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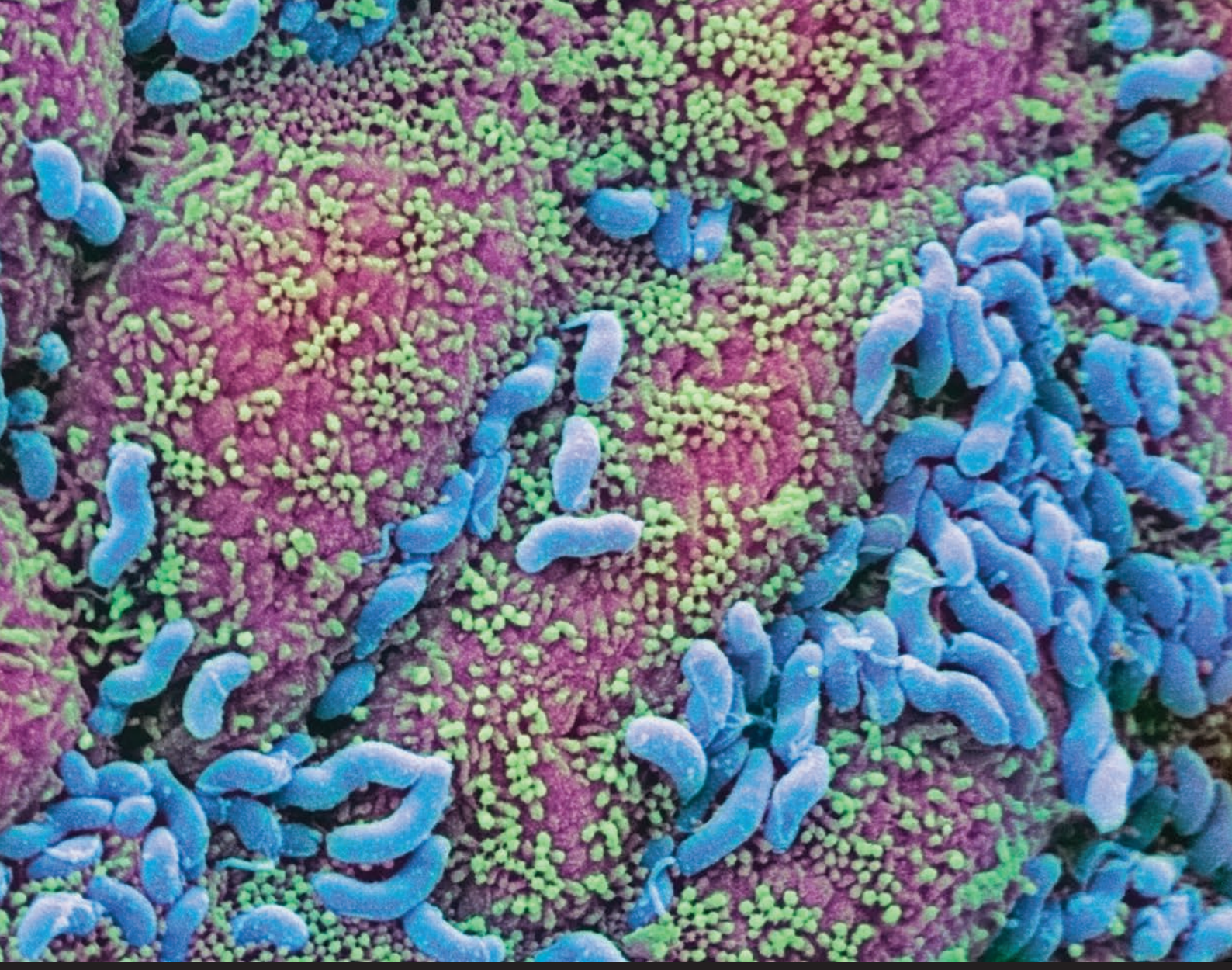
RED TAPE

How sulfur-free adhesive is helping archaeology

S24-7 PROTECTION
Good stomach bacteria boost immunity

CIRCUIT BREAKER
Hybrid system heralds next quantum leap

POWER PACKED
Ultrathin solar cell for wearable electronics



▲ **Good versus bad stomach bacteria**
A scanning electron micrograph (SEM) showing *Helicobacter pylori* bacteria (blue) and yeast (green) on the mucous lining of the stomach. RIKEN researchers have shown that bacteria in the stomachs of mice can induce an immune response against *H. pylori*, which is a bacteria that can cause stomach ulcers in humans.

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RIKEN Research is published by RIKEN in collaboration with Nature Research Custom Media, a part of Springer Nature.

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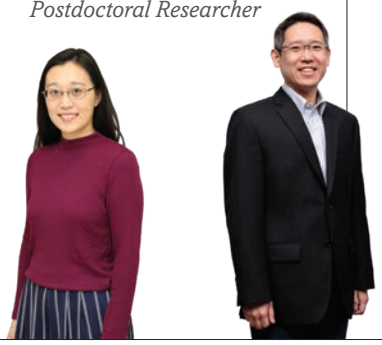
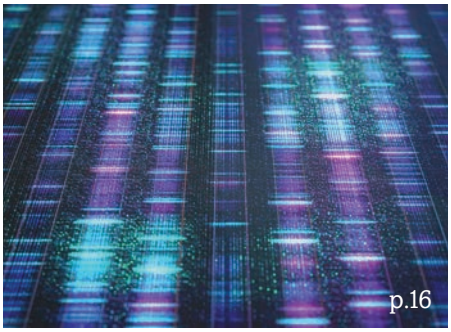
ISSN 1883-3519
www.riken.jp/en



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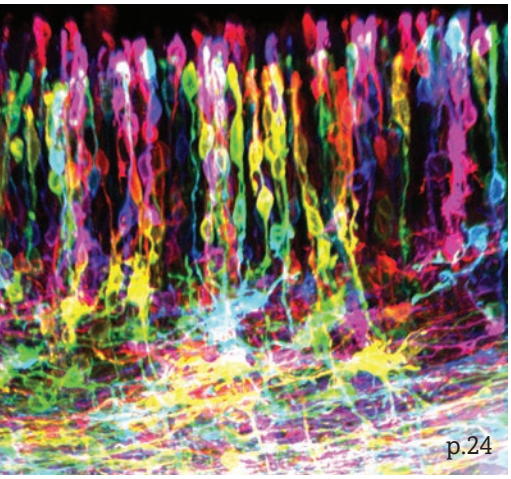
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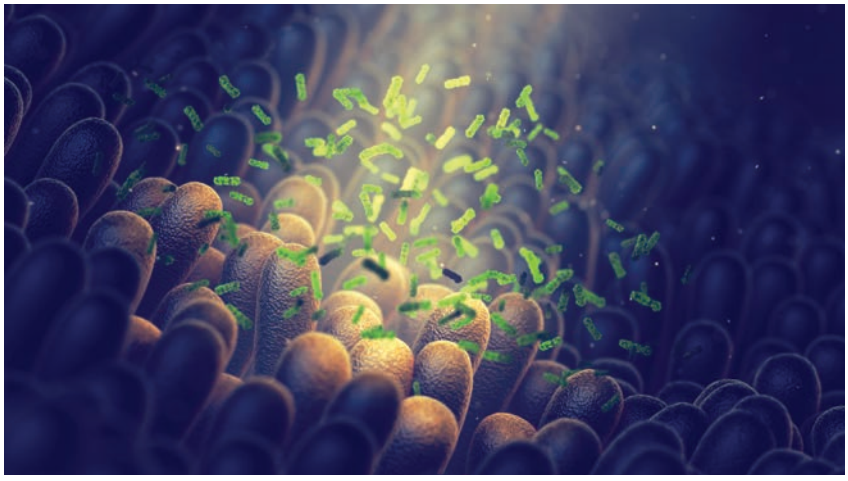

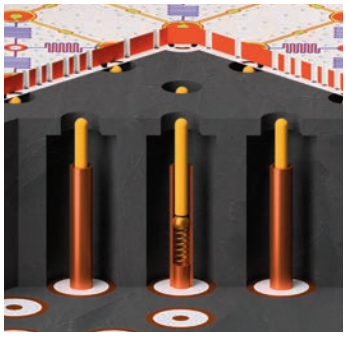

RIKEN's responses to COVID-19

Hiroshi Matsumoto
President, RIKEN

Normally choosing a topic for the editorial column of *RIKEN Research* is a source of joy to us, but today that is very much tempered by the fact that the world is embroiled in the midst of this terrible pandemic. I would like to express my solidarity with all our collaborators and readers around the world. I hope that you have been spared the worst of COVID-19 and that we may soon be able to see the light at the end of the tunnel. Also, as the situation is rapidly evolving, I am sure you will understand that there may have been recent developments, occurring while the magazine was under production, that I have failed to touch upon.

Our own response at RIKEN to the pandemic has been two fold. First and foremost, we have striven to keep our personnel as safe as possible and to help prevent the further spread of the virus through a variety of measures. These include encouraging teleworking, making sure that personnel who may have been exposed to the virus remain at home, introducing staggered working and lunch hours, and canceling all business trips, as well as most events.

Second, we have launched a series of initiatives to make use of our research infrastructure and research capacity to help develop models that may help to contain the spread of the disease and therapeutics that will be of use to patients. For details on these programs, including one that offers the use of the resources of the new Supercomputer Fugaku, see page 7.

Finally, I would like to express our readiness to work with our partners around the world to help overcome the pandemic and help those suffering. Now, more than ever, it has become clear that scientific research is an undertaking that must be carried out beyond the borders between nations, institutions, and disciplines and in the spirit of open science.

COVER STORY:
Sulfur-free sticky tape can be used to sample the red mineral vermilion on archaeological objects with minimal damage. *Page 13*

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Minute-to-minute weather prediction

Takemasa Miyoshi
Team Leader, Data Assimilation Research Team
RIKEN Center for Computational Science

Explain how data assimilation contributes to predicting weather.
To simulate weather with great precision, we have to feed a prediction system with real data, such as temperature, atmospheric pressure and prior forecasts. That's data assimilation. How observational data is assimilated significantly affects the accuracy of weather predictions, and it needs to be processed carefully. My research is about how to do this processing effectively, which is a challenge today because we have more and more data and it's hard to incorporate all of them into our models.

How much will Supercomputer Fugaku improve the capability of your simulations?
The Fugaku will achieve a 100-fold improvement in application capability compared to RIKEN's recently decommissioned, world-leading supercomputer, the K computer. If we can only do one simulation with the K computer, we will be able to run 100 simulations in parallel at the same time using Fugaku. In this way, we can measure a range of uncertainties.

You've helped improve predictions of torrential rainfall. How will that make people's lives better?
Without our unique Big Data assimilation system, we essentially have no predictive power for small-scale, localized torrential rainfall. While we received new data every 30 seconds, our models sometimes rejected it because real-world data has noise and missing values. Now we can find out what might happen 30 minutes in the future. For disaster prevention, it could help decide when to evacuate or move things.

Obviously, you can't use such advanced computers all the time. How are conventional weather forecasting computers advancing?
In Japan, the Japan Meteorological Agency operates their own supercomputer dedicated to weather prediction. And that computer has something like a tenth of the capability of the most powerful computer right now. That is still quite powerful. What we can do with the K computer or Fugaku is actually to explore what we will be able to do 10 years in the future, when meteorological agencies may have similarly powerful systems.

> *Without our unique system, we have no predictive power for small-scale, localized torrential rainfall.*

What is your dream as a researcher?
My dream is to develop a new fundamental theoretical framework with which to think about prediction in general. That's a whole new field of science, but I'm ready to dig into that direction because of advances in big data and computation technologies.

Why did you choose RIKEN?
Simply stated, it was because of the K computer. I was a professor at the University of Maryland in the United States. I had great freedom to do what I wanted because academic freedom is very important at universities in the United States. I was very happy, but I wanted to do something ground-breaking. ■

Microfluidics that shape drug delivery

Leung Hei Man
Special Postdoctoral Researcher, Nano Medical Engineering Laboratory
RIKEN Cluster for Pioneering Research

Describe your role at RIKEN.
I joined the Nano Medical Engineering Laboratory at RIKEN as a Special Postdoctoral Researcher in 2019. My current goal is to develop a new drug-delivery system by controlling the size and shape of drug carriers using microfluidic devices.

Please briefly describe your current research.
Drug-delivery agents are used to enhance the specificity and stability of drug molecules. However, the physical properties of the drug carrier may influence its cellular uptake. To control this, I'm currently developing a microfluidic system that allows the manipulation of a microgel carrier's size and shape.

How did you become interested in your current field?
I was working on polymer nanoparticles for drug delivery as part of my PhD and I soon realized the limitation on manipulating the size and shape of nanoparticles created by batch-top synthesis. I then became interested in microfluidics for nanoparticle synthesis.

What excites you the most about your current research?
Turning my design into a working device gives me a great sense of achievement. I really enjoy observing my device under a microscope and seeing how microgels are formed in it.

What made you decide to become a scientist?
When I was young, I never dreamed I would become a scientist. However, I enjoy doing experiments, including designing an experiment, testing a hypothesis, and collecting and analyzing data.

I'm currently developing a microfluidic system that allows the manipulation of a microgel carrier's size and shape.

What has been the most interesting discovery in your field in the last few years?
To me, the most interesting advances have been organs-on-chips, specially engineered microfluidic culture devices that recreate the microarchitecture and functions of living human organs. Currently, many of the beneficial effects of drug carriers observed *in vitro* aren't observed *in vivo*. I think organs-on-chips can improve this by providing a new observation platform in addition to conventional cell culture experiments and animal studies.

What RIKEN technologies and facilities do you use?
I often use the clean room facility at the Emergent Matter Science Research Laboratory to fabricate microfluidic devices. Here, I use the maskless ultraviolet photolithography system to make devices with channels at a micrometer scale. Also, I use a surface profiler to characterize the geometry of my channel. In addition, I wouldn't be able to even start my research without the help and support of technicians.

What is the best thing about working at RIKEN?
Being encouraged to do interdisciplinary research. Following my drug carrier fabrication and synthesis work, I am expecting to carry out cell uptake experiments to evaluate the performance of my carriers. Although I have little experience with cell experiments, I'm looking forward to learning about this from other researchers at RIKEN. ■

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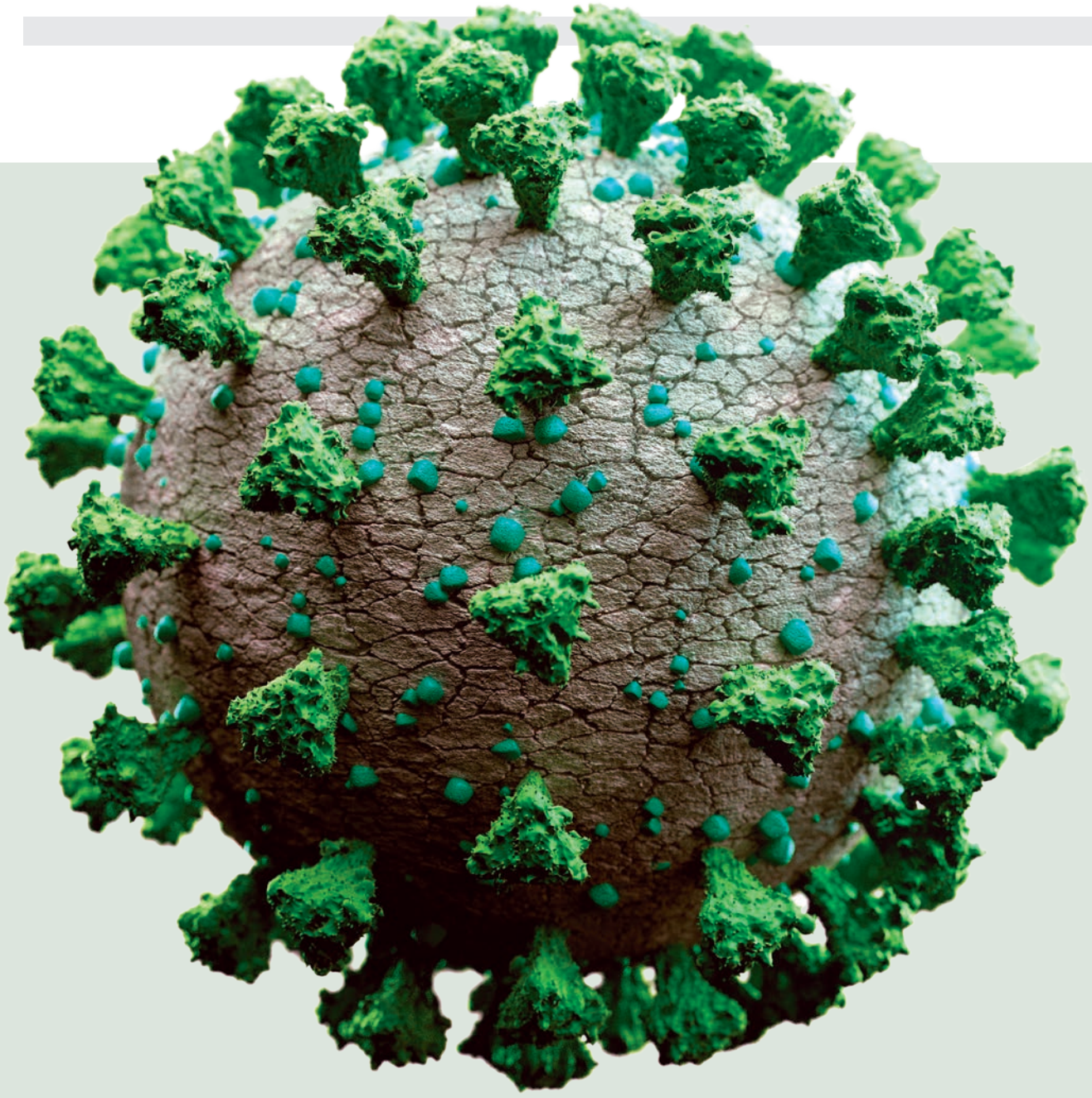


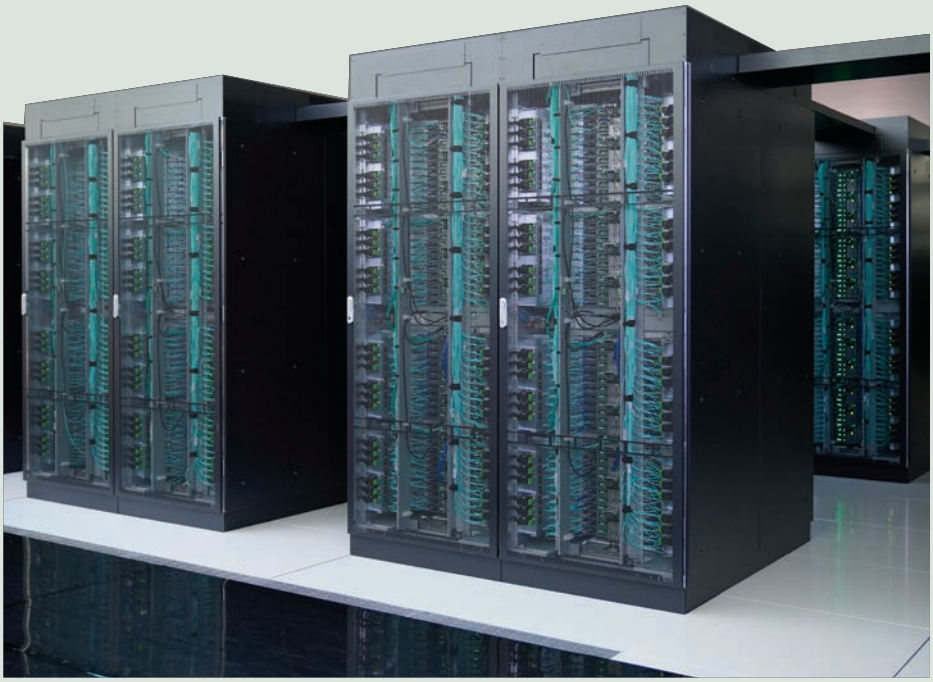
HELPING TO STEM THE PANDEMIC

In the hope of making some contribution to easing the burden of the COVID-19 pandemic, RIKEN has initiated several programs aimed at therapeutics and modeling of the virus.

COVID-19

Early use of new super-computer

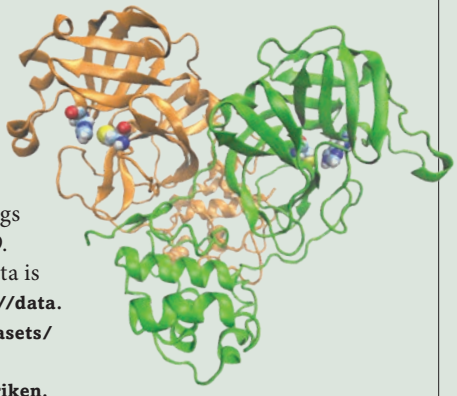
To aid COVID-19 research, RIKEN has decided to begin using the functioning parts of RIKEN's exascale supercomputer Fugaku, before its official 2021 launch. Supercomputer Fugaku is being used for applications related to COVID-19, using the nodes that have already been installed. This resource has been made available for research into new therapeutics, diagnostics, and modeling of the spread of the pandemic.



The supercomputer Fugaku is being used for applications related to COVID-19 using the parts that have already been installed.

Simulation of one of COVID-19's main replication enzymes

In March, a group from the Center for Biosystems Dynamics Research published on a molecular dynamics simulation of the main protease of the new coronavirus on the online database Mendeley Data. The simulation was performed on MDGRAPE-4A, a RIKEN supercomputer that specializes in drug development. Computing the 10-microsecond-long simulation of the system took ten days. Proteases are one of the main types of enzymes that viruses use to create new replicas of themselves and could be one of the targets for drugs against COVID-19. The simulation data is available at: **https://data.mendeley.com/datasets/vpps4vhryg/.** Read more: **www.riken.jp/en/news_pubs/news/2020/20200323_1/index.html**



A RIKEN simulation of the main protease that the COVID-19 virus uses to replicate.

RIKEN's COVID-19 therapy initiative

In March, it was announced that a number of RIKEN life-science centers will work with the RIKEN Program for Drug Discovery and Medical Technology Platforms (DMP), and external partners, to help develop therapies for COVID-19. The plan is to use RIKEN's resources, such as expertise in protein analysis using structural biology, molecular simulations and artificial intelligence, and in immunotherapy research using artificial adjuvant vector cells. **www.riken.jp/en/news_pubs/news/2020/20200330_2/index.html**

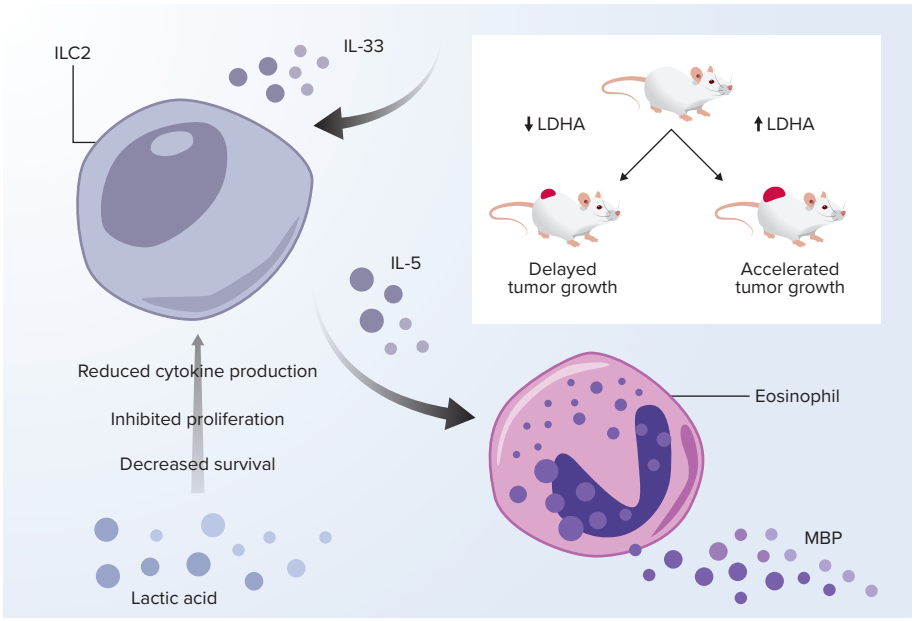
D3G Omics Database for non-human primates

A collaborative group led by Jun Kawai, Deputy Director of the RIKEN Program for Preventative Medicine, has published a database of omics information. The D3G Omics Database includes information from mice, humans and two non-human primates, cynomolgus monkeys (also known as crab-eating macaques) and marmosets. The aim is to provide a genomic dataset to support the development of oligonucleotide therapeutics, an emerging type of drug that focuses on modulating gene expression by targeting RNA or the genome itself. It's believed these therapies will help treat areas not available to small molecules and biologics, providing new options for diseases that currently have limited or no therapeutic options.
The database consists of data derived from RIKEN's own experiments as well as publicly available databases, including genome sequences, gene models, and expression data sets.
The database is available at: **https://d3g.riken.jp/release/latest/**
Read more: **www.riken.jp/pr/news/2020/20200325_2/index.html**

A database of genetic information from humans, cynomolgus monkeys (above), marmosets and mice will facilitate the research on drugs that modulate gene expression by targeting RNA or the genome.

Lactic acid helps tumors grow

RIKEN researcher Marek Wagner, and a collaborative group at the RIKEN Center for Integrative Medical Sciences, has found that lactic acid produced by tumors promotes the growth of cancer cells. Lactic acid promotes cancer cell growth by inhibiting the actions of ILC2, a type of immune cell that is known to be involved in the body's fight against parasitic worms and now believed to also play a key role in anti-cancer immunity. For example, the RIKEN study found that ILC2s are involved in eosinophil-associated anti-tumor responses in melanoma. The study also found that lactic acids decrease both the function and survival of ILC2s and that tumors with increased lactic acid production had fewer ILC2s in them. The study, published in *Cell Reports*, could lead to the development of new targets for cancer treatment.



The enzyme lactate dehydrogenase A (LDHA) is known to play a role in the development of malignancies. Lactic acid accumulation associated with LDHA is linked to fewer ILC2s (a type of innate immune cell), eosinophils and major basic proteins (MBPs). Eosinophils and MBPs have been correlated with improved cancer prognoses.

Modeling the insides of a neutron star

Astrophysicists at RIKEN have developed an improved model for the interior structure of neutron stars. It agrees well with observations, and, unlike previous models, it can be extended to consider what happens when two neutron stars merge.

Neutron stars are incredibly dense, being the size of a medium asteroid but having masses similar to that of the Sun. They have an onion-like structure, which theorists have been trying to model.

Previously, Tetsuo Hatsuda of the RIKEN Interdisciplinary Theoretical and Mathematical Sciences Program and his co-workers had developed a model that consists of three layers: an outer layer made up mostly of neutrons, an inner core consisting of quarks—the building blocks of neutrons—and a transitional region between these two layers.

Hatsuda's team has now taken this model a step further by using a more general equation to describe the outer layer. The improved model agrees well with observational data obtained so far. For example, it predicts that the maximum mass of neutron star is 2.35 times that of the Sun, which is close to the mass of the largest neutron star observed to date. The team is using their model to model mergers between two neutron stars and obtain predictions about the gravitational waves they will generate.

www.riken.jp/en/news_pubs/research_news/rr/20200207_2/index.html

RIKEN and JAXA sign agreement on habitation of outer space

RIKEN and the Japan Aerospace Exploration Agency (JAXA) have had a long partnership in space science, which includes exciting areas such as cosmic-ray research. On March 26, they signed a new collaboration agreement to begin research into paving the way for human habitation of outer space. The agreement covers collaborative research, exchanges of personnel, paths for nurturing young researchers, and shared use of facilities and instruments. The agreement was signed at a ceremony by RIKEN President Hiroshi Matsumoto (left) and JAXA President Hiroshi Yamakawa (far left).

www.riken.jp/pr/news/2020/20200326_1/index.html

NON-CODING RNA

Mapping the interaction of RNA with chromatin

A new technique reveals how RNA interacts with chromatin in different types of cells

A new RNA-mapping method developed by RIKEN researchers reveals how RNA interacts with the genome via chromatin—the structure used to tightly fold DNA[1]. This knowledge will be valuable for helping develop new therapies.

Decades ago, RNA was generally believed to act just as an intermediary for translating DNA into proteins. However, the decoding of the human genome in the early 2000s led to the realization that a large amount of RNA—dubbed junk RNA at the time—did not code for proteins. Subsequent work revealed that large numbers of long, non-protein-coding RNAs in the genomes of mammals interact with DNA. Many of these RNAs are found in the cell nucleus and are attached to chromatin. But it was unclear which RNAs interact with which DNA regions in different cells.

"This study is a first step toward understanding how the interplay between RNA and chromatin ensures proper genome function"

To gain a better understanding of these interactions and to determine whether RNA is a part of the chromatin structure, Piero Carninci and Alessandro Bonetti, both at the RIKEN Center for Integrative Medical Sciences, and their co-workers have developed a new technology that maps genome-wide RNA–chromatin interactions in intact nuclei. It can identify distinct patterns of genome occupancy for different transcript classes as well as RNA–chromatin interactions that are specific to certain cell types.

To demonstrate the potential of their method, the team used it to look at two transcripts that are preferentially expressed in certain types of cells. The first, known as nuclear enriched abundant transcript 1 (NEAT1), may be involved the formation of a mysterious structure known as paraspeckles found in the cell nuclei of mammals. The researchers found that in mouse embryonic stem cells NEAT1 acts almost exclusively on genomic regions of chromosome 19, from which NEAT1 itself derives from. NEAT1 interacts with a wide range of genomic regions on other chromosomes as well in oligodendrocyte progenitor cells—a later type of developmental cell that can differentiate into brain cells.

In contrast, the second transcript, fibroblast growth factor receptor 2, which is involved in embryonic development and tissue repair, mostly interacts with genomic regions on its own chromosome.

"This study is a first step toward understanding how the interplay between RNA and chromatin ensures proper genome function," says Bonetti. "Our data indicate that RNAs may exert more widespread effects on gene regulation and chromatin organization than previously thought."

"The broad, genome-wide applications of this technology will help us to understand the fundamental role of non-coding RNA as a regulator of genome activity, which could lead to future applications and therapies," adds Carninci.

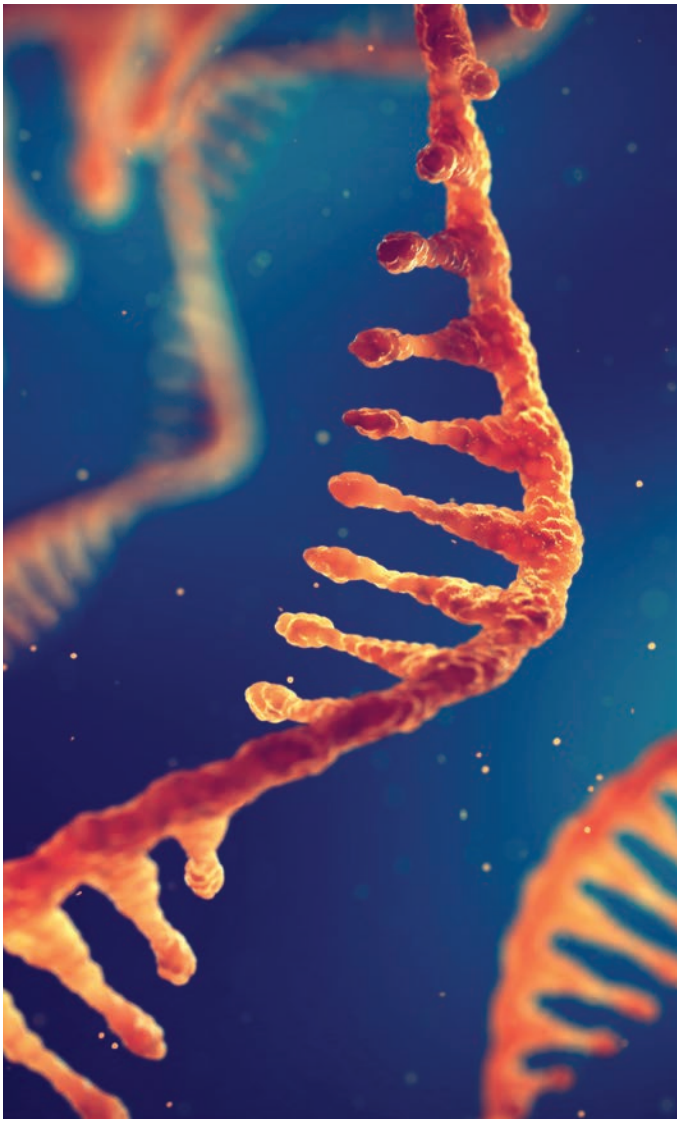


Illustration of RNA molecules. RIKEN researchers have developed a new method for mapping RNA and have used it to investigate how a transcript called fibroblast growth factor receptor 2 interacts with the genome via chromatin. They found that it mostly interacts with genomic regions on its own chromosome.

Reference

1. Bonetti, A., Agostini, F., Suzuki, A. M., Hashimoto, K., Pascarella, G., Gimenez, J., Roos, L., Nash, A. J., Ghilotti, M., Cameron, C. J. F. *et al.* RADICL-seq identifies general and cell type–specific principles of genome-wide RNA-chromatin interactions. *Nature Communications* **11,** 1018 (2020).

EXCITONS

When the dark side of nanotubes is good

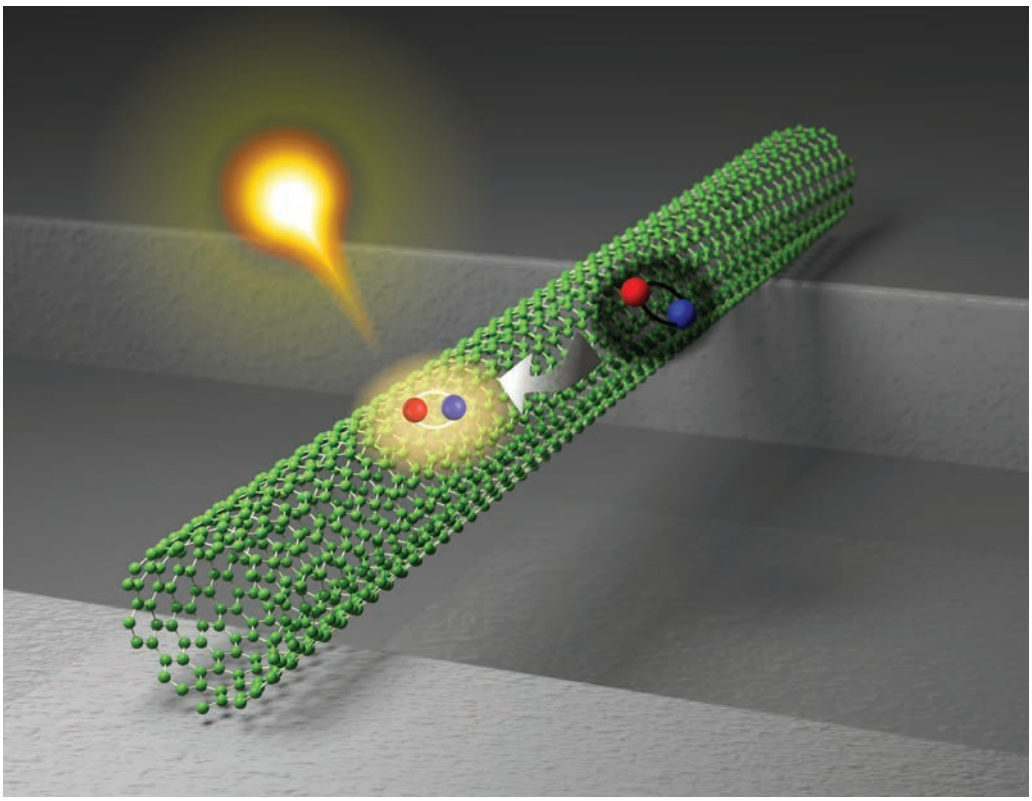
The high conversion of dark to bright excitons in long carbon nanotubes can lead to more efficient optoelectronic devices

Tailoring the dimensions and other attributes of carbon nanotubes can substantially boost the amount of light they emit, three physicists at RIKEN have discovered[1]. This finding promises to lead to the development of highly efficient photonic devices.

Carbon nanotubes are tiny cylinders that are just a nanometer to a few nanometers in diameter but can be up to several micrometers in length. Their excellent electronic and mechanical properties make them attractive for use in energy-efficient devices. In particular, a defect in the otherwise pure atomic carbon structures of nanotubes can emit single photons of light—a vital component for many nanoscale devices that are needed for quantum computation and communications.

In a typical light-emitting device, laser light or an electric field creates pairs of electrons and holes known as excitons. Sometime later, the electron and hole recombine and the exciton annihilates. Depending on the symmetry of the exciton, annihilation can result in the emission of light or not.

About half of the created excitons are bright, while the other half are dark and recombine without emitting light. Some dark excitons can become bright excitons and then emit light on annihilation. But carbon nanotubes tend to have low light-emitting efficiencies, mainly because dark excitons often recombine before they can turn into bright excitons (see image).



Schematic drawing showing a dark exciton converting into a bright exciton before emitting light. Three RIKEN physicists have shown that the conversion rate of this process is higher in longer nanotubes.

Now, Yuichiro Kato and two colleagues, all at the RIKEN Nanoscale Quantum Photonics Laboratory, have discovered that by tailoring the specifications of the nanotubes more than half of the dark excitons can be converted into bright ones, thereby greatly enhancing the light output of the nanotubes.

The researchers performed time-resolved luminescence measurements on a range of carbon nanotubes. By fitting the time-resolved luminescence traces with a model, they found that the conversion rate between dark and bright excitons depends on the length, diameter and chirality of the nanotubes. The trio estimated that in longer nanotubes, the conversion rate of dark to bright excitons was so high that more than half of the dark excitons contributed to the total luminescence.

"This shows that dark excitons can significantly affect the emission kinetics in low-dimensional materials such as nanotubes," says Kato. "They thus point to the potential of using surface interactions to engineer the dark-to-bright conversion process."

The team now intends to explore the potential of harnessing this effect. "We are interested in using this efficient conversion process to achieve carbon-nanotube single-photon emitters that have better performance," says Kato. ●

Reference

1. Ishii, A., Machiya, H. & Kato, Y. K. High efficiency dark-to-bright exciton conversion in carbon nanotubes. *Physical Review X* **9,** 041048 (2019).

A human fetus in the womb with the placenta at the bottom. RIKEN researchers have identified the importance of a certain protein in the early development of mouse embryos.

DEVELOPMENTAL BIOLOGY

Probing problems in the placenta

A placental protein offers insights into developmental abnormalities associated with higher risk of miscarriage

RIKEN scientists have determined how a protein that transports essential amino acids across the placenta contributes to normal embryonic development in mammals[1].

The placenta provides a supportive environment for developing mammalian fetuses. It supplies nutrients, including amino acids, from the mother. But the molecular mechanisms behind the supply of amino acids are not well understood.

Now, a team led by Atsuo Ogura of the RIKEN BioResource Research Center has conducted a genetic study that explores the roles amino-acid transporters in the placenta play in development. Their major interest is cloning mammalian cells in a process known as somatic cell nuclear transfer (SCNT), which offers tremendous potential for producing livestock with useful genetic traits, generating animal models for disease, and reproductive medicine.

"However, SCNT-generated embryos frequently show various developmental abnormalities, including an abnormally large placenta," says Shogo Matoba, a senior research scientist in Ogura's lab. "Only 1–5% of SCNT-cloned mouse embryos develop to term."

A search for abnormally regulated genes in the placentas of these cloned embryos led the researchers to small neutral amino-acid transporter 4 (SNAT4), which belongs to a larger family of proteins that facilitate the delivery of a variety of amino acids. Ogura and Matoba made a series of genetic manipulations to better understand this protein's importance in the early development of mouse embryos.

After confirming that SNAT4 is specifically expressed in the healthy placenta, the researchers used CRISPR–Cas9 gene-editing technology to generate mouse embryos that were deficient in SNAT4. The resulting pups were severely underweight, and only 28% were alive two weeks after delivery.

The researchers then bred SNAT-4-deficient males with normal females, and found that the resulting pregnancies still yielded severely underweight embryos with equally underdeveloped placentas. These changes were associated with reduced amino-acid levels in the circulation of fetal mice, hinting at a likely cause for this impaired development.

Since SNAT4 is strikingly overexpressed in SCNT-generated embryos, this could potentially explain the abnormally large placentas observed in this context.

These results also have implications for normal human reproduction. "The SNAT4-knockout mice showed phenotypes similar to those seen in intrauterine growth retardation," says Matoba, referring to a developmental abnormality that can potentially lead to miscarriage. "These animals could be a valuable model for studying the mechanisms of this phenomenon in mammals—including humans."

Matoba intends to investigate further how amino-acid transporters shape normal fetal development by knocking out other SNAT-encoding genes alongside SNAT4. He also wants to explore SNAT4's function in non-placental tissues such as the liver. ●

Reference

1. Matoba, S., Nakamuta, S., Miura, K., Hirose, M., Shiura, H., Kohda, T., Nakamuta, N. & Ogura, A. Paternal knockout of *Slc38a4*/SNAT4 causes placental hypoplasia associated with intrauterine growth restriction in mice. *Proceedings of the National Academy of Sciences USA* **116,** 21047–21053 (2019).

ARCHAEOLOGICAL SCIENCE

Sulfur-free tape the answer to a sticky problem

Sticky tape and a highly sensitive analysis technique will allow archaeologists to analyze ancient artifacts with minimal damage

Using a new technique, RIKEN researchers have found evidence suggesting trade occurred between Japan's northern island of Hokkaido and the western part of Japan's mainland as long as 3,500 years ago. The technique involves analyzing extremely small samples of vermilion from artifacts.

A bright red mineral, vermilion was used in paintings, statues and ceramics dating back almost 9,000 years across Europe, Asia and the Americas. Batches of vermilion can be distinguished by measuring the ratio of two isotopes of sulfur. Because this ratio remains constant over time, it can be used as a fingerprint to identify where samples came from.

Recently, Kazuya Takahashi and Yuko Motizuki of the RIKEN Nishina Center for Accelerator-Based Science and their colleagues developed a highly sensitive method for analyzing sulfur isotope ratios that only requires 1 microgram of vermilion—about 500 times less than other methods. This is important because smaller samples mean less damage to the artifacts being tested.

After developing the technique, Takahashi looked for a way to collect tiny samples. The easiest way was to use a 3-millimeter-long square of adhesive tape to pick up vermilion from an artifact, but most tape contains sulfur and even the tiniest amount of sulfur would throw off the results.

After trying several commercial tapes, Takahashi got lucky. "By chance, I met an old friend who works in a company that sells different kinds of tape," he recalls. "She knew of one tape that could be sulfur free, which was a great suggestion for me!" The team tested this polyester adhesive tape and found it was sulfur free.

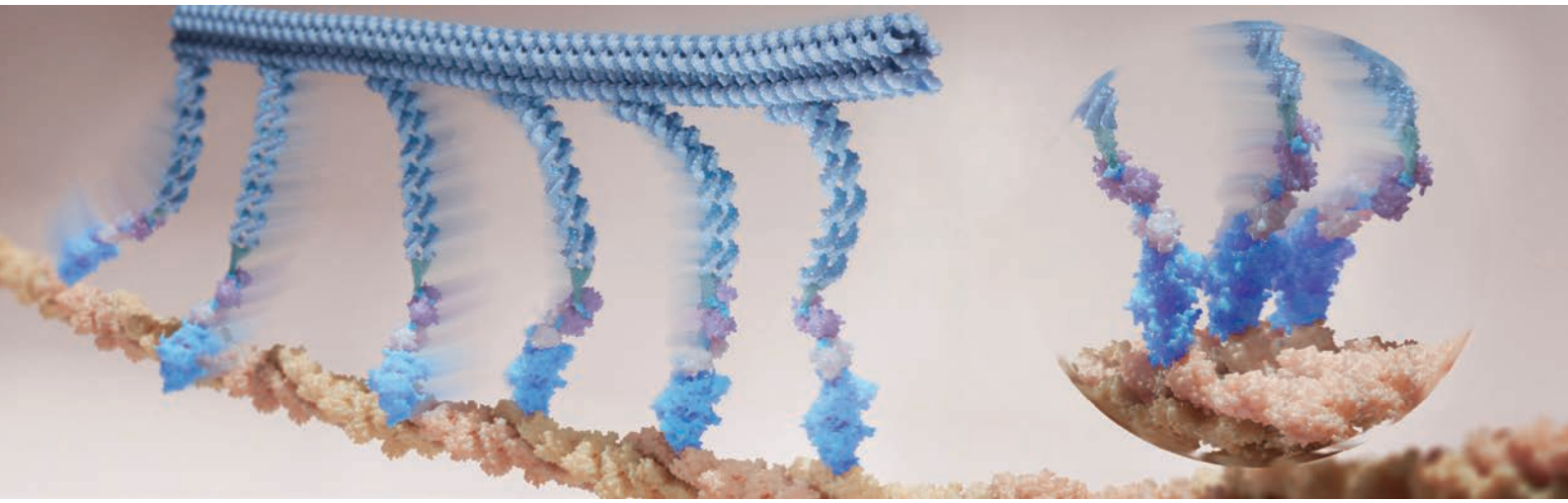
An area in western Japan called Izumo contains an archaeological site with artifacts from a settlement dated about 3,500 years ago. Its inhabitants are thought to have traded extensively within Japan. The researchers collected vermilion samples from two earthenware fragments, a stone tool and a potsherd excavated at the site and used their technique to determine their sulfur isotope ratios. They then compared the sample ratios to ratios measured at eight cinnabar ore mines across Japan. They found that most of the artifacts contained vermilion that was likely mined in the northern island of Hokkaido, more than 1,600 kilometers away, rather than in closer mines in western Japan.

Archaeologists often want to analyze the origins of pigments on wall paintings or pottery, but the artifacts are often too important to damage even a small amount for sample collection. "Our method might open the doors for new research into ancient trade routes and the history of individual works of ancient art," notes Takahashi.

Reference

1. Minami, T., Hatanaka, K., Motizuki, Y., Nakai, Y. & Takahashi, K. A method of collecting trace amounts of vermilion from artifacts for source estimation by sulfur isotope ($\delta^{34}S$) analysis: use of sulfur-free adhesive tape to minimize damage to the artifact body during sampling. *Journal of Archaeological Science: Reports* **28,** 102027 (2019).

Red crystals of vermilion (also known as cinnabar), a mercury sulfide mineral. It was used as a red pigment in many archaeological objects, including artifacts from a 3,500-year-old archaeological site in western Japan.



A rod structure based on DNA origami allows for precise positioning of the myosin molecules.

MOLECULAR BIOLOGY

Myosin molecules in action

Single-molecule imaging reveals how myosin moves to bring about muscle contraction

In a research first, molecular biologists at RIKEN have directly visualized the motion of a critical motor protein at the single-molecular level[1]. This achievement could aid in the hunt for new ways to treat diseases associated with myosin malfunction.

Muscles contract by sliding between thick filaments of myosin and thin filaments of actin. But there has been a long-standing controversy about the dynamics of this molecular machine. Researchers have been debating whether myosin travels by ratcheting along actin or simply by marching progressively forward in a series of power strokes.

To resolve this question, a team led by Mitsuhiro Iwaki of the RIKEN Center for Biosystems Dynamics Research watched individual myosin molecules in action. They did this by assembling strands of DNA into bundles of rope-like fibers, creating rods that resembled the thick filaments found in muscle tissue. The researchers then attached myosin proteins along the DNA structures in precise positions (see image), and, using advanced imaging techniques, snapped atomic-scale pictures of myosin interacting with its partner protein actin under biologically realistic geometric conditions.

The team showed with microsecond resolution that the head of myosin first binds weakly to actin. That bond strengthens, however, as myosin moves along the actin filament and finds the position for maximal force generation. Once in place, the lever arm below the myosin head swings in a two-step fashion, eliciting an oar-like stroke that powers muscle contraction. That motion is flexible and reversible, though, allowing multiple myosins to work cooperatively and in unison for efficient muscle function.

"...we can precisely examine the effect of drug candidates on myosin function."

This demonstration of how myosin moves to bring about muscle contraction reveals that both proposed mechanisms, namely the ratchet one and the power-stroke one, occur in tandem.

According to Iwaki, his team's state-of-the-art visualization technique—which takes advantage of 3D DNA origami and high-speed atomic force microscopy—now offers a platform for scientists to better understand why mutant forms of myosin can cause forms of heart failure in which the cardiac muscle thickens, making it hard for the organ to pump blood. That kind of information should help pharmaceutical companies to search for drug compounds that can coax malfunctioning myosin in the heart to do its job properly.

"Because our novel assay system can visualize the basic mechanical processes of myosin, we can precisely examine the effect of drug candidates on myosin function," Iwaki says. "We can thus contribute to advancing precision medicine approaches to heart disease." ●

Reference

1. Fujita, K., Ohmachi, M., Ikezaki, K., Yanagida, T. & Iwaki, M. Direct visualization of human myosin II force generation using DNA origami-based thick filaments. *Communications Biology* **2**, 437 (2019).

ORGANIC SOLAR CELLS

A flexible and efficient solar cell that lasts longer

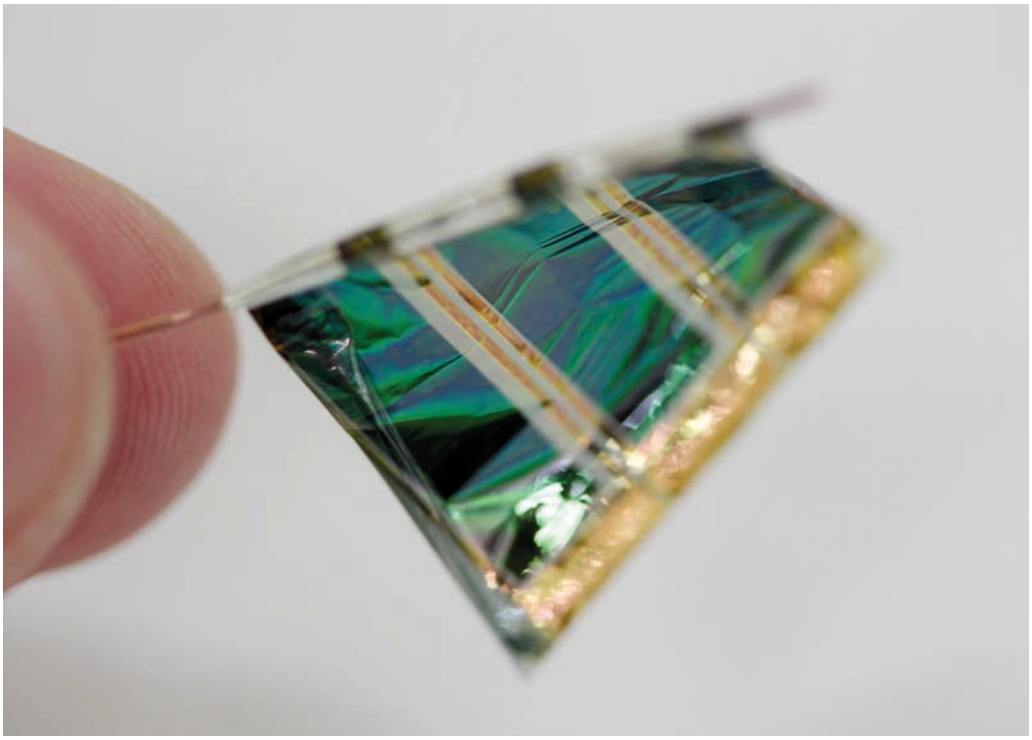
A robust and flexible ultrathin organic solar cell holds promise for powering wearable electronics

An ultrathin organic solar cell that is simultaneously flexible, durable and efficient has been demonstrated by physicists at RIKEN[1]. In the future, it could be used to power wearable electronics and in sensors that attach to clothing.

Organic solar cells are promising alternatives to conventional silicon-based films, being cheaper to produce and more environmentally friendly. Ultrathin solar cells are particularly attractive as they are flexible and could provide a high power per weight, making them suitable for powering wearable electronics and as sensors and actuators in soft robotics.

However, the energy-conversion efficiencies of ultrathin organic films (typically 10–12%) are usually significantly lower than those of silicon solar cells (up to about 25%) and of rigid organic solar cells (up to around 17%). Furthermore, ultrathin organic films also tend to degrade rapidly when exposed to sunlight (clearly problematic for solar cells), heat or oxygen. Researchers are trying to create ultrathin organic films that are both energy efficient and durable, but it is often difficult to overcome the trade-off between these two qualities.

Now, a team that included Kenjiro Fukuda of the RIKEN Center for Emergent Matter Science has demonstrated an ultrathin organic solar cell that converted light into electricity with an efficiency of more than 13% and whose efficiencies degraded by less than 5% when exposed to atmospheric conditions for more than 4,700 hours. Furthermore, the shelf life of the organic solar cell is estimated to be longer than 11 years.



A photograph of an ultrathin organic solar cell developed by RIKEN researchers that could be used to power wearable electronics.

"...ultrathin organic solar cells can be used to supply high power in a stable way..."

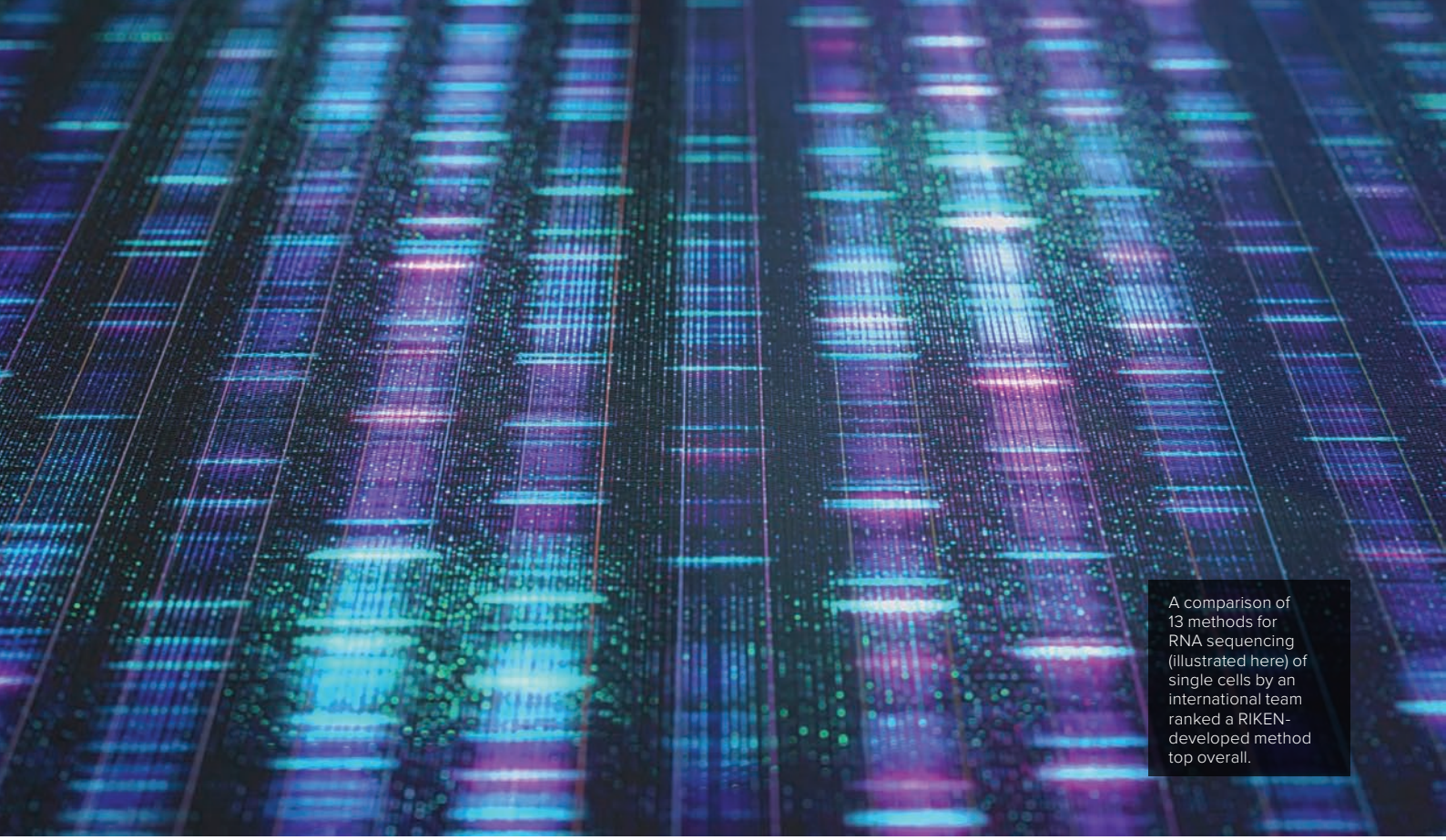
The team increased the thermal stability of the film by using a semiconducting polymer for the donor layer and a non-fullerene acceptor. In addition, they made the ultrathin film more durable by creating a stable interface between the layers through employing a simple post-heating process.

"By combining a new power-generation layer with a simple post-annealing treatment, we have achieved both a high energy-conversion efficiency and a long-term storage stability in ultrathin organic solar cells," explains Fukuda. "Our research shows that ultrathin organic solar cells can be used to supply high power in a stable way over long periods of time, and can be used even under severe conditions such as high temperature and humidity."

The findings demonstrate the promise of flexible organic solar cells that can be stably used as power sources in wearable electronics. "I very much hope that this research will contribute to the development of long-term stable power-supply devices that can be used in wearable electronics such as sensors attached to clothes," Fukuda says. ●

Reference

1. Jiang, Z., Wang, F., Fukuda, K., Karki, A., Huang, W., Yu, K., Yokota, T., Tajima, K., Nguyen, T.-Q. & Someya, T. Highly efficient organic photovoltaics with enhanced stability through the formation of doping-induced stable interfaces. *Proceedings of the National Academy of Sciences of the USA* **117,** 6391–6397 (2020).



A comparison of 13 methods for RNA sequencing (illustrated here) of single cells by an international team ranked a RIKEN-developed method top overall.

SINGLE-CELL RNA SEQUENCING

Best of the bunch

A technique developed at RIKEN for sequencing the RNA of single cells was evaluated to be the best overall method

In a benchmark of 13 single-cell RNA-sequencing methods by an international team, a RIKEN-developed method came out top overall[1].

A lack of benchmarking of genomic analysis methods has caused problems since different groups use different methods that have varying standards and come up with different results. With this in mind, several groups working on the analysis of single-cell RNA came together to evaluate different methods to ensure good reproducibility.

Single-cell RNA sequencing is seen as the next major project in genomic research. Initially, genomic research sought to determine the DNA sequence found in all cells of an organism. But although the cells in an organism share the same DNA code, different genes are expressed in them based on epigenetic factors. Understanding the genetic makeup of individual cells would allow scientists to identify how individual cells differ in conditions such as cancer and how cells change during development.

Led by Holger Heyn of the Centro Nacional de Análisis Genómico in Spain, the group used the 13 single-cell RNA-sequencing methods to analyze a set of about 3,000 cells. This set fulfilled four conditions: it included various cell types; some of the cells were very similar, having only subtle differences in gene expression; the cells had trackable markers; and they included cells from different species (most of the cells were human peripheral blood and mouse colon cells, but some were dog cells).

The methods were evaluated based on how precisely they could detect cell profiles and marker expression. The group evaluated the methods using six metrics: gene detection, overall level of expression in transcriptional signatures, cluster accuracy, classification probability, cluster accuracy after integration, and mixability. These metrics were selected to compare the methods in terms of their accuracy, applicability to various cell types, ability to distinguish between closely related cell types, ability to produce reproducible profiles, ability to detect population markers, compatibility with other methods, and good predictive value for cell mapping.

The team found that the Quartz-Seq2 method developed by researchers at the RIKEN Center for Biosystems Dynamics Research was particularly accurate, scoring highest in the benchmark.

"We were very happy that our method was selected as overall best, and plan to further improve it so that we can achieve the best results in projects such as the Human Atlas Project," says Itoshi Nikaido, who led the group that developed the method.

"The protocols showed profound performance differences and we hope that our work contributes to developing standards and guidelines towards the production of high-quality data sets for the Human Cell Atlas and broader single-cell community," says Heyn. ●

Reference

1. Mereu, E., Lafzi, A., Moutinho, C., Ziegenhain, C., McCarthy, D. J., Álvarez-Varela, A., Batlle, E., Sagar, Grün, D., Lau, J. K. *et al.* Benchmarking single-cell RNA-sequencing protocols for cell atlas projects. *Nature Biotechnology* **59,** 9744–9750 (2020).

DEVELOPMENTAL BIOLOGY

Fold along the fuzzy line

Mechanical forces generate straight folds in fly embryos despite sloppy reading of the blueprint

A mechanism that helps animals to develop with precise and constant form has been identified by RIKEN researchers in fruit fly embryos[1]. This resolves a long-standing question in developmental biology and could have implications for tumor formation and cancer metastasis.

The reproducibility of form, shape and characteristic appearance—a key feature of our development—are coded in our DNA. But it had been unclear how this reproducibility is achieved in the face of genetic variation and developmental 'noise' resulting from environmental, physical and chemical fluctuations.

Recent work in fruit flies has suggested that noise-canceling mechanisms in embryos rely on a detailed and highly reproducible genetic blueprint with instructions down to the single-cell level.

Now, a team led by Yu-Chiun Wang at the RIKEN Center for Biosystems Dynamics Research has found that the mechanical forces that sculpt the embryo both produce noise and ensure precision.

The team investigated a structure called the cephalic furrow in fruit fly embryos, where the surface of the embryo folds along a straight line (see image). This fold forms through cells deploying a molecule called myosin to exert mechanical forces that shorten the cells making up the fold.

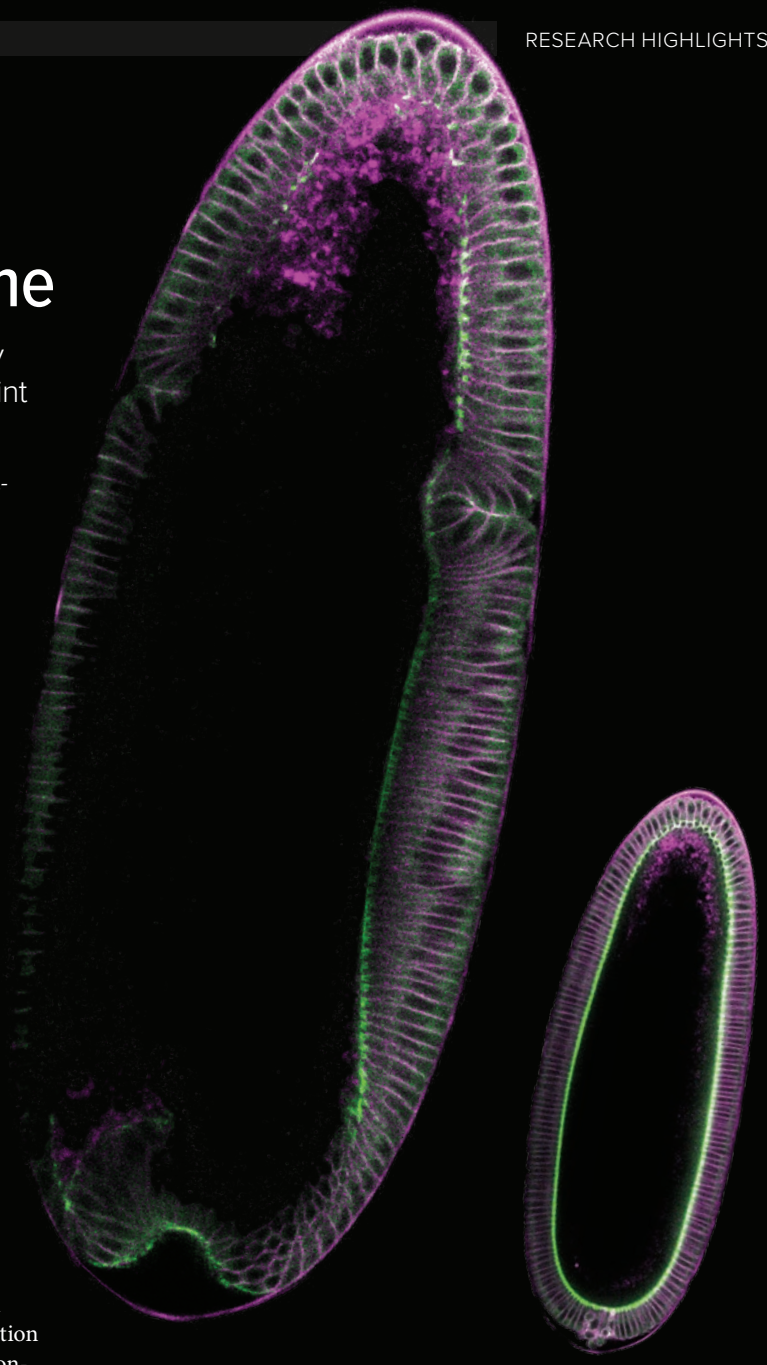
However, the team found that about 20% of the cells did not receive the instructions to become part of the cephalic furrow. While the information on where to make a fold was precise, reading of this information was unexpectedly sloppy. Consequently, myosin distribution was highly variable, resulting in discrepancies between the blueprint and cell behavior.

"These results were very puzzling as generations of developmental biologists were in awe of how the genetic blueprint could instruct machine-like precision of development," says Wang.

Realizing that myosin is polarized parallel to the forming crease, the researchers hypothesized that, powered by myosin, the cell membranes pull on each other, creating a form of mechanical communication that allows a straight, ribbon-like structure to emerge out of a fuzzy zone of membrane contraction. This myosin-dotted ribbon appeared to be the crease of the developing cephalic furrow.

To demonstrate this, the scientists inactivated myosin in a few cells by cutting the ribbon using a laser beam. The cephalic furrow developed a kink, indicating that the straightness of the folding requires an intact ribbon of contractile membranes.

This shows that the constancy of animal form requires more than just the deterministic process of genetic inheritance and networks—it also relies on the stochastic and emergent behaviors of mechanical forces. "Constancy in biology stems not only from its regulatory complexity, but also from the unique noise-and-self-correction principle of self-organization," Wang says. "This is a missing chapter in developmental biology textbooks." ●



Fluorescence micrographs of a developing fruit fly embryo (left image is of a later stage than the right one). The small bulge in the top right of the left image is the beginning of the cephalic furrow.

Reference

1. Eritano, A. S., Bromley, C. L., Albero, A. B., Schütz, L., Wen, F.-L., Takeda, M., Fukaya, T., Sami, M. M., Shibata, T., Lemke, S. *et al.* Tissue-scale mechanical coupling reduces morphogenetic noise to ensure precision during epithelial folding. *Developmental Cell* **53,** 212–228 (2020).

CATALYSIS

Back to basics to build esters

A small change in the chemical structure produces a big improvement in performance for a continuous-flow catalyst

Recalling basic textbook chemistry has enabled RIKEN researchers to develop a better solid catalyst for producing important industrial chemicals known as esters[1]. This advance promises to benefit the manufacture of fuels, pharmaceuticals, resins, paints, adhesives and perfumes.

Esters form in the chemical reaction between the hydroxyl (OH) group of alcohols and the carboxyl (COOH) group of carboxylic acids. When these groups combine, a water molecule (H_2O) is released, leaving the remainder of the alcohol and carboxylic acid molecules bound together as an ester. Many school students perform this simple reaction during their first introduction to organic chemistry.

"All companies that produce organic chemicals should be interested."

Although esters can easily be made in low yields, it is challenging to produce them at the high yields needed by industry. "Achieving the complete conversion into esters is difficult," notes Yoichi Yamada of the RIKEN Center for Sustainable Resource Science. Esterification is an equilibrium reaction—one that settles into a state where both the forward and reverse reactions proceed at the same rate. The challenge is to minimize the reverse reaction so that the production of ester dominates.

Yamada and his colleagues met the challenge by remembering their school textbooks. "We were surprised to find that knowledge from beginner organic chemistry courses helped us to develop a new cutting-edge catalyst," he says.

Basic chemical theory says that a small change in the relative positions of two groups bonded to a ring of six carbon atoms can greatly affect a molecule's stability. This inspired the researchers to modify the placement of the groups they had used in an earlier but unstable version of their catalyst. Changing the structure of the key starting material produced a solid catalyst that is more stable, more active, reusable and robust.

This new catalyst has the great advantage that it can work under continuous flow conditions. The alcohol and carboxylic acid are pumped into a column packed with the catalyst powder, allowing high yields of the desired ester to flow out from the other end. This process outperformed other commercial catalysts in trials producing an ester-based biofuel. In addition, the catalyst is mass producible so that it can be manufactured on the large scales needed by industry.

Going back to high-school chemistry has enabled RIKEN chemists to develop a catalyst that can produce esters at high yields in a continuous-flow process.

Yamada believes that the catalyst could eventually significantly impact the chemical industry. "All companies that produce organic chemicals should be interested," he comments.

The RIKEN team is now seeking to extend the usefulness of their catalyst by exploring other reactions for which it could be used. ●

Reference

1. Hu, H., Ota, H., Baek, H., Shinohara, K., Mase, T., Uozumi, Y. & Yamada, Y. M. A. Second-generation *meta*-phenolsulfonic acid–formaldehyde resin as a catalyst for continuous-flow esterification. *Organic Letters* **22,** 160–163 (2020).

EPIGENETICS

Evidence that dad's diet can affect the kids

A low-protein diet in mice can turn on genes in their offspring that metabolize cholesterol

The molecular mechanism behind the development of metabolic disorders in the offspring of mice fed a low-protein diet has been discovered by RIKEN researchers[1]. This will help identify diets that will cause problems for the next generation.

Children of parents who eat low-protein diets often develop metabolic disorders such as diabetes. This phenomenon is thought to be regulated by epigenetics—heritable changes in which genes are turned on and off without actually altering an individual's DNA. However, the details of this process were unknown.

Now, a team led by Keisuke Yoshida and Shunsuke Ishii at the RIKEN Cellular Memory Laboratory has discovered that a protein called ATF7, which regulates when genes are turned on and off, is essential for the intergenerational effect in mice.

The diets of parents can affect their children. Scientists at RIKEN have found how a low-protein diet in mice can turn off genes in their offspring that metabolize cholesterol.

This demonstrates that a male mouse's diet can influence its children's health.

The researchers fed male and female mice normal or low-protein diets and then allowed them to mate. Comparing gene expression—which genes were turned on—in the fully grown offspring, they found that expression differed for hundreds of genes in the liver, many of which are involved in cholesterol metabolism. In contrast, gene expression did not differ between the offspring of parents that had been genetically engineered to lack one copy of the *ATF7* gene, regardless of which diet they had been fed.

The team found genes in sperm cells that are controlled by ATF7, including those for fat metabolism in the liver and cholesterol production. Experiments revealed that when fathers-to-be ate low-protein diets, ATF7 no longer bound to these genes. This, in turn, reduced a particular modification to histone proteins, with the effect that these sperm-cell genes, which are normally turned off, were turned on.

This demonstrates that a male mouse's diet can influence its offspring's health. "The most surprising and exciting discovery was that the epigenetic change induced by the paternal low-protein diet is maintained in mature sperm during spermatogenesis and transmitted to the next generation," Ishii says.

This helps to clarify parental diets that could lead to the development of metabolic disorders such as diabetes in offspring as well as the molecular mechanism behind this inheritance. It should also make it possible to predict metabolic changes in the next generation by measuring epigenetic changes in the identified genes of paternal sperm cells.

"We hope that people, especially those who have poor nutrition by choice, will pay more attention to their diet when planning for the next generation," says Ishii. "Our results suggest that diets with more protein and less fat are healthier not just for everyone's own body, but also for sperm and the health of potential children." ●

Reference

1. Yoshida, K., Maekawa, T., Ly, N. H., Fujita, S., Muratani, M., Ando, M., Katou, Y., Araki, H., Miura, F., Shirahige, K. *et al.* ATF7-dependent epigenetic changes are required for the intergenerational effect of a paternal low-protein diet. *Molecular Cell* **78,** 445–458 (2020).

QUANTUM COMPUTING

Measuring without demolishing

Repeated measurements of a quantum dot are now possible without affecting its spin

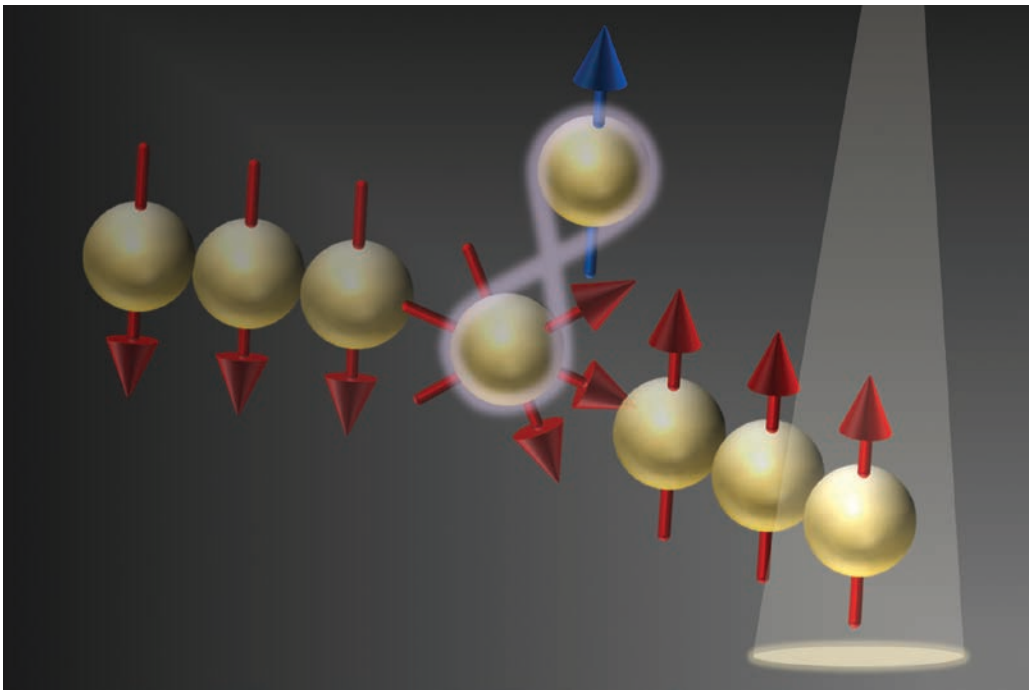
RIKEN physicists have repeatedly measured the spin of an electron in a tiny silicon spot known as a quantum dot without altering the spin in the process[1]. This is an important step toward creating fault-tolerant quantum computers.

Quantum computers promise to perform certain classes of calculations in a fraction of the time that it takes conventional computers. Quantum computing calculations involve measuring a parameter of a quantum system. Unlike transistors in conventional computers, which are either on or off, such systems never exist in a single state, but rather are in a superposition of two states. They can be used to conduct calculations with qubits—the quantum equivalent of classical bits—and the correct result can be statistically determined.

Quantum computers that use single electron spins in silicon quantum dots are attractive due to their potential scalability and because silicon is already widely used in electronics technology.

"We could potentially build a variety of fault-tolerant quantum information processing systems"

However, quantum computers are very sensitive to external noise, making it critical to correct errors. Researchers have developed single electron spins in silicon quantum dots with long data-retention times and high-precision quantum operation, but quantum non-demolition measurements—a key to effective error correction—have proven elusive. The conventional method for reading out single electron spins in silicon is to convert the spins into electric charges that can be rapidly detected, but the detection process affects the electron spin.



By coupling two quantum dots, physicists at RIKEN could transfer the spin (blue arrow) of an electron in one of the quantum dots to an electron (gold sphere with three red arrows) in the other one, which can then be read (gold sphere on far right). Because this process leaves the spin of the first electron unchanged, it permits repeated and rapid measurements of the first electron spin.

Now, a team led by Seigo Tarucha of the RIKEN Center for Emergent Matter Science has achieved such a non-demolition measurement.

They were able to transfer the spin information—up or down—of an electron in a quantum dot to another electron in a neighboring quantum dot by coupling the two quantum dots (see image). The team then measured the spin of the neighbor using the conventional method, while leaving the original spin unaffected. In this way, they could perform repeated and rapid measurements of the neighbor.

"Through this, we were able to achieve a non-demolition fidelity rate of 99%, and by using repeated measurements would get a readout accuracy of 95%," explains Tarucha. "We have also shown that, theoretically, this could be increased to readout 99.6%, and we plan to continue work toward reaching that level."

"This is very exciting because, if we can combine our work with high-fidelity single- and two-qubit gates, which are currently being developed, we could potentially build a variety of fault-tolerant quantum information processing systems using a silicon quantum-dot platform," Tarucha adds. ●

Reference

1. Yoneda, J., Takeda, K., Noiri, A., Nakajima, T., Li, S., Kamioka, J., Kodera, T. & Tarucha, S. Quantum non-demolition readout of an electron spin in silicon. *Nature Communications* **11,** 1144 (2020).

The dwarf galaxy Fornax contains stars where the s-process may be responsible for enriching strontium levels.

ELEMENTAL ABUNDANCE

Galaxy simulation traces strontium's origins

Neutron-capture processes in various stars are responsible for making the metallic element strontium

Simulations of a dwarf galaxy by RIKEN astrophysicists have revealed the various processes by which moderately heavy metals such as strontium are birthed[1]. They have found that at least four kinds of stars are needed to explain the observed abundance of these metals in dwarf galaxies.

Stars are the alchemists of the cosmos. Many of the lighter elements in the periodic table are generated by nuclear fusion in stars, for example. But the origins of some heavier elements are more mysterious.

Fusion reactions can make elements as heavy as iron and nickel, while even heavier elements are created when nuclei capture extra neutrons. Extreme conditions, such as those in a supernova or a merger between two neutron stars, drive the rapid neutron-capture process (r-process). In contrast, the slow neutron-capture process (s-process) happens more gradually, for example in so-called asymptotic giant branch stars at the ends of their lives. Each process—and each environment—generates a different blend of heavy elements.

The metals forged in these processes are eventually ejected into space as the star dies and may be incorporated into new stars. Tracking the distribution of these inherited elements can help to understand how they were made.

Strontium, for example, is one of the lightest elements created in the r-process. Some stars in dwarf galaxies close to the Milky Way have unusually high strontium-to-barium ratios, which suggests they are being produced in different environments.

To examine the provenance of this strontium, Yutaka Hirai at the RIKEN Center for Computational Science and two colleagues simulated a dwarf galaxy with a similar distribution of metals as those observed in nearby dwarf galaxies. Then they looked at which stellar processes led to strontium enrichment.

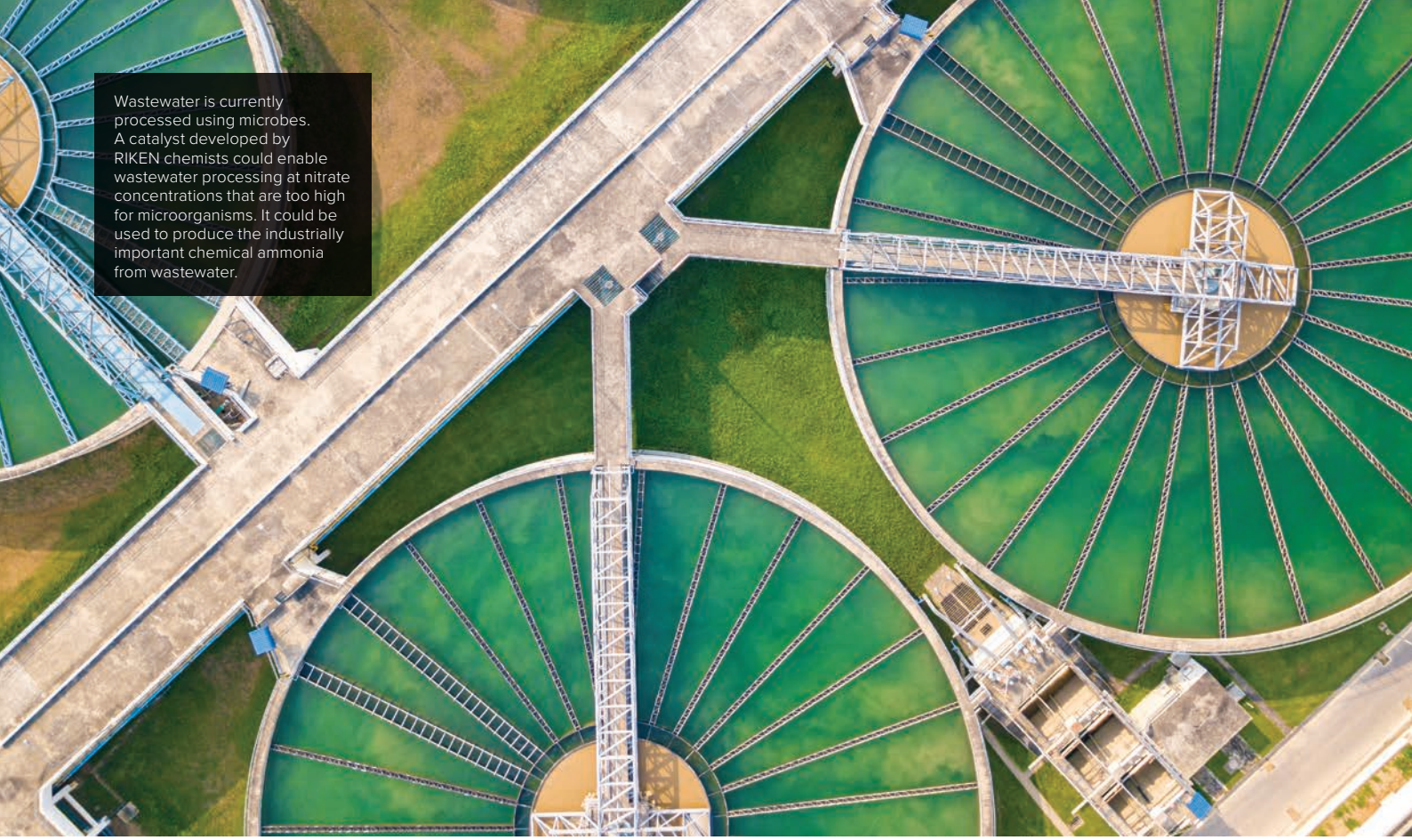
The researchers found that neutron-star mergers and asymptotic giant branch stars could not explain all of the strontium enrichment in their simulation. Some of the enrichment came from rotating massive stars, where the mixing of materials inside the star can generate neutrons for a particular form of s-process.

"But our most important finding is that ejecta from electron-capture supernovae can form stars with highly enhanced in strontium-to-barium ratios," Hirai says. "An electron-capture supernova explosion is expected to occur in the lowest mass range of massive stars, eight to ten times the mass of the Sun." These stars are notable for having cores rich in oxygen, neon and magnesium.

Hirai's team now intends to carry out a more detailed comparison between simulations and observations of the elemental abundances of stars in and around the Milky Way. ●

Reference

1. Hirai, Y., Wanajo, S. & Saitoh, T. R. Enrichment of strontium in dwarf galaxies. *The Astrophysical Journal* **885,** 33 (2019).



Wastewater is currently processed using microbes. A catalyst developed by RIKEN chemists could enable wastewater processing at nitrate concentrations that are too high for microorganisms. It could be used to produce the industrially important chemical ammonia from wastewater.

NITRATE REDUCTION

Efficient catalyst imitates nature

A promising artificial catalyst for nitrate reduction has a similar reaction active site to that of a natural enzyme found in microbes

Ammonia, an industrially important chemical, could one day be synthesized from wastewater. Chemists at RIKEN have identified the mechanism that enables a catalyst to efficiently transform nitrate into nitrite—an environmentally important reaction—at moderate temperatures and acidity[1].

Wastewater is processed using microbes, but sometimes nitrate concentrations are too high for microorganisms to survive. Some expensive rare-metal catalysts can perform the same task, but they require high temperatures, ultraviolet light or high acidity. Thus, the development of catalysts that can cheaply perform the transformation at ambient temperatures is a major research goal.

In a previous study, a team led by Ryuhei Nakamura of the RIKEN Center for Sustainable Resource Science (CSRS) used the same method as nitrate reductase—an enzyme used by microorganisms—to chemically synthesize oxo-containing molybdenum sulfide, which can catalyze nitrate into nitrite in an aqueous electrolyte at neutral pH.

Now, Nakamura and his team have discovered that their catalyst contains a reaction active site similar to that found in natural nitrate reductase. They had known that oxo-containing molybdenum sulfide worked better than other catalysts, but had not known why. The researchers studied it by observing chemical species on its surface in the presence of a reducing agent using molecular spectroscopy.

"We hypothesized that the oxo-molybdenum sulfide catalysts may have active sites similar to those in enzymes," says Yamei Li, who was at the RIKEN CSRS and is currently at the Tokyo Institute of Technology. "To test this hypothesis, we attempted to track how chemical species on the catalyst surface change using molecular spectroscopy."

The researchers discovered that pentavalent molybdenum with oxygen ligands—one of the intermediate products—functioned as an active species that accelerated the reaction. They showed that this active species has a similar structure to the active core of natural nitrate reductase. Spectroscopic measurements confirmed this, showing that the oxygen and sulfur ligands of the molybdenum also play an important role in efficiently producing the pentavalent oxo-molybdenum species on the catalyst surface.

"This result shows that nitrate ions can be detoxified in a mild environment without depending on rare-metal catalysts," says Nakamura. "We hope that this will make possible the development of new technology for synthesizing ammonia from waste liquid."

Reference

1. Li, Y., Go, Y. K., Ooka, H., He, D., Jin, F., Kim, S. H. & Nakamura, R. Enzyme mimetic active intermediates for nitrate reduction in neutral aqueous media. *Angewandte Chemie International Edition* **59,** 9744–9750 (2020).

OPTOGENETICS

Light causes marmosets to raise a paw

Marmosets move their forelimbs on optical stimulation of their brain for the first time

RIKEN neuroscientists have succeeded in causing marmosets to move their forelimbs when they shine laser light on the motor cortex—the brain region responsible for planning, conducting and controlling voluntary movements[1]. This will help researchers discover what different circuits in the motor cortex of marmosets do, with a view to gaining valuable insights into equivalent circuits in the human brain.

In optogenetics, researchers use light to stimulate specific neurons in the brain, allowing them to probe the brain and discover what different neural circuits do. This technique has been widely used on mice, but scientists are keen to apply it to primates because their brains more closely resemble human brains.

Researchers have used optical stimulation to induce mice to move their front and rear paws, but until now no one has managed to achieve the same thing in primates. Indeed, it was proving so challenging that some prominent neurobiologists had even speculated that it was not possible.

Now, after more than three years of trying, Masanori Matsuzaki of the RIKEN Center for Brain Science and co-workers have succeeded where many have failed. They have developed a low invasive way to cause marmosets to move their forelimbs in response to laser light illumination.

The researchers improved the standard technique for optical stimulation of brain areas.

RIKEN researchers can cause marmosets to move their forelimbs in response to optical stimulation.

Importantly, they used young marmosets, rather than larger monkeys. "The marmoset brain is about ten times smaller than the macaque brain, which means that forelimb movement in marmosets should be controlled by fewer motor cortical neurons," explains Matsuzaki.

Also, instead of inserting an optical fiber into the brain, which is invasive and can only illuminate a small area, the team installed a transparent window in the scalp and shone the laser light through it. This allowed them to stimulate a much larger area. "An optical fiber can only illuminate an area that is about half a millimeter in diameter, whereas our technique could realize diameters that are two to four times larger than that," says Matsuzaki. "Furthermore, by moving the fiber, we can easily change the illumination area to cause different forelimb movements."

In addition to directly controlling the forelimbs of marmosets, the team was able to modify a movement that a monkey was in the process of making by shining a lower intensity light. The secret to this part of the experiment was the methods that the team had developed for training marmosets to perform tasks with their forelimbs. "So far, only our lab can train marmosets to perform such tasks," Matsuzaki comments.

In the long term, the knowledge gained by the technique could help researchers gain a better understanding of how the motor cortex in the human brain responds to injury and stroke. ●

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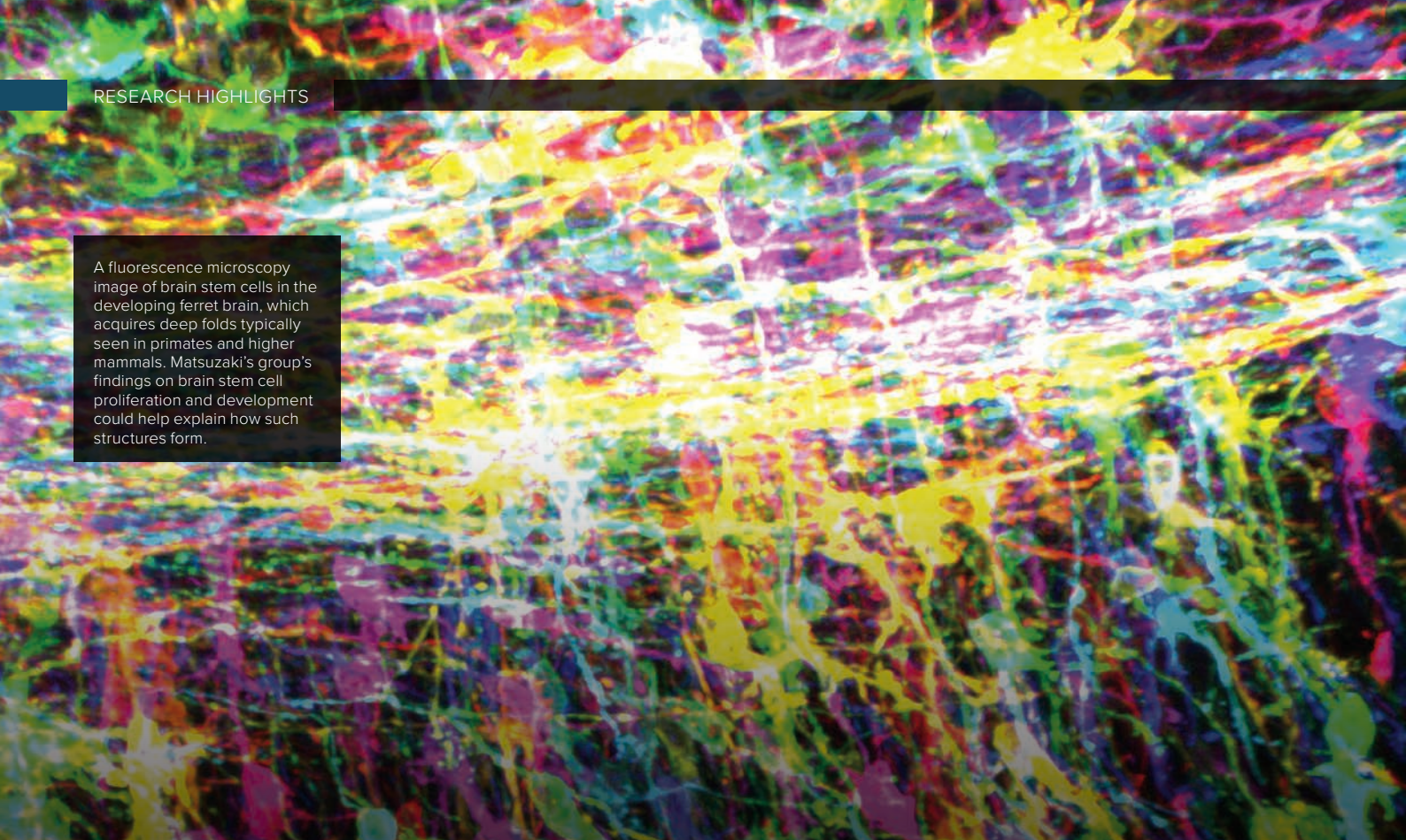

A fluorescence microscopy image of brain stem cells in the developing ferret brain, which acquires deep folds typically seen in primates and higher mammals. Matsuzaki's group's findings on brain stem cell proliferation and development could help explain how such structures form.

BRAIN DEVELOPMENT

Timing is everything for developing brains

Insights into mechanisms controlling early brain development could also help scientists understand this organ's evolution

Neural stem cells affect the timing and trajectory of division in brain development more than previously thought, RIKEN researchers have found[1]. This discovery could have important implications for our understanding of the evolution of the mammalian brain.

"We've been interested in the general design principles underlying how brains are built," says Fumio Matsuzaki of the RIKEN Center for Biosystems Dynamics Research.

Matsuzaki and his team have focused on brain stem cells known as radial glia (see image). These cells, which give rise to all the neurons in the cerebral cortex, are stretched between two surfaces, known as the apical and basal membranes.

Radial glia initially divide laterally in a symmetric fashion, yielding two daughter radial glia that are anchored to both surfaces. Over time, some of these cells begin dividing asymmetrically, pushing at the basal surface and causing the developing brain to expand outward. These asymmetric divisions yield more-mature cells that ultimately produce neurons and other brain cells.

For decades, developmental biologists have postulated that this transition is governed by changes in the orientation of the cellular spindles—molecular machines that govern mitotic division—relative to the apical surface.

But previous work by Matsuzaki and colleagues has called that model into question. "Our findings have provided strong evidence that mitotic spindle orientation does not determine whether self-renewal or differentiation occurs; rather it determines the position of radial glia," he says.

The latest findings by his team reinforce this hypothesis, and offer an alternative mechanism.

The team manipulated the spindle orientation of early stage radial glia and then imaged what happened. Altered orientation caused radial glia to detach from the apical side, but did not necessarily lead to the migration of these radial glia. Instead, radial glia have the capacity to extend membrane projections or 'endfeet' that can reattach to the apical surface, allowing symmetric division to proceed.

"This ability to regenerate prevents radial glia from detaching and migrating," explains Matsuzaki. "Only later in development do these detachment events lead to the formation of a new stem cell zone and the generation of a large number of neurons."

This is not just important for brain development; it also has evolutionary consequences since this process governs the expansion of cortical layers near the brain surface and complex folds seen in the brains of primates and other higher mammals.

Matsuzaki is now keen to understand the forces that control when and why radial glia 'let go' and begin to differentiate. "We don't yet know the exact mechanisms by which one daughter cell self-renews while the other differentiates," he says. "It's an enigma in our field." ●

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SUPRAMOLECULAR POLYMERIZATION

Chain reaction feels the heat, and the cold

Computational analysis unravels the complex behavior of a polymer with great potential for greener plastic production

A polymer that can be broken down into its molecular building blocks, which can then be recombined by either heating or cooling—but by different mechanisms in each case—has been developed by RIKEN chemists[1]. This could lead to intrinsically recyclable and sustainable plastics that depolymerize on demand.

Polymers are long-chain molecules formed by connecting long strings of small molecules called monomers. In conventional polymers, the monomers connect via covalent bonds. Because these bonds are so strong, it is extremely difficult to recover the monomer at the end of a plastic's useful life.

Takuzo Aida at the RIKEN Center for Emergent Matter Science has been developing supramolecular polymers, in which the monomers connect via readily reversible noncovalent interactions.

"We initially just wanted to synthesize a thermally stable supramolecular polymer using a disk-shaped monomer having eight hydrogen-bonding amide units in its side chains," Aida says. A team that included his former colleagues Venkat Rao and Daigo Miyajima developed a porphyrin-based monomer that formed a stable polymer in hydrocarbon solvents, but which readily depolymerized on adding an alcohol, which disrupted the hydrogen bonds holding the polymer together.

As expected, this depolymerized mixture repolymerized on cooling. "But to our great surprise, the depolymerized mixture also repolymerized upon heating," Aida recalls.

Conventional plastics such as these plastic chips from recycled water bottles are difficult to breakdown into their monomer building blocks. Now, RIKEN researchers have unraveled the complex depolymerization behavior of a material with the potential for sustainable plastic production.

To investigate this unusual phenomenon, the RIKEN group teamed up with E. W. 'Bert' Meijer's group at Eindhoven University of Technology, the Netherlands, where Mathijs Mabesoone had developed a computational method for analyzing supramolecular polymerization.

The analysis revealed competing processes at play. Upon cooling, the eight alcohol molecules complexing to each monomer dropped off at once to allow repolymerization. If the depolymerized mixture was heated, however, the alcohol molecules dropped off one by one.

"Before the computational analysis, none of us had predicted that such an interesting decomplexation mechanism was operating," Meijer says. "Such complex and competitive molecular processes are a key element of biology, but have only recently been recognized in supramolecular chemistry. Our polymer is thus a step toward closing the gap between synthetic and natural systems."

The discovery could lead to the development of supramolecular polymers that are very stable in use, but highly dynamic when the material needs to be recycled.

It could also make industrial-scale solution processing of polymers less energy hungry. Polymer solutions are highly viscous and hard to process, but the supramolecular polymer is depolymerized at room temperature, and so should have a low viscosity.

"This may cause a paradigm shift in the polymer industry," Aida says. "The next step is to tweak the polymer structure to control the non-polymerizable temperature range and to design very cheap monomers." ●

Reference

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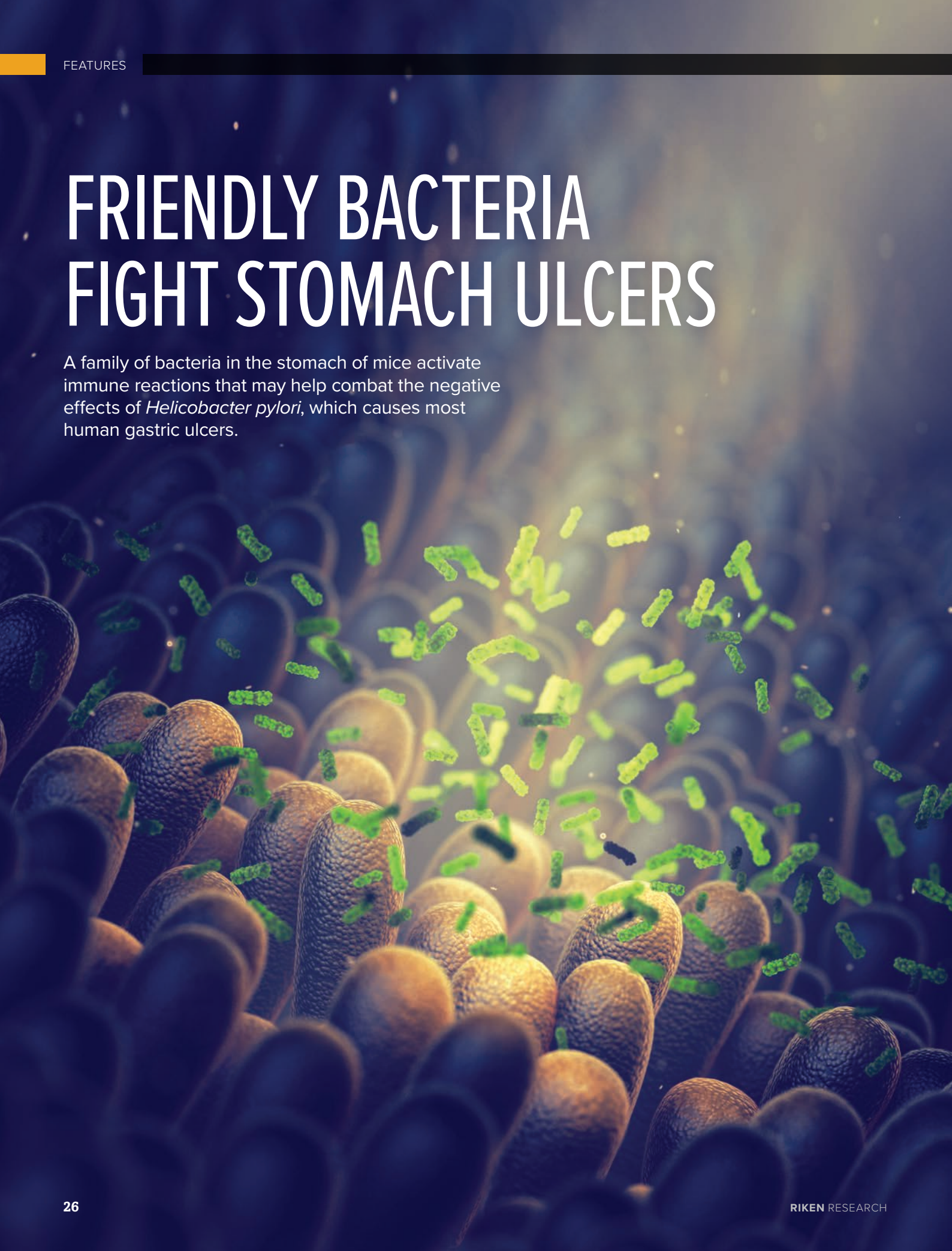
FRIENDLY BACTERIA FIGHT STOMACH ULCERS

A family of bacteria in the stomach of mice activate immune reactions that may help combat the negative effects of *Helicobacter pylori*, which causes most human gastric ulcers.



A group from the RIKEN Center for Integrative Medical Sciences has shown how a family of bacteria stimulates the stomach's immune system to produce a protective antibody coating. This coating is thought to ameliorate the impact of pathogens, such as the bacterium *Helicobacter pylori*, which is linked to most gastric ulcers and also potentially to stomach cancer. Revealing a similar mechanism in humans could lead to new probiotics to treat, or prevent, stomach ulcers and cancers.

A FRIENDLY BACTERIA FOUND

To understand how the stomach typically manages *H. pylori* infections and other pathogens, the RIKEN team, led by Naoko Satoh-Takayama, wanted to understand which immune cells were at play.

The human immune system has three broad groups of immune cells. The main two are linked to innate and adaptive immunity. Innate immune cells respond rapidly to pathogens, but lack specificity—a kind of first-line-of-defense, shotgun approach. In contrast, adaptive immune cells take longer to respond, but are much more targeted in their attack on harmful bacteria and viruses. The latter's B- and T-cells are more like guided missiles.

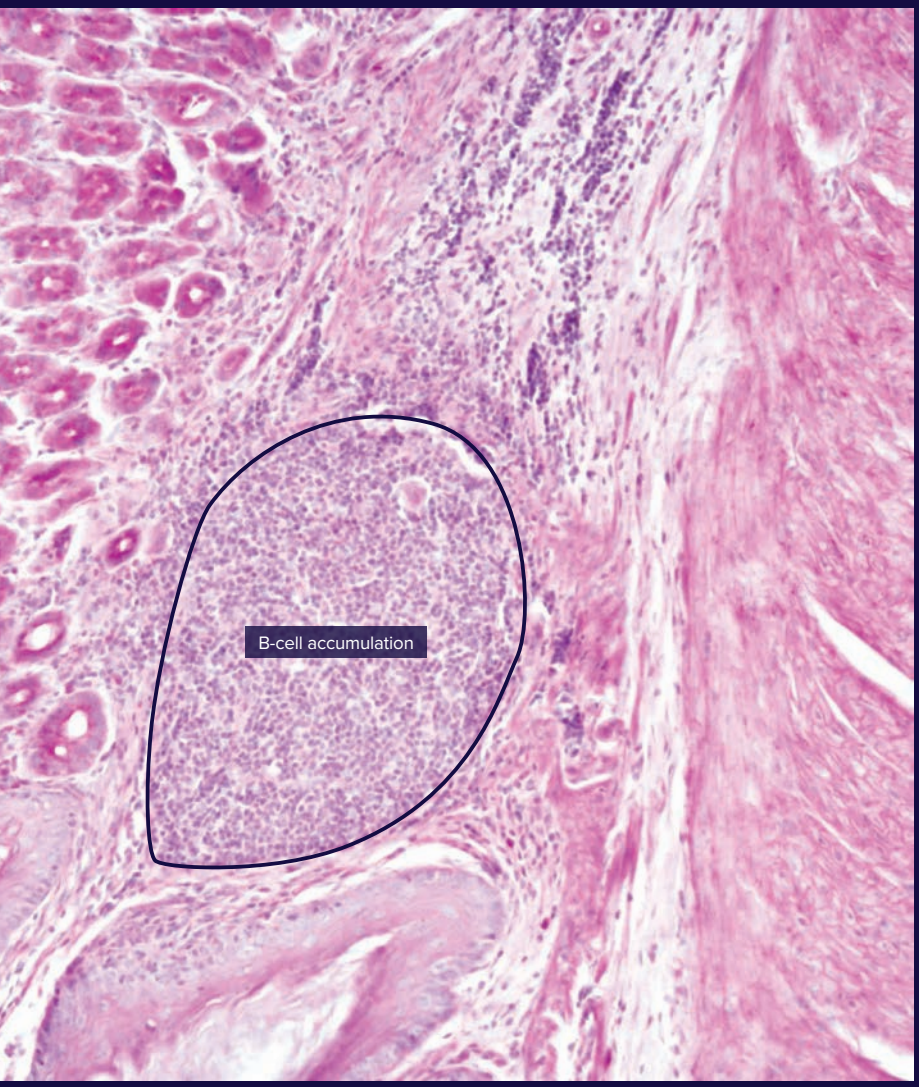
In between these two groups (in terms of function) are innate lymphoid cells (ILCs). Like innate immune cells, ILCs respond quickly and lack the receptors for antigens that give adaptive immunity cells their specificity. But like T-cells, they emit a cocktail of proteins that prime the immune system for a more specific response. Satoh-Takayama was part of the team that discovered these cells while working at the Institut Pasteur in Paris. That group became the first to publish on ILCs in 2008 when they discovered ILC3, one of the three known types.

To better understand stomach ILCs, Satoh-Takayama and her RIKEN co-workers started checking for ILC3 populations in the stomachs of mice. These ILCs are abundant in mice intestines, and so the group assumed it would be the same in the stomach. "But we found nothing at all—no ILC3s!" Satoh-Takayama says. "My initial reaction was: Where do we go from here?" The group then checked ILC1s and ILC2s, and found that of the three ILCs, ILC2s were most plentiful in the stomachs of mice.

ILC2s were then found to be rapidly produced in the stomach in response to *H. pylori* infection. By tracing the interactions back from these cells, the team found that the S24-7 bacteria family (commonly found in human and mouse stomachs) were also associated with an increase of ILC2s. They then showed that S24-7 bacteria stimulate production of two proteins that cells use to communicate—interleukins 7 and 33—and, in turn, these trigger the propagation and activation of ILC2s. ILC2-derived

This feature looks at the work of NAOKO SATOH-TAKAYAMA

Naoko Satoh-Takayama received her PhD from the University of Tokyo in 2007 under the direction of Hiroshi Kiyono. After graduating, she joined James Di Santo's group in the Institut Pasteur, France, on a scholarship. In 2008, she identified and reported a novel cell subset of innate lymphoid cells, a world first, and became an assistant professor at the Institute Pasteur in 2010. She moved to RIKEN Center for Integrative Medical Sciences in 2015 and joined Hiroshi Ohno's lab. She is currently investigating the importance of commensal and pathogenic bacteria in the function of innate lymphoid cells as a senior research scientist.



The proliferation of B-cells seen here after two weeks of infection by *Helicobacter pylori* is a slower adaptive immune response. A RIKEN team's insights into the role of the S24-7 bacteria family in supporting a slightly faster response from innate lymphoid cells may lead to a probiotic to treat stomach infections.

IL-5 then results in the production of the blood protein antibody immunoglobulin A, which coats stomach microbes, effectively controlling potentially harmful bacteria.

A PROBIOTIC FOR ULCERS?

Many studies have looked at how microbes in the large and small intestines interact with the immune system, but because of its acidic nature, the stomach—one of the first port of calls for food entering our digestive system—has been largely ignored until recently, says Satoh-Takayama. "That's because it was thought unlikely that bacteria could endure the highly acidic conditions of the stomach," she explains.

But since *H. pylori* bacteria were found in the stomach and linked to ulcers in the 1980s (a discovery that earned Barry Marshall and Robin Warren the Nobel Prize in Physiology or Medicine in 2005), stomach bacteria have come increasingly into the spotlight.

The right balance of bacteria across the whole digestive system has also recently been linked to many beneficial effects, such as helping the immune system fight pathogens and break down food, and providing protection against diabetes, obesity, colon cancer and depression. As a result, some companies already make probiotics, doses of beneficial bacteria, that they claim better regulate the bacterial balance in the digestive system to then boost the immune system.

Most reliably, several combined analyses of dozens of studies have concluded that probiotics may help prevent some of the common side effects of antibiotics. Antibiotics disrupt communities of beneficial bacteria in the gut and these emptied niches are sometimes filled by harmful bacteria that secrete toxins, causing inflammation and diarrhea. Adding yogurt or other probiotics to a diet during and after a course of antibiotics seems to decrease the chances of subsequently developing opportunistic infections in the intestine.

Could something similar be true for *H. pylori*? *H. pylori* infections are found in about 60% of adult stomachs across the world, but only about 10% will develop a stomach ulcer. Generally, this happens if a treatment of non-steroidal anti-inflammatory drugs damages the stomach lining and an *H. pylori* infection gets out of hand and causes an ulcer at the site. If that's the case, could a dose of specific beneficial stomach bacteria have a protective effect when taking anti-inflammatory drugs?

Moreover, if an *H. pylori* strain proves to be one of a growing number of antibiotic-resistant bacteria (sometimes known as superbugs), taking S24-7 inducible bacteria as a probiotic could provide one possible alternative treatment, Satoh-Takayama says.

But before these possibilities can be addressed, researchers need to understand how much the recent findings carry over to humans—something that Satoh-Takayama and her team are keen to investigate. "Unfortunately, the function of IL-5 is a little bit different in mice. But there is another, similar mechanism with IL-13, for example," she says. "We're trying to find medical researchers to collaborate with so that we can further investigate this link between gut microbes and immune cells in humans."

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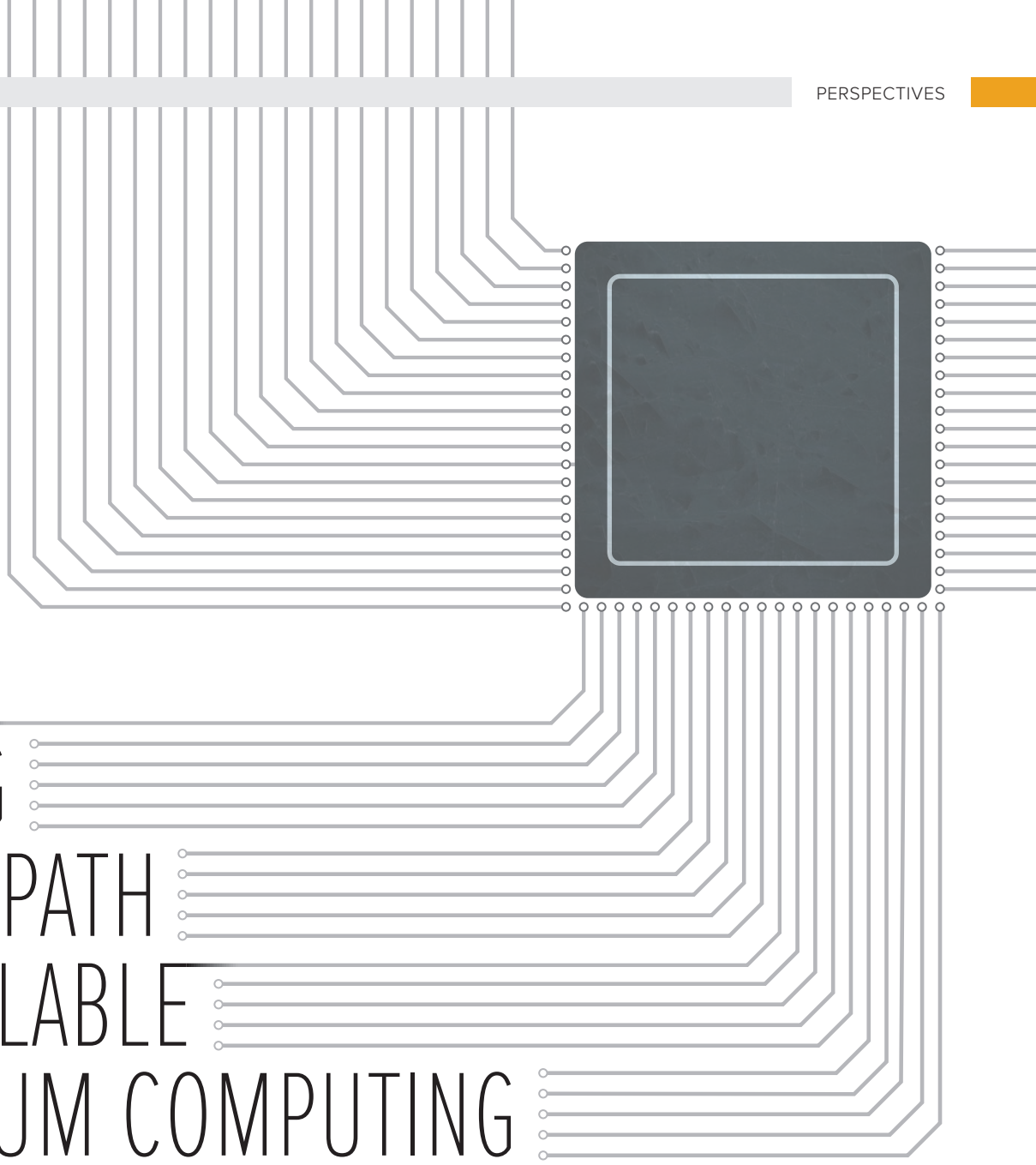


WIRING A NEW PATH TO SCALABLE QUANTUM COMPUTING

Clever wiring architecture will soon produce bigger and better quantum circuits, says Yasunobu Nakamura.

Last year, Google produced a 53-qubit quantum computer that could perform a specific calculation significantly faster than the world's fastest supercomputer. Like most of today's largest quantum computers, this system boasts tens of qubits—the quantum counterparts to bits, which encode information in conventional computers.

To make larger and more useful systems, most of today's prototypes will have to overcome the challenges of stability and scalability. The latter will require increasing the density of signaling and wiring, which is hard to do without degrading the system's stability. I believe a new circuit-wiring scheme developed over the last three years by RIKEN's Superconducting Quantum Electronics Research Team, in collaboration with other institutes, opens the door to scaling up to 100 or more qubits within the next decade. Here, I discuss how.

CHALLENGE ONE: SCALABILITY

Quantum computers process information using delicate and complex interactions based on the principles of quantum mechanics. To explain this further we must understand qubits. A quantum computer is built from individual qubits, which are analogous to

YASUNOBU NAKAMURA
Team Leader, Superconducting Quantum Electronics Research Team

Since 2014, Yasunobu Nakamura has been a principal investigator and team leader of the Superconducting Quantum Electronics Research Team at the RIKEN Center for Emergent Matter Science (CEMS). He is also a professor at the University of Tokyo. Until 2012, he worked for NEC Corporation. Nakamura was a Thomson Reuters Highly Cited Researcher in 2014 and was named as one of the world's top innovators in the *MIT Technology Review* magazine in 2003. He has also been awarded the Sir Martin Wood Prize (1999), Nishina Memorial Prize (1999), Agilent Technologies Europhysics Prize (2004), Simon Memorial Prize (2008), Leo Esaki Prize (2014), JSAP Outstanding Achievement Award (2018).

the binary bits used in conventional computers. But instead of the zero or one binary states of a bit, a qubit needs to maintain a very fragile quantum state. Rather than just being zero or one, qubits can also be in a state called a superposition—where they are sort of in a state of both zero and one at the same time. This allows quantum computers based on qubits to process data in parallel for each possible logical state, zero or one, and they can thus perform more efficient, and thus faster, calculations than conventional computers based on bits for particular types of problems.

However, it is much harder to create a qubit than a conventional bit, and full control over the quantum-mechanical behavior of a circuit is needed. Scientists have come up with a few ways to do this with some reliability. At RIKEN, a superconducting circuit with an element called a Josephson junction is used to create a useful quantum-mechanical effect. In this way, qubits can now be produced reliably and repeatedly with nanofabrication techniques commonly used in the semiconductor industry.

The challenge of scalability arises from the fact that each qubit then needs wiring and connections that produce controls and readouts with minimal crosstalk. As we moved past tiny two-by-two or four-by-four arrays of qubits, we have realized just how densely the associated wiring can be packed, and we've had to create better systems and fabrication methods to avoid getting our wires crossed, literally.

At RIKEN, we have built a four-by-four array of qubits using our own wiring scheme, where the connections to each qubit are made vertically from the backside of a chip, rather than a separate 'flip chip' interface used by other groups that brings the wiring pads to the edges of a quantum chip. This involves some sophisticated fabrication with a dense array of superconducting vias (electrical connections) through a silicon chip, but it should allow us to scale up to much larger devices. Our team is working toward a 64-qubit device, which we hope to have within the next three years. This will be followed by a 100-qubit device in another five years as part of a nationally funded research program. This platform should ultimately allow up to a 1,000 qubits to be integrated on a single chip.

CHALLENGE TWO: STABILITY

The other major challenge for quantum computers is how to deal with the intrinsic vulnerability of the qubits to fluctuations or noise from outside forces such as temperature. For a qubit to function, it needs to be maintained in a state of quantum superposition, or 'quantum coherence'. In the early days of superconducting qubits, we could make this state last for just nanoseconds. Now, by cooling quantum computers to cryogenic temperatures and creating several other environmental controls, we can maintain coherence for up to 100 microseconds. A few hundred microseconds would allow us to perform a few thousand information processing operations, on average, before coherence is lost.

In theory, one way we could deal with instability is to use quantum error correction, where we exploit several physical qubits to encode a single 'logical qubit', and apply an error correction protocol that can diagnose and fix errors to protect the logical qubit. But realizing this is still far off for many reasons, not the least of which is the problem of scalability.

QUANTUM CIRCUITS

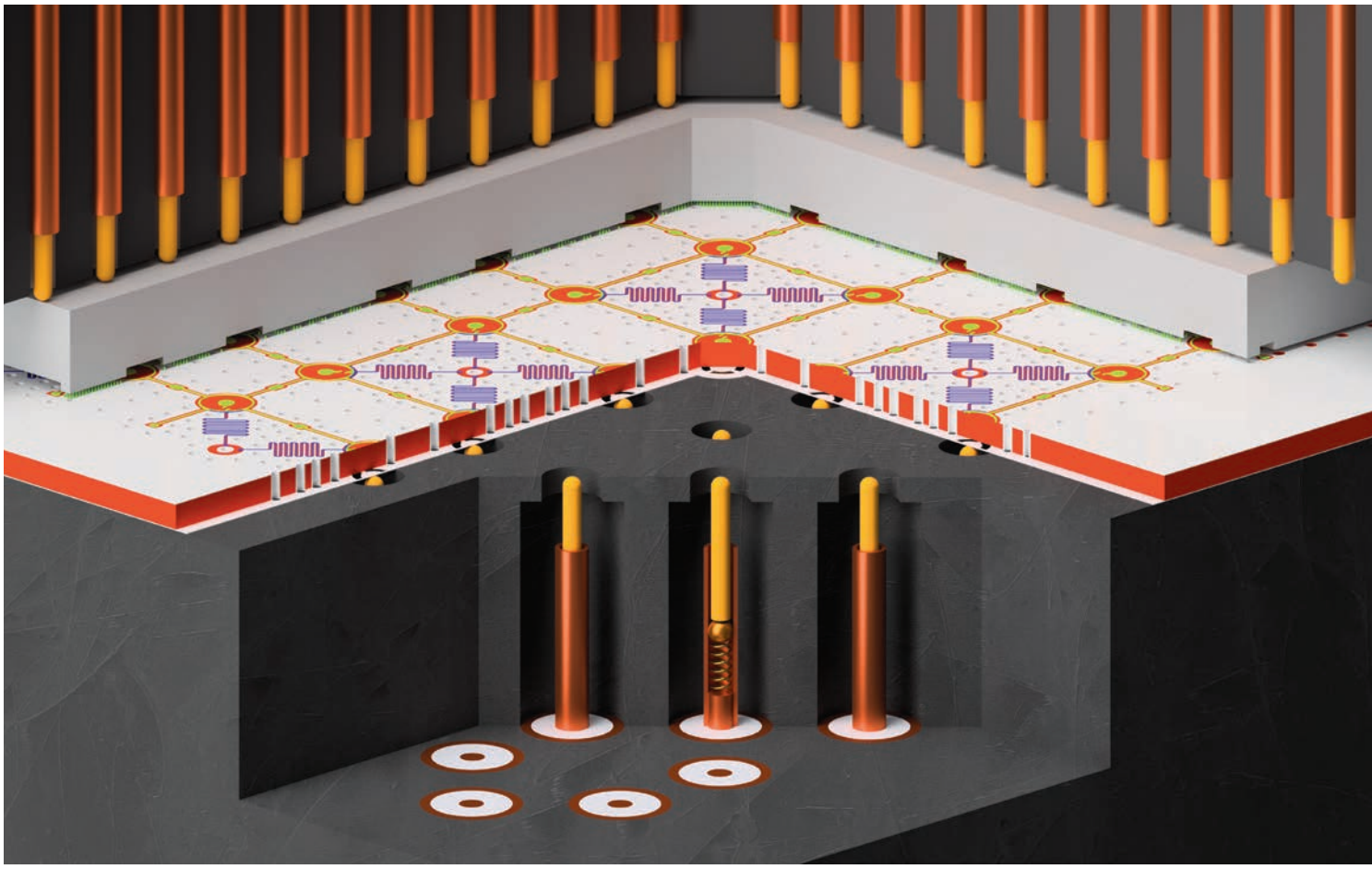
I have been researching quantum circuits since the 1990s, before quantum computing became a big thing. When I began, I was interested in whether my team could create and measure quantum superposition states within electric circuits. At the time, it wasn't at all obvious if electric circuits as a whole could behave quantum mechanically. To realize a stable qubit in a circuit and create switch-on and -off states in the circuit, the circuit also needed to be capable of supporting a superposition state.

We eventually came up with the idea of using a superconducting circuit. The superconducting state is free of all electrical resistance and losses, and so it is streamlined to respond to small quantum-mechanical effects. To test this circuit, we used a microscale superconducting island made of aluminum, which was connected to a larger superconducting ground electrode via a Josephson junction—a junction separated by a nanometer-thick insulating barrier—and we trapped superconducting electron pairs that tunneled across the junction. Because of the smallness of the aluminum island, it could accommodate at most one excess pair due to an effect known as Coulomb blockade between negatively charged pairs. The states of zero or one excess pairs in the island can be used as the state of a qubit. The quantum-mechanical tunneling maintains the qubit's coherence and allows us to create a superposition of the states, which is fully controlled with microwave pulses.

HYBRID SYSTEMS

Because of their very delicate nature, quantum computers are unlikely to be in homes in the near future. However, recognizing the huge benefits of research-oriented quantum computers, industrial giants such as Google and IBM, as well as many start-up companies and academic institutes around the world, are increasingly investing in research.

A commercial quantum-computing platform with full error correction is probably still more than a decade away, but state-of-the-art technical developments are already bringing about the possibility of new science and applications. Smaller scale quantum circuits already perform useful tasks in the lab.



This schematic image of integrated superconducting qubits and their packaging, shows the qubits as green dots with rings, which are laid out on top of a silicon chip (in red). A number of holes through the chip electrically connect the top and bottom surfaces. The blue wires on top are circuit elements for the readout of the qubits. Coaxial wiring (with gold-plated spring-loaded pins) is connected to the backside of the chip, and these control and read the qubits.

For example, we use our superconducting quantum-circuit platform in combination with other quantum-mechanical systems. This hybrid quantum system allows us to measure a single quantum reaction within collective excitations—be it precessions of electron spins in a magnet, crystal lattice vibrations in a substrate, or electromagnetic fields in a circuit—with unprecedented sensitivity. These measurements should advance our understanding of quantum physics, and with it quantum computing. Our system is also sensitive enough to measure a single photon at microwave frequencies, whose energy is about five orders of magnitude lower than that of a visible-light photon, without absorbing or destroying it. The hope is that this will serve as a building block for quantum networks connecting distant qubit modules, among other things.

QUANTUM INTERNET

Interfacing a superconducting quantum computer to an optical quantum communication network is another future challenge for our hybrid system. This would be developed in anticipation of a future that includes a quantum internet connected by optical wiring reminiscent of today's internet. However, even a single photon of infrared light at a telecommunication wavelength cannot directly hit a superconducting qubit without disturbing the quantum information, so careful design is a must. We are currently investigating hybrid quantum systems that transduce quantum signals from a superconducting qubit to an infrared photon, and vice versa, via other quantum systems, such as one that involves a tiny acoustic oscillator.

Although many complex issues need to be overcome, scientists can see a future enhanced by quantum computers on the horizon. In fact, quantum science is already in our hands every day. Transistors and laser diodes would have never been invented without a proper understanding of the properties of electrons in semiconductors, which is totally based on understanding quantum mechanics. So through smart phones and the internet, we are already totally reliant on quantum mechanics, and we will only become more so in the future.

REFERENCE

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

HITTING SAVE ON COMPUTING

Daily computing demands more energy every year, and operating the world's current fastest supercomputer consumes the energy equivalent of 16% of US desktops. In fact, energy is the leading design constraint on supercomputers that might otherwise be predicting natural disasters or discovering new drugs. Luckily, RIKEN is at the forefront of efficiencies in computing.

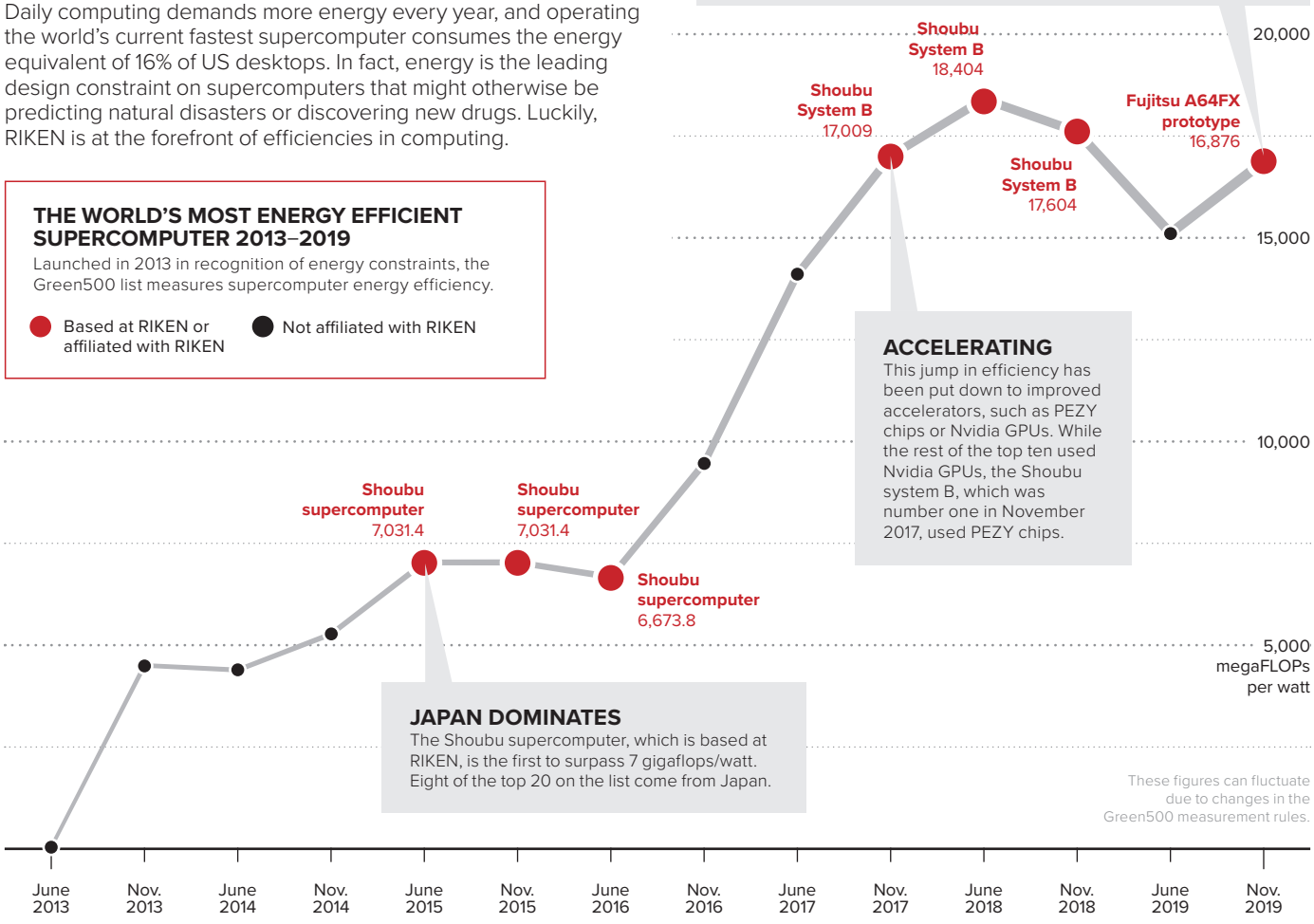
PROTOTYPING THE FUTURE

This is a prototype of RIKEN's Supercomputer Fugaku, developed with Fujitsu. Its efficiency is partly due to data-processing hardware (the CPU) that consumes about 2/3 less energy than similar systems. Many other highly efficient supercomputers use processing accelerators to add efficiencies, but in this round of testing the Fujitsu A64FX didn't need to.

THE WORLD'S MOST ENERGY EFFICIENT SUPERCOMPUTER 2013–2019

Launched in 2013 in recognition of energy constraints, the Green500 list measures supercomputer energy efficiency.

- Based at RIKEN or affiliated with RIKEN
- Not affiliated with RIKEN



ACCELERATING

This jump in efficiency has been put down to improved accelerators, such as PEZY chips or Nvidia GPUs. While the rest of the top ten used Nvidia GPUs, the Shoubu system B, which was number one in November 2017, used PEZY chips.

JAPAN DOMINATES

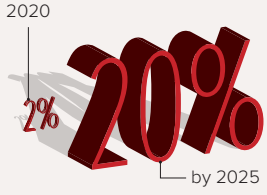
The Shoubu supercomputer, which is based at RIKEN, is the first to surpass 7 gigaflops/watt. Eight of the top 20 on the list come from Japan.

These figures can fluctuate due to changes in the Green500 measurement rules.

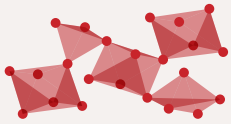
DATA STORAGE

The electricity needs of cloud-based data services (such as Facebook and Google) are predicted to reach 20% of global use by 2025. Data is stored using an electrical current that changes the magnetic state of a core into a one or zero. About 40% of data center energy goes to cooling this process. In 2019, a team led by Vilmos Kocsis at the RIKEN Center for Emergent Matter Science made a new core material changed at near room temperature.

GLOBAL CLOUD-DATA ELECTRICITY CONSUMPTION



COOLER CRYSTAL CORE



'Hexaferrite' crystal magnetism can be switched using a voltage close to room temperature.

QUANTUM COMPUTING

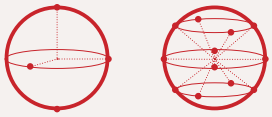
Quantum computing's tiny, agile mechanisms (see below) will be more energy efficient. In 2019, a team led by Chia Cheng Chang, a RIKEN iTHEMS fellow at the Berkeley Lab's Nuclear Science Division, developed a quantum annealing algorithm, which has the potential to solve a system of equations more efficiently for subatomic physics.

CLASSICAL STATES

Off On

Traditional computing uses bits with two states as a basic unit of information.

QUANTUM STATES



1 qubit (2^2) 4 qubits (2^4)

Quantum computing's qubit system allows for more than two states per qubit.

RIKEN'S CENTERS AND FACILITIES

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- ● Interdisciplinary Theoretical and Mathematical Sciences Program (iTHEMS)
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- ◆ SACLA

NAGOYA

KEIHANNA
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- ■ BioResource Research Center (BRC)

KOBE
- ● Center for Biosystems Dynamics Research (BDR)
- ■ Center for Computational Science (R-CCS)
- ▲ Cluster for Science, Technology, and Innovation Hub (CSTIH)
- ◆ Molecular Imaging

OSAKA
- ● Center for Biosystems Dynamics Research (BDR)

Since relocating its original campus from central Tokyo to Wako on the city's outskirts in 1967, RIKEN has rapidly expanded its domestic and international network. RIKEN now supports five main research campuses in Japan and has set up a number of research facilities overseas. In addition to its facilities in the United States and the United Kingdom, RIKEN has joint research centers or laboratories in Germany, Russia, China, South Korea, India, Malaysia, Singapore and other countries. To expand our network, RIKEN works closely with researchers who have returned to their home countries or moved to another institute, with help from RIKEN's liaison offices in Singapore, Beijing and Brussels.

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