RIKEN RESEARCH

FALL 2019

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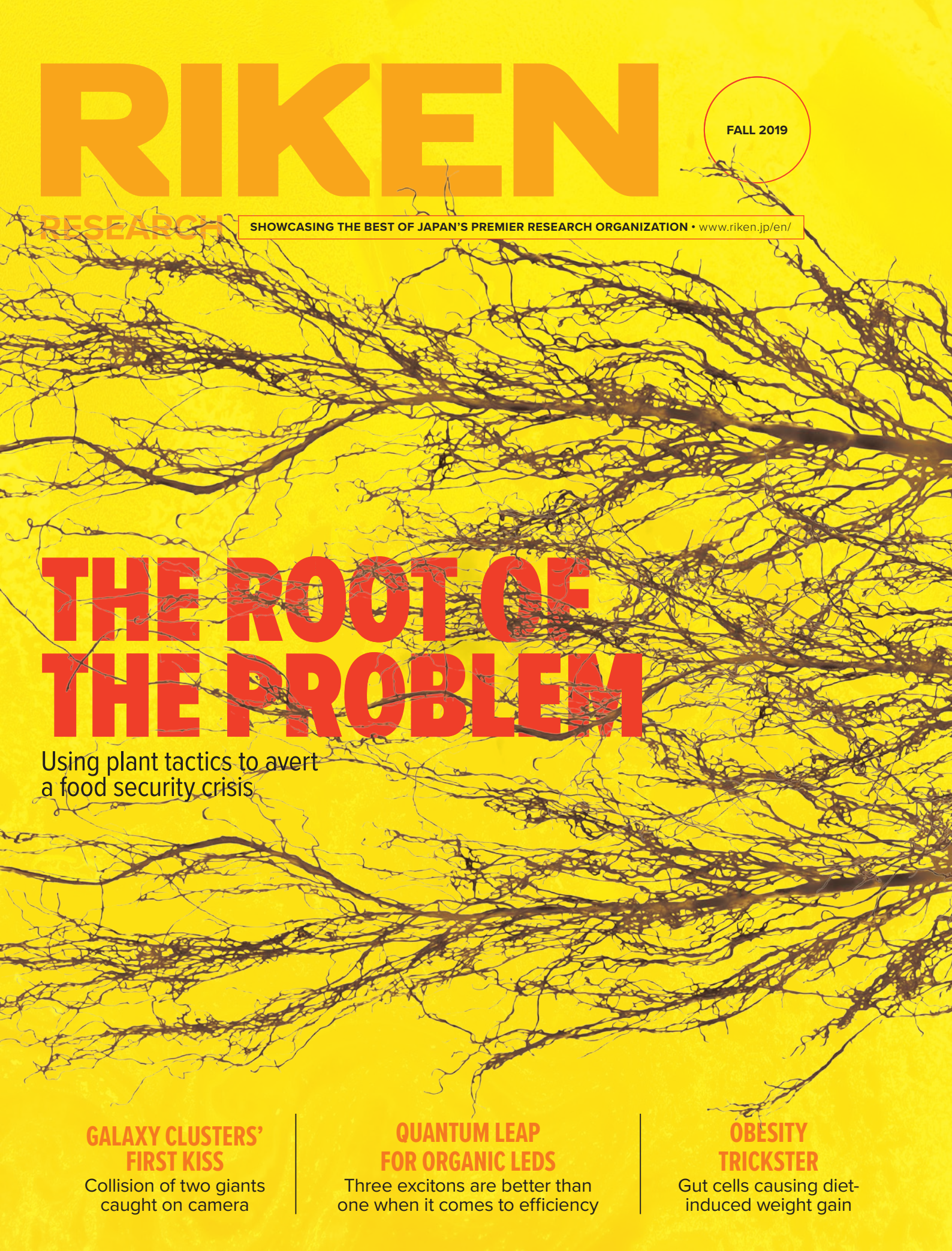


THE ROOT OF THE PROBLEM

Using plant tactics to avert a food security crisis

GALAXY CLUSTERS' FIRST KISS

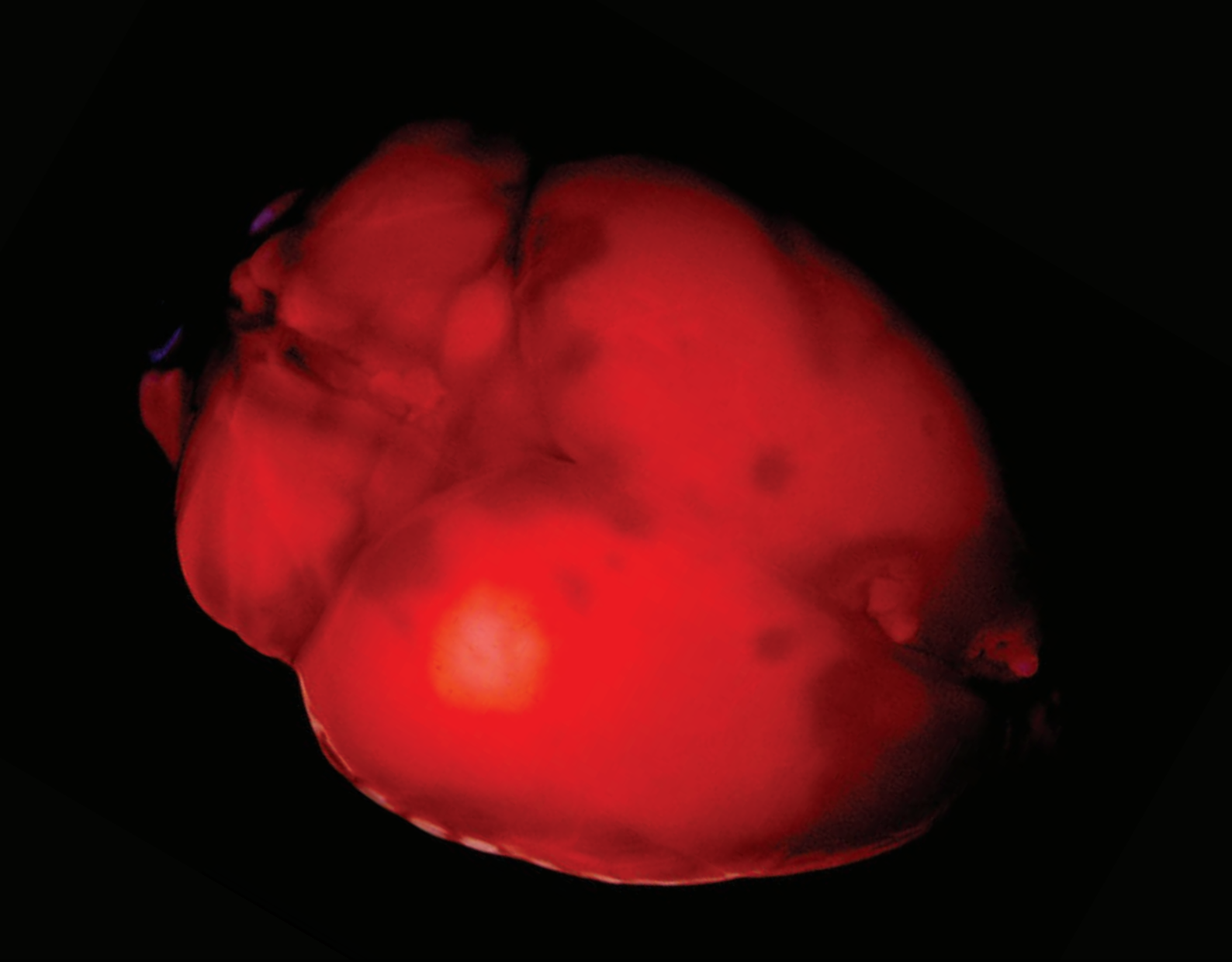
Collision of two giants caught on camera

QUANTUM LEAP FOR ORGANIC LEDS

Three excitons are better than one when it comes to efficiency

OBESITY TRICKSTER

Gut cells causing diet-induced weight gain



▲ **Restraining damage caused by a stroke**
A whole mouse brain showing that administrating a drug cocktail that blocks the adrenergic receptor after a stroke stops the area damaged by the stroke (light region in image) from spreading, thereby limiting the effects of a stroke.

RIKEN RESEARCH

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

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

RIKEN Research is an online and print publication that highlights the best research published by RIKEN. This publication is a selection of the articles published by RIKEN at: www.riken.jp/en/. Please visit the website for recent updates and related articles. Articles showcase RIKEN's groundbreaking results and are written for a non-specialist audience.

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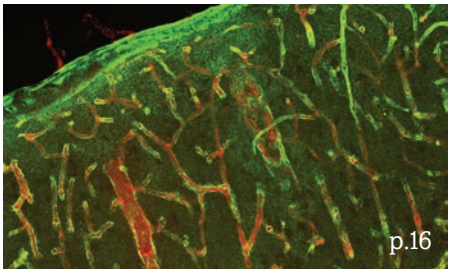
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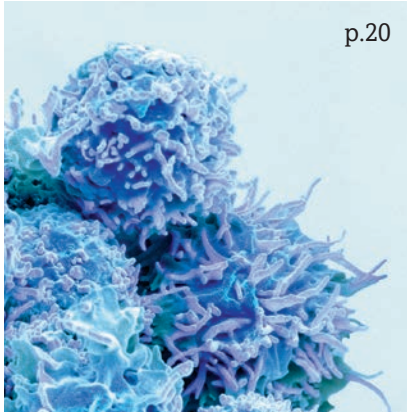
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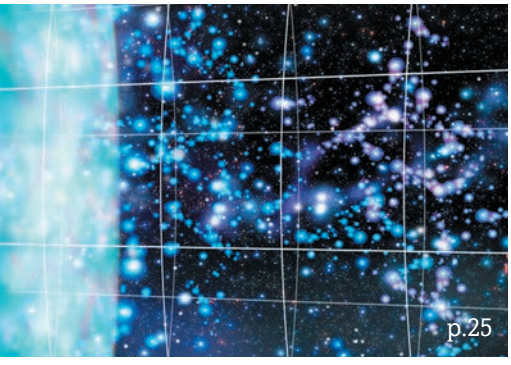
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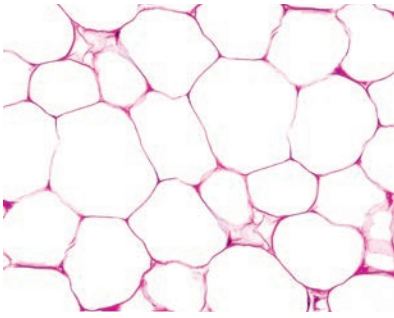
A tiny population of immune cells in the small intestine may trigger diet-induced weight gain: *A recent finding shows that understanding a very specific population of immune cells in the small intestine might be key to keeping obesity at bay on a high-fat diet*



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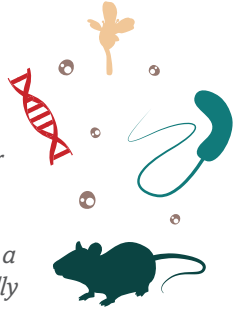


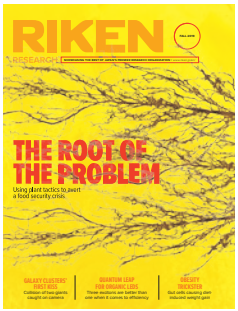
Interdisciplinary culture, the All-RIKEN Projects and beyond

Shigeo Koyasu
Executive Director, RIKEN

One of RIKEN's strengths is that our researchers work in many different disciplines and the barriers between them are quite low. We have developed this culture by encouraging researchers to participate in collaborative projects. In particular, an internal program called the Pioneering Projects of the Competitive Program for Science and Technology supports interdisciplinary collaborations. Within this program, we like to help our researchers propose projects that pioneer new research fields that involve taking interdisciplinary research beyond organizational boundaries; the aim is to support work that leads to big leaps in science and technology. Occasionally, these projects result in the establishment of new research centers, such as the Interdisciplinary Theoretical and Mathematical Sciences (iTHEMS) program led by Tetsuo Hatsuda.

Another program that encourages collaborations beyond organizational boundaries is the cross-organizational All-RIKEN Projects—which was originally designed to enhance collaborations between the life science centers. At the RIKEN Epigenome Manipulation Project, we are developing methods to replicate the actions that environmental factors exert on the epigenome, redress epigenetic abnormalities, and use epigenetic changes to create more robust living things. Through the RIKEN Integrated Symbiology (iSYM) project, we are seeking to gain a comprehensive understanding of microbe–host symbiotic systems in both animals and plants (see page 29).

We have many other interdisciplinary projects as well, such as one to develop quantum technology and another to understand the aging process, both involving a number of centers. Through these programs, we plan to use our research capabilities to drive Japan's innovation efforts and to generate world-class R&D results, while also fostering research excellence and contributing to knowledge circulation on a global scale. Several articles in this issue (see 'Cutting the energy of OLED displays' on page 22 and 'New metalloenzyme targets cancer cells' on page 24) highlight some of the interdisciplinary research we are doing.



COVER STORY:
To solve a growing resistance to agro-chemicals, scientists are looking more closely at the microbiomes of plants and how they manage disease.

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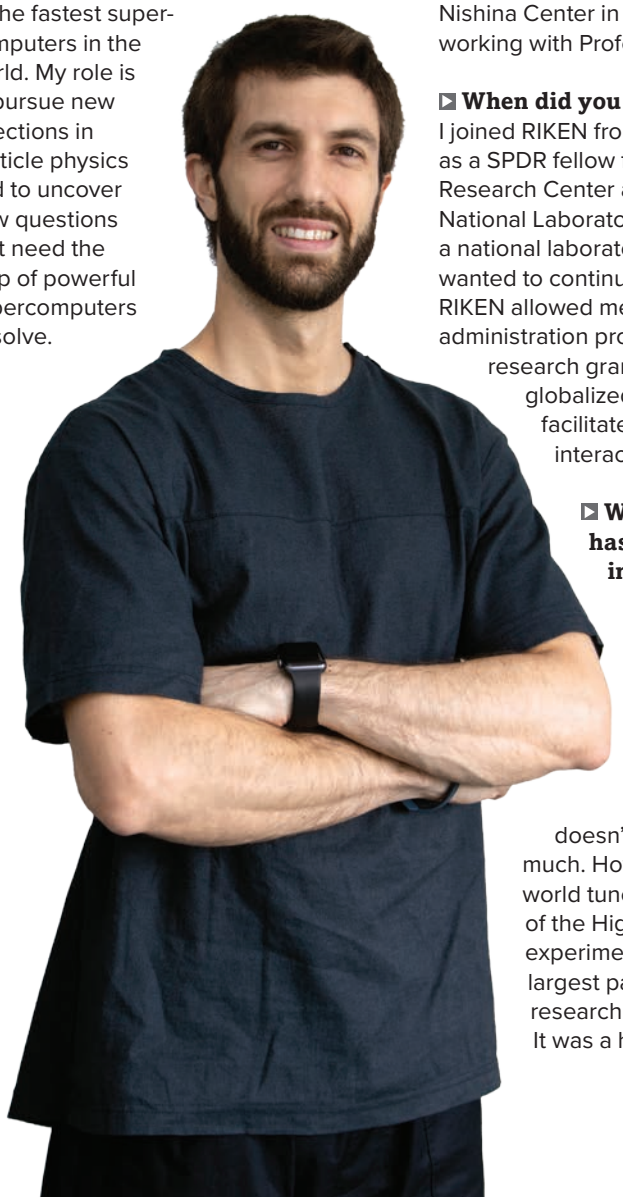
Investigating dark matter, from New York to Tokyo

Enrico Rinaldi
Special Postdoctoral Researcher, Computational Group at RIKEN BNL Research Center/RIKEN Nishina Center for Accelerator-Based Science

Describe your role at RIKEN
I have a Special Postdoctoral Researcher (SPDR) fellowship, which allows me to investigate the nature of dark matter using some of the fastest supercomputers in the world. My role is to pursue new directions in particle physics and to uncover new questions that need the help of powerful supercomputers to solve.



I work as part of the Computational Group at the RIKEN BNL Research Center in the United States, led by Taku Izubuchi. I've also been a member of the Quantum Hadron Laboratory at the Nishina Center in Japan since April, working with Professor Tetsuo Hatsuda.

When did you join RIKEN?
I joined RIKEN from New York in 2016 as a SPDR fellow for the RIKEN BNL Research Center at Brookhaven National Laboratory. I had come from a national laboratory in the US and wanted to continue my research. Joining RIKEN allowed me to do that, and the administration provided a substantial research grant together with a globalized environment that facilitates interdisciplinary interactions.

What do you think has been the most interesting discovery in your field recently?
Generally, high-energy particle physics (just a fancy way of describing work on tiny, tiny particles) doesn't make the news much. However, the whole world tuned into the discovery of the Higgs boson in 2012 by experimentalists at CERN, the largest particle-accelerator research center in the world. It was a huge breakthrough, and the two physicists who predicted the existence of the Higgs boson years earlier received a Nobel Prize just a year later. The Higgs discovery relates very directly to my work because I work on particle theories in which the Higgs boson is not what the standard model predicts, and so I eagerly await new experimental measurements of the particle.

What technologies do you use?
Until recently, RIKEN hosted one of the world's top-ten supercomputers, the K computer, at the R-CCS in Kobe. Soon the R-CCS will have a successor, Supercomputer Fugaku, and RIKEN will have one of the fastest supercomputers in the world. Right now, I also have access to some of the world's fastest computers through some US partnerships.

> *It's about figuring out why we are here, what happened during the Big Bang and what dark matter is*

Describe your current research
My current research is about understanding the interactions among elementary particles in the standard model of particle physics, and working on theories that go beyond and extend the standard model. It probably sounds very abstract and complicated, but it's about figuring out why we are here, what happened during the Big Bang and what dark matter is.

What is the best thing about working at RIKEN?
The best thing about RIKEN is its highly interdisciplinary approach to research. I'm a theoretical particle physicist, but I'm also a computational physicist. I have direct contact with both worlds at RIKEN. Moreover, being able to talk to experimental particle physicists is also important, and working at the RIKEN BNL Research Center in New York made that easy for me. ■

Crafting conversations on Alzheimer's

Shoko Hashimoto
Special Postdoctoral Researcher, Laboratory for Proteolytic Neuroscience, RIKEN Center for Brain Science

Describe your role at RIKEN
My group aims to elucidate the etiologic mechanisms (the source) of Alzheimer's disease, the world's most common form of dementia.

Describe your current research
Of the neuropathological hallmarks of Alzheimer's, senile plaque and neurofibrillary tangle are the best known and believed to be key to the disease's progression. But senile plaque begins forming more than 10 years before symptoms begin. We believe there are changes within that 10 years that either greatly progress or suppress the development of symptoms, and we want to understand these changes better. I study 'oxidative stress' and 'novel Alzheimer-related proteins' in mouse models, which are linked to one of three main areas believed to cause the symtoms of Alzheimer's.

We believe there are changes within that 10 years that either greatly progress or suppress the development of symptoms

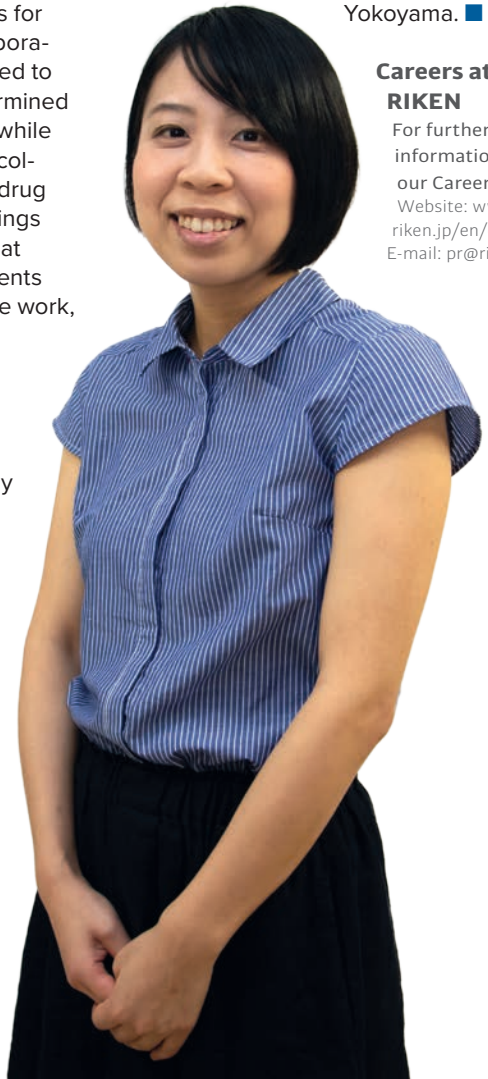
How did you become interested in your current field of research?
The misfolding of proteins leads to an accumulation and aggregation of proteins in the brain, and these are linked to neurodegenerative diseases, including Alzheimer's. I studied enzyme protein folding in graduate school and wanted to understand what triggers protein misfolding and how a misfolded protein kills neuronal cells.

When did you join RIKEN?
I joined RIKEN seven years ago, when my lab was recruiting researchers for a pharmaceutical company collaboration. Through that project, I learned to produce results within a predetermined period, to advance our research while keeping up communication with colleagues, about the difficulties of drug development, and many other things besides. In particular, I noticed that research isn't just about experiments and writing papers, but also office work, communication, and so on.

Describe some of the technologies that you use
I use magnetic resonance imaging (MRI) on mice. MRI clearly shows brain shrinkage, and this has been important to the development of my publications. A cryo-electron microscope has also enabled us to observe molecules at atomic resolution, resolving the structure of pathogenic protein aggregates seen in brains with Alzheimer's.

What's the best thing about working at RIKEN?
The Special Postdoctoral Researcher program lets us perform independently planned research by giving us a budget and salary. The program helps foster responsibility and leadership in young scientists.

What has been your most memorable experience at RIKEN?
Two years ago, I gave a presentation at a Brain Lunch Seminar held by the RIKEN Brain Science Institute (BSI). Before the presentation, Charles Yokoyama, a research coordinator at the BSI, taught me how to tell a compelling story, make my English easier to understand and how to create slides with impact. Consequently, I felt confident presenting in English and the attendees had a lively discussion on the topics I presented. After this experience, I began to want to present my research and to be part of discussions at international conferences, and this has definitely helped me write better papers. I'm deeply thankful to Dr Yokoyama. ■



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Website: www.riken.jp/en/careers
E-mail: pr@riken.jp

GLOBAL VISITORS

Italian minister visits after G20

GIULIA GRILLO

In July, Italian Minister of Health Giulia Grillo visited RIKEN's Yokohama Campus following the G20 summit in Osaka. Executive Director Hidetoshi Kotera and Yokohama Branch Director Naoki Saito spoke about the institute. Piero Carninci, deputy director of the Center of Integrative Medical Sciences (IMS), summarized the IMS's activities, and three other IMS principal investigators talked about their research projects and how they are helping to translate basic research into future therapies.

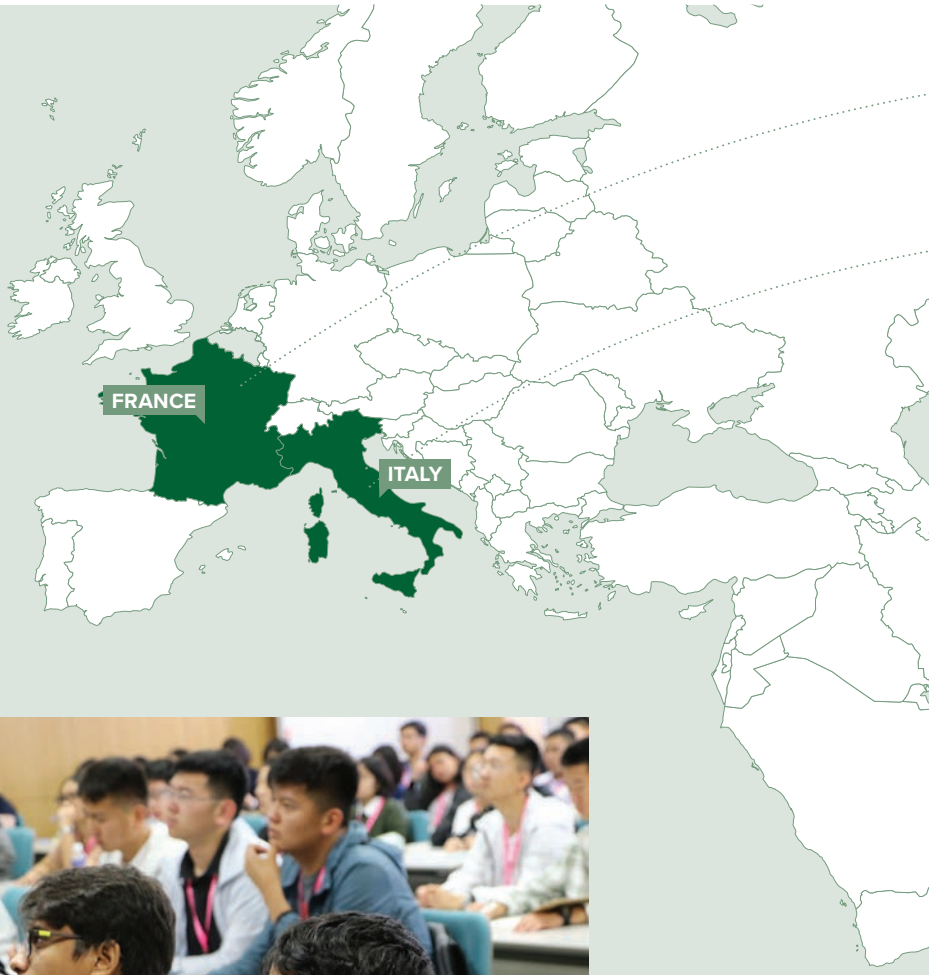
www.riken.jp/en/pr/topics/2019/20190704_1/

Incoming Korean ambassador touches base at Kobe campus

NAM GWAN-PYO

In June, a delegation led by South Korean ambassador to Japan Nam Gwan-pyo visited RIKEN's Kobe campus just three weeks after the new ambassador's appointment. RIKEN Executive Director Shigeharu Kato gave Nam an overview of the institute. Deputy director of the Center for Biosystems Dynamics Research Tomoya Kitajima and research scientist Ahn Kyungmin presented on their center, after which BDR staff showed off samples, such as their iPS cells, from the center's laboratories.

www.riken.jp/en/pr/topics/2019/20190612_3/



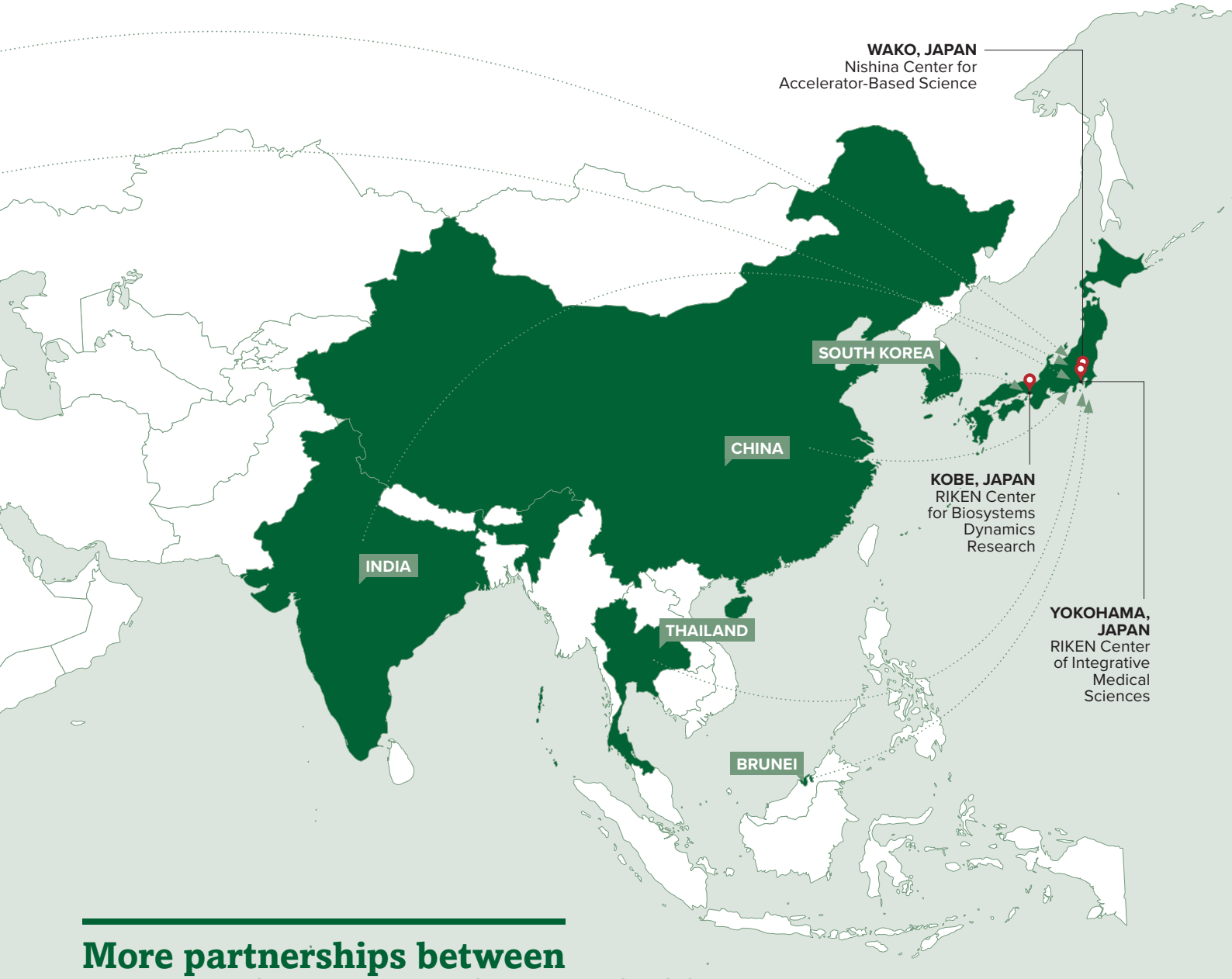
As part of the Sakura Science Plan, bright young teenagers traveled to Japan from China, India, Brunei and Thailand.

Sakura Science Plan: Youth travel to Japan

In June, as part of the Sakura Science Plan RIKEN welcomed 93 high school students from China, India, Brunei and Thailand to its Wako campus. The goal of the program, organized by the Japan Science and Technology Agency (JST), is to bring talented high school students from overseas to Japan to gain some exposure to Japanese science and technology.

During their visit, the students visited the RIKEN Nishina Center for Accelerator-Based Science and attended a lecture from Hideto En'yo, director of the center, about the discovery of nihonium and the center's work on superheavy elements. Three researchers also spoke about Nishina and the RIKEN Center for Sustainable Resource Science.

https://ssp.jst.go.jp/EN/outline/index.html



More partnerships between Japan and France on the roundtable

In June, the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) and the French Ministry of Higher Education, Research and Innovation (MESRI) hosted a partnerships roundtable. Following opening remarks by MESRI Minister Frédérique Vidal and MEXT Deputy Minister Yoshio Yamawaki, a number of representatives from research institutes, universities and funding agencies gave their views on the current state and future of collaboration between the two countries. In his remarks, President Hiroshi Matsumoto pointed out that "RIKEN places extremely high value on strengthening collaborations with Europe, including France". As an exmple, he highlighted the opening of RIKEN's Europe Office last November. Matsumoto pointed to RIKEN's many ties with organizations including the French National Center for Scientific Research (CNRS) and the French Alternative Energies and Atomic Energy Commission (CEA), and said that he expects to further strengthen ties in important areas such as health, AI and computational science, and sustainability.

www.riken.jp/en/pr/topics/2019/20190701_2/

Yokozuna: K computer remains undefeated in the Graph500 ranking

Japan's K computer has taken the top spot on the Graph500 ranking for the ninth consecutive time. The Graph500 is a benchmark that gauges the ability of supercomputers to process data-intensive loads.

This time the ranking was won through the efforts of a collaboration involving RIKEN, Kyushu University, the Tokyo Institute of Technology, the Barcelona Supercomputing Center, Fujitsu, Fixstars Corporation, and the Japan Science and Technology Agency.

The Graph500 is designed to reward computing ability to process big data in areas such as cybersecurity, medical informatics, data enrichment, social networks, symbolic networks, and modeling neuronal circuits in the brain. The benchmark has become particularly important because the big data acquired by technologies such as the Internet of Things (IoT) will need to be converted into this type of graph data and processed at high speed to realize new business applications.

To encourage future development, the K computer group published the program they developed for the ranking measurement as open-source code on the GitHub repository.

Additionally, the group is working to develop new large-scale graph analysis algorithms and programs to operate on RIKEN's soon-to-be completed exascale supercomputer, Supercomputer Fugaku, which is scheduled to succeed the K computer in 2021.

Two research projects funded by the Japan Science and Technology Agency (JST) CREST programs contributed the K computer's recent ranking sucess:

1. The first project is called, Advanced Computing and Optimization Infrastructure for Extremely Large-Scale Graphs on Post Peta-Scale Supercomputers. The Principal Investigators are Professor Katsuki Fujisawa of Kyushu University and Professor Toyotaro Suzumura of Barcelona Supercomputing Center. This project is encompassed by an umbrella project called the Development of System Software Technologies for Post-Peta Scale High Performance Computing. The latter is run by Mitsuhisa Sato, Deputy Director of the RIKEN Center for Computational Science.

2. The second project is called EBD: Extreme Big Data — Convergence of Big Data and HPC for Yottabyte Processing and it is run by Satoshi Matsuoka, Director of the RIKEN Center for Computational Science. This project is part of the Advanced Core Technologies for Big Data Integration area, run by Masaru Kitsuregawa, Director General of the National Institute of Informatics.

The K computer has been leading the field on the Graph500 ranking since 2015.

www.riken.jp/en/pr/topics/2019/20190619_1/

Visitors took a test on the periodic table sourced from the Genso Club, a Japanese association set up to accredit people in their knowledge of the elements.

Welcoming Nihonium Street

In May, an event celebrated the new Nihonium Street at RIKEN's Wako campus. About 100 people were invited to see the RI Beam Factory (RIBF) facilities and to undergo a test to evaluate their knowledge of the elements.

Nihonium Street, which was completed in March this year, commemorates the discovery of the element nihonium in Wako with a series of plaques, running from Wakoshi Station to the entrance of RIKEN's Wako campus. The street features plaques inscribed with each of the elements from hydrogen (atomic number 1) to nihonium (113) and further to oganesson (118), the heaviest element synthesized so far.

After arriving, the visitors gathered at the RIBF building, where they underwent either a level 2 or 3 test sourced from the Genso Club, a Japanese association set up to accredit people in their knowledge of the elements and the periodic table.

Wako Mayor Takehiro Matsumoto joked during his introduction that even he had found some of the test difficult, though he had passed. Following the test, the 100 people were offered a tour of the RI Beam Factory and insights into the work of the Nishina Center for Accelerator-Based Science from Center Director Hideto En'yo.

Congratulations to the EIHO and BAIHO awardees

Each year, RIKEN gives out a number of RIKEN EIHO Awards to researchers who have made major achievements during their research and it's thought that these achievements could have a major impact on society or lead to prizes. RIKEN also gives RIKEN BAIHO Awards to researchers who have had unique results that could receive the attention of scientific society meetings or that made major contributions to knowledge both inside and outside RIKEN.

EIHO AWARDS — RIKEN SIGNIFICANT ACHIEVEMENT AWARD

Kenjiro Fukuda, Takao Someya, Soo Won Heo and Keisuke Tajima: Wearable electrocardiogram monitoring devices with ultrathin, high-performance and highly stable organic solar cells

Saori Takahashi, Hisashi Miura and Ichiro Hiratani: Development of a single-cell genome-wide DNA replication sequencing method, scRepli-seq

Yasujiro Taguchi and Kosuke Karube: Discovery of chiral magnets hosting skyrmions above room temperature and their topological properties

Hideaki Otsu, Teiichiro Matsuzaki and Hiroyoshi Sakurai: Reduction and resource recycle of high-level radioactive waste with nuclear transmutation

BAIHO AWARDS — RIKEN EXCELLENT ACHIEVEMENT AWARD

Juan Pascual Anaya: Inferring the Hox system in the last common ancestor of vertebrates

Masahiko Iwasaki: Observation of a strange nuclear bound state made of a K meson and two protons

Gang Niu: Robust machine learning with less supervised information

Yukihide Momozawa: Development of a pathogenic variant database for breast cancer

Harumichi Ishigame: Elucidation of differentiation mechanisms of multipotent memory $CD8^+$ T cells

Satomi Matsuoka: Single-molecule imaging analysis for mutual inhibition between PTEN and PIP3 that generates polarity in motile cells

Haruhiko Ehara: Structural basis of nucleosome transcription by RNA polymerase II

Hiroshi Shiozaki: Development of a novel paradigm to study the mechanisms of cognition in *Drosophila*

Fuminori Takahashi: Discovery of a small peptide that modulates stomatal control via abscisic acid in long-distance signaling

Naoki Ogawa: Optical spectroscopy on topological electron/spin properties

Keisuke Tajima: Study on structure control by surface segregated monolayers in organic semiconductor thin films

Yuxi Fu: Development of ultrastrong infrared lasers and their application to the generation of intense coherent soft x-ray lights

Atsushi Hori: Study on novel in-node parallel execution model

Masahiro Nakao: Development of an optimization algorithm for order/degree problems

www.riken.jp/en/pr/topics/2019/20190620_1/

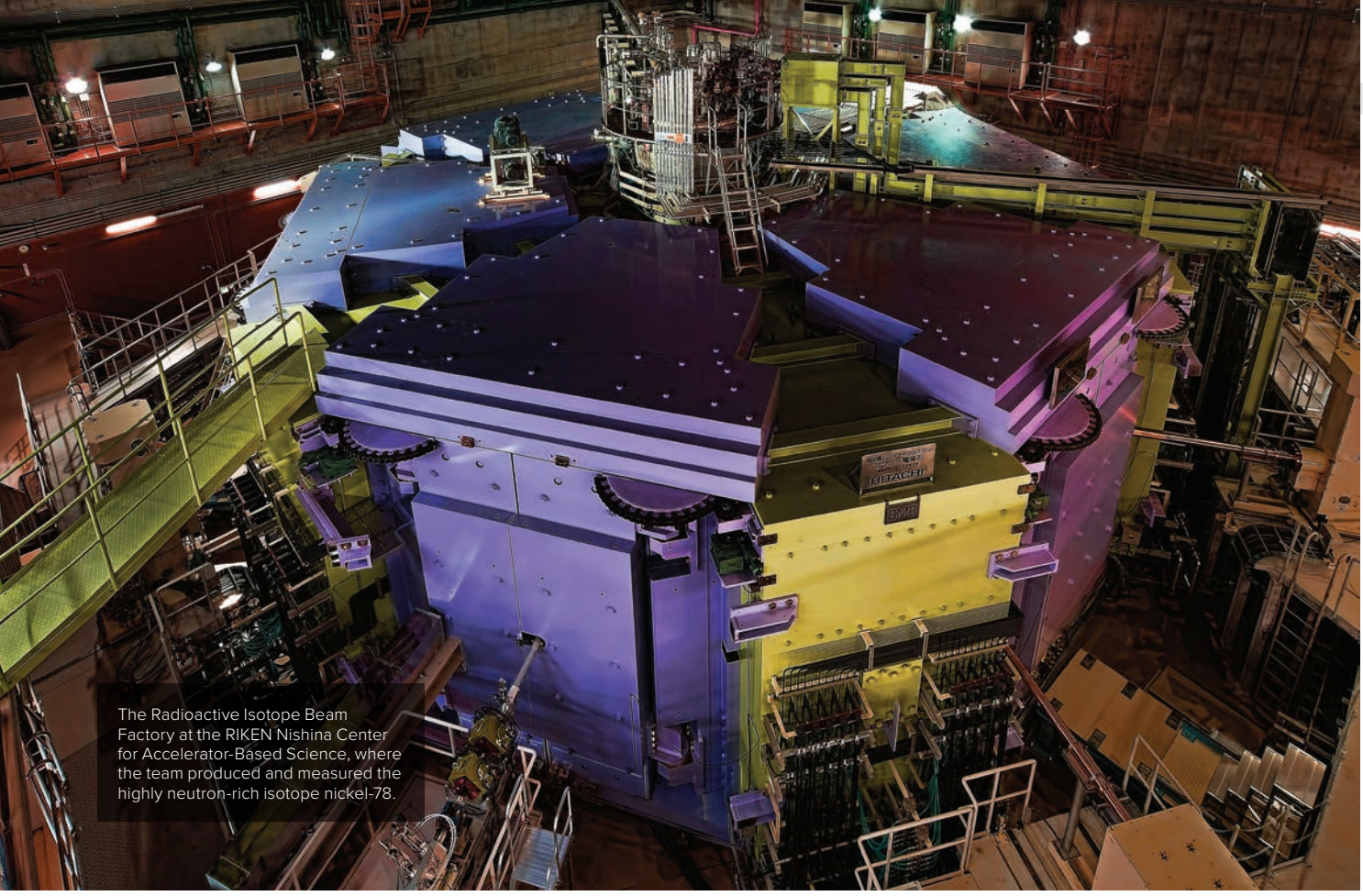
IN HONOR OF PAST TRAILBLAZERS

These RIKEN awards honor **Jokichi Takamine**, who proposed that RIKEN be established; **Eiichi Shibusawa**, who helped build RIKEN's foundation; and **Umetaro Suzuki**, a famous chief scientist who did pioneering work on vitamin A.

TAKAMINE

SHIBUSAWA

SUZUKI



The Radioactive Isotope Beam Factory at the RIKEN Nishina Center for Accelerator-Based Science, where the team produced and measured the highly neutron-rich isotope nickel-78.

NUCLEAR PHYSICS

Magic still happens at 78

Nickel-78 remains spherical despite being extremely neutron rich

The 'doubly magic' nucleus nickel-78 is spherical, allowing it to be relatively stable, despite having nearly twice as many neutrons as protons (28 protons and 50 neutrons), nuclear physicists at RIKEN have demonstrated[1].

Under normal conditions, nuclei having certain numbers of neutrons or protons, known as magic numbers, are particularly stable. Determining whether these magic numbers are valid in extremely neutron-rich nuclei is crucial for determining why the Universe has the mix of nuclei we see today.

Elements heavier than iron are mainly created through two processes in which nuclei capture extra neutrons. In one of these processes, nuclei accumulate neutrons until they reach a state—known as a waiting point—where they can no longer accept them. They then undergo beta decay, where they convert a neutron into a proton, allowing them to begin accepting new neutrons. This process occurs only in extraordinarily neutron-rich environments, such as supernova explosions and neutron star mergers.

However, the precise location of waiting points is not well understood. What complicates the process is that magic numbers of neutrons make the nuclei more resistant to capturing further neutrons. A well-known magic number is 50 neutrons, but it has been unclear whether it is preserved for extremely neutron-rich nuclei.

To get an answer, the group produced nickel-78, a doubly magic isotope, by firing an uranium-238 beam at a beryllium target. This caused the uranium to split into isotopes such as copper-79 and zinc-80—both of which have 50 neutrons. These two beams then hit a hydrogen target, where they sometimes produced nickel-78, the focus of the research.

Using gamma-ray detectors, the group found that nickel-78 is relatively stable and is spherical rather than deformed in shape, which agrees with theoretical calculations.

"We were happy to be able to show experimentally that nickel-78 does maintain the spherical shape that calculations predicted it would," says Ryo Taniuchi of the RIKEN Nishina Center for Accelerator-Based Science (RNC). "We were surprised, however, to discover that the nucleus also has a competing shape, which is not spherical, and that any lighter isotone than the one we used would be subject to this deformation and would not maintain its magic nature."

"This is an important finding, as it gives us new insights for how magic numbers appear and disappear across the nuclear landscape and affect the process of nucleosynthesis that led to the abundance of isotopes that we see in the Universe today," says Pieter Doornenbal, who is also at the RNC. "We intend to do further experiments with even lighter isotones with 50 neutrons to experimentally demonstrate this finding."

Reference

1. Taniuchi, R., Santamaria, C., Doornenbal, P., Obertelli, A., Yoneda, K., Authelet, G., Baba, H., Calvet, D., Château, F., Corsi, A. *et al.* ^{78}Ni revealed as a doubly magic stronghold against nuclear deformation. *Nature* **569,** 53–58 (2019).

X-RAY FREE-ELECTRON LASERS

More x-rays for your buck

An optical scheme that sharpens the spread of photon energies of x-ray beams promises to increase both the number and type of experiments that can be performed

A simple way to greatly improve the brilliance of x-ray lasers has been demonstrated by RIKEN researchers[1]. This advance promises to both free up precious experimental time on big x-ray laser facilities and enable new experiments.

X-rays are routinely used for scanning bags at airports and capturing medical images. In both cases, x-rays are generated by x-ray tubes, the x-ray equivalent of the electric light bulb. The x-ray beams they produce are weak and the waves making up the beams are out of sync with each other.

"I'm really excited about the experimental results that this method will enable"

For more demanding applications, such as taking picosecond snapshots of chemical reactions and studying the structures of biomolecules, viruses, and smart materials, researchers need much more intense x-ray beams whose waves are in sync. For these applications, they use large x-ray facilities known as x-ray free-electron lasers (XFELs).

But XFEL beams have quite a wide spread of x-ray photon energies. Since many experiments require x-ray beams with a narrow range of photon energies, researchers often have to throw away many of the x-ray photons to narrow the photon-energy spread. This makes experiments take longer to complete, which is a problem as the competition to get time on the handful of XFEL facilities around the world is intense.

Now, Ichiro Inoue of the RIKEN SPring-8 Center and co-workers have demonstrated a straightforward way, called self-seeding, to generate x-ray beams with a sharp distribution of photon energies without sacrificing beam intensity. They boosted the spectral brightness six times compared to conventional XFELs.

The researchers achieved this by placing a monochromator—a device designed to narrow the photon-energy spread of an x-ray beam—between two long banks of magnets, or undulators. The first undulator creates an x-ray laser beam, and the monochromator selects a narrow-band x-ray beam, which is used as a 'seed beam' and amplified in the second undulator.

The team's monochromator uses reflection between two silicon crystals. It generates the seed beam more efficiently and is easier to use than earlier monochromators based on transmission through a thin diamond crystal.

As well as freeing up XFEL facility time for more experiments, it will let physicists explore new phenomena that occur only at very high x-ray energies. "This method can be easily implemented at current XFEL facilities," notes Inoue. "Colleagues at other XFEL facilities have told me they are considering trialing our seeding method at their facilities. I'm really excited about the experimental results that this method will enable." ●

The monochromator developed by Ichiro Inoue and his team enables the spectral brightness of x-ray free-electron lasers (XFELS) to be enhanced six times compared to conventional XFELs.

Reference

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MULTIFERROICS

Crystals could cut energy consumption

Crystals with special magnetic and electrical properties could help reduce the power consumed by memory storage devices

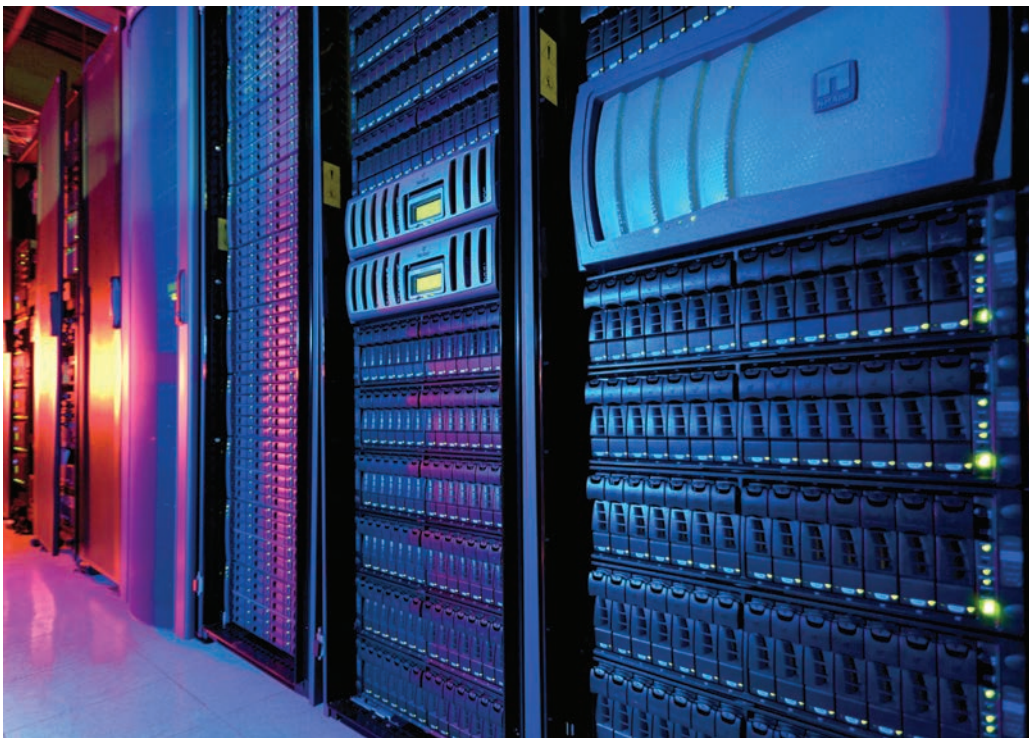
A vital step toward realizing memory storage devices that consume a tiny fraction of the power needed for current devices has been made by a RIKEN team. They have developed a material whose magnetism can be switched by applying a voltage at temperatures close to room temperature[1].

When you use cloud-based services such as Facebook and Google, your data is stored in huge data centers, which globally consume an estimated 200 terawatt hours a year—more energy than some countries consume. And this energy use by data centers is set to increase in the future.

Data storage is quite energy intensive because present devices store data by using an electrical current to change the magnetic state of a memory element. If the same thing could be done using a voltage instead of a current, it is estimated that power consumptions would drop somewhere between 100 and 1,000 fold.

Special materials known as magnetoelectric multiferroics are promising for realizing this because their magnetism can be flipped by applying a voltage rather than a current. But few such materials exist, and those that do, exhibit this property at temperatures well below room temperature, which makes them unsuited for practical applications.

Now, Vilmos Kocsis of the RIKEN Center for Emergent Matter Science and his colleagues have made crystals whose magnetism can be controlled using a voltage at temperatures close to room temperature. They achieved this by fine-tuning the chemical composition of their 'hexaferrite' crystals and then heating them in oxygen at high pressure.



Data storage systems would consume a lot less power if they were based on materials whose magnetization could be switched by applying a voltage. Researchers at RIKEN have developed such a material that works at near room temperature.

In addition to simultaneously measuring the magnetization and polarization of the crystals, the team used magnetic force microscopy to visualize the changes induced in microscopic magnetic domains when a voltage was applied.

According to Kocsis, the hardest part of the experiment was making the crystals. "It was challenging," he recalls. "Growing these crystals is not easy at all, and the biggest challenge was to produce really good quality material." He needed to make six crystals on average for each measurement, because many of the crystals were destroyed by the high electric fields applied during measurements.

Kocsis was also a bit apprehensive about what might happen if a major earthquake struck. "Working with high-pressure oxygen is not recommended in such an event!"

But it was worth the effort. "I was happy with such beautiful results," he says.

The team is currently preparing a second paper for publication that delves into more detail about the mechanism behind the coupling of the material's magnetic and electric properties.

Reference

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An image showing two galaxy clusters on the verge of merging.

X-ray: NASA/CXC/RIKEN/L. Gu *et al*; Radio: NCRA/TIFR/GMRT; Optical: SDSS

ASTROPHYSICS

Galaxy clusters caught in a first kiss

Two galaxy clusters that are on the verge of merging have been spotted

For the first time, astronomers have found two giant clusters of galaxies that are just about to collide[1]. This observation can be seen as a missing piece of the puzzle in our understanding of the formation of structure in the Universe, since large-scale structures—such as galaxies and clusters of galaxies—are thought to grow by collisions and mergers.

Clusters of galaxies are the largest known bound objects and consist of hundreds of galaxies that each contain hundreds of billions of stars. Ever since the Big Bang, these objects have been growing by colliding and merging with each other. Because of the massive size of these clusters, which are a few million light years across, these collisions can take about a billion years to complete. After the dust has settled, the two colliding clusters will have merged into one bigger cluster.

Because the merging process takes much longer than a human lifetime, we see only snapshots of the various stages of these collisions. The challenge is to find colliding clusters that are just at the stage of first touching each other. This stage is relatively brief, and so it is hard to find. Astronomers have found a lot of single clusters and merged clusters, but until now they had not spotted two clusters that are just about to touch each other.

Now, an international team of astronomers has discovered two clusters that are on the verge of colliding (see image). This enabled astronomers to test their computer simulations, which predict that in the first moments a shock wave is created between the clusters and travels out perpendicular to the merging axis.

"These clusters show the first clear evidence for this type of merger shock," says Liyi Gu of the RIKEN High Energy Astrophysics Laboratory. "The shock created a hot belt region of 100-million-degree gas between the clusters, which is expected to extend up to, or even go beyond, the boundary of the giant clusters. Therefore, the observed shock has a huge impact on the evolution of galaxy clusters and large-scale structures."

Astronomers are planning to collect more snapshots to ultimately build up a continuous model describing the evolution of cluster mergers. "More merger clusters like this one will be found by eROSITA, an x-ray all-sky survey mission that will be launched this year," says Hiroki Akamatsu of SRON Netherlands Institute for Space Research. "Two other upcoming x-ray missions, XRISM and Athena, will help us understand the role of these colossal merger shocks in the structure formation history."

Reference

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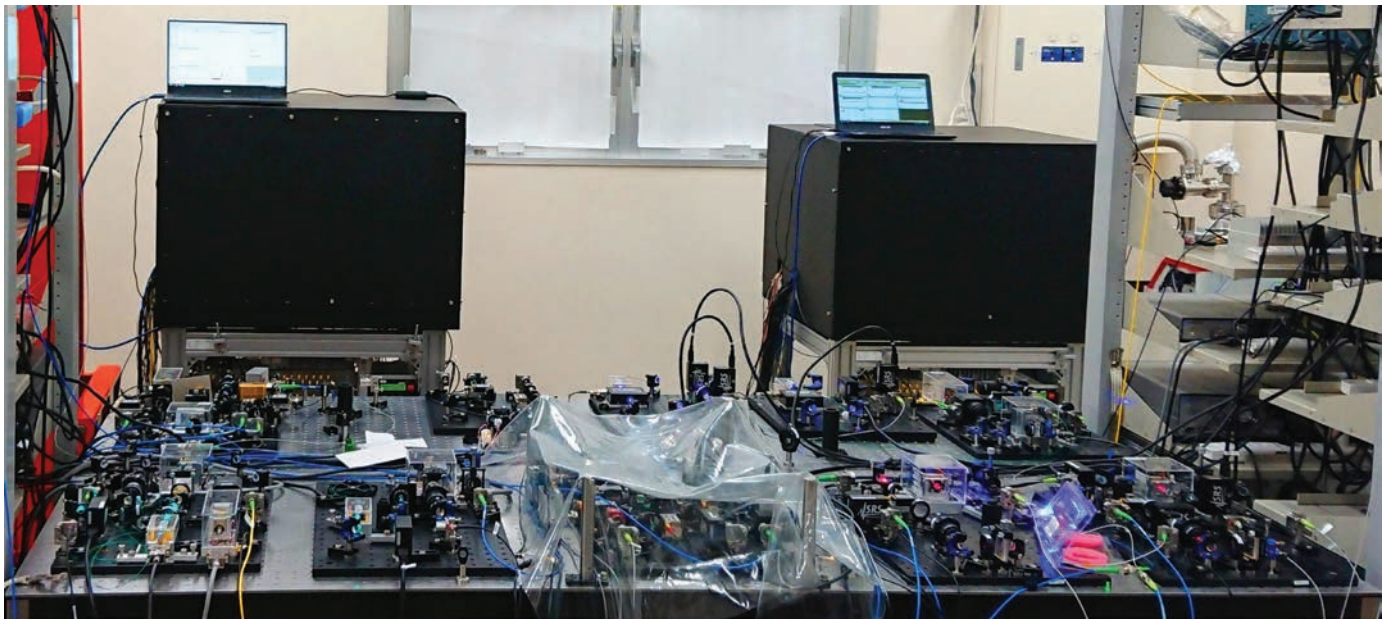

These two optical lattice clocks use strontium atoms to keep time with incredible accuracy.

ATOMIC CLOCKS

A matter of time

A lattice of strontium atoms could 'tick' with unprecedented accuracy

A significant step toward building an optical lattice clock that will set a new record for accuracy has been taken by RIKEN researchers[1]. Such clocks could be used to measure millimeter-level differences in height.

The astonishing precision with which atomic clocks keep time sees them used in applications as diverse as global positioning systems and telecommunications. Conventional atomic clocks contain a thin gas of atoms, such as cesium, which act as pendulums. The atoms absorb and emit energy at a specific microwave frequency, and this frequency is used to define the duration of 1 second.

In contrast, optical clocks use visible light to make atoms 'tick' at frequencies tens of thousands of times higher than microwave frequencies. "That makes optical clocks far more precise than conventional microwave atomic clocks," notes Hidetoshi Katori of the RIKEN Quantum Metrology Laboratory.

Optical clocks are so accurate that they lose less than 1 second in 16 billion years—longer than the age of the Universe. They thus have a fractional uncertainty of roughly 10^{-18}.

But further improvements in accuracy could open up new applications. For example, according to the general theory of relativity, two clocks at different heights above the Earth's surface will tick at slightly different rates. If those clocks operated with an uncertainty of 10^{-19}, it should be possible to measure height differences between them with millimeter precision, which may lead to applications such as detecting tiny anomalies in the Earth's gravitational field to improve earthquake-warning systems.

The leading method to achieve this uses lasers to confine thousands of atoms in a lattice. The laser would normally affect the atoms' ticking, but researchers can eliminate most of this perturbation by using a carefully chosen 'magic frequency' of laser light.

Katori's team has now developed a way to fine-tune the intensity of this laser light to further reduce any perturbations of the atoms. This 'magic intensity' could improve the accuracy of the optical lattice clock to unprecedented levels.

The team cooled strontium atoms to a fraction of a degree above absolute zero (–273.15 degrees Celsius) and loaded them into an optical lattice trap. They then carefully monitored how very tiny shifts in the frequency of the atoms varied with the laser intensity and frequency. These measurements allowed the team to calculate the precise laser intensities and frequencies that should enable them to reduce the clock's uncertainty down to 10^{-19}.

"This will lead to exciting applications"

The researchers are now building two optical lattice clocks so that they can apply these predicted magic frequency and intensity conditions, and measure how closely the clocks agree. "This will lead to exciting applications in the future," predicts Katori. ●

Reference

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WATER OXIDATION

Using an overlooked catalyst to produce hydrogen

An Earth-abundant catalyst promises to make the production of hydrogen fuel more feasible

A low-cost, stable catalyst for generating hydrogen fuel from water has been found by RIKEN researchers[1]. This development could make the production of hydrogen from water and sunlight more economically viable.

Hydrogen is a highly attractive, energy-efficient renewable fuel source that produces only water when burned. It can be generated from sunlight using proton-exchange membrane electrolysis cells. But because the conditions in these electrolysis cells become acidic, most catalysts corrode in them.

The only catalysts that have been found to be stable under such conditions are those based on iridium oxide, but iridium is scarce and expensive.

"Iridium is rarer than gold," says Hideshi Ooka of the RIKEN Center for Sustainable Resource Science (CSRS). "One study found that there simply isn't enough iridium in the world to meet the global energy demand."

Now, Ailong Li, also of the CSRS, Ooka and their coworkers have discovered a stable catalyst, gamma manganese oxide (γ-MnO_2), for proton-exchange membrane electrolysis cells that is about a million times more abundant than iridium. They found that γ-MnO_2 is stable in acid in a specific range of potentials.

The material had been overlooked previously because predictions based on thermodynamics indicated that it should be unstable in acid. But it dawned on Li that since γ-MnO_2 is generally made using concentrated acid, it may be stable in acid under certain conditions.

Hydrogen fuel could be used to power the cars of the future.

"Li's knowledge of the synthetic procedures in acid was critical for us to test this material," explains Ooka. "Otherwise, we would have ignored this material, just as many other groups have in the past."

To check the effect of the potential on the catalyst's stability, the team analyzed the catalyst and the water it was immersed in using ultraviolet–visible spectroscopy. They found that in a narrow potential window of 0.1 volts it was so stable that it has not degraded significantly even after more than a year of continuous electrolysis.

Ooka explains that the lesson from the study is not to rely on oversimplified analyses based on thermodynamics. "Thermodynamics just tells you that this material could dissolve," he says. "But it doesn't mean it will."

The team is now optimizing their catalyst toward industrial hydrogen production. They also plan to use their spectroscopic technique to see whether any other materials have similar windows of stability. Looking further ahead, Ryuhei Nakamura, who led the team, says: "We will seek to combine this technique with carbon dioxide fixation. That would allow us to produce chemicals and fuels from water and carbon dioxide, mimicking photosynthesis, which would truly bolster the sustainability of human society." ●

Reference

1. Li, A., Ooka, H., Bonnet, N., Hayashi, T., Sun, Y., Jiang, Q., Li, C., Han, H. & Nakamura, R. Stable potential windows for long-term electrocatalysis by manganese oxides under acidic conditions. *Angewandte Chemie International Edition* **58,** 5054–5058 (2019).

STROKE

Drug cocktail helps mice bounce back after stroke

Stroke-induced brain damage in mice can be reduced by using drugs that block adrenergic receptors

A promising experimental treatment that could supplement current post-stroke treatments has been demonstrated by RIKEN researchers. They have shown that brain fluids after a stroke can be normalized by using a combination of drugs to block the activity of noradrenaline in the brain, by aiding motor recovery and reducing cell death in mice[1].

Brain injuries such as stroke can be devastating and require time-sensitive treatment. Clotting factors like thrombin are commonly administered to patients, but many other stroke-related signs can be targeted, such as swelling and ion imbalances in the surrounding fluids. A major consequence of stroke is an immediate imbalance in the ion concentrations of fluids that bathe brain cells. Potassium levels spike and fluid accumulates, which leads to swelling, a major cause of stroke injury.

"We know that the water dynamics in the brain immediately during and after a stroke are critical, so we focused on the pathways that move fluids in and out of cells," explains Hiromu Monai of the RIKEN Center for Brain Science.

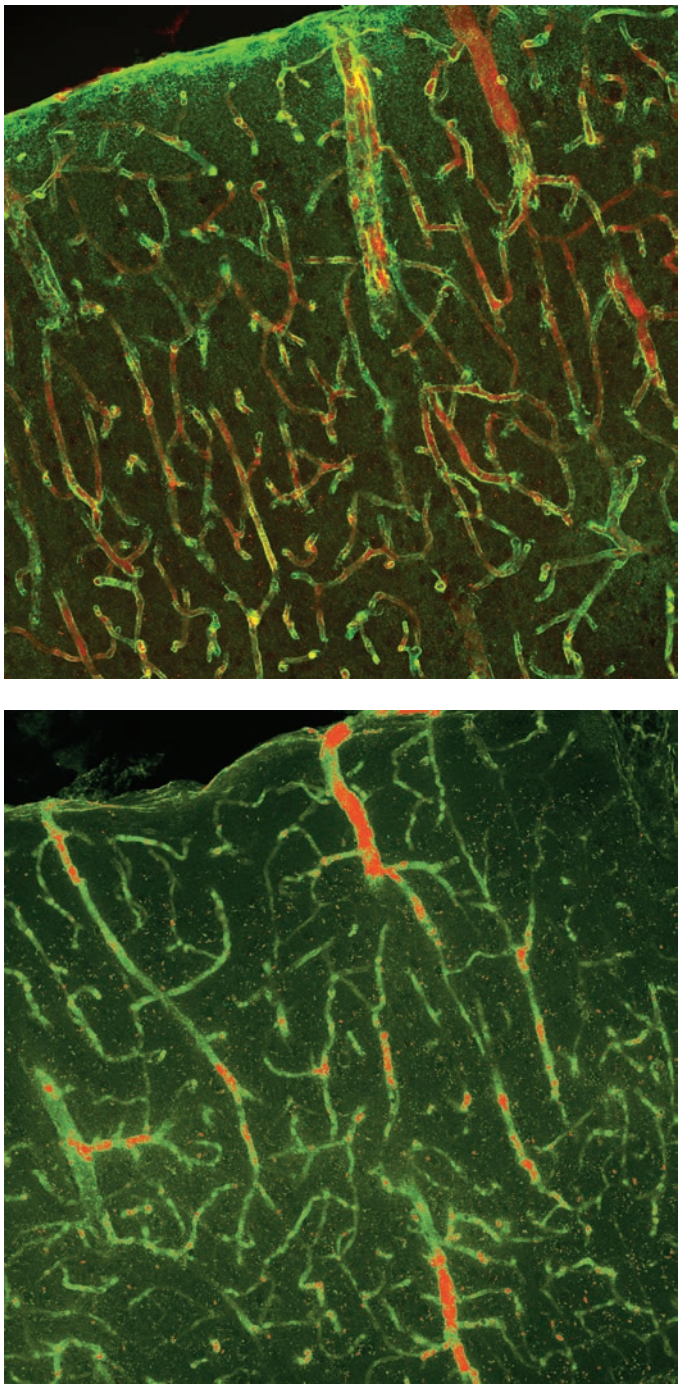
One way to lower potassium levels and get neurons active again is to administer adrenergic receptor (AdR) antagonists, drugs that counteract the electrical and chemical disturbances that accompany a stroke. These antagonist drugs have been found to promote fluid exchange in normal brains.

A cocktail of AdR blockers reduced both the area of tissue damage and potassium levels in mice that had had strokes. Moreover, administrating AdR blockers even 1 or 2 hours after a stroke stopped the infarction from spreading. Mice were also able to recover the use of their forepaws much more quickly when treated with AdR blockers. The researchers found that levels of a water channel called aquaporin 4 were lower following a stroke. "We think that preserving aquaporin levels is critical to protecting brain tissue during stroke," says Monai.

To test this idea, they used genetically engineered mice that lacked the aquaporin 4 water channel. These mice did not benefit from AdR blocker treatment and their brain potassium levels remained high after stroke, supporting the idea that the neuroprotective effect occurs through the action of aquaporin 4 water channels.

"Keeping potassium levels in balance is an alternative therapeutic strategy for stroke, and we found that adrenergic receptor blockers promote this normalization," says Monai. "Recovering motor function following a stroke is so important, and we also saw improvements in the mice treated with AdR blockers."

A patent application for AdR blocker treatment for stroke has been filed in Japan. ●



Damage to brain tissue in mice after a stroke was less when adrenergic receptor antagonists were administered (top) compared to control mice (bottom).

Reference

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AUTISM

Link between autism symptoms and brain anatomy

A connection between two autistic symptoms and brain anatomy has been uncovered

An anatomical link between the cognitive and perceptual symptoms of autism has been found by RIKEN neuroscientists[1].

Mental inflexibility, which is exhibited in restricted and repetitive behaviors, is a hallmark symptom of autism spectrum disorder (ASD). People with ASD can also exhibit less flexible perception. Until now, these two autistic symptoms were only related conceptually.

The team sought to find a physical neuroanatomical link between these two characteristics of autism. They asked people with and without ASD to perform two simple computer-based tests and to undergo an MRI scan.

The first computer test assessed perceptual stability. Participants viewed a bistable image in which the front and back of a cylindrical shape switch back and forth. The second test evaluated cognitive rigidity. Participants were shown shapes on a display and asked to choose a rule to follow: select the brightest shape or a specific shape. The researchers counted how many times each participant reported a switch in perception during the first test and how many times they spontaneously switched rules in the second test. These measures allowed the researchers to quantify perceptual stability and cognitive rigidity for each participant.

As expected, perception of the bistable image switched much less frequently in people with ASD than in the control participants. In addition, people with ASD repeated the same rule choice—brightness or shape—for longer periods before switching rules.

The results from the rule-switching task were particularly encouraging. "Cognitive rigidity in high-functioning autism is known to be difficult to detect and quantify in conventional psychological paradigms," explains Takamitsu Watanabe from the RIKEN Center for Brain Science. "We overcame this issue with a new spontaneous task-switching test." With these results, the team was confident that their tests were good measures of perceptual stability and cognitive rigidity.

The researchers then tested whether these individual scores correlated with the brain anatomy seen in the MRI scans. They found that one part of the brain in particular was related to both perceptual stability and cognitive rigidity. A lower density of neurons in the posterior superior parietal lobule was associated with both less frequent perceptual switching and less frequent rule switching, and was also associated with the severity of the participant's restricted and repetitive behaviors.

"We think that the posterior superior parietal lobule is the neural basis for both overly stable perception and cognitive inflexibility, two seemingly different symptoms in autism," says Watanabe. "Knowing the importance of this brain region, we can now work to identify how it produces its effects and test whether manipulating its neural activity can mitigate these ASD symptoms." ●

Reference

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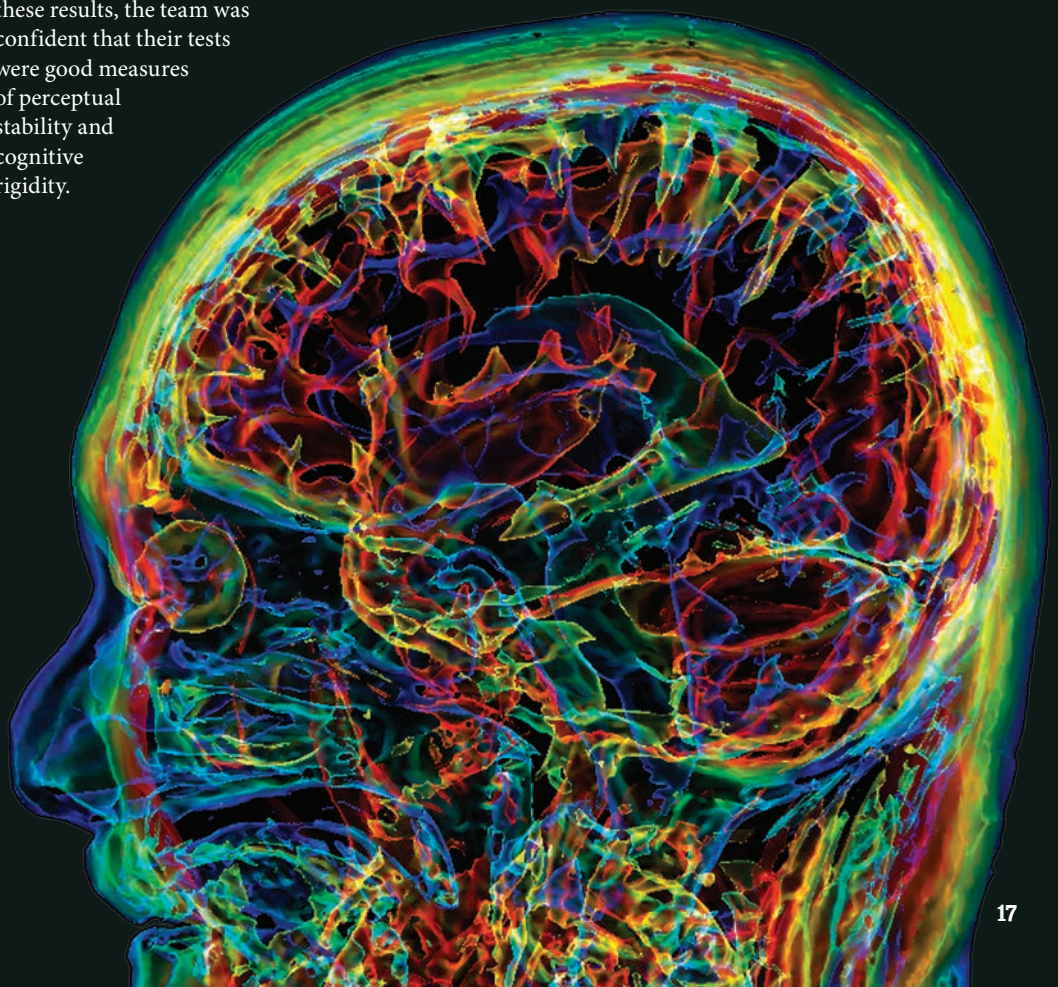

By comparing brain anatomy seen in magnetic resonance imaging (MRI) scans with results obtained in tests designed to measure cognitive rigidity and perceptual stability, RIKEN researchers have found an anatomical link between the cognitive and perceptual symptoms of autism.

SCHIZOPHRENIA

Common chemical may help treat schizophrenia

Boosting low levels of betaine in people with schizophrenia could assist with treating the condition

Supplementation of a chemical found in many foods can counteract psychiatric symptoms in mice, RIKEN researchers have found[1]. This may lead to new ways for treating schizophrenia.

Many psychiatric drugs act on the receptors or transporters of certain neurotransmitters in the brain. However, there is a great need for alternatives, and research is looking at other targets along the brain's metabolic pathways.

Betaine is found in various foods, such as cereals, beets, spinach, seafood and wine. It is also synthesized in the body, where it contributes to metabolism in various ways, including as an anti-inflammatory agent. Levels of betaine (glycine betaine or trimethylglycine) in the blood plasma of patients with schizophrenia have previously been found to be low, which suggested it is a possible therapeutic target.

Betaine is found in various foods, including spinach. Boosting its levels in the brain could help treat schizophrenia.

In the new study, mice missing a gene that is involved in making betaine showed depressive behaviors and greatly reduced betaine levels in both the brain and blood. Betaine levels in the brain recovered when it was given to the mice as a supplement in drinking water, demonstrating that betaine can pass through the blood–brain barrier.

Psychedelic drugs like PCP and methamphetamine can also produce schizophrenia-like behaviors in both humans and mice. The researchers tested whether betaine supplementation could help alleviate symptoms induced by PCP and methamphetamine in mice. They found that betaine not only improved cognitive deficits and behavioral abnormalities, it also reversed oxidative stress at the molecular level. Oxidative stress is thought to be one mechanism by which these drugs cause psychiatric symptoms in humans.

Finally, investigation of post-mortem human brain samples revealed reduced betaine levels in patients with schizophrenia, which was unrelated to the amount of antipsychotic drugs taken before death. Some of the brains exhibited 'betaine-deficit oxidative stress', a pathology that occurred in cases with severe psychotic symptoms. The researchers were able to replicate this pathology in induced pluripotent stem cells that simulate the oxidative stress condition, and counteract it with the betaine treatment.

"We suggest that one of betaine's functions is to promote antioxidant activity in the metabolic cycles in which it participates," says Takeo Yoshikawa of the RIKEN Center for Brain Science. "However, supplementation of betaine is not a silver bullet for schizophrenia or other psychiatric conditions."

The researchers also identified a genetic variant that could predict betaine's treatment efficacy, a potential example of precision medicine in psychiatry. Betaine is already used as a drug for the autosomal recessive metabolic disorder homocystinuria, so it could be considered as therapy for psychiatric conditions with minimal concern for adverse effects.

Reference

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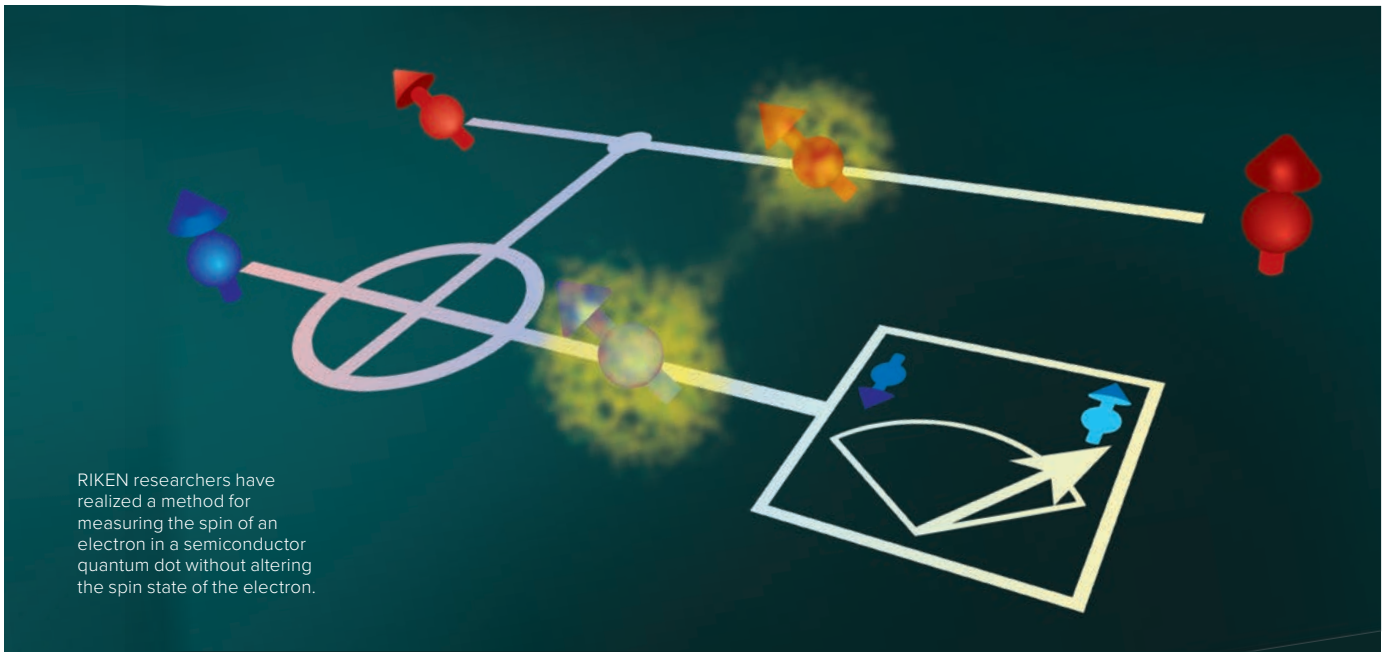

RIKEN researchers have realized a method for measuring the spin of an electron in a semiconductor quantum dot without altering the spin state of the electron.

QUANTUM COMPUTING

Measuring without demolishing

Accurate quantum computing is closer to reality, thanks to quantum non-demolition measurements

RIKEN researchers have performed repeated measurements of a semiconductor quantum system without disturbing the property they are measuring[1]. This is promising for the development of quantum computers based on such systems.

One dictum of quantum physics is that it is impossible to perform a measurement on a quantum system without disturbing it. This is problematic for quantum computing because it means that you get only one chance to read a qubit—the quantum equivalent of bits in classical computers. This in turn implies that it is not possible to detect and correct errors in qubits, which is vital for achieving accurate calculations.

One way to overcome this problem is to use a special type of measurement known as a quantum non-demolition measurement (QND), which is designed such that the property being measured remains unchanged (other properties of the system will be altered). This permits multiple measurements to be performed on the system without affecting the property being measured.

While QND measurements have been performed in various systems, until now they had not been realized in semiconductor quantum dots—tiny semiconductor regions that accommodate only a few electrons. Semiconductor quantum dots are especially attractive for quantum computers because they have the key advantage of being able to use existing manufacturing technology.

"Semiconductor devices are particularly good for larger-scale quantum computers because we can employ existing technologies of the integrated circuit industry," explains Takashi Nakajima at the RIKEN Center for Emergent Matter Science.

Now, Nakajima and his co-workers have succeeded in realizing QND measurements in a device containing semiconductor quantum dots.

By entangling two quantum dots to a third one, they could use the two quantum dots as probes to measure the spin of an electron in the third quantum dot. A single measurement of the spin of a quantum dot was not particularly accurate, but performing multiple measurements on the quantum dot allowed a much higher accuracy to be realized.

Their technique will allow errors to be corrected in quantum computers. "Being able to detect an error in a qubit without disturbing the qubit further, will allow us to correct the error by an appropriate control pulse," says Nakajima. "Such an error-correcting protocol is essential for realizing a fault-tolerant quantum computer."

In the present study, the team used gallium arsenide as the semiconductor. They note that the next challenge will be to realize QND measurements in silicon, as that will enable accuracies of more than 99% to be achieved.

Reference

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Colored scanning electron micrograph (SEM) of a clump of activated T cells from a human blood sample. RIKEN researchers have found that a protein known as CIN85 inhibits the activation of T cells.

IMMUNE SIGNALING

Protein puts the brakes on immunity

In a surprise finding, a versatile protein has been shown to inhibit the activation of immune cells

The immune response of mice to pathogens is curbed by a multitasking protein, CIN85, which applies the brakes to immune cells called T cells, researchers at RIKEN have shown[1]. This finding could assist scientists to find new ways to tinker with the body's immune system so that it attacks cancer cells more effectively.

A type of white blood cell, T cells are a key player in the body's immune response to pathogens such as bacteria and viruses. They are activated by proteins known as antigens, which are found on the surfaces of pathogens. T-cell activation triggers a highly complex cascade of reactions involving many different molecules. Some of these reactions reduce the strength and duration of positive signals to prevent T cells from being excessively activated, which could lead to harmful effects such as inflammation and autoimmune disorders.

Now, Takashi Saito at the RIKEN Center for Integrative Medical Sciences and his colleagues have shown that the protein CIN85 curtails the activation of T cells.

CIN85 plays different roles in different cells. To discover its function on T cells, the researchers produced mice that lacked CIN85 and then compared their immune response with that of normal mice. Saito and his team found that the mice lacking CIN85 produced more T cells as well as interleukin-2, a signaling molecule in the immune system, after antigen stimulation.

The result came as a surprise since CIN85 had been found to have the opposite effect in B cells, another key type of immune cell. "We had expected the opposite finding because CIN85 promotes B-cell receptor signaling, and B cells are similar to T cells from a signaling point of view," explains Saito.

Interestingly, the researchers found that a close cousin of CIN85 called CD2AP does not inhibit the activation of T cells. There had been speculation that CD2AP would have similar effects on cells as CIN85 because it contains similar sequences of amino acids as CIN85. But when Saito's team examined mice lacking CD2AP, they found that their T-cell activation did not differ from that of normal mice.

The team also clarified the mechanism by which CIN85 inhibits T-cell activation: they found that CIN85 recruits an inhibitory phosphatase known as Sts-2 to dampen activation signals.

Saito notes that the finding is very topical at the moment, since there is a lot of interest in finding affordable ways to manipulate the immune system so that it can attack tumors more effectively. ●

Reference

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EPILEPSY

Trigger region found for epileptic seizures

By monitoring irregular brain activity in mice, scientists have determined the brain regions responsible for triggering one type of epileptic seizure

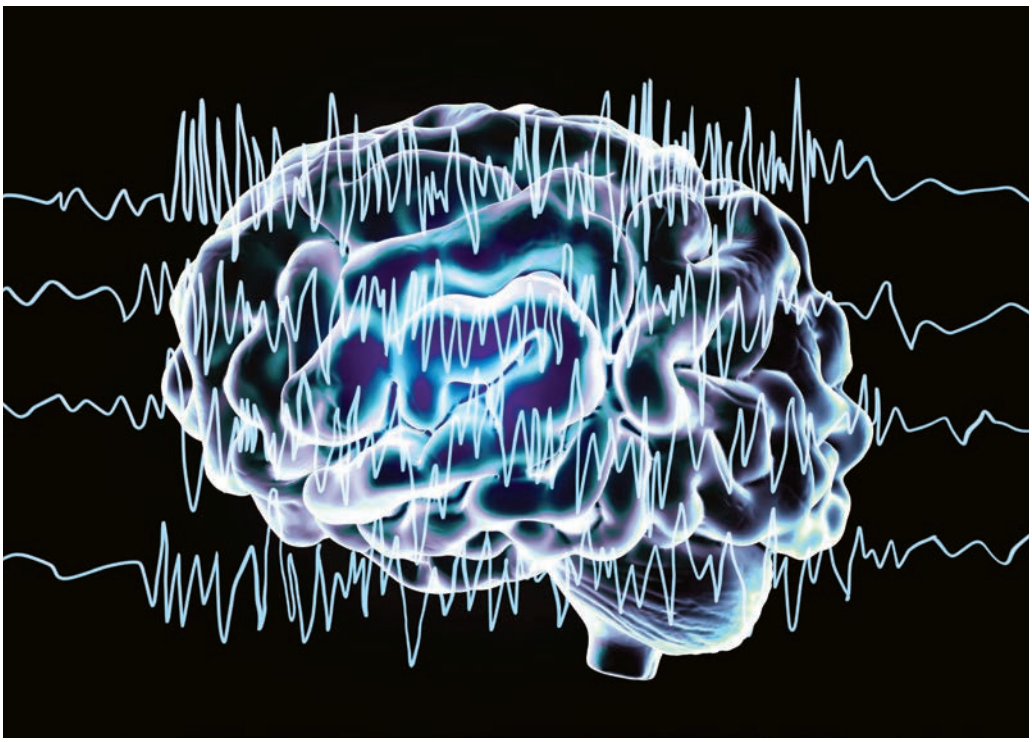
In a major step forward for epilepsy research, a neurological explanation for one type of seizure has been discovered by RIKEN neuroscientists[1].

Epileptic seizures come in several varieties. The most familiar are characterized by large convulsions, but several kinds of childhood epilepsy involve absence seizures in which children are unconscious for a few seconds due to widespread erratic brain activity. Absence seizures are associated with spike-wave discharges—irregular brain activity that can be recorded on electrocorticograms.

Now, by using a mouse model of childhood epilepsy, a team led by Kazuhiro Yamakawa at the RIKEN Center for Brain Science has shown that absence epilepsy can be triggered by impaired communication between two brain regions: the cortex and the striatum.

Because children with these types of epilepsy often have mutations in the *STXBP1* or *SCN2A* genes, the team created mouse models of these childhood epilepsies by mutating these genes. For both genes, they created mice with one normal gene and one mutated gene. After establishing that their mice experienced absence seizures, as evidenced by spike-wave discharges over the somatosensory cortex, the researchers performed a series of experiments to determine how they were triggered.

Spike-wave discharges can be blocked by drugs that inhibit neurons from exciting each other. The scientists injected a neuronal inhibitor into several brain regions and discovered that three regions—the somatosensory cortex, the thalamus and a part of the striatum beneath the cortex—are related to the seizures.



By monitoring irregular brain activity in mice using electrocorticogram recordings, RIKEN neuroscientists have determined the brain regions responsible for absence seizures, a type of epileptic seizure.

Although many researchers consider that the somatosensory cortex and the thalamus are the primary sources for absence seizures, further experiments showed that the striatum was actually the region critical for triggering the seizures.

After finding that injecting a neuron-exciting drug into only the striatal region of the model mice reliably induced spike-wave discharges, the researchers created mice with mutations limited to neurons in the somatosensory cortex that were connected to the striatum. These mice showed the same spike-wave discharges, indicating that absence seizures were triggered by faulty signals arriving in the striatum. Another experiment showed that the problem arose because transmission specifically to fast-spiking interneurons in the striatum was too weak.

These findings were unexpected. "Although the cortico-thalamic circuit has long been assumed to be the sole and exclusive causal source for absence epilepsy, we showed that it is actually triggered by impaired cortico-striatal excitatory transmission," Yamakawa explains. "This could be a paradigm shift for epilepsy research." ●

Reference

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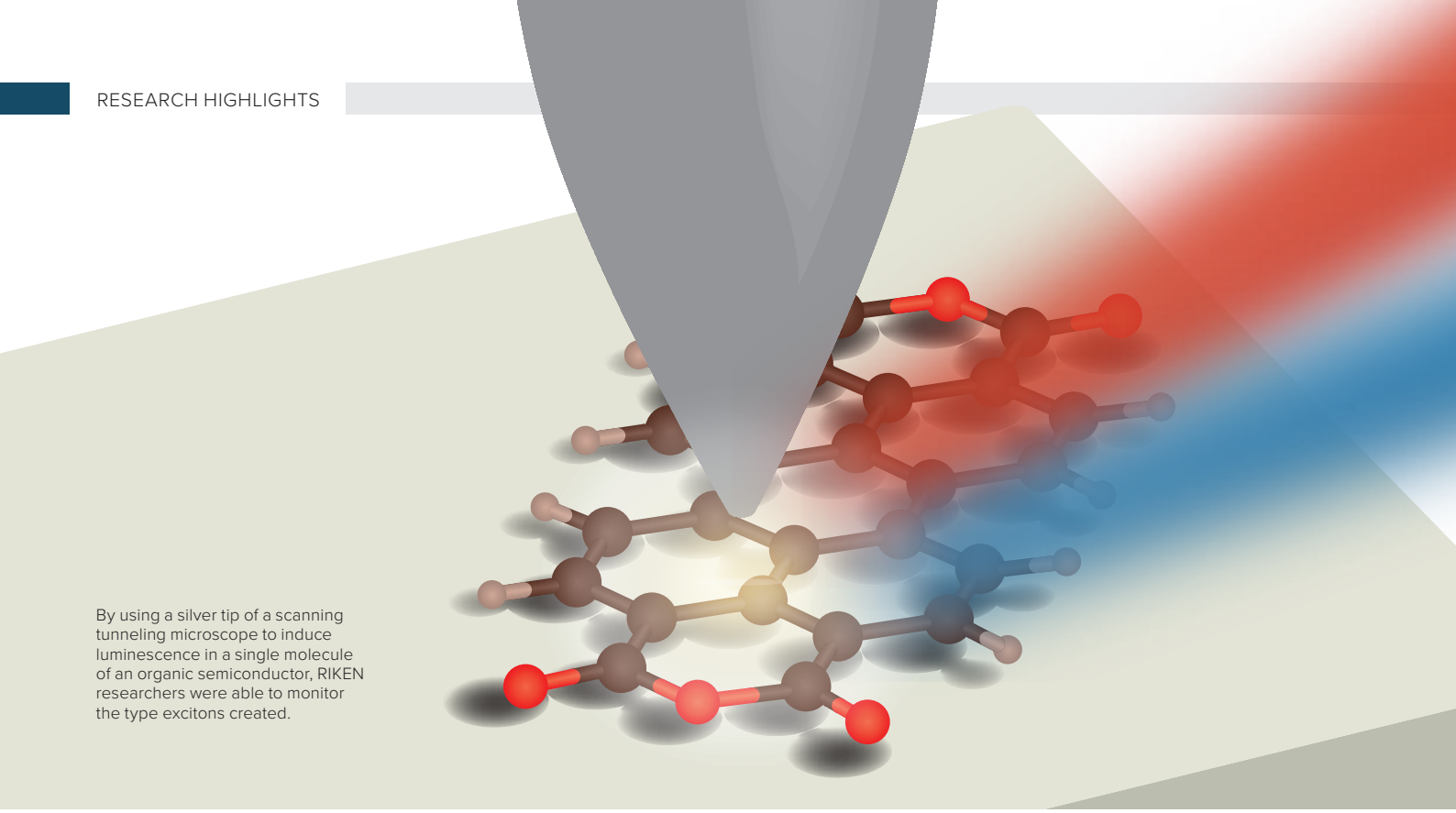


By using a silver tip of a scanning tunneling microscope to induce luminescence in a single molecule of an organic semiconductor, RIKEN researchers were able to monitor the type excitons created.

ORGANIC LIGHT-EMITTING DIODES

Cutting energy consumed by displays

A new way to manipulate excitons in OLEDs cuts their energy demand

More energy efficient displays could be possible thanks to physicists at RIKEN finding a way to significantly reduce the amount of energy that organic light-emitting diodes (OLEDs) require[1].

OLEDs are flat and flexible light-emitting devices, consisting of a series of organic thin films sandwiched between two conductors. They are attractive replacements for liquid-crystal diodes because they are thinner and more efficient since they do not need a backlight.

Passing a current through an OLED creates pairs of negatively charged electrons and positively charged holes known as excitons that are key for OLEDs. Excitons emit light when they drop to a lower energy level.

Normally, the spins of excitons in OLEDs point in either the same or opposite directions. Excitons with parallel spins—known as triplet excitons—are three times more common than singlets, which have antiparallel spins. Singlets, which are created along with the triplets, require more energy, and though they can be converted into triplets, the device as a whole still requires the energy to create them initially.

Now, a group of RIKEN and international researchers has found a way to lower the voltage of OLEDs so that only triplets are formed.

"We believe that these findings could become a general working principle for novel OLEDs with low operating voltage"

They started by investigating the basic physics behind the creation of excitons using precise electroluminescence measurements of single molecules using a scanning tunneling microscope combined with an optical detection system. The researchers prepared a model system based on an isolated molecule of an organic semiconductor adsorbed on a metal-supported ultrathin insulating film. They used a special technique to impart a negative charge to the molecule. Then, the team used the current from a scanning tunneling microscope to induce luminescence in the molecule, and monitored what type of exciton was created based on the emission spectrum (see image).

The measurements showed that only triplets formed at low voltage. Theoretical calculations by Kuniyuki Miwa and Michael Galperin at the University of California San Diego confirmed the experimental results, substantiating the mechanism.

"We believe that we were able to do this thanks to a previously unknown mechanism, where electrons are selectively removed from the charged molecule depending on their spin state," says Kensuke Kimura of the RIKEN Surface and Interface Science Laboratory.

"It was very exciting to discover this new mechanism," says Yousoo Kim, who leads the laboratory. "We believe that these findings could become a general working principle for novel OLEDs with low operating voltage." ●

Reference

1. Kimura, K., Miwa, K., Imada, H., Imai-Imada, M., Kawahara, S., Takeya, J., Kawai, M., Galperin, M. & Kim, Y. Selective triplet exciton formation in a single molecule. *Nature* **570,** 210–213 (2019).

STRUCTURAL BIOLOGY

Preventing that stalling feeling

The smooth copying of genetic information in cells is facilitated by two protein factors that act as bearings against chromatin structures

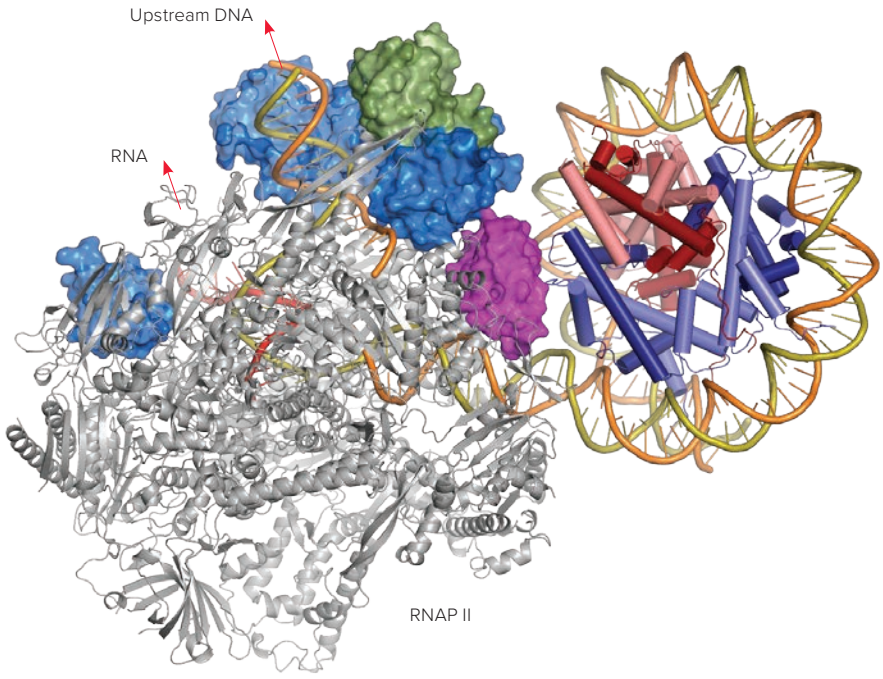
Two protein factors play a critical role in ensuring that transcription of DNA into RNA does not grind to a temporary standstill when it hits structures known as nucleosomes, RIKEN researchers have shown[1]. This finding has important implications for research into new strategies for treating diseases such as cancer.

As you read this, an enzyme known as RNA polymerase II is busy transcribing genetic information stored in DNA into messenger RNA, much of which is then converted into proteins needed for various cellular processes in your body.

The familiar double helix of DNA is not arranged in straight lengths; rather, it is wrapped around spool-like structures known as nucleosomes, which are connected by short, linear sections of DNA. While this arrangement allows more compact storage of DNA than a linear structure, it complicates transcription because RNA polymerase II has to negotiate nucleosomes—the building blocks of chromatin—when it is transcribing.

"How RNA polymerase II manages to do this has been a long-standing question in cell biology," says Shun-ichi Sekine of the RIKEN Center for Biosystems Dynamics Research (BDR).

When proteins called elongation factors are not present, the transcription of DNA by RNA polymerase II stalls at several locations within the nucleosome, a previous study by Sekine and collaborators had shown.



The elongation factors Elf1 (magenta) and Spt4/5 (blue and green) come between RNA polymerase II (RNAP II) and a nucleosome to ensure smooth transcription of DNA. The colored rods on the right make up the nucleosome.

Now, they have identified two particular elongation factors—Elf1 and Spt4/5—that prevent RNA polymerase II from stalling. By examining the structures of Elf1 and Spt4/5, the team has also revealed some of their inner workings.

The researchers found that by itself Elf1 did not prevent transcription from stalling, while Spt4/5 had only a limited effect. But when both elongation factors were present, transcription proceeded unimpeded. "This was a very surprising finding," says Haruhiko Ehara, also of BDR. "Especially for the small Elf1 factor, since very little was known about it."

The team then used cryo-electron microscopy to examine the structures of these two elongation factors and how they help RNA polymerase II to pass through the nucleosome. They discovered that Elf1 and Spt4/5 squeeze in between RNA polymerase II and the nucleosome and effectively act as bearings, enabling transcription to occur smoothly. "The two elongation factors prevent direct contact between the polymerase and the nucleosomes that cause stalling, and they facilitate the smooth rotation of the nucleosome in front of RNA polymerase II," notes Sekine.

This information will be foundational for future research into diseases such as cancers that involve the improper transcription of genetic information. "By studying such structures we can gain a better understanding of disease mechanisms, which will provide valuable clues for drug development and other therapies," says Sekine. ●

Reference

1. Ehara, H., Kujirai, T., Fujino, Y., Shirouzu, M., Kurumizaka, H. & Sekine, S. Structural insight into nucleosome transcription by RNA polymerase II with elongation factors. *Science* **363,** 744–747 (2019).

METALLOENZYME

New weapon against cancer cells

An artificial enzyme combined with a sugar and a metal ion can be used to deliver drugs to cancer cells

A promising method for delivering a drug to cancer cells without affecting surrounding tissues has been developed by RIKEN chemists[1].

Many metal catalysts have been developed for synthesizing molecules such as drugs and functional materials. Recently, researchers have begun to focus on chemical reactions in living bodies catalyzed by transition metals—elements belonging to groups 3 to 12 on the periodic table. However, transition-metal catalysts are easily inactivated by substances such as antioxidants, so it has been difficult to get them to perform chemical reactions in organisms.

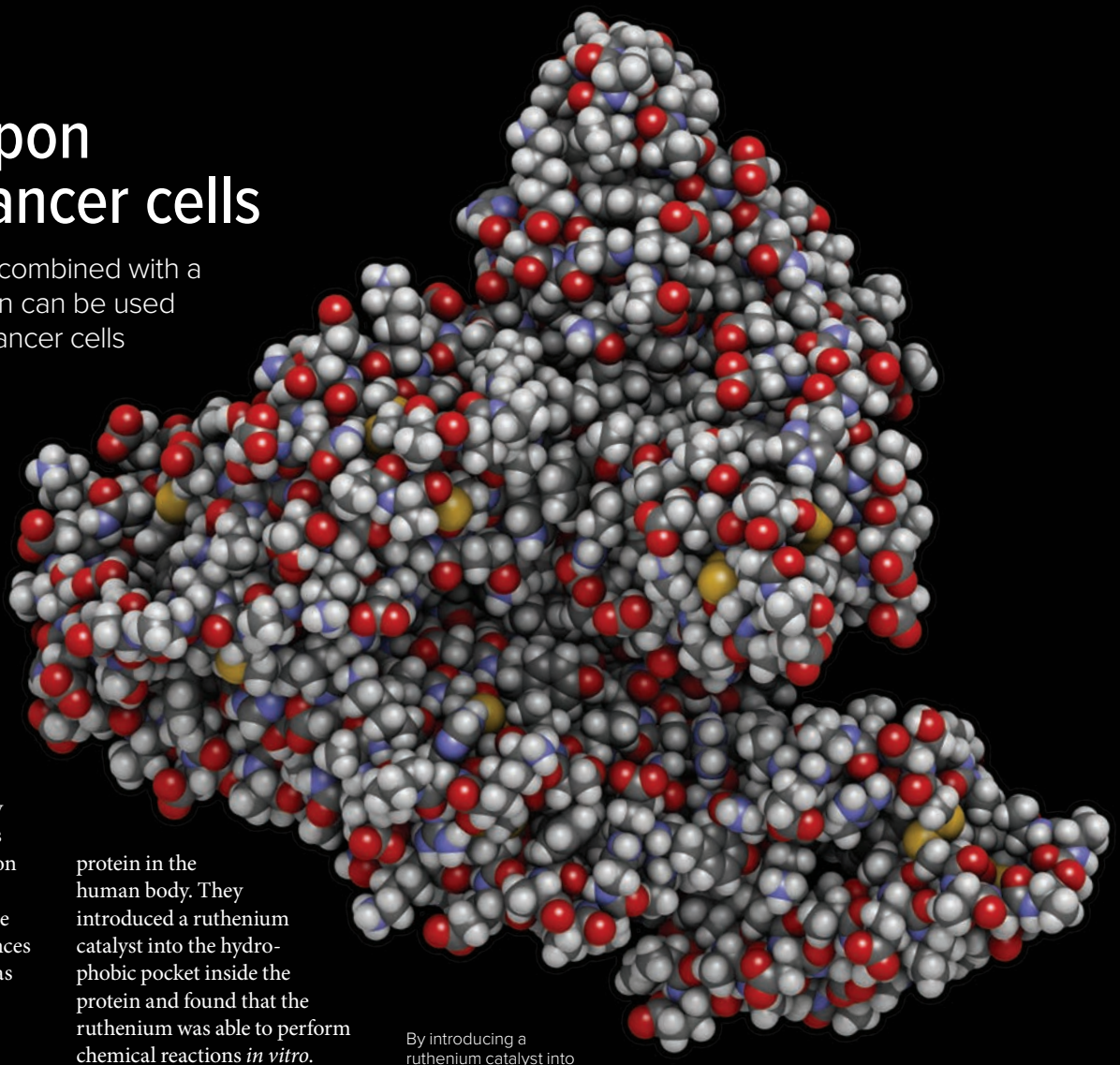
Now, a team led by Katsunori Tanaka of the RIKEN Biofunctional Synthetic Chemistry Laboratory has developed an artificial metalloenzyme that contains a metal ion and is able to save the ion from being inactivated, making it possible for the chemical reaction to occur *in vivo*. The metal ion in this case was ruthenium, which catalyzes a drug precursor into umbelliprenin, a plant-derived compound known to have anti-cancer activity. Further, attaching a sugar 'delivery tag' to the surface of the artificial metalloenzyme caused the drug to target cancer cells.

The group worked with human serum albumin, an abundant protein in the human body. They introduced a ruthenium catalyst into the hydrophobic pocket inside the protein and found that the ruthenium was able to perform chemical reactions *in vitro*.

"We were pleasantly surprised that our newly developed metalloenzyme worked well in the presence of glutathione, an antioxidant that is abundant in actual cells and can inactivate ruthenium," says Tanaka.

The researchers then modified the surface of the albumin, attaching sugar chains that allowed it to be transported to specific cells of interest. Target cells are recognized by the pattern of sugar chains. Doing this, they delivered the catalyst to cancer cells, and used it to produce umbelliprenin, which they determined had cytotoxic effects on the cancer cells.

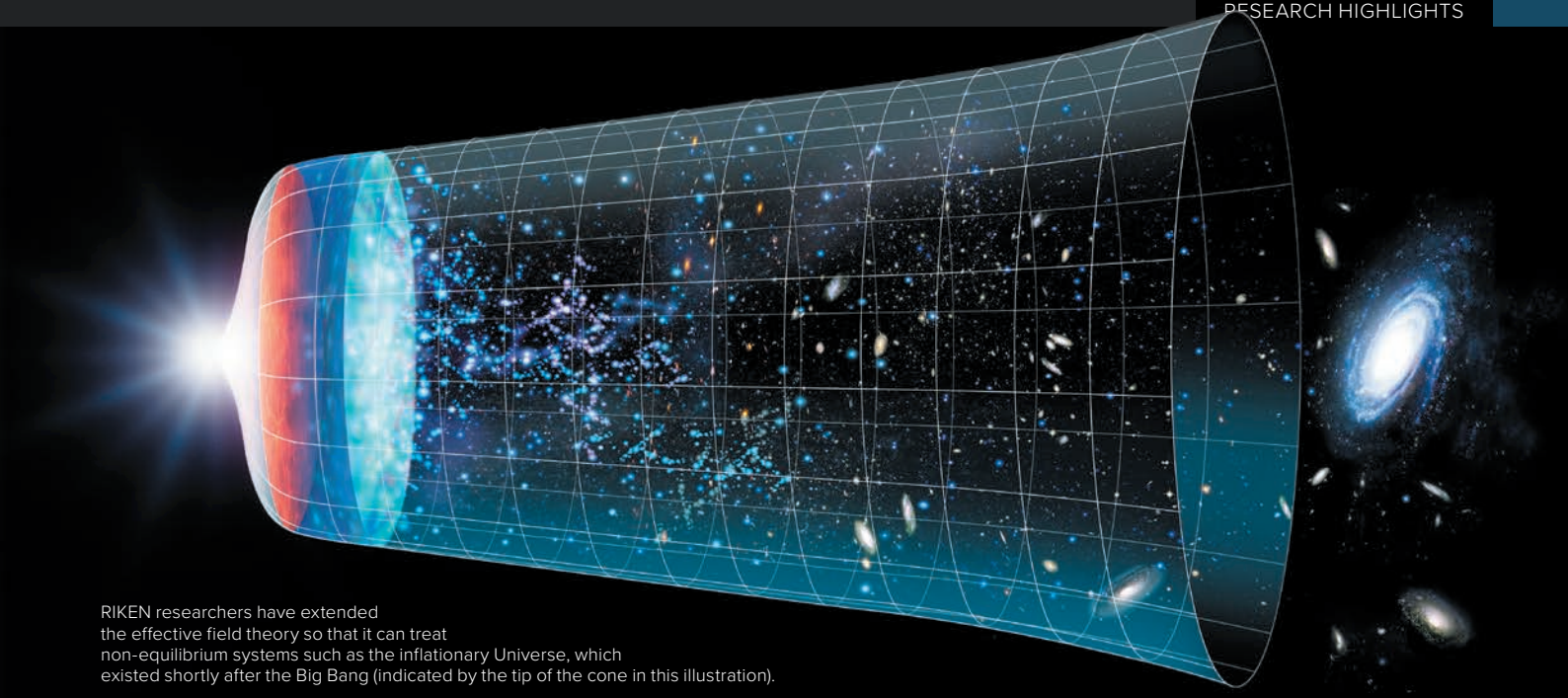
"We confirmed that the method we developed can be applied to metal-catalyzed reactions using other catalysts such as gold, and the artificial metalloenzyme could be generally used *in vivo*," adds Tanaka. "If transition-metal catalysis can be performed on specific organs or diseased cells in the body, it will allow us to rapidly and stably synthesize drugs there, minimizing side effects. Our findings could become a key in the fight against such diseases," he explains. "Furthermore, we can consider using other natural compounds, which show strong anti-cancer activity but have not been used so far. We have opened a door to a new era where we can synthesize and activate natural chemical compounds in actual organisms."



By introducing a ruthenium catalyst into a hydrophobic pocket inside the protein human serum albumin (shown here) and modifying the surface of the albumin with sugar chains, RIKEN researchers were able to deliver the catalyst to cancer cells, where it produced an anticancer molecule.

Reference

1. Eda, S., Nasibullin, I., Vong, K., Kudo, N., Yoshida, M., Kurbangalieva, A. & Tanaka, K. Biocompatibility and therapeutic potential of glycosylated albumin artificial metalloenzymes. *Nature Catalysis* **2,** 780–792 (2019).



RIKEN researchers have extended the effective field theory so that it can treat non-equilibrium systems such as the inflationary Universe, which existed shortly after the Big Bang (indicated by the tip of the cone in this illustration).

EFFECTIVE FIELD THEORY

Calculations emerge from equilibrium

An extension to a powerful mathematical technique makes it applicable to a broader range of physical and biological systems

A powerful mathematical method for simplifying the analysis of highly complex systems has been extended by a RIKEN-led team[1]. This will enhance its usefulness for researchers in a wide range of fields.

Attempting to mathematically describe the world around us is profoundly difficult. Most real systems have so many interacting elements that the equations quickly become impossible to solve.

A common approach is to simplify the situation by removing interactions that have a negligible effect on the characteristic being modeled.

"When considering the thermodynamic properties of water, for example, we don't need to think about its microscopic components, such as the elementary particles," explains Masaru Hongo from the RIKEN Interdisciplinary Theoretical and Mathematical Sciences (iTHEMS) program. "We need only consider information such as whether it is in the liquid phase or is forming solid ice."

This concept is embodied in modern physics by the effective field theory, which looks only at interactions on the same, or greater, length scale at which the physical phenomenon acts. Interactions that occur at shorter distances are averaged into a 'field' that acts on the whole system uniformly, and this can often be simplified further by identifying symmetries within the system.

Effective field theory has been successfully applied to a wide range of physical systems in fields such as cosmology, condensed-matter physics and particle physics. But, until recently, the approach has been mainly applied to equilibrium systems; that is, those that have settled into their lowest energy state. Non-equilibrium 'open' systems offer an even broader range of fascinating phenomena including the expanding Universe and even the synchronization of fireflies.

"An interesting motivation for looking at these systems is that we now have the possibility of breaking time translational symmetry, which cannot be broken in conventional equilibrium systems," says Hongo.

Hongo, along with colleagues Suro Kim and Toshifumi Noumi from Kobe University and Atsuhida Ota from Utrecht University in the Netherlands, has now developed an effective field theory that can be applied to non-equilibrium systems with time-dependent physical quantities, which captures their macroscopic behavior based only on the symmetry-breaking patterns.

The team used their approach to model the simplest situation with a time-dependent variable, which can be regarded as a 'toy model' for inflation in flat space-time. They think it should be straightforward to extend the argument to a realistic inflation in curved space-time. It may also be possible to apply the concept to chemical or biological systems.

"We considered the most basic type of symmetry: time translational symmetry," says Hongo. "We will next consider constructing an effective field theory for spontaneous breaking of the symmetries seen in systems such as solids, liquid crystals, superfluids and magnetic materials." ●

Reference

1. Hongo, M., Kim, S., Noumi, T. & Ota, A. Effective field theory of time-translational symmetry breaking in nonequilibrium open system. *Journal of High Energy Physics* 2019, **131** (2019).

A tiny population of immune cells in the small intestine may trigger diet-induced

WEIGHT GAIN

A recent finding shows that understanding a very specific population of immune cells in the small intestine might be key to keeping obesity at bay on a high-fat diet.

Confusingly, a distinct population of immune cells in the small intestine could be helping to stimulate diet-induced obesity, while the same cells in white fats have previously been shown to help burn energy.

What does this mean? It may mean that, after much more research, specifically targeting these particular immune cells could prevent weight gain and obesity, even for those eating a lot of fat.

"We were very surprised to find that the same kinds of cells appear to exert completely different functions in different tissues," says Takaharu Sasaki, who, along with Shigeo Koyasu and Kazuyo Moro, led the study at the RIKEN Center for Integrative Medical Sciences.

The team drew their conclusions after a series of mouse experiments on a recently identified lymphocyte known as the innate lymphoid cell (ILC). The experiments showed that a particular subset of ILCs, known as small-intestine group-2 innate lymphoid cells (SI-ILC2s), may trigger the development of obesity, while a similar group of ILC2s located in white fat do not.

WEIGHING IN ON HIGH-FAT DIETS

For the study, the group put two types of genetically engineered mice on a high-fat diet or on a regular diet. After 8 weeks, mice that lacked all lymphocytes and were fed a high-fat diet were not obese and had put on about as much weight as the same type of mice on a normal diet. In contrast, genetically engineered mice with no acquired immune cells, but with ILCs, had put on significantly more weight.

Further testing showed that in addition to gaining weight, these mice also displayed other hallmarks of obesity, such as greater amounts of white fat tissue, larger livers and impaired insulin resistance.

To probe further, the team used bone marrow cell transplants to introduce ILCs into non-obese mice that lacked all lymphocytes, and found that when fed on the 8-week high-fat diet, these mice were not resistant to weight gain or other symptoms of obesity.

The next stage of testing focused on location subsets of ILCs. The team looked at the effects of transferring small-intestine-derived ILC2s and white-fat-derived ILC2s into mice lacking all ILCs. They found that only the mice with ILC2s from the small intestine showed signs of obesity after being fed a high-fat diet. The researchers concluded that ILC2s specifically from the small intestine appear to be linked to the development of diet-induced obesity.

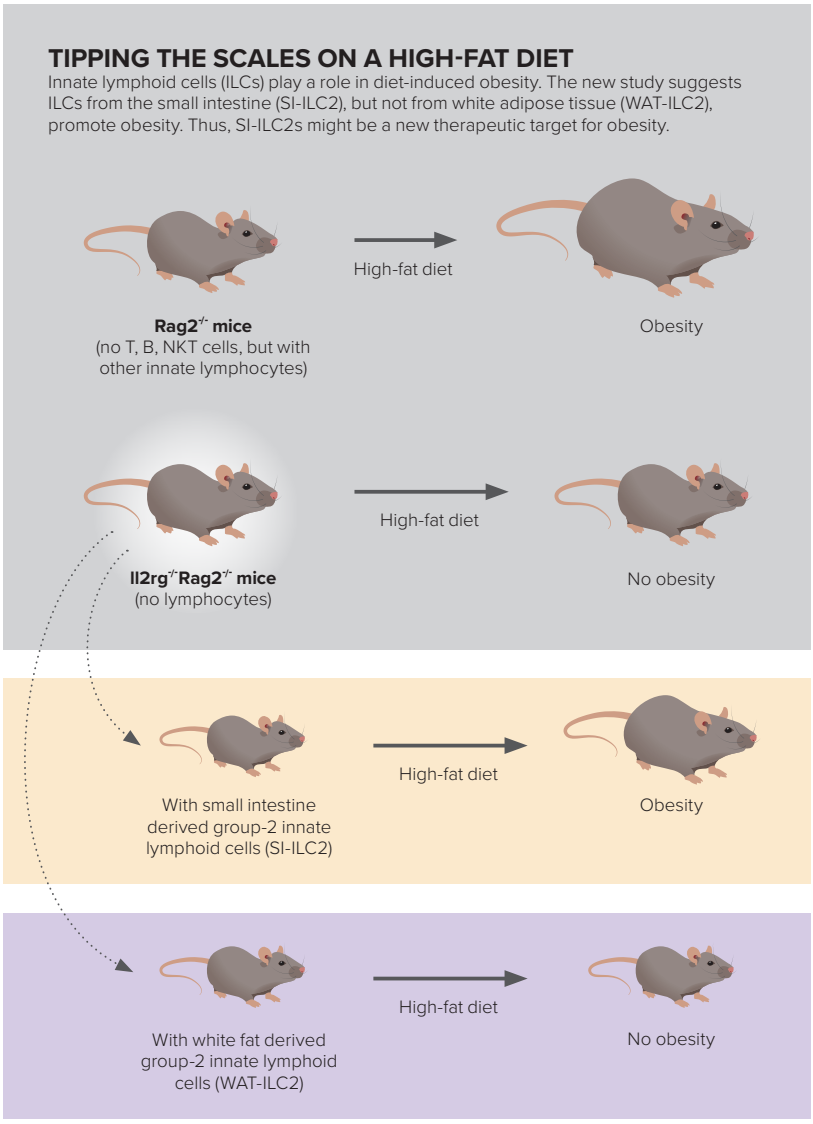
Sasaki hypothesizes that "an imbalance between the function of small-intestine ILC2 and white-fat ILC2 may be one of the accelerators for obesity."

The researchers also noted that despite being fed on a high-fat diet, mice lacking ILCs were found to have lower levels of inflammation promoting M1 macrophages in their white fat tissue, which is linked to

This feature looks at the work of
TAKAHARU SASAKI

Takaharu Sasaki received his PhD from the Graduate School of Pharmaceutical Sciences at the University of Tokyo, while supported by the Junior Research Associate program in RIKEN. During his PhD course, he studied innate lymphoid cells in the Laboratory for Immune Cell Systems and the Laboratory for Innate Immune Systems. After graduating from the PhD course in 2016, he moved to the Laboratory for Intestinal Ecosystem to become a research scientist. His research interests include innate lymphoid cells as well as the interplay between food and the gut immune system, and diseases such as tumors and disorders associated with obesity.

Innate immune cells in the small intestine could be causing diet-induced obesity, while the same cells in adipose tissue (pictured) were previously shown to burn energy.



insulin resistance. They suggest these may prove to be key factors in ILC2's role in diet-induced weight gain.

OBESITY'S NEW LINK TO THE IMMUNE SYSTEM

One of the reasons this link is being uncovered now is that scientists have only known that ILCs exist for roughly a decade. This recent work built on research published in 2010 by Moro and Koyasu, which helped to lay the groundwork for the surge of interest in ILC2s.

In 2010, Moro and Koyasu reported on the discovery of unusual lymphoid clusters in adipose tissue, which they named fat-associated lymphoid clusters (FALCs). During the course of their investigations, they identified ILC2s, a set of innate immune cells that produce T helper 2 (Th2) cytokines—proteins that play a critical role in the body's inflammatory response.

Since then, the newly discovered immune cells have begun to be classified. They have been found to reside in barrier tissues—such as the skin, lungs and intestine—where they are thought to respond to signals from infected or damaged tissues by producing cytokines, which then launch other immune responses.

Of these, two big groups of ILCs have been shown to be involved in fighting off infections: ILC1s are linked to combating viruses and intracellular bacterial infections, and ILC3s are linked to combating extracellular bacterial infections.

So far, ILC2s have been implicated in the body's response to allergies and helminth (parasitic worm) infections. Those factors need to be carefully examined before any ILC2 therapies would be considered.

ILCs have also flown under the radar because they don't have antigen-specific receptors, which means they don't engage in the more frequently studied immune responses triggered by acquired immune cells, such as T cells, B cells and natural killer T (NKT) cells.

Another technical challenge is presented by the rarity of ILC2s. It takes some effort to collect enough of them, because they are relatively scarce in the bodies of mice.

All of these factors mean this new aspect of our metabolism is only just beginning to be explored, and all three major ILC groups are currently being intensively investigated in live mouse models.

HOPE FOR EPIDEMIC OBESITY

Billions of people are affected by obesity and related issues. The World Health Organization estimates that the global prevalence of obesity nearly tripled between 1975 and 2016. As a result, a large community of researchers is working on prevention and treatment options, exploring everything from gut bacteria to brown fat.

RIKEN researchers are not ignoring the complexity or the interrelated factors that may be contributing to obesity. In the present study, the team took care to show that resistance to obesity in ILC-deficient mice could not be due to the workings of the gut microbiota alone. However, they caution that "it is still possible that interactions between microbiota and ILCs contribute to the induction of obesity."

Sasaki says that one of the next steps will be to investigate the involvement of signaling molecule interleukin-2 (IL-2) in more detail, as the study also indicated that small intestine ILC2s express higher levels of IL-2 than white fat ILC2s. The paper's findings further suggest that IL-2 is linked to both obesity-related insulin resistance and the maintenance of ILC2s and ILC3s in the small intestine.

REFERENCE

Sasaki, T. *et al.* Innate lymphoid cells in the induction of obesity. *Cell Reports* **28,** 202–217 (2019).

Source: Ref 1. Sasaki, T. *et al*

WE SHOULD LEARN TO FIGHT LIKE A PLANT

To tackle threats to global food security, symbiologists need to understand the natural balance between plants, pathogens and their environment, says Ken Shirasu

The well-stocked shelves of our supermarkets hide a food fight happening in and on the ground. Crops are becoming more vulnerable to agrochemical-resistant pathogens—pathogens such as fungi, bacteria and nematodes.

We need new strategies to combat these threats, and we can learn important lessons from the complex defenses put up by plants.

The pathogen problem is layered. While increasing plant domestication and monoculture have allowed more intensive cropping to feed multiplying mouths, these trends come with the risk of pathogen outbreaks freed from diversity's protections. Food and human movement add to the problem, with pathogens becoming frequent international travellers. On top of that, agrochemicals are increasing selective pressures, so when a fungus, bacterium or nematode finds a way to survive, it emerges into a landscape without competitors and can spread like wildfire.

Fungal diseases are of particular concern to crops. Between 2016 and 2019, a blast fungus spreading in key farming regions reduced Bangladeshi wheat yields, the country's second most important staple, by half; India recently announced a three-year wheat growing "holiday" in neighbouring areas. In Africa, wheat stem rust fungus UG99 has been aggressively mutating and causing havoc for decades, and a 2016 outbreak in Sicily was dubbed one of the worst European outbreaks in 50 years. Bananas have also weathered a series of crises from fungal Panama disease. Recently, the popularity of a few banana species has exacerbated the problem. In 2015, Asian banana exports dropped 46 percent, a figure attributed to both storms and the disease.

Monoculture is increasing, but even in the 1800s it had devastating consequences. Ireland's dependence on one potato species, *Solanum tuberosum*, and the spread of water mould, *Phytophthora infestans*, led to famine and the death of more than a million people during the Irish Potato Famine.

Wheat crops in Kenya. Across Africa, wheat stem rust fungus UG99 has been aggressively mutating and causing havoc for decades. In Europe, a 2016 outbreak of UG99 in Sicily was dubbed one of the worst European outbreaks in 50 years.

We have a similar, if less extreme problem with strawberries in Japan, of which more than 100,000 metric tonnes are grown each year. Our soft, sweet strawberry varieties are vulnerable to necrosis, wilt and rot from fungi of the genus *Colletotrichum*.

Fungi have a unique relationship to plants. They are often necessary for plant survival, many living symbiotically, exchanging nutrients for energy. But in more destructive forms they're wily, often able to clone themselves. Cloning encourages species to hoard genetic tricks, such as transposable elements, which can change a fungus's genome by jumping spots and replicating in a cut-and-paste action. Cloning then allows strains with useful mutations to replicate and rapidly spread.

At RIKEN, my team recently identified a particularly virulent species of *Colletotrichum*, known as *C. fructicola*. In a soon-to-be published paper, we found evidence of huge genome and chromosome reorganisation in *C. fructicola*'s most virulent phenotypes. The study shows how quickly *C. fructicola* has adapted to fungi-resistant strawberry cultivars developed by Japanese strawberry breeders, and why it continues to cause expensive export problems.

SYMBIOLOGY AS A SOLUTION

Containing plant pathogens by harnessing the same strategies used by plants isn't simple. Until now, scientists have largely avoided studying the incredible complexity of whole-system molecular interactions. But now symbiologists—the scientists interested in organism-to-organism interactions—use high-throughput sequencing. Using this, they can track changes in microbe genomes in response to their environment, which has led to a renewal in international efforts to understand microbial environments holistically.

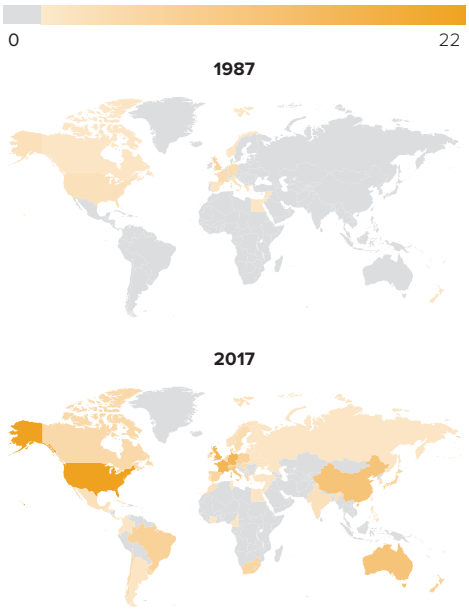
The advantage of this approach is robustness. Agrochemicals tend to target a single protein, while an ecosystem's defences are systems-based and multifaceted, making it more difficult for pathogens to mutate to overcome them.

While there's still a lot of groundwork to lay, we've made headway. RIKEN recently contributed some promising efforts to halt the expansion of Striga weeds, a major food security threat affecting more than 60 percent of farmland in sub-Saharan Africa. Striga weeds leach off the roots of important African cereal crops such as sorghum, millet, sweetcorn and rice. The weed causes crop losses each year estimated at roughly US$1 billion, and it's spreading.

In 2015, another RIKEN researcher and I were part of an American, Australian and Japanese collaboration that in *Science* described the strigolactone

REPORTS OF ANTIFUNGAL RESISTANCE, BY COUNTRY

Between 1987 and 2017, the number of peer-reviewed publications that reported resistance to Azole antifungals, the world's most used fungicides, increased dramatically.



Source: Fisher, M., Hawkins, N., Sanglard, D. & Gurr, S. Worldwide emergence of resistance to antifungal drugs challenges human health and food security. *Science* **360(6390)**, 739-74

hormone chemical receptor, KARRIKIN INSENSITIVE 2. Plants release strigolactone to promote symbiotic interactions with soil microbes. Striga seeds detect plants by germinating in the presence of strigalactone in order to take advantage of a nearby host.

Our 2015 study helped stimulate several projects on strigolactones. Groups in Canada, the Netherlands and at Nagoya University in Japan began developing chemicals mimicking the function of the hormone.

At the end of 2018, the Nagoya team developed a molecule designed partly around our receptor work that was published in *Science*. The idea is that by applying low concentrations of the Nagoya team's molecule to uncultivated soil, farmers could stimulate the germination of Striga seeds already in the ground. Without a host, the parasites would germinate and die.

While this new molecule needs to be thoroughly tested to make sure it doesn't have a negative effect on crops, it could be a huge leap forward in the fight against the weed.

THE CHALLENGE: CORE MICROBIOMES

We need many more of these findings, but symbiologists work in a black box. Why? For one, we need to have isolates of all the microbes in a system, such as a soil, to understand whole-system interactions. Not only are isolates diverse, they aren't always easy to grow in a lab; for example, some estimate that only one percent of bacteria are culturable.

Plants and soils also function in an open environment, which means their microbes are more diverse than those in a closed environment, such as the gut, which is one of the fastest growing areas of symbiology. Nonetheless, there's a lot to learn from gut research's successes.

For example, we must start to understand plant microbiomes, which are common groups of microbes that, as a community, become very robust and stable. Gut researchers have identified roughly 2,000 core microbiomes.

Right now, large efforts are underway in Germany and the USA to sequence plant microbes. If some prove common, they should eventually resolve into core microbiomes.

The German government, despite boasting one of the world's largest agrochemical industries, has recognized the importance of symbiology. In 2017, Germany's main research funder, the German Research Foundation (DFG), launched a huge program to study the rhizosphere—the chemicals, minerals, microbes and fungi that interact around a plant's roots. The program has been dubbed one of five new life-science priority programs. This is a clear mandate to move large symbiological projects in plant science forward.

Unfortunately, while important, the 2014 Nagoya Protocol on Access and Benefit Sharing has made symbiological study trickier. The biodiversity protocol limits the movement of samples internationally to preserve global biodiversity, and importing or exporting samples now requires more paperwork. However, it will also force us to do the hard work on local microbes and soils, which will ultimately benefit Japanese farmers.

To accelerate the process, the Integrated Symbiology (iSYM) program at RIKEN, which was established in 2018, is in the process of sequencing a lot of Japanese pathogens and establishing a plant phenotyping platform. We expect this to have a huge impact, allowing us to monitor plant parasite movement. It will help us hunt evolving pathogens and resistant cultivars at both a genome and phenotypic level.

We hope that Japan will follow a route similar to Germany and issue a strong financial mandate to construct Japanese symbiological models.

Eventually, we hope we will learn to fight the pathogens affecting Japanese farmers in whole-of-system ways; in other words, to fight like a plant.

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

KEN SHIRASU
Group Director, Plant Immunity Research Group, RIKEN Center for Sustainable Resource Science

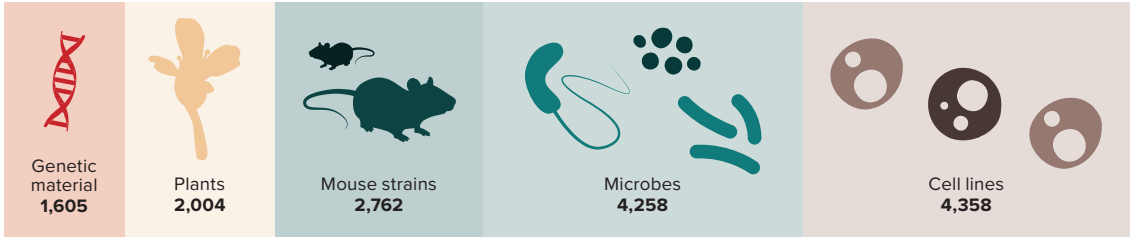
Ken Shirasu is the Group Director of the Plant Immunity Research Group. After graduating with a degree in Agricultural Chemistry from the University of Tokyo, Shirasu did a PhD in genetics at the University of California, Davis, and then went on to work as a Postdoctoral Fellow at The Salk Institute/ Nobel Foundation in the USA. After becoming a group leader at the Sainsbury Laboratory in Norwich, UK, he moved to a group leader position at RIKEN in 2006. He has previously been director of the International Society for Molecular Plant Microbe Interactions and Chair of International Committee of The Japanese Society of Plant Physiologists. He was a Thomson Reuters highly cited researcher from 2014–2018.

BIORESOURCE RICH

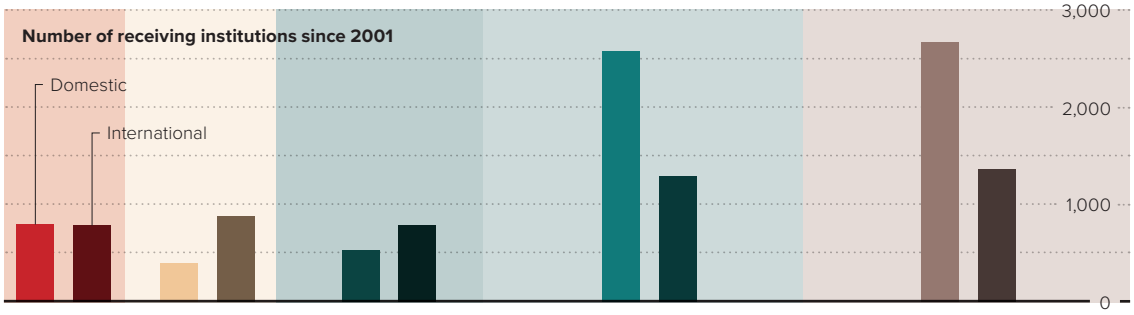
The RIKEN BioResource Center (BRC) focuses on collecting and distributing plant and animal resources originally developed for research in Japan. Opened in 2001, the BRC is now a major repository drawn upon by researchers globally.

BIORESOURCES ORDERED IN 2018
Almost 15,000 bioresources were sent out in 2018. Since 2001, the BRC has supplied almost 70 countries.

14,987 RESOURCES (IN 2018)



SUPPLYING 12,000 INSTITUTIONS
Proportionally more of its plant materials and mouse strains go overseas, while Japanese institutions order more cell lines and microbes. Genetic material is almost evenly split.



GLOBAL TOP THREE
The BRC one of the top three repositories for each of its resources in the world.

3.8 MIL CLONES	838K ITEMS	8,849 STRAINS	28,575 STRAINS	15,590 LINES
	One of three major centers in the world	The second largest repository in the world	The second largest collection of newly identified microorganisms	The world's largest collection, and one of two to take direct overseas orders

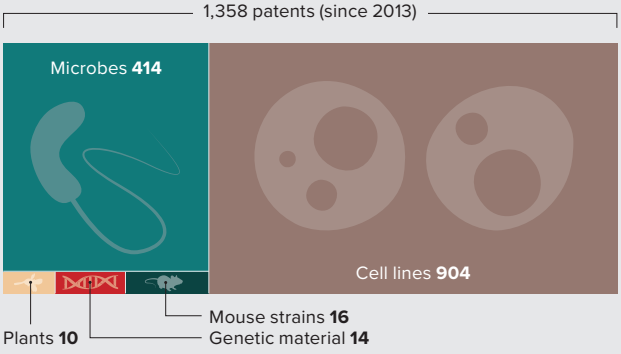
No.1

NATIONAL TREASURE

Japan's National BioResource Project (NBRP) facilitates the work of life scientists by providing research resources. It was initiated by the Ministry of Education, Culture, Sports, Science and Technology and the Japan Agency for Medical Research and Development in 2002. The BRC is one of the NBRP's core facilities, although almost 30 similar centers are involved.

PATENT PRODUCER

95% of the patents granted to the National BioResource Project stemmed from BRC resources



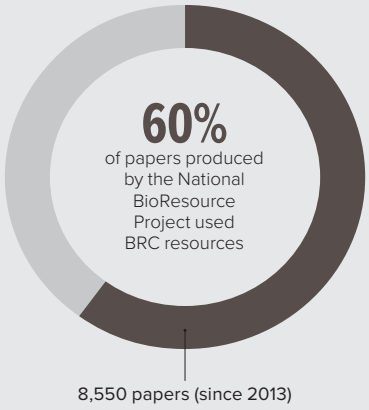
TOP PATENT USING BRC RESOURCES

Title: Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors
Journal: *Cell*

PATENT CITATIONS*
1,058

SCHOLARLY CITATIONS*
12,878

PAPERS ON THE PLANET



*Source: lens.org

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:
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