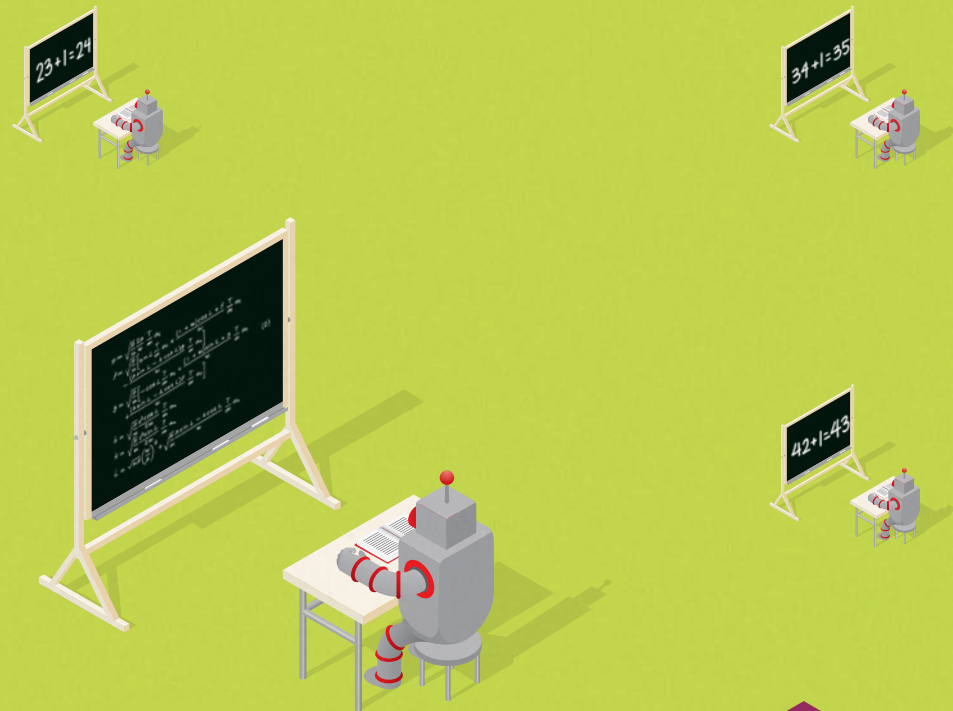


# RIKEN

WINTER 2018

## RESEARCH

SHOWCASING THE BEST OF JAPAN'S PREMIER RESEARCH ORGANIZATION • [www.riken.jp/en/research/rikenresearch](http://www.riken.jp/en/research/rikenresearch)



## MACHINE LEARNING

*Japan is poised to reap the benefits of clever artificial intelligence algorithms*

### SNAP FREEZE

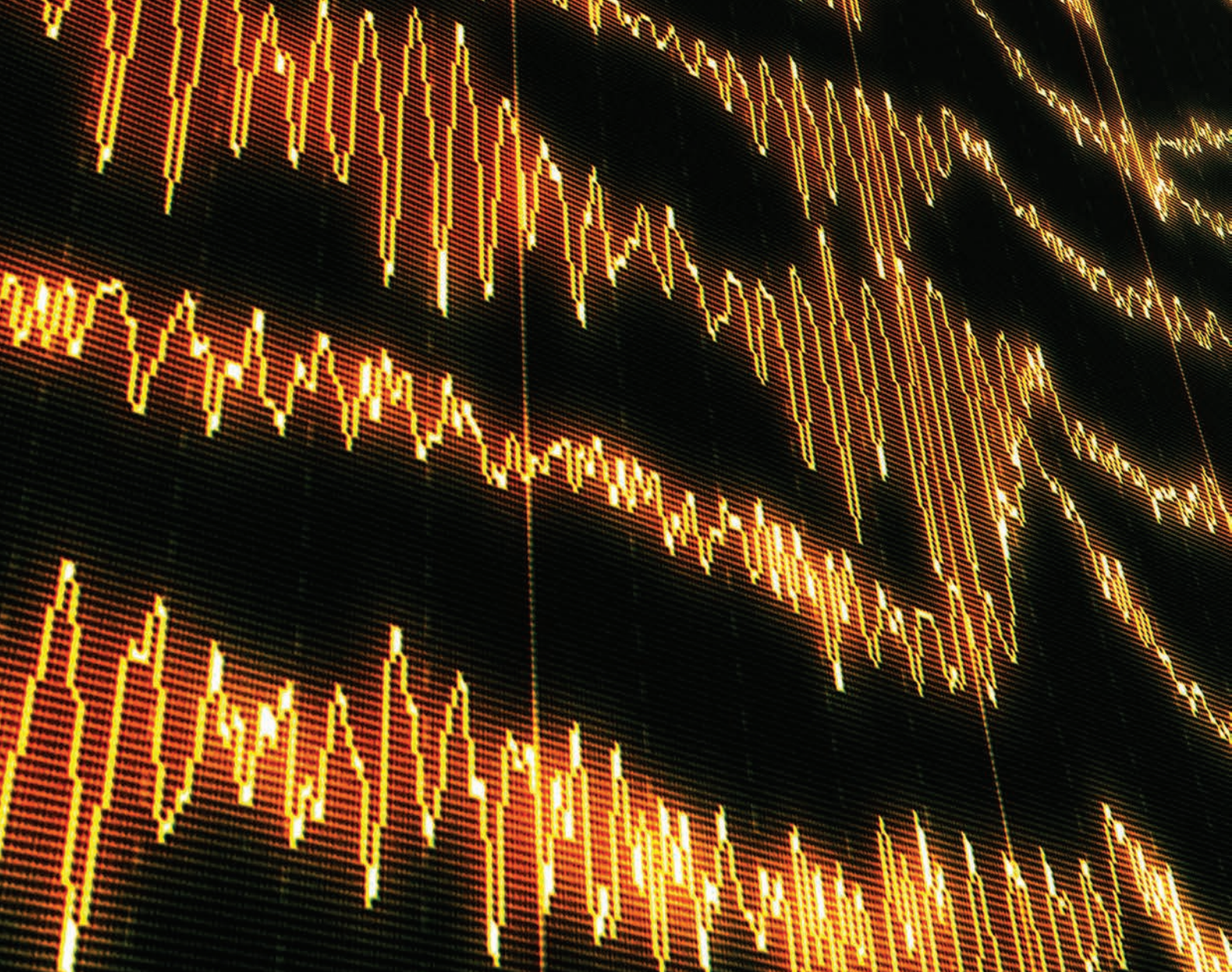
Quick cooling reveals new superconductors

### FLY BY THE SEAT OF THEIR PANTS

These insects find each other via fecal pheromones

### DREAM GENES

Two DNA markers control our most vivid sleep state



▲ **RIKEN Center for Biosystems Dynamics Research**

Rapid eye movement (REM) sleep is when animals dream. An international team, led by RIKEN's Hiroki Ueda, has identified two genes that regulate REM (above are brain waves of REM sleep). Removing the genes caused REM sleep in mice to drop to almost undetectable levels (see page 11).

## 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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## 3 Editorial

Harnessing artificial intelligence for society

## 4 People

Seeing the promise in plant plasticity

Keiko Sugimoto  
*Team Leader*

Instrumental advances in physics

Christopher Butler  
*Special Postdoctoral Researcher*



## 10 Research highlights

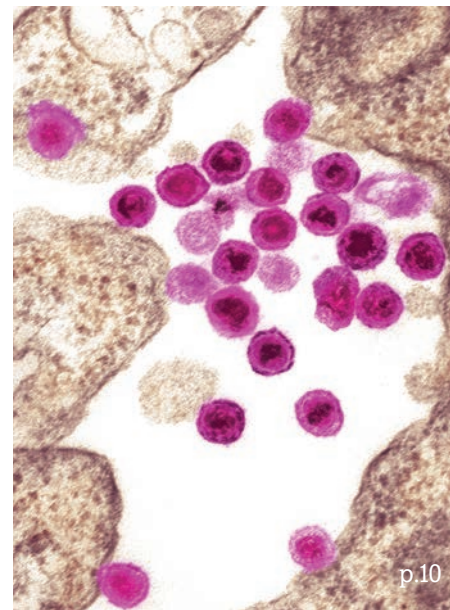
- 10 Silencing ancient viruses in the genome

### COVER STORY

- 11 Genes that regulate how much we dream
- 12 How light catalyzes bond breaking in molecules
- 13 Proximity boosts efficiency
- 14 The versatility of spin

### COVER STORY

- 15 Fruit fly's droppings attract other flies
- 16 Detecting fetal heart problems
- 17 Protein subunits increase in active bacterial energy channel



p.10



p.15

## 6 Briefs

Symposium: How AI will affect the life sciences

Thailand National Science and Technology Fair

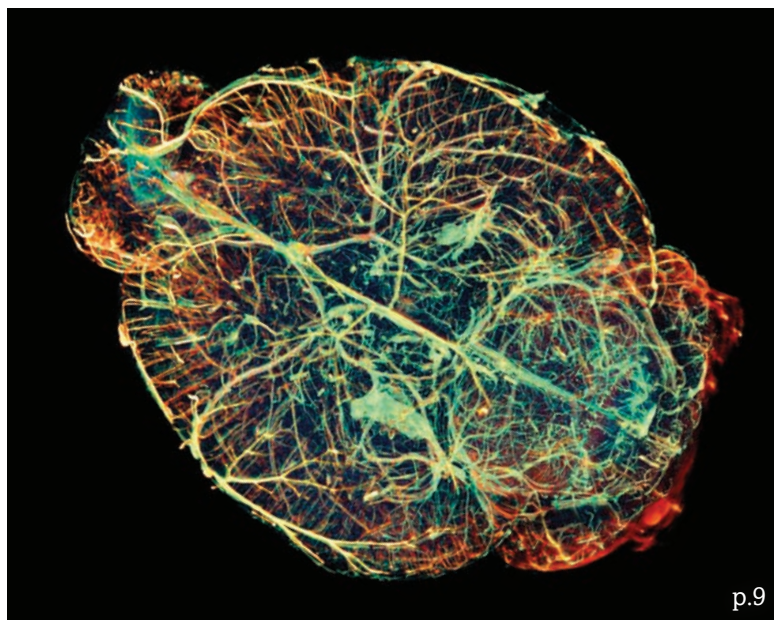
Thoughts from a world-leading quantum physicist

Seventh Global Summit of Research Institute Leaders

Tatarstan president visits Kobe campus

A joint laboratory established with Zhejiang Ivy Institute of Technology, China

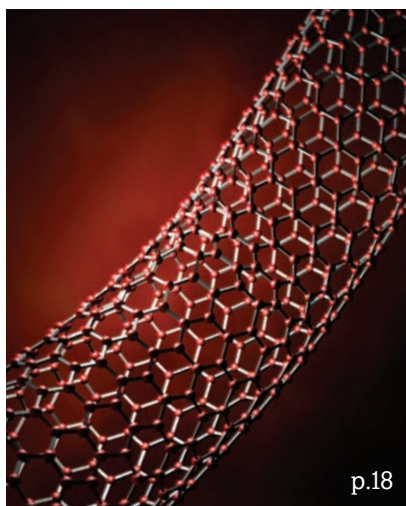
RIKEN Center for Brain Science Kickoff Symposium



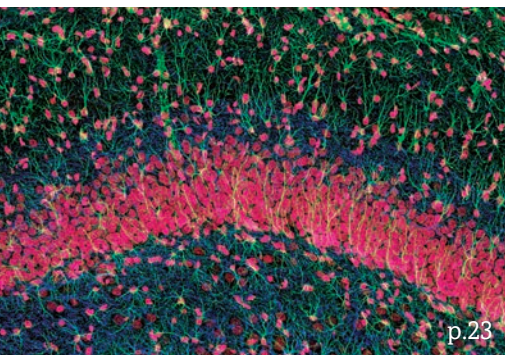
p.9

## 18 Research highlights

- 18 Enhanced emission of single photons realized
- 19 A switch in perspective
- 20 How plants beat the heat
- 21 Growing salivary glands in the lab
- 22 Two ways to pair up
- 23 Enigma of engram cells solved
- 24 A solar-powered heart monitor taped to the skin
- 25 Removing barriers to cloning mice



p.18



p.23

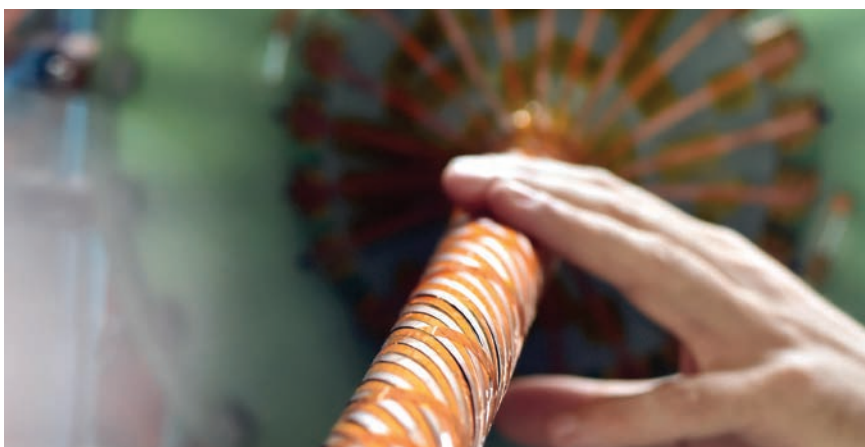
## 26 Perspectives COVER STORY

**By (artificially) intelligent design:** Japanese artificial intelligence researchers are working on deep-learning algorithms that glean advanced insights from Japanese types of data.



## 29 Feature COVER STORY

**Rapid cooling reveals superpowers:** Rapid electrical cooling bypasses other states and turns on a superconducting state in materials that were previously not superconductors



## 32 Infographic

**Productive partnerships:** Large-scale collaborations are increasingly recognized as a means of solving big, complex problems. Fortunately, big projects, big facilities and collaborations are among RIKEN's strengths.

# Harnessing artificial intelligence for society



**Michihiko Minoh**  
Executive Director, RIKEN

**T**oday, there are high hopes that artificial intelligence (AI) will soon be deployed in society to help enrich our lives. The RIKEN Center for Advanced Intelligence Project (AIP) was established in 2016 to promote research related to AI.

It is interesting to note that even in the AI community, there is no clear consensus on what AI actually is. Instead, people make excited pronouncements that AI will soon replace humans or that the singularity—a tipping point in technological advancement—is just around the corner. It is true that due to advances in computing power and machine learning technology, it has become possible for computers to solve complex pattern-recognition problems—which human brains can solve easily, but that stump computers. What makes it difficult to define AI is that there are, in a sense, two streams of thought on what to do with the large amount of data that is generated by modern society. On one hand, many computer scientists are striving to use AI to make computers that can do things like humans, such as understanding language or faces. In contrast, others are using mathematics to try to develop new fundamental ways to have

computers learn or solve problems in the most optimal ways, by using deep learning based on neural networks, for example. AIP is focusing its work on the development of such new methods.

In addition to this fundamental research, scientists at AIP are focusing on research that will be of benefit to society. Information systems, which have become the key infrastructure of modern society, generate large amounts of data related to human activities, and scientists can make use of this to create better lives.

AIP's research strategy and plans, which were adopted based on the context I have outlined, are introduced in this issue by Center Director Masashi Sugiyama (see page 26). Today, many researchers around the world are actively engaged in competition in this area. I am very much looking forward, as I believe many of our readers are as well, to soon seeing innovative research emerging from AIP.



**COVER STORY:**  
RIKEN is building artificial intelligence capabilities for Japan, as new machine learning technology ushers in exciting possibilities.  
Page 26

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# Seeing the promise in plant plasticity

## Keiko Sugimoto

Team Leader, Cell Function Research Team  
RIKEN Center for Sustainable Resource Science

### ▣ Please describe your role at RIKEN

I lead a research group investigating how plants grow and respond to a changing environment. Plants are very clever in deciding how far to grow and when to stop under given conditions—so, I'm trying to understand how they make these decisions. Compared to animals, plants are also very good at making new tissues and organs from wound sites and so I also study how plants regenerate when they're injured.

### ▣ Please briefly describe your current research. Why is it important?

My research helps advance our understanding of how plants sense the



environment and optimize their growth. I'm trying to understand how plant cells divide and expand to make new organs, as well as how environmental stimuli intervene with these cellular processes to fine-tune organ growth. I hope my research will contribute to fundamental biology and eventually to developing new molecular tools to improve crop yield and quality.

### ▣ How did you become interested in your current field of research?

I was fascinated with plants as a child. As an undergrad, I dearly wanted to have my own *Arabidopsis* mutants. Thanks to my PhD supervisors, Geoffrey Wasteneys and Richard Williamson, I did get a few, even today I still love identifying new mutants and phenotypes.

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

We are making advances in understanding how plants reprogram their cell fate after injury, a mystery to plant biologists for some time. Only now are we starting to find clear molecular answers, which is very exciting.

### ▣ What has been the most interesting discovery in your field recently?

My team has discovered that fully differentiated plant cells retain the capacity to 'de-differentiate' and

they actively suppress this potential through epigenetic mechanisms during normal development. In the absence of this repression, fully differentiated somatic cells revert to an embryo-like state, which highlights plant cells' developmental flexibility. We have also learned that plants have an additional mechanism to prevent spontaneous reprogramming, and we aim to uncover how severe injuries can overcome this repression.

### ▣ "My research is important for society because...."

...we can improve the yield and quality of important plant species. We depend heavily on plants as food and medicine sources. Plants' capacity to provide these resources is far from being maximized because we don't know enough about how they produce them. Understanding how plants grow should help, for instance, secure our food supplies through improving agricultural sustainability.

“Plants are very clever in deciding how far to grow and when to stop under given conditions”

### ▣ How has being at RIKEN helped your research?

State-of-the-art facilities always help. My lab has also made extensive use of Minami Matsui's *Arabidopsis* mutant collections, and Hitoshi Sakakibara's and Yuji Kamiya's groups, among others, have helped with characterizing plant hormones.

### ▣ How do you balance family life with your work at RIKEN?

Being a mother in science means I get to see both my lab and family develop. I try to stay focused on my research when I'm at work, so I can accomplish interesting things in a limited time frame. But I'm also careful to ask for help, since there's no way I can do both perfectly. ■

# Instrumental advances in physics

## Christopher Butler

Special Postdoctoral Researcher, Emergent Phenomena Measurement Research Team, RIKEN Center for Emergent Matter Science

### ▣ Please describe your role at RIKEN

I work in condensed matter physics in Dr Tetsuo Hanaguri's Emergent Phenomena Measurement Research Team. We use scanning tunneling microscopy (STM) to visualize the behavior of electrons at crystal surfaces, especially the peculiar collective behavior of a large number of interacting electrons.

### ▣ How has being at RIKEN helped your research?

As part of Dr Hanaguri's team, I feel like I have moved from the outskirts of the STM community to somewhere close to the center, as we develop and use STM instruments that are among the most advanced in the world.

*Crystalline materials are like mini-universes, with their own physical laws and 'fundamental particles'...*



### ▣ Please briefly describe your current research.

#### Why is it important?

I'm investigating a type of material called a Mott insulator. This material should conduct electricity but doesn't, because electrons get stuck in a 'traffic jam' due to their strong interactions with each other. Useful phenomena can emerge from this behavior, like high-temperature superconductivity, which is the disappearance of electrical resistance.

### ▣ What do you think has been the most interesting discovery in your field in the last few years? How has it influenced your research?

Many recent high-profile discoveries suggest the collective behaviors of a huge number of electrons are better described as new kinds of particles—'quasiparticles'. In this sense, crystalline materials are like mini-universes, with their own physical laws and their own 'fundamental particles' that differ from the fundamental particles of our wider Universe. Quasiparticles can mimic theoretical particles we haven't yet observed, such as Majorana particles, fermions with their own antiparticle and zero charge. One of our aims is to understand how such Majorana quasiparticles come to exist, and how they could be controlled and perhaps put to use for quantum computing.

### ▣ "My research is important for sustainable development because..."

... with the right electronic behavior in the right materials, scientists may be able to build a quantum computer, and there is no major problem we face as a society that is not made easier to solve by having a better computer!

### ▣ How did you find moving to Japan?

Having lived in Taiwan for eight years meant I was culturally well prepared for Japan, and I was hugely helped by organizers from the Special Postdoctoral Researchers Program and lab assistant Ms Naoko Mitsuzawa in all aspects of moving and adapting to life in the lab.

### ▣ What are some technologies you use?

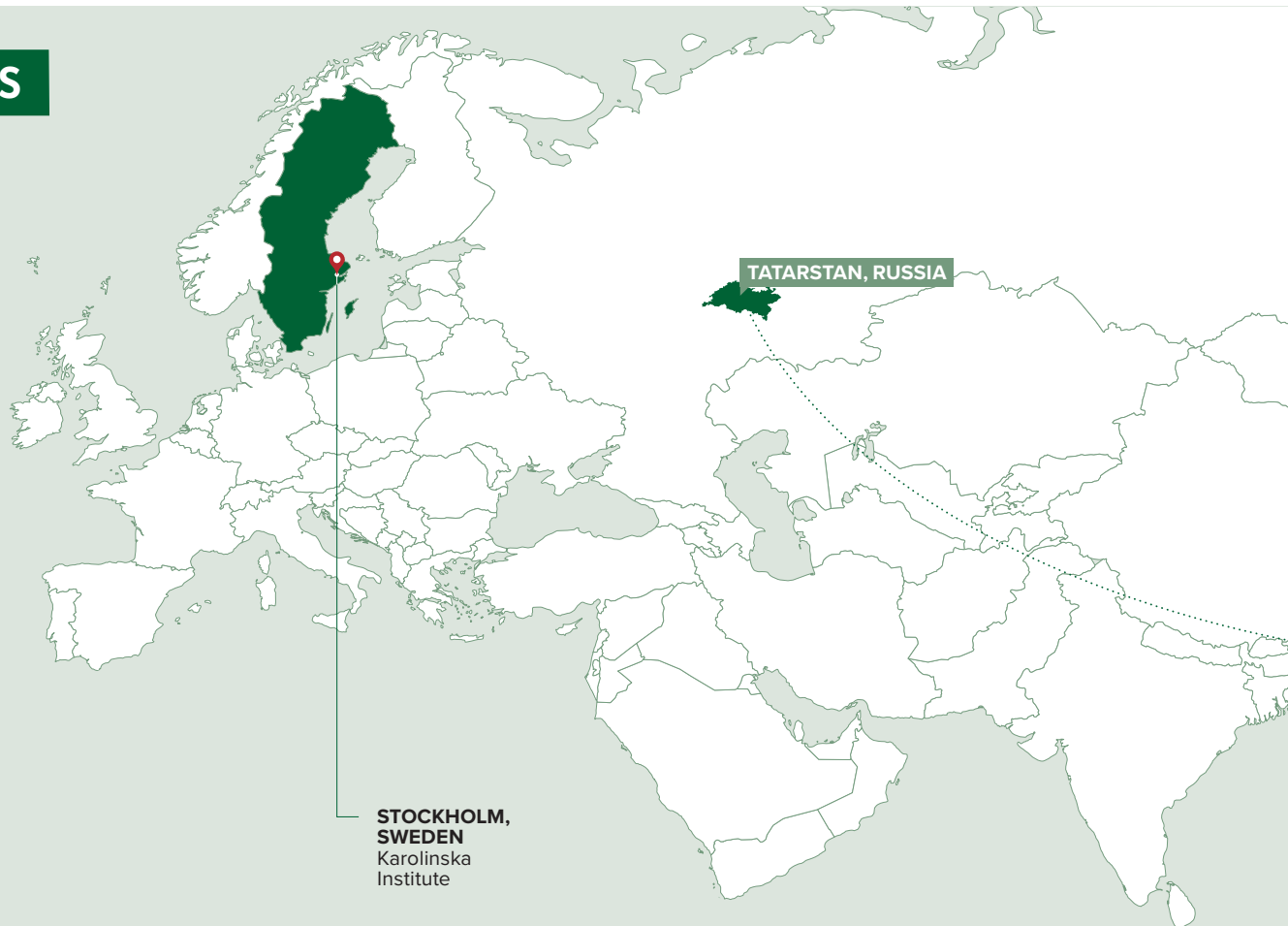
I use a scanning tunneling microscope that scans samples in an ultrahigh vacuum (comparable to outer space) at about 0.4 degrees above absolute zero (much colder than outer space!), and in a 12-tesla magnetic field (a few thousand times stronger than a refrigerator magnet). One of our team members, Dr Tadashi Machida, has built an ultrahigh-vacuum scanning tunneling microscope cooled to below 0.1 degrees above zero by a dilution refrigerator, with a 17.5-tesla magnet. The overall performance of this dilution-refrigerator microscope may well be the best in the world at this time. ■

### Careers at RIKEN

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## EVENTS



## Symposium: How AI will affect the life sciences

In September 2018, at the fifth joint symposium between RIKEN and Karolinska Institute/SciLifeLab, researchers met to discuss topics that included the clinical applications of artificial intelligence, using artificial intelligence in bioimage informatics and current challenges in applying artificial intelligence in the life sciences. The symposium was held at SciLifeLab, Karolinska Institute in Sweden. It began with addresses by SciLifeLab Director Olli Kallioniemi, Karolinska Institute President Ole Petter Ottersen and Piero Carninci, the deputy director of the RIKEN Center for Integrative Medical Sciences.



Piero Carninci (left), deputy director of the RIKEN Center for Integrative Medical Sciences (IMS), and Olli Kallioniemi (right), director of SciLifeLab, discuss how artificial intelligence will affect the life sciences.





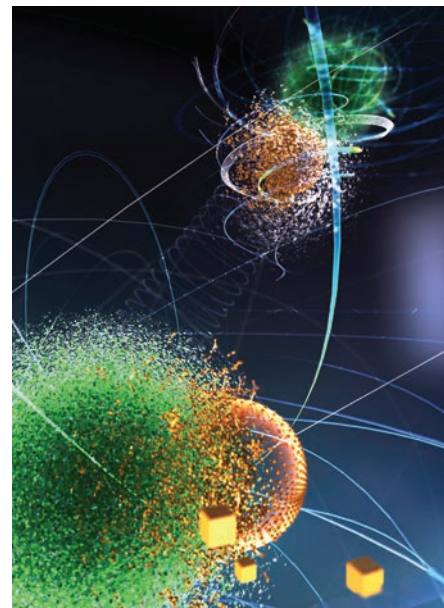
Genichi Tsuzawa, director of RIKEN's Singapore office, introduces RIKEN to Thai students.

## Thailand National Science and Technology Fair

Last August, RIKEN took part in the Thailand National Science and Technology Fair 2018, the largest fair of its kind in Thailand. More than a million people, most of them Thai students, visited the fair. RIKEN joined the fair

as a part of the Japan Pavilion, which was visited by Thai Prime Minister Mr Prayut Chan-o-cha and Thailand's Minister of Science and Technology Suvit Maesincee. The RIKEN booth featured an introduction to RIKEN and information on programs for young researchers. It also showcased RIKEN's research collaboration with Chulalongkorn University in Thailand.

<http://www.sg.riken.jp>



Anthony James Leggett discussed how Bell's theorem makes teleportation (concept above) and secure-in-principle cryptography possible.

## Thoughts from a world-leading quantum physicist

In July, more than 150 people attended the iTHEMS–CEMS Joint Colloquium to hear a talk by Anthony James Leggett, a world-leading theorist in quantum physics, a professor at the University of Illinois at Urbana-Champaign and a laureate of the Nobel Prize in Physics in 2003. He began by introducing basic classical radiation. Leggett later discussed 'objective local theory' in which local causality, induction and microscopic realism are assumed, and he noted that an inequality holds for certain correlation measurements (Bell's theorem). Since this inequality is violated in quantum mechanics, he pointed out, it follows that microscopic realism is not satisfied in quantum mechanics and information is stored non-locally by entanglement. Leggett then noted that Bell's theorem makes possible quantum phenomena in which entanglement plays an essential role, such as quantum teleportation, quantum cryptography and quantum computing.

<https://ithems.riken.jp/en/events/ithems-cems-joint-colloquium-leggett>



## Seventh Global Summit of Research Institute Leaders

In October, the leaders of 22 national research institutes in 11 countries gathered in Kyoto for the Seventh Global Summit of Research Institute Leaders, which was themed *Interacting with Society: Tasks for Global Research Institutes*. The meeting was jointly organized by RIKEN and the National Institute of Advanced Industrial Science and Technology (AIST), and

co-chaired by RIKEN and the Leibniz Association. This year, the participants heard two keynote presentations, one by Yumiko Kajiwara of Fujitsu in Japan and the second by Ranga Yogeshwar, a science journalist from Germany. Representatives attended from Australia, Canada, France, Germany, Indonesia, Japan, Korea, Singapore, Sweden, Thailand and the United States.



## A joint laboratory established with the Zhejiang Ivy Institute of Technology, China

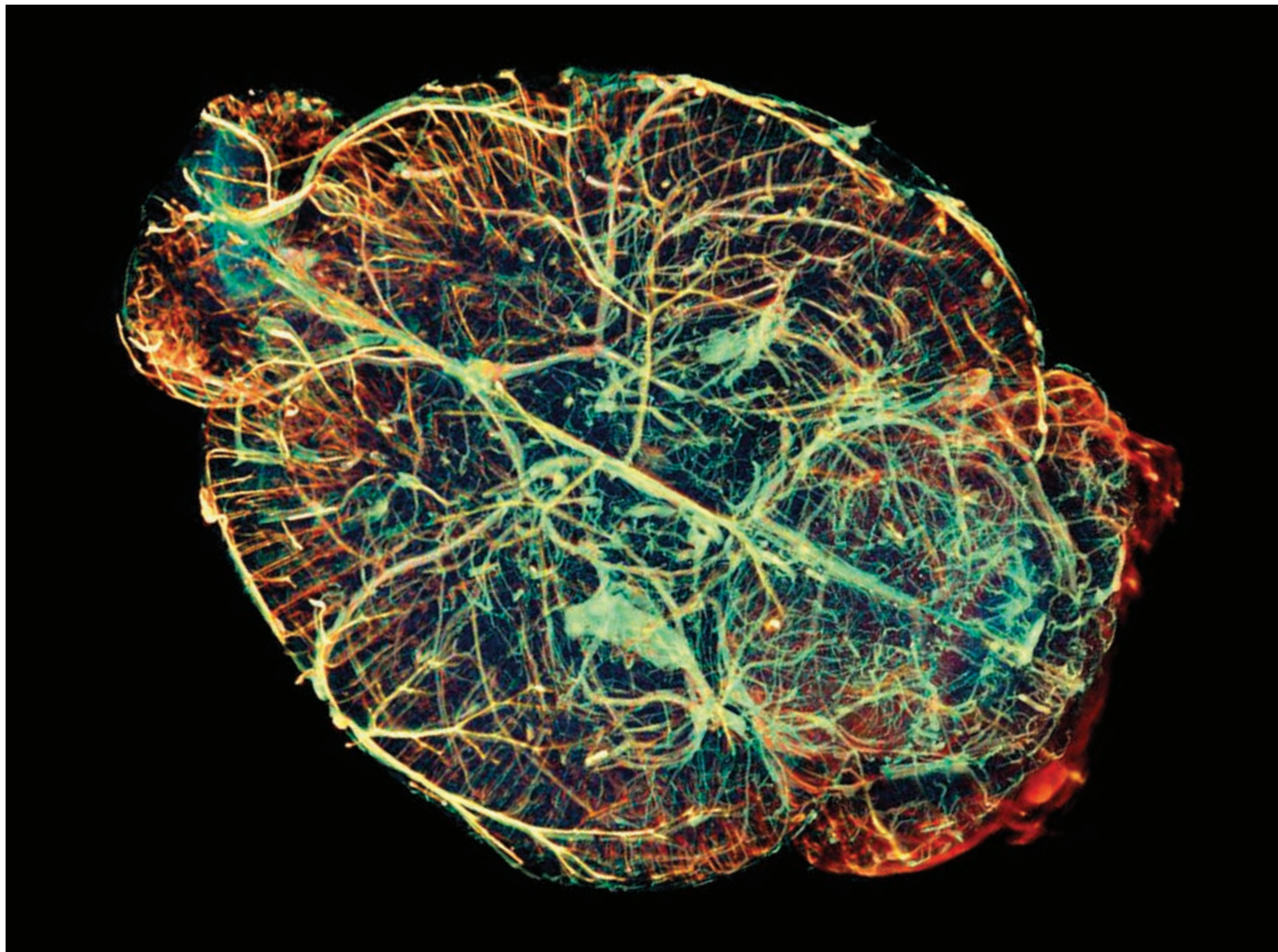
On 13 September 2018, RIKEN signed a joint statement with Zhejiang Hangzhou Future Science and Technology City Management Committee and Zhejiang Ivy Institute of Technology that will strengthen the relationship between the institutes and collaborations in chemical biology. A joint laboratory will be established to promote researcher exchange and expand capacity in this field for both countries.

## Tatarstan president visits Kobe campus

In October 2018, Rustam Minnikhanov, president of the Republic of Tatarstan, visited the RIKEN Kobe campus, accompanied by Tatarstan's Minister of Health Marat Sadykov, Kazan Federal University Rector Ilshat Gafurov and others. The delegation was given a presentation on the RIKEN Center for Biosystems Dynamics Research (BDR) by Center Director Eisuke Nishida, followed by an introduction to regenerative medicine using induced pluripotent stem (iPS) cells by Masayo Takahashi, a project leader at BDR. Takahashi then led the delegation on a tour of her laboratory, demonstrating the use of the Maholo robotic cell manipulation system. Following the RIKEN visit, the delegation visited the Kobe mosque, which was built in 1935 thanks to donations from people including Tatar merchants.



Tatarstan's president, Rustam Minnikhanov (front right), looking at iPS cell-derived retinal cells developed at RIKEN. These stem cells are being clinically tested to see if they can be transplanted into human eyes to treat retinal diseases.



Brain research has become more and more sophisticated, noted speakers at the CBS Kickoff Symposium. For example, mouse brain gene expression has been systematically characterized at a cellular level through approaches that have included optical projection tomography data (above) and whole mount data.

## RIKEN Center for Brain Science Kickoff Symposium

The RIKEN Center for Brain Science (CBS) Kickoff Symposium was held on 19 June at the Marunouchi My Plaza Hall in Tokyo. CBS Deputy Director Hiroyuki Kamiguchi introduced the history of CBS and its 33 research teams. He described how their work spans topics ranging from the tangible, such as synapses and neural circuits, to the intangible, such as decision making and self-reflection. Japan Neuroscience Society president and

Kyoto University professor Tadashi Isa talked about a paradigm shift that occurred in neuroscience research in the 1980s due to advances in molecular neurobiology, technology for genetically modified animals, and the identification of disease-causing genes. CBS Director Yasushi Miyashita spoke about CBS's goals, including using brain science to alleviate conditions such as dementia, depression and development disorders. He described several projects,

including a collaborative project with Toyota that is researching feelings of agency and free will in humans vis-à-vis self-driving vehicles. He also discussed the ground-breaking work being done by principal investigators who have joined CBS on self-reflection and intuition, metacognition and metamemory (the locations and structures of memory systems) and the development of specialized laboratory animals and of new techniques for studying brains.

## GENE SILENCING

# Silencing ancient viruses in the genome

Systematically knocking out genes from embryonic stem cells reveals which genes are needed for protecting against retroviral elements

**G**enes in mouse embryonic stem cells that are required to prevent gene disruption from ancient viruses have been identified by RIKEN researchers<sup>1</sup>. This catalogue of genes will greatly benefit future studies of the silencing mechanism.

The genomes of mammals contain relics of ancient viral infections—fragments of viral sequences known as retroelements. Since these fragments can jump around the genome, they still pose a risk to genome stability, and so it is important for the host genome to inactivate them.

## He sees his team's knockout mouse embryonic stem cell lines as a great resource for researchers

Yoichi Shinkai of the RIKEN Cellular Memory Laboratory considers the regulation of retroelements one of the most important questions in biology. He has long been interested in the role of methylation in gene silencing, particularly the methylation on lysine 9 of histone H3 (H3K9me3), a protein that is part of nucleosomes that condense DNA into tight chromatin.

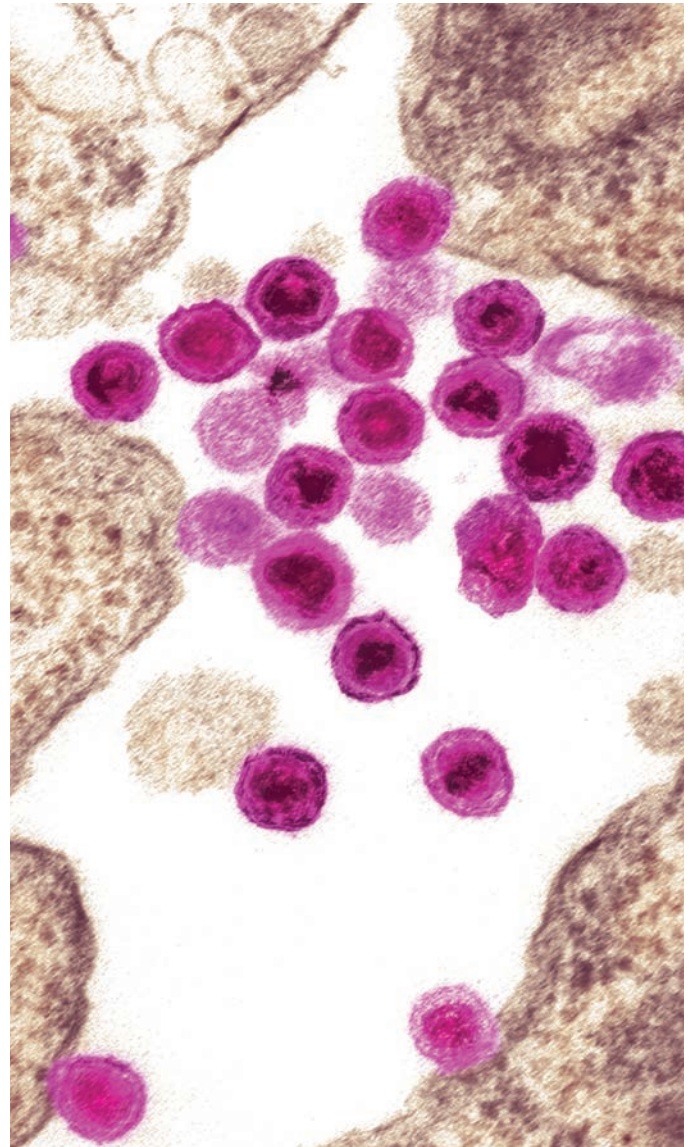
Retroelements present a good model system for his team to study this process.

To uncover the components needed to silence retroelements, Shinkai's team produced a mouse embryonic stem cell line that expressed a fluorescent molecule driven by a viral enhancer and promoter. They used this cell line in a genome-wide knockout screen, in which they systematically removed more than 19,000 genes that encode proteins.

The team found more than 80 genes that contributed to retroelement silencing. Their top eight candidates are known to be involved in the process, and included the gene *Setdb1*, which encodes for an enzyme responsible for methylating H3K9.

One candidate the researchers analysed in detail was a novel molecule they named RESF1. They showed that it interacts with SETDB1 and binds to the SETDB1-targeted genome loci. The team confirmed this by removing the *Resf1* gene from cells and observing that the fluorescent viral gene was no longer silenced. They also confirmed that RESF1 silenced endogenous retroviral elements in the mouse genome.

Many of the genes found by the screen were part of a diverse range of protein complexes, which indicates unexpected complexity. "SETDB1 cooperates with different protein complexes depending



By using a mouse retrovirus (purple circles) as a reporter provirus, RIKEN researchers were able to identify over 80 genes involved in silencing retroelements in mouse embryonic stem cells.

on the type of retroelement for silencing," explains Kei Fukuda, a postdoctoral researcher in Shinkai's lab who analyzed *Resf1* and identified other genes. "It's unclear what determines the specificity."

Shinkai next plans to explore the functions of other candidate genes and unveil their detailed mechanisms. He sees his team's knockout mouse embryonic stem cell lines as a great resource for researchers investigating

other physiological roles of H3K9me3, such as telomere maintenance or the silencing of exogenous viruses. ●

### Reference

1. Fukuda, K., Okuda, A., Yusa, K. & Shinkai, Y. A CRISPR knockout screen identifies SETDB1-target retroelement silencing factors in embryonic stem cells. *Genome Research* **28**, 846–858 (2018).

## SLEEP SCIENCE

# Genes that regulate how much we dream

Two genes that play key roles in regulating sleep in mice have been identified

A pair of genes that regulates how much rapid eye movement (REM) and non-REM sleep an animal experiences has been identified by an international team led by RIKEN researchers<sup>1</sup>.

Sleep re-energizes animals and consolidates their memories. In vertebrates such as mammals and birds, sleep has two phases: REM sleep and non-REM sleep. REM sleep is a mysterious stage of sleep in which animals dream. It plays an important role in maintaining a healthy mental and physical life, but the molecular mechanisms behind it are barely understood.

Now, a team led by Hiroki Ueda at the RIKEN Center for Biosystems Dynamics Research and the University of Tokyo has identified two genes involved in regulating REM sleep. The amount of REM sleep dropped drastically to almost undetectable levels when both genes were knocked out in a mouse model.

Several studies have suggested that acetylcholine—the first identified neurotransmitter—and its receptor are important for regulating REM sleep. Acetylcholine is abundantly released in some parts of the mammalian brain during REM sleep and wakefulness. However, it was unclear which receptor or receptors were directly involved in the regulation of REM sleep due to the complexity of the underlying neural network.

The researchers used cutting-edge genetic tools to modify mouse genes and conduct genetic screening for factors whose inhibition would cause



Scientists have identified two genes that regulate rapid eye movement sleep in mice.

sleep abnormalities. After knocking out a number of genes encoding various acetylcholine receptors, they found that the loss of two receptors—*Chrm1* and *Chrm3*—induced a characteristic short-sleep profile. These two receptors are widely distributed in distinct brain regions. The knockout of *Chrm1* reduced and fragmented REM sleep, whereas knocking out *Chrm3* reduced the length of non-REM sleep. When both genes were knocked out, mice failed almost entirely to experience REM sleep, but survived nonetheless.

“The surprising finding that

mice are viable despite the almost complete loss of REM sleep will allow us to rigorously verify whether REM sleep plays a crucial role in fundamental biological functions such as learning and memory,” says Yasutaka Niwa, the first author of the study.

These findings strongly suggest that these two receptors are essential for sleep regulation, especially REM sleep, and function in different ways. “The discovery that *Chrm1* and *Chrm3* play a key role in REM sleep opens the way to studying its underlying cellular and molecular mechanisms

and will eventually allow us to define the state of REM sleep, which has been paradoxical and mysterious since its original report,” Ueda says. ●

## Reference

1. Niwa, Y., Kanda, G. N., Yamada, R. G., Shi, S., Sunagawa, G. A., Ukai-Tadenuma, M., Fujishima, H., Matsumoto, N., Masumoto, K., Nagano, M. *et al.* Muscarinic acetylcholine receptors *Chrm1* and *Chrm3* are essential for REM sleep. *Cell Reports* **24**, 2231–2247 (2018).

## PHOTOCATALYSIS

# How light catalyzes bond breaking in molecules

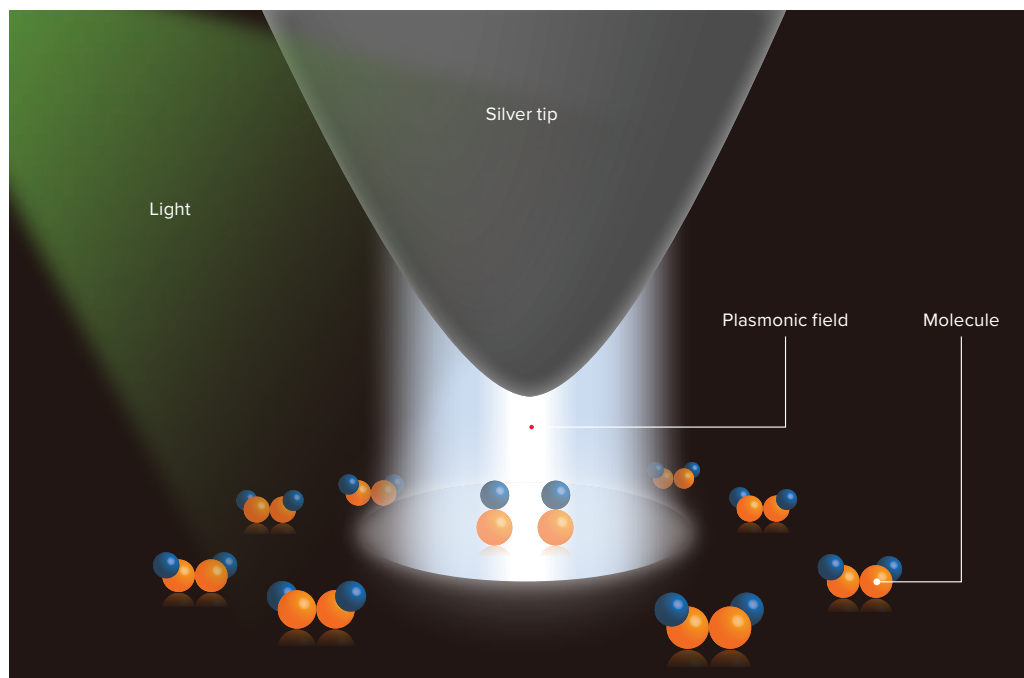
Scanning tunneling microscopy observations of a single molecule provide new insights into photocatalytic reactions

Using a special type of electron microscope, RIKEN researchers have observed a single molecule sitting on a metal surface split into two due to electron vibrations set off by the interaction of light with the microscope tip<sup>1</sup>. This observation has revealed the mechanism of this light-induced catalytic reaction for the first time.

The interaction of light with metal nanoparticles can be used to catalyze chemical reactions. Such photocatalysts are attractive from an environmental perspective since chemical reactions could be assisted by sunlight. But to design more-efficient photocatalysts for chemical reactions requires a deep understanding of the catalytic process at the molecular level.

Light can excite collective oscillations of electrons on the surfaces of metal nanoparticles. Known as localized surface plasmons (LSPs), these oscillations can be used to efficiently transfer energy to molecules adsorbed on their surface and thereby trigger reactions. However, the mechanism for this transfer has been unclear because the reaction occurs on such a small scale. In particular, it has not been clear whether the light-induced LSPs interact directly with the molecules or whether the LSPs decay and generate energetic electrons ('hot electrons'), which then interact with the molecules.

Previous studies have favored the indirect mechanism via hot electrons. "The indirect hot-electron transfer has been put forward as the mechanism for



Schematic representation of the experimental setup for the direct observation of plasmon-induced molecular dissociation. The silver tip of a scanning tunneling microscope is positioned about 1 nanometer above a metal surface on which dimethyl disulfide molecules are adsorbed. The irradiated plasmonic field then initiates dissociation of the molecule.

the plasmon-induced break up of oxygen and hydrogen molecules on metal surfaces," notes Emiko Kazuma of the RIKEN Cluster for Pioneering Research. "However, this proposal arises from several indirect observations and thus is controversial."

Now, by using a scanning tunneling microscope to observe plasmon-induced rupture of a single molecule of dimethyl disulfide ( $C_2H_6S_2$ ) on silver and copper surfaces (see image), Kazuma and her co-workers have found that LSPs can directly interact with the adsorbed molecule.

Light excited LSPs in the nanogap between the silver tip of the scanning tunneling

microscope and the metallic surface. These LSPs then directly transferred their energy to molecules adsorbed on the metal surface, exciting electrons in the molecule, which caused the molecule to split into two due to the breaking of the bond between its two sulfur atoms.

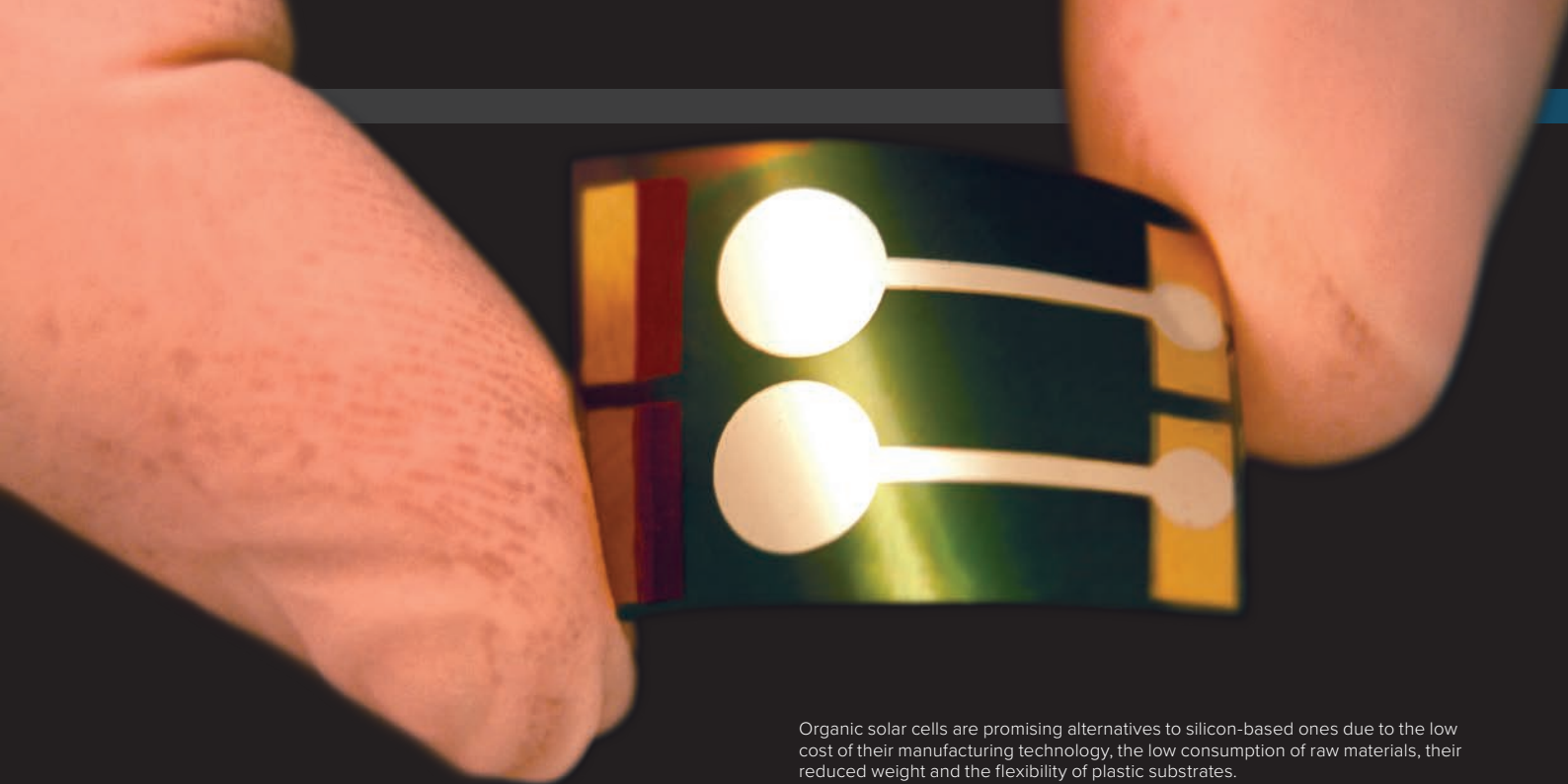
Kazuma and co-workers found that the mechanisms of plasmon-induced reaction, direct or indirect, can in principle be guided by tuning how strongly an adsorbed molecule is bound to the catalyst surface. Strongly adsorbed molecules such as oxygen and hydrogen would dissociate through an indirect hot-electron transfer mechanism, whereas weakly

adsorbed molecules prefer a direct intramolecular excitation mechanism, as in the case of dimethyl disulfide.

"These findings provide deep insights into the interaction between LSPs and molecules at metal surfaces for designing efficient plasmon-induced photocatalysis in a highly controlled fashion," Kazuma comments. ●

## Reference

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Organic solar cells are promising alternatives to silicon-based ones due to the low cost of their manufacturing technology, the low consumption of raw materials, their reduced weight and the flexibility of plastic substrates.

## ORGANIC PHOTOVOLTAICS

# Proximity boosts efficiency

Fine-tuning the structures of polymers can maximize the light-conversion ability of organic solar-cell systems

Improving the recipe of organic solar materials and precisely controlling how the ingredients mix could significantly improve their light-conversion performance, an all-RIKEN team has shown<sup>1</sup>.

Organic photovoltaics are potential low-cost rivals to silicon solar cells. Some of the most efficient organic photovoltaics consist of long-chain semiconducting polymers mixed with spherical fullerene molecules—a combination called a mixed bulk heterojunction, whose structure is reminiscent of spaghetti and meatballs in miniature. When the polymer component captures light, an excited electron is generated, which is then transferred to the electron-accepting fullerene before traveling through the material to the electrode.

But the way the two components of the bulk heterojunction structure interact has been a black box, says Keisuke Tajima

from the RIKEN Center for Emergent Matter Science. “We think it’s time to take molecular design to the next level by considering how we can arrange the molecules in mixed bulk heterojunctions,” Tajima says. “Our study is the first step toward molecular design for more precise control of the interfacial structures in bulk heterojunctions.”

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**“We think it’s time to take molecular design to the next level”**

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Tajima’s team produced two semiconducting polymers that differed only in the positions of the side chains along their backbones. “We wanted to change only one parameter while keeping others the same to see its

effects,” Tajima explains. These side chains control how close the fullerene molecules can get to the polymer backbone.

Equally importantly, the polymers contained methoxy groups, which give a clear and unambiguous nuclear magnetic resonance (NMR) signal. This allowed the team to use two-dimensional NMR analysis to assess how close the fullerene was to each polymer.

Fullerene proximity did significantly impact the materials’ photovoltaic efficiency, the team discovered. Rather like a good spaghetti dinner needs intimately mixed noodles and meatballs, bulk heterojunction performance was maximized in materials where the side chains allowed close contact between the fullerene and electron-accepting segments of the polymer strands, Tajima’s team showed.

As the polymers were designed for an investigative

study rather than for maximum performance, the team has not broken any bulk heterojunction photovoltaic efficiency records yet. “However, the same principle should apply to high-performance polymers with more complicated structures,” Tajima says.

Recently, the fullerene component has been replaced with alternative electron-acceptor molecules in top-performing organic photovoltaics. “The next challenge will be to extend our concept and methodology to non-fullerene acceptors,” Tajima adds. Controlling the new acceptors’ orientation and proximity to the polymer chain could lead to a breakthrough in organic photovoltaic performance. ●

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## SPINTRONICS

# The versatility of spin

A nanodevice that generates an electrical current from a spin current, which in turn is generated by mechanical oscillations, demonstrates the versatility of electron spin to convert between energy forms

**A** nanoscale device that converts mechanical ripples into an electrical current via a ‘spin current’ has been made by RIKEN researchers<sup>1</sup>. Further development of this technology could see it used in devices that permit sound waves to pass in one direction but block them in the opposite direction.

Conventional electronic devices are based on shunting electrons around circuits. Because electrons possess charge, they give rise to electric currents when they move. The emerging field of spintronics, however, harnesses another property of electrons: their spin. Spin currents are the spintronic equivalent of electric currents, but unlike electric currents, they can flow without the electrons actually moving since spin can be transferred between stationary electrons.

## People might find this approach cheaper to produce real devices

As well as holding out the promise of resistance-free energy flow, electron spin can be used to convert between various forms of energy, including electricity, light, sound, vibrations and heat. This ability to switch between different energy forms

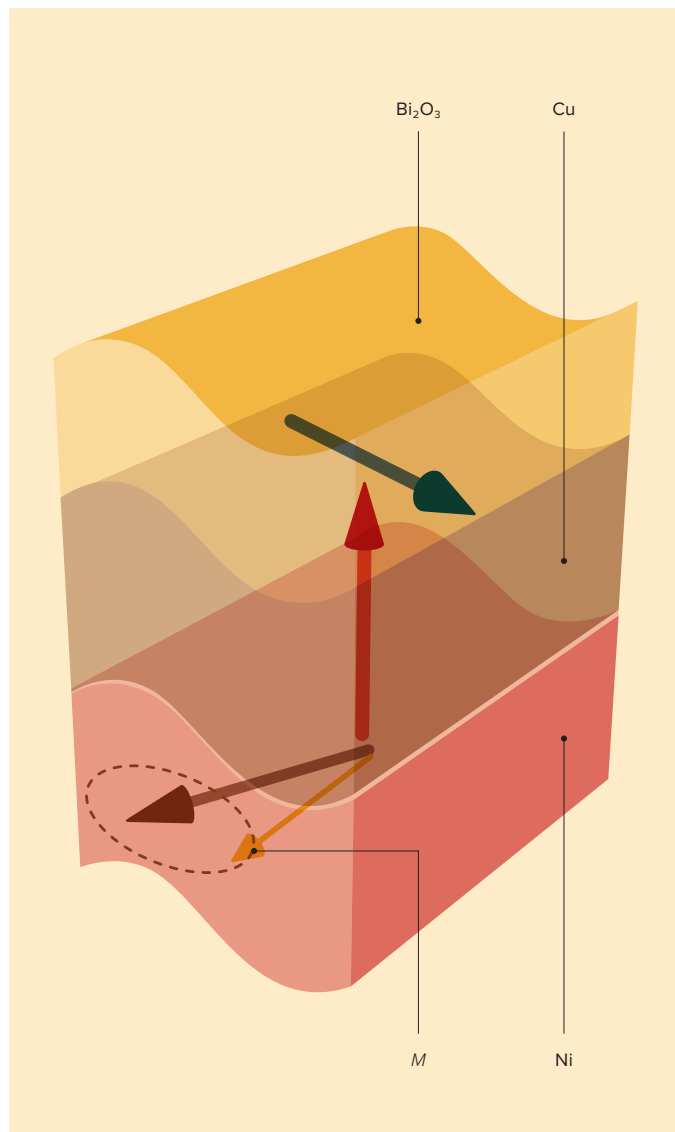
will lead to a wide range of versatile devices.

Jorge Puebla at the RIKEN Center for Emergent Matter Science and Mingran Xu at the University of Tokyo and colleagues have made a three-layered nanodevice that converts mechanical vibrations into electric current. Waves generated on the surface of a substrate cause the magnetization of the bottom nickel layer of the device to sweep out arcs (see image). This periodic motion of the magnetization generates a spin current in the second copper layer. Finally, the spin current is converted into an electric current at the top bismuth oxide layer.

The team found that the spin current generated in the second layer was particularly large. “In our field, researchers are seeking to generate higher spin currents,” explains Xu. “Our method produces quite a huge spin current.”

“We’re approaching spin currents that are large enough to move magnetic domain walls, which could be used in memory devices,” adds Puebla. “We’re still below the spin currents needed, but believe we should be able to get close by optimizing our devices.”

Another advance was the use of a relatively new way to convert a spin current into an electrical one. Often expensive metals such as platinum are



Surface waves in the substrate (not shown) cause the magnetization (orange arrow) in the bottom nickel layer to precess, which generates a spin current (red arrow) in the second copper layer. This is converted into electric current (dark arrow) at the interface with the top bismuth oxide layer.

required for this conversion, but the method the team used worked with copper. “I think in terms of technology, people might find this approach cheaper to produce real devices,” comments Xu.

Since the output varied with direction, a potential application is audio devices that allow sound to flow in one direction but not the opposite one. “You could have headphones that allow

you to listen to music and hear what others are saying, but other people cannot hear what you’re listening to,” says Puebla. ●

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## BEHAVIORAL SCIENCE

# Fruit fly's droppings attract other flies

Flying in the face of conventional wisdom, scientists find that chemicals in droppings, and not on flies' bodies, attract other flies

**B**y monitoring the brain activity of freely interacting fruit flies, RIKEN scientists have discovered that males signal their presence by placing droppings that act as calling cards for flies to find each other and even lure females to designated locations<sup>1</sup>.

Many animals from flies to mammals use signaling molecules called pheromones to attract mates and communicate socially. These pheromones may waft off the body or be excreted. Hokto Kazama of the RIKEN Center for Brain Science and co-workers have now found that pheromone-laced fecal landmarks, rather than the flies' bodies, are strong attractors for fellow flies.

In their experiments, *Drosophila* flies moved around untethered in a small arena while their neural activity and behavior were monitored by photodetectors and a thermal camera, respectively. The researchers were interested in responses of both male and female flies to the male pheromone cVA, which activates only a specific class of odor-sensing neurons. In genetically engineered flies that have bioluminescent molecules, these neurons glow when activated.

"This simultaneous neural and behavioral recording is the first for investigating social communication in such small organisms," observes Kazama. "The fly environment is a rich landscape of pheromones changing over space and time, and this kind of naturalistic observation can change our understanding of what drives flies' behavior."



Fruit flies (*Drosophila*) use droppings laced with pheromones, rather than pheromones on their bodies, to attract other flies.

Observing male flies in the arena, the researchers found that odor-sensing neurons were triggered most strongly by a particular place—the location of a dropping—rather than interactions between flies, whose bodies had previously been thought to be the main, if not the sole, source of cVA.

"We have seen cases where the odor-sensing neurons respond only after a marking," says Kazama. "And the closer the flies are to these fecal landmarks, the more bioluminescence we see."

On their own in the arena, male flies will circle the perimeter and deposit droppings, with a tendency to revisit and spend

more time around the marked regions. Flies with blocked cVA-sensing neurons did not show this attraction.

In another experiment with a male and female fly, the female's droppings were not attractive, whereas the male's markings attracted both sexes—even during courtship when a male chases a female. Fecal landmarks thus function as a social hub, indicating the identity of the marking fly and increasing mating chances.

The system for monitoring bioluminescence has applications beyond fruit flies. Traditionally, neural recording has required wires or tethering, but now

scientists can use these glowing brains to get a real-time look at activity during social communication. "Emerging genome-editing technologies combined with bioluminescent probes are giving us a powerful window into observing natural behavior and how it arises in the brain," notes Kazama. ●

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## MEDICINE

# Detecting fetal heart problems

A system that harnesses the power of artificial intelligence can detect congenital heart problems before a baby is born

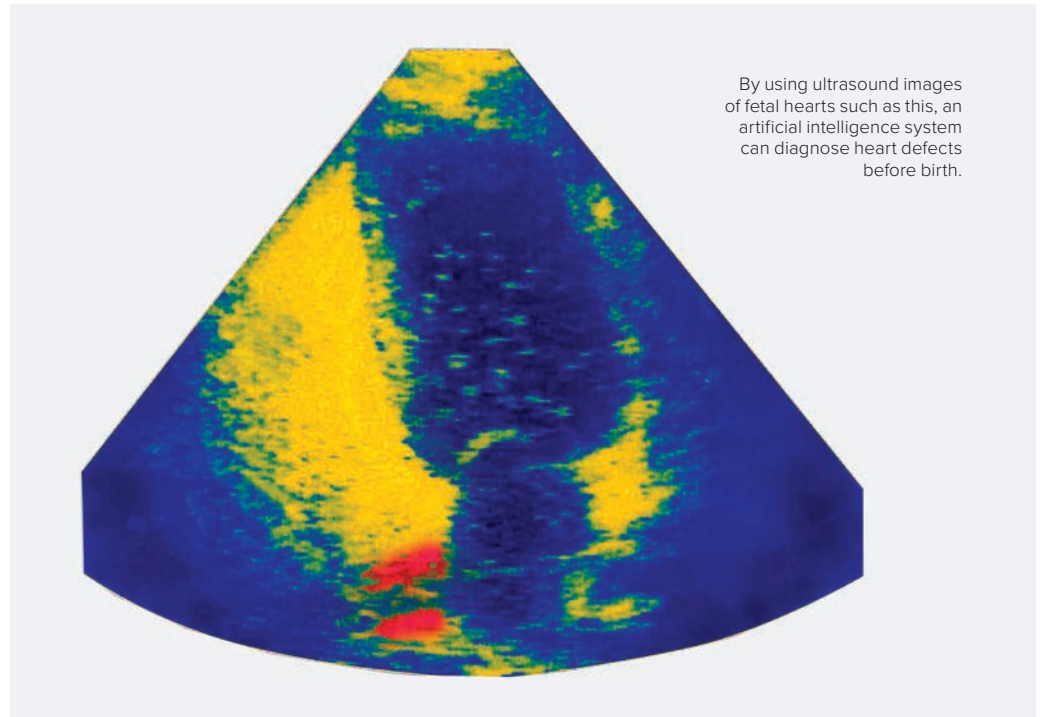
**A**n artificial intelligence system that can automatically detect abnormalities in fetal hearts in real time has been developed by RIKEN researchers. It promises to assist examiners to detect congenital heart abnormalities that require prompt treatment.

Congenital heart problems account for about one in five newborn deaths. As diagnosis before a baby is born markedly improves prognosis, many attempts have been made to develop technology that enables accurate and rapid diagnosis. But fetal diagnosis depends on observations by experienced examiners using ultrasound imaging, so sometimes children are born without having been properly diagnosed.

Machine learning techniques have been developing rapidly, and there is great interest in applying them to medical applications. Machine learning allows diagnostic systems to detect diseases more quickly and accurately than human beings, but this requires the availability of adequate datasets on normal and abnormal subjects for a certain disease. However, the relative rarity of congenital heart problems in children means there are no complete datasets for it.

To overcome this problem, the researchers developed a new machine learning technology that can accurately predict diseases using relatively small and incomplete datasets.

Experts of fetal heart diagnosis generally seek to find whether certain parts of the



By using ultrasound images of fetal hearts such as this, an artificial intelligence system can diagnose heart defects before birth.

heart are in incorrect positions by comparing normal and abnormal fetal heart images based on their own judgement. The researchers found that this process is similar to the object detection technique, which allows artificial intelligence to distinguish the position and classify multiple objects appearing in images.

## The process can be performed in real time

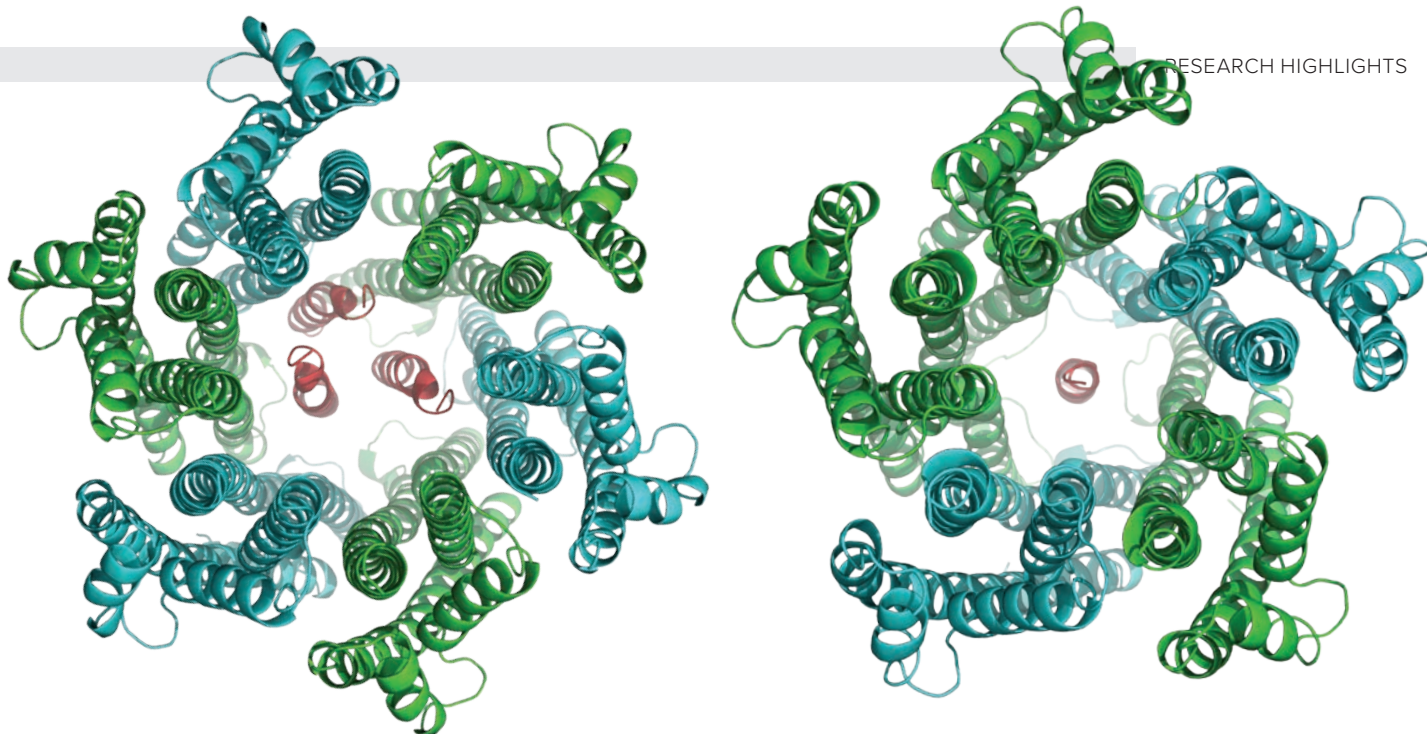
A set of ‘teacher’ data—that is, data from which artificial intelligence learns—is prepared

through ‘annotation’ or the attachment of meanings of objects, and used to train the object detection system. To develop the system, the researchers used normal heart images to annotate correct positions of 18 different parts of the heart and peripheral organs, and developed a novel fetal heart screening system, which allows heart abnormalities to be automatically detected from ultrasound images. The system judges that there is an abnormality if the difference between the test and learned data exceeds a specific confidence value. The process can be performed in real time, with the results appearing immediately on the examination

screen. The system can also help harmonize diagnoses among different hospitals with different levels of medical expertise or equipment.

“This breakthrough was possible thanks to accumulated discussions among experts on machine learning and fetal heart diagnosis,” says Masaaki Komatsu of the RIKEN Center for Advanced Intelligence Project. “We hope the system will go into widespread use through cooperation among clinicians, academia and companies.”

The researchers plan to perform clinical trials at university hospitals in Japan, adding more fetal ultrasound images to improve screening accuracy. ●



The hexameric (left) and pentameric (right) structures of the ExbB/ExbD complex in the Ton system obtained from x-ray crystallography and single-particle cryo-electron microscopy. ExbB subunits are shown in cyan and green, and ExbD in red.

## MEMBRANE BIOLOGY

# Protein subunits increase in active bacterial energy channel

A bacterial engine turns on and off as the number of its protein units changes

**T**he two structures of a protein complex that provides energy for transporting materials across bacterial membranes have been elucidated by RIKEN researchers<sup>1</sup>. This will help deepen our understanding of how to use a fundamental energy source, the proton motive force, in living organisms.

Many essential biological processes are powered by ions flowing across cell membranes. A protein complex known as the Ton system in the inner membrane of many bacteria harnesses the energy generated when protons flow into the cell to transport compounds, including essential nutrients, across the outer membrane. Determining the complex's structure and function could help researchers develop drugs that attach to pathogenic bacteria.

The Ton complex is formed from three proteins: ExbB, ExbD and TonB. Researchers have clarified some aspects of its structure and function, but its working mechanisms remain unclear. “The ExbB/ExbD complex is a challenging target as it is difficult to crystallize for x-ray diffraction and relatively small for single-particle cryo-electron microscopy (cryo-EM),” explains Koji Yonekura of the RIKEN SPring-8 Center.

By combining both techniques, Yonekura's team gained a more detailed understanding of the proteins' structures. They separated ExbB and ExbD proteins from bacterial membranes and were able to obtain sample crystals that gave good x-ray diffraction images for ExbB but not for ExbD. The researchers also placed the

ExbB/ExbD protein complexes in different levels of acidity, froze them and obtained cryo-EM images, from which they generated three-dimensional models of the protein complex for both ExbB and ExbD.

Scientists have long debated how many ExbB and ExbD subunits are in the Ton complex. Yonekura's team discovered that the numbers vary depending on the local acidity in the bacterial membrane.

In higher acidity, the ExbB/ExbD complex consists of five ExbB (pentamer) and one ExbD subunits. In contrast, in lower acidity, the complex consists of six ExbB (hexamer) and three ExbD subunits (see image). The hexamer complex represents an open, active channel, whereas the narrower pentamer channel represents an inactive state. This

is reasonable since accumulating too many protons inside a cell is toxic to bacteria. This mechanism could be used to activate and inactivate this system.

The team hypothesizes that protons move through the spiral-shaped group of six ExbB proteins, generating a torsional force that rotates the three ExbD subunits. This energy is transferred to the TonB protein part of the complex, which reaches out and connects to receptors on the outer layer of the bacterial cell membrane. This connection changes the receptors' structures such that they release substances bound to them for transfer into the cell.

“Our findings could provide a new vision of dynamic membrane biology,” says Yonekura. ●

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## QUANTUM PHOTONICS

# Enhanced emission of single photons realized

Carbon nanotubes coated onto a holey silicon substrate emit a superabundance of single particles of light

**B**y coating chemically doped carbon nanotubes on a silicon substrate riddled with tiny holes, RIKEN researchers have demonstrated a powerful source of single particles of light, or photons<sup>1</sup>. It can spew out up to about 17 million single photons a second, making the source promising for use in quantum information technologies, which could be used to send uncrackable messages.

Light is already used to carry information at high speeds around the globe via a vast network of fiber-optic telecommunications cables. These systems carry data using classical states of light—but light is also a citizen of the quantum world, sometimes behaving like a wave and sometimes like a stream of particles called photons. These light particles carry quantum information that can be used to encode data, says Akihiro Ishii, a researcher at the RIKEN Nanoscale Quantum Photonics Laboratory led by Yuichiro Kato.

**This coupling enhanced light emission from the nanotubes by about 50 times**

Communication systems based on quantum information are of great interest as it is impossible

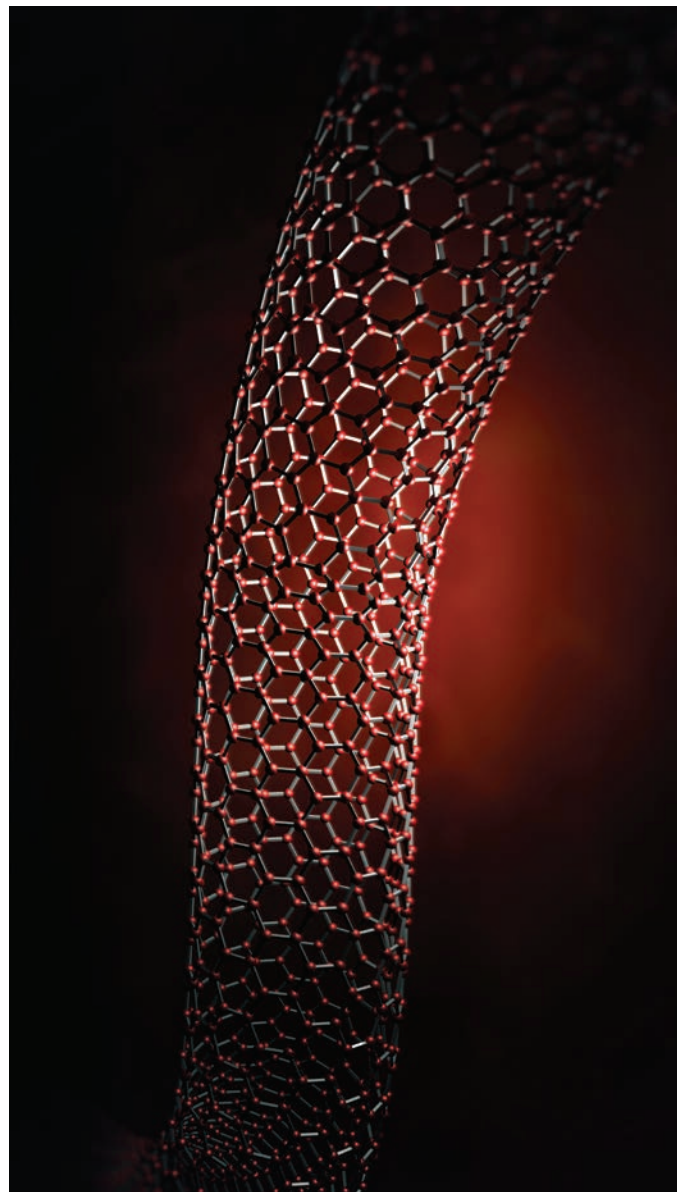
to intercept data without disturbing the data itself, preventing covert eavesdropping. But early systems for generating single photons were the size of a room. For practical applications, nanomaterials that emit single photons are eagerly sought.

Single-walled carbon nanotubes—structures akin to a flat sheet of carbon atoms rolled up into a cylinder—had previously been shown to emit single photons when excited by a laser. Kato, Ishii and their colleagues have now dramatically enhanced their photon emission by integrating them on silicon containing a regular array of holes.

The team coated a thin film of chemically doped carbon nanotubes onto a silicon substrate that had tiny holes etched into its surface so as to form photonic-crystal microcavities. They then excited the nanotubes with a laser.

A small proportion of the nanotubes aligned perfectly with one of the microcavities on the silicon. “When a carbon nanotube is coupled to a microcavity that has a very small volume, the photon emission efficiency is enhanced by a phenomenon known as the Purcell effect,” Ishii explains. The team found that this coupling enhanced light emission from the nanotubes by about 50 times.

What’s more, the device produced single photons with



When carbon nanotubes (schematically depicted here) are coated on a silicon substrate that has holes in it, they emit many single particles of light.

high purity at room temperature, even when the intensity of the laser beam was ramped up. “This result means that our devices are durable and can offer good performance,” Ishii says. “High-power excitation yields bright single-photon emission.”

The team is now working on modifying the carbon nanotubes and the underlying silicon microcavities so that they emit bright single photons

at the main wavelength used for telecommunications. ●

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## DEVELOPMENTAL BIOLOGY

# A switch in perspective

A surprising ‘switch’-based signaling mechanism governs tissue formation in developing fly embryos

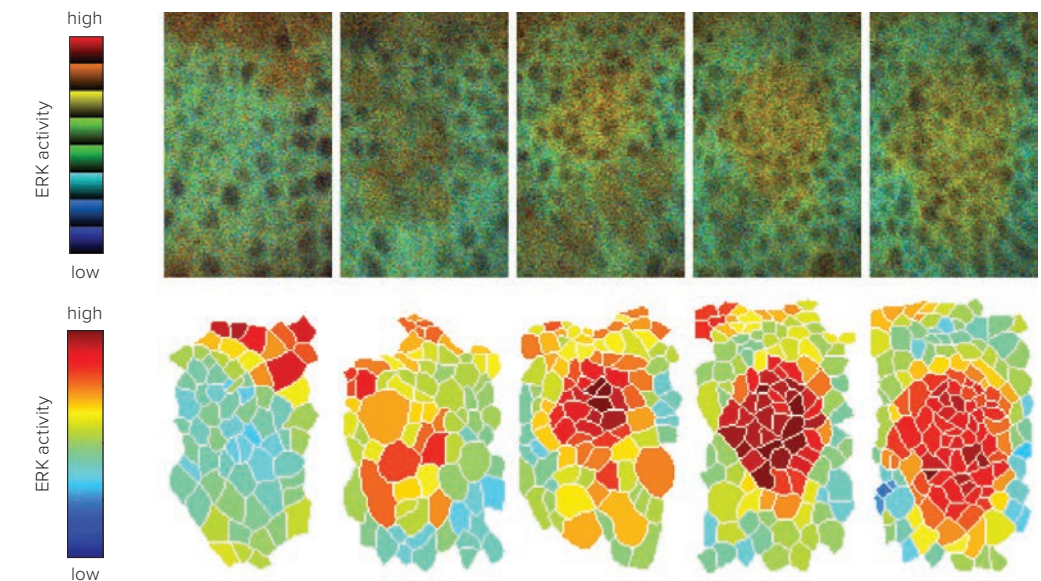
**A** well-studied signaling molecule employs an unexpected mechanism to coordinate the formation of the respiratory system in fruit flies, RIKEN researchers have discovered<sup>1</sup>. This discovery will prompt fresh evaluation of the previously accepted model for this process.

The development of embryos is orchestrated through the complex interplay of many cellular signaling pathways, which collaboratively steer the organization of various body structures. Epidermal growth factor receptor (EGFR) sits at the center of many critical cellular processes, governing both normal development and the abnormal growth that occurs in tumors.

A team led by Shigeo Hayashi of the RIKEN Center for Biosystems Dynamics Research was interested in discovering how EGFR leads to the activation of the key kinase—extracellular signal-regulated kinase (ERK)—in this signaling pathway in fruit fly embryos.

**“This mechanism is advantageous for some aspects of the developmental process.”**

“Our previous work had indicated that EGFR activity spreads in a tissue,” Hayashi says. “We thus wanted to capture the spread of EGFR activity in a real-time video.”



Live imaging analysis (top) reveals the activation pattern of EGFR-ERK signaling that spreads throughout the cell layer that gives rise to tracheal tissue. The lower panel illustrates relative activation levels.

Fruit flies breathe through tube-like structures known as tracheae, which are formed by the inward folding of embryonic cell layers. Researchers have long believed that the timing and location of this folding is governed by a gradient of EGFR-induced ERK activation, where the strength of EGFR-ERK signaling drops off gradually with distance from the site of initial activation. However, an alternative hypothesis suggests that these signals may instead propagate like a wave, with each cell in the outer boundary of this wave successively undergoing EGFR-ERK activation.

By using a fluorescent sensor to visualize this process in developing embryos, Hayashi’s team has now confirmed that the wave model reflects successive activation of EGFR ligand production.

“This switch-like response allows for a domino-like chain reaction of persistent signal propagation without decay,” says Hayashi. “This mechanism is advantageous for some aspects of the developmental process.”

His team confirmed this by performing computer simulations of the two different signaling mechanisms. Their simulations revealed that the gradient fails to induce proper cell layer folding. The researchers also identified a genetic mutation that essentially disables this relay-signaling process, producing a gradient-like profile of EGFR-ERK activation that is incapable of coordinating tracheal formation.

Hayashi notes that this does not entirely invalidate the gradient model of EGFR activation, which is likely to play

a role in other developmental processes. “A single molecular toolkit like EGFR can possibly produce two different modes of output—a ‘tuner’ and a ‘switch’—depending on the cellular context,” he comments.

His team intends to explore the other molecular factors that determine which mechanism is employed, and where these different systems may prove advantageous in development. ●

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When 14-day-old plants were exposed to heat shock, the *hili1* mutants (withered plants in bottom right octant) fared poorly.

## PLANT RESILIENCE

# How plants beat the heat

A novel approach enables researchers to pinpoint the gene that imparts plants with heat tolerance

**A** gene in plants that helps protect them from excessive heat has been identified by researchers at RIKEN<sup>1</sup>. This finding will inform future research into developing heat-tolerant plants.

Excessive heat can cause plants to wither and die by damaging the membranes of their chloroplasts—organelles that capture sunlight and use it to produce food for plants.

But plants have a natural defense against this type of stress that involves modifying plant fats that make up chloroplast membranes. Polyunsaturated fatty acids stabilize the membranes. Heat causes the fatty acids to be removed, thereby destabilizing the chloroplast membranes.

The RIKEN team quickly found the gene responsible for this process by adopting an innovative approach.

“We hypothesized that the breaking down of chloroplastic lipids would be controlled by some unidentified genes that encode lipases localized in chloroplasts and which are induced by heat stress,” explains Yasuhiro Higashi of the RIKEN Center for Sustainable Resource Science.

The researchers performed a transcriptome analysis to identify candidate genes that code for lipases—enzymes that break lipids apart. They then used proteomics databases to narrow the search by predicting which of the candidate genes are localized in chloroplasts.

To test the most likely candidate gene—which the team named *Heat Inducible Lipase 1 (HILI)*—they created a mutant *Arabidopsis* plant in which the gene was disrupted. They then compared mutant responses to heat stress to those of normal plants and found that the mutant plants were more sensitive to heat—their condition worsened more than the control plants in extreme heat and they had a much lower survival rate (see image).

Closer examination showed that membrane remodeling in the mutant chloroplasts was partially disrupted, and not all polyunsaturated fatty acids were removed from a key glycerolipid.

These experiments were performed in the plant *Arabidopsis*, the most common plant used in plant research. The team

also did a gene coexpression analysis using public microarray data, which revealed a conserved network associated with *HILI* in several plant species, including rice, tomatoes, corn and soybeans.

“We are interested in discovering the function of the *HILI* homologous genes in major crop species,” notes Higashi. “We hope our knowledge about *HILI* might aid in the development of new heat-stress-tolerant plant varieties, which could help improve crop yield in hot environments.”

Team leader Kazuki Saito is also looking at the big picture. “This natural response to heat is not new, but understanding how it works is a step forward in fighting global warming,” he says. ●

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## ORGANOGENESIS

# Growing salivary glands in the lab

By harnessing the power of stem cells, scientists have produced tissue that enables mice to salivate

**S**alivary gland tissue that produced saliva like normal glands when implanted in mice has been grown in the lab for the first time by RIKEN researchers<sup>1</sup>. This achievement could give doctors new options for treating patients who have damaged salivary glands.

Growing functional organoids—simplified three-dimensional tissues that resemble the structures of real organs—in the lab could restore at least partial organ function to patients with failing organs. Stem cells are promising for realizing this since they can transform into many different types of cell.

Salivary glands are needed to digest starch and facilitate swallowing, but they can be damaged by an autoimmune condition known as Sjogren's syndrome and by radiation therapy for cancer. They develop from an early structure called the oral ectoderm, but the process is not fully understood.

**“It was incredibly exciting to see that the tissues we created actually functioned in a living animal”**

Now, a team led by Takashi Tsuji of the RIKEN Center for Biosystems Dynamics Research and Kenji Mishima of Showa University has unraveled the important cytokine signaling and changes in gene expression that occur in the



A micrograph showing an induced salivary gland with a branching structure.

development of salivary glands. They identified two transcription factors that are important for the differentiation of stem cells into salivary gland tissue—Sox9 and Foxc1. The scientists also identified a pair of signaling factors that induced cells expressing those transcription factors to differentiate into salivary gland tissue.

The team used a chemical and cytokine cocktail to induce embryonic stem cells to form an ectoderm and then used viral vectors to get the cells to express Sox9 and Foxc1. This induced the cells to form tissue that genetic analysis revealed was very similar to developing salivary glands in the embryo (see image).

The final step was to test whether the organoid would

function in mice. When the organoids were transplanted alone or with mesenchymal tissue—embryonic tissue that forms mesenchyme of salivary glands—into salivary gland-dissected mice, the implanted tissues properly connected to the nerve tissue. Furthermore, the glands secreted a substance remarkably similar to real saliva when the mice were stimulated by citric acid.

“It was incredibly exciting to see that the tissues we created actually functioned in a living animal,” says Mishima. “This is an important proof of concept that organoids are a valid alternative to actual organs.”

The team is enthusiastic about the potential of their approach.

“We continue to work to develop functional tissues to replace the functions of various organs, and we hope that these experiments will soon find their way into the hospital and help patients suffering from a variety of disorders,” comments Tsuji. ●

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## SUPERCONDUCTIVITY

## Two ways to pair up

Evidence that electrons form pairs in two distinct ways in iron-based superconductors will help theorists unravel the mechanism of unconventional superconductivity

**B**y mapping uneven patterns of electrons in iron-based superconductors, RIKEN researchers have found evidence that electrons can pair up in two different ways, depending on the crystal structure<sup>1</sup>. This finding could help scientists in their quest to design materials that superconduct at relatively mild temperatures.

Superconductors carry electrical current with no resistance and are used to create powerful electromagnets and sensitive magnetic detectors. However, most superconduct only at extremely low temperatures, limiting their practical application. So physicists are investigating high-temperature superconductors that operate well above  $-196$  degrees Celsius, the temperature of liquid nitrogen.

**“This may lead to the design of as-yet-unknown exotic, and hopefully high-temperature, superconductors”**

Superconductivity occurs when electrons pair up, which slightly lowers their energy and creates an energy gap that stops them scattering as they flow through the material. In some copper- or iron-based

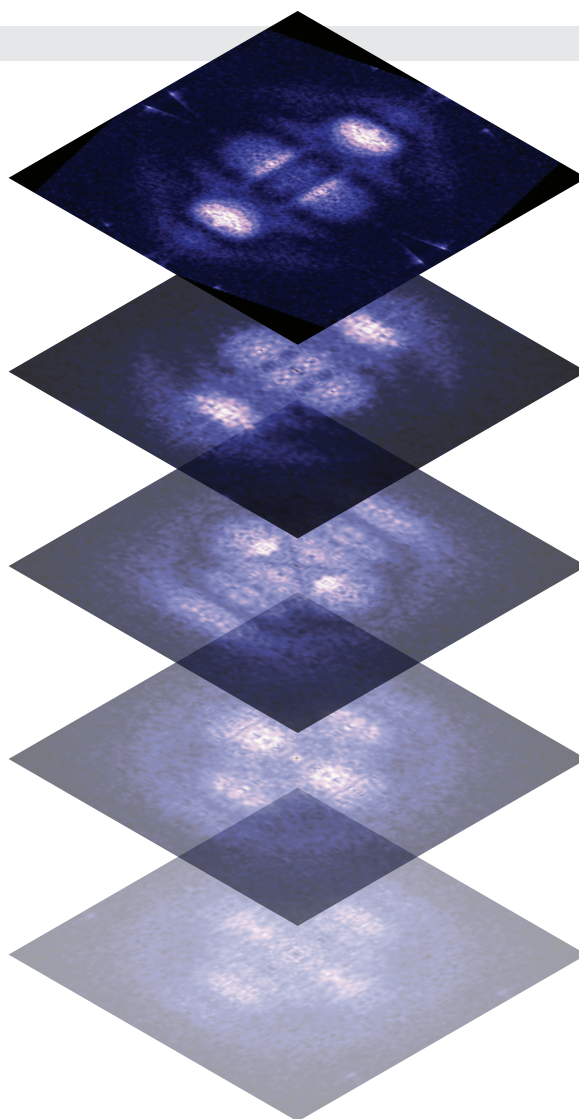
superconductors, this pairing is closely related to a distortion in the material’s structure known as the nematic phase. As a result, certain electrons around the metal atoms can adopt different energy states, giving them a more uneven distribution than in the non-nematic phase.

Tetsuo Hanaguri of the RIKEN Center for Emergent Matter Science and colleagues have now probed the relationship between nematicity and superconductivity in a family of materials based on iron selenide.

Iron selenide enters its nematic phase below about  $-183$  degrees Celsius. Swapping some of the material’s selenium atoms for sulfur ones weakens this nematicity, and once the ratio of sulfur atoms to selenium ones exceeds about one fifth (known as the nematic end point), the temperature at which the transition to the nematic phase occurs begins to fall.

The researchers studied crystals of iron selenide sulfide with varying sulfur content using a technique called spectroscopic imaging scanning tunneling microscopy. This allowed them to measure the precise chemical compositions of the samples as well as key electronic properties of the material (see image).

As the sulfur content increased up to the nematic end point, the energy gap of superconducting electron pairs did not change.



By mapping electron patterns in crystals of iron selenide containing increasing amounts of sulfur, RIKEN researchers have found evidence that electrons in the superconductor pair up in two different ways.

However, the energy gap suddenly shrank beyond the nematic end point. This suggests that the superconducting electrons could pair up in two different ways, depending on the material’s nematicity.

“Our data clearly indicate that there is an intimate relationship between nematicity and superconductivity,” says Hanaguri. “This is an important constraint for the theory of iron-based superconductivity, because the correct theory must account for this characteristic behavior.”

The researchers now plan a more detailed investigation of the superconducting energy gaps in the nematic and non-nematic phases of iron selenide sulfides,

and they aim to study other superconducting materials in the same way.

“This may lead to the design of as-yet-unknown exotic, and hopefully high-temperature, superconductors,” notes Hanaguri. ●

### Reference

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## NEUROSCIENCE

# Enigma of engram cells solved

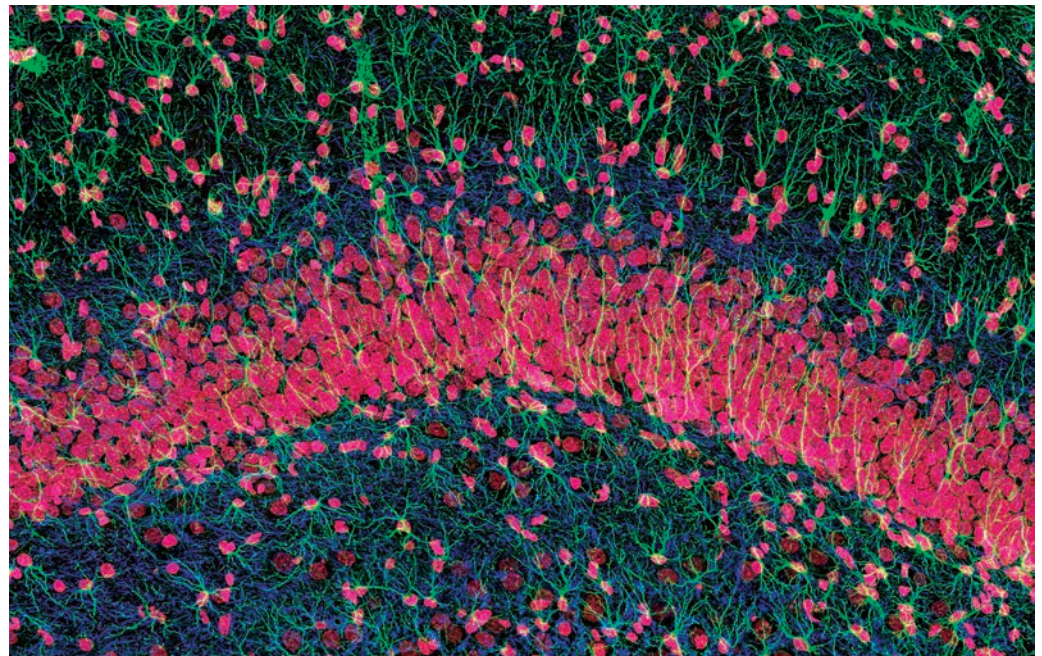
Experiments reveal that brain cells thought to be involved in making mental maps actually store experiences

**T**he brain does not store all memories in ‘place cells’, the main type of neuron in the hippocampus, a structure crucial for navigation and memory. Instead, memories seem to be powered by a subset of hippocampal cells that have more to do with context or episodes than location, RIKEN researchers have found<sup>1</sup>.

The hippocampus contains place cells, which construct mental maps of space, and engram cells, which store memories of experiences. Memory engrams had been assumed to be just a type of place cell, but experiments by Thomas McHugh of the RIKEN Center for Brain Science and co-workers suggest otherwise.

To identify the brain cells involved in creating a memory of a new environment, the researchers used optogenetic methods to identify cells activated while mice explored a cage. These cells represented only a fraction of hippocampal place cells and had larger place fields—the area in the real world excites a place cell when the mouse is exploring—than other place cells.

Analysis of the activity across many cells revealed that, while most place cells kept the same spatial map during an initial and later visit to the cage, the engram cells had uncorrelated activity between the two visits. The only exception was very early during both visits when the cells’ activity was similar, which is consistent with them being involved in recalling the context.



An image of the hippocampus, which contains place cells that function as engram neurons.

## The researchers could tell the two environments apart by comparing the activity of these cells

When the mice were placed in a different cage, the engram cells remained inactive—they were already ‘occupied’ with the previous memory. In fact, the researchers could tell the two environments apart by comparing the activity of these cells. The engram cells are active only when recalling the general context, not specific locations,

whereas place cells are active during exploration, creating and updating a spatial map. Since recognizing a context or environment does not occur during exploring, location cells appear to be distinct from memory cells.

The instability of the spatial information signaled by engram cells compared with most place cells indicates that they deal with the ‘big picture’, the macroscale of a context and not a specific location therein.

The researchers propose that engram cells may not store memories per se but act as an index that ties memory-relevant details together, wherever they may be in the brain. “Their role is to track elements of a

memory, whether those are from sound or vision or other senses, and then trigger their recall by activating other parts of the brain like the cortex,” McHugh hypothesizes.

While the hippocampus clearly does underlie spatial memory, this newly revealed function as an index for contextual identity shows that this brain region is about more than just maps. ●

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## ORGANIC PHOTOVOLTAICS

# A solar-powered heart monitor taped to the skin

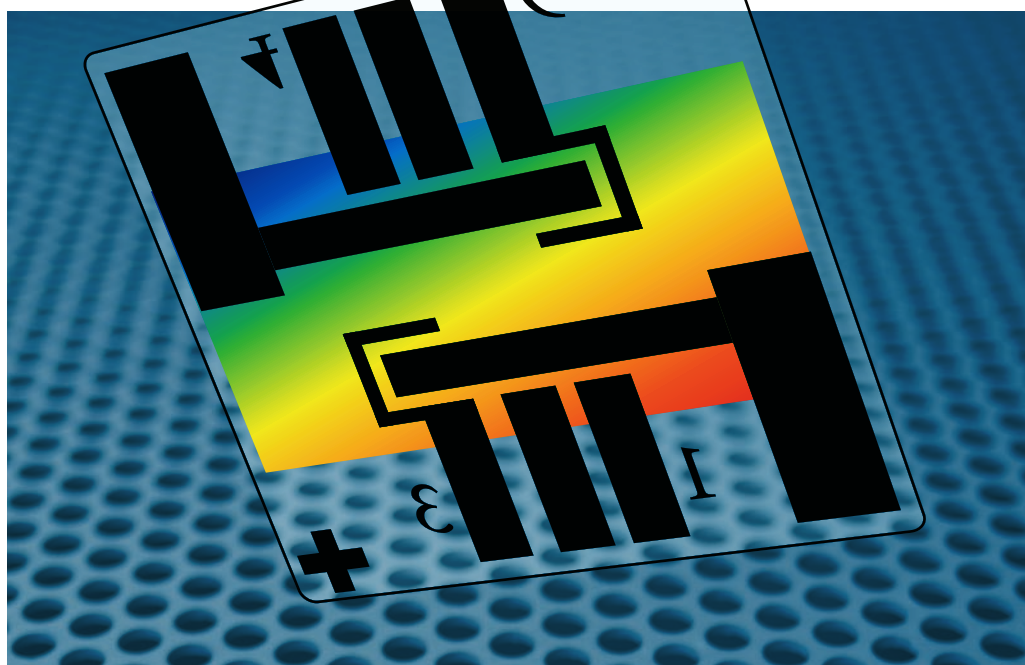
A self-powered device that attaches to the skin can measure the heartbeat of a rat

**A** human-friendly, ultra-flexible organic sensor powered by sunlight, which acts as a self-powered heart monitor, has been developed by scientists at RIKEN<sup>1</sup>. They directly integrated a sensory device called an organic electrochemical transistor—an electronic device that can be used to measure a variety of biological functions—into a flexible organic solar cell. The sensor enabled them to measure the heartbeats of rats and humans under bright light.

Self-powered devices that can be fitted directly on human skin or tissue have great potential for medical applications. For example, they could be used as physiological sensors for the real-time monitoring of heart or brain function in the human body. However, practical realization has been hindered by bulky batteries and inadequate power supplies. Also, noise interference from the electrical supply impedes long-term operation.

**“This is a nice step forward in the quest to make self-powered medical monitoring devices that can be placed on human tissue”**

The key requirement for such devices is a stable and adequate power supply. Now,



Self-powered devices with flexible organic solar cells such as this one can serve as self-powered heart monitors on the skin.

Kenjiro Fukuda of the RIKEN Center for Emergent Matter Science and his co-workers have used a nanograting surface on the light absorbers of the solar cell, allowing for a high photoconversion efficiency of 10.5 percent, which is approaching the ‘magic number’ of 15 percent that will make organic photovoltaics competitive with their silicon-based counterparts.

To demonstrate a practical application of this technology, the Kenjiro and his team integrated organic electrochemical transistors with organic solar cells on an ultrathin substrate and then used the devices to perform self-powered detection of heartbeats on the skin and

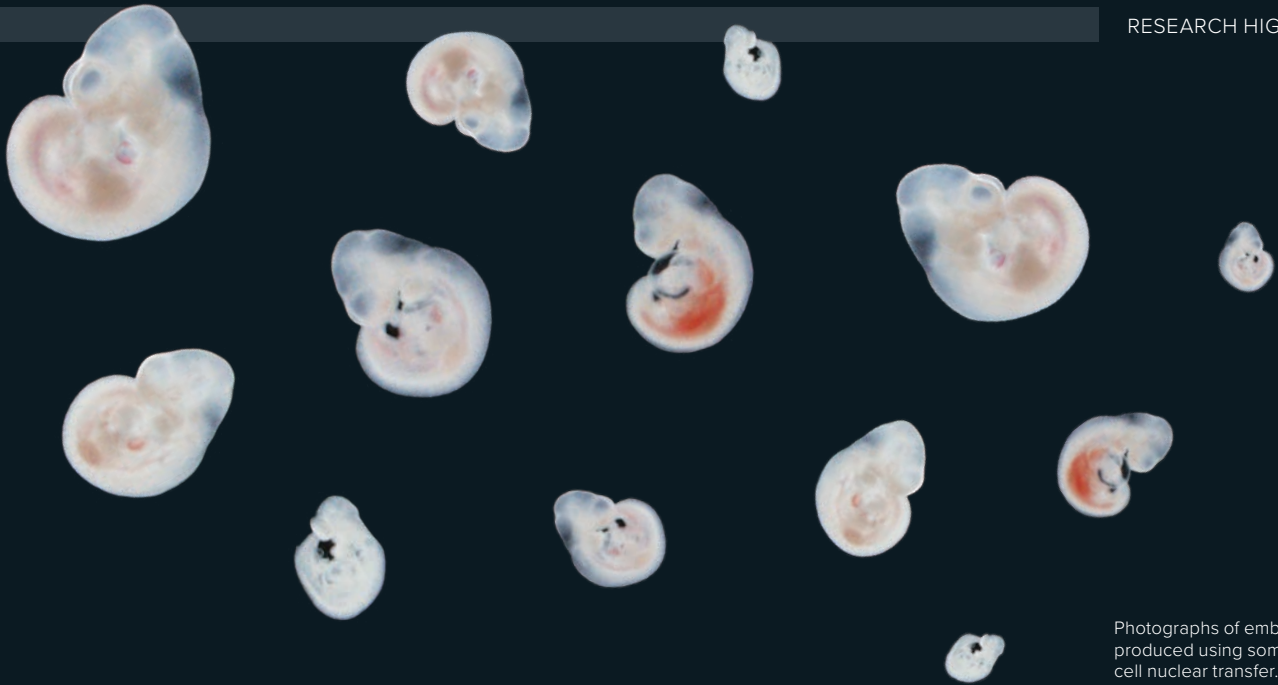
to record electrocardiographic signals directly from the heart of a rat. The device worked well at a lighting level equivalent to that in the shade on a sunny day. Furthermore, it exhibited less noise than similar devices connected to a battery, presumably because it did not have electrical wires.

“This is a nice step forward in the quest to make self-powered medical monitoring devices that can be placed on human tissue,” says Fukuda. “There are some important remaining tasks, such as the development of flexible power storage devices, and we will continue to collaborate with other groups to produce practical devices.

“Importantly, for the current experiments, we worked on the analog part of our device, which powers the device and conducts the measurement. There is also a digital silicon-based portion, for the transmission of data, and further work in that area will also help to make such devices practical,” he adds. ●

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Photographs of embryos produced using somatic cell nuclear transfer.

## ANIMAL CLONING

# Removing barriers to cloning mice

Removal of two epigenetic barriers has boosted the chances of mice successfully birthing clones

The probability of producing cloned mice has been dramatically increased by RIKEN researchers<sup>1</sup>. They have also identified barriers that, when overcome, will raise the success rate for birthing clones even more.

Cloned animals like Dolly the sheep are created through a process called somatic cell nuclear transfer (SCNT). This involves transplanting the nucleus of a normal body cell, which contains the DNA of an individual, into an egg cell. The nucleus is reprogrammed by its host egg cell so that the cell can form all the cell types in the body. If all goes well, a genetically identical clone of the donating individual is created. But things do not usually go well. For example, in the case of Dolly, the procedure had to be performed manually more than 270 times before the first fetus was brought to term.

Two epigenetic factors—changes to the chemical

modifications of DNA or histone proteins rather than to the genetic code itself—play a key role in hampering the proper development of SCNT clones.

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**“We will continue studies to find ways to overcome this further barrier”**

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The first one is called histone H3 lysine 9 trimethylation. Removing this factor by injecting a demethylation factor called *Kdm4d* boosts the rate of successful implantation of the cloned embryos. The other epigenetic factor is an RNA called *Xist*. It is normally only expressed from the paternal X chromosome but is expressed from both X chromosomes in SCNT, leading to developmental problems after implantation. These two barriers

contribute to the low success rate—about 1 percent of SCNT embryos in mice are brought to term.

Now, Shogo Matoba of the RIKEN BioResource Research Center and co-workers have brought about 20 percent of implanted cells to term. They achieved this by removing both barriers through using cells in which the *Xist* gene was knocked out and then injecting *Kdm4d* messenger RNA.

The team found that even when embryos implanted successfully, they often had abnormalities preventing normal development and the placenta had abnormalities too. Further work revealed that although fertilized embryos and SCNT embryos had similar levels of epigenetic marks, the genes that methylation silenced often differed. The scientists also discovered a set of genes that were not expressed from the maternal chromosome

in fertilized embryos, but were expressed from both the paternal and maternal chromosomes in SCNT embryos. These genes are involved in fetal and placental development, providing a likely explanation for the failure of development after implantation.

“We have definitively shown that epigenetic modifications will need to be modulated to further improve the efficiency of SCNT,” comments Matoba. “We will continue studies to find ways to overcome this further barrier, hopefully leading to even better efficiency of cloning.” ●

### Reference

1. Matoba, S., Wang, H., Jiang, L., Lu, F., Iwabuchi, K. A., Wu, X., Inoue, K., Yang, L., Press, W., Lee, J. T. *et al.* Loss of H3K27me3 imprinting in somatic cell nuclear transfer embryos disrupts post-implantation development. *Cell Stem Cell* **23**, 343–354 (2018).

# BY (ARTIFICIALLY) INTELLIGENT DESIGN

*Japanese artificial intelligence researchers are working on deep-learning algorithms that glean advanced insights from Japanese types of data.*

Roughly 40 percent of Japan's infrastructure will be 50 years old or older by the 2020 Tokyo Olympics. AI from RIKEN will help the Japanese government assess what needs to be fixed using drones.

**H**uman wisdom is the result of accumulated experiences, and soon machines will be wiser too. Sound like science fiction?—It isn't. Powerful artificial intelligence (AI) algorithms are already driving 'deep learning' programs that use complex pattern reinforcement so that machines can 'learn' from data. This technology will enhance human analytics so much that it could add US\$3.5 trillion annually to the global economy, according to a report released in April 2018 by the McKinsey Global Institute.

The RIKEN Center for Advanced Intelligence Project (AIP) was set up in 2016, following extensive discussions with Japan's Ministry of Education, Culture, Sports, Science and Technology on the best ways to invest in intelligent computing. I became the inaugural director, a role I took alongside a professorship at the Graduate School of Frontier Sciences at The University of Tokyo.

Even in the short time the AIP has been around, AI technologies—including speech recognition, image analysis and language interpretation—have made huge inroads, and the young AIP quickly established links with more than 50 academic groups and research teams.

However, researchers around the world are still working on AI capable of higher level thinking—machines that could, for example, interpret the underlying meaning of sentences in the context of a whole conversation. As a result, we're still working closely with neuroscientists and psychologists on useful learning phenomena and behaviors that we could replicate within computer programs.

All of this work ties into the first of the AIP's five main missions: to continue developing fundamental AI technologies, which will help AI move beyond working on well-defined data to being able to recognize patterns in more complex data.

Japan, it turns out, has to develop smarter algorithms. For a variety of reasons (including population and language), we don't have access to the same amount of data as the USA and China, from where a lot of advances in AI research are emanating. We will have to develop smarter technology to be able to learn from limited information.

Fortunately, AI has recently moved on from being about better data or bigger computers. In 2017, David Silver, the principal researcher on Google's highly publicized deep-learning project, Go, pointed out that today "it is the novel algorithms that really matter." He made his point just after his team published a paper on a particularly game-changing algorithm, AlphaGo Zero. It represented a huge leap forward for AI algorithms. Smart algorithms like AlphaGo Zero will hopefully have many additional advantages.

### **JAPANESE AI FINDS NEW DRUGS AND SOLAR MATERIALS**

This leads us to our second mission, which is to help

accelerate and augment scientific research. Our AI software can already help scientists search through literature for relevant findings, and collate or summarize measurements across several papers.

Scientists today can also generate increasingly large datasets and use them to simulate phenomena such as the behavior of biological proteins or climate change, for which millions of calculations must be performed over large, fine-scale grids, taking up unwieldy amounts of computational power and time. We can help our computer science colleagues to streamline this process by providing software tools to help build models to limit the computing power needed to run simulations.

We have already had some great results assisting geoscientists simulating earthquakes, tsunamis and floods in collaboration with the RIKEN Center for Computational Science, which operates the super-computer known as the K computer.

Alongside this work, the AIP is helping to simulate complex chemistry and quantum physics to find new functional materials for electronics and manufacturing. For example, in 2018 we applied this technology to finding molecules suitable for organic photovoltaic cells useful to solar technology, photofunctional sensors and ultraviolet filters, among other things. By using a combination of known chemistry and deep learning, in 10 days a collaboration that included AIP was able to identify five synthesizable and stable organic molecules possessing target properties.

Perhaps our most active multidisciplinary efforts are in applying AI to medicine, including image analysis tools to extract information from x-rays, MRI scans and other imaging systems, as well as statistical software that helps biologists to understand the immense datasets generated by genomics, molecular biology, government surveys and clinical records. Deep learning machines interrogating these 'big data' sets help to produce fast diagnoses or can suggest relevant directions for research.

AIP teams are also applying similar algorithms to design drug compounds that can match up the shapes of disease-related proteins and neutralize them.

With about 15–20 percent of drug development costs seen in the discovery phase, this could soon be a huge boon to medicine. In the USA, for example, there is a program to show researchers how proteins fold to help them build drugs against various viruses that is already seeing heavy investment.

### **THE SOCIAL BENEFITS OF AI: EVERYTHING FROM FIXING BRIDGES TO WELLBEING**

Of course, we have a duty to focus on projects that will benefit society, and this is reflected in our third mission, which is to use AI to find solutions to critical domestic problems.



**MASASHI SUGIYAMA**  
Director of the RIKEN  
Center for Advanced  
Intelligence Project

Masashi Sugiyama has been the director of the RIKEN Center for Advanced Intelligence Project (AIP) since it was set up in 2016. He is also a professor at the Graduate School of Frontier Sciences at the University of Tokyo, and was the first Asian program chair at the Neural Information Processing Systems (NeurIPS) conference in 2015. NeurIPS is the largest international conference in the machine learning field. In 2012, he published a book with The MIT Press, *Machine Learning in Non-Stationary Environments*.



The RIKEN Center for Advanced Intelligence Project (AIP) is helping assess the condition of infrastructure by using drones and AI-driven image analysis to spot cracks in hard to reach places.

To this end, the AIP has been helping the Japanese government address the fact that roughly 40 percent of Japan's infrastructure will be 50 years old or older by 2020, the year of the Tokyo Olympics. The total cost of Japan's infrastructure, including its roughly 700,000 bridges and 100,000 tunnels, has been estimated at ¥700 trillion, so it seems logical to fix these structures rather than replace them. To do this, our AI is being used to control fleets of drones that will use various cameras to inspect hard-to-reach parts of bridges, and these will automatically identify cracks or other damage through image analysis.

As AI enters the practical world, ethical implications also become more important, and staying on top of this area is our fourth mission. Some people believe that AI will polarize people due to concerns about the loss of jobs and privacy. Data privacy is already contentious, with big companies being forced to restructure their business models as regulation tightens, most notably through the General Data Protection Regulation (GDPR) introduced by the European Union in May 2018.

As a result, we have dedicated teams investigating societal attitudes to AI, monitoring international information laws, and working to make sure that interactions between humans and machines are pleasant experiences.

#### **BUILDING TALENT AND WORKING ALONGSIDE CORPORATE R&D**

However, all of these tasks are impossible if our fifth mission fails: Japan's next generation of AI researchers and data scientists must be nurtured. Due to its structure, the AIP is lucky to have very broad academic links. For example, 35 out of the 51 team leaders at AIP are professors at other Japanese universities and we have ongoing partnerships with a number of institutions. We have also hosted more than 70 graduate students doing internships for periods ranging from a few months to a year.

While we find many of our talented students are enticed into jobs in Japan's strong corporate R&D sector, we still have the chance to collaborate with them. Many multinationals already have collaboration centers with us, including Fujitsu, Toshiba, NEC and Fujifilm. Our projects include improving the efficiency of their manufacturing plants. And while these industrial research partners benefit from our fundamental research and software, we benefit from their wide range of resources and learn from their experiences of bringing AI into the real world. ●

👂 We will have to develop smarter technology to be able to learn from limited information

For a full list of references, please visit the online version of this article: <http://www.riken.jp/en/research/rikenresearch/perspectives/2018winter/>

A superconductor model cable on display in a museum in Germany. Germany has been one of the first countries to use superconductor cables to supply electricity.

## RAPID COOLING REVEALS SUPERPOWERS

*Rapid electrical cooling bypasses other states and turns on a superconducting state in materials that were previously not superconductors*

**R**IKEN researchers have developed a brand-new method for inducing superconductivity, by very rapidly cooling a target material using electrical pulses and effectively bypassing other states that might be more stable. RIKEN's Hiroshi Oike says it will vastly broaden the range of known superconducting materials.

In most conductors, the natural kinetic motion of warm atoms somewhat disrupts the flow of electrons (electricity), some of which are lost as heat. However, when a superconductor's atoms are very cold, they stop vibrating around as vigorously, and electrons are

free to zoom along the material without resistance because of quantum mechanical effects. Because of this, superconductors don't suffer from energy scattering and loss, and they can harness larger electric currents.

What Oike and his colleagues from the RIKEN Center for Emergent Matter Science and the University of Tokyo realized is that electron ordering takes time, so reducing the temperature of a potential superconductor extremely fast could circumvent other non-superconducting states that might otherwise take precedence. The group describe it as a "thermal quenching approach" based on the fact that within a time range, a system may be trapped



Massive cooling systems are part of what make magnetic resonance imaging machines so bulky. This is down to the fact that most harness superconductors that need to be very cold.

in a local minimum state. In an overview on Oike's study, *Nature* compared the idea to plunging hot steel into cold water to harden it, which bypasses small changes that happen during drawn out cooling.

Excitingly, the group found that, in the right conditions, superconductivity does indeed emerge as 'a metastable state'—the state with the longest lifetime against other excited states—even if more stable competing orders were bypassed during cooling.

Important implications exist if new superconductors are found that operate at higher temperatures than those we already know. Currently, superconducting materials only exhibit this state at very low temperatures—the highest temperature a superconductor is known to operate at is  $-70^{\circ}\text{C}$ . Finding higher temperature superconductors could vastly reduce the need for cumbersome cooling apparatus. This change could quickly dovetail into more efficient computing and electrical devices, and MRI machines would be able to finally shed their distinct bulky doughnut shape, which is created by huge liquid cooling systems surrounding superconductors emitting the powerful magnetic fields essential to an MRI's function.

#### AN ENERGETIC BALANCING ACT

Since the discovery of superconductivity in 1911, scientists have tweaked superconductors by making small changes to their composition or increasing physical/chemical pressure, both as a means of ensuring that the superconducting state is the lowest energy state. They do this because it's fundamental to thermodynamics that a system will eventually settle into the state with the lowest energy. According to Oike, the problem for many potential superconductors previously had been the fine energetic balance between a superconducting state and its alternatives.

He explains that localized particles have greater kinetic energy, but smaller repulsion energy, than delocalized ones, and so localized and delocalized states are in very close energetic competition. "Electrons at low temperatures are often localized to minimize the energy cost of their mutual repulsion," Oike says. "But electrons in a superconducting state are delocalized and consequently pay a larger energetic cost because a delocalized electron has more chance to get close to, and repel, other electrons." As a result, for many materials another state takes precedence over a superconducting state.

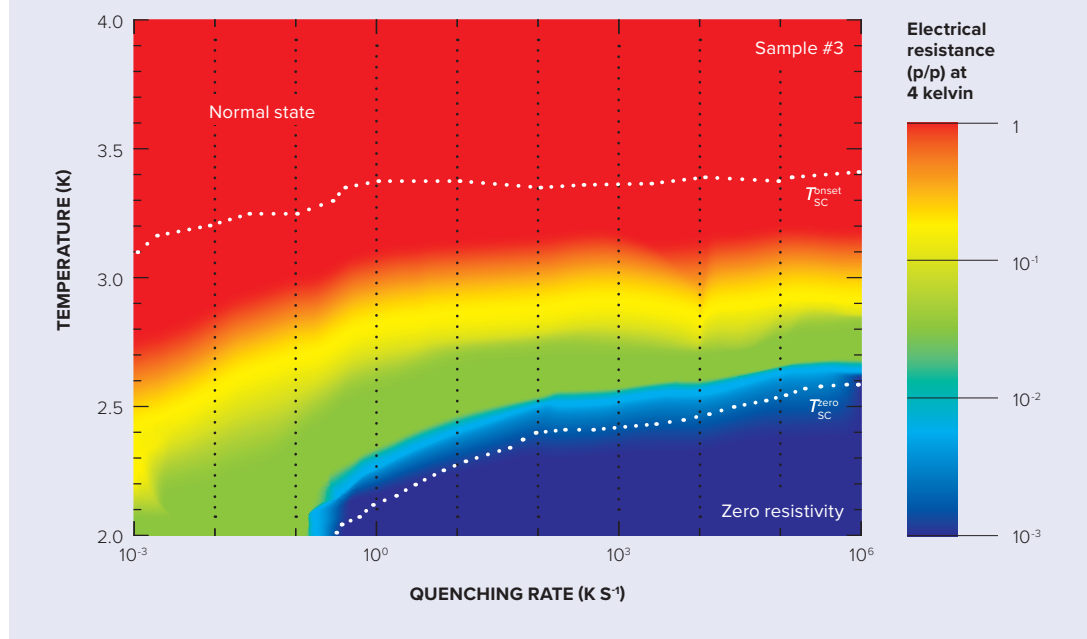
#### QUICK COOLING VERY EFFECTIVELY BYPASSES OTHER STATES

To prove experimentally that their quick cooling idea could effectively line-jump other states, Oike's team selected a non-superconducting material called iridium ditelluride. The electrons in iridium telluride are delocalized at high temperatures, but usually



## ELECTRICALLY ASSISTED COLD SNAP FOR ZERO RESISTIVITY

This chart represents an interplay between the quenching rate and the emergent superconductivity in non-doped iridium ditelluride (IrTe<sub>2</sub>).



This feature looks at the work of **HIROSHI OIKE**

Hiroshi Oike received his PhD from the Department of Applied Physics at the University of Tokyo, while supported by a Research Fellowship for Young Scientists from the Japan Society for the Promotion of Science (DC2). After working at the University of Tokyo as a postdoctoral researcher, he joined the Dynamic Emergent Phenomena Research Unit at the RIKEN Center for Emergent Matter Science in 2013. In 2018, he became a research associate in the Department of Applied Physics at the University of Tokyo. His research interests include phase control of correlated electrons based on the understanding of phase transitions, such as metal–insulator transitions, superconducting transitions, and magnetic transitions.

form an ordered state when slowly cooled. It's also known from previous research that this material has a superconducting state 'nearby' its natural state, which makes it the perfect choice for this experiment.

To cool their iridium ditelluride, the team placed the sample on a cold substrate and then passed rapid pulses of electrical current through it. This, in effect, temporarily turns the sample into an electrical heater, and, every time the current is switched off, the surroundings get warmer but the iridium ditelluride gets much colder.

"In a conventional heater in air, the element cools down by several degrees per minute when it is switched off," says Oike. "But when the size of the heater is very small and it is attached to a cold substrate, the cooling rate can exceed 10,000,000 degrees per second." In less than 10 microseconds the pulses heated the metal to more than 27°C before cooling it to -269°C.

The RIKEN team confirmed the creation of a superconducting state by measuring a zero electrical-resistance in their sample at its coolest, and they observed that this non-resistant state remained intact for a week.

### POTENTIAL SUPERCONDUCTING CIRCUITS

"I think that the most exciting message from our work is that a non-superconducting material such as iridium

ditelluride has the potential to exhibit reversible and non-volatile switching to a superconducting state," says Oike. "Our scheme means that materials that have been categorized as non-superconducting now have a fresh chance to yield metastable superconducting behavior."

Achieving this switching phenomenon electrically means that it could also potentially be applied to devices such as superconducting circuits, which are seen as one possible route to quantum computers. And the team is not stopping here: they next hope to investigate other ways of achieving this approach to creating a superconductor.

"Although we used electric current in this study, the temperature of materials can also be controlled with high-intensity light," says Oike. "When we control the local temperature of a non-superconducting material with focused light, we expect that the illuminated area turns to a superconducting state, thus affording us the ability to write a superconducting area in a non-superconducting material." ●

### REFERENCE

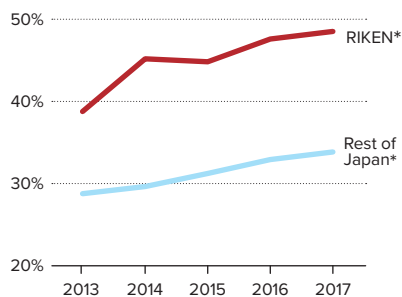
Oike, H., Kamitani, M., Tokura, Y. & Kagawa, F. Kinetic approach to superconductivity hidden behind a competing order. *Science Advances* **4**, eaau3489 (2018).

# PRODUCTIVE PARTNERSHIPS

Large-scale collaborations are increasingly recognized as a means of solving big, complex problems. Fortunately, big projects, big facilities and collaborations are among RIKEN's strengths.

## PAPERS WITH OVERSEAS AUTHORS

RIKEN is far above the Japan average in terms of international collaboration, with almost 50% of its papers citing international partners in 2017



## RIKEN'S TOP 10 INTERNATIONAL COLLABORATORS



**30+ YEAR PARTNERS**  
A 1984 cooperating agreement led to significant early overseas researcher recruitment at RIKEN.

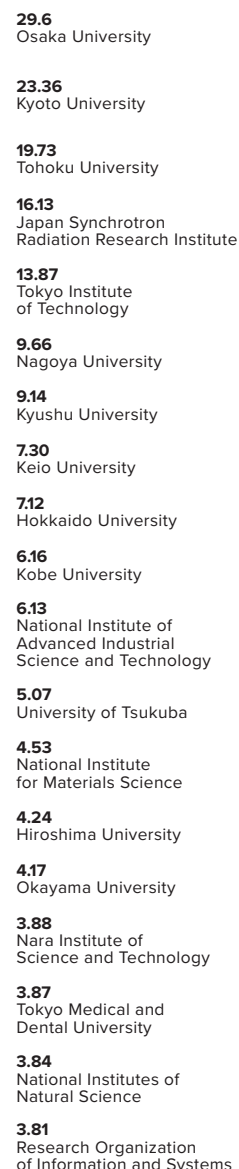
## WHAT DO THE LINES MEAN?

\*The bar widths and number correspond to each institution's **bilateral collaboration score**, a measure of authors who collaborated on papers published within the Nature Index's chosen, high-impact journals in 2017.

## RIKEN'S TOP 20 DOMESTIC COLLABORATORS

### THE UNIVERSITY OF TOKYO 120.11\*

One of the most fertile U Tokyo collaborations is with the **RIKEN Center for Emergent Matter Science**, which is the most productive academic partnership in Tokyo and the 15th most productive in the world



# RIKEN'S CENTERS AND FACILITIES

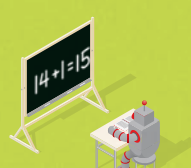
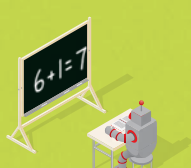
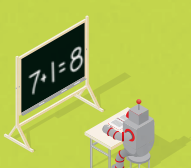
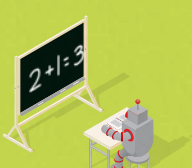
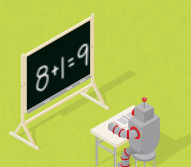
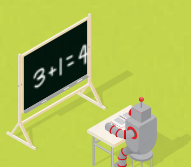
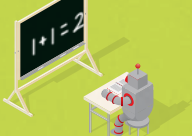
across Japan and around the world



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,

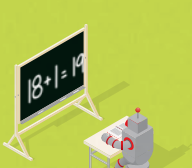
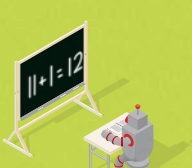
India and Malaysia. To expand our network, RIKEN works closely with researchers who have returned to their home countries or moved to another institute, with help from RIKEN's liaison offices in Singapore, Beijing and Brussels.

For more information, please visit:  
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