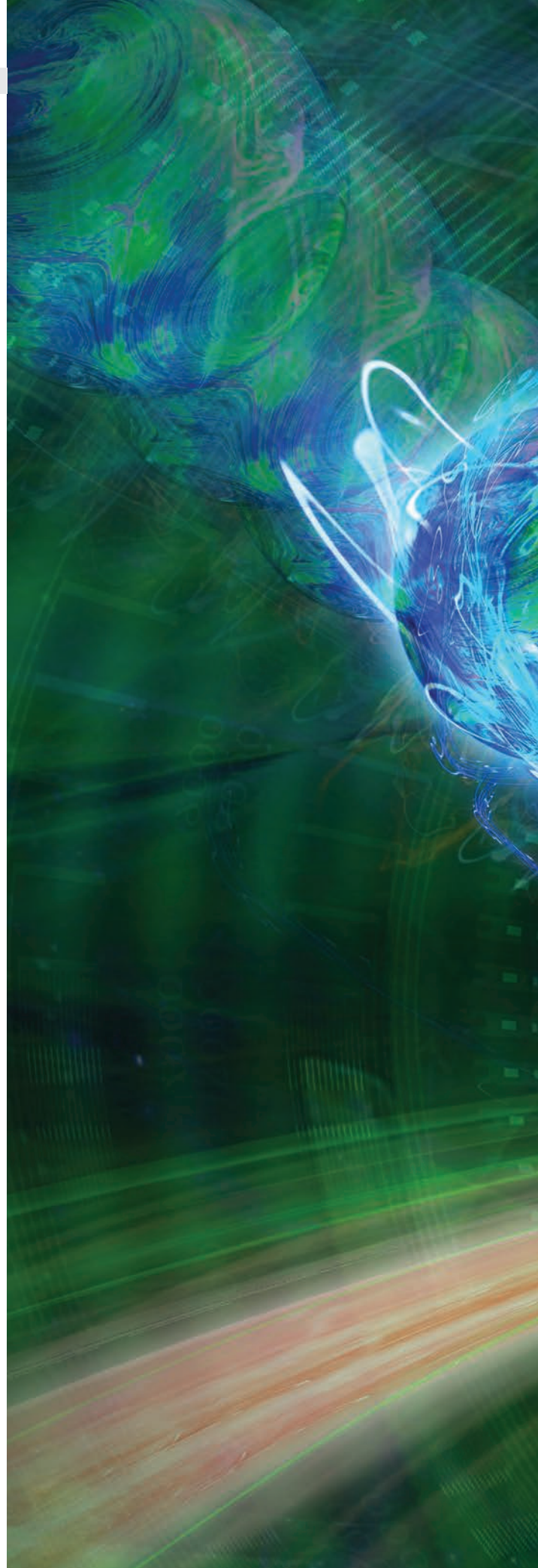
“We have shown that mesons can exist in nuclear matter as a real particle—like sugar that is not dissolved in water,” says Masahiko Iwasaki, the team leader. “This opens up a whole new way to look at and understand nuclei.”

The finding has important implications for the physics of both nuclei and neutron stars, Iwasaki says. “Understanding such exotic nuclei will give us insights into the origin of the mass of nuclei, as well as to how matter forms in the core of neutron stars.”

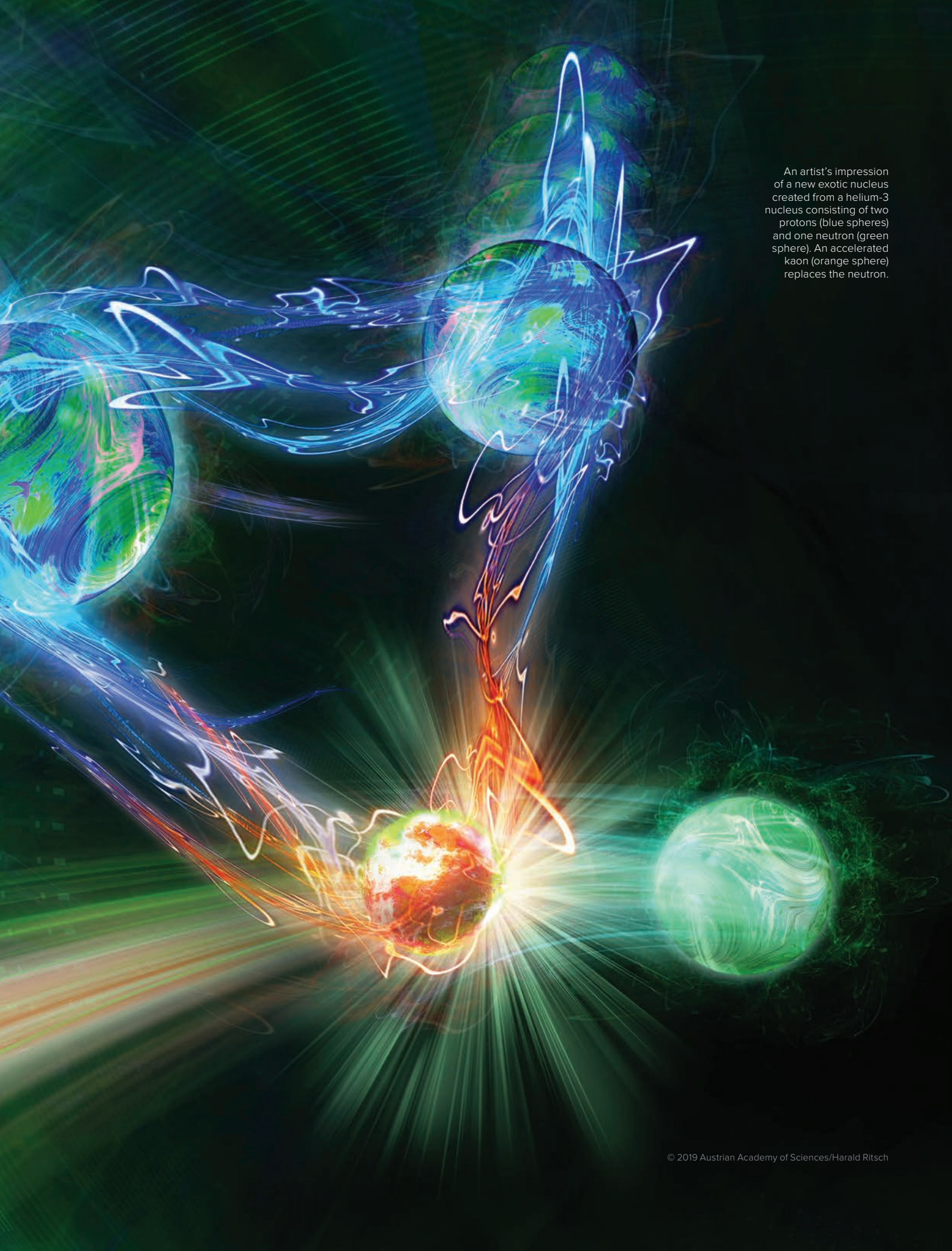
“We intend to continue experiments with heavier nuclei to further our understanding of the binding behavior of kaons,” says Iwasaki. “It will be a tremendous breakthrough if we can successfully repeat the experiment with higher precision and do it with heavier nuclei than helium,” notes Johann Zmeskal of the Austrian Academy of Sciences. “We could then produce extremely dense nuclear matter under laboratory conditions and at normal temperatures.” ●

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An artist's impression of a new exotic nucleus created from a helium-3 nucleus consisting of two protons (blue spheres) and one neutron (green sphere). An accelerated kaon (orange sphere) replaces the neutron.



An artist's impression of a gamma-ray burst, one of the Universe's most energetic events.

## GAMMA-RAY BURSTS

# Tracking down the origin of photons in gamma-ray bursts

The source of one of the Universe's most energetic events has been located

The photons released by long gamma-ray bursts—the most powerful electromagnetic phenomena in the Universe—originate in the photosphere, the visible portion of the ‘relativistic jet’ emitted by exploding stars, according to simulations by RIKEN researchers<sup>1</sup>.

Gamma-ray bursts (GRBs) release as much energy in about a second as the Sun will release over its entire lifetime. After their discovery in 1967, decades of study finally revealed that long bursts of a type of GRB originate from relativistic jets of

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**“This strongly suggests that photospheric emission is the emission mechanism of GRBs”**

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matter ejected during the death of massive stars. However, exactly how the gamma rays are produced from the jets is still a mystery today.

The Yonetoku relation, which provides the tightest correlation

yet between the spectral peak energy and peak luminosity of observed GRBs, acted as a diagnostic breadcrumb for an international team of researchers from Japan, the UK and the USA, to follow in their attempts to explain the emission mechanism.

The group focused on the photospheric emission model, one of the leading models for GRB emission. This model postulates that the GRB photons visible on Earth are emitted from the photosphere of the relativistic jet. As the jet expands, it becomes

easier for photons to escape from within it, since there are fewer objects available to scatter the light.

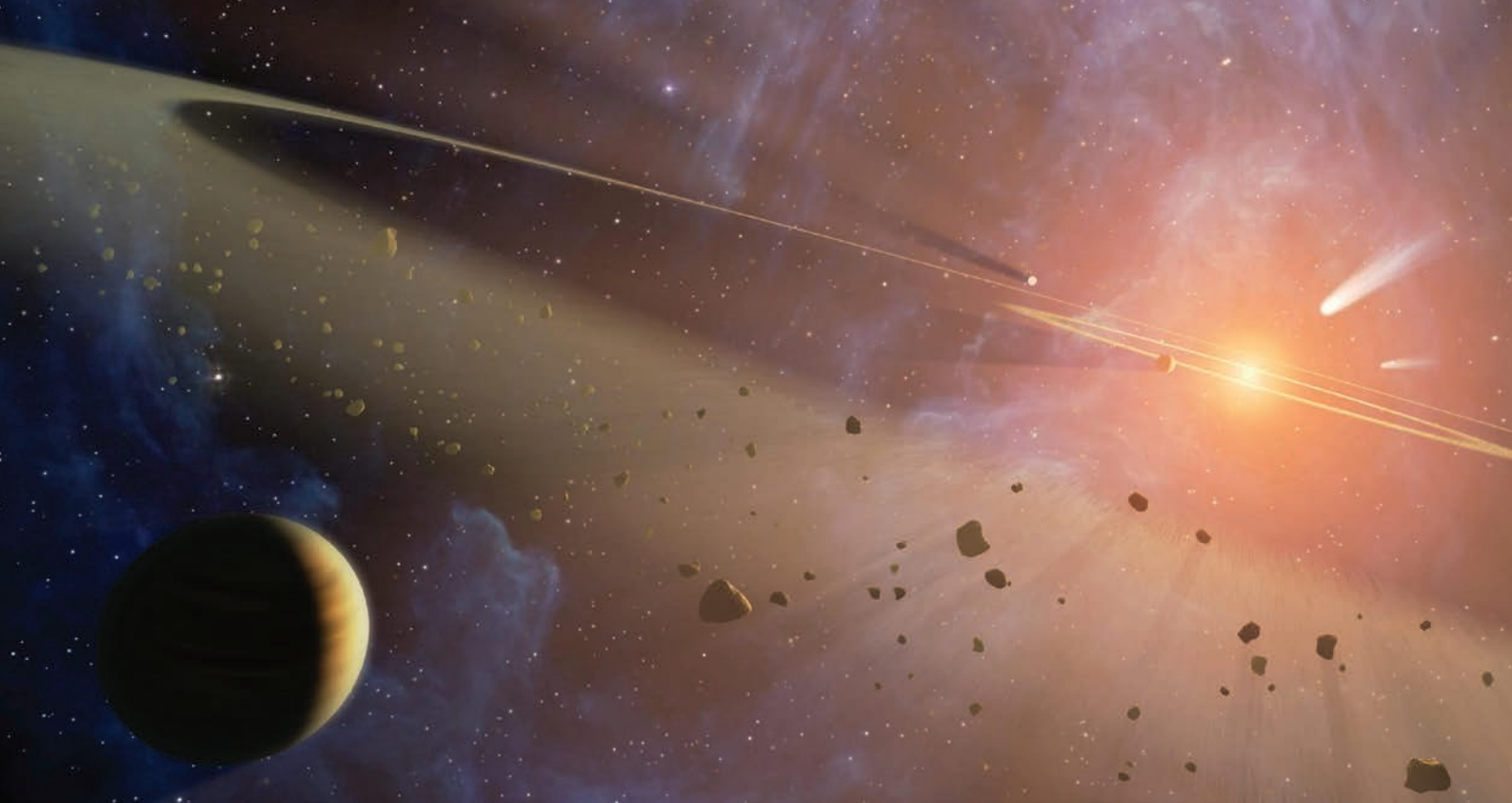
To test the validity of the model, the researchers took into account the global dynamics of relativistic jets and radiation transfer. By employing a combination of three-dimensional relativistic hydrodynamical simulations and radiation transfer calculations to evaluate photospheric emissions from a relativistic jet breaking out of a massive star's envelope, they were able to determine that at least in the case of long GRBs—the type associated with such collapsing massive stars—the model worked.

Their simulations, performed on several supercomputers, revealed that the Yonetoku relation could be reproduced as a natural consequence of the jet-stellar interactions. “This strongly suggests that photospheric emission is the emission mechanism of GRBs,” says Hirotaka Ito of the RIKEN Astrophysical Big Bang Laboratory.

“While we have elucidated the origin of the photons, there are still mysteries concerning how the relativistic jets themselves are generated by the collapsing stars. Our calculations should provide valuable insights for looking into the fundamental mechanism behind the generation of these tremendously powerful events,” he adds. ●

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An artist's impression of a planetary system in which planets are being birthed. Astronomers at RIKEN have discovered a protoplanetary system that consists of two clouds rotating in different planes.

## PLANETARY SYSTEMS

# Warping begins early in life

The observation of two clouds rotating in different planes around a protostar hints at an early origin of the misalignment of planets' orbits

**A** warped disk around an infant protostar that formed a mere several tens of thousands of years ago has been observed by RIKEN astronomers<sup>1</sup>. This suggests that early distortions in planet-forming disks may be responsible for the misalignment of planet orbits seen in many planetary systems, including our own Solar System.

The planets in the Solar System orbit in planes inclined by up to about 7 degrees relative to the Sun's equator. The Solar System is not unique in this respect—planets in many other planetary systems do not orbit in the plane of the equator of their star, and their orbits are often in different planes from each other.

One explanation for this is that some of the planets may have collided with other objects in the system or have been perturbed from their initial orbital planes by stars passing by the system.

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### The disk is very young and still growing

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Another possibility is that warping of the star-forming cloud that birthed the planets caused the planets to be formed in a different plane from the star's equator. Recent images of protoplanetary disks—rotating disks in which planets form

around a star—have shown such warping, but it is unclear how early this happened.

Now, by using the ALMA radio telescope in Chile, Nami Sakai of the RIKEN Star and Planet Formation Laboratory and her co-workers have discovered that an infant protostar still embedded within a cloud has a disk that has two parts—an inner one rotating in one plane and an outer one in a different plane. The disk is very young and still growing.

“This observation shows that it is conceivable that the misalignment of planetary orbits can be caused by a warped structure formed in the earliest stages of planetary formation,” says Sakai, who led the team. “We will have to

investigate more systems to find out if this is a common phenomenon or not.”

Sakai suggests two hypotheses for what caused the warping of the disk. “One possibility is that irregularities in the flow of gas and dust in the protostellar cloud are still preserved and manifest themselves as the warped disk,” she says. “A second possibility is that the magnetic field of the protostar is in a different plane from the rotational plane of the disk, and that the inner disk is being pulled into a different plane from the rest of the disk by the magnetic field.”

The team plans to do further work to determine which explanation best explains the disk's warping. ●

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## SMALL-MOLECULE DRUGS

# Small molecule kills tumors, not trees

Insights into the structure of an anti-cancer drug compound made by the Chinese perfume tree could lead to new precision therapeutics

**T**he discovery by RIKEN researchers of why a natural drug compound kills tumor cells—but not the plant from which it is derived—could help researchers develop new therapeutic weapons against cancer<sup>1</sup>.

The leaves of the Chinese perfume tree *Aglaiia odorata* contain a potent inhibitor of cancer proliferation. This drug, known as rocaglamide A (RocA), was thought to work by targeting an enzyme called eIF4A, which is needed to produce proteins in cells.

## The team is now turning to nature for insights into the molecular basis of various resistance pathways

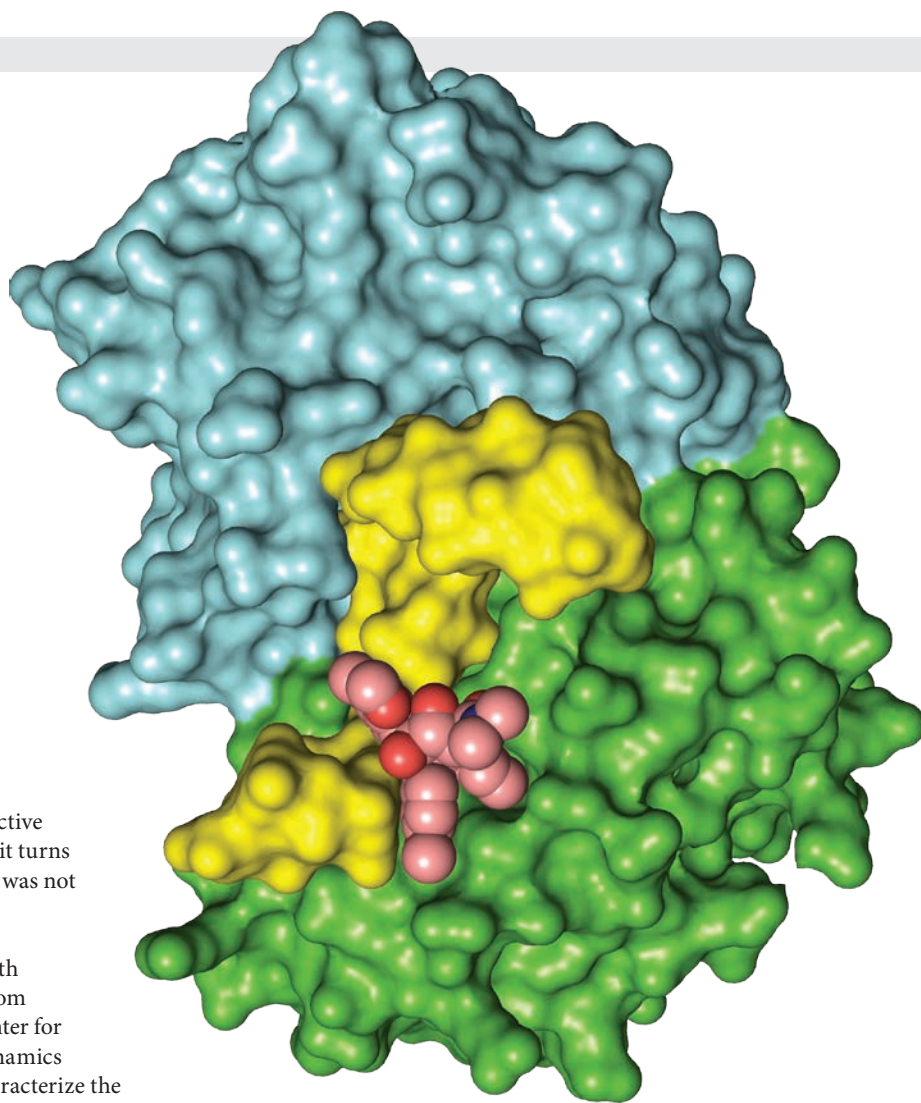
A few years ago, Shintaro Iwasaki from the RIKEN RNA Systems Biochemistry Laboratory showed that RocA clamps onto eIF4A at a specific RNA sequence, one jam-packed with consecutive adenines (As) and guanines (Gs). The drug then locks the complex into place and leads to defects in protein synthesis. It was the first time anyone had described

a drug capable of stabilizing RNA–protein interactions in a sequence-selective manner. But as it turns out, the picture was not yet complete.

Iwasaki collaborated with Takuhiro Ito from the RIKEN Center for Biosystems Dynamics Research to characterize the three-dimensional structure formed between RocA, eIF4A1 and target RNA. They showed that the long stretch of As and Gs produces a sharp bend in the RNA, creating a molecular cavity that fits the cancer-killing drug like a glove (see image). “To our surprise, RocA directly senses the RNA sequence on eIF4A, without affecting the protein’s shape,” Iwasaki explains.

That mechanistic insight could help drug developers design potent derivatives of RocA that nestle even more tightly into the cavity, says Iwasaki. Or it could lead to compounds modeled after RocA that bind structural pockets formed by different types of RNA sequences.

The RIKEN team also discovered why the Chinese perfume tree does not poison itself with its own drug compound. The researchers showed that the *Aglaiia* version of eIF4A contains



The anti-cancer drug rocaglamide A (pink) nestles into a cavity formed when the enzyme eIF4A1 encounters RNA sequences containing long stretches of adenines and guanines.

a small difference that changes the protein shape and prevents the formation of the usual RocA-binding pocket.

What is more, similar alterations were found in human cells that were resistant to the drug, suggesting it may be possible to design a predictive test for whether an individual patient will respond to RocA treatment or not.

Iwasaki and his team are now turning to nature for insights into the molecular basis of various resistance pathways. They are studying a parasitic fungus that lives on the leaves of the *Aglaiia* tree. RocA is supposed to protect the plant

from invaders, yet the fungus manages to escape the drug’s toxic effects. “We’re actively working on the mechanism,” Iwasaki comments. “Hopefully, it can help with precision medicine.” ●

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## MOTT INSULATORS

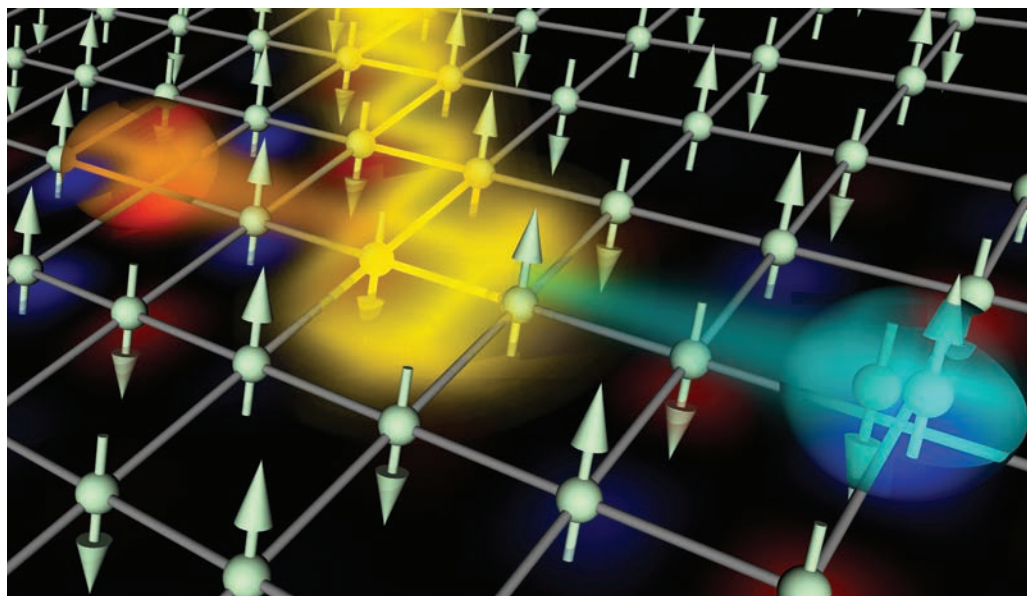
# Light may turn insulator into superconductor

Calculations suggest a new way to enhance superconductivity that uses light pulses

**L**ight pulses could transform a special type of electrical insulator known as a Mott insulator into a superconductor, which conducts electricity with no loss of energy, theoretical calculations by an all-RIKEN team indicate<sup>1</sup>. If confirmed experimentally, this effect could provide an alternative mechanism for enhancing superconductivity and hence lead to the development of new superconductors that could superconduct at high temperatures.

Mott insulators are examples of a class of materials that has been attracting much interest recently because they exhibit unusual phenomena due to the strong interactions between their electrons. For example, Mott insulators ought to conduct electricity according to conventional theory based on the energy bands of electrons, but they do not due to the interactions among their electrons. One reason for the interest in Mott insulators is that some of them can become superconductors under certain conditions.

Recent experiments have shown that solids can exhibit many intriguing phenomena when they are not under equilibrium conditions. Now, by performing numerical simulations, four RIKEN researchers have shown that non-equilibrium conditions could give rise to an unconventional type of superconductivity in strongly correlated materials due to a phenomenon known as eta ( $\eta$ ) pairing (see image).



Calculations by RIKEN researchers indicate that eta ( $\eta$ ) pairing of electrons (spheres, with arrows indicating their spin) induced by light pulses could cause a Mott insulator to superconduct.

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**“Our calculations showed that this takes place based on the beautiful mathematical structure that Yang and his followers formulated so many years ago”**

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Theoretical physicist Chen-Ning Yang first proposed the idea of  $\eta$  pairing three decades ago, but it was viewed as a virtual phenomenon that would not take place in the real world. However, when the researchers used non-equilibrium dynamics to

analyze the effect of pulses of light on a Mott insulator, they discovered that the effect could in fact happen in the real world.

“What is interesting is that our calculations showed that this takes place based on the beautiful mathematical structure that Yang and his followers formulated so many years ago,” notes Tatsuya Kaneko of the RIKEN Computational Condensed Matter Physics Laboratory.

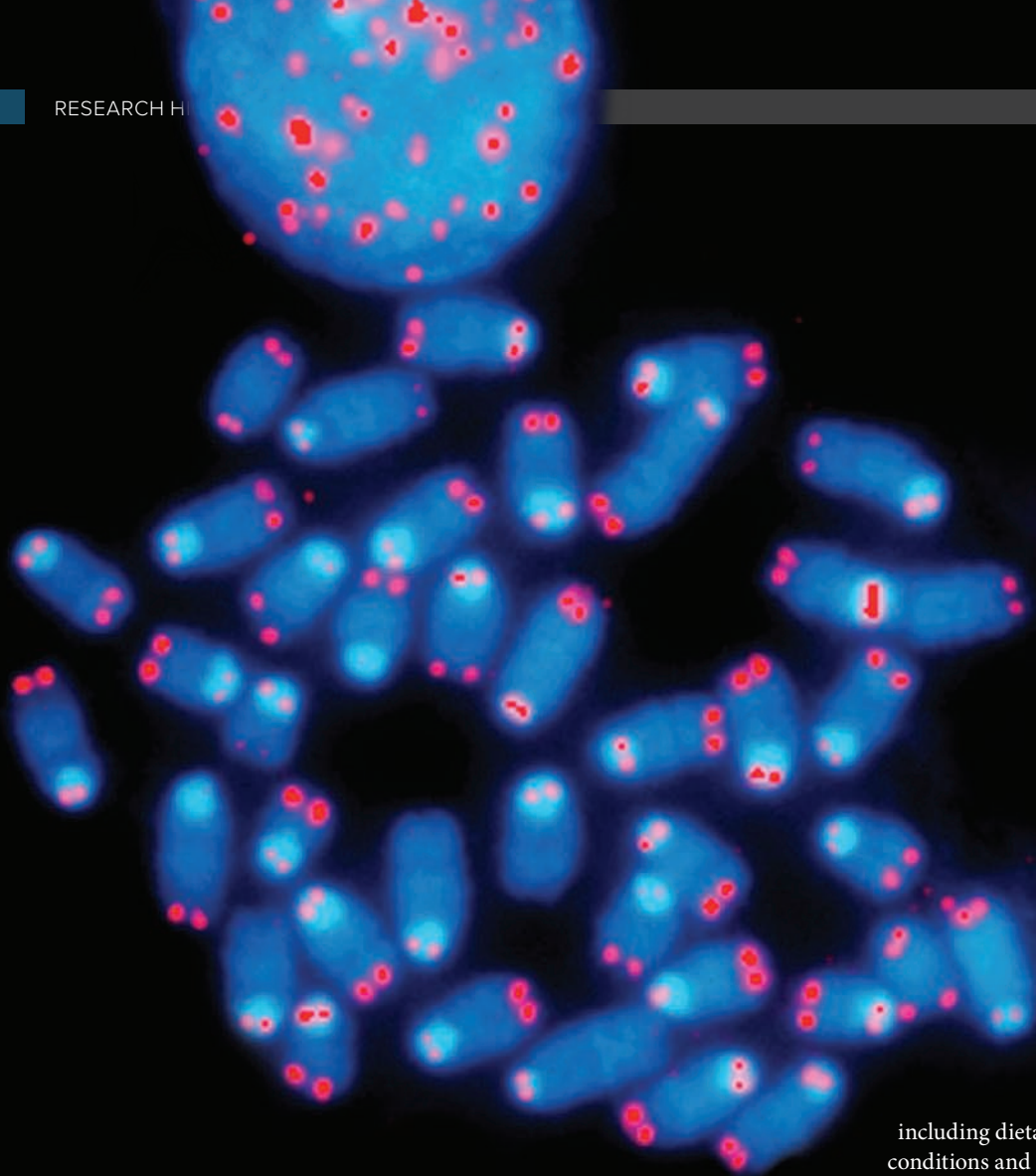
This  $\eta$ -pairing mechanism for superconductivity is thought to involve repulsive interactions between certain electrons within the structure. This mechanism differs both from that observed in the same strongly correlated materials under equilibrium conditions and from conventional superconductivity, which arises due to interactions

between electrons and vibrations of the atoms forming the crystal structure.

“This work not only provides new insights into the phenomenon of non-equilibrium dynamics, but also it could lead to the development of new high-temperature superconductors, which could be useful in applications,” says Seiji Yunoki, who led the team. “What remains is to perform actual experiments with Mott insulators to verify that this process actually takes place.” ●

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The red spots in this fluorescence light micrograph of human chromosomes are telomeres, which provide essential protection for the ends of the chromosomes. Premature telomere shortening may be associated with a variety of health problems.

## TELOMERE SHORTENING

# Stress runs in the family

The physiological effects of stress on male mice promotes chromosomal shortening, normally associated with early aging, in their offspring

**P**arents' experience of stress may negatively affect their children's health through a previously unknown genetic mechanism, a team of RIKEN scientists has shown<sup>1</sup>.

Up until relatively recently, the genes children received from their parents were considered to be passed on unchanged to their offspring. But there has been much interest of late in ways in which environmental factors can modify DNA and how these modifications can be passed onto the next generation. In this way,

a parent's lifestyle could affect their children's health.

One such modification involves telomeres—long stretches of repetitive DNA that cap the ends of the chromosomes and insulate our genes from damage. They shorten over the course of our lives, and this is thought to contribute to the biological process of aging, although external factors also promote premature telomere shortening. “A series of studies has demonstrated that various environmental factors,

including dietary conditions and psychological stress, shorten telomere length,”

explains Shunsuke Ishii at the RIKEN Cluster for Pioneering Research.

Previous studies have found evidence that children whose parents have experienced high stress levels may inherit shorter telomeres and consequently poorer health. But there has been no clear demonstration of cause and effect.

Now, by looking at how the effects of stress in adult mice affect the telomere integrity of their children, Ishii and his team have found a mechanism by which stress shortens telomeres in offspring.

The researchers had previously shown that injecting mice with a protein called tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )—a pro-inflammatory signal produced by the body during psychological

stress—triggered telomere shortening. “Thus, in this study, we tested whether injecting TNF- $\alpha$  into father mice can induce telomere shortening in their offspring,” Ishii says.

Following TNF- $\alpha$  injection, the germ cells that give rise to sperm produced elevated levels of telomere repeat-containing RNA (TERRA). These RNA transcripts selectively inhibit telomere maintenance and can thereby contribute to the shortening of these chromosomal structures. Importantly, the sperm produced by these mice retained the excess TERRA, and male offspring resulting from fertilization with these sperm exhibited significantly shorter telomeres.

Ishii believes this finding is an important step toward demonstrating that parental stress can potentially have a causal effect on a child's long-term health. “The main reason why the heritable effect of stress hasn't been widely accepted was that its mechanism was unknown,” he notes.

It should be straightforward to measure TERRA levels in human sperm, and Ishii now intends to conduct more tests of the extent to which different stressors trigger this effect. ●

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## METABOLOMICS

# Finding potential drugs from natural resources

New software can identify ten times more metabolites than existing methods

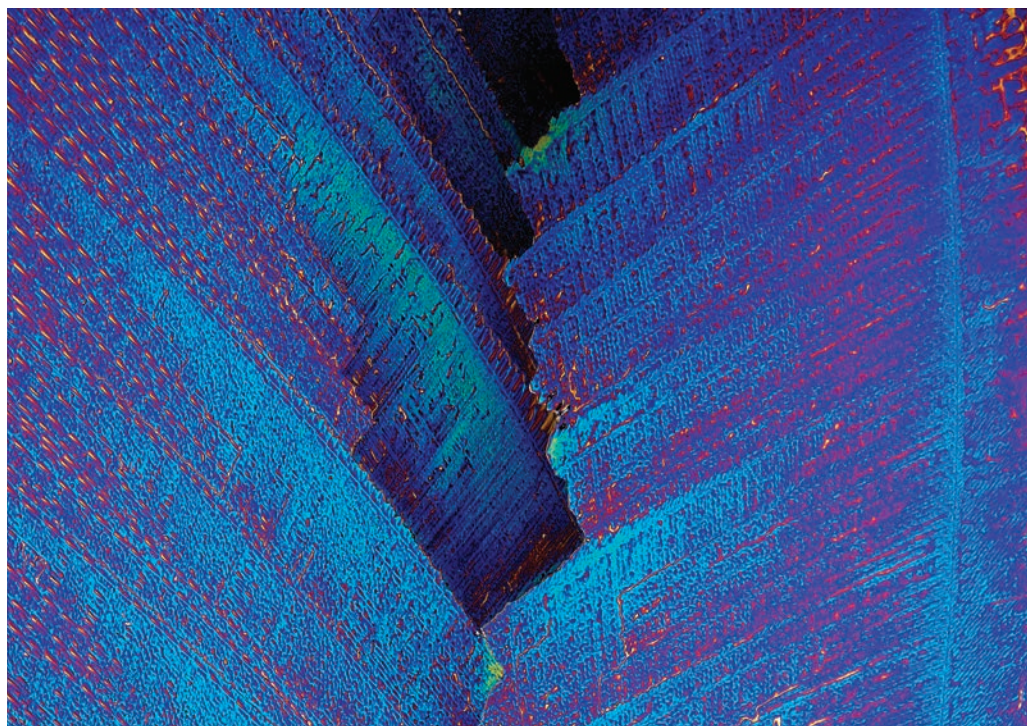
Over 1,000 metabolites, dozens of which had never been found before, some with antibiotic and anticancer properties, have been identified from 12 plant species. This demonstrates the potential of a new computational mass-spectrometry system for identifying metabolomes—sets of metabolites present in living organisms—that has been developed by RIKEN researchers<sup>1</sup>.

Computational mass spectrometry is a growing research field that focuses on finding previously unknown metabolites and predicting their functions. A team at the RIKEN Center for Sustainable Resource Science, led by Hiroshi Tsugawa and Kazuki Saito, has spent several years developing a system that can quickly identify large numbers of plant metabolites, including those that have not been identified before.

“While no software can comprehensively identify all the metabolites in a living organism, our program incorporates new techniques in computational mass spectrometry and provides ten times the coverage of previous methods,” explains Tsugawa.

## The new system will speed up the discovery of natural products that could be used in drugs

In tests, mass spectrometry-based methods only noted about 100 metabolites, whereas the team’s new system was able to



RIKEN scientists have developed a new method for identifying metabolomes, such as carbamide, shown here in crystal form.

find more than 1,000.

Their technique relies on several new algorithms that compare mass spectrometry outputs from plants labeled with carbon-13 to those that are not. The algorithms can predict the molecular formula of the metabolites and classify them by type. They can also estimate the substructures of unknown metabolites, and based on similarities in structure, link them to known metabolites, which can help predict their functions.

The ability to find unknown metabolites is a key selling point for the new software. In particular, the system was able to characterize a class of antibiotics (benzoxazinoids) in rice and maize as well as a class with

anti-inflammatory and antibacterial properties (glycoalkaloids) in the common onion, tomato and potato. It was also able to identify two classes of anticancer metabolites, one (triterpene saponins) in soy beans and licorice, and the other (beta-carboline alkaloid) in a plant from the coffee family.

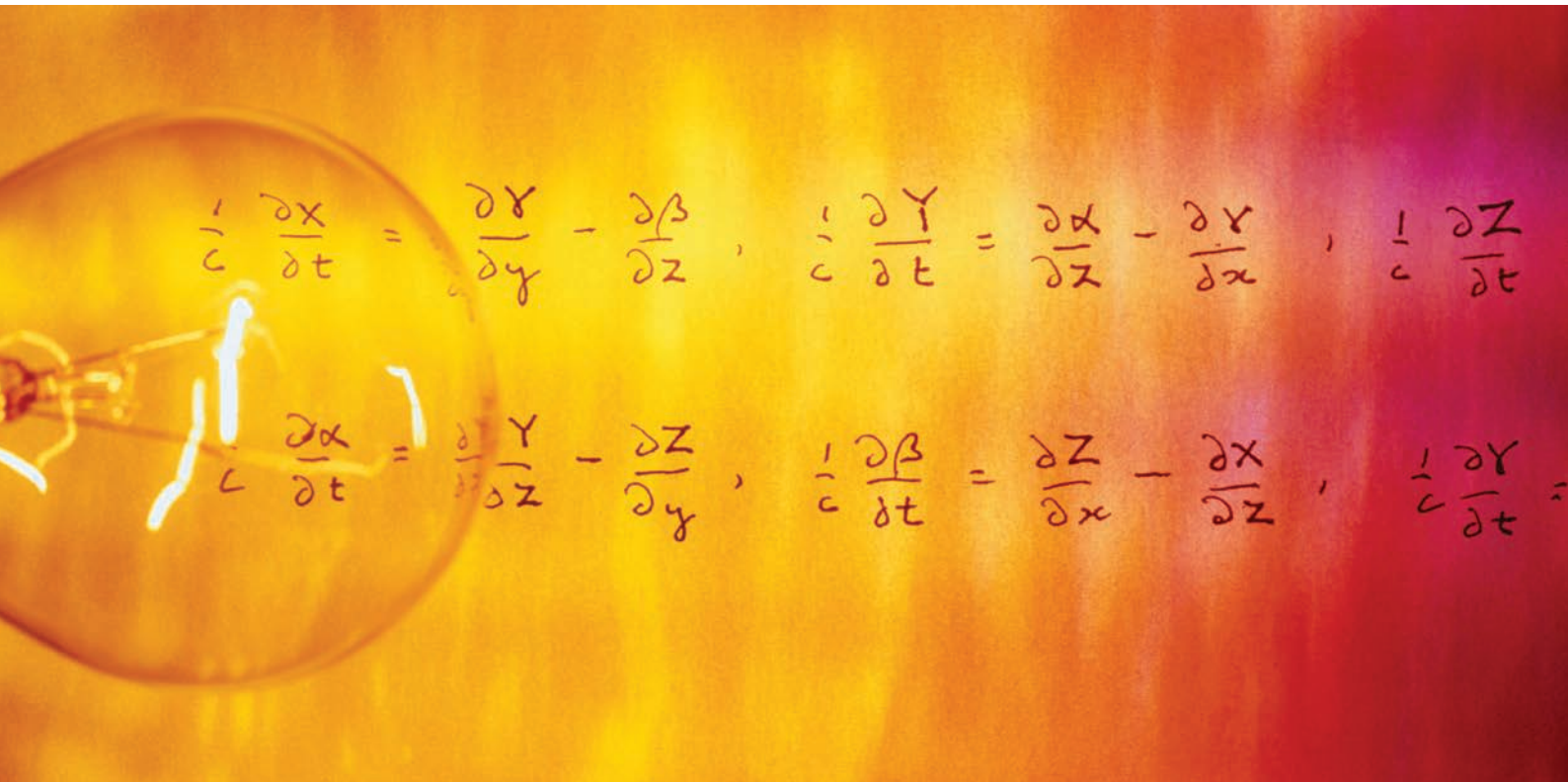
In addition to facilitating the screening of plant-specialized metabolomes, the new system will speed up the discovery of natural products that could be used in drugs and increase our understanding of plant physiology in general.

This method is not limited to plants. “I believe that computationally decoding metabolomic mass spectrometry data is linked to a deeper understanding of all

metabolisms,” explains Tsugawa. “Our next goal is to improve this methodology to facilitate global identification of human and microbiota metabolomes as well. Newly found metabolites can then be further investigated via genomics, transcriptomics and proteomics.” ●

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Surface electromagnetic waves that arise at interfaces between two materials whose optical properties are uniform and the same in all directions are given by solutions to the well-known Maxwell's equations (shown here). RIKEN researchers have now shown that they also have a purely topological origin.

## ELECTROMAGNETISM

# A new way of looking at surface waves

Some electromagnetic waves that occur at interfaces between two materials can be described in topological terms

**E**lectromagnetic waves that arise at interfaces between two homogeneous materials with certain optical properties, have a purely topological origin, physicists at RIKEN have shown<sup>1</sup>. In addition to providing a new way to describe such surface electromagnetic waves, this theoretical finding has repercussions for other areas of physics that involve waves besides electromagnetism.

Formulated more than a century and a half ago, James Maxwell's theory of electromagnetism was one of the greatest breakthroughs in physics. It united electricity and magnetism and provided a complete description of electromagnetic waves, including light waves.

Six decades ago, scientists found that electromagnetic radiation such as light can not only propagate in free space,

but can also form surface waves at interfaces between different optical media, such as metals and air or glass. This discovery has led to the development of the emerging fields of plasmonics and optical metamaterials, where surface electromagnetic waves are harnessed to achieve new applications that cannot be realized using conventional optical materials.

In recent years, the mathematical concept of topology has been applied to the quantum theory of solids, where it has resulted in many exciting new insights. For example, it can explain why certain materials conduct electricity on their surfaces but are insulators inside. Such topological systems are robust against small perturbations and continuous deformations.

Until now, electromagnetic waves that are topological in

nature have been demonstrated only in intricate nanostructures that have been carefully engineered. Now, Konstantin Bliokh and Franco Nori from the RIKEN Theoretical Quantum Physics Laboratory and two co-workers have shown that surface electromagnetic waves that arise at interfaces between two simple materials whose optical properties are uniform and the same in all directions have a purely topological origin.

Such waves have traditionally been described using Maxwell's equations, but this topological approach provides an alternative way of describing them that provides new insights. In particular, it illuminates the origin of surface electromagnetic waves and explains why these waves appear at interfaces where one



## NEUROSCIENCE

# Brain clock ticks differently in autism

Individual brain regions have been found to exhibit different time scales in people with autism

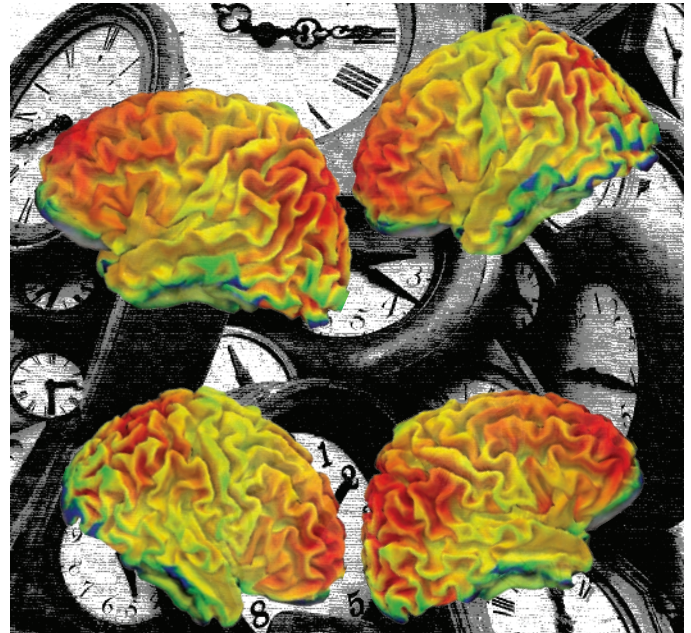
**T**he severity of autistic symptoms is linked to how long information is stored in certain small regions in the brain, a RIKEN researcher and his two UK colleagues have discovered<sup>1</sup>. Such differences in neural time scales could be useful as a future diagnostic tool.

Autism is a brain disorder that affects how people interact with others. While the brain as a whole is known to show less coordinated activity in autism, it had been unclear whether individual brain regions function differently in autism. To investigate this, the researchers compared magnetic resonance images of the brains of male adults with relatively mild autism with those of people without autism.

The trio found that the usual neural time scales—namely that sensory brain areas that receive input from the eyes, skin and muscles have faster processing times than higher order areas that integrate information and control memory and decision making—is disrupted in autism. This is one of the first indications that small-scale temporal dynamics could have an outsized effect.

“Shorter time scales mean higher sensitivity in a particular brain region, and we found the most sensitive neural responses in those individuals with the most severe autistic symptoms,” says lead author Takamitsu Watanabe of the RIKEN Center for Brain Science.

The researchers uncovered the opposite behavior in the brain area known as the right caudate. Here, the neural time



People with autism have been shown to have different time scales in individual brain regions compared to people without autism.

scale was longer than normal in the autistic group, particularly in individuals with more severe repetitive, restricted behaviors.

These differences in brain activity were also found in separate scans of autistic and non-autistic children.

The team considers that structural changes in small parts of the brain link these local dynamics to the symptoms of autism spectrum disorders. They observed changes in grey matter volume in the areas with atypical neural time scales. A greater density of neurons can contribute to recurrent, repetitive neural activity patterns, which underlie the longer time scales observed in the right caudate and the shorter ones found in the sensory and visual cortices.

“The neural time scale is a measure of how predictable the activity is in a given brain region. The shorter time scales we observed in the autistic individuals suggest their brains have trouble holding onto and processing sensory input for as long as neurotypical people,” explains Watanabe. “This may explain one prominent feature of autism, the great weight given by the brain to local sensory information and the resulting perceptual hypersensitivity.” ●

## Reference

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of the optical parameters that appear in Maxwell's equations changes its sign.

The researchers note that this topological approach is not limited to electromagnetism. “Our theory extends the range of applicability of the topological approach to other wave systems,” explains Bliokh. “It provides a new twist and insights for several areas of wave physics, including Maxwell electromagnetism, topological quantum states, plasmonics and metamaterials,” Nori adds. ●

## Reference

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## PARTICLE PHYSICS

# Trapping single antiprotons

A highly sensitive trap enables the magnetic properties of antimatter to be measured thousands of times more precisely than previously

**A** newly designed trap that can isolate single protons and their antimatter counterparts—antiprotons—better than ever before could help reveal why there is such a paucity of antimatter in the Universe<sup>1</sup>.

A conundrum that has long vexed physicists is why there is vastly more matter in the Universe than antimatter, despite the standard model of particle physics predicting that they should exist in equal quantities. “A big question in modern physics is what happened to all the antimatter after the Big Bang?” says Stefan Ulmer from the RIKEN Ulmer Fundamental Symmetries Laboratory.

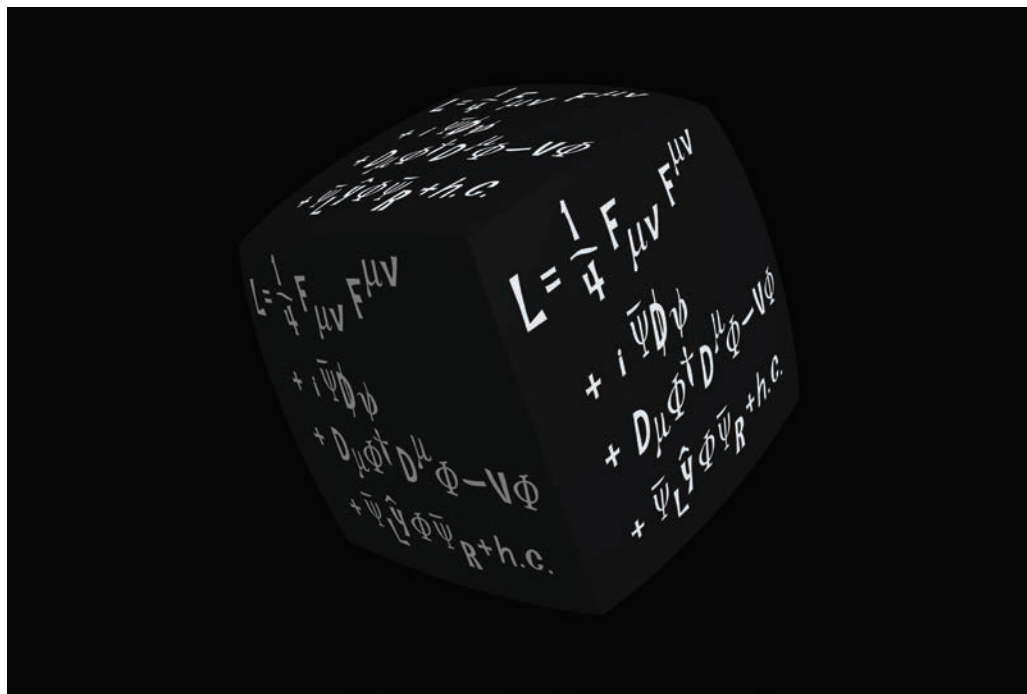
One way to search for answers is to compare the properties of particles and their antiparticle counterparts and see whether there are tiny deviations between them.

Isolated from its environment, a proton will behave according to the fundamental laws of physics. For this reason, getting a single proton on its own offers a fascinating way to observe these natural laws and compare them to the predictions of our best theoretical models.

“In the search for new physics, the strategy is always to observe a well understood system and search for deviations from our understanding,” explains Ulmer.

A good technology for isolating antiprotons is an ion trap, which employs crossed electric and magnetic fields to stably store a particle.

The cryogenic ion trap developed by Ulmer and



The standard model of particle physics predicts that there should be equal amounts of matter and antimatter in the Universe. A new ion trap that allows ultraprecise measurements of the magnetic moments of protons and antiprotons may help scientists discover why this prediction does not hold.

colleagues isolates either protons or antiprotons to enable measurement of their magnetic moment: a measure of the intrinsic magnetic field they produce. They hope to identify some asymmetry between the properties of protons and antiprotons that would explain why matter is tremendously more abundant than antimatter.

The challenge is to make these measurements as precise as possible. One particular problem is anomalous heating: quantum-mechanical changes in the particle motion driven by noise in the system that can alter the particle’s energy and fundamentally limit the precision of measurements.

Until now, measured heating rates have been several orders of magnitude higher than those predicted by theory. In this study, heating rates were measured in a cryogenic Penning trap for the first time and were found to be orders of magnitude lower than those observed before, resulting in quantum stabilities that are 100 times higher than previously achieved.

“The current ultralow-noise conditions in our system are the results of many years of noise decoupling and technical improvements,” notes Matthias Borchert, the first author of the study.

With such a stable system, the team could determine

the antiproton magnetic moment with a precision 3,000 times better than previous experiments. “To put this into context, 1,000-fold improvements in precision-measurement studies,” comments Ulmer. ●

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RIKEN researchers have used the Atacama Large Millimeter/Submillimeter Array (ALMA) telescope array in Chile to study a molecular cloud in which two massive protostars are forming.

## BINARY STARS

# Witnessing the birth of a massive binary star

Astronomers have glimpsed two massive protostars that will eventually form a pair of orbiting stars

**A** molecular cloud that is collapsing to form two massive protostars, which will eventually form a binary star system, has been observed by RIKEN researchers<sup>1</sup>. This adds weight to the hypothesis that binary stars are born from the same stellar ‘womb’.

Most massive stars have orbiting stellar companions, but it has been unclear how such systems form. The two stars may form together from the same spiraling gas disk at the center of a collapsing cloud or they could pair up later through a chance encounter in a crowded star cluster.

Discovering the dynamics of forming binaries has been difficult because the protostars in these systems are enshrouded by thick clouds of gas and

dust, which prevent most light from escaping. But they can be observed using radio waves, provided they can be imaged at a sufficiently high spatial resolution.

Now, researchers led by Yichen Zhang of the RIKEN Star and Planet Formation Laboratory have observed a star-forming region at high spatial resolution using the Atacama Large Millimeter/Submillimeter Array (ALMA) telescope array in Chile.

Their observations revealed that already at this early stage, the cloud contains a massive primary central star and a secondary forming star, also of high mass. The team found that the two forming stars are quite far apart, being separated by a distance about 180 times that from the Earth to the Sun.

“This is an exciting finding because we have long been perplexed by the question of whether stars form into binaries during the initial collapse of the star-forming cloud or whether they are created during later stages,” says Zhang. “Our observations clearly show that the division into binary stars takes place early on, while they are still in their infancy.” He adds that it is important to look at other systems to see whether this is a special case or is common for the birth of all massive stars.

The observations also showed that the binary stars are being nurtured from a common disk fed by the collapsing cloud. This favors a scenario in which the secondary star forms due to fragmentation of the disk that was originally around the

primary star. The initially smaller secondary protostar can thus ‘steal’ infalling matter from its sibling and eventually they should emerge as quite similar twins.

“This is an important result for understanding the birth of massive stars,” adds second author Jonathan Tan. “Such stars are important throughout the Universe, not least for producing, at the ends of their lives, the heavy elements that make up our Earth and are in our bodies.” ●

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# NOW POLYMERS CAN SELF-HEAL, EVEN WHEN WET

*New spontaneously self-healing polymers don't mind a bit of wetness, and they may be useful in everything from dentistry to liquid crystal display (LCD) screens*

**I**magine if a crack in your smartphone screen disappeared in minutes. At RIKEN, several new polymers that can heal with great strength, without outside energy input, and even in water, or acidic and alkaline solutions, hint at this possibility.

It's the latter three conditions that sets us on the path of everyday use in self-healing liquid crystal display (LCD) screens. While self-healing materials have been on the radar for more than a decade, most conventional self-healing polymers face at least two barriers: one, some kind of energy, such as heat or pressure, needs to be applied to stimulate healing, and, two, these materials don't heal well when wet.

Both of these problems are linked to fact that these materials typically manipulate particular bonds, such as hydrogen bonds, covalent bonds or ionic interactions—covalent bonds require extra energy to re-form, and hydrogen and ionic bonds can be broken in water, and acidic or alkaline liquids.

Now, a team led by Zhaomin Hou of the RIKEN Center for Sustainable Resource Science, has developed a number of self-healing polymers in which physical bonds spontaneously reform when ruptured. And, because these bonds are unique, contact between the polymer and water, acid or base solutions—as is the case in liquid crystal display screen construction—doesn't inhibit self-healing.

The scientists have been able to create a number of polymer materials, including soft viscoelastic materials, tough elastomers—materials able to be stretched and return to their original shape—and rigid plastics.

Initially, the stretchy elastomers have shown the most promising self-healing properties, says Hou. For example, in one test, when one of the elastomer polymers was cut in two with scissors, when held together the parts recombined within minutes. After five days of self-healing at room temperature, this process had created bonds so strong that the polymer didn't break along the cut when stretched to several times its original length. The authors describe this measured strength as “the highest ever reported for an autonomously repaired material...even higher than most pristine autonomous self-healing materials reported to date.”

#### USING PHYSICAL FORCE

The secret lies in the polymers' structure, composed of long, spaghetti-like molecules that are formed by two monomers—the building blocks from which polymer molecules are made. One is ethylene ( $C_2H_4$ ),



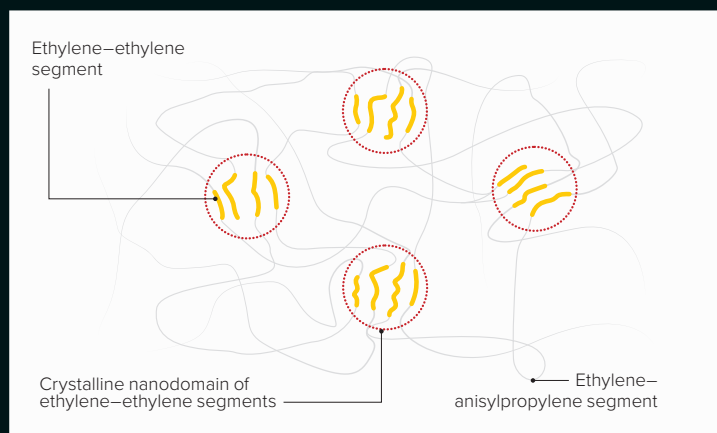
**This feature looks at the work of ZHAOMIN HOU**

Zhaomin Hou obtained his PhD in chemistry from Kyushu University in Japan in 1989. After postdoctoral training at RIKEN and the University of Windsor in Canada, he joined RIKEN in 1993. Since 2013, he has worked as the Deputy Director of the RIKEN Center for Sustainable Resource Science (CSRS), concurrent to his work as Group Director of the Advanced Catalysis Research Group at the CSRS and the Director of the Organometallic Chemistry Laboratory at RIKEN. His research interests include the activation and utilization of small molecules such as nitrogen gas and carbon dioxide and the development of more efficient, selective catalysts for synthesizing functional molecules and polymers.

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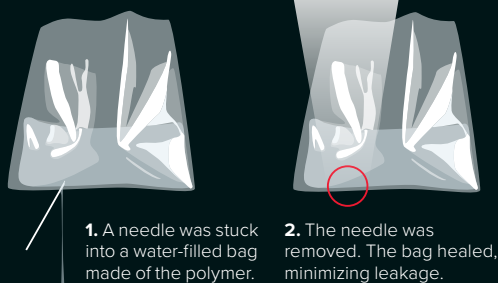
## THE NEW ORDER

RIKEN's new self-healing polymer is made of long ethylene–anisylpropylene strings and shorter ethylene–ethylene segments. The ethylene parts of the polymer tend to cluster into crystalline islands, and that clumping is believed to drive the self-healing.



## NO MORE LEAKS

One of the benefits of polymers that self-heal in the presence of water is that they can stem small leaks in packaging, which is something the RIKEN team tested.



1. A needle was stuck into a water-filled bag made of the polymer.
2. The needle was removed. The bag healed, minimizing leakage.

the same monomer that makes up polyethylene, the most popular plastic in the world, used to make plastic bags, shampoo bottles and toys. The other monomer is known as anisylpropylene.

Normally, it would be next to impossible to combine these two monomers in the desired manner. They are not usually attracted to each other, as anisylpropylene is polar, meaning that it contains units in which one end is slightly positively charged and the other end is slightly negatively charged, while ethylene is non-polar. Usually, anisylpropylene is also much less reactive than ethylene for polymerization.

Hou's team was able to overcome the reluctance of the two monomers to combine by using a catalyst—tiny amounts of a rare-earth metal called scandium. They also combined the two monomers in a controlled manner, so that by varying the initial conditions, they could make a whole series of polymers with slightly different properties.

The copolymers created consist of relatively long segments, in which ethylene alternates with

anisylpropylene, and these are punctuated by shorter strings of ethylene units. Weak physical bonds form between the alternating segments, as well as between the ethylene segments. Consequently, when these bonds are ruptured by cutting the polymer, they will try to reform, and it is this that creates the elasticity and self-healing properties of the polymer.

## PLENTY OF REAL-WORLD POSSIBILITIES

Hou and his team didn't set out to make self-healing polymers. "It was a serendipitous discovery," he says. "We knew we could make new structures, but we had no way of predicting what their mechanical properties would be. It was only after we made the polymer and checked its properties that we discovered it could self-heal."

Even after making the polymer, Hou's team were in the dark about how it was healing itself. "We're synthetic chemists, and so it was challenging for us to understand the physical properties of the resulting polymer," explains Hou. "To pin down how it was self-healing, we had to collaborate with some polymer physics specialists at Kyushu University."

The teams were soon demonstrating just how useful the new polymers could be. For example, the team made a bag from one polymer and filled it with water. When punctured with a needle, this polymer's self-healing process was so fast that little water dripped out as the needle was removed and the bag self-healed. This, says Hou, could pave the way for more robust or reusable food packaging or blood transfusion bags.

Their elastomer polymers are also strong and have good elasticity, one able to be stretched to 20 times its original length. Both the flexible and rigid plastics the teams created had excellent shape memory, meaning that they can return to their original shapes after being stretched and distorted at a high temperature and cooled and then heated. It will mean these polymers can be molded into industrially useful forms, explains Hou.

"The potential is huge," he enthuses. "There are many, many potential applications." His team has already received enquiries from companies in various fields ranging from automobiles to cell phones, and medical care. But Hou says the first step will be to team up with a chemical company to work out how to produce large quantities of the polymers, which he says should be able to be made relatively cheaply. The group will also continue to try using other combinations of monomers to see what other kinds of polymers they can materialize. ●

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**MOTOKO KOTANI**  
Executive Director,  
RIKEN

Motoko Kotani has been executive director for international affairs since 2017. She has a doctorate in mathematics. She became associate professor at the Mathematical Institute at Tohoku University in 1999 and then a professor in 2004. Since 2012, she has been Director for the WPI Advanced Institute for Materials Research at Tohoku University. She is also an executive member of the Japanese government's Council for Science, Technology and Innovation.

# RIKEN'S GLOBAL GOALS

*RIKEN's strong international links will be expanded by new organizational commitments, says RIKEN Executive Director Motoko Kotani*

**D**uring my more than ten years at the forefront of Japan's international research network expansion, I have seen global agendas become more vital. The areas that need our attention most have been highlighted in the form of 17 Sustainable Development Goals (SDGs), adopted by the United Nations in 2015. These address the global challenges we face to achieve a better and more sustainable future. All will need to be addressed via coordinated multinational research efforts.

In 2016, the Japanese government began to look at how to act on these issues through research, as part of its Science, Technology and Innovation for SDGs (STI for SDGs) roadmap. In 2017, among the points outlined in the STI for SDGs basic promotion document, policy-makers stated that: "In order to enhance and develop the efforts of the STI for SDGs continually, it

is essential to foster human resources who can connect science with politics, administrations, and various sectors in and outside Japan, with historical and international perspectives and geopolitical knowledge."

The Japanese government has made it clear that research institutions, including RIKEN, have a responsibility to reach out and continue to make the most of their strong international connections, not just with other academic organizations, but with many stakeholders.

As the executive director in charge of international affairs at RIKEN, I have often discussed Japan's excellent research reputation with other leaders around the world. In the past, however, the Japanese research community was not fully aware of its responsibility to become part of global conversations. Today, RIKEN is expected to play a central role in making these connections and to become a hub that gathers research talent from around the world.

At the new MPG-PTB-RIKEN Centre, opened in January 2019, the world's leading physicists will collaborate to measure time and fundamental physics using ultraprecise equipment. RIKEN physicist Stefan Ulmer (top left) is a spokesperson for both the new center and the BASE project at CERN, which is a series of studies trying to establish the differences between matter and antimatter.

RIKEN comes to this mission from a position of strength. In September 2018, about 20 percent of the almost 2,000 researchers at RIKEN hailed from foreign countries, which is a contrast compared to roughly five percent across Japan. Despite this, increasing organization-to-organization efforts are important to ensure RIKEN's voice continues to be a part of key global conversations, beyond the impressive input of its individual researchers.

**BALANCING TOP-DOWN AND BOTTOM-UP COLLABORATIONS**

My perspective on how to create a vibrant international community comes from more than a decade of experience working on building a successful, world-class research environment. During an intensification of research globalization that began in the mid-2000s, the Japanese government encouraged universities to cultivate highly

autonomous and “globally visible” research hubs, one of which I lead.

One of the biggest challenge in creating these hubs is how to balance top-down and bottom-up approaches. Research collaborations should be based on bottom-up ideas and personal connections between individual researchers. However, a bottom-up approach on its own rarely translates into bigger and more multidisciplinary projects that bring long-term benefits to an entire organization.

Top-down, organization-to-organization collaborations have become the focus of many research administration efforts. However, I would also emphasize that this top-down approach is only effective when researchers already have strong ties with organizational partners. Our challenge, in the International Affairs Division, has been to identify bottom-up collaborations with the potential to apply or extend into other research areas and

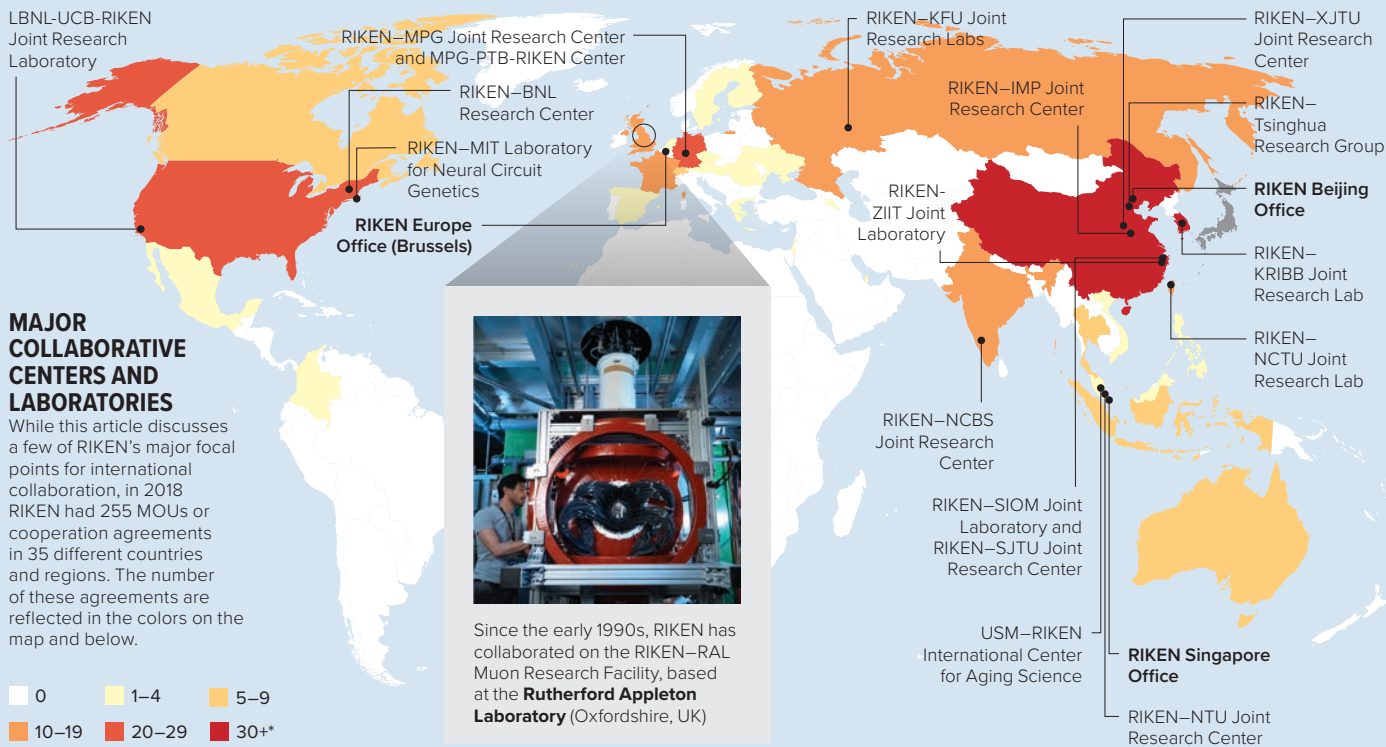
become fruitful, long-term organization-to-organization collaborations.

**STRATEGIC RESEARCH PARTNERS**

RIKEN has recently chosen to invest in a number of both top-down and bottom-up collaborations with existing overseas partners. This has been achieved through the International Collaborations with Strategic Research Partners initiative, a key pillar of RIKEN's mid- to long-term management plan, which runs from 2018 to 2025.

After an internal callout, four projects became the first to be adopted by the initiative in 2018.

The first will explore fundamental physics by using ultraprecision frequency measurements in collaboration with long-time collaborator, the Max Planck Society (MPG), and the National Metrology Institute of Germany (PBT). The MPG was an organizational inspiration when RIKEN was



\*As of March 31, 2019, © 2019 STFC Rutherford Appleton Laboratory



established, and has been a key research partner for more than 30 years.

The second project is aimed at strengthening international alliances in genome research between Japan, the United States and Europe. This will mean additional support for the Human Cell Atlas, a project aiming to understand the roughly 37 trillion cells of the human body. RIKEN will lead this global project's efforts in Asia through the work of its Single Cell Project.

The third initiative, a collaboration with the Cincinnati Children's Hospital in the US, will work on advanced organoid medical research. As RIKEN does not own a hospital, collaborating with major hospitals is vital to advance RIKEN's clinical research.

The fourth project will develop an innovative drug-delivery system using glycan pattern recognition and synthetic chemotherapy *in vivo*, with Kazan Federal University in Russia. The Russian university and RIKEN's biofunctional synthetic chemistry team have already achieved impressive results together, and we will support their moves to develop practical medical treatments from their findings.

### CONNECTING WITH ASIA, EUROPE, AND THE UNITED STATES

In recent years, we have focused on forging global collaborations, including with government-related bodies. While RIKEN already has 255 research cooperation agreements and memoranda of understanding, recently we increased our presence in Europe, the United States and China.

In addition to our facilities in the United States and United Kingdom, we have joint research centers or laboratories in China, Germany, India, Korea, Malaysia, Russia, Singapore and other countries.

RIKEN's international offices in Singapore, which opened in 2006, and Beijing, which opened in 2010, are identifying potential research partnerships and strengthening links with Asian government officials, as well as building an alumni network and helping to recruit promising young researchers from Asia.

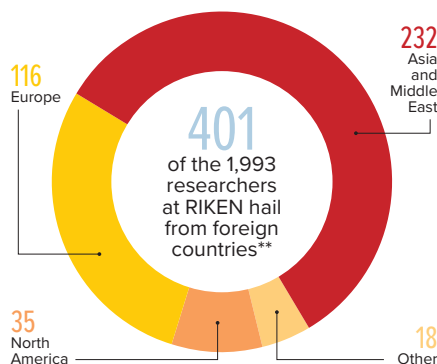
China is vigorously developing science and technology infrastructure, and a number of Chinese organizations have already noted that RIKEN has experience building big facilities, such as the SPring-8 large synchrotron radiation facility and the K computer. A number of Chinese institutes

have expressed a desire to cooperate with RIKEN on infrastructure construction and operation, which will likely be a fertile basis for future collaborations.

European intuitions are among our most valued partners, given their high productivity and research impact; their experience creating frameworks and rules; and the existence of various important initiatives within the European Union (EU), at both the national and regional level. A quarter of RIKEN's international researchers also came to us from Europe. It is therefore natural that our third overseas office was opened in the European quarter of Brussels in November 2018. The new office's

### INTERCONNECTED

A range of international researchers work at RIKEN, which has ties with China, Europe and North America reaching back to the 1980s and 1990s. (See left and page 32)



mission is to contribute to enhancing RIKEN's research excellence and capacity. The Europe Office is working to raise RIKEN's visibility in Europe, through the promotion of collaborative research and innovation; facilitating of mutual access to resources; systematic collection and analysis of information on STI policies and programs; and the creation of strong links with European research institutions, EU and governmental organizations, funding organizations and other relevant bodies. To reach out to some of these partners, we will host a symposium in Brussels for the first anniversary of the opening of the Europe Office, in December 2019.

In the United States, RIKEN's Interdisciplinary Theoretical and Mathematical Science (iTHEMS) program owns a laboratory within the well-known Lawrence Berkeley National Laboratory at

the University of California, Berkeley. In the near future, we also hope to make space there available for RIKEN's other centers to enhance collaborations along the Pacific Rim.

### INTERNATIONALIZING LIFE AND WORK

RIKEN is also already well ahead in terms of the structures needed work with a global research cohort.

I believe RIKEN is an ideal place for young foreign researchers to begin their careers. It has an international and open atmosphere, in which researchers can pursue research excellence in a world-class environment, with strong support both in work and life. In this area, RIKEN leads the pack.

RIKEN also provides exciting opportunities for young scientists from all over the world during the crucial early years of their careers. For example, the Special Postdoctoral Researcher Program offers young scientists a three-year position and funding for an autonomous research project under the direction of a RIKEN laboratory head. RIKEN also accepts non-Japanese PhD candidates as International Program Associates (IPA) through collaborations with partner universities. IPAs are doctoral candidates attending a Japanese or overseas graduate school at the partner university, who also conduct research at RIKEN under the supervision of RIKEN scientists as part of the process of obtaining their PhD. RIKEN has also recently set up the RIKEN Hakubi Fellows Program, which offers exceptionally talented junior principal investigators positions for a maximum of seven years, and the Kato Sechi Program for women who are outstanding researchers. Ensuring career opportunities at this level will be important for both young researchers and also for the continued development of science and technology research networks into the future.

Finally, to support the researchers who come to Japan from elsewhere, RIKEN has developed strong family, language and cultural support: health insurance is covered; English-speaking childcare facilities have been set up around Japan; and an international secondary school is located near the main campus in Wako. Most importantly, researchers themselves have much to gain from RIKEN's scientific cohort and cutting-edge equipment, and will benefit from the ample opportunities for promotion.

We are always looking to further expand our network, so please get in contact with us to discuss future collaborations. ●

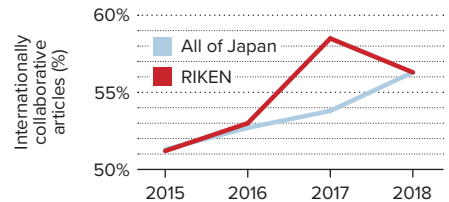
# WORLD WISE

While RIKEN has rapidly expanded its international links during the last two decades, this has been built on a foundation of long-term work with some of the world's most important research bodies, particularly huge accelerator facilities. This **timeline** represents some of the major agreements and memorandums of understanding RIKEN has made with international bodies, as well as the opening of international offices.

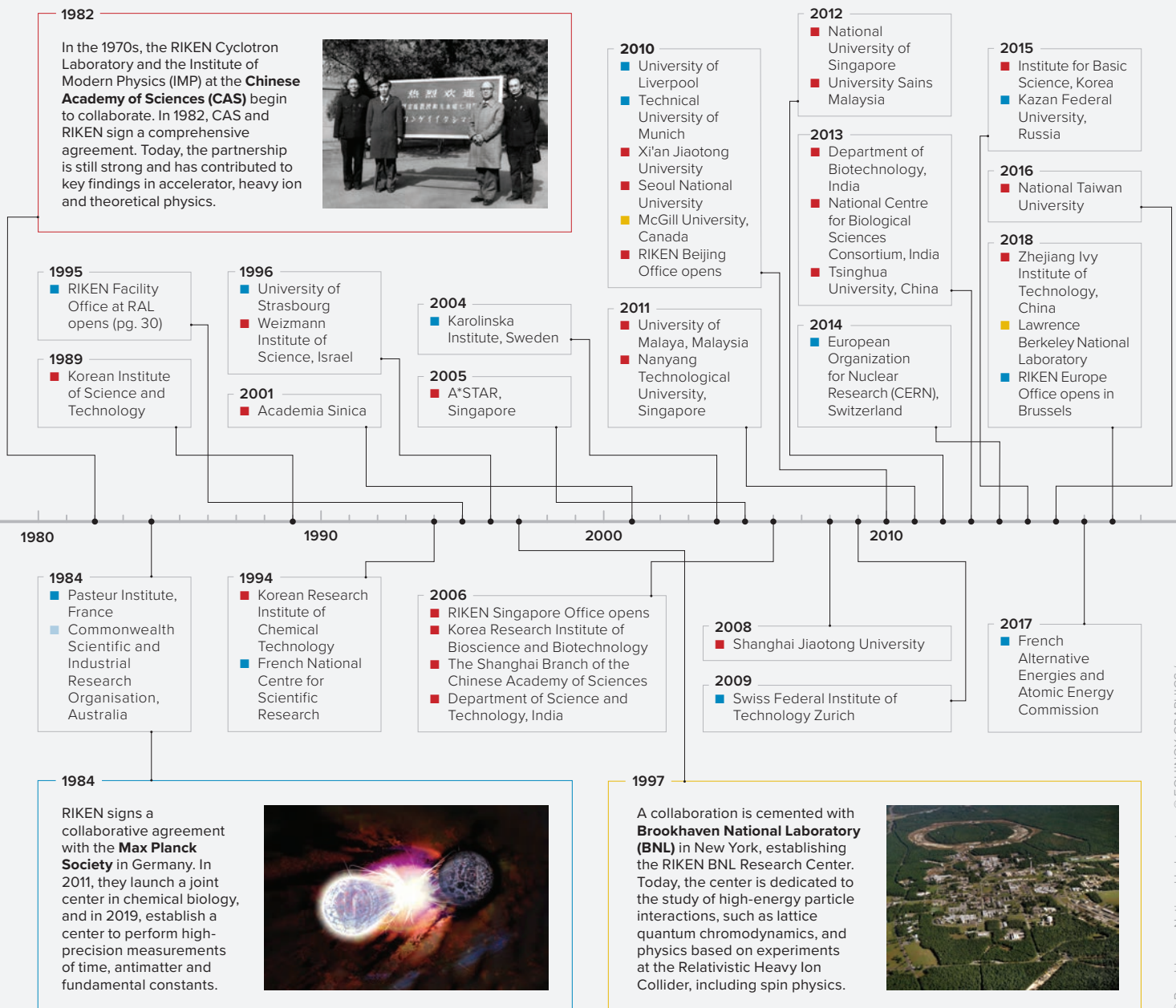
■ Asia/Middle East ■ Europe ■ North/South America ■ Oceania

## PAPER PLANES

More than 50% of RIKEN's collaborative articles are produced with overseas partners, and this figure is on the rise.



Source: Nature Index



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# RIKEN'S CENTERS AND FACILITIES

across Japan and around the world



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.

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