RIKEN
RESEARCH
WINTER 2019
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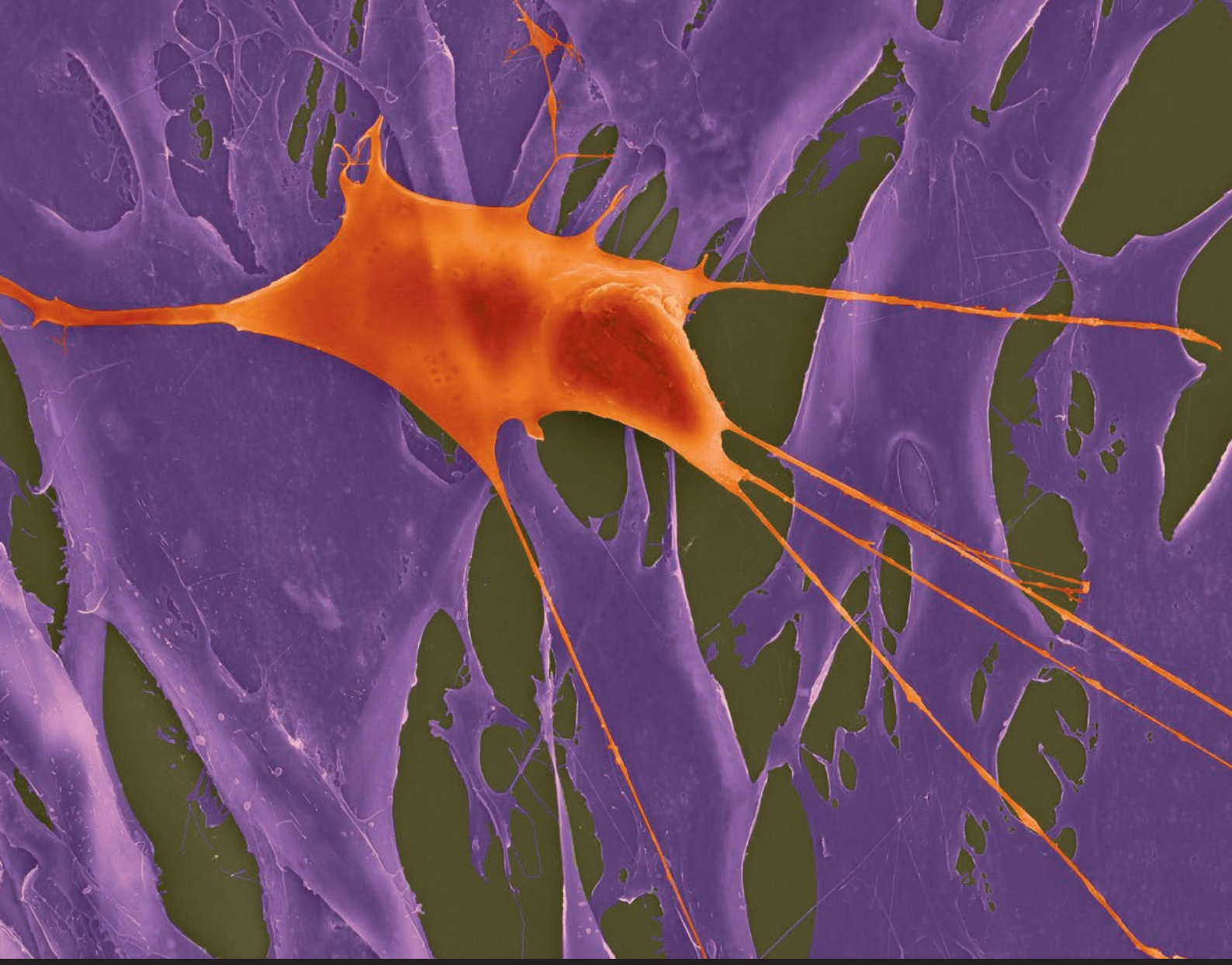
LEAVING NO CELL UNTURNED

Mapping the human body in its entirety

WORM POWER
Device powered by muscles from earthworms

GENEROUS THINKING
The neural origins of generosity uncovered

IMAGING A COSMIC WEB
Gas filaments that birthed galaxies spotted



▲ **UNDERSTANDING ACTIVATED CANCER CELLS**
A human lung fibroblast cancer cell (orange) among healthy fibroblasts (purple). Lung cancer, also called lung carcinoma, is a malignant lung tumor. It is characterized by uncontrolled cell growth in the tissues of the lung, especially lung epithelial cells. One of the aims of the Human Cell Atlas (see page 29) is to understand the different states of cells, such as how healthy fibroblasts become 'activated' and cancerous.

RIKEN RESEARCH

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

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

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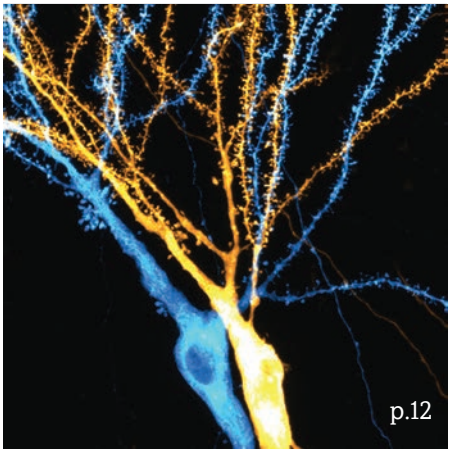

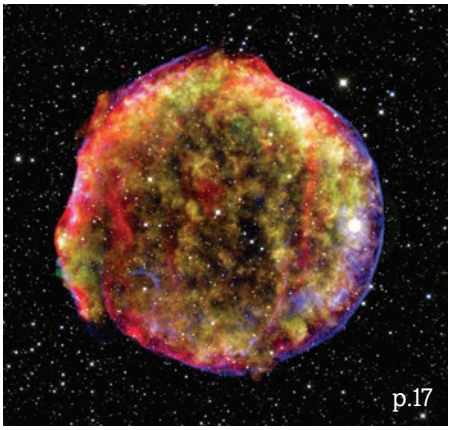

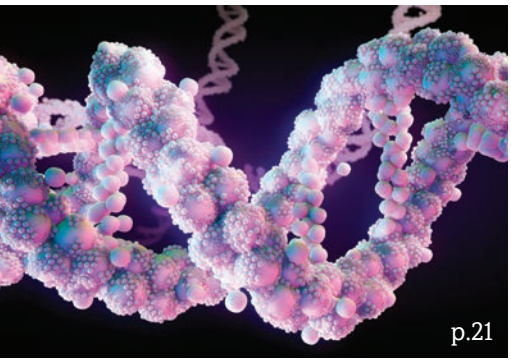
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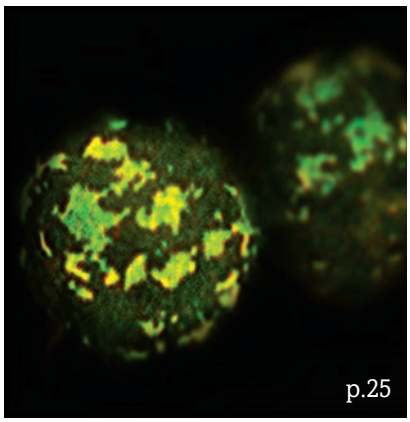
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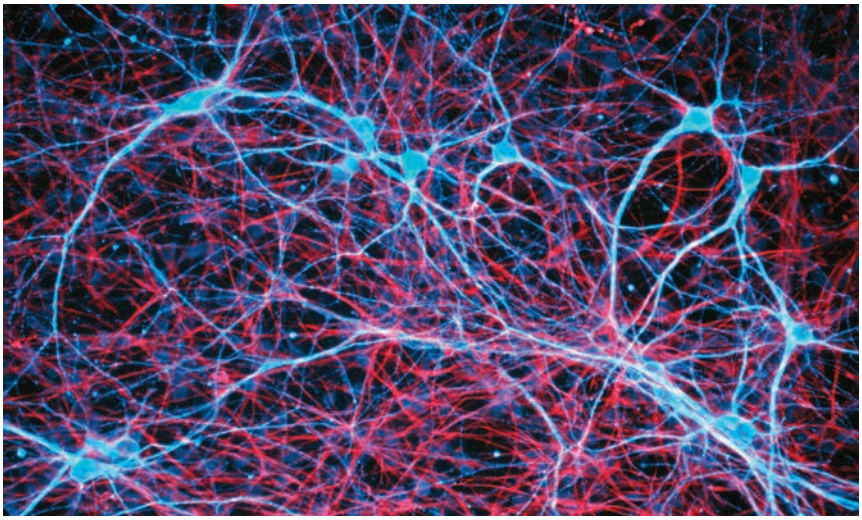

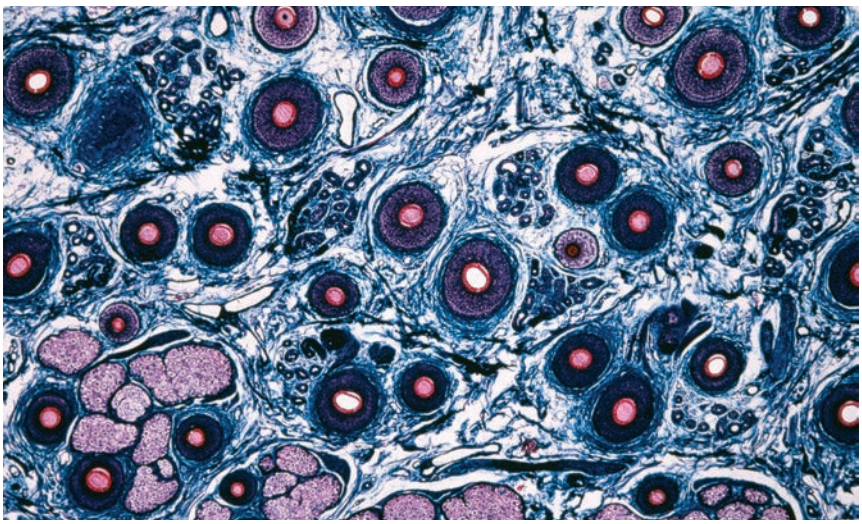

New subsidiary to bring findings to fruition

Hiroshi Matsumoto
President, RIKEN

I have some exciting news to report. On September 5, RIKEN established a fully owned subsidiary called RIKEN Innovation, which will work closely with our laboratories and industry partners to ensure that the fruits of our research are used to benefit society. The company will be staffed by professionals skilled at identifying potentially useful discoveries and finding suitable partners, both in Japan and overseas.

The Japanese name of the subsidiary is RIKEN Teigyo, which includes the Japanese character (鼎) for a bronze vessel with three legs. In the case of RIKEN Teigyo, the three legs signify the pillars of the new company: management, technology and social responsibility.

RIKEN has a reputation for focusing on fundamental research, but in reality many of our research advances have been used by industry. In fact, when RIKEN was established in 1917, its main mission was to contribute to the development of Japanese industry. And in the 1920s and 1930s, several companies—many still active today—were established under RIKEN's umbrella. RIKEN is one of Japan's leading innovators, as our research papers are frequently cited in patent applications filed by private companies.

Like past issues, this issue of RIKEN Research contains several examples of research that could lead to commercial applications. For example, RIKEN researchers have developed an earthworm muscle-derived valve that can operate without electricity (page 13) and a simple chemical reaction that could make radioactive particles more efficient at destroying cancer cells (page 15).

I hope you will find this issue enlightening, and I look forward to working ever more closely with our partners around the world to solve the major challenges confronting humanity.

COVER STORY:
RIKEN is leading the Human Cell Atlas' efforts in Asia to create a baseline reference dataset of human cells. *Page 29*

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How mitochondria influence our mood

Emilie Kristine Bagge
Research Scientist, Laboratory for Molecular Dynamics of Mental Disorders, RIKEN Center for Brain Science

Please describe your current research at RIKEN
I'm a research scientist at the RIKEN Center for Brain Science, where I study the influence of mitochondria on neuropsychiatric disorders, especially mood disorders (bipolar and depression). While we know very little about the molecular pathology of these disorders—one theory is that mitochondria and their loss of functionality may be involved. At the RIKEN Laboratory for Molecular Dynamics of Mental Disorders we are trying to elucidate the molecular mechanisms of such mitochondrial dysfunction on whole cell function.

Describe your role at RIKEN
I am employed as a research scientist at the RIKEN Center for Brain Science. That means I'm responsible for my own research projects, from coming up with research ideas and performing experiments to data analysis in close collaboration with other lab members and the lab's team leader, Tadafumi Kato.

How did you become interested in your current field of research?
I have always been very interested in how cells integrate all the signals they are constantly exposed to, as there is a constant need to respond and adjust to different cues to ensure the stability of not just the cell, but the entire organism. This is especially true in the brain. Add to that a disease state, and signal integration becomes extremely complex—and extremely exciting!

What excites you the most about your current research?
Probably that the area is still so poorly understood—we recognize and treat mood disorders, but can't really explain how they manifest. There are so many questions waiting to be answered. We're often looking to find a risk gene, but sometimes overlook genomic structure in our search to understand disease; I think we need to have a keen focus on that when we study mood disorders.

"My research is important for society because…."
Many think of neuropsychiatric disorders as 'mental disorders', separate from the physical body. I hope that discovering and describing the molecular mechanisms in patients can help alleviate the taboo often associated with these disorders.

What made you decide to become a scientist?
I am not sure I ever decided to become a scientist—I often think it kind of just happened! My plan was to study English at university, but then I discovered molecular biology during my first year of high school and was hooked.

> *We are often looking to find a risk gene, but in our search to understand disease we sometimes overlook genomic structure*

How and when did you join RIKEN?
I joined RIKEN in September 2017, a few months after finishing my PhD. I was hoping to find a position in Wako or Tokyo, and when I was preparing my application for this position I was surprised how much my skills in molecular biology and genomics could actually contribute to neurobiology. I had no prior experience in the area, so I was extremely appreciative of RIKEN's open-minded approach to hiring new staff. I think this is one of RIKEN's real strengths—an interdisciplinary mindset.

How has being at RIKEN helped your research?
RIKEN is inhabited by excellent researchers—there's always an expert around! I'm also constantly impressed by the willingness of others to help you and contribute to your ideas and projects I think this is very much in the spirit of RIKEN. ■

The dynamics of single cells

Hirofumi Shintaku

RIKEN Hakubi Research Team Leader, Microfluidics RIKEN Hakubi Research Team, Cluster for Pioneering Research

Please describe your role at RIKEN
I joined RIKEN in April 2018 to lead the Microfluidics RIKEN Hakubi research team, which consists of engineers and scientists with backgrounds in mechanical engineering, biophysics and biology. We develop new microfluidic technologies to uncover the hierarchical systems underlying the apparently stochastic behavior of single cells.

Please briefly describe your current research?
In 2014, I found that an electric field can selectively break down the plasma membrane of eukaryotic cells while retaining the integrity of nuclei membrane. This discovery led me to develop a new approach to separating cytoplasmic contents from nuclear components in single cells. My team exploits this approach to study localization and regulation of transcript abundance across the nuclear membrane in single cells. We are now working to extend the approach to do sequencing-free characterization of single cells. I believe this series of studies will contribute to understanding the most basic elements of life.

What has been the most interesting discovery in your field in the last few years?
Single cells are known to be unique, even if they are from a same population. This diversity is important to complex biological functions and hierarchical structures. However, until recently we had no means to explore these differences in more depth, because of limitations in throughput and sensitivity of measurements. During the last decade, the field of microfluidics has offered number of disruptive technologies that allowed researchers to characterize single cells at unprecedented resolution and throughput.

How did you become interested in your current field of research?
I started my research career as a mechanical engineer with an emphasis on microelectromechanical systems and fluid dynamics. I have always been passionate about applying new technologies to solve biological questions. Ultimately, I would like to describe single cells with a physical model, and develop a mathematical description that predicts the future fate of single cells.

What excites you the most about your current research?
We are now putting our efforts into developing a sequencing-free approach to understand new molecular mechanisms within single cells. This approach will complement state-of-the-art sequencing technology to reveal dynamics and real instantaneous snapshots of single cells—I'm really excited about this project, both as an engineer and as a scientist.

How has being at RIKEN helped your research?
RIKEN is a research institute that embraces scientists from many fields. The Cluster for Pioneering Research, which I belong to, is a real melting pot of all kinds of scientists. I've noticed a wider variety of people expressing interest in my work since I moved to RIKEN.

What is the best thing about working at RIKEN?
Great staff. They think of researchers first—which allows us to focus on the science. My team started from scratch, and so we renovated our research space. Although I knew zero about the basics like air conditioning, lighting, water supply, etc., we accomplished the renovations thanks to the support of RIKEN staff. ■

Careers at RIKEN

For further information, visit our Careers page:
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Center for Brain Science Summer Program participant, Maria Scala, discusses sex-specific brain activation networks in zebrafish during a poster session.

Center for Brain Science Summer Program

From early June to early August 2019, the Center for Brain Science (CBS) hosted roughly 40 young neuroscientists and emerging researchers.

The selection for the CBS Summer Program is highly competitive, with only about one in six applicants being selected. The main theme of the lecture course changes every year. The topic of the 2019 lecture course was "Neurotechnology—Understanding the brain in health and disease". Keynote speaker Susumu Tonegawa, Nobel laureate and RIKEN fellow, spoke on the mechanisms underlying the encoding, consolidation and retrieval of memories.

Since the program began in 1999, nearly 300 prominent researchers and more than 800 students have participated. The Summer Program consists of two courses: a two-month internship course or a week-long lecture course. The lecture course features presentations from prominent scientists and poster sessions from CBS laboratories and program participants.

Panels discussed a wide range of topics including what to think about when looking for a postdoc lab.

The program provided lots of opportunities for extracurricular interaction, also, including an optional Tokyo Bay cruise and a discussion session with CBS postdoctoral fellows.

https://cbs.riken.jp/en/summer

A new ultraviolet eye on our planet

Mini-EUSO (below) was made at RIKEN and has been delivered to the International Space Station by a Russian Soyuz rocket to carry out the first ever night observations of the Earth's atmosphere from space in the near-ultraviolet band.

On 22 August 2019, a Russian Soyuz rocket took off from the Baikonur launch site on an experimental mission to the International Space Station (ISS). Hitching a ride on the flight was a revolutionary telescope developed by an international team led by Japan's RIKEN national laboratory. The experiment, dubbed Mini-EUSO, will look down at the Earth's night atmosphere from the ISS, essentially using the atmosphere as an enormous observatory for exploring poorly understood phenomena, carrying out the first night observations of the Earth's atmosphere from space in the near-ultraviolet band. It has been installed in front of the ultraviolet-transparent window in the Russian Zvezda module on the ISS, looking at Earth in a nadir position.

Mini-EUSO will have a long list of scientific missions. First, it will observe the near-ultraviolet background level in preparation for ultrahigh-energy cosmic-ray space observatory missions. Second, it will look for strange quark matter, a type of hypothesized super-dense matter that has never been observed but might create traces by burning up in the atmosphere. Small pieces of this type of matter, called strangelets, are one candidate for dark matter, which is currently the subject of a massive scientific search. A failure to see such traces could help the search for dark matter by putting upper limits on the mass of such objects.

Another goal is to look at ultrahigh-energy cosmic rays, with energies above 10^{21} electron volts. There are no certain observations of events at this energy, with the highest energy recorded on the ground being 3×10^{20} electron volts, so the observations may find that they do not exist.

Other goals are to look at bioluminescence from plankton in the oceans, helping to understand sea life and pollution, and to observe high-altitude atmospheric lighting and meteoroids entering the atmosphere. Those these phenomena have been examined in other light bands; seeing them from above in ultraviolet could reveal new findings regarding their mechanisms.

Mini-EUSO was developed by the JEM–EUSO collaboration, which brings together 306 researchers from 84 institutes in 16 countries. The entire detector was realized in-house, with the large Fresnel lenses manufactured at RIKEN and the detectors and electronics integrated and tested at the various institutes, leading to a significant cost reduction compared to other detectors.

www.riken.jp/en/news_pubs/news/2019/20190820_1

RIKEN opens joint lab in Luxembourg

On 9 July, a ceremony was held in Luxembourg to commemorate a memorandum of understanding between RIKEN and the University of Luxembourg's Luxembourg Center for System Biomedicine (LCSB) and the Luxembourg Institute of Health. Based on this agreement, a joint laboratory will be established.

RIKEN's ties with Luxembourg began with an agreement between RIKEN and LCSB in 2014, and a joint annual symposium has been held since then. In 2015, RIKEN and the Luxembourg National Research Fund signed another agreement. The joint laboratory will work on several areas, including immunology, microbiome and inflammation research.

Luxembourg is a world leader in the collection and management of data related to clinical specimens, and the joint research will take advantage of this strength. The plan is to develop a comprehensive medical data system that records patient-derived data in disease models and to research neuroinflammation using human-derived induced pluripotent stem cells.

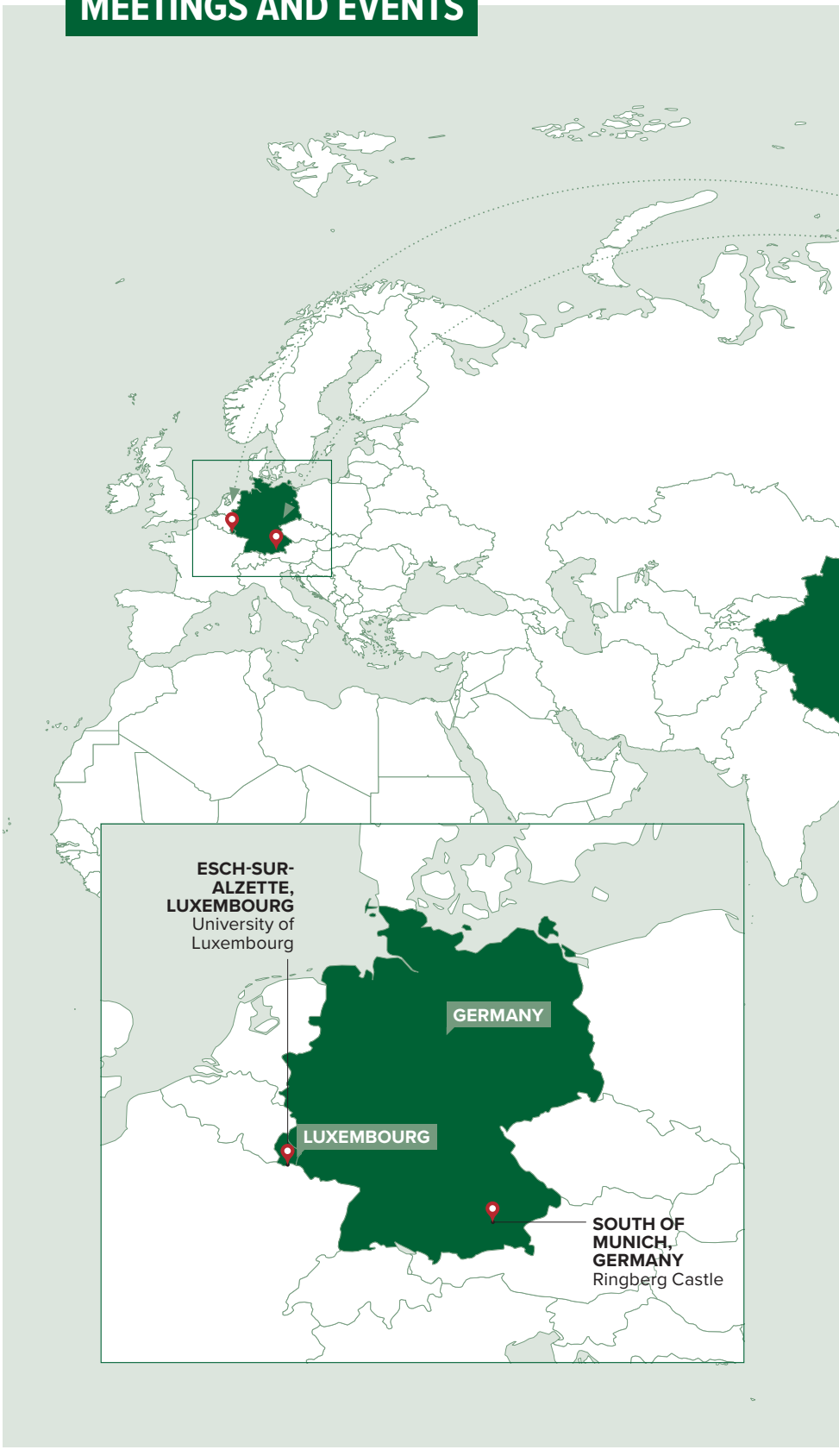
www.riken.jp/en/news_pubs/news/2019/20190806_1/index.html

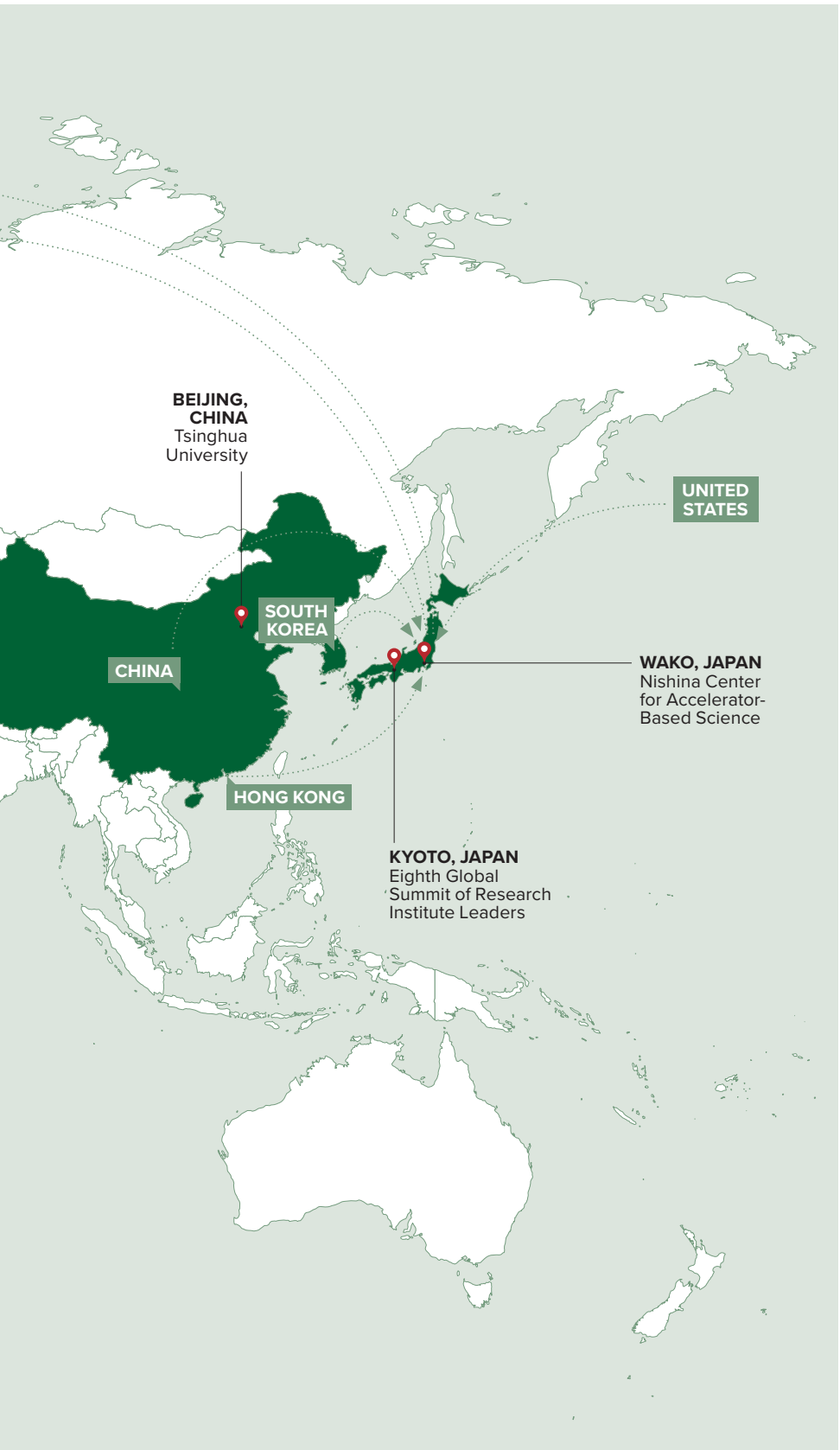
Eighth Global Summit of Research Institute Leaders

For the eighth consecutive year, prominent academics from 21 institutes and 12 different countries came to Kyoto to attend the Eighth Global Summit of Research Institute Leaders, which was held in conjunction with the 16th Annual Meeting of the Science and Technology in Society (STS) forum. The Japan Science and Technology Agency (JST) and the US Department of Energy provided guest speakers and mechanisms to support multilateral collaboration were discussed. The meeting was co-hosted by RIKEN and the Japan Advanced Institute for Science and Technology (AIST) and co-chaired by Matsumoto Hiroshi, president of RIKEN, and Matthias Kleiner, president of the Leibniz Association.

www.riken.jp/en/news_pubs/news/2019/20191021_3/index.html

MEETINGS AND EVENTS





RIKEN–Max Planck joint symposium

Researchers from RIKEN and the Max Planck Society in Germany gathered at Ringberg Castle in the Bavarian Alps to discuss systems chemical biology. The meeting, held in September 2019, was the seventh in a series of joint symposiums between the two organizations. A jointly managed center is led by Herbert Waldmann, director of the Max Planck Institute of Molecular Physiology, Peter Seeberger, director of the Max Planck Institute of Colloids and Interfaces, Hiroyuki Osada, director of the RIKEN Center for Sustainable Resource Science's RIKEN–Max Planck Joint Research Division for Systems Chemical Biology, and Chief Scientist Katsunori Tanaka.

www.riken.jp/en/news_pubs/news/2019/20191025_1/index.html

Tsinghua University–RIKEN IMS joint summer program

In June 2019, the RIKEN Center for Integrative Medical Sciences (IMS) co-organized an international summer school in Beijing with Tsinghua University Institute of Immunology. Seminars by leading international researchers discussed immunology, genomics and medical science. About 50 young researchers participated. The summer school will be held again in 2020 at the IMS in Yokohama, Japan.

www.ims.riken.jp/english/jobs/summer_program.php

Nishina School

In July and August 2019, 22 students were shown nuclear physics experiments at the RI Beam Factory located on RIKEN's Wako campus as part of the 13th Nishina School. Participants arrived from: Peking University, China; Rikkyo University, Japan; Seoul National University, Korea; Tohoku University, Japan; Hong Kong University, China; and, as guests, Phillips Exeter Academy, United States. This year, the school focused on reactions involved in the process of stellar nucleosynthesis.

https://indico2.riken.jp/event/3068

Astronomers at RIKEN have mapped in detail the filaments in a massive protocluster of galaxies that lie about 12 billion light years away.

INTERGALACTIC MEDIUM

Massive filaments fuel the growth of galaxies

Gas filaments that spanned millions of light years and spawned galaxies have been spotted for the first time

Gas filaments that connected galaxies in a large protocluster in the early Universe were extensive, extending over more than 3 million light years, RIKEN astronomers have found[1]. This finding provides important insights into how galaxies formed in the early Universe.

Most of the gas in the Universe lies in intergalactic space, where it forms filaments that make up a cosmic web. Cosmologists conjecture that, in the early Universe, galaxies and supermassive black holes formed at the intersection of these filaments, where matter was concentrated. Although this model is well supported by simulations, it has been difficult to demonstrate through observations.

Now, an international team that included Hideki Umehata of the RIKEN Star and Planet Formation Laboratory has found observational confirmation of this model of galaxy formation. They created a very detailed map of the filaments in a massive protocluster of galaxies located about 12 billion light years away—making it a structure that existed when the Universe was only about 1.8 billion years old. The team found that the intersection between the enormous filaments they identified is home to supermassive black holes, which act as active galactic nuclei, and 'starbursting' galaxies that have very active star formation.

"This suggests very strongly that gas falling along the filaments under the force of gravity triggers the formation of starbursting galaxies and supermassive black holes, giving the Universe the structure that we see today," comments Umehata. "Previous observations had shown that there were emissions from blobs of gas extending beyond the galaxies, but now we have been able to clearly show that these filaments are extremely long, going even beyond the edge of the field that we viewed. This adds credence to the idea that these filaments are actually powering the intense activity that we see within the galaxies inside the filaments."

Their observations are based on the detection of ultraviolet light that is produced when neutral hydrogen gas is ionized and returns to its ground state. The radiation was found to be intense—too high to originate from the ultraviolet background radiation of the Universe. Their calculations indicated that the high radiation was likely triggered by star-forming galaxies and forming black holes.

"It's very exciting to clearly see for the first time multiple and extended filaments in the early Universe," says co-author Michele Fumagalli from Durham University in the UK. "We finally have a way to map these structures directly, and to understand in detail their role in regulating the formation of supermassive black holes and galaxies."

Reference

1. Umehata, H., Fumagalli, M., Smail, I., Matsuda, Y., Swinbank, A. M., Cantalupo, S., Sykes, C., Ivison, R. J., Steidel, C. C., Shapley, A. E. *et al.* Gas filaments of the cosmic web located around active galaxies in a protocluster. *Science* **366,** 97–100 (2019).

NUCLEAR PHYSICS

New magic number confirmed

Measurements on calcium nuclei show that 34 should join the ranks of magic numbers, which confer greater stability to nuclei

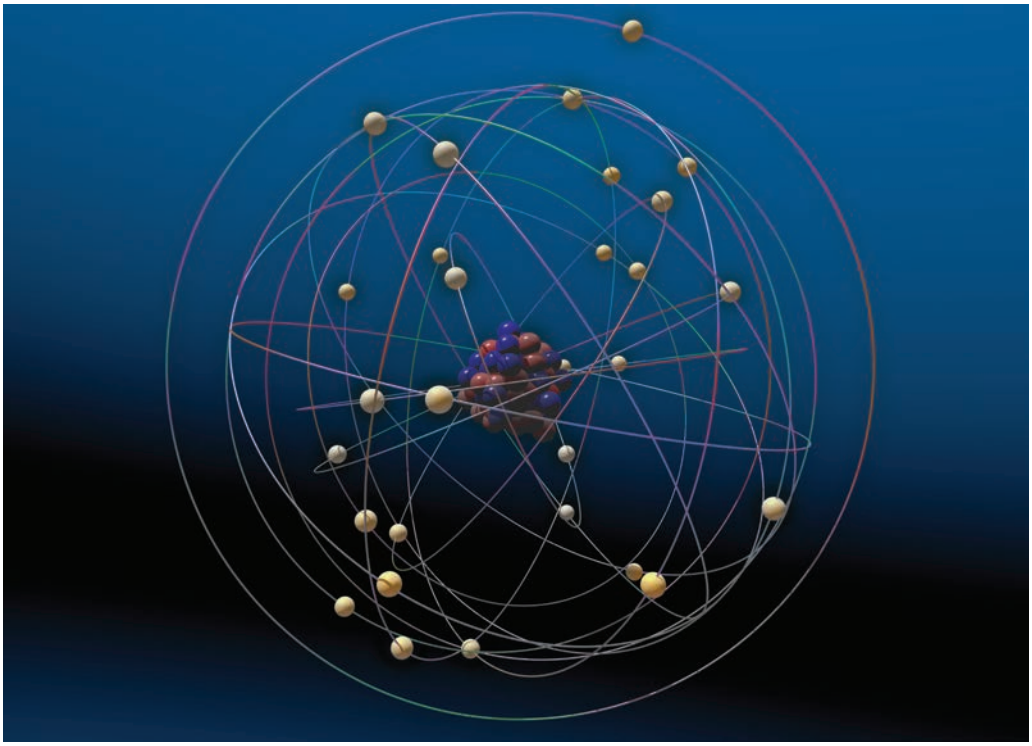
Nuclear physicists at RIKEN have shown that 34 is a 'magic number' for neutrons, meaning that atomic nuclei with 34 neutrons are more stable than would normally be expected[1]. This confirms the suggestions of earlier experiments and provides physicists with greater insight into the structure of the nucleus.

Protons and neutrons are organized in shells within a nucleus. A nucleus that has a full shell—in other words, one that has a magic number of protons or neutrons—is particularly stable. This high stability is reflected in nuclear properties, which can be probed in experiments using nuclear-beam facilities such as RIKEN's Radioactive Isotope Beam Factory (RIBF).

Recent studies on neutron-rich nuclei have hinted that new numbers should be added to the known magic numbers of 2, 8, 20, 28, 50, 82 and 126. Initial tests at the RIBF in 2013 on calcium-54, an unstable nucleus with 20 protons and 34 neutrons, had suggested that 34 was one such missing magic number.

Now, by painstakingly knocking out neutrons one at a time, a team led by Sidong Chen of the University of Hong Kong has directly measured how many neutrons occupy each shell of calcium-54. They found that calcium-54 exhibits strong shell closure. This finding demonstrates that 34 is a part of the set of magic numbers, though its appearance is restricted to a very limited region of the nuclear chart.

"For the first time, we were able to demonstrate quantitatively that all the neutron shells are completely filled in calcium-54, and that 34 neutrons is indeed a good magic number," says Pieter Doornenbal of the RIKEN Nishina Center for Accelerator-Based Science.



By performing experiments on calcium-54, nuclear physicists at RIKEN have shown that 34 is a magic number for neutrons.

"This finding demonstrates that 34 is a part of the set of magic numbers"

The team accelerated a beam containing calcium-54 to about 60% of the speed of light. They used a specially designed isotope separator to select and identify calcium-54 nuclei and then collided this beam into a target of thick liquid hydrogen, or protons, cooled to 20 kelvin. The researchers could infer the detailed shell structure of the isotope from the cross-sections of the neutrons knocked out as they collided with the protons, allowing them to associate them with different shells.

"Major efforts in the future will focus on delineating this region," says Chen. "Moreover, for more neutron-rich systems, like calcium-60, further magic numbers are predicted. These exotic systems are currently beyond the reach of the RIBF for detailed studies, but we believe that thanks to its increasing capabilities, they will become accessible in the foreseeable future." ●

Reference

1. Chen, S., Lee, J., Doornenbal, P., Obertelli, A., Barbieri, C., Chazono, Y., Navrátil, P., Ogata, K., Otsuka, T., Raimondi, F. *et al.* Quasifree neutron knockout from ^{54}Ca corroborates arising N = 34 neutron magic number. *Physical Review Letters* **123,** 142501 (2019).

NEUROSCIENCE

Tuning neurotransmission

The different regulation of signal strength in neurons across the two sides of a synapse contributes to information processing in the brain

Synaptic strength is regulated differently in response to activity across the two sides of a synapse in mice, RIKEN neuroscientists have found[1]. The finding provides evidence for a neural mechanism that compensates for the plastic changes within a single synapse.

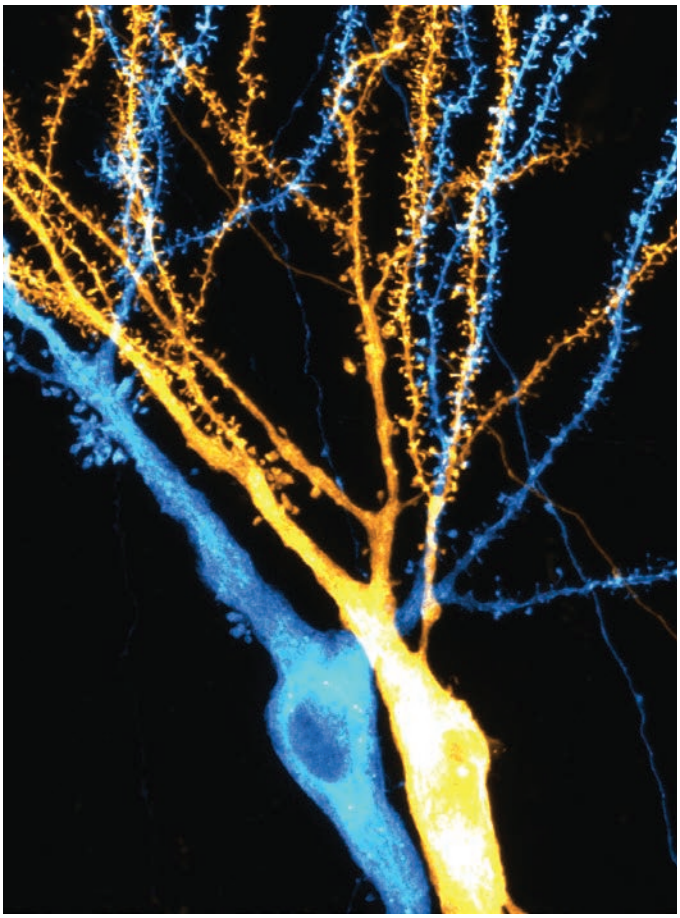
Neurons receive, integrate and transmit information as electrical or chemical signals. Importantly, neurons can alter the strength of their connections, or synapses, in response to the inputs they receive. This synaptic plasticity controls how effectively two neurons communicate with each other and is crucial for memory formation, consolidation and retrieval. However, little is known about how changes in individual synaptic strength are regulated within neurons and across networks.

This mismatch between the regulation of synaptic strength at pre- and postsynaptic sites was unexpected.

Now, by combining electrophysiological recordings with live-cell imaging of pyramidal neurons from the hippocampus of mice, Yukiko Goda at the RIKEN Center for Brain Science, Japan, and Mathieu Letellier at the University of Bordeaux, France, have assessed the strengths of individual synapses and explored how they are modified by neural activity in relation to neighboring synapses.

They found that the efficacy of neurotransmitter release from presynaptic sites, which correlates with presynaptic strength, depends on both the identity of the presynaptic cell and the location of the presynaptic site along the dendrite. A branch of the tree-like extension in the postsynaptic cell, the dendrite receives the input from other cells (see image). By contrast, the postsynaptic strengths of individual synapses, determined from dendritic spine size, depended less on the identity of the presynaptic cell and mainly on local synaptic contacts along the dendritic branch of the postsynaptic cell.

These findings highlight a role for local interactions between postsynaptic compartments along the dendritic branch that could lead to the sharing of plasticity-related molecules and spine clustering or, alternatively, to competition for such molecules and an overall reduction in postsynaptic strengths. The resulting synaptic strength distribution in the dendrite will ultimately determine how each input is integrated in the postsynaptic neuron to produce an output signal.



Dendrites of hippocampal neurons receive and process information from other neurons in the brain.

The researchers also showed that presynaptic cell stimulation, which led to a normalization of presynaptic strengths, whereby synapses with a low initial neurotransmitter release probability showed a large increase in this parameter and vice versa, was accompanied by a decrease in postsynaptic strengths.

This mismatch between the regulation of synaptic strength at pre- and postsynaptic sites was unexpected. "Our findings indicate that the directions of synaptic strength changes between the pre- and postsynaptic sites are not necessarily parallel and may represent a means to preserve network stability without compromising the specificity of incoming information," Goda explains.

The team is now seeking to determine how activity-dependent synaptic strength regulation produces effective signal integration and processing. "We aim to understand the relevance of synaptic strength tuning to hippocampal memory circuits and make this knowledge available for the design of efficient artificial networks," she adds. ●

Reference

1. Letellier, M., Levet, F., Thoumine, O. & Goda, Y. Differential role of pre- and postsynaptic neurons in the activity-dependent control of synaptic strengths across dendrites. *PLoS Biology* **17,** e2006223 (2019).

BIOMEMS

Harnessing the muscle power of worms

By using the muscles of earthworms as a power source, researchers have created a valve that can operate without electricity or fluid pressure

A microchip valve powered by earthworm muscle—the first valve to be powered by living cells—has been developed by RIKEN scientists[1]. It doesn't need an external power source, making it promising for use in biomedical applications.

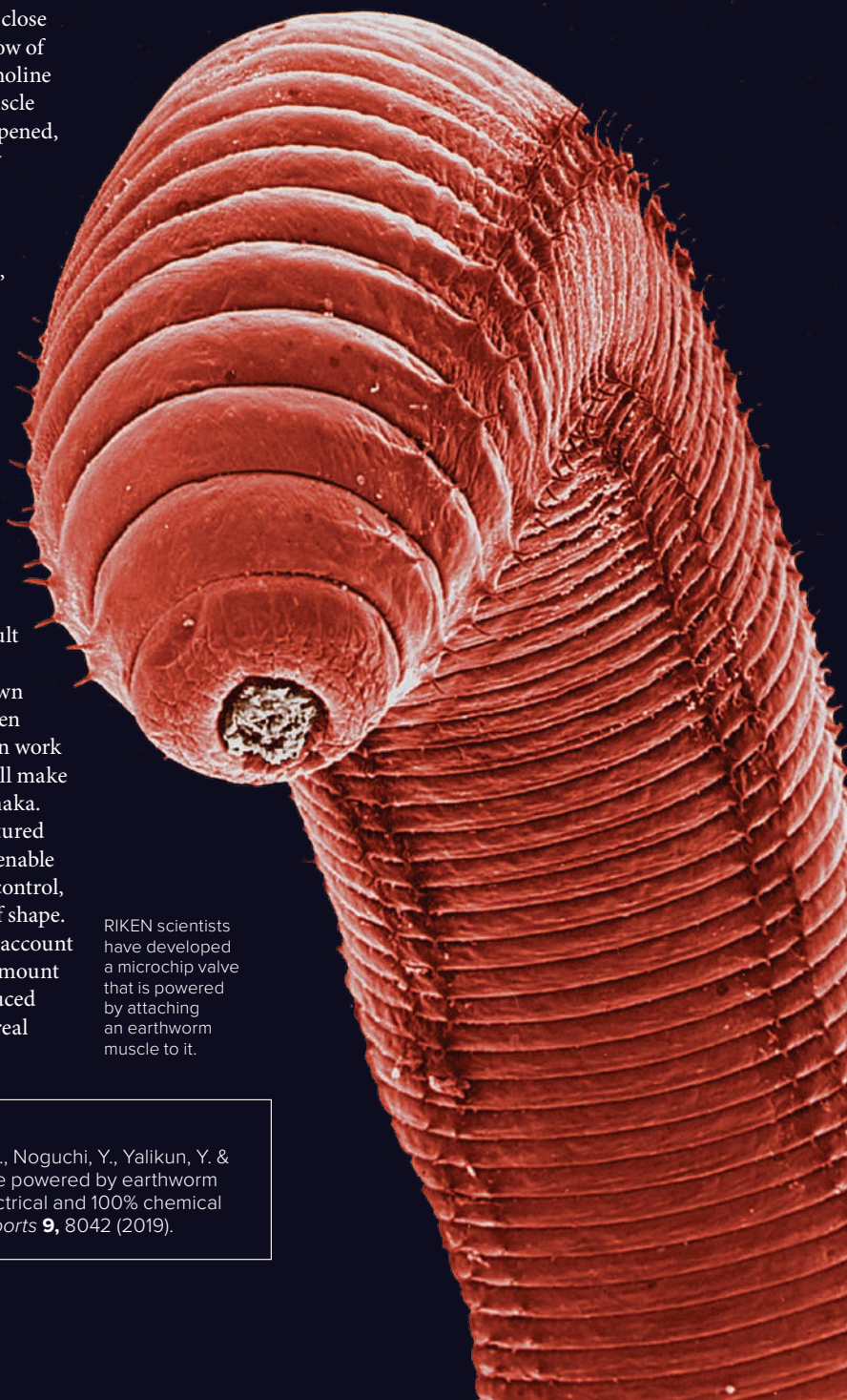
An actuator is a mechanical component that converts energy into motion in response to a signal. A common example is a valve, which can open and close. Actuators are typically powered by electricity or fluid pressure. But using muscles as actuators in a biomedical microelectromechanical system (bioMEMS) would have the advantage that they can be powered chemically—the same way as muscles are powered in living bodies. For muscles, the signal for contraction is the molecule acetylcholine, which is delivered by neurons, while the energy source is adenosine triphosphate (ATP), which is stored in muscle cells.

Now, Yo Tanaka from the RIKEN Center for Biosystems Dynamics Research and his co-workers have produced a bioMEMS valve that uses earthworm muscle tissue to generate a high contractile force that can be sustained for minutes. The team built a microfluidic channel and valve on a microchip that could be controlled by the contraction and relaxation of earthworm muscle stimulated by a very small amount of acetylcholine.

The researchers then used a microscope to monitor fluorescently labeled microparticles in liquid as they flowed through the microchannel. When acetylcholine was applied, the muscle contracted. The resulting force was transduced to a bar that was pushed down to close the valve, stopping the flow of liquid. When the acetylcholine was washed away, the muscle relaxed and the valve reopened, allowing the fluid to flow again.

"Not only can our bioMEMS work without an external power source, but unlike other chemically driven valves that are controlled by acids, our muscle-driven valve runs on molecules that are naturally abundant in living organisms," says Tanaka. "This makes it biofriendly and especially suited for medical applications in which the use of electricity is difficult or not advised."

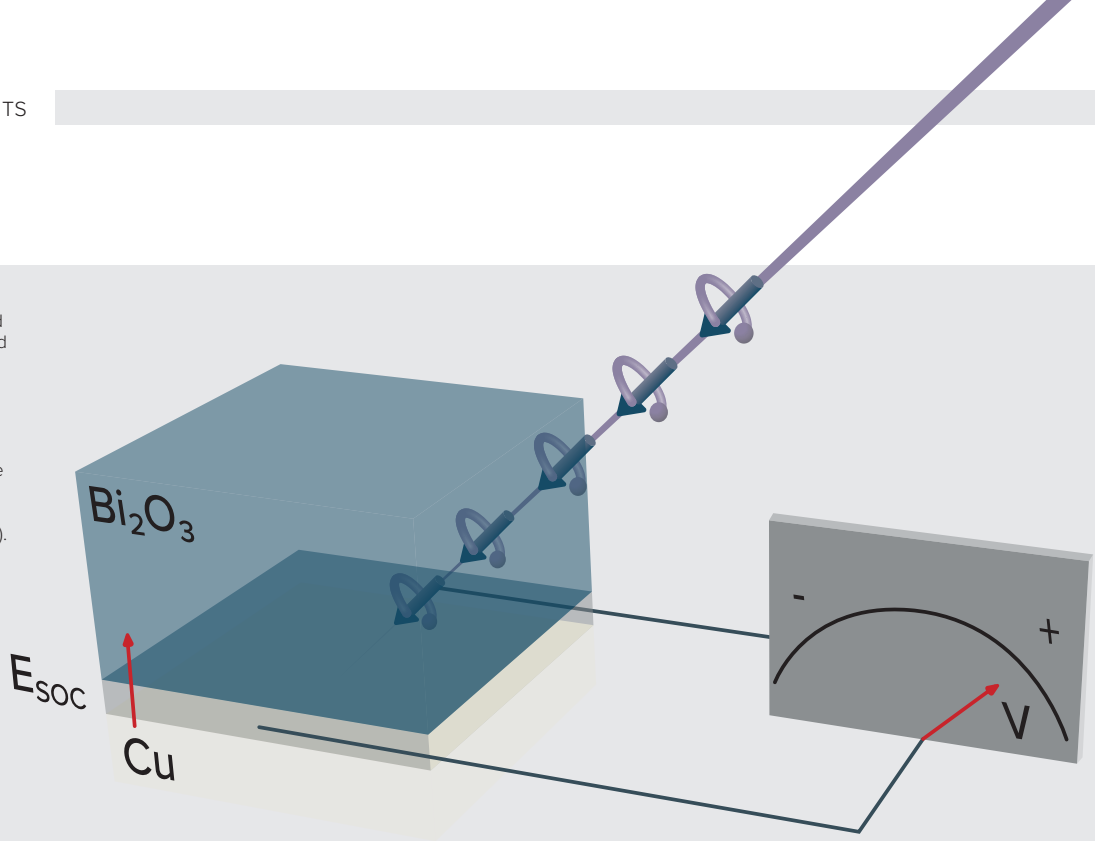
"Now that we have shown that on-chip muscle-driven valves are possible, we can work on improvements that will make it practical," explains Tanaka. "One option is to use cultured muscle cells. This might enable mass production, better control, and flexibility in terms of shape. However, we will have to account for the reduction in the amount of force that can be produced this way compared with real muscle sheets." ●



RIKEN scientists have developed a microchip valve that is powered by attaching an earthworm muscle to it.

Reference

1. Tanaka, Y., Funano, S., Noguchi, Y., Yalikun, Y. & Kamamichi, N. A valve powered by earthworm muscle with both electrical and 100% chemical control. *Scientific Reports* **9,** 8042 (2019).



Electron spin created by circularly polarized light (purple arrows, with pink arrows indicating direction of polarization) is converted to an electric current at the interface between copper (Cu) and bismuth oxide (Bi_2O_3).

SPINTRONICS

Light puts electrons in a spin

The interface between a metal and an oxide creates the right conditions for optically controlling electrons

A combination of two materials that can detect rotating light has been demonstrated by physicists at RIKEN[1]. This approach could help develop information processing devices that have ultralow power consumption.

In addition to their mass and electrical charge, electrons have a property called spin. Spin can be thought of as the electron's rotation on its own axis, and it takes one of two values: clockwise or counter clockwise, which are often more simply referred to as just 'up' and 'down'. And just like a flow of electrons generates an electrical current, a flow of electrons of the same spin creates a spin current, which has been heralded as the future of low-power electronic devices.

One way to create a spin current is to use light. Circularly polarized light, because it also rotates about its axis of propagation (see image), can create spin-polarized electrons when it is absorbed by an appropriate material. But this list of materials is small and limited to those that are intrinsically magnetic.

"We demonstrated the absorption of light with spin information"

Now, Jorge Puebla and Florent Auvray from the Quantum Nano-scale Magnetism Research Team (led by Yoshichika Otani) at the RIKEN Center for Emergent Matter Science and their co-workers have created a non-magnetic material in which they could optically induce a spin current and then convert it to a measurable electrical current.

They took advantage of a phenomenon called the Rashba effect. This effect couples the spin of the electrons to their spatial motion, which can convert spin current to electrical charge current.

"The effect of this 'Rashba field' is that up and down spin-polarized electrons move in opposite directions perpendicular to the direction that the electrons are flowing," explains Puebla. "In this way, an electrical current can be converted into a spin current and vice versa."

Again, the family of materials that intrinsically exhibit the Rashba effect is small because it requires a very specific asymmetric arrangement of atoms. So instead, Puebla's team showed that a very large Rashba effect can be produced at the interface between copper and bismuth oxide.

To experimentally demonstrate this idea, the team shone a spiraling beam of laser light on the interface. They were able to measure a large light-induced voltage across the materials. "We demonstrated the absorption of light with spin information," says Puebla.

This effect cannot be seen in either of the two materials separately. "Our work motivates us to explore whether other interfaces have properties that differ drastically from those of the materials that make up the interface," says Puebla. ●

Reference

1. Puebla, J., Auvray, F., Yamaguchi, N., Xu, M., Bisri, S. Z., Iwasa, Y., Ishii, F. & Otani, Y. Photoinduced Rashba spin-to-charge conversion via an interfacial unoccupied state. *Physical Review Letters* **122,** 256401 (2019).

RADIOTHERAPY

RIKEN click reaction weaponizes antibodies

A simple reaction can arm an antibody with a radioactive element that enables it to destroy cancer cells

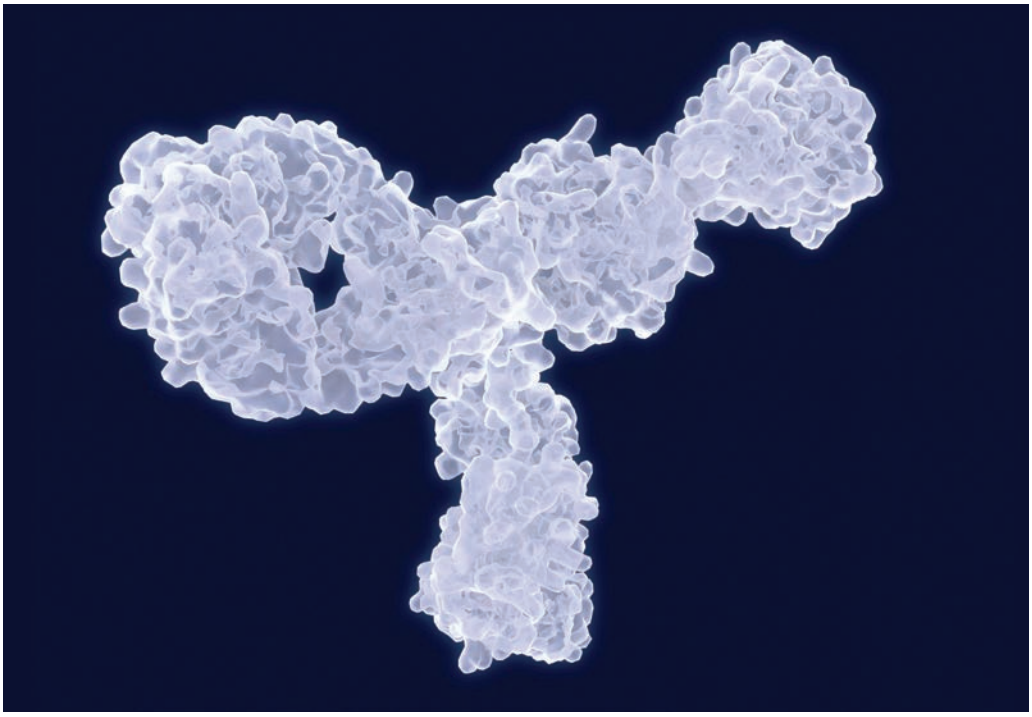
RIKEN chemists have come up with a potent weapon against tumors in mice by adding a radioactive element to an antibody[1].

Tumor-targeting therapy is sometimes referred to as 'missile therapy' by researchers in Japan, says Katsunori Tanaka, who heads the RIKEN Biofunctional Synthetic Chemistry Laboratory (BSCL). That is because two components are needed: a guided missile and a warhead. In the case of radiotherapy, the warhead is a radioactive isotope that kills tumors by subjecting them to high doses of radioactivity.

Most isotopes used in radiotherapy are beta-particle emitters—that is, they give off electrons when they decay. But alpha-particle emitters, which release helium nuclei consisting of two protons and two neutrons, are much preferred since alpha particles are more than 7,000 times more massive than electrons. As a result, they travel far shorter distances before stopping, thereby minimizing collateral damage to healthy cells near a tumor.

But Tanaka notes there are two problems to using alpha-particle emitters in radiotherapy: producing alpha-particle emitters and then chemically attaching them to antibodies. Now, he and his colleagues have overcome both problems.

To make an alpha emitter, Tanaka and Katsumasa Fujiki, also at BSCL, teamed up with physicists at the RIKEN Nishina Center for Accelerator-Based Science to use its world-class cyclotron facility to produce astatine-211.



Chemists at RIKEN have used the RIKEN click reaction to attach the alpha-emitter astatine-211 to antibodies (depicted) to target skin cancer cells.

They then used a reaction they had previously developed, the RIKEN click reaction, to attach astatine-211 to antibodies to target skin cancer cells. The reaction is very attractive, having many advantages over conventional reactions. "Since it is a 'one-pot' reaction you don't have to make each reaction, sequence of the reactions, and isolate each compound and then go to the next step," says Tanaka. "We just take the components we need and mix them together."

Furthermore, the RIKEN click reaction can be performed under mild conditions, which is important since the harsh conditions of conventional reactions can destroy antibodies.

The RIKEN click reaction was crucial for combining astatine-211 to antibodies, Tanaka notes. "The RIKEN click reagents just go to the surface locations of the antibodies—they don't react indiscriminately with all sites on the antibody," he says. "This ensures that the antibody retains its activity."

With help from colleagues at the RIKEN Center for Biosystems Dynamics Research, the researchers demonstrated the effectiveness of their compound by using it to target skin cancer tumors in mice. They showed that it accumulated at tumors and suppressed their growth.

The team intends to investigate other vehicles for conveying astatine-211 to tumors such as glycoclusters. They are also keen to partner with medical researchers to bring the therapy to patients. ●

Reference

1. Fujiki, K., Kanayama, Y., Yano, S., Sato, N., Yokokita, T., Ahmadi, P., Watanabe, Y., Haba, H. & Tanaka, K. ^{211}At-labeled immunoconjugate via a one-pot three-component double click strategy: practical access to α-emission cancer radiotherapeutics. *Chemical Science* **10,** 1936–1944 (2019).

CATALYSIS

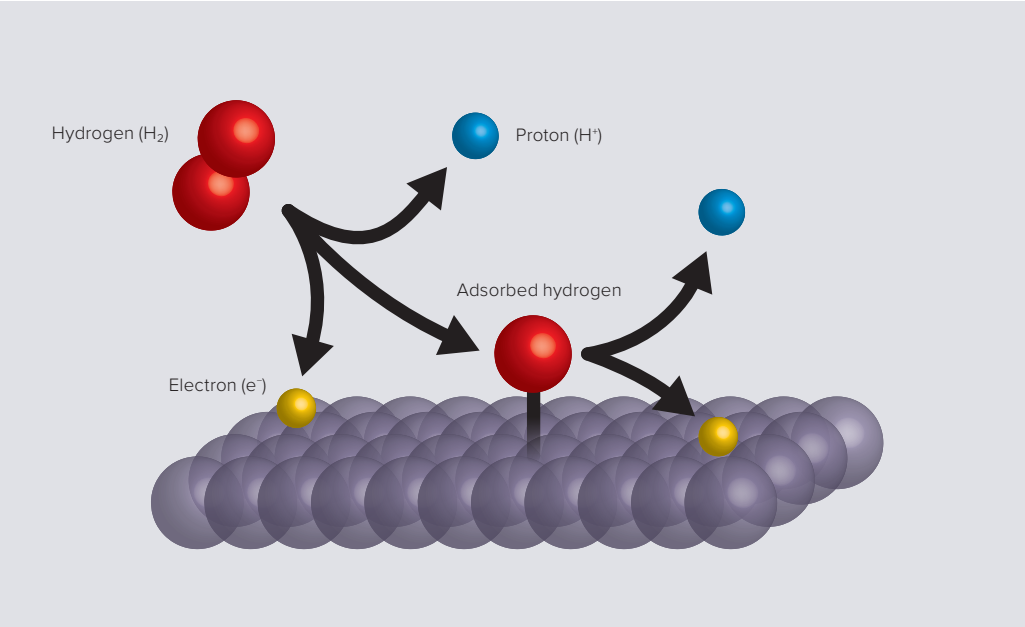
Revisiting catalyst calculations after a century

Improving on a hundred-year-old approach for analyzing heterogeneous chemical reactions could lead to cheaper, more ecofriendly catalysts

In a discovery that could lead to novel catalysts that do not contain expensive rare metals, two RIKEN chemists have shown that traditional catalyst-design strategies based on equilibrium thermodynamics may be inapplicable at high reaction rates and have created a framework for performing more-accurate calculations[1]. This means that the design of catalysts will need to be reconsidered to achieve the highest activities.

Determining the optimal binding energies for heterogeneous chemical reactions—where usually the reactant is in the gas or liquid phase and the catalyst is a solid—is critical for many aspects of modern society, as we rely on such reactions for processes as diverse as the production of fertilizers and plastics. The binding energy between the reactants and the catalyst needs to be optimized to ensure the process is as efficient as possible: if the binding energy is too positive, the reactants will not react with the catalyst, whereas if it is too negative they will remain bound to the catalyst.

In 1911, French chemist Paul Sabatier proposed the existence of an optimum binding energy that maximizes the catalytic activity. Recent advances in computational chemistry have provided a framework that is commonly used today to calculate this optimal binding energy. These calculations are based on equilibrium thermodynamics and assume that a process will proceed smoothly if all of the steps in the process are thermodynamically favorable. Within this framework, the role of the catalyst is to improve the thermodynamics of the most unfavorable step.



Two RIKEN chemists have improved chemical century-old calculations for catalysts and demonstrated it using the hydrogen oxidation reaction in which a hydrogen molecule (two red spheres on the left) is converted into two protons (blue spheres) and two electrons (gold spheres) on a catalyst surface.

> **"We were happy to see that our calculations predict new strategies of catalyst design"**

The catch with this approach is that 'optimum' is usually taken to mean that the driving force required to initiate the reaction is minimized, so that it is thermodynamically efficient. But in the real world, it is often more practical to have a higher rate of catalysis, even if a larger driving force is needed.

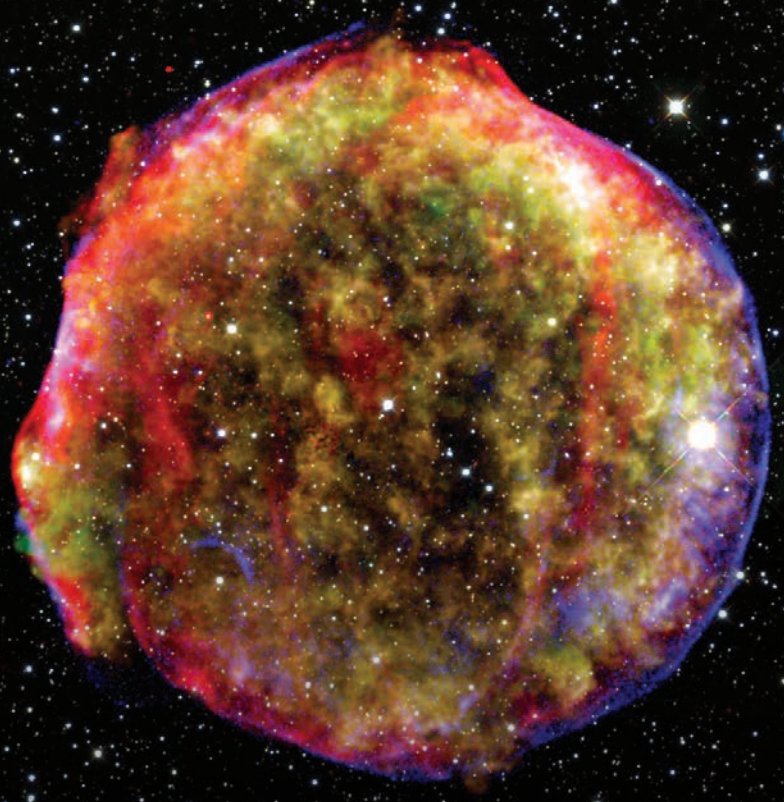
Now, Hideshi Ooka and Ryuhei Nakamura of the RIKEN Center for Sustainable Resource Science have performed a new set of calculations based on reaction kinetic modeling that accounts for this discrepancy.

Their calculations of the hydrogen oxidation reaction using heterogeneous catalysis show how the optimal binding energy can deviate from the traditional understanding at high reaction rates. "We were happy to see that our calculations predict new strategies of catalyst design which could not have been obtained using the traditional, thermodynamic approach," says Ooka.

"We plan to look for new catalysts, using elements such as copper or nickel, that can push heterogeneous catalytic reactions forward. They would be less costly and more environmentally friendly than the current ones, which often require precious metals such as platinum and palladium," adds Nakamura.

Reference

1. Ooka, H. & Nakamura, R. Shift of the optimum binding energy at higher rates of catalysis. *Journal of Physical Chemistry Letters* **10,** 6706–6713 (2019).



Combined x-ray and infrared image (released by NASA in 2009) of the Tycho supernova remnant. The blast's outer shockwave is seen here in blue.

X-ray data: NASA/CXC/SAO; Infrared data: NASA/JPL-Caltech; Optical data: MPIA, Calar Alto, O. Krause et al.

SUPERNOVAE

Blasts from the past

The evolution of an exploding star begins more haphazardly than previously thought

RIKEN astrophysicists have bridged the gap between studies of supernova and those of their remnants by using the output of a supernova model as the input for a model of a supernova remnant[1]. This approach offers a way to assess the validity of supernova models.

Supernovae are the dazzling displays of dying stars and the birthplace of many heavy elements, yet how these explosions originate and evolve is not fully understood. The initial burst of light fades after a few weeks, but an invisible shockwave continues to spread out, driving an ever-expanding shell of gas and dust that emits radiation for thousands of years. X-ray telescopes have picked up several of these supernova remnants, which is allowing astronomers to glean insights into their evolution.

In 1572, a supernova was spotted—one of a handful ever seen with the naked eye—and named Tycho, after the astronomer Tycho Brahe. Almost 450 years later, x-ray emissions from Tycho's remnant are providing astrophysicists a portal to its past (see image).

Previous supernova remnant simulations assumed they explode in a sphere, but these simplified, often one-dimensional models fail to reproduce the clumpy, irregular structure of Tycho's remnant.

Now, Gilles Ferrand at the RIKEN Astrophysical Big Bang Laboratory and his international team have used recent three-dimensional (3D) simulations of a Tycho-like supernova as the starting point for a more realistic remnant simulation.

"We're bridging the gap between the separate groups modeling supernovae and those studying the remnants," says Ferrand. "We want to see if we can use visible remnants as a probe for the explosions themselves."

Ferrand's team modeled the dynamics of the gas as it evolved over the 450 years since the supernova occurred. Because their realistic 3D model of the explosion captured the instability within the original blast, the team was able to closely recreate the random, clumpy structure of Tycho seen today.

"We didn't know how long we would see an imprint of the explosion," says Ferrand, "but now I think some of Tycho's fluffy, irregular appearance was there from the very beginning."

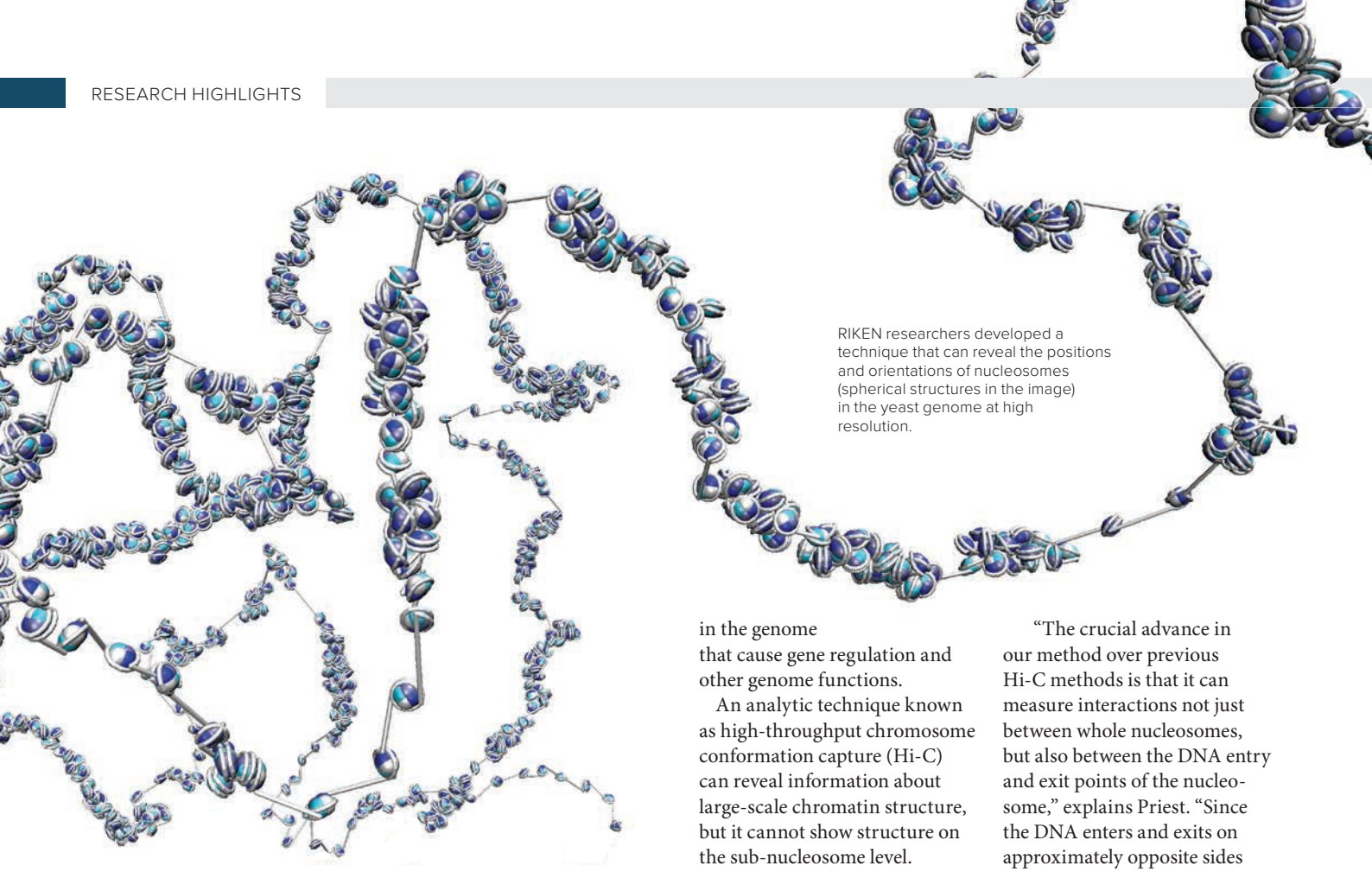
"We want to see if we can use visible remnants as a probe for the explosions themselves."

The team has created 3D models for many different types of supernova that a dying white dwarf star can produce. "We now have a way of testing whether we can tell them apart," says Ferrand. "This will enable astronomers to assess the different ways white dwarfs can meet their end."

Many supernova mysteries still remain to be solved, such as the appearance of heavy elements. "A clump at the edge of Tycho's shell is rich in iron, which is surprising as iron usually forms at the center," says Ferrand. "We want to compute the x-ray emissions from the different elements, so that we can model their distribution within the remnant."

Reference

1. Ferrand, G., Warren, D. C., Ono, M., Nagataki, S., Röpke, F. K. & Seitenzahl, I. R. From supernova to supernova remnant: The three-dimensional imprint of a thermonuclear explosion. *The Astrophysical Journal* **877,** 136 (2019).



RIKEN researchers developed a technique that can reveal the positions and orientations of nucleosomes (spherical structures in the image) in the yeast genome at high resolution.

CHROMATIN STRUCTURE

Analyzing genome structure at ultrahigh resolution

The ability to explore the genome on a sub-nucleosome level promises to lead to new discoveries about how chromatin structure is linked to epigenetics

A powerful method that can pinpoint the positions and orientations of individual nucleosomes—one of the building blocks of chromatin, which contains the genetic material of a cell—has been demonstrated on yeast by a RIKEN team[1]. It will help researchers to explore the relationship between chromatin structure and function.

While the molecular structure of DNA has been known for over 60 years, more recent research has shown how DNA is packaged into cell nuclei as thread-like chromatin interspersed with nucleosome 'beads'. But despite recent advances, there is still a blind spot in our understanding of genome structure, namely the details of how nucleosomes are folded. Such knowledge is important because nucleosome positioning and orientation can couple with molecular reactions in the genome that cause gene regulation and other genome functions.

An analytic technique known as high-throughput chromosome conformation capture (Hi-C) can reveal information about large-scale chromatin structure, but it cannot show structure on the sub-nucleosome level.

"The three-dimensional nucleosome folding structure across the genome was still unknown," comments Yuichi Taniguchi of the RIKEN Center for Biosystems Dynamics Research (BDR). "If we can achieve a nucleosome-level resolution, I anticipate we will see a very strong connection between genome structure and function. I think it's the next frontier in genetics."

The low resolution of Hi-C means it cannot reveal the orientations of nucleosomes—an important aspect of chromatin structure. "Just like you can't play dominoes without specifying the orientation of each domino tile, you can't know chromatin structure without knowing the nucleosome orientations," says David Priest, who was a postdoctoral researcher at BDR at the time of the study.

Now, by combining Hi-C with molecular dynamics simulations, Taniguchi and colleagues have been able to reveal the positions and orientations of nucleosomes in the yeast genome at high resolution (see image).

"The crucial advance in our method over previous Hi-C methods is that it can measure interactions not just between whole nucleosomes, but also between the DNA entry and exit points of the nucleosome," explains Priest. "Since the DNA enters and exits on approximately opposite sides of the nucleosome, this sub-nucleosome interaction data will allow us to map nucleosome orientations."

Using their technique, the researchers discovered that the nucleosomes in yeast exhibit two folding motifs: four adjacent nucleosomes can form a pyramid-like structure or a flat rhombus. This finding could explain two competing models of chromatin structure proposed in earlier studies.

The team intends to apply the technique to more complex situations. "Our next challenge is to apply the technique to the human genome and expand our findings to more general cases," says Masae Ohno, the first author of the study.

Reference

1. Ohno, M., Ando, T., Priest, D. G., Kumar, V., Yoshida, Y. & Taniguchi, Y. Sub-nucleosomal genome structure reveals distinct nucleosome folding motifs. *Cell* **176,** 520–534 (2019).

STRUCTURAL BIOLOGY

Structural study reveals secret of stressed cells

A study of molecular structure reveals how a small chemical change can make a big difference to function in a cell's response to stress

Structural biologists at RIKEN have discovered how a small modification to a key molecule can shut down a cell's protein-producing machinery when the cell is stressed[1]. This finding could help to find new treatments for neurodegenerative diseases and traumatic brain injury.

Before a stressful event such as giving an important speech, many people experience loss of appetite as the body redirects resources from digestion to 'fight or flight' responses. A similar thing happens on a cellular level—cells will stop producing proteins when subject to a wide range of stresses, including starvation or viral infection.

"I was totally shocked by the difference. I couldn't believe it."

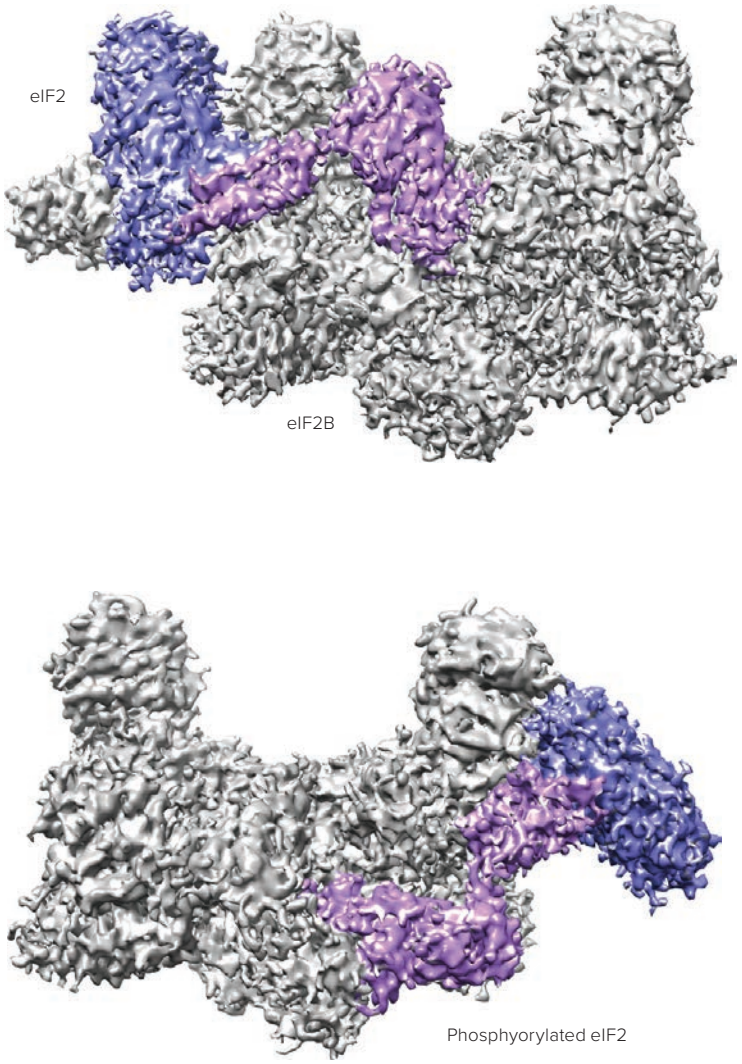
The key event in this stress response is the addition of a phosphate group (PO_4^{3-}) to a protein called eukaryotic translation initiation factor 2 (eIF2). As its name suggests, this protein plays a key role in initiating the translation of messenger RNA into proteins in the cells of eukaryotes. However, the addition of a phosphate group stops it from performing this role, putting the brakes on protein production so that the cell can concentrate its resources on processes more necessary for survival. But it wasn't clear how adding such a small group could have such a big effect on eIF2's function.

Now, Takuhiro Ito and Kazuhiro Kashiwagi of the RIKEN Center for Biosystems Dynamics Research and their co-workers have used x-ray diffraction and cryo-electron microscopy to determine the molecular structure of eIF2 when it is bound to eIF2B, which activates eIF2. They found that eIF2 binds to eIF2B in a completely different way when it is phosphorylated compared to its unphosphorylated form (see image).

"This difference in binding was really surprising for me," recalls Ito. "When Kashiwagi showed me the density maps for the first time, I was totally shocked by the difference. I couldn't believe it."

This finding was the culmination of about 15 years of work for Ito as he started investigating the structure of eIF2 when he was a postdoc in 2004. "It's an interesting and nice result at the end of a long investigation," he comments. It was also a race against time as other groups were studying the same system. Another study covering a different aspect of the eIF2–eIF2B system was published in the same issue of *Science* as Ito's paper.

The team intends to determine the structure of another initiation factor associated with the system. They are also interested in finding out more about the mechanism of eIF2 and eIF2B in the stress response of cells. ●



Unphosphorylated (top) and phosphorylated (bottom) forms of eIF2 (pink and purple complex) bind in completely different ways to eIF2B, explaining why eIF2 is inactivated by phosphorylation in a cell's response to stress.

Reference

1. Kashiwagi, K., Yokoyama, T., Nishimoto, M., Takahashi, M., Sakamoto, A., Yonemochi, M., Shirouzu, M. & Ito, T. Structural basis for eIF2B inhibition in integrated stress response. *Science* **364,** 495–499 (2019).

PLURIPOTENT STEM CELLS

Turning stem cells into blastocyst-like structures

Mice stem cells have been used to produce structures closely resembling blastocysts

In an achievement that holds promise for fertility and regenerative medicine research, structures like the first stage of an embryo have been generated from mice stem cells by RIKEN researchers[1].

After fertilization, an egg divides into two cells that can become any cell type. After many more cell divisions, the embryo becomes a ball of cells called a blastocyst and implants in the womb, where it differentiates and grows into a fetus. A blastocyst consists of pluripotent cells—cells that can become any type of cell in the body, but not the placenta—and cells that form the placenta.

Previously, a team that included Cody Kime of the RIKEN Center for Biosystems Dynamics Research noticed structures resembling blastocysts when they converted pluripotent mouse cells from an implanted-like state to a pre-implanted state. "Our reprogramming experiments suggested we had found a way to increase cell potency beyond pluripotency, which was unlikely and had not been seen before," Kime explains. "We decided to find out if it was real."

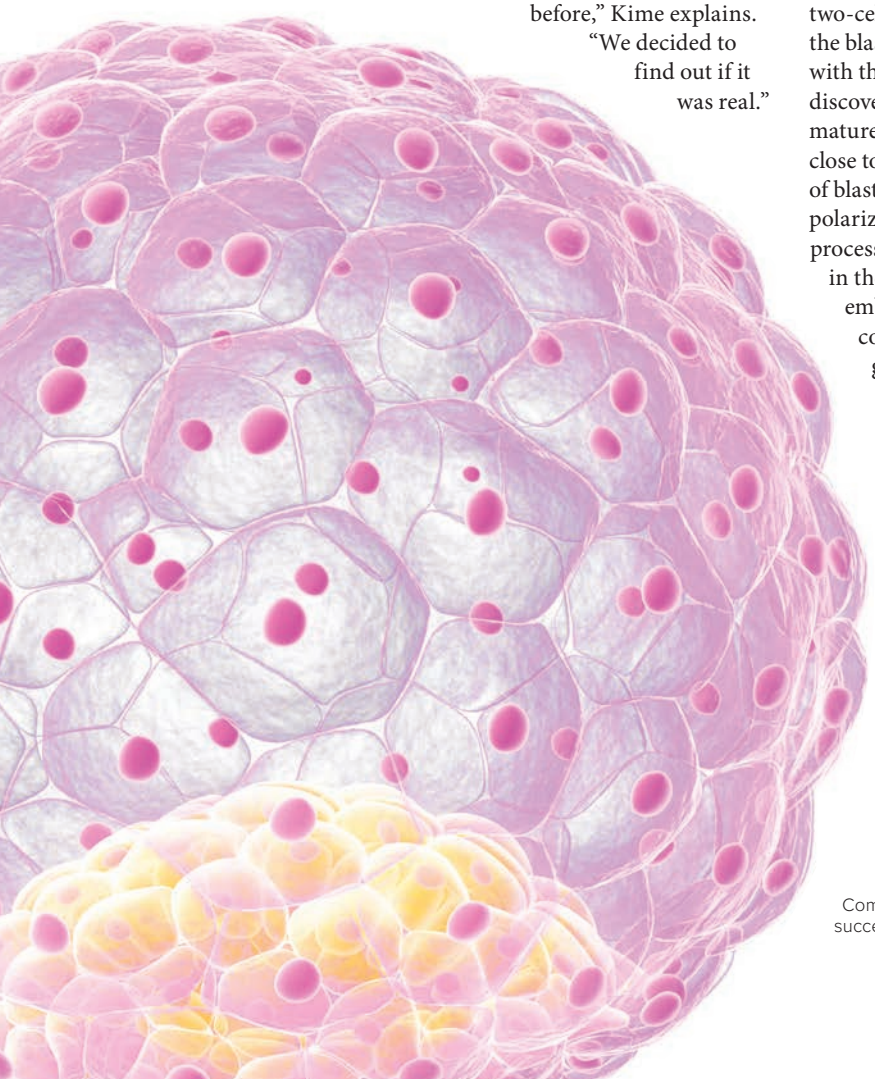
Now, the team has refined their reprogramming technique to produce embryo-like structures that are closer to real embryos. "Perhaps our most important finding was that natural molecules found in the early mouse embryo can reprogram cultured cells to become surprisingly similar in function to early embryos," says Kime.

The researchers examined small clusters of cells a few days before they matured into the blastocyst-like structures and found that the cells contained gene expression for totipotency, which is found in two-cell embryos. Comparing the blastocyst-like structures with their precursors, they discovered that cells in the matured structures were bound close together—a hallmark of blastocyst formation and polarization that is the result of a process called compaction. Cells in the precursors resembled embryos at a stage before compaction, which was good evidence that the precursor clusters might include totipotent cells.

When transplanted to the womb of a pseudo-pregnant mouse, the blastocyst-like structures frequently induced changes to the uterus needed for blastocyst implantation. The implanted structures often grew and produced many types of cells that resembled those naturally found in early developing embryos. The embryos were eventually resorbed, and the surrounding tissue showed signs similar to cases of natural resorption.

"Natural molecules found in the early mouse embryo can reprogram cultured cells to become surprisingly similar in function to early embryos"

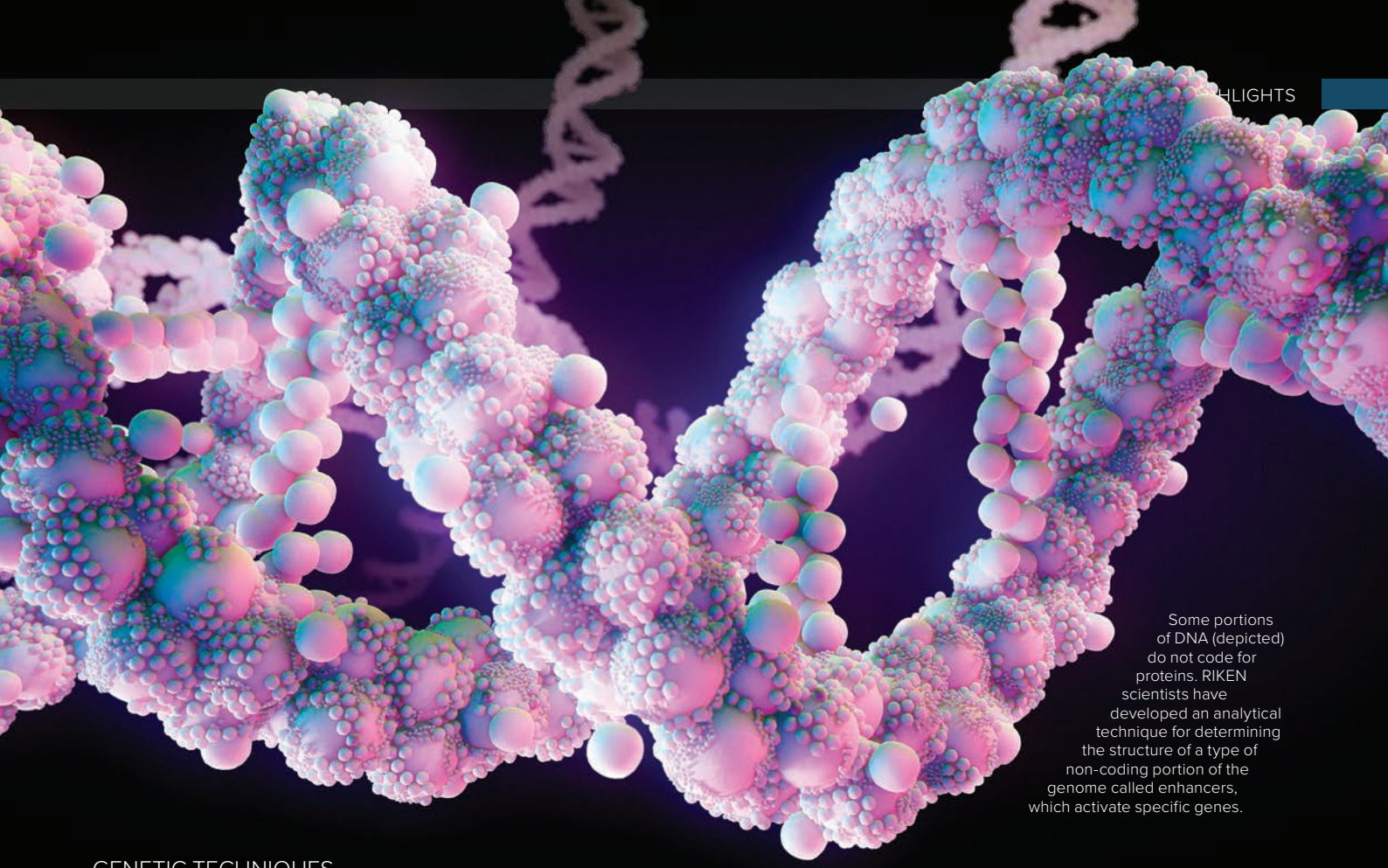
"Totipotency is the highest order of cell potency: one totipotent cell can form the placenta and the body," says Kime. "If our system can be improved to fully reach that state, we will be able to improve basic research in the fields of embryogenesis and fertility, as well as basic and clinical research in regenerative medicine." ●



Computer artwork of a 100-cell blastocyst embryo. RIKEN researchers have succeeded in converting mice stem cells into blastocyst-like structures.

Reference

1. Kime, C., Kiyonari, H., Ohtsuka, S., Kohbayashi, E., Asahi, M., Yamanaka, S., Takahashi, M. & Tomoda, K. Induced 2C expression and implantation-competent blastocyst-like cysts from primed pluripotent stem cells. *Stem Cell Reports* **13,** 485–498 (2019).



Some portions of DNA (depicted) do not code for proteins. RIKEN scientists have developed an analytical technique for determining the structure of a type of non-coding portion of the genome called enhancers, which activate specific genes.

GENETIC TECHNIQUES

Enhancing enhancers

By improving a technique for analyzing non-coding regions of the genome, researchers shed new light on them

A new technique for elucidating the structure of a type of non-coding portion of the genome called enhancers, which activate specific genes, has been developed by RIKEN scientists[1]. The technique will be useful for shedding light on a previously overlooked part of the genome.

Non-coding parts of the genome used to be dubbed junk DNA because they were not considered to play any useful role. But they are now known to be associated with various diseases, and understanding their function has become an important goal in genomic research.

Two types of genomic regions, known as promoters and enhancers, coordinate the activation of protein-coding genes, essentially by switching them on. Promoters are located next to the genes they activate, whereas enhancers are far away, but still manage to act on the genes. Although various techniques have been developed to map enhancers, they all have limitations. For example, some lack identification sensitivity, others cannot pinpoint the location of the regions, while still others are ill-suited for use on frozen cells.

To overcome these limitations, a team led by Yasuhiro Murakawa and Hideya Kawaji of the RIKEN Center for Integrative Medical Sciences has developed a method called NET-CAGE, which is an extension of the CAGE technology developed at RIKEN to identify non-coding regions of the genome with high sensitivity. They used it to examine five commonly used cancer cell lines and were happy to find that the method can be used on cryopreserved cells.

"Our new method can be used to study many aspects of biology," says Murakawa. "In the long term, it can be implemented in next-generation genomic medicine."

The researchers used NET-CAGE to make a series of interesting discoveries about enhancers. They identified as many as 20,000 new enhancers in humans. The team found that while promoters are activated in a variety of cell types, enhancers tend to function in just one cell type, thus showing an important difference between the two types of region.

The team also uncovered an intriguing link between promoters and enhancers, finding that they are linked topologically according to their cell type specificities. In addition, they pinpointed the exact location of active enhancers at high nucleotide resolution within cluster regions known as super enhancers.

"Using this technology, we are making a comprehensive map of enhancer activation in the human body," says Murakawa. "By integrating the knowledge with data on mutations associated with disease and cancer genomics data, we hope to increase our understanding of the mechanisms of diseases."

The group is currently collaborating with a genomics technology company to commercialize a NET-CAGE kit. ●

Reference

1. Hirabayashi, S., Bhagat, S., Matsuki, Y., Takegami, Y., Uehata, T., Kanemaru, A., Itoh, M., Shirakawa, K., Takaori-Kondo, A., Takeuchi, O. *et al.* NET-CAGE characterizes the dynamics and topology of human transcribed *cis*-regulatory elements. *Nature Genetics* **51,** 1369–1379 (2019).

TISSUE CULTURE

Brain tissue kept alive for weeks

Tissue taken from animals can be kept alive longer in the lab thanks to a new microfluidic device

A technique developed by an all-RIKEN team that keeps brain tissue alive in the laboratory for about 50 times longer than the conventional method and will facilitate longer-term studies[1].

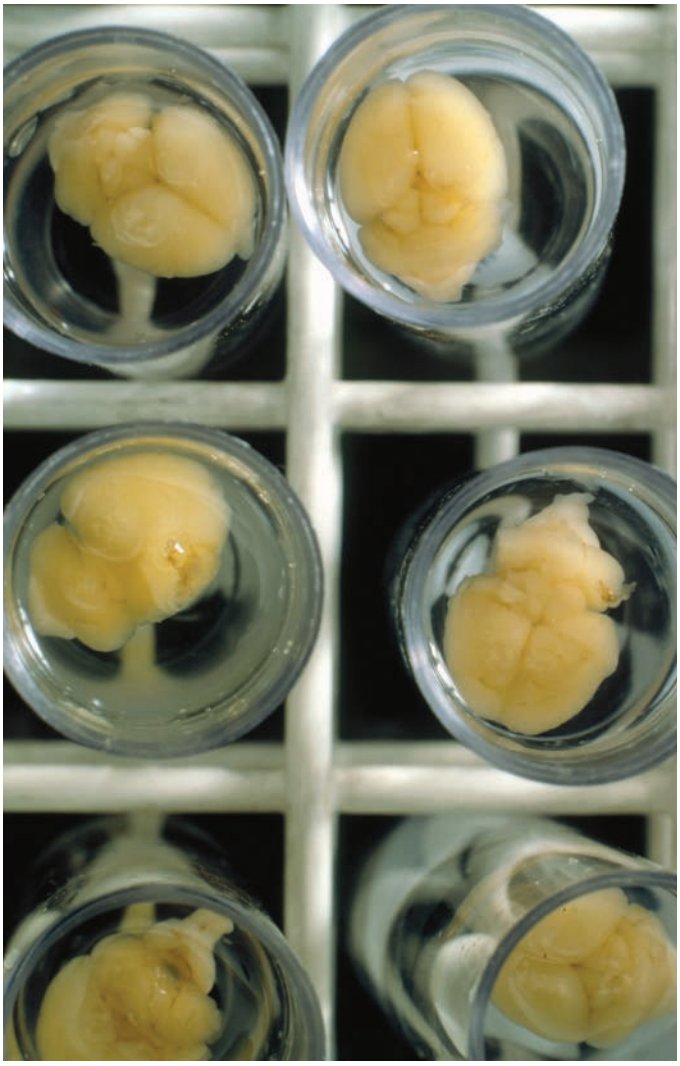
Experimenting on tissues in culture can facilitate drug discovery because researchers can systematically manipulate the tissue and test different drugs or drug combinations. However, when studying a whole system in which many cells interact with each other, it has been difficult to keep the tissue 'alive' for more than a few days. Tissue dries out quickly and dies unless it is placed in a culture medium containing appropriate nutrients. On the other hand, immersing complex tissue in fluid can damage it because the normal transfer of gases cannot occur.

Now, Nobutoshi Ota and colleagues at the RIKEN Center for Biosystems Dynamics Research have developed a microfluidic device made from polydimethylsiloxane (PDMS), a material often used as a defoamer in over-the-counter drugs. The device had a semi-permeable channel surrounded by an artificial membrane and solid PDMS walls. The tissue was not constantly immersed in fluid; rather the culture medium circulated within the microchannel and passed through the semi-permeable membrane, which allowed proper gas exchange.

The system will be useful for observing biological development and testing how tissues respond to drugs.

It was challenging to find the optimal settings. "Controlling the medium flow was difficult because the microchannel that formed between the PDMS walls and the porous membrane was unusual," Ota notes. "However, we had success after trial-and-error modifications to the porous membrane and adjustments of the inlet/outlet flow rates."

The team tested the device using tissue from the mouse suprachiasmatic nucleus—a complex part of the brain that governs circadian rhythms. The mice were knock-in mice in which circadian rhythm activity in the brain was linked to the production of a highly fluorescent protein. By measuring the level of bioluminescence from the brain tissue, the researchers were able to see that tissue kept alive by their system stayed active and functional for over 25 days with nice circadian activity. In contrast, neural activity in tissue kept in a conventional culture decreased by 6% after only 10 hours.



An all-RIKEN team has developed a microfluidic system that can keep mouse brains (yellow tissue in image) viable in culture for almost a month.

In the short term, the system will be useful for observing biological development and testing how tissues respond to drugs. The long-term benefits are also clear. "This method will also improve research into organogenesis through long-term culturing and observation, which is necessary for growing tissue and organs," says Ota.

The team is planning to use their system to observe the formation of blood vessels and cell movement during organoid formation. ●

Reference

1. Ota, N., Kanda, G. N., Moriguchi, H., Aishan, Y., Shen, Y., Yamada, R. G., Ueda, H. R. & Tanaka, Y. A microfluidic platform based on robust gas and liquid exchange for long-term culturing of explanted tissues. *Analytical Science* **35,** 1141–1147 (2019).

EPIGENETICS

Catching chromosomes changing their shape

Movements of chromosomal domains between compartments have been captured during differentiation of mouse embryonic stem cells

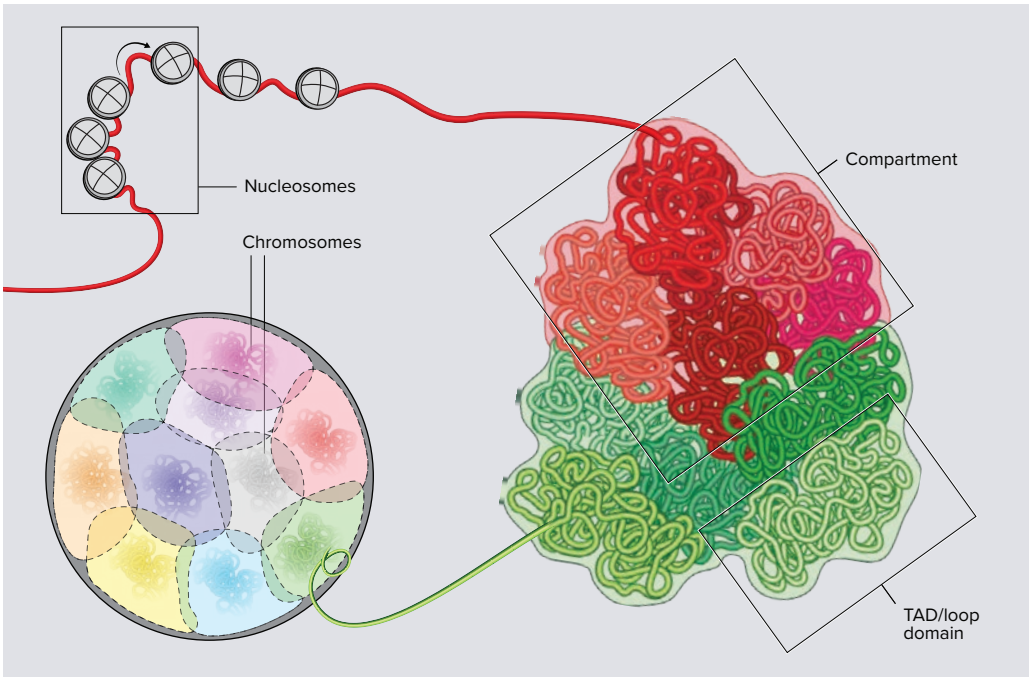
RIKEN geneticists have observed how chromosomes change their shape during cell differentiation in detail using genomics-based approaches[1]. The finding provides insights into changes in chromosome organization on the scale of millions of base pairs—base pairs being the building blocks of the DNA double helix.

The human genome consists of 46 chromosomes, which are each about 100–200 million base pairs long. Each chromosome contains nucleosomes—146-base-pair-long DNA strands wrapped around eight histone protein molecules.

Recently, novel structural units called topologically associating domains (TADs) have been discovered on mammalian chromosomes, which are about one million base pairs in size. Multiple TADs assemble to form subnuclear compartments: TADs with many active genes form A compartments, whereas TADs with few or no active genes form B compartments. The positions of boundaries between A and B compartments are known to change during differentiation, but such changes had not been observed directly as they occurred.

Now, Ichiro Hiratani of the RIKEN Center for Biosystems Dynamics Research and co-workers have observed changes between A and B compartments during the differentiation of mouse embryonic stem cells.

The researchers discovered many genomic regions that switched compartments, from A to B or vice versa, which correlated well with genomic regions that switched their replication timing (the temporal order of genomic DNA replication) from early to late or vice versa, respectively. A to B compartment changes were accompanied by movement from the nuclear interior to the periphery and gene repression, whereas B to A compartment changes were accompanied by movement from the nuclear periphery to the interior and gene activation. These results strongly suggest that A/B compartment changes represent physical movements of portions of chromosomes within the three-dimensional nuclear space, accompanied by changes in gene expression and replication timing.



Geneticists at RIKEN have observed how structures known as compartments, which are made up of multiple topologically associating domains (TADs), change during the differentiation of mouse embryonic stem cells.

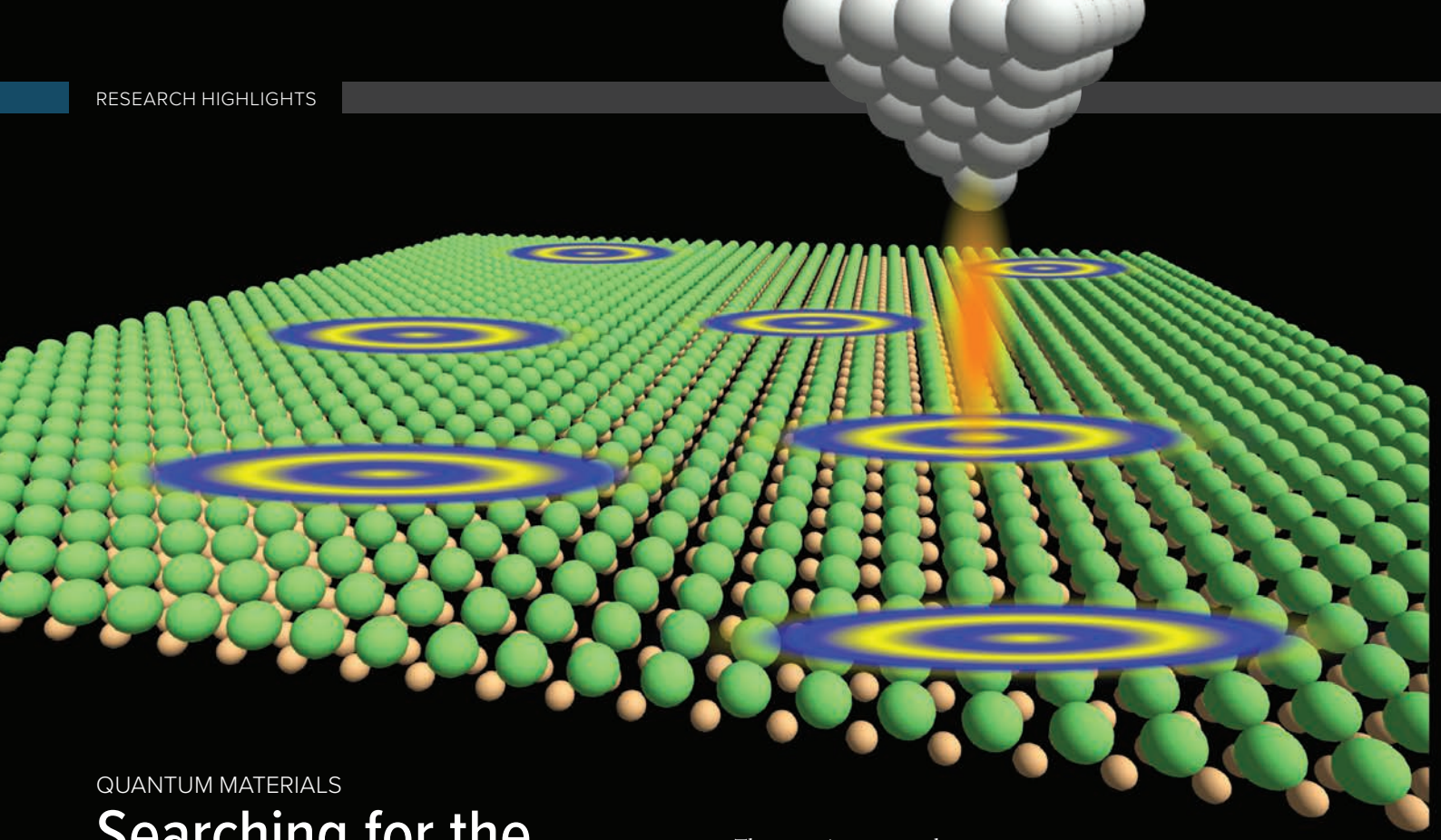
The team found that genomic regions that switched from B to A compartments did so one to two days before gene activation and replication timing varied from late to early. This raises the intriguing possibility that compartment changes might be a prerequisite for gene activation and replication timing changes.

The findings suggest that A/B compartments change primarily by the relocation of single TADs facing the A/B compartment interface to the opposite compartment. "It's possible that the accumulation of these compartment switching events may reflect or represent changes in differentiation states such as from embryonic stem cells to epiblast-derived stem cells," says Hiratani.

"Our study is the first to clearly demonstrate that changes in chromosome conformation precede changes in DNA-based transactions, such as gene expression and DNA replication timing," adds Hiratani. ●

Reference

1. Miura, H., Takahashi, S., Poonperm, R., Tanigawa, A., Takebayashi, S. & Hiratani, I. Single-cell DNA replication profiling identifies spatiotemporal developmental dynamics of chromosome organization. *Nature Genetics* **51,** 1356–1368 (2019).



QUANTUM MATERIALS

Searching for the Majorana quasiparticle

A potential host of the Majorana quasiparticle—a component of quantum computers of the future—has been observed

Conditions appropriate for generating a particle-like entity useful for quantum computing have been induced by RIKEN physicists[1]. They have detected a zero-energy state in a superconducting material, bringing researchers closer to realizing controllable Majorana quasiparticles—particle-like entities that are their own antiparticles[1].

The Majorana quasiparticle has recently been observed experimentally in various materials. The challenge now is to create easily controllable Majorana quasiparticles that can be used in quantum computing.

The quasiparticle is thought to exist in vortices that form on superconducting materials since several telltale signs hinting at the presence of Majorana quasiparticles in bound states have been seen.

Now, Tadashi Machida of the RIKEN Center for Emergent Matter Science and co-workers have found strong evidence that the zero-energy states in the vortex cores of the iron-based topological superconductor Fe(Se,Te) may host Majorana quasiparticles.

"We believe that our finding is a first step towards moving quantum computing from vision to reality"

They used the tip of a scanning tunneling microscope to reveal the zero-energy states on the surface of vortices in Fe(Se,Te). These vortices emerged on applying a magnetic field.

"The material possesses features of a trivial superconductor in the bulk but has the features of a topological insulator at the surface," says Machida. "As a result, topological superconductivity, and hence Majorana quasiparticles in the vortex cores, may be induced at the surface without the need for any fabrication processes."

The imaging of the zero-energy state requires spectroscopic imaging with an ultrahigh energy resolution. Specifically, the energy resolution of the imaging must be lower than the lowest energy of the trivial bound states, which are also found in the vortex core of topological superconductors.

By using a spectroscopy technique employing a scanning tunneling microscope at ultralow temperatures, Machida and his colleagues achieved a high enough energy resolution to detect the zero-energy state in the presence of bound states (see image).

Only a fraction of vortices in Fe(Se,Te) host the zero-energy state, and this fraction increases with a decreasing magnetic field.

The detection of electronic states at a vortex core of a topological superconductor using the tip of a scanning tunneling microscope.

This observation is a vital clue for the control of Majorana quasiparticles—namely that it is important to keep the magnetic field low.

"In Majorana-based quantum computing, it is envisaged that pairs of Majorana quasiparticles function as fundamental quantum bits and the computation can be executed by the exchange of their locations," says Machida. "Realizing this process is the next challenge."

"Although there is a long way to go, we believe that our finding is a first step towards moving quantum computing from vision to reality," he adds. ●

Reference

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CELL POLARITY

A polarizing influence in cells

A method for inducing polarization in cells will allow scientists to explore the real-time processes that occur during cell polarization

RIKEN researchers have found an intrinsic way to induce cell polarity—the asymmetry observed in the shape, structure, or organization of cells—in fruit fly cells[1]. This method provides a useful means for studying the dynamics of cell polarization on a micrometer scale.

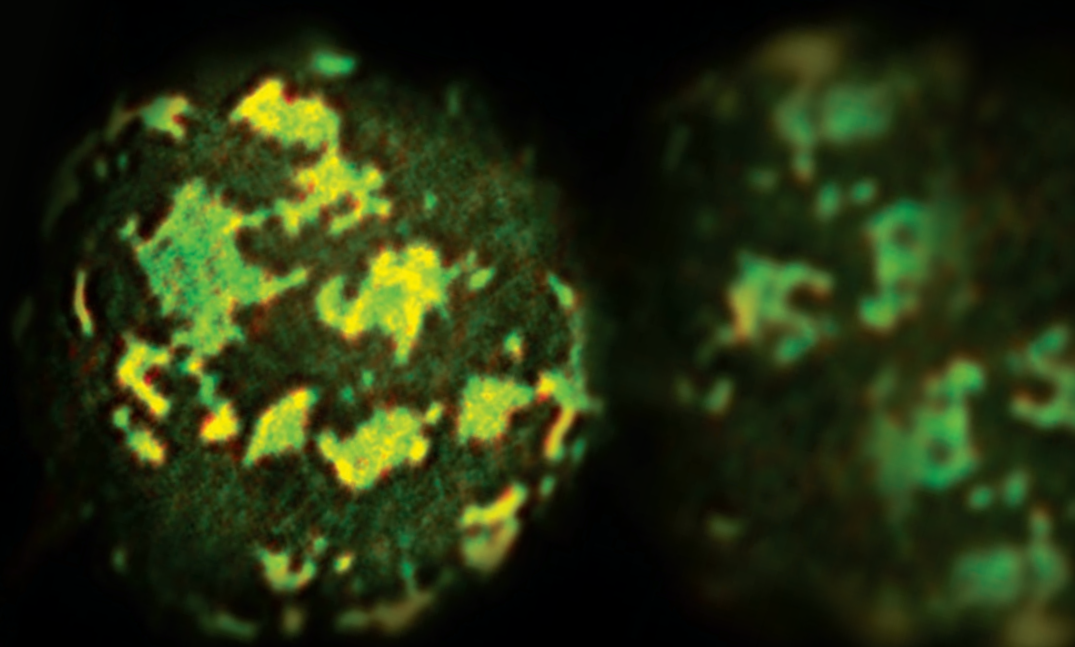
Animals consist of many different types of cells, all of which originate from a single cell—the fertilized egg. To generate this huge diversity in cells, the egg and its descendants must divide unevenly to produce new cells with different fates. Thus, asymmetric cell division, which generates two different daughter cells, is a critical step in cell development. Cell polarity plays a crucial role in asymmetric division.

Much work has been done on discovering the factors that drive cell polarity. In particular, the Par family of proteins has been found to play a crucial role in establishing polarity.

"As our understanding of cell polarity advanced, we noticed that the Par complex operates in a context-specific way," says Fumio Matsuzaki of the RIKEN Center for Biosystems Dynamics Research. "This has made it difficult to study the general features of the cell polarization process."

To gain a better picture of polarization dynamics, the team focused on generating Par-dependent polarity using non-polar cells.

The idea behind this approach had been simmering in Matsuzaki's mind for more than a decade, but work did not begin in earnest until graduate student Kalyn Kono took on this challenging project four years ago. By investigating changes in the expression level of each of the major components of the Par complex, the team hit on their method for inducing polarity through overexpressing Par3—one of the three core proteins of the Par family—in non-polar fruit fly cells called Schneider 2 cells, or S2 cells.



A super-resolution micrograph of artificially polarized Schneider 2 cells, or S2 cells.

Using their reconstruction system, the researchers observed clusters, or what they call Par-complex islands, that are composed of a meshwork containing unit-like segments, which dynamically associated and dissociated with each other. As these island structures resemble patch-like features known to exist in the neural stem cells of fruit flies, their method appears to closely model the autonomous process of polarization.

"Our success in polarizing S2 cells implies that, in principle, any cell can be polarized if a certain set of conditions is met," comments Matsuzaki.

A remaining question is why the Par-complex islands do not appear to merge into one large island under the cell membrane, even when polarized. "We have started collaborating with physicists and biophysicists to tackle this interesting problem," Matsuzaki adds.

The team intends to explore what determines whether the Par-complex islands cluster asymmetrically or evenly. Going beyond polarization, a future goal is to reconstruct asymmetric cell division. ●

Reference

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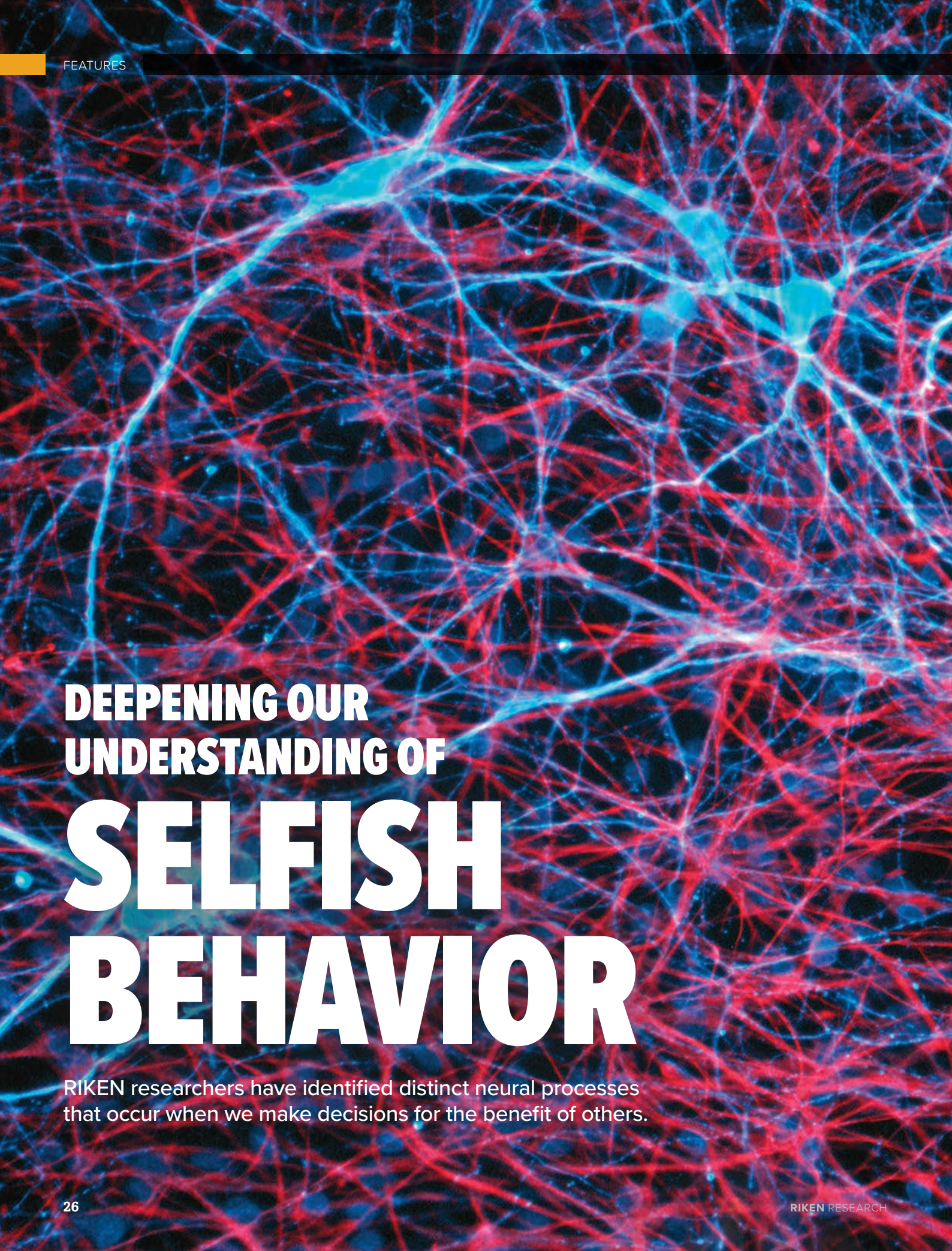
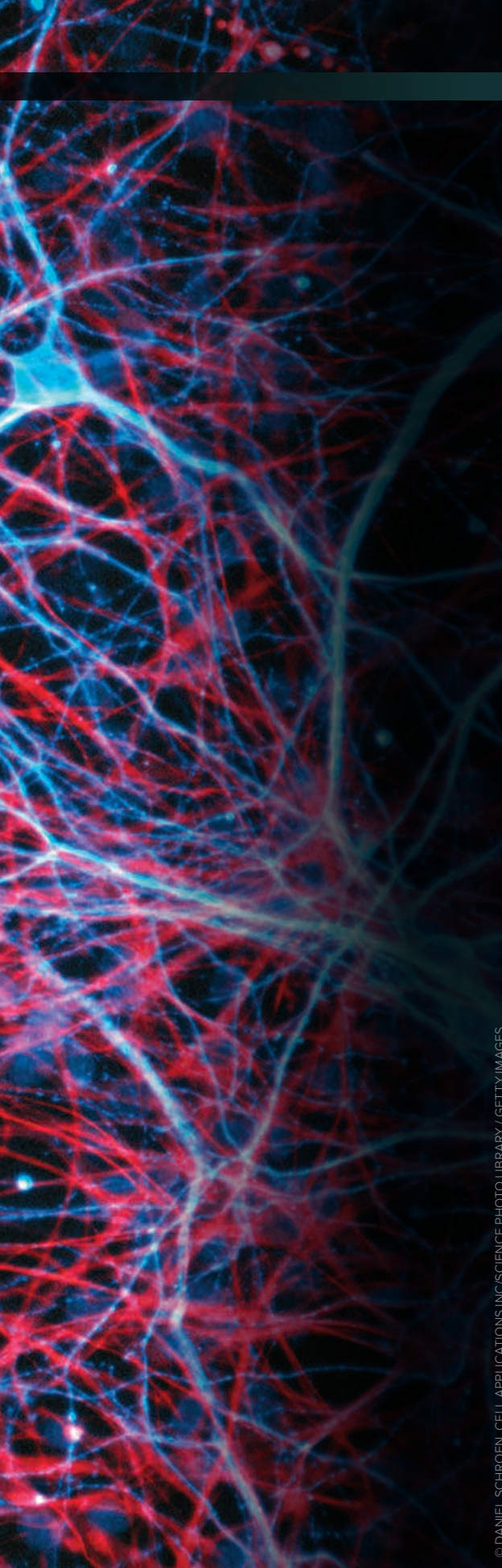


DEEPENING OUR UNDERSTANDING OF SELFISH BEHAVIOR

RIKEN researchers have identified distinct neural processes that occur when we make decisions for the benefit of others.



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Is a selfish person just processing the decisions that result in rewards to others differently? Perhaps, suggests a recent RIKEN study.

A RIKEN team, led by Hiroyuki Nakahara of the Laboratory for Integrated Theoretical Neuroscience at the RIKEN Center for Brain Science, discovered this when they examined 36 healthy volunteers aged between 20 and 32 years. Their aim was to find out which parts of the brain are activated when considering giving rewards to others.

These volunteers were asked to choose one of two options, each with a baseline reward to themselves. One option then involved an extra financial reward for the participants and the other, a reward to 'others'—in this case a series of well-known charities.

The group looked at the what happened when a person is giving an extra reward to one of the charities, using functional magnetic resonance imaging (fMRI) and a computational modeling method called a connectivity analysis. They discovered that there is a three-stage cascade process involved.

In the first stage, the brain detects a perceived benefit to others. The first stage was accompanied by neural activity in the right temporoparietal junction (right TPJ) and the left dorsolateral prefrontal cortex (left dlPFC)—regions that are well known to play a role in attention and social interaction.

The second stage involves understanding the impact of the offer of value on the outcome. This corresponded to activity in the right anterior insula (right AI), a key node of a brain circuit called the salience network, which has been associated with empathy.

The third stage is the actual decision-making process. Decision-making corresponded to activity in the medial prefrontal cortex (mPFC), supporting findings from previous studies that have implicated the mPFC in strategic reasoning.

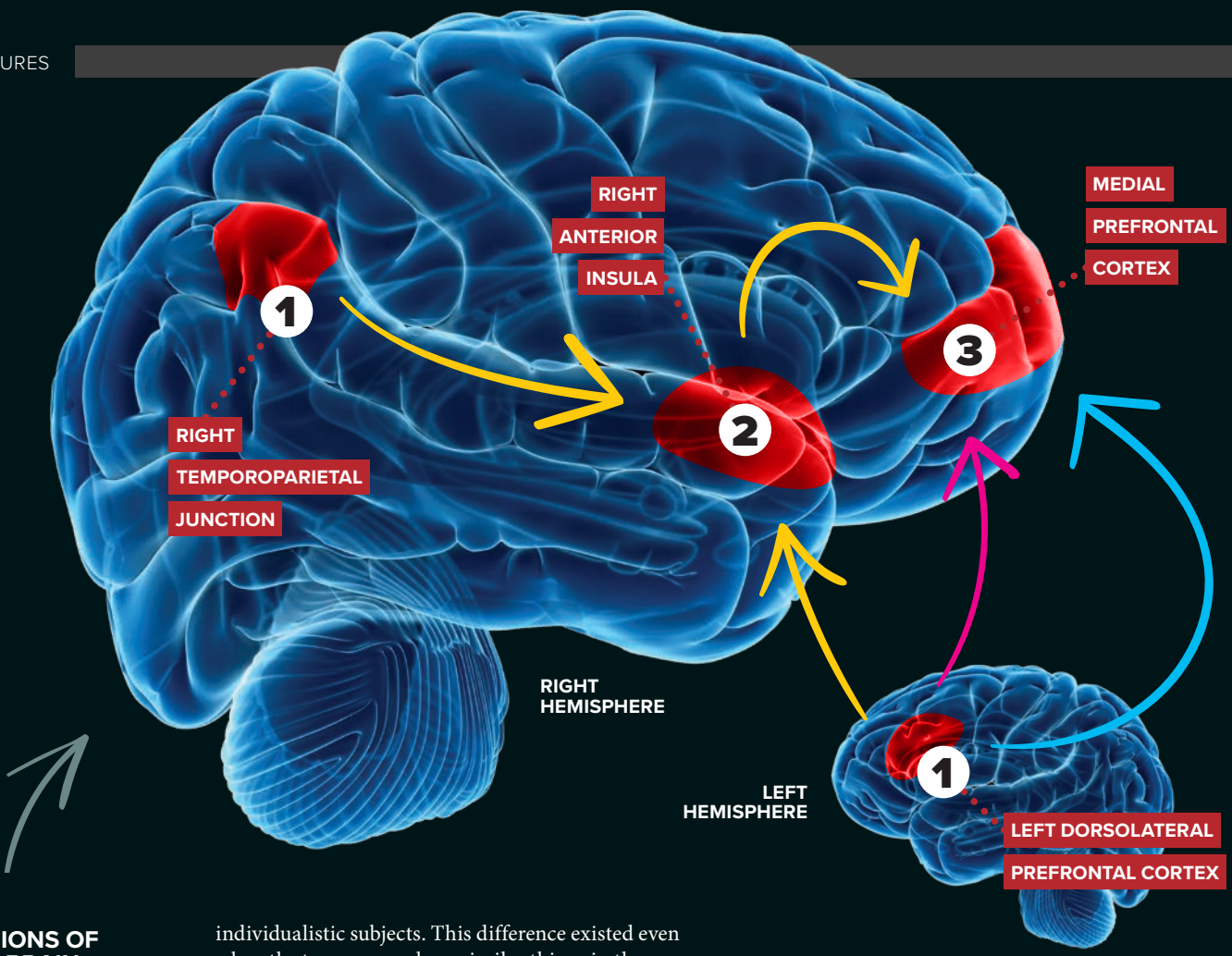
Next, the team explored whether there might be any common patterns in the neural pathways involved in the choice to give to others in individuals who can broadly be described as either generous or selfish. For this, the team used a test established by social psychologist Paul A. M. Van Lange of Vrije Universiteit Amsterdam in the 1990s. The test enables scientists to gauge a person's preference regarding the allocation of rewards to themselves and others. This social value orientation (SVO) test is widely used in social psychology and other disciplines, such as economics.

The volunteers took the SVO test in the form of a questionnaire and were subsequently classified as either prosocial (i.e. having a tendency towards generous behavior) or individualistic (having a tendency towards selfish behavior).

One of the most striking findings was that there was a distinct difference in the neural processes involved in giving to others between prosocial and

This feature looks at the work of HIROYUKI NAKAHARA

Hiroyuki Nakahara earned his PhD at the University of Tokyo studying sequential decision-making in biological systems. He then joined Shun-ichi Amari's laboratory at the RIKEN Brain Science Institute (BSI), and later started his own lab at BSI. His Laboratory for Integrated Theoretical Neuroscience aims to understand the computational principles that underlie the way neural systems realize adaptive behavior, decision-making, and associated learning; in particular, reward-based learning and social decision-making. They build computational and mathematical models, while also using human functional magnetic resonance imaging (fMRI) in combination with quantitative approaches.



REGIONS OF THE BRAIN

The **right temporoparietal junction** and the **left dorsolateral prefrontal cortex** play a role in attention and social interaction.

The **right anterior insula** has been associated with empathy.

The **medial prefrontal cortex** has been implicated in strategic reasoning.

1. Perceived benefits
2. Impact of benefits on the choice
3. Decision

Other benefits (individualistic and social)

Other benefits (social)

Self benefits

individualistic subjects. This difference existed even when the two groups chose similar things in the original task.

Nakahara considered it particularly intriguing that prosocial subjects used a similar brain process for other-bonus and self-bonus choices, mediated via the left dlPFC–mPFC pathway. Individualist subjects, on the other hand, mediated the process of weighing up giving to others in a different way to the self-reward choice. In the second stage of the process, more 'selfish' subjects mediated the choice to give to others by the right AI, which represents where the brain may digest the implications of the benefit-to-others option.

This isn't all about selfishness and generosity, but rather perceptions of value, emphasize the researchers. Rather than being altruistic, a generous subject may be perceiving more value in social contributions or be subject to predispositions such as inequity aversion and guilt. The team have called the process of deciding to give to others 'social value conversion'. In the paper, the team predicted that social value conversion is actually a primitive computation that may be essential for different forms of social behavior.

The team's findings provide building blocks for investigating more complex forms of social decision-making. Exploring ideas about generosity and selfishness would call into question the role of cultural and religious factors, and variations across countries and regions, for example, in accounting for how we each perceive and take on board consideration for others.

These multifarious factors "would certainly contribute to shape more complex types of social behaviors," Nakahara explains. "Through repeated experiences in daily life, they would be built-in as part of the neural circuitry of social behavior and decision-making. The building blocks of the social conversion process would then be modulated and integrated with those processes to produce a final behavior and decision."

Another promising research direction, albeit one that goes beyond the scope of the present study, would be to look at the possibility that the process involved in giving to others might in some way be different in people with antisocial disorders. Such differences, if identified, may contribute to understanding of the neural correlates of antisocial behavior.

Nakahara's team is continuing to work on uncovering further insights into of social decision-making. "One of our ongoing studies investigates how people seek to make better decisions by predicting the decisions of others, and we are getting some interesting results," he says.

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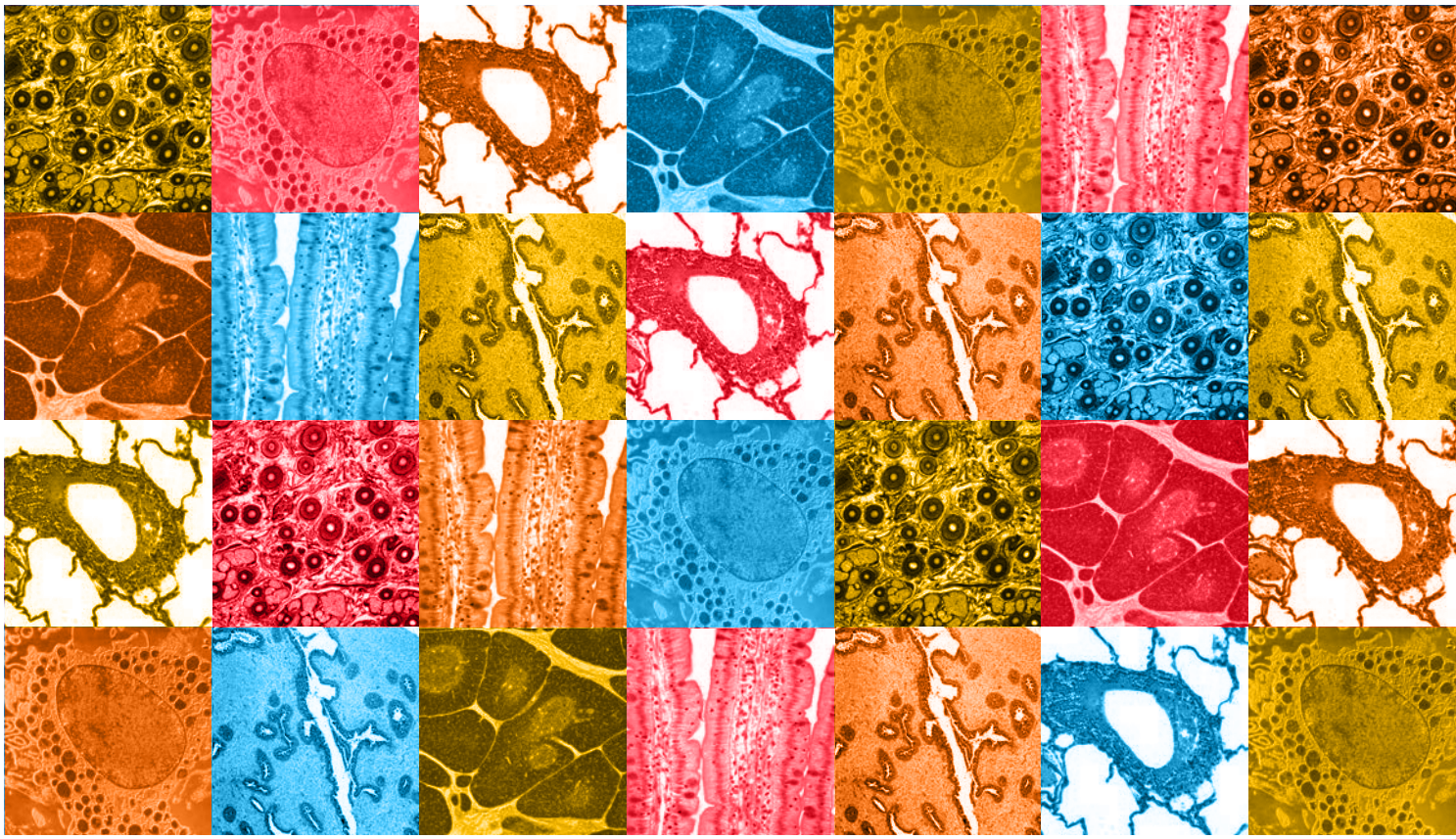


WHY MAP EVERY CELL IN THE HUMAN BODY?

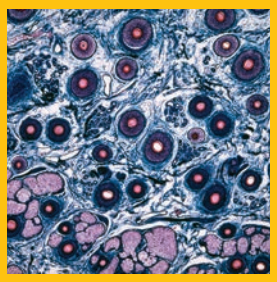
RIKEN is spearheading Asia's efforts for the Human Cell Atlas, a push to understand the regulatory networks that make human cells unique.

PIERO CARNINCI: A highly standardized reference dataset of human cells is currently being created under a project called the Human Cell Atlas (HCA). This international consortium aims to create a common database consisting of millions of single-cell data points in order to map out all the cell types and their relationships. This will help better understand health and identify triggers that cause disease. The database aims to be open to the public to accelerate research for better medical research, diagnostics and drug discovery.[1]

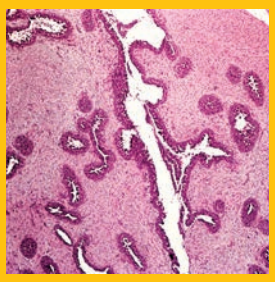
I am part of the original HCA Organization Committee with Jay W. Shin, a team leader for the Laboratory for Advanced Genomics Circuit at the RIKEN Center for Integrative Medical Sciences. This committee consisted of 31 scientists from 10 countries and established the guidelines and scientific policies to make the HCA database an accessible resource to the global community. As of September 2019, more than 1,000 research institutes and 1,500 scientists from 60 countries and regions are now participating as members of the HCA.

RIKEN IMS HUMAN CELL ATLAS TISSUES

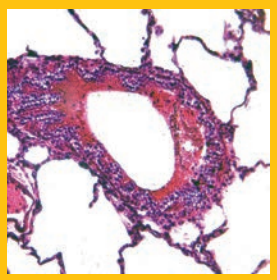
At the RIKEN Center for Integrative Medical Sciences, a number of researchers are charged with leading efforts to profile single-cell regulatory networks and identify new cell types within specific tissues, with the aim of feeding this information into the Human Cell Atlas.



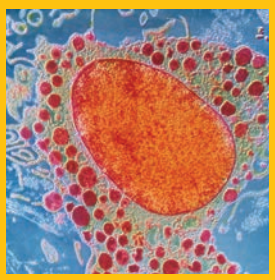
SKIN from Keio University



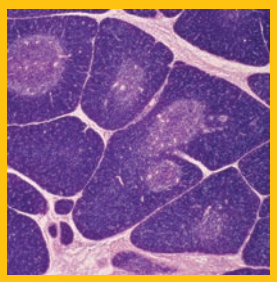
CHEST (BREAST) from St. Marianna University School of Medicine



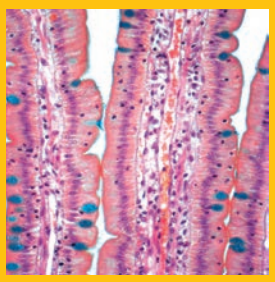
LUNG from National Cancer Center Japan and Juntendo University



BLOOD from Toranomon Hospital and RIKEN



THYMUS from the University of Tokyo



INTESTINE from the National Cancer Center Japan, Chiba University and Keio University

As one of its key aims, the consortium is collecting data across broad ethnic and geographic regions to provide an equitable and globally representative picture of the human body. RIKEN is one of four Executive Offices (EOs) that will regularly coordinate general HCA activities, alongside the Wellcome Sanger Institute for the United Kingdom, the Broad Institute of MIT and Harvard for the United States, and the Karolinska Institutet for the European Union. RIKEN will act as the EO in Asia.

FANTOM SYNERGY

RIKEN was perfectly positioned to take part in this project. It already has decades of experience mapping the gene expression and regulatory networks that define the different types of cells through its leadership of the international consortium working on FANTOM (Functional Annotation of the Mammalian Genome).

Among the many findings of the FANTOM projects, we cataloged the genomic regions critical in controlling the expression of RNAs, known as promoters and enhancers, and measured their activities across the major primary cells and tissues.[2] The FANTOM database allowed us to understand the interplay of the regulatory proteins that defines a cell type, known as transcription factors. We also created an atlas of non-coding RNAs (ncRNAs) and revealed their importance in human genetics and gene control. In fact, in the current sixth edition of FANTOM (FANTOM6), we are aiming to understand the functions of long ncRNA.[3]

Because of this history, there is a natural synergy with the HCA and we will work closely with them to build the atlas of promoters and enhancers at a single-cell resolution, as well as to profile millions of single cells across many tissues across populations.

TOWARD THE ANALYSIS OF SINGLE CELLS

The HCA will start by sampling a comprehensive set of organs and tissues, followed by dissociating these samples into single cells or profiling gene expression within a tissue's spatial context. The combined information will lead us to define the identity of each cell, based on the level of RNA, chromatin states and to a certain extent protein expression. We will employ expert-guided curation and data-driven definitions to reach a consensus about the boundaries of how each cell should be classified by type and state, and this will create a common language for the global community.

RIKEN has started with a project to analyze blood samples from multiple ethnic groups in Asia including those in South Korea, Singapore (India, Malay, Chinese), and Japan funded by a grant from the Chan Zuckerberg Initiative (CZI). The project aims to compare cell-type compositions and RNA

expression signatures in immune cells and cross-reference them to their sources' genetic background, as well as to environmental factors, to identify the causal regulators of the immune system. Several bioinformaticians are on board and will work together with clinicians and ethicists to make the data meaningful and accessible to the community.

In addition to the CZI grant, RIKEN is spearheading a Single Cell Medical Network where samples from clinical collaborators in Japan will be profiled using the latest single-cell RNA sequencing and spatial technology.

In FANTOM5, we profiled large numbers of samples using CAP Analysis of Gene Expression (CAGE), which was developed at RIKEN. The CAGE method precisely determines where the gene is generated in our DNA, giving us a good sense of how the gene is controlled. However, in FANTOM5, we profiled bulk samples. Now, because of advancing technologies, we're able to profile RNAs at a single-cell level using a modified version of the CAGE method that we recently developed.

JAY W. SHIN: Early in 2019, I led a team, together with Dr. Piero Carninci, to combine a microfluidic technique with CAGE to better and more systematically profile RNA transcripts at the single-cell level.

We used a microfluidic platform called C1, which isolates, processes and prepares individual cells for analysis, and we integrated a highly sensitive version of CAGE with this system, which we refer to as C1 CAGE. The team compared the C1 CAGE method with a standard protocol for profiling RNA's 5'ends in single cells and found it to be more sensitive, detecting more genes including non-coding RNAs.[4]

With the support of the HCA, we continue to develop and benchmark RNA profiling methods in single cells as one of our key contributions to the HCA community. With these new technologies we can measure individual RNA molecules within single cells, enabling us identify rare cell types or states in a sample with heterogeneous cell populations, which is particularly important for the interpretation of disease pathology in clinical samples of complex tissues.[5]

The ultimate aim of the HCA is to help treat diseases and improve diagnostics. There are many ways we can approach this. For example, it has become apparent that the risk of disease onset is usually linked to changes in the genome through single nucleotide polymorphisms, which can influence the functions and expression levels of the proteins that cause diseases. Analysis of RNA expression in single cells should shed light on exactly how each polymorphism affects expression levels and functions, helping us to vastly better understand diseases. By looking at deviations from the baselines set by the HCA, we should also be able to ascertain drug efficacy and safety with high precision.

The HCA will also help us look at diseases by revealing more cell subtypes. The brain, for example, has many subtypes of neurons, and some may only be discovered by looking at gene expression. In 2015, researchers at the Karolinska Institutet in Sweden discovered a much greater diversity of glial cells—a type of cell that supports and shields neurons—by looking at gene expression alone. We also know that certain subtypes of neurons are particularly affected in Parkinson's disease, so to understand this type of disease, we must understand the brain's cell types and the expression levels that make them unique.

In addition, cell states are important—for example, cells located near cancer cells may respond to signals from them and change states, becoming directly involved in cancer progression and metastasis. However, previous methods that relied upon the averaged values for groups of cells could not help us understand changes in cell states. The new single-cell CAGE could help us spot dynamic levels of RNA expression in cells in a disease state, as a means of early detection. For example, in Parkinson's disease, cells that produce the neurotransmitter dopamine are lost in specific regions of the brain. As many as 70% of dopamine-producing cells are lost by disease onset, implying that these cells must show some markers earlier than that. We have already found that the level of a certain ncRNA in the blood increases in the early phase of Parkinson's disease, which may lead to a means for early detection. Many more RNA and protein biomarkers are likely to be found in this way through the HCA.

Last but not least, a better understanding of cells will very likely help us when we differentiate induced pluripotent stem cells into specific cells to replace and repair damaged or defective tissues in the body.

Advances based on the HCA findings will likely be quick. The first cell atlas that will be published in a few years' time will most likely be a draft of each healthy tissue and organ. New research can begin from the moment such an atlas is published, ranging from research into the similarities and differences between Asian and American lung cells, to differences by sex and age. It is likely that this research will also compare healthy tissues and organs characterized by the HCA with the cells of disease tissues and organs, opening up a whole range of exciting new insights.

For a full list of references, please visit RIKEN's website.

PIERO CARNINCI
Deputy Director of the RIKEN Center for Integrative Medical Sciences (IMS)

After arriving at RIKEN in 1995, Carninci played a critical role in many key projects, including the FANTOM Consortium. In 2018, he became deputy director of the IMS. He also leads the Laboratory for Single Cell Technologies, which is describing samples as populations of single cells classified by RNAs. He is an organizing committee member of the HCA.

JAY W. SHIN
Team Leader at the RIKEN Center for Integrative Medical Sciences (IMS)

Shin studied computer science at Boston College in the United States and gained a PhD in life sciences at Swiss Federal Institute of Technology in Zürich, Switzerland. Today, he leads RIKEN's Laboratory for Advanced Genomics Circuit, co-leads the FANTOM6 consortium and is an organizing committee member of the HCA.

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PROGRAMS FOR YOUNG RESEARCHERS

INTERNATIONAL PROGRAM ASSOCIATE

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

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

RIKEN HAKUBI FELLOWS PROGRAM

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

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

SPECIAL POSTDOCTORAL RESEARCHERS PROGRAM

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

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

JUNIOR RESEARCH ASSOCIATES

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

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

RIKEN'S CENTERS AND FACILITIES

across Japan and around the world

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

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

SENDAI
- ● Center for Advanced Photonics (RAP)

YOKOHAMA
- ● Center for Integrated Medical Sciences (IMS)
- ● Center for Biosystems Dynamics Research (BDR)
- ● Center for Sustainable Resource Science (CSRS)
- ■ SPring-8 Center (RSC)
- ▲ Cluster for Science, Technology, and Innovation Hub (CSTIH)
- ◆ Genome Sequencing
- ◆ Nuclear Magnetic Resonance (NMR)

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

TOKYO
- ● Center for Advanced Intelligence Project (AIP)
- ▼ Innovation Design Office

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

NAGOYA

KEIHANNA
- ● Center for Advanced Intellegence Project (AIP)
- ■ 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.

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

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