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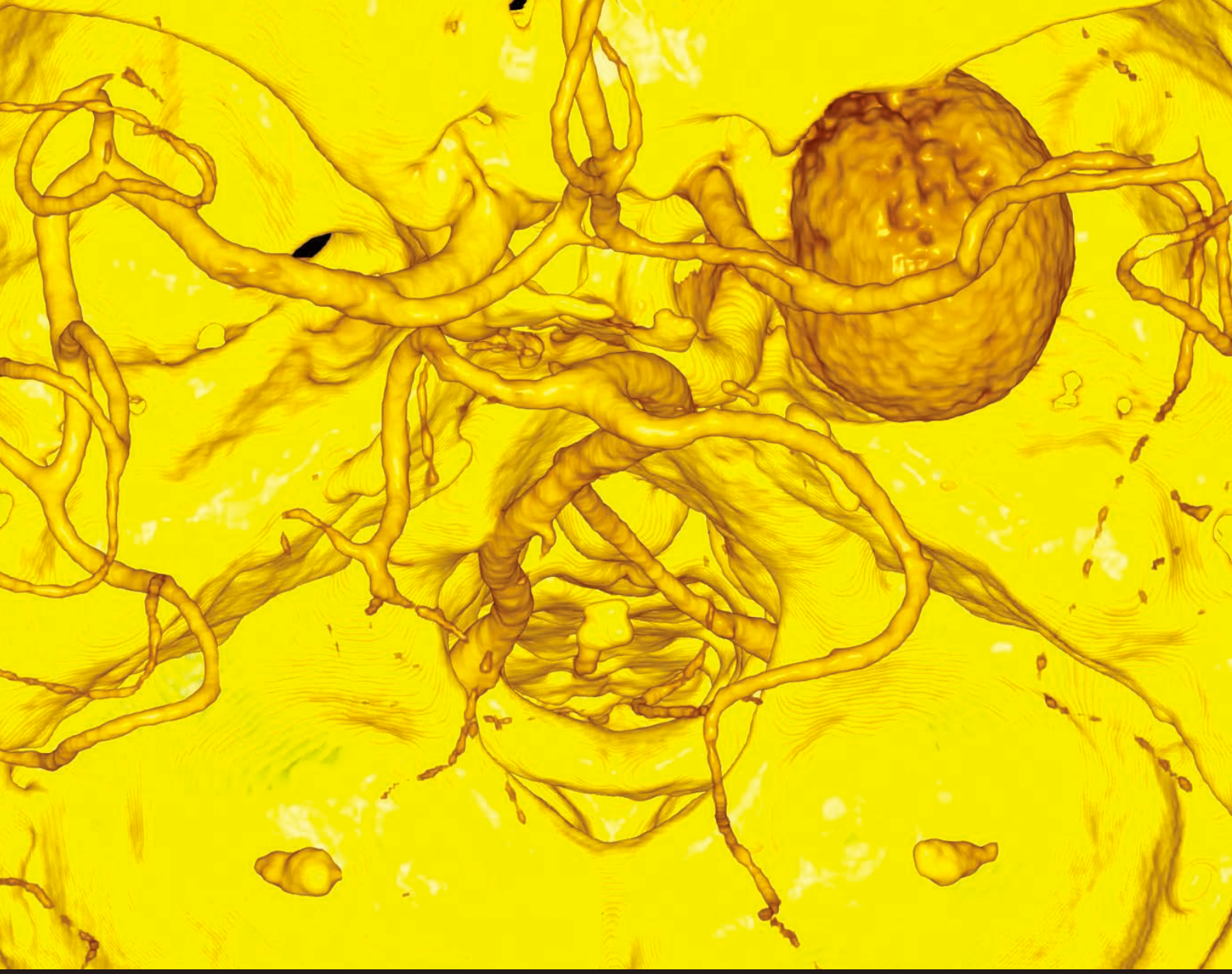
TARGETED FOR DESTRUCTION
Treatment strikes multiple cancers

CRYSTAL CONVENIENCE
Cheap and efficient hydrogen storage

DRUG-RESISTANT FUNGI
Halting infections that kill millions



▲ **ARTERIAL DANGER**
RIKEN researchers found that more than 90% of people with intracranial aneurysms—where weakened arteries in the brain dangerously balloon with blood (top right)—shared common mutations in their genes.

RIKEN RESEARCH

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

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

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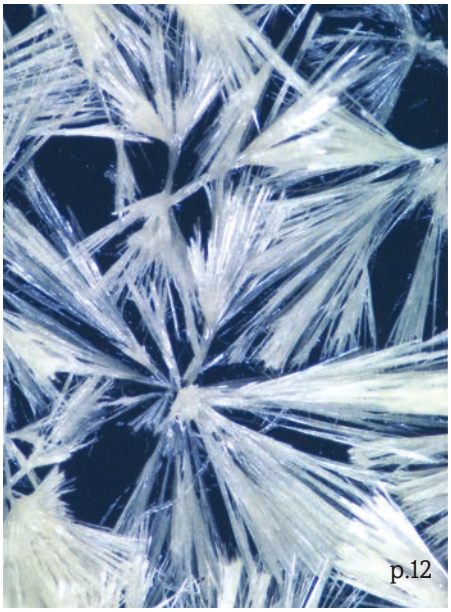
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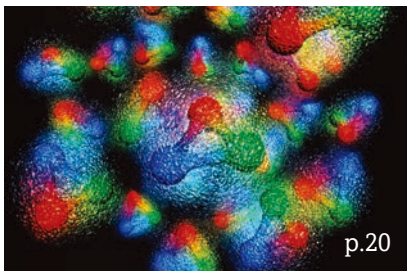
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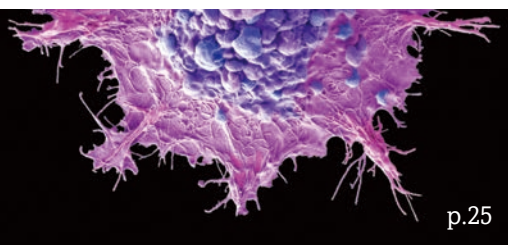
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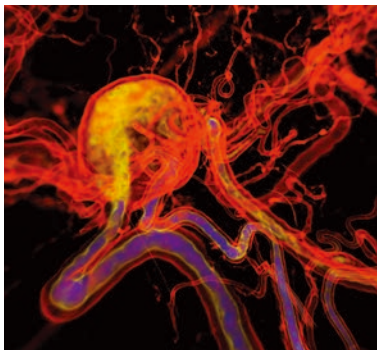
Treating brain aneurysms before they burst: studies reveal new potential drug targets to fix the problem of common, and potentially deadly, weakened arteries in the brain.



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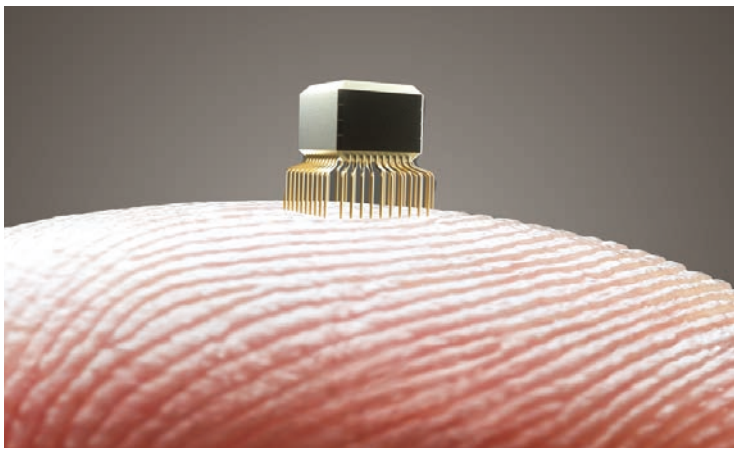

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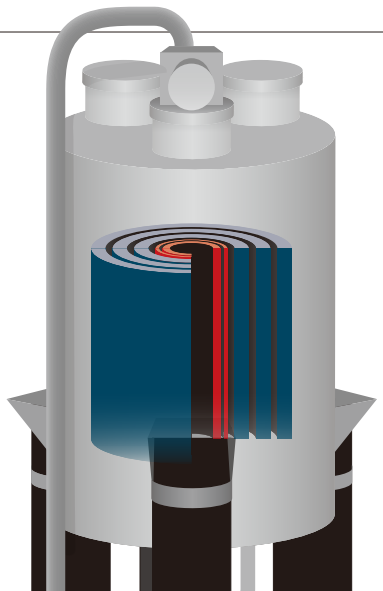
Small, but mighty: A joint research team led by Yoshinori Yanagisawa at the RIKEN Center for Biosystems Dynamics Research has developed the world's lightest and most compact nuclear magnetic resonance (NMR) system.



A melting pot of scientific fields

Minoru Yoshida
Executive Director, RIKEN

Though I began my term as executive director in April this year, I began working at RIKEN in 2002 as a chief scientist and continued in that capacity until 2018. The chief scientist system, which was launched in 1922, was the soil within which RIKEN was able to become a "free paradise for scientists". RIKEN was free of organizational barriers like those of university faculties, and researchers in various fields such as physics, chemistry, biology, and engineering could have free discussions. This system has survived to the present day as the heart of RIKEN.

RIKEN has grown rapidly since 1990. During that time, we have established strategic research centers to address important policy issues and research infrastructure centers to provide world-class infrastructure, some created with chief scientists at their core.

In order to solve social issues, researchers from diverse fields must come together to pioneer new areas. For instance, the Center for Sustainable Resource Science, to which I belong, was founded with chief scientists in a variety of areas, and we were able to create a new discipline of environmental resource science, bringing together researchers from different fields, including plant science, catalytic chemistry, and chemical biology.

In April 2013, at the start of RIKEN's Third Mid-Term Plan, chief scientists were redefined as the "core of RIKEN's comprehensive capabilities", and it was clearly stipulated for the first time that the chief scientist system would extend to all of RIKEN, including the research centers.

Furthermore, two bodies were merged to form the new RIKEN Science Council. The council makes proposals on the research directions to be pursued by RIKEN and formulates strategies and tasks based on these directions. It also recommends and evaluates projects under the Competitive Program for Creative Science and Technology, which aims to encourage the exploration of new research areas and interdisciplinary research. Via this council, chief scientists can help to identify the research fields that RIKEN should explore, allowing the recruitment of outstanding individuals who will carry out this research, mainly in the Cluster for Pioneering Research.

While collaboration under a new cutting-edge research platform named the Transformative Research Innovation Platform of RIKEN platforms (TRIP), which launched this fiscal year, brings together all of RIKEN's resources to solve pressing issues, the chief scientist system and the RIKEN Science Council lay a foundation for a long-term strategy to solve future problems. Both require a fusion of different disciplines, and RIKEN is a well-designed melting pot for this purpose.

吉田 稔

COVER STORY:
Modeling by RIKEN researchers suggests that small changes could have big effects on extreme weather events. *Page 16*

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Plant-derived medical chemicals

Amit Rai
Research Scientist, Metabolomics Research Group
RIKEN Centre for Sustainable Resource Science

Please describe your role.
I work as a research scientist in the Metabolomics Research Group under the leadership of Kazuki Saito, who is also the director of the RIKEN Center for Sustainable Resource Science. In my present role, I study Japanese plants, such as *Panax japonicus* and *Glycyrrhiza uralensis* among others, to understand why and how these plants synthesize chemicals with medicinal properties.

> *Phytochemicals are used in drugs that treat various diseases, including cancer and hypertension.*

Please describe your current research.
My interest lies in delving into the biosynthesis and regulation of a group of medicinal plant-derived chemicals known as phytochemicals. These phytochemicals are used in drugs that treat various diseases, including cancer, hypertension and non-insulin dependent diabetes.

Specifically, I investigate the biosynthesis of bioactive metabolites, including alkaloids. My aim is to develop strategies to enhance their production and achieve sustainable supplies. As these phytochemicals are essential to the plant stress response, understanding their biosynthesis pathways and regulatory mechanisms is also vital to cultivating next-generation crops with heightened nutritional value, increased production rates and enhanced resistance to pests and environmental fluctuations.

What advanced technologies do you use at RIKEN?
One important technology that is very useful is a platform my group uses for identifying new metabolites using highly sophisticated and sensitive mass spectrometry instruments.

Why did you join RIKEN?
While working at Chiba University, I collaborated with members of the Metabolomics Research Group. My interactions allowed me to see RIKEN's capabilities in terms of performing big-data research. That's how I heard of this position, which is focused on genomics and multiomics with the aim of enhancing phytochemical production.

What has been your most memorable experience at RIKEN?
I received a Letter of Appreciation from the president of RIKEN for my research in March 2022. That was a memorable moment for me.

What excites you the most about your research?
Today, thanks to advances in technology, we have gained access to thousands of plant genomes that represent diverse lineages. These give us insight into their mechanisms.

How did you become interested in your field of research?
Coming from a family of farmers in India, I was fortunate to have my grandfather to teach me about the fundamentals of cultivating and harvesting crops.

While his explanations were primarily rooted in personal experience, I found myself grasping the underlying scientific principles as I delved into my studies.

Then, after my undergraduate and doctoral studies, I had the privilege of joining Kazuki Saito's group while he was at Chiba University in Tokyo, Japan. This invaluable opportunity granted me access to an extensive collection of Japanese medicinal plants.

I was intrigued that medicinal plants are a major source of health worldwide, and yet little is known about their evolution, biosynthesis and regulation of phytochemicals, nor the mechanisms behind their medicinial properties. Advances in genomics and metabolomics further helped me to ask difficult questions. ■

All in the mind's eye

Alexandra Wolf
Special Postdoctoral Researcher, Cognitive Behavioral Assistive Technology Team
RIKEN Center for Advanced Intelligence Project

Please describe your role.
I am a Special Postdoctoral Researcher at the RIKEN Center for Advanced Intelligence Project in Tokyo, Japan. I am part of a program that aims to nurture young scientists to help them make significant global contributions to research. This program provides creative researchers like me with the opportunity to pursue self-directed and independent research aligned with RIKEN's objectives.

My focus lies in exploring eye movements in two groups: healthy older adults and older adults with mild cognitive impairment (MCI). By studying eye movements, I aim to contribute to our understanding of age-related cognitive decline and potentially develop diagnostic tools and interventions for MCI.

How did you become interested in your current field of research?
My passion for psychology and photography sparked a deep curiosity about how people perceive the world. This led me to delve into the fascinating field of eye tracking. Initially captivated by studying eye movements among healthy participants during my PhD projects, I soon recognized the need to expand my research to include clinical groups. Exploring gaze patterns in individuals with clinical conditions allowed me to uncover unique insights and understand the impact of these conditions on visual perception and cognition. This broader perspective revealed diverse visual impairments within clinical populations.

Why is your research important?
Addressing age-related cognitive decline, particularly in those with MCI, is the driving force behind studying eye movements in older adults. Eye movements provide valuable insights into attention, perception and memory. By examining eye movements in both healthy older adults and those with MCI, we aim to uncover potential biomarkers and early indicators of cognitive decline. This research holds the potential to develop practical and effective diagnostic tools for MCI and other age-related cognitive disorders.

Eye movements provide valuable insights into attention, perception and memory.

Why did you become a scientist?
My decision to pursue a career as a scientist evolved gradually, influenced by mentors from prestigious institutions like Warsaw University of Life Sciences, Technical University Munich and Kyushu University. I participated in exceptional international exchanges, which nurtured my curiosity and instilled the confidence needed to make a meaningful impact through my work. Hence, it was through the accumulation of these experiences and the unwavering support of my parents that the picture of my career as a scientist began to crystallize during my years of education.

Please tell us about your professional and personal goals.
Despite my origins in Europe, I have been raised with the mindset of considering myself a 'global citizen'. I totally embrace this perspective, which motivates me to fulfill my responsibilities and obligations to my family, community and society as a whole.

I believe in embracing the inherent equality and dignity of all individuals, regardless of their background. The values of active engagement, meaningful science communication, and striving for the betterment of society should be universal and inclusive. By upholding these ideals, I seek to promote positive change—for all. ■

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E-mail: pr@riken.jp

Director-elect of the Brookhaven National Laboratory in the United States JoAnne Hewet (at left) and RIKEN President Mokoto Gonokami signed a new agreement to foster collaboration on spin physics research.

New spin on RIKEN and Brookhaven National Laboratory collaboration

On June 22, 2023, RIKEN and Brookhaven National Laboratory (BNL) in the United States celebrated 25 years of partnership. At an event to mark the milestone, RIKEN President Makoto Gonokami signed a new agreement with BNL's Director-elect JoAnne Hewett to extend the RIKEN–BNL Memorandum of Understanding (MoU) to 2028. The MoU fosters collaboration on spin physics research.

Since 1997, the RIKEN BNL Research Center (RBRC) at BNL has hosted theory, computational and experimental groups. The theory group conducts research on hot and cold quantum chromodynamics (QCD), the study of the force that holds quarks in a nucleon, using the Relativistic Heavy Ion Collider (RHIC) at BNL. The members of the computational physics group carry out precise calculations that are essential to understanding various aspects of QCD from first principles, largely using lattice QCD. Experimental scientists explore the spin structure of nucleons and the physics of quark gluon plasma (QGP), a 'soup' of quarks and gluons at close to kinetic and chemical equilibrium.

The RBRC has already achieved some outstanding research results in spin physics using RHIC. These include a study revealing the formation of quark–gluon plasma and the measurement of QGP temperatures exceeding 2 trillion degrees Celsius.

Another recent achievement showed that the spin of gluons in a proton nucleus is aligned in the same direction as that of the proton. In the future, the recently completed sPHENIX detector, a new detector at RHIC with exceptional capabilities for particle jet measurements, will be used for heavy-ion and polarized-proton collisions.

www.riken.jp/en/news_pubs/news/2023/20230710_2

Arabidopsis in focus

The 33rd International Conference on Arabidopsis Research (ICAR2023) was held as a hybrid event in Chiba, Japan, on June 5–9, 2023.

ICAR is an annual conference that rotates between North America, Asia-Oceania and Europe. It covers all aspects of plant biology research on Arabidopsis, as well as other plant species.

ICAR2023 hosted 1,209 participants, 95% of which were in-person, including 792 people from 41 countries and regions outside of Japan.

The theme was Arabidopsis for Sustainable Development Goals (SDGs), and the event featured many presentations on basic plant science using Arabidopsis and translational crop science aiming to contribute to achieving the SDGs. ICAR2023 provided students and early career professionals with a chance to connect with global cutting-edge research. Two team leaders at the RIKEN Center for Sustainable Resource Science, Motoaki Seki and Keiko Sugimoto, chaired the organizing committee. Altogether, there were 899 oral and poster presentations at the event.

https://twitter.com/ICAR_2023
https://icar2023.org/

The 33rd International Conference on Arabidopsis Research hosted 1,209 participants from more than 40 countries and regions.

A new super-fast probe (right) helps a solid-state nuclear magnetic resonance machine (left) observe the molecular structure and physical properties of a trace amount of a solid sample. It has greatly enhanced spectral resolution and almost doubled the sensitivity of a conventional detector for a given sample amount.

An ultrasensitive nuclear magnetic resonance probe

A team from the RIKEN Center for Biosystems Dynamics Research, in conjunction with its partners, has developed a new, super-fast probe that allows researchers to observe the molecular structure and physical properties of a tiny solid sample. Led by Yoshitaka Ishii, the team believes this is the world's fastest, spinning at 180 kilohertz (1 kilohertz is 1,000 hertz) in magic-angle spinning experiments for solid-state nuclear magnetic resonance (NMR).

The results of this research are expected to enhance the sensitivity of solid-state NMR. Potential applications include the detection of miniscule biological samples and nanomaterials, such as hints of beta-amyloid in brain tissue from people with Alzheimer's disease.

The ultrafast magic angle spinning (MAS) method uses NMR with high spectral resolution and high sensitivity by rotating it at an extremely high speed. With their new device, the joint research team demonstrated solid-state NMR measurements at the world's fastest rotation of 180 kilohertz. They achieved this by developing an NMR detector equipped with a MAS device that rotates a microsample tube with a diameter of about 0.4 millimeters with high-speed gas flow.

Rotation at 180 kHz is equivalent to 180,000 rotations per second, and the peripheral speed at the outside of the tiny rotor reaches up to 813 kilometers per hour, more than 2.5 times faster than the Japanese bullet train, the Shinkansen.

This ultrahigh-speed rotation has almost doubled the sensitivity of a conventional detector. The team also successfully performed 2D NMR measurements of a trace protein sample at 160 kilohertz.

This achievement was made by a team led by Yoshitaka Ishii from the RIKEN Center for Biosystems Dynamics Research. Also on the team are Tatsuya Matsunaga from the Tokyo Institute of Technology; Yuki Endo, vice chief of JEOL Ltd (a developer and manufacturer of the NMR, electron microscopes and other scientific instruments); Takahiro Nemoto and Kenichi Hachitani, who are group leaders at JEOL; and Michitaka Ono, a program manager at the Japan Science and Technology Agency (JST).

Without helium's help: a new, compact nuclear magnetic resonance system

See infographic about this topic on **page 32**.

A new take on a scientific instrument known as a nuclear magnetic resonance (NMR) machine has achieved an unprecedented magnetic field at less than a tenth the weight of existing machines (see page 32). The new system also promises to be more cost effective and environmentally friendly than its larger counterparts, say RIKEN researchers.

NMR machines are used for everything from chemical analysis and drug discovery to material science. They function by analyzing the behavior of atomic nuclei in extremely strong magnetic fields to understand the properties of substances.

While they are extremely useful, these magnetic fields are produced by superconducting magnets that need large amounts of expensive helium to stay cool. Because of this, there is a strong demand for machines that reduce helium use.

With this in mind, RIKEN researchers developed a compact 1 gigahertz system that is about one-tenth the weight of a conventional system, using bismuth-based high-temperature superconducting (HTS) coil technology.

The group has been able to increase the current density of the HTS inner coil by a factor of 1.5, allowing them to develop a compact 1.01 GHz NMR system weighing approximately 1.6 tons. This is about one-tenth the weight of a 1.02 GHz system that had the highest magnetic field in the world in 2015.

The design group included researchers from RIKEN, Japan Superconductor Technology, Inc., Tokyo Institute of Technology, JEOL Ltd. and the Japan Science and Technology Agency (JST).

According to RIKEN's Yoshinori Yanagisawa, "We believe that this technology will facilitate the use of high-performance NMR systems and allow researchers to carry out advanced research, such as the analysis of amyloid-β peptide, which is involved in the development of Alzheimer's disease. It is also exciting that we were able to operate the machine for several months without any replenishment of helium."

The new nuclear magnetic resonance machine weighs about one-tenth the weight of existing systems.

Summer program participants and CBS PDFA members had candid discussions.

Center for Brain Science summer program

After a three-year on-site hiatus, the Center for Brain Science (CBS) welcomed 40 young neuroscientists and emerging researchers to the RIKEN Wako campus near Tokyo.

This year's program focused on the theme of 'Learning and Imagination—Neural Mechanisms in Humans and Animals', with lecturers sharing their research on learning, memory, cognition, sleep, functional magnetic resonance imaging techniques and neurosurgical approaches.

In addition to the lectures, participants visited labs, engaged in hands-on experiments, presented posters and engaged in candid discussions with their peers and CBS researchers, all helping to foster future research ideas. A highlight of the program were two casual discussions featuring principal investigators and the Postdoctoral Fellows Association (PDFA), a self-governed organization of CBS postdoctoral fellows.

During these sessions, principal investigators and postdocs addressed questions raised by participants regarding career development, scientific pursuits, life in Japan, and more, creating a valuable and insightful exchange of ideas.

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

AI center hosts Singapore's deputy prime minister

On April 25, 2023, Heng Swee Keat, Singapore's Deputy Prime Minister and Coordinating Minister for Economic Policies, visited RIKEN's Tokyo office. He met with RIKEN President Makoto Gonokami to learn about the RIKEN Center for Advanced Intelligence Project.

The Deputy Prime Minister was accompanied by a delegation from various Singaporean ministries and government organizations, including Andy Hor, Deputy CEO of A*STAR, with which RIKEN has a research collaboration memorandum of understanding.

www.riken.jp/en/about/president/

French minister visits medical and biology research centers

On May 11, 2023, a delegation led by the French Minister of Higher Education and Research, Sylvie Retailleau, visited the RIKEN Center for Integrative Medical Science (IMS) and the RIKEN Center for Biosystems Dynamics Research (BDR) in the city of Yokohama.

Following discussions with RIKEN Executive Director Makiko Naka, the delegation was given an introduction to the site by campus director Minemasa Suehiro, and an overview of the RIKEN IMS by Center Director Kazuhiko Yamamoto. The delegation was also taken on a tour of the IMS genomics facility and shown BDR's new super-compact nuclear magnetic resonance (NMR) machine (see pages 7 and 8).

Quantum computing before fault tolerance

Quantum computing promises to offer substantial speed benefits over its classical counterpart. However, more research is needed on integrating fault-tolerant quantum circuits with current processors.

Yantao Wu from the RIKEN iTHEMS group and his colleagues from multinational computing company IBM and the University of California, Berkeley in the United States has reported progress in a recent paper. They measured accurate expectation values on a noisy IBM-Q 127-qubit processor for circuit volumes at scales beyond classical computation.

Using strong entanglement of the temporal dynamics of the transverse-field Ising model, the quantum computer provides correct results, when other leading classical approximations break down.

This represents evidence that quantum computing can be used in a pre-fault-tolerant system. At the same time, their results will advance classical approximation methods, as it serves as a valuable benchmark.

CRYSTALLOGRAPHY

Resolving hydrogen atoms in organic molecules

Beams of electrons and x-rays give complementary information on hydrogen in small organic molecules

Extremely intense x-ray pulses can determine the positions of some hydrogen atoms in organic molecules that form small crystals, an all-RIKEN team has shown[1]. Many areas, including drug discovery and materials research, stand to benefit from this demonstration.

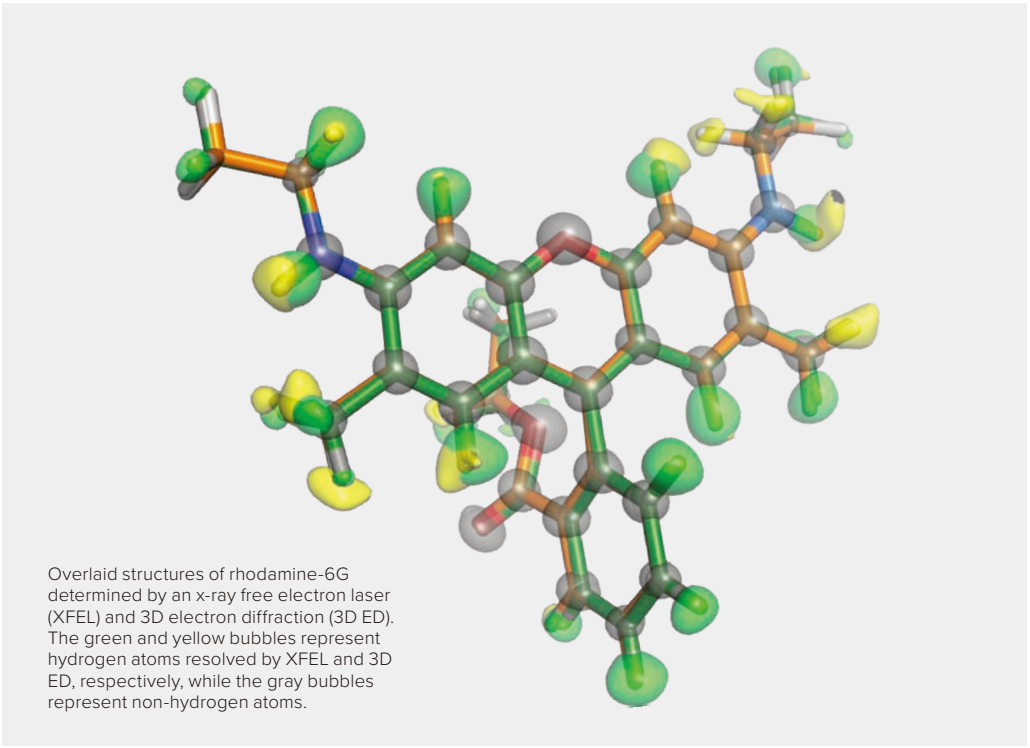
Ever since British physicists William Lawrence Bragg and his father William Henry Bragg demonstrated that x-rays scattered from crystals produce distinctive patterns 110 years ago, x-ray diffraction has been the technique for determining the structure of crystalline materials. However, many materials form crystals that are too small to be analyzed by x-ray diffraction.

"Because many compounds cannot be obtained in large crystals, the ability to analyze the structures of small crystals is important in fields such as synthetic organic chemistry, pharmaceutical science and materials science," says Koji Yonekura of the RIKEN SPring-8 Center.

Switching from x-rays to electrons can allow the structures of smaller crystals to be determined, but it has the downside that it requires very thin samples.

Another promising approach is to use the x-ray free electron laser (XFEL) facility SACLA, which produces ultra-intense, ultrashort x-ray pulses.

Now, Kiyofumi Takaba, Saori Maki-Yonekura, Yonekura and co-workers have used x-rays from an XFEL to determine the structure of a small organic molecule, a fluorescent dye called rhodamine-6G. They also compared the results with those obtained using 3D electron diffraction for the same molecule.



Overlaid structures of rhodamine-6G determined by an x-ray free electron laser (XFEL) and 3D electron diffraction (3D ED). The green and yellow bubbles represent hydrogen atoms resolved by XFEL and 3D ED, respectively, while the gray bubbles represent non-hydrogen atoms.

Using both techniques, the researchers were able to resolve the positions of some of the hydrogen atoms, which is remarkable since they are the smallest atom, consisting of just a proton and electron. The positions of the hydrogen atoms resolved by the two techniques depended on the type of bonds between hydrogen atoms.

"This is the first time anyone has demonstrated that hydrogen atoms in small crystals of organic compounds can be visualized by XFEL diffraction," notes Takaba. "It is an important achievement because the position of a hydrogen atom reveals the polarity of chemical bonds and because hydrogen atoms can significantly affect an organic molecule's properties and functions."

While the molecular structures obtained by the two techniques were very similar to each other, they also provided complimentary information since electrons and x-rays interacted differently with the samples. "XFEL and electron crystallography can reveal different and detailed features of organic compounds," says Maki-Yonekura. Specifically, XFEL could determine atomic coordinates more accurately, whereas electron diffraction was more sensitive to the distribution of electric charges in the molecule.

Importantly, no special sample preparation was needed for either method, making them practical to perform.

The team intends to continue to explore how specimens interact with different probes. "We expect this will extend not only the application of these techniques but also our theoretical understanding of the techniques themselves," says Takaba.

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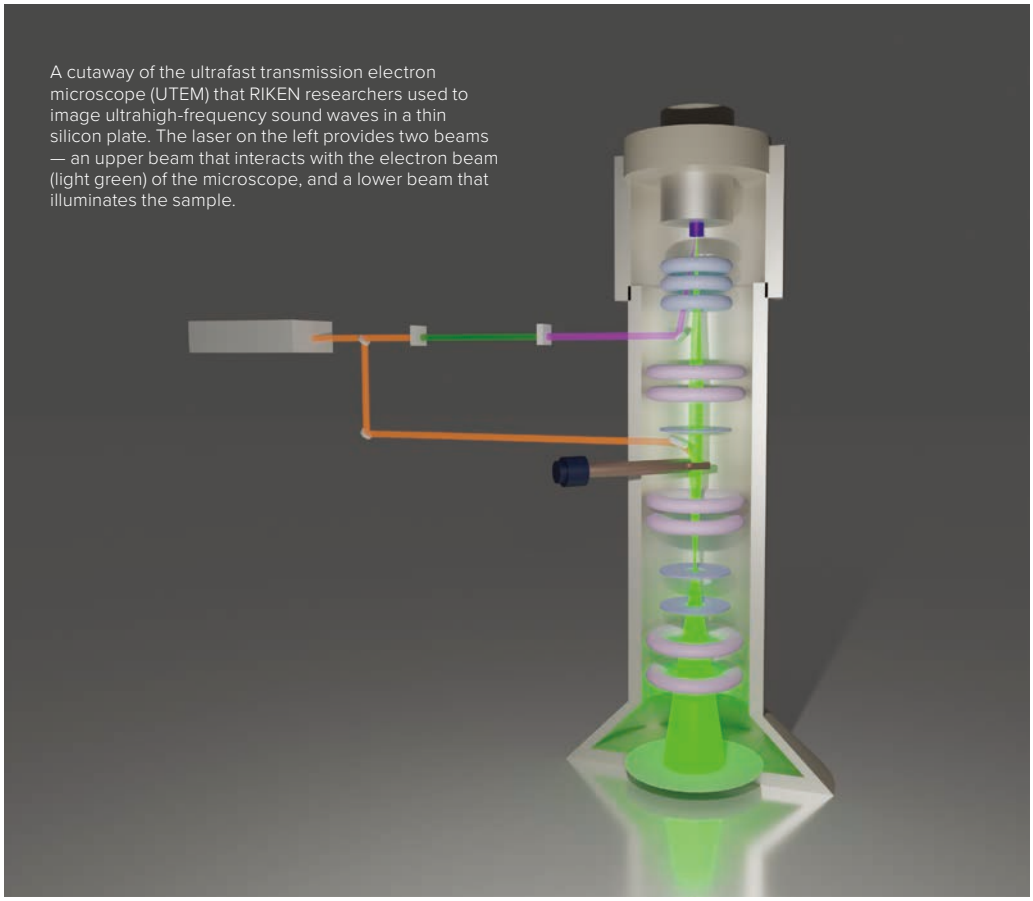
1. Takaba, K., Maki-Yonekura, S., Inoue, I., Tono, K., Hamaguchi, T., Kawakami, K., Naitow, H., Ishikawa, T., Yabashi, M. & Yonekura, K. Structural resolution of a small organic molecule by serial X-ray free-electron laser and electron crystallography. *Nature Chemistry* **15,** 491–497 (2023).



A cutaway of the ultrafast transmission electron microscope (UTEM) that RIKEN researchers used to image ultrahigh-frequency sound waves in a thin silicon plate. The laser on the left provides two beams — an upper beam that interacts with the electron beam (light green) of the microscope, and a lower beam that illuminates the sample.

ACOUSTIC WAVES

Using sound to see nanostructures

Sound waves that have tiny wavelengths can be detected using a special electron microscope

The potential of an ultrafast form of transmission electron microscopy to measure sound waves in nanostructures has been demonstrated by three RIKEN physicists[1]. This could help realize a high-resolution imaging method that uses ultrahigh-frequency sound waves to image structures that are nanometers in size.

Ultrasound is routinely used in clinics and hospitals to image internal organs and babies in the womb. The sound waves used are usually a few millimeters in wavelength, and so they can image structures down to that scale.

While such a resolution is sufficient for medical imaging, physicists would like to use sound waves to image structures in materials that are a few nanometers in size.

"If we can use sound waves that have wavelengths of about 100 nanometers or so, we can use them for inspecting materials [and]...finding defects," explains Asuka Nakamura of the RIKEN Center for Emergent Matter Science (CEMS). "But the sensitivity to small defects really depends on the wavelength."

This requires generating and detecting sound waves that have much smaller wavelengths (and hence higher frequencies). Creating such high-frequency sound waves is relatively easy—ultrashort laser pulses have been used to generate them in metals and semiconductors for several decades. But detecting them is much more challenging since it requires developing detectors capable of achieving a resolution of nanometers in space and picoseconds in time.

Now, Nakamura, along with CEM colleagues Takahiro Shimojima and Kyoko Ishizaka, have demonstrated the potential of a special type of electron microscope for imaging such ultrahigh-frequency sound waves.

Specifically, they used an ultrafast transmission electron microscope (UTEM) to detect sound waves generated by a 200-nanometer hole in the center of an ultrathin silicon plate. A UTEM uses two laser beams with a slight delay between them (see image). One beam illuminates the sample, while the other generates an ultrashort pulse of electrons in the microscope. This setup enables very short timescales to be resolved.

When the trio simulated the waves theoretically and compared the simulations with experimentally obtained images, they found good agreement.

The quality of the images exceeded the team's expectations, allowing them to perform Fourier-transform analysis—a commonly used mathematical analytic technique—on the images. "Before performing these experiments, we didn't intend to characterize the sound waves," says Nakamura. "But after taking the data, we noticed they were very beautiful, and we could apply Fourier transformation. That was surprising for me."

The researchers now intend to investigate ultrafast structural and magnetic dynamics in solids induced by such nanometric sound waves using UTEM. ●

Reference

1. Nakamura, A., Shimojima, T. & Ishizaka, K. Characterizing an optically induced sub-micrometer gigahertz acoustic wave in a silicon thin plate. *Nano Letters* **23,** 2490–2495 (2023).

HYDROGEN STORAGE

A safe, easy and affordable way to store and retrieve hydrogen

A crystal that can readily incorporate and release ammonia is promising for storing hydrogen

A compound that offers a potentially safe and convenient way to store ammonia—an industrially important chemical used for making fertilizers, drugs and textiles—has been discovered by RIKEN chemists[1]. Since ammonia is also useful for storing hydrogen, this finding could help to realize a practical hydrogen economy.

Hydrogen is the ideal clean fuel, producing only water as a waste product. But since it is highly combustible, a safe way to store and transport hydrogen is needed. One way would be to store hydrogen as part of another molecule and extract it as required.

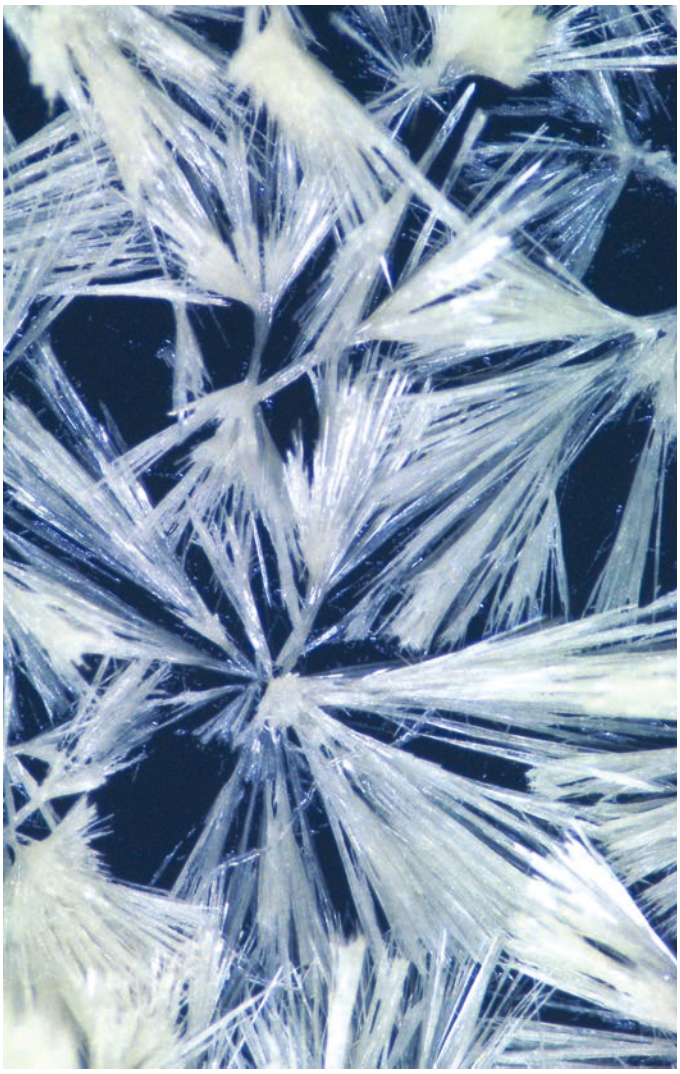
"To our surprise, ammonia stored in ethylammonium lead iodide could be easily extracted by heating it gently"

Ammonia (NH_3) makes a good hydrogen carrier as each molecule has three hydrogen atoms. However, being a highly corrosive gas, ammonia is difficult to store and use. It is generally stored by liquefying it at 33 degrees Celsius in pressure-resistant containers. Porous compounds can store ammonia at room temperature and pressure, but they have low storage capacities and it can be difficult to retrieve ammonia from them.

Now, a team led by Masuki Kawamoto of the RIKEN Center for Emergent Matter Science (CEMS) has discovered a crystalline material that can easily store and release ammonia at relatively low temperatures.

The team found the 1D columnar structure of the crystal ethylammonium lead iodide reacts chemically with ammonia at room temperature and pressure, dynamically transforming into a 2D layered structure called lead iodide hydroxide (see image). This process stores ammonia within the layered structure through chemical conversion. Thus, ethylammonium lead iodide can safely store ammonia as a nitrogen compound in a process that is much cheaper than liquification.

More importantly, retrieving the stored ammonia is just as simple. "To our surprise, ammonia stored in ethylammonium lead iodide could be easily extracted by heating it gently," says Kawamoto. The stored nitrogen compound undergoes a reverse reaction at 50 °C under vacuum and returns to ammonia, which is much lower than the 150 °C or more that is needed to extract ammonia from porous compounds.



Crystals of lead iodide hydroxide. These can be used to store ammonia, which holds promise as carrier of hydrogen.

Additionally, after returning to the 1D columnar structure, the crystal can be reused, allowing ammonia to be repeatedly stored and extracted.

An added bonus was that the yellow compound became white after the reaction. "The compound's ability to change color when storing ammonia means that color-based ammonia sensors can be developed to determine the amount of ammonia stored," says Kawamoto.

"In the long term, we hope that this simple and efficient method can be a part of the solution for achieving a decarbonized society through the use of ammonia as a carbon-free hydrogen carrier," says Yoshihiro Ito, also of CEMS. ●

Reference

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INFLAMMAGING

How immune systems overactivate in old age

By engineering mice lacking a key signaling molecule, researchers have shed light on how the immune system causes problems in elderly people

The lack of a key signaling molecule in certain immune cells can induce various age-related diseases in young mice, RIKEN researchers have shown[1]. This finding eventually could help to develop new treatments for age-related diseases.

Aging isn't kind to our immune systems, causing over-activation of the system, so that inflammation occurs even when there are no pathogens in sight. Dubbed inflammaging, this chronic, low-grade inflammation damages tissue, making elderly people more susceptible to infection and a wide range of diseases, including cancer, type 2 diabetes and heart disease.

Inflammaging causes T cells—immune cells that recognize, respond to, and remember specific pathogens—to go into overdrive, producing inflammation-causing compounds such as cytokines and chemokines. This is known as the senescence state of T cells.

"People often have the impression that aging makes cells less active," says Takashi Saito of the RIKEN Center for Integrative Medical Sciences. "However, some aged immune cells enter an activated phase, and the resulting inflammaging can give rise to various age-dependent diseases."

A signaling molecule called receptor-interacting protein kinase 1 (RIPK1) controls cell death through two different paths, depending on which compounds it combines with. Recent studies had found that people with a RIPK1 deficiency are more susceptible to inflammatory disorders.

Now, Saito and co-workers have engineered mice that lack RIPK1 just in their T cells. They found that these mice developed inflammatory diseases at a young age and died much earlier than normal mice.

Interestingly, the T cells lacking RIPK1 behaved similarly to T cells in aged mice.

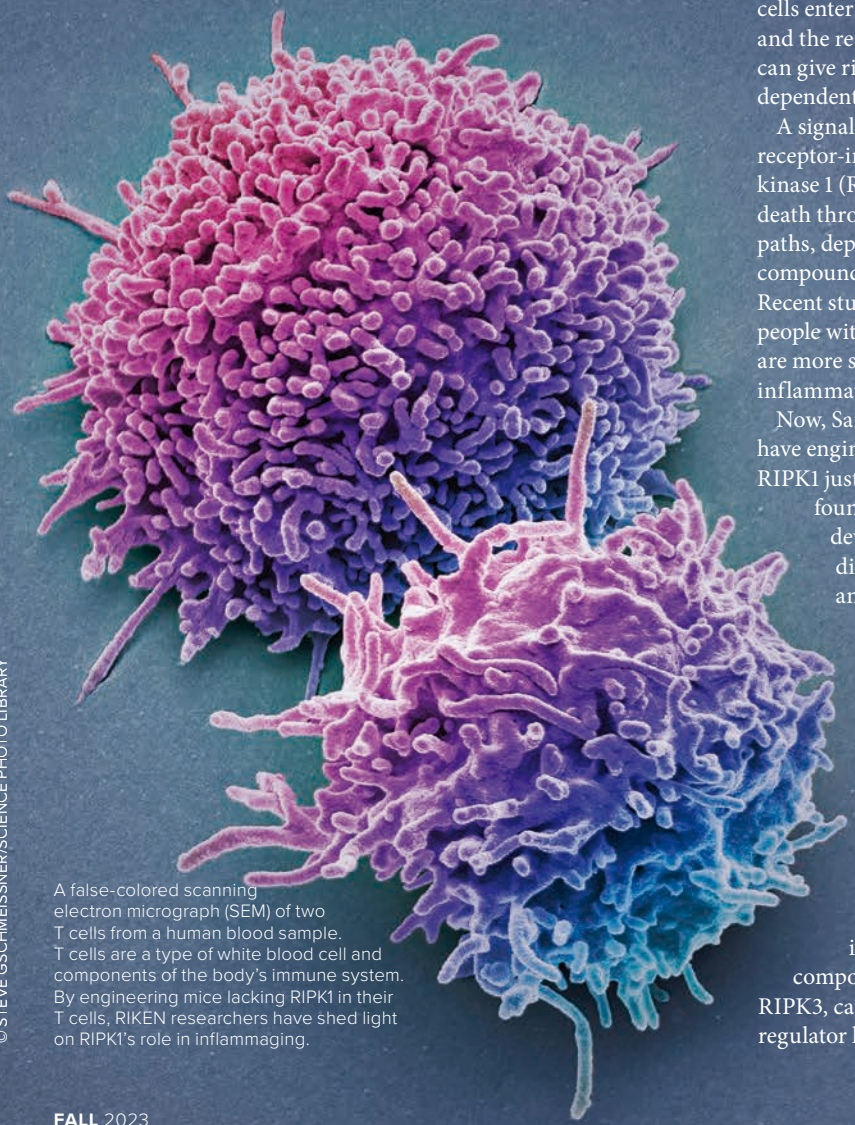
The team uncovered how this premature inflammaging occurs. When RIPK1 is not present, two compounds, caspase-8 and RIPK3, cause a cell-growth regulator known as mTORC1 to be excessively activated. This in turn promotes T cell senescence by inducing the expression of senescence-related genes, resulting in the production of various cytokines and chemokines.

This mechanism was unexpected. "Caspase-8 and RIPK3 are well known to induce cell death," says Saito. "But we've shown that they also help to activate mTORC1 and induce inflammaging in cellular senescence."

This discovery opens up the possibility of finding new ways to treat inflammaging. "We could target caspase-8 and RIPK3 to counteract inflammaging induced by T cell senescence," says Saito.

A further surprise was that when the team put the senescent T cells into normal mice, they reverted to normal, non-senescent T cells, indicating that environmental factors play an important role in regulating T cell senescence.

The team is now investigating what happens before activation of RIPK3 and caspase-8. They also want to explore what environmental factors allow senescent T cells to revert to normal T cells.



A false-colored scanning electron micrograph (SEM) of two T cells from a human blood sample. T cells are a type of white blood cell and components of the body's immune system. By engineering mice lacking RIPK1 in their T cells, RIKEN researchers have shed light on RIPK1's role in inflammaging.

Reference

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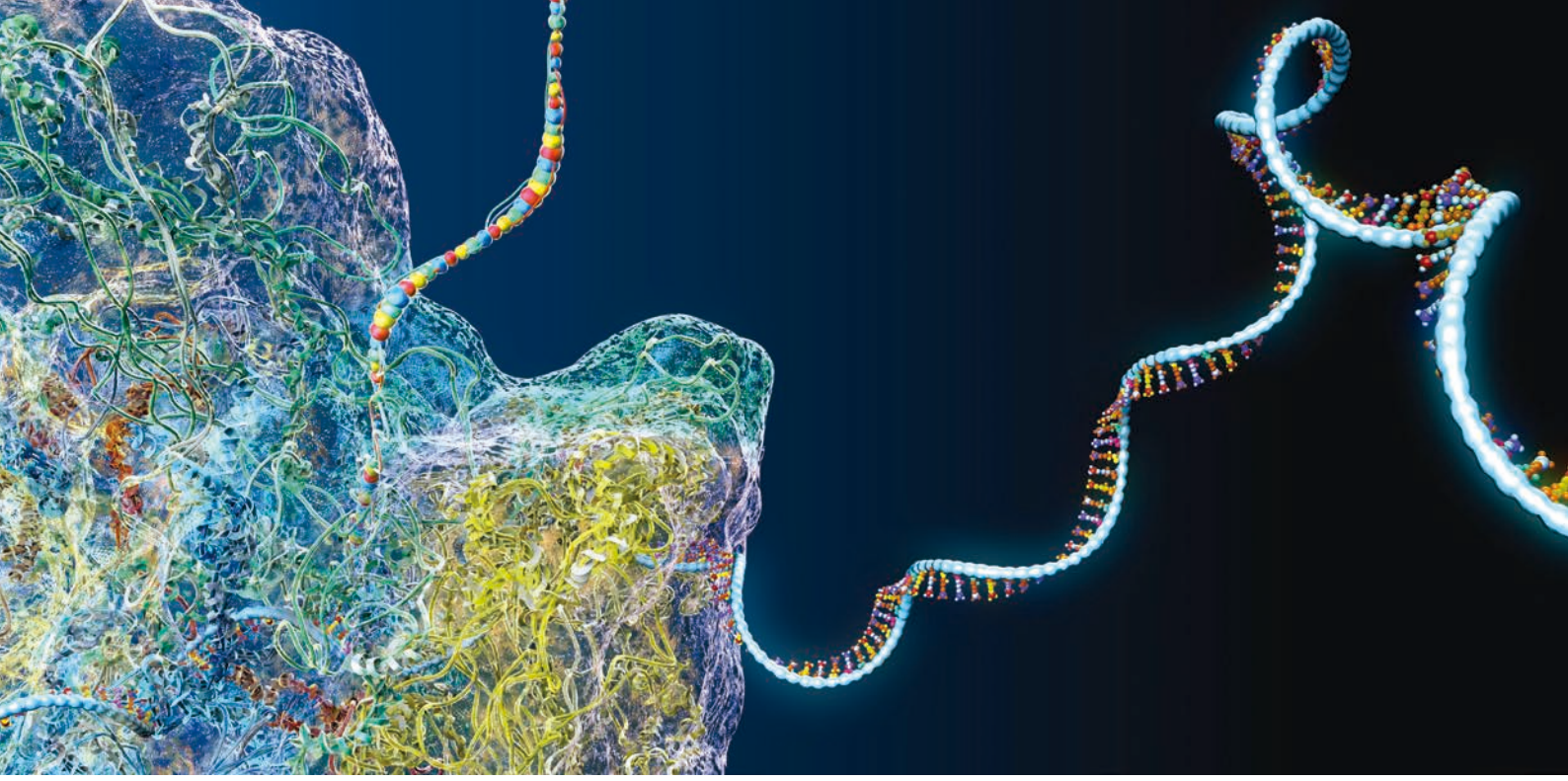

An artist's impression of a ribosome. Ribosomes convert genetic material (half helix on the right) into proteins (coloured beads on top left) that allow cells to function. RIKEN researchers have now found a connection between cognitive disorders and dysregulation of ribosome-associated quality control of protein production.

COGNITIVE DISORDERS

Making a bad situation worse

An over-reaction when protein synthesis stalls can lead to neurodevelopmental disorders in mice

The link between quality control during protein synthesis in cells and neurological disorders has been made clear for the first time by RIKEN researchers[1]. This discovery could help to develop new treatments for such cognitive disorders.

Complex molecular factories inside cells, ribosomes convert genetic code into protein molecules. This protein synthesis proceeds in fits and starts, and sometimes it grinds to a complete halt.

When this happens, an important quality-control process kicks in and degrades the incomplete protein threads that have been made, which would otherwise damage cells. This mop-up operation is known as ribosome-associated quality control (RQC).

Recently, there has been some evidence suggesting that various brain disorders result when RQC goes awry, but no-one knew how this occurs.

"Previous studies had suggested that dysfunction of RQC may lead to neurodegenerative disorders," says Motomasa Tanaka of the RIKEN Center for Brain Science. "So we are really interested in what happens in neurons, but most studies so far have focused on cultured cell lines or yeast cells."

Now, Ryo Endo, also of RIKEN, Tanaka, and their team have discovered that removing a key gene in RQC in mice neurons leads to developmental defects in neurons.

Specifically, the team found that mice lacking an enzyme known as LTN1 had higher levels of two signaling molecules: TTC3 and UFMylation.

"The abundance of the protein TTC3 increased more than tenfold," notes Tanaka. "That was really surprising as it's an overkill."

These signaling molecules serve to turn off the translation of genetic material into proteins—a beneficial effect. But they go too far and apply the brakes to the growth of neurites—projections from neurons that go on to form connections with other neurons. It is this inhibition of neurites that is thought to lead to problems in neurons.

"Overexpression of TTC3 definitely helps to stop translation, which is a good thing," says Tanaka. "But it also curbs neurite extension, reducing communication between neurons. This is probably the cause of cognitive dysfunction."

Tanaka likens this creation of a more dire situation due to overcompensating for the initial problem of an overactive immune system that can cause serious conditions such as chronic inflammation and allergies.

The finding could help to develop new therapies. "We think some therapeutic strategies to target TTC3 or illumination signaling factors may also be interesting in the future," says Tanaka.

The team now intends to explore the relationship between the accumulation of signaling dysfunction and human brain disorders. ●

Reference

1. Endo, R., Chen, Y.-K., Burke, J., Takashima, N., Suryawanshi, N., Hui, K. K., Miyazaki, T. & Tanaka, M. Dysregulation of ribosome-associated quality control elicits cognitive disorders via overaccumulation of TTC3. Proceedings of the *National Academy of Sciences* **120,** e2211522120 (2023).

IMAGE RECOGNITION

Using AI to take Alice out of Wonderland

The development of robotic avatars could benefit from an improvement in how computers detect objects in low-resolution images

Just making a small tweak to algorithms typically used to enhance images could dramatically boost computer vision recognition capabilities in applications ranging from self-driving cars to cybernetic avatars, RIKEN researchers have shown[1].

Unlike most artificial intelligence (AI) experts, Lin Gu from the RIKEN Center for Advanced Intelligence Project began his career as a therapist. This background gave him unique insight into scale variance—a critical issue facing computer vision that refers to the difficulty of accurately detecting objects at different scales in an image. Because most AI systems are trained on high-resolution images, realistic low-quality pictures with blurry or distorted features pose a challenge to recognition algorithms.

The situation reminded Gu of 'Alice in Wonderland syndrome', a distorted vision condition that causes objects to appear smaller or larger than they actually are. "Human vision has size constancy, meaning we perceive objects as being the same size despite how the retinal image changes," says Gu. "In contrast, existing computer vision algorithms lack that constancy, like Alice."

Now, inspired by hippocampal replay techniques used by the brain to form memories, Gu and co-workers have developed a model that randomly degrades the resolution, blurriness, and noise of a high-resolution image—searching for features that stay the same after repeated changes.

Self-driving cars could benefit from enhanced object detection by using self-supervised learning.

By training on the generated data, the algorithm can perform self-supervised learning: helping other image-processing algorithms figure out what objects are in the image and where they are located without human intervention. The result: a more computationally efficient method of encoding and restoring the critical details in an image.

"In typical self-supervised learning methods, training data is modified by either masking part of the image or changing contrast before learning the supervisory signal," explains Gu. "We propose using resolution as a self-supervision clue for the first time."

Aside from typical computer vision uses, Gu notes that perceptual constant representation will be a fundamental part of technologies related to cyborgs and avatars. As an example, he cites his participation in a futuristic project by Japanese science agencies to create a realistic digital version of a government minister that can interact with citizens.

"For the artificial memory mechanism, representations that are invariant to resolution changes can act as a keystone," says Gu. "I'm working with neuroscientists in RIKEN to explore the relation between artificial perpetual constant representation and the real one in the brain."

This method is also being applied to terahertz imaging—an emerging non-destructive imaging technique with much potential in biomedicine, security and materials characterization. "As part of an ongoing collaboration with Michael Johnston's team at Oxford University, we're developing a new generation of terahertz imaging devices by using AI to enhance its quality and resolution," Gu says. ●

Reference

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EXTREME WEATHER

Small tweaks may mitigate extreme weather

Managing the impact of climate-change-induced increases in extreme weather events might one day be possible using clever simulations

RIKEN scientists have demonstrated how small changes in weather systems could prevent, or reduce, the severity of extreme weather events, such as torrential rain, that have become more common in recent years due to climate change[1].

The simulation experiment essentially showed that small perturbations—which might, for example, involve making tiny changes in wind speed—could prevent a typhoon with winds that are many times more powerful. If these changes could be made strategically, they could perhaps prevent a weather system from entering an undesired area, for example, says Takemasa Miyoshi from the RIKEN Center for Computational Science.

Being a chaotic dynamical system, weather is highly sensitive to initial conditions. "Using the chaos inherent in systems such as the weather is attractive," says Miyoshi. "It is generally accepted that we need to learn how to predict severe weather events so that we can prepare for them, but it could also be desirable to be able to mitigate the events themselves."

"Using the chaos inherent in systems such as the weather is attractive"

Previously, Miyoshi's group had used a simple Lorenz 63 weather model, which only has a few variables, and showed the possibility of inducing small perturbations in a weather system to keep it on one side of a 'butterfly' pattern that was the beginning of an extreme weather event.

Extreme weather events could be averted or their intensity reduced by making small tweaks, a simulation by RIKEN researchers suggests.

The latest study goes beyond that simpler model. In it, Miyoshi's group adopted the Lorenz 96 model. It shows weather variables for 40 points along a line of latitude around the Earth, and looks at how each of these points change as they interact with neighboring points throughout the year.

Approximately once or twice a year, the points show large variations, which correspond to extreme weather events. In a 100-year simulation, the team was able to eliminate some extreme events by making small tweaks.

While the exact means of changing weather and the ethical considerations around these actions are not yet clear, the benefits could be huge, says Miyoshi.

Scientists aiming to counteract global warming have focused on large geoengineering projects, such as carbon dioxide removal and solar radiation management, he says. However, this entails large costs and associated risks. "It might be better in some instances, to do the minimum required to prevent small-scale, but extreme weather events," he muses.

"In the future, we plan to continue our experiments with more realistic weather models," says Miyoshi. "It is important also to note that there are ethical, legal, and social issues that must be thoroughly discussed, such as the risks involved in making the changes compared to the gains that will come from them." ●

Reference

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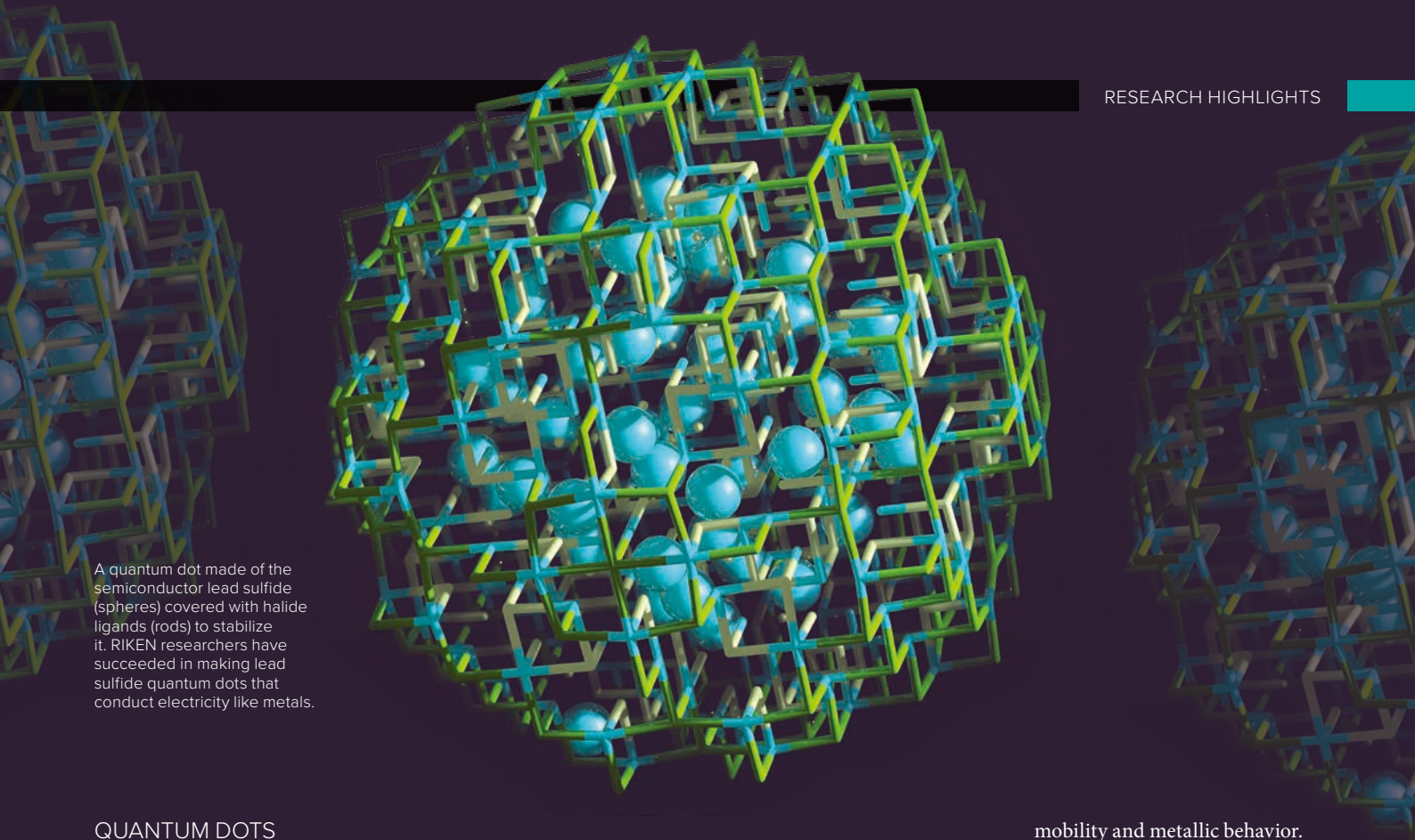

A quantum dot made of the semiconductor lead sulfide (spheres) covered with halide ligands (rods) to stabilize it. RIKEN researchers have succeeded in making lead sulfide quantum dots that conduct electricity like metals.

QUANTUM DOTS

Forging a dream material with semiconductor quantum dots

A material made from an array of semiconductor quantum dots behaves like a metal when it comes to conducting electricity

A superlattice of semiconductor quantum dots—nanoscale blobs of semiconductors—that can conduct electricity like a metal has been created by RIKEN researchers[1]. This demonstration could lead to the development of a whole range of new devices based on quantum dots.

Semiconducting quantum dots have been attracting tremendous interest, mainly due to their special optical properties. They are being used in solar cells, bioimaging, displays and quantum computing.

However, getting semiconductor quantum dots to efficiently conduct electricity has been a major challenge, impeding their full use. This is primarily due to their lack of orientational order in assemblies.

"Making them metallic would enable, for example, quantum-dot displays that are brighter yet use less energy than current devices," says Satria Zulkarnaen Bisri, who conducted the research at the RIKEN Center for Emergent Matter Science (CEMS) but is now at the Tokyo University of Agriculture and Technology.

Now, a team led by Bisri and Yoshihiro Iwasa of CEMS has taken a large step towards reaching that goal by creating a superlattice of colloidal quantum dots made from the semiconductor lead sulfide that conducts electricity like a metal.

The key to achieving this was to get the individual quantum dots in the lattice to directly attach to one another and to do this with their facets oriented in a precise way.

When the researchers measured the conductivity of the material while increasing the carrier density, they found that at a certain point it became a million times more conductive than what is currently available from quantum-dot displays. Importantly, the quantum confinement of the individual quantum dots was maintained, so that they didn't lose their functionality despite the high conductivity.

"Semiconductor quantum dots have always shown promise for their optical properties, but their electronic mobility has been a challenge," says Iwasa. "Our research has demonstrated that precise orientation control of the quantum dots in the assembly can lead to high electronic mobility and metallic behavior. This breakthrough could open up new avenues for using semiconductor quantum dots in emerging technologies."

"We plan to carry out further studies with this class of materials, and believe it could lead to vast improvements in the capabilities of quantum-dot superlattices," says Bisri. "In addition to improving current devices, it could lead to new applications such as true all-quantum-dot direct electroluminescence devices, electrically driven lasers, thermoelectric devices, and highly sensitive detectors and sensors, which previously were beyond the scope of quantum-dot materials."

Reference

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Suddenly encountering a bear while walking in a forest would imprint both the bear and the location in the walker's memory. RIKEN researchers have discovered how this information is integrated into pre-existing mental maps in rats.

PLACE CELLS

Replaying bad memories marks them on our mental maps

The mechanism by which places associated with negative experiences are burned into our memories may have been revealed

Three RIKEN neuroscientists have found that rats reinforce the memories of negative experiences in familiar locations by preferentially replaying them over in their minds[1]. This finding could have implications for treating conditions in people such as post-traumatic stress disorder (PTSD).

When an animal explores a new place, it generates a mental map of the area, which it can later recall. This mental map is created by special neurons known as place cells, which reside in the hippocampus. Different place cells fire as the animal moves around the area, but when it returns to a spot it has visited before, the same place cell fires again.

This mapping mechanism is well understood now, but it wasn't clear how animals incorporate memories of things that happen to them while revisiting a previously mapped-out location.

Significant events get burned in our memories along with the place where they happened, whereas we tend to forget about details that don't matter.

"For example, if you're hiking along a familiar trail, you're probably not going to remember all the details of the trail," says Joshua Johansen of the RIKEN Center for Brain Science. "But if a bear comes out and attacks you, you're going to remember a lot of the details about the bear and also the surrounding environment. We want to understand how these more complex memories are formed."

Now, Johansen, along with Jake Ormond and Simon Serka, has found that the neurons where negative experiences are stored are separate but adjacent to the place cells in the hippocampus and that the memories are reinforced by replaying the experience.

Specifically, the team found that a specific population of place cells 'remapped', changing their firing location to reflect the aversive experience, while other place cells did not change their firing location during learning, providing a stable representation of the physical environment. Notably, the cells associated with the negative experience were preferentially reactivated during rest periods between trials.

This finding could inform the development of new treatments for psychiatric disorders such as PTSD. "We've made much headway in understanding how simple forms of learning such as fear conditioning occur," notes Johansen. "But that hasn't really brought us that much closer to being able to treat conditions such as PTSD."

This might be because we lack a good understanding of the higher-order processing systems in the brain that are altered in PTSD, Johansen thinks. "Understanding how higher-order systems such as the hippocampus alter the record of unpleasant experiences could give basic insights into how these systems are altered and dysregulated in conditions such as PTSD," he says.

Reference

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PLANT CELL BIOLOGY

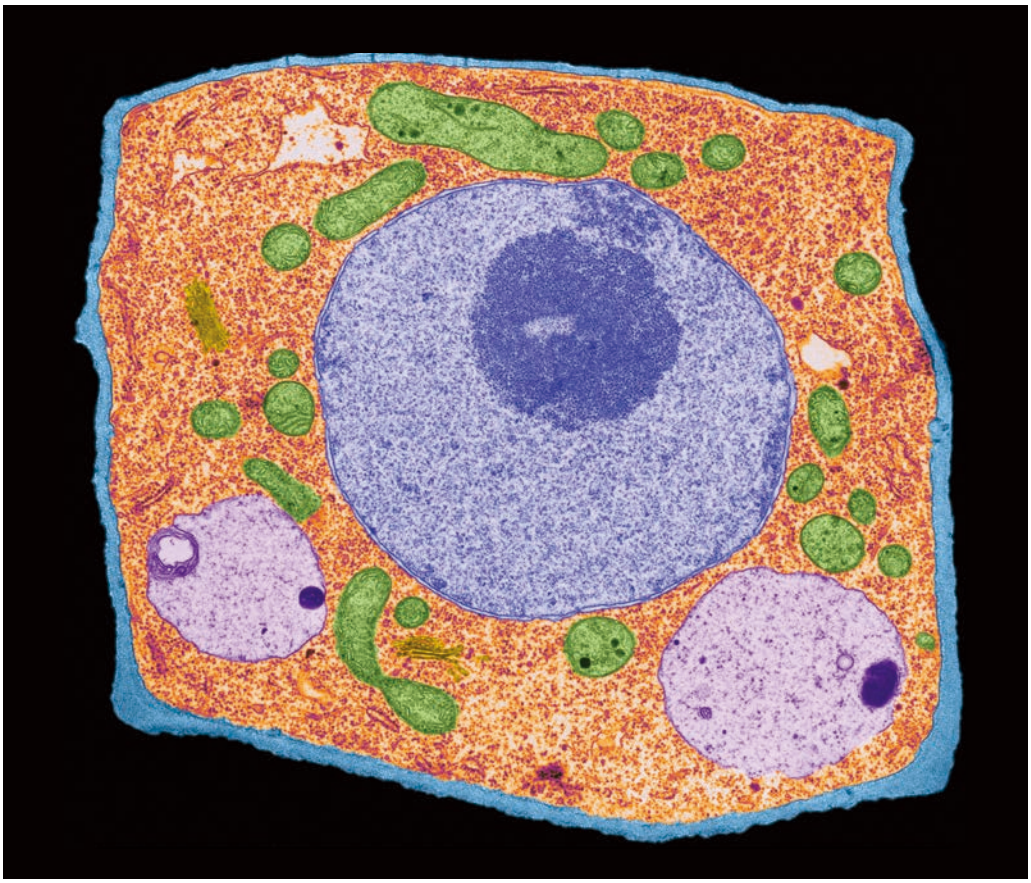
Lipid making in plants involves two organelles

Two enzymes that catalyze an essential reaction for producing plant oils are found in different organelles

Two enzymes that plants need to make oils live in different organelles, a pair of RIKEN researchers has found[1]. This finding will help inform efforts to tweak the metabolism of plants to boost their production of oils, which can be used as biofuels among other things.

As well as forming the building blocks for the cell membranes of plants, membrane lipids are the precursors for the oils stored in seeds. They are thus attracting attention in research looking into modifying plant metabolism to boost the production of industrially useful oils.

"Oil is the main storage lipid of seeds and is not only important for plant growth, but also as a raw material for various industrial products, including biodiesel," explains Yuki Nakamura of the RIKEN Center for Sustainable Resource Science (CSRS). "Since oils are derived from sugars produced from carbon dioxide in the atmosphere through photosynthesis in plants, research into lipids is expected to contribute to biomanufacturing, which will help to realize a low-carbon society."



Color-enhanced transmission electron micrograph of a thale cress cell. RIKEN researchers have discovered that two enzymes essential for making lipids actually reside in different organelles, namely the endoplasmic reticulum (purple blobs) and chloroplasts (green blobs).

Oils are formed in the endoplasmic reticulum—a large structure in plant cells that performs multiple functions. A key step in lipid synthesis is catalyzed by an enzyme known as phosphatidic acid phosphatase. It has a dozen or so different forms that have slightly different sequences of amino acids, but it wasn't known which of these forms are essential for lipid synthesis.

Now, Nakamura and Van Nguyen, also at the CSRS, have shown that two forms of phosphatidic acid phosphatase, LPPα2 and LPPε1, are required to make lipids in thale cress.

When the researchers knocked out the genes that code for LPPα2 and LPPε1, the resulting plants didn't survive.

In a surprising twist, the researchers found that the forms don't reside in the same organelles: LPPα2 is in the endoplasmic reticulum, whereas LPPε1 is found nearby in chloroplasts—the site where photosynthesis occurs.

"It makes sense that one enzyme is in the endoplasmic reticulum, because that is where the pathway is happening, but we don't yet know why the other enzyme is in the chloroplast," comments Nakamura.

This finding implies that the two organelles have to talk to each other in order to produce lipids—something that Nakamura is keen to explore in the future.

The discovery was particularly gratifying for Nakamura as it answers a question he had while doing his PhD about 15 years ago. "I'm very happy with this finding because it resolves a question that's been nagging at me for a very long time," he says. ●

Reference

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NUCLEAR PHYSICS

Probing the properties of vacuum in nuclei

The effect of high densities on the properties of vacuum have been quantitatively deduced for the first time

By creating special atoms, RIKEN physicists have measured how the extremely high density of atomic nuclei influences the properties of vacuum[1]. This could help to shed light on where matter gets most of its mass.

As its name implies, the strong force is the strongest of the four fundamental forces, being about 100 times stronger than the electromagnetic force, the second strongest force. It is so strong that it causes pairs of quarks—the building blocks of protons and neutrons—and antiquarks (the antiparticles of quarks) to spontaneously form in vacuum.

"We were surprised at the consistency between the achieved result and the fundamental theories."

While these quark–antiquark pairs are not directly observable, they alter the properties of vacuum and can be detected through their effects on other processes. In particular, they break the symmetry of vacuum.

This symmetry breaking of vacuum has surprising effects. Both protons and neutrons are made up of three quarks, but the masses of the quarks only account for about 1% of the total mass of a proton or neutron. A significant proportion of the remainder of their mass is thought to come from the symmetry breaking of vacuum.

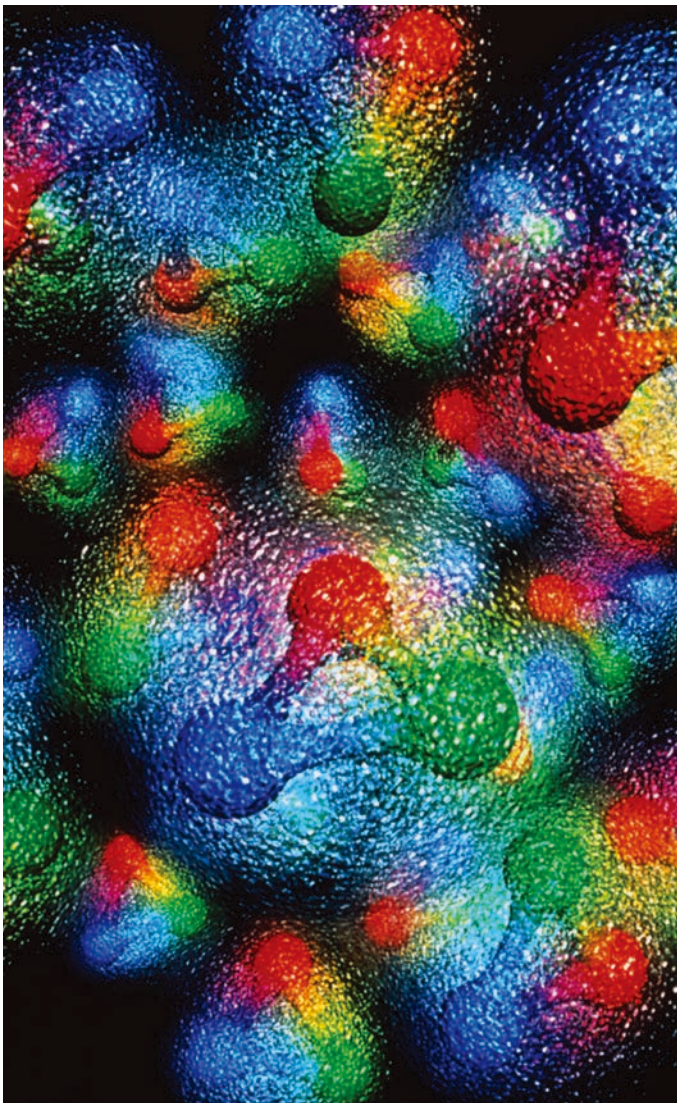
Increasing either the temperature or the density of matter present is theoretically predicted to partially restore the symmetry of vacuum. While several experiments have verified this effect at high temperatures, none have been done at high matter densities.

Now, Kenta Itahashi of the RIKEN Nishina Center for Accelerator-Based Science and co-workers have measured with high precision the partial restoration of vacuum symmetry at high densities, obtaining excellent agreement with theory.

They did this by creating special atoms of the metal tin using the RIKEN Radioactive Isotope Beam Factory, a facility that creates beams of heavy ions by accelerating them in stages. Instead of having electrons circling the nucleus, these atoms had a pion—an extremely short-lived particle consisting of a quark and antiquark. Unlike electrons, which only experience the electromagnetic force, pions interact with the nucleus through both the strong and electromagnetic forces. Since a nucleus is about 100 trillion times denser than normal matter, this enabled the researchers to probe the effect of high density on the symmetry of vacuum.

The experiment itself only took ten days, but the subsequent analysis of the results took about nearly ten years to complete. The initial results overlapped only slightly with those predicted by theory, but after correcting various effects and updating parameters as more accurate ones became available, the results agreed very well with theory.

"We were surprised at the consistency between the achieved result and the fundamental theories," says Itahashi. "Thanks to the continuous efforts of our collaborators, we were able to achieve unprecedented accuracy." ●



A depiction of an atomic nucleus, showing protons and neutrons, which are composed of three quarks held together by the strong force. RIKEN researchers have measured the effect of the nucleus' high density on the symmetry of vacuum.

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ANTIFUNGALS

Combating deadly antifungal resistance

Blocking fungi from making fatty acids offers a new way to address a problem that kills millions annually

RIKEN researchers have discovered a new way to attack fungal infections that involves blocking fungi from being able to make fatty acids[1]. Because it affects a broad range of fungal species, this approach is promising for tackling the growing resistance to existing antifungal drugs.

Athlete's foot is a relatively harmless health issue that can be solved by a trip to the drug store, but other fungal infections are more serious, with the *Candida*, *Cryptococcus* and *Aspergillus* families of fungi claiming millions of lives every year. Similar to bacterial resistance to antibiotics, fungal resistance to medications is also growing worldwide, and the death toll will likely rise unless action is taken.

Antifungal medications work by destroying the barrier surrounding fungal cells. Despite this common mechanism, current treatments are highly specific, killing some fungal species but not others.

A collaboration between the RIKEN Center for Sustainable Research Science (CSRS) and the University of Toronto is looking to combat fungi in a different way. They screened the structurally diverse RIKEN natural product depository against four pathogenic yeasts—three *Candida* and one *Cryptococcus* species—identified as critical human pathogens by the World Health Organization. They were looking for something that would affect all four species, which would indicate that it might be effective against a broad range of fungi.

The screening identified several compounds that reduced fungal growth by at least 50% in each of the four species. After eliminating known compounds, three new possibilities remained. Of these, the one least toxic to human cells (NPD6433) also reduced growth of *Aspergillus fumigatus*, an extremely common fungal mold that can be deadly to immuno-compromised individuals.

For almost 1,000 genes, the researchers assessed how much NPD6433 suppressed growth in yeast missing one copy of the gene. They found that removing the gene encoding *fatty acid synthase* made yeast more susceptible to NPD6433, indicating that it probably works by inhibiting *fatty acid synthase* and so preventing fatty acids from being made inside fungal cells.

The researchers tested NPD6433 in nematodes, which have similar intestinal tracts as humans. Using NPD6433 to treat nematodes infected with pathogenic yeast that invades through the intestines reduced the number of nematode deaths by about 50%. Importantly, this still held in worms that were resistant to a standard antifungal medication.

"Drug-resistant fungi are a growing problem, and leads for the development of new drugs offer hope against these evolving pathogens," says Yoko Yashiroda, who leads the CSRS team. "Our research indicates that targeting fatty acid synthesis is a promising alternative therapeutic strategy for fungal infections, and one which might not require tailor-made solutions for individual species."

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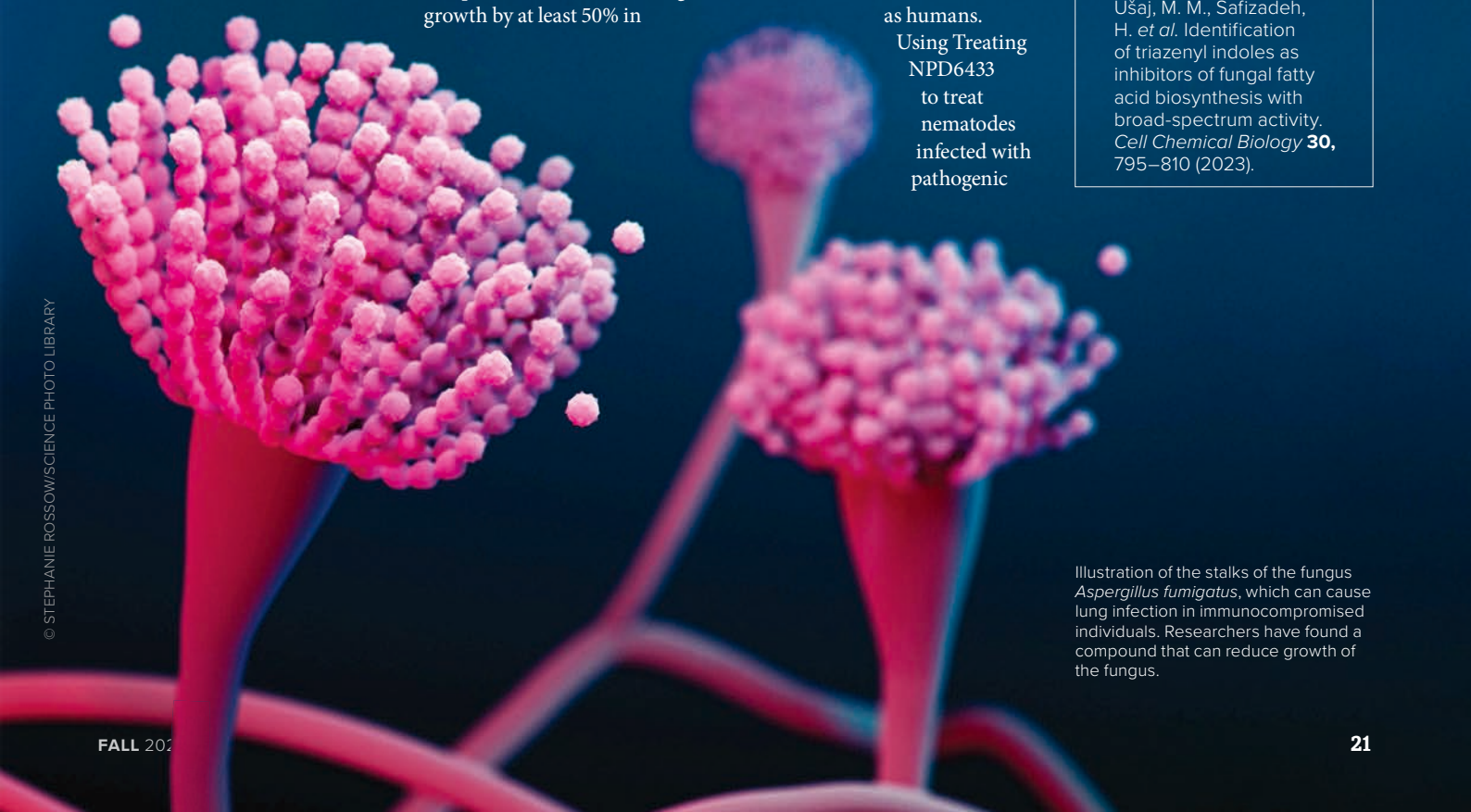

Illustration of the stalks of the fungus *Aspergillus fumigatus*, which can cause lung infection in immunocompromised individuals. Researchers have found a compound that can reduce growth of the fungus.

APOPTOSIS

Flies aren't freaks when it comes to cell death

Despite what's written in textbooks, fruit flies use a similar cell-stress sensor as mammals to initiate programmed cell death

RIKEN geneticists have uncovered a protein in fruit flies that many textbooks say doesn't exist[1]. The protein detects stress in cells and sets them on a pathway to self-destruction when they are overly stressed.

Damaged cells in our bodies eliminate themselves by initiating a suicidal process of programmed cell death known as apoptosis. This process is essential for our health and for ensuring that cells don't become cancerous.

"It means that fruit flies aren't an exception or a bit weird."

The molecular cascade behind this process is highly complex, but it is triggered by a single protein that belongs to a family of proteins known as BH3-only proteins. These proteins sense stress in cells and are found in many animals including mammals and nematodes.

However, for the last two decades, fruit flies, and possibly all insects, were thought to lack BH3-only proteins. Instead, they were believed to rely on a different cell-death program.

But now, in a surprise discovery, Sa Kan Yoo of the RIKEN Center for Biosystems Dynamics Research and co-workers have found that fruit flies do indeed harbor a BH3-only protein. They named the gene that encodes for it *sayonara* after the Japanese word for 'farewell'.

When the team caused the *sayonara* gene to be expressed in fruit-fly wings, they observed apoptosis occurring, resulting in withering of the wings (see image).

According to Yoo, the gene was hidden in plain sight. "We didn't do anything fancy," he says. "We used the genetic sequence for a human BH3-only protein and checked whether the genome of fruit flies has a similar sequence—it's a very common way to find genes in fruit flies that correspond to human ones."

Yoo suspects that incomplete sequencing of the fruit fly's genome may explain why researchers didn't find the gene in fruit flies 20 years ago. "Genomic sequencing was incomplete back then, so probably scientists couldn't find the gene and after a while they just gave up."

The fruit fly's lack of a BH3-only protein subsequently became enshrined in textbooks. But for Yoo it posed an interesting challenge. "I thought it might be fun to check it," he says. "And after just a few hours, I found something that looked suspiciously like a BH3-only protein."

The finding implies that fruit flies, and probably other insects, aren't so different when it comes to apoptosis. "It means that fruit flies aren't an exception or a bit weird," says Yoo. "Rather we found they have a similar mechanism for regulating apoptosis as humans and nematodes."

The team is now exploring exactly what happens after the BH3-only protein is activated. They are also investigating if other insects have BH3-only proteins. ●

Expression of the *sayonara* gene in the wings of a fruit fly causes the wings to shrivel due to apoptosis.

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PLANT–FUNGUS INTERACTIONS

How a fungus sidesteps a plant's defenses

An anti-fungal compound produced by plants doesn't work on at least one fungus

RIKEN scientists have discovered how a parasitic fungus renders harmless a powerful anti-fungal compound produced by some plants[1]. As well as providing a fascinating glimpse into the ongoing arms race between plants and parasites, the finding could be useful for developing new therapies for people.

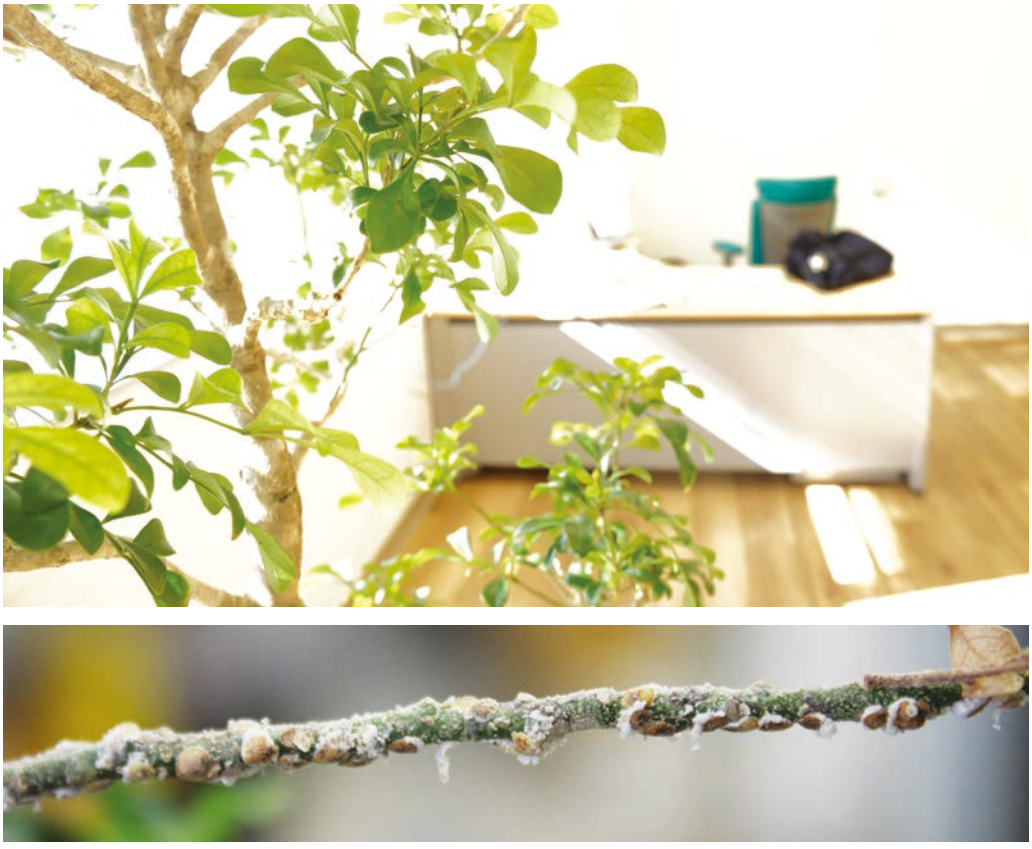
Parasitic fungi that infect plants are a major economic burden as they cause significant loss of crops. This provides a big incentive for scientists to understand the interactions between plants and fungi.

Many plants ward off fungi by producing small molecules that kill fungi. Rocaglates are one such family of antifungals that work by binding to a molecule called eIF4A, which fungi, in common with plants and animals, need to make essential proteins.

Now, Shintaro Iwasaki of the RIKEN RNA Systems Biochemistry Laboratory and co-workers have discovered a fungal species that can avoid the lethal effects of rocaglates.

The discovery owed a lot to serendipity. "It was a fortuitous accident," Iwasaki comments. At the time, he had been in the United States researching a common house plant called *Aglaia* (also known as the Chinese perfume plant). Iwasaki subsequently moved to Japan to start working at RIKEN but was unable to take the plant with him due to import restrictions on foreign plants.

"So I asked a student in the lab to water the plant and keep it healthy, since it might be needed for further experiments," says Iwasaki. "But the student overwatered it."



The *Aglaia* plant in Shintaro Iwasaki's former office in the USA became infected with a fungus (bottom) despite producing rocaglate, an antifungal compound. His team has discovered how the fungus is able to evade the effects of rocaglate.

As a consequence, the plant became infected by a fungus. But that took Iwasaki by surprise since *Aglaia* produces rocaglates and so should have been protected from fungal infection.

Curious as to how the fungus could survive, Iwasaki and his team started to analyse it. They discovered that its gene for encoding eIF4A differed in just one place from that of the usual gene for eIF4A. This point mutation produced a slightly modified form of eIF4A that rocaglates cannot bind to, thus protecting them from the fungus.

To demonstrate that this was the case, Iwasaki transferred the gene to a cucumber-infecting fungus and found that the fungus thrived on cucumber even when treated with a chemical derived from rocaglates.

Interestingly, it is the same strategy that rocaglate-producing plants employ to prevent themselves from being poisoned by rocaglates.

Since rocaglates are attracting interest for treating diseases such as COVID-19 and cancer, the finding may be relevant to future therapies. "Some people may have a similar mutation as the fungus and thus not benefit from treatments based on rocaglates," says Iwasaki. ●

Reference

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GUT BACTERIA

Gut microbe causes flies to live fast and die young

The connection between a species of gut microbe in flies and an early death has been unraveled

RIKEN researchers have uncovered how one species of gut bacteria causes fruit flies to perish early[1]. This discovery illuminates the complex interactions between the microbes in our guts and our health.

The human gut is home to somewhere between 200 and 1,000 species of bacteria. The vast majority of these species are beneficial, converting food into useful compounds that the human body cannot make by itself. But some bacterial species have a negative impact on health.

The sheer number of bacterial species in the human gut makes it extremely challenging to untangle their individual effects on our health. Researchers find it much simpler to look at the gut microbiome of fruit flies since they only have about two to five bacterial species in their guts.

RIKEN researchers have discovered how a species of gut microbe causes flies to die young.

"*Acetobacter persici* has a drastic impact on fly lifespan, curtailing it by about 20–30%."

In a previous study, Fumiaki Obata of the RIKEN Center for Biosystems Dynamics Research had found that one of these species, *Acetobacter persici*, accelerated aging in flies, causing them to die early. "*A. persici* has a drastic impact on fly lifespan, curtailing it by about 20–30%," says Obata. "But just how the gut microbe caused this big change in lifespan was unclear."

Now, by feeding flies with a diet of dead *A. persici*, Obata and his co-workers have discovered the connection between *A. persici* and shortened fly lifespans.

To their surprise, the team found that the shortened lifespan is not due to a compound produced by *A. persici*. Rather, a component in the bacterium's cell wall triggers a receptor in the fly's gut, which stimulates the immune system, boosting the production of antimicrobial compounds and activating intestinal stem cells. It's this enhanced immunity that causes the flies to die young.

In an intriguing twist, the team discovered that these effects also boost a fly's resistance to infection by a harmful bacterium that can kill flies. It thus provides flies with a short-term advantage in exchange for an early death—a tradeoff that the researchers dubbed a 'live fast, die young' lifestyle.

"This increased resistance to infection explains why the vast majority of flies in the wild have *A. persici* or other *Acetobacter* species in their guts," says Obata. "It's better to have a strong resistance to stressors such as infection rather than to live to a ripe old age."

The finding raises the possibility that 'postbiotics' with health benefits could be developed; postbiotics are food and drinks that contain dead gut microbes (as opposed to 'prebiotics' containing live ones).

The team aims to determine the genes involved in the immune signaling that leads to shorter lifespans. They also want to see if the same mechanism occurs in other animals such as mice and humans. ●

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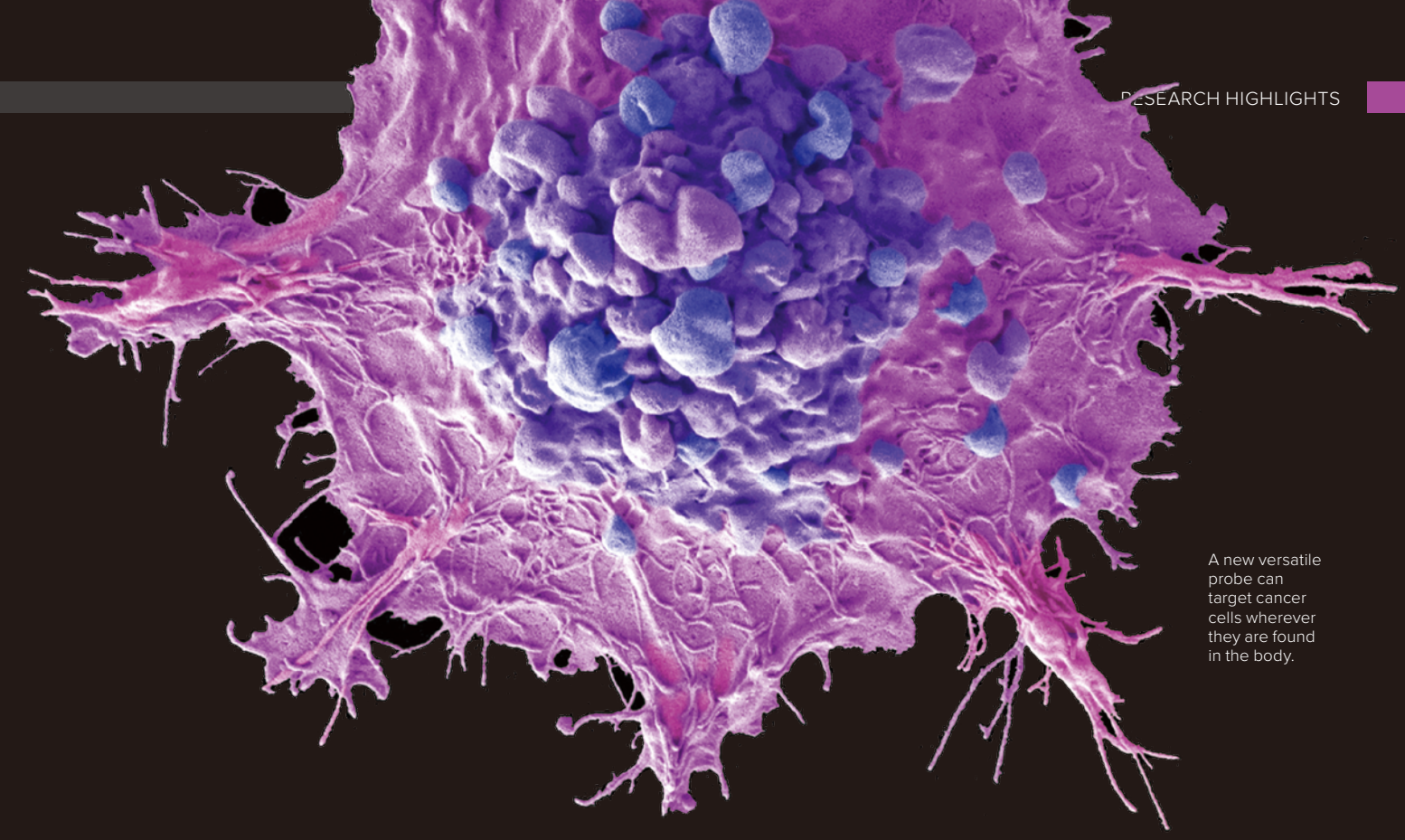

A new versatile probe can target cancer cells wherever they are found in the body.

ANTICANCER DRUGS

A versatile treatment for multiple types of cancer

A targeting technique has the potential to generically treat several kinds of cancer

RIKEN researchers have shown that tumors in mice grew almost three times less after just one injection of a compound designed to emit small amounts of alpha radiation from the inside of cancer cells, thus killing them but sparing healthy tissue[1].

Side effects of radiation treatment can be devastating, and the eradication of all cancer cells is not guaranteed, especially when the cancer has spread throughout the body. Therefore, most current research aims to find a way to specifically target cancer cells so that treatments only affect tumors. While some targeted treatments do exist, they cannot be applied to all cancers.

"Our new method can be used to treat many kinds of cancer without any targeting vectors, such as antibodies or peptides," explains Katsunori Tanaka of the RIKEN Biofunctional Synthetic Chemistry Laboratory.

The new technique relies on acrolein that accumulates in cancer cells. Tanaka's team had previously used a similar technique to detect individual breast cancer cells. They attached a fluorescent compound to a specific type of azide—an organic molecule with a group of three nitrogen atoms at the end.

When the azide and acrolein meet inside a cancer cell, they react, and the fluorescent compound becomes anchored to structures inside the cell. Because acrolein is almost absent from healthy cells, this technique acted like a probe to light up cancer cells in the body.

Now, the team has targeted cancer cells for destruction. Instead of attaching the azide to a fluorescent compound, they attached it to something that can kill a cell without harming surrounding cells. They used astatine-211, a radionuclide that emits a small amount of radiation in the form of alpha particles when it decays.

Alpha particles are more deadly than other radiation therapies, but they can only travel about 0.05 millimeter. In theory, when astatine-211 is anchored inside a cancer cell, the emitted alpha particles should damage the cell, but not much beyond.

The team attached astatine-211 to the azide probe and implanted human lung-tumor cells in mice. They tested the treatment under three conditions: injecting astatine-211 into the tumor; injecting the astatine-211-azide probe into the tumor; and injecting the astatine-211-azide probe into the bloodstream.

Without targeting, tumors continued to grow, and mice did not survive. But when the azide probe was used, tumors grew almost three times less and more mice survived—100% when injected into the tumor and 80% when injected into the blood.

"We can use this method to treat very early-stage cancer even if we don't know where the tumor is," says Tanaka.

Reference

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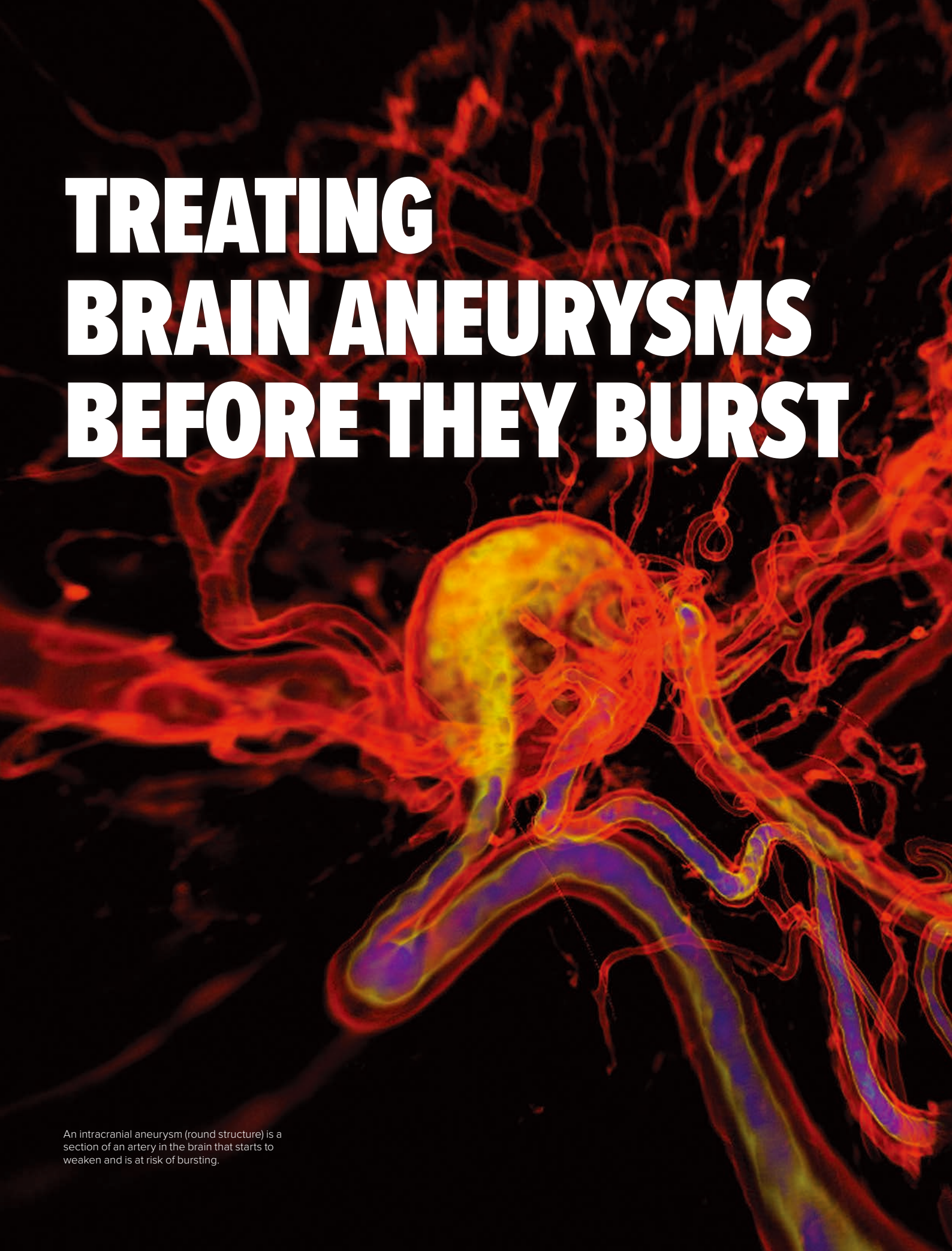
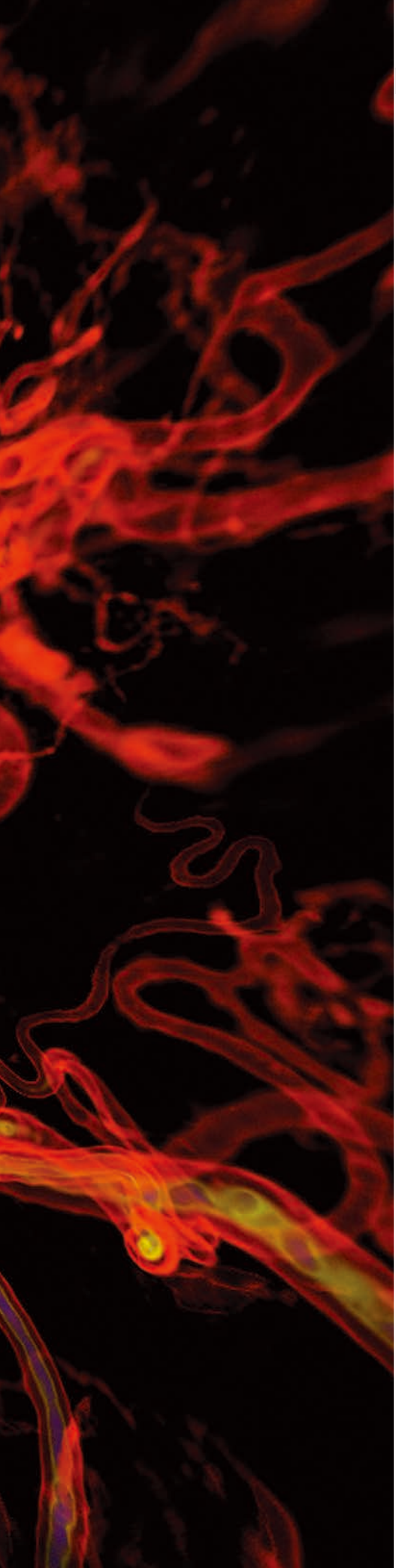
TREATING BRAIN ANEURYSMS BEFORE THEY BURST



An intracranial aneurysm (round structure) is a section of an artery in the brain that starts to weaken and is at risk of bursting.



K H FUNG / SCIENCE PHOTO LIBRARY

Studies reveal new potential drug targets to fix the problem of common, and potentially deadly, weakened arteries in the brain.

Deadly danger lurks in the brain of one in 20 people. A section of an artery in the brain can start to weaken, ballooning into something called an intracranial aneurysm (IA) that is at risk of bursting.

As Hirofumi Nakatomi of the RIKEN Center for Brain Science explains, "The growth of an aneurysm increases the risk of its rupture, but there is currently no other treatment than surgery." If an IA bursts, the bleeding often causes brain damage or death, even if a patient reaches a hospital quickly.

To find better treatments, scientists hope to unravel the biology behind these arterial bulges in the brain. Until recently, says Nakatomi, "the cause of intracranial aneurysms was largely unknown." So researchers at RIKEN set out to find the answers.

A CLUSTER OF CONCERN

While our genes account for about 10% of IAs—age, high blood pressure and alcohol consumption also increase the risk—Nakatomi wanted to dig deeper, especially into potential genetic causes. In a recent study[1], he and his colleagues applied whole-exome sequencing of protein coding regions to samples from 65 human arteries, both with and without aneurysms.

"Unexpectedly, we found that more than 90% of the aneurysms had mutations in a common set of genes," Nakatomi says.

In particular, tissues from cerebral aneurysms usually included mutations in a group of 16 genes in the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway. This pathway is known to play a role in inflammatory responses and the formation of tumors.

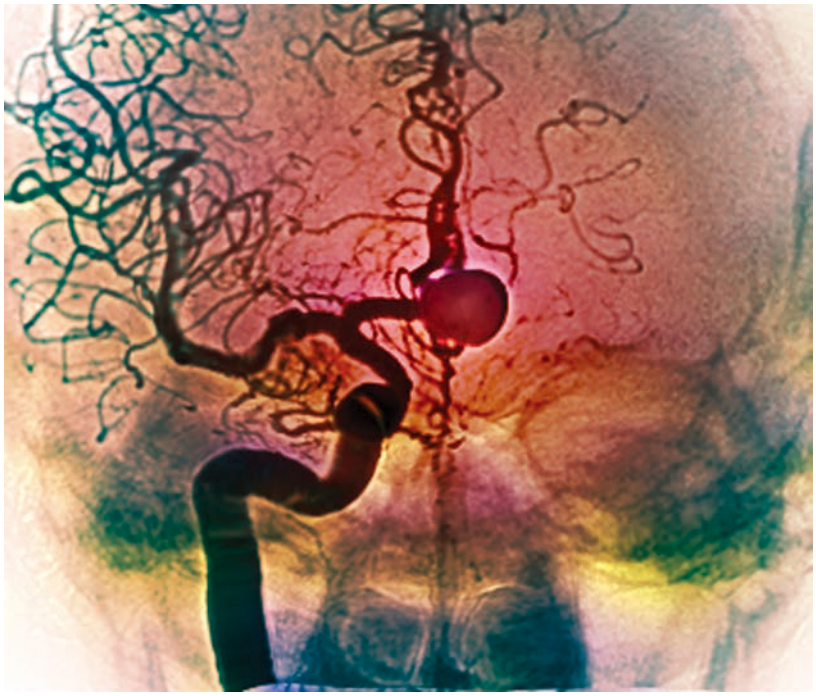
Six of those genes also included mutations that change the platelet-derived growth factor receptor β (PDGFRβ), which is part of a protein family that transmits signals from the cell surface into the cell. Aberrations in PDGFRβ have also been linked to tumor cell proliferation, invasion, metastasis and development.

Many of the variants identified in the study arose from 'missense' mutations, which are changes in one base in a gene that swaps in a new amino acid. "These findings indicate that mutations are the major trigger of IA development in most cases," Nakatomi says.

Although part of his ongoing work involves looking for more IA-related mutations, he doesn't expect the list to grow. He says, "I am accumulating data on

This feature looks **at the work of**
HIROFUMI NAKATOMI

Hirofumi Nakatomi graduated from the University of Tokyo (UTokyo) School of Medicine in 1993. After a number of years as a practicing neurosurgeon in Japan, he returned to UTokyo to finish a PhD in Neurology in 1999. After this were stints at the Mayo Clinic and University of Cincinnati in the United States. Nakatomi returned to Japan to continue practicing and teaching. In 2018, he joined the Neurodynamic Medical Science Collaboration at the RIKEN Brain Science Center to study aneurisms, while also working as chief of the Department of Neurosurgery at The University of Tokyo Hospital. In 2021, he left UTokyo Hospital to also become a professor of at Kyorin University School of Medicine in Tokyo, also in conjunction with his work at RIKEN.



Researchers found that 90% of the aneurysms (pictured) they tested had mutations in a common set of genes.

around 160 patients, and a second report could lead to a more precise percentage, but I am assuming the top two or three genes will be the same."

ZEROING IN ON THE PROBLEM

Beyond showing up in six of the IA-related genes, mutations in PDGFRβ appear in most of the weakened arteries. Importantly, IAs with a poor clinical prognosis (based on being deeper in the brain) included mutations in PDGFRβ in more than half of the cases of giant IAs.

In an effort to show the causal effect of PDGFRβ on IAs, the scientists created a mouse model of a rare IA, characterized by the invasion of cells (PDGFRB positive mural cells) into the wall of an artery, called an intracranial fusiform aneurysm (IFA).

"A variant of the PDGFRβ gene identified by our analysis was introduced into a mouse's cerebral artery vessel wall with a viral vector," Nakatomi says. The group then confirmed that 28 days after introduction of the mutant gene, aneurysm-like changes occurred in the main artery that supplies blood to the 'inferior' portion of the mouse brain around the brain stem. These changes were a spindle-like shape or 'fusiform' widening of the blood vessel, which is observed in human aneurysms.

Nakatomi's team also revealed that PDGFRβ mutations appear most often in pericytes, which are cells on the outer membrane side of a blood vessel developing an aneurysm. Furthermore, they found that mutations in PDGFRβ triggered a process that can ultimately cause an enlargement of tissue hyperplasia. This was due to an increase in the reproduction of pericytes in the outermost 'adventitial' layers of capillaries first, then progressing into the inner media and endothelial layers.

At this point, Nakatomi and his colleagues started to think of ways that they could use this information to treat IAs. They started with a number of inhibitors that target tyrosine kinase receptors, a protein family transmits signals from a cell surface into the cell. These tyrosine kinase inhibitors have been developed for cancer therapy and Nakatomi's group started by adding sunitinib—used to treat renal cancer—to human cells with a mutated PDGFRβ gene in a lab. They found that this inhibitor suppressed activity. The scientists also showed again that sunitinib suppressed the development of IAs in their IFA-like arterial expansion model in mouse populations.

Thus, they established for the first time a means of using genetic insertions to create a mouse model of cerebral aneurysm formation, and also a means of suppressing the their development in these models. But most excitingly, this finding indicates that intracranial aneurysms might one day be successfully treated with drugs, says Nakatomi.

FINDING MORE THERAPIES

The team are now looking at other cancer drugs that might inhibit the development of IAs. "Many of the 16 genes that were frequently mutated in the cerebral aneurysm samples are cancer-related genes, some of which have already been identified as causes of solid tumors and for which molecular-targeted drugs and small-molecule compounds are being developed," says Nakatomi.

Nonetheless, more research lies ahead. "If the inhibitory effect of sunitinib administration on aneurysm formation is verified in large mammals and then in human clinical trials, it could lead to the practical application of a completely new therapeutic agent for cerebral aneurysms," he says.

Nakatomi and his colleagues also plan to explore the potential of targeting genes beyond PDGFRβ. They will start with AHNAK, the second most frequently detected mutated gene in IA samples.

If the scientists do come up with a drug treatment for IAs, the impact could be life changing for many. "We want to find an additional tool, one that prevents the need for surgery," says Nakatomi, "and a drug would be almost as magical as a lightsaber."

For more information, watch this video.

www.youtube.com/watch?v=5ydVLtOz2mc

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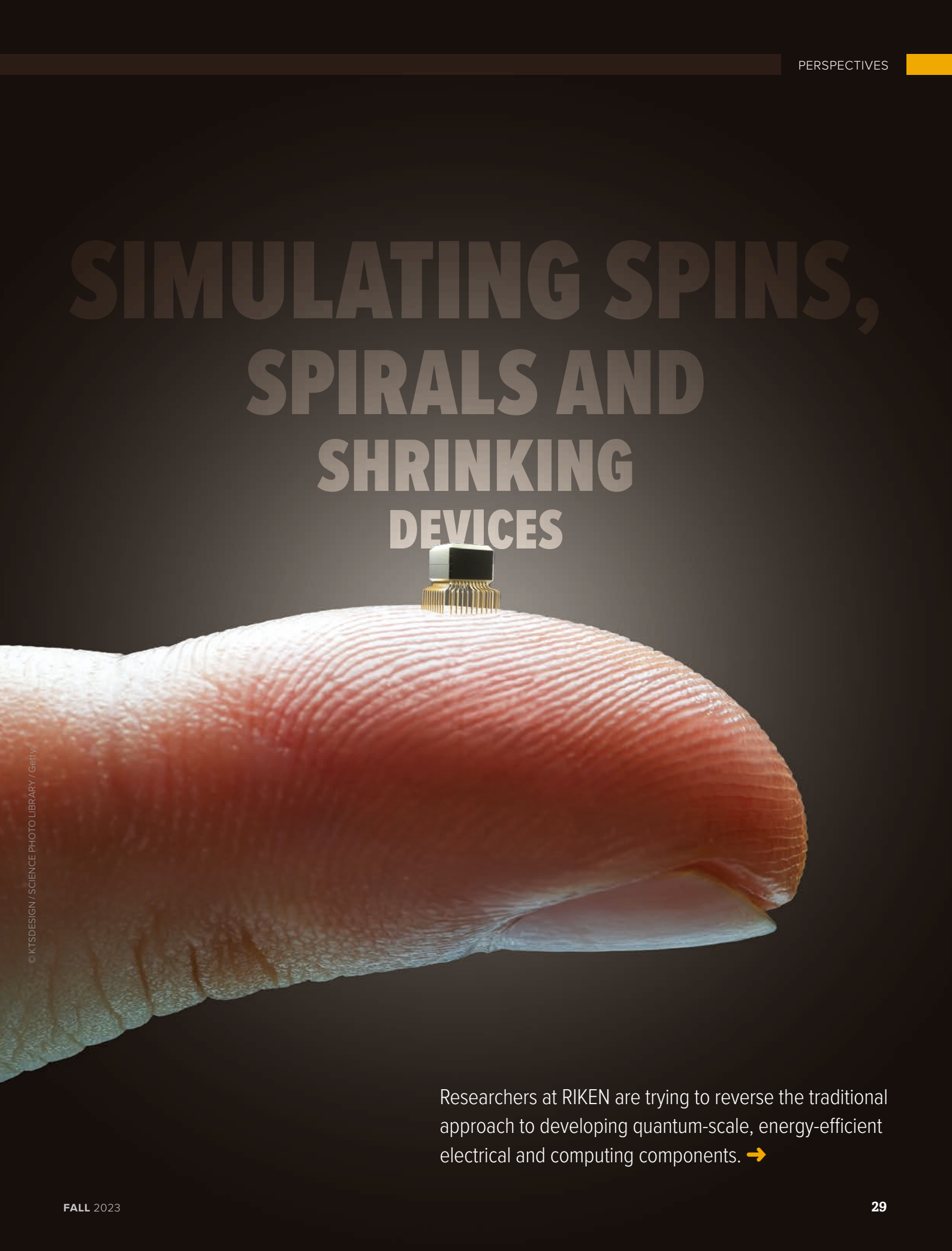
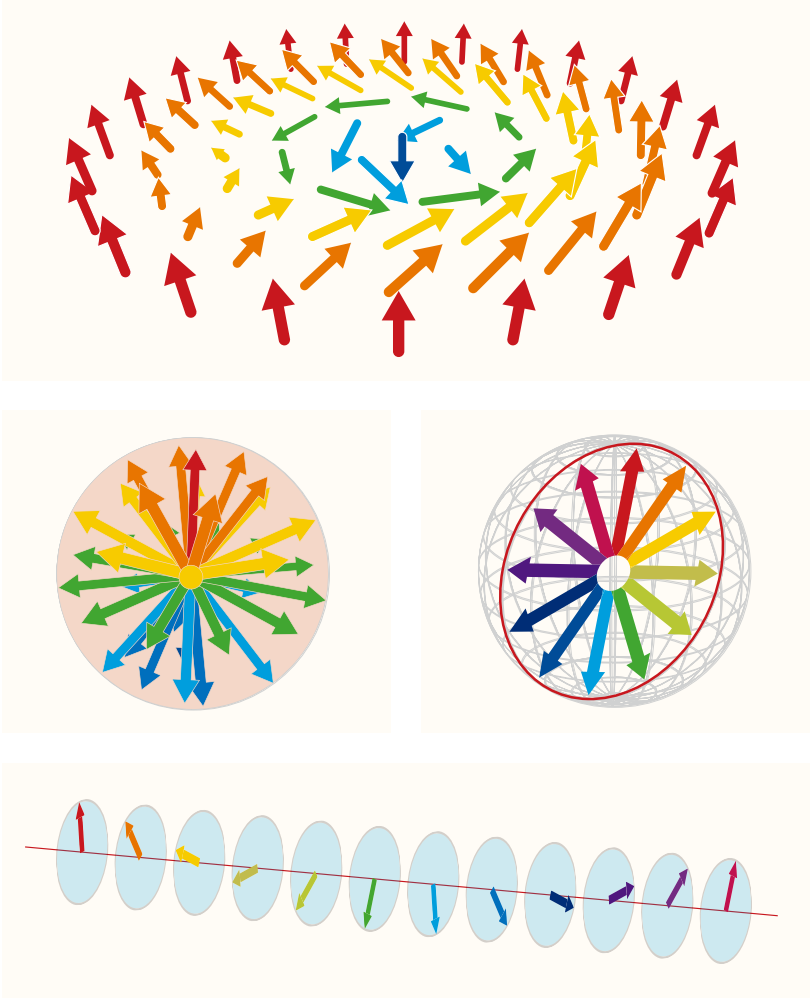
SIMULATING SPINS, SPIRALS AND SHRINKING DEVICES



Researchers at RIKEN are trying to reverse the traditional approach to developing quantum-scale, energy-efficient electrical and computing components. ➜

The diamond in an engagement ring, the wonder-material graphene and the 'lead' in a humble pencil are all formed from carbon, but display profoundly different characteristics. Carbon materials such as these are among the most famous examples of how diverse properties can emerge in materials, based only on the rearrangement of the structure of atoms.

The goal of the RIKEN Center for Emergent Matter Science (CEMS) in Saitama, Japan, is to develop materials for new, energy-efficient technologies. The usual approach to synthesizing new materials involves looking for improved properties such as strength and durability, or enhanced conduction of electricity and heat. But CEMS is pioneering an alternative approach that turns that standard approach on its head. First, we think of the properties needed for a new device, use data from RIKEN's new repository and simulation platform to calculate the atomic structure that provides these features and then build the bespoke material.



Helimagnets are a set of naturally occurring materials in which the electrons arrange themselves into spirals (below). Some tiny electrically-conducting helimagnets could mimic an inductor (bottom)—coils of wire that control the flow of electrical current in a circuit by storing it as magnetic field energy.

SUSTAINABLY SMALL

CEMS is working to shrink electronics, but engineers are hitting many limits in size reduction. For example, you might look at an 'inductor', a standard component found in devices such as smart phones. These coils of wire control the flow of electrical current in a circuit by storing it as magnetic field energy.

At first glance, physicists might assume that the inductor can be made smaller by reducing the size of the coil, but this decreases its ability to store energy.

A few years ago, physicists at CEMS hit upon an innovative solution. They realized that a peculiar property of certain exotic magnetic materials could mimic an inductor, without needing a wire.[1] The feature relates to a quantum characteristic inherent to all electrons called 'spin', which turns electrons on an invisible axis that points in a specific direction.

In normal magnets, the spins of electrons align in one direction, creating the magnetic effect. But the CEMS physicists were intrigued by helimagnets, a set of naturally occurring materials in which the electrons arrange themselves into spirals.

They thought some electrically-conducting helimagnets could mimic a coil of wire, serving as a tiny inductor: that notion was borne out in CEMS experiments in 2020.[1]

While the first helimagnets investigated operated only at energy intensive ultra-cold temperatures, CEMS researchers found one that works at room temperature, in collaboration with the University of Tokyo.[2]

There are, however, other obstacles to overcome. For example, helimagnets only work below the megahertz regime, but devices such as a cellphones operate at frequencies in the much higher gigahertz range.

MAGNETIC MEMORY

Another tiny, twisting technology being investigated at CEMS could help revolutionize memory storage in electronics.

It involves skyrmions—spherical knots of electrons oriented so that their spins all point outwards, a bit like a curled-up hedgehog. These configurations are very stable because they only unfurl when extra energy is put into the system.

Skyrmions act like particles because they are easy to move around with an external magnetic field and are difficult to destroy. This makes them an attractive tool for storing information, which would be encoded in the position of the skyrmion. Since they are so stable, they are also robust against errors and memory corruption.

Crucially, they are also minuscule: a skyrmion can be smaller than one hundredth of a micrometer, which means you can pack 10,000 skyrmions into just 1 μm^2 (micrometer squared), which is one tenth to one hundredth the width of a human hair.

This would enable very high-density memory storage and smaller memory storage devices.

A TRIP into the future of material science

There are only 80 or so kinds of elements that humans can play with in the lab when trying to engineer novel components for devices. But the atoms of these 80 elements can be re-arranged to design an almost infinite number of new materials, and this means that studying this involves mind-blowing amounts of data.

With this in mind, RIKEN's Center for Emergent Matter Science (CEMS) is contributing to the promotion of 'TRIP', or 'Transformative Research Innovation Platform of RIKEN Platforms,' a RIKEN-wide initiative aimed at linking the various data platforms within RIKEN to develop new scientific paradigms. CEMS is participating in the initiative through a repository that combines knowledge gained from real-lab experiments with simulations of predicted material properties made by super-computers. Artificial intelligence, or AI, can then be harnessed to help design useful new materials based on the properties that are wanted, which scientists that can then synthesize.

Takahisa Arima, deputy director of CEMS, says that despite being based in physics, the project takes inspiration from biology, where AI has shown considerable success in recent years at correctly predicting how proteins will fold—once one of the biggest outstanding problems for biologists. "But the challenge for material science is far harder because there are many more building blocks," says Arima.

Looking toward the future, TRIP aims to include simulations and predictions made by quantum computers—machines being developed that have the potential to outperform today's supercomput-ers—to tackle these problems. "We are pioneering the digital transformation of science," says Arima.

Growing up, Arima had a very different ambition. "I wanted to become a meteorolo-gist and forecast the weather. But I changed my mind at university, when I realized just how many complex factors come into play when trying to predict—let alone manipulate—the route of a typhoon, say," he says.

"By contrast, condensed matter physics offers an enticing clarity and control. Material properties are very diverse, but they are generated by simple behaviors of electrons and nuclei in atoms." This combined with increasing computing power, he says, means that materials should have the power to transform our lives sooner than we may think.

TAKA-HISA ARIMA
Deputy Director, RIKEN Center for Emergent Matter Science

Taka-hisa Arima received his PhD in science from the University of Tokyo in 1994. He worked as an assistant professor at the University of Tokyo, an associate professor at the University of Tsukuba, and a professor at Tohoku University. He was a team leader at RIKEN SPring-8 Center from 2007 to 2014, and then worked as a team leader at CEMS. He is leading the Strong Correlation Quantum Structure Research Group of RIKEN Center for Emergent Matter Science (CEMS). He is now a Deputy Director of CEMS. He is also a professor at the University of Tokyo. He studies material science to explore novel properties of condensed matters.

But, once again, there is a stumbling block. So far, physicists have been able to easily manipulate skyrmions in materials with lower densities of the electron knots, but not in the high-density knots they are most interested in.

> A major frustration is that there is no real strategy behind finding the right skyrmion-hosting material. It's all trial-and-error. CEMS is setting up a new digital platform to make this process more efficient.

A major frustration is that there is no real strategy behind finding the right skyrmion-hosting material. The present approach is to make a compound, measure it, see if it fits and make another compound if it doesn't.

Typically, it is chemists who discover new materials, by tweaking the structures of familiar materials. Physicists then catalogue any new properties that emerge from them, by meticulously measuring their optical, electrical, magnetic, thermal and mechanical characteristics. Finally, engineers take a material that has useful features and build a device to capitalize on them. It's all trial-and-error.

Worse still, scientists only tend to report successful attempts to their peers. This means a lot of time and resources are wasted by different groups repeating the same mistakes.

CEMS is setting up a new digital platform to make this process more efficient by systematically combining data from lab experiments with supercomputer simulations via an online platform that can be accessed from within RIKEN (see box: *A TRIP into the future of material science*). The aim is to make it easier for scientists to start with a vision of the device they need and work backwards to create the bespoke material that matches their requirements.

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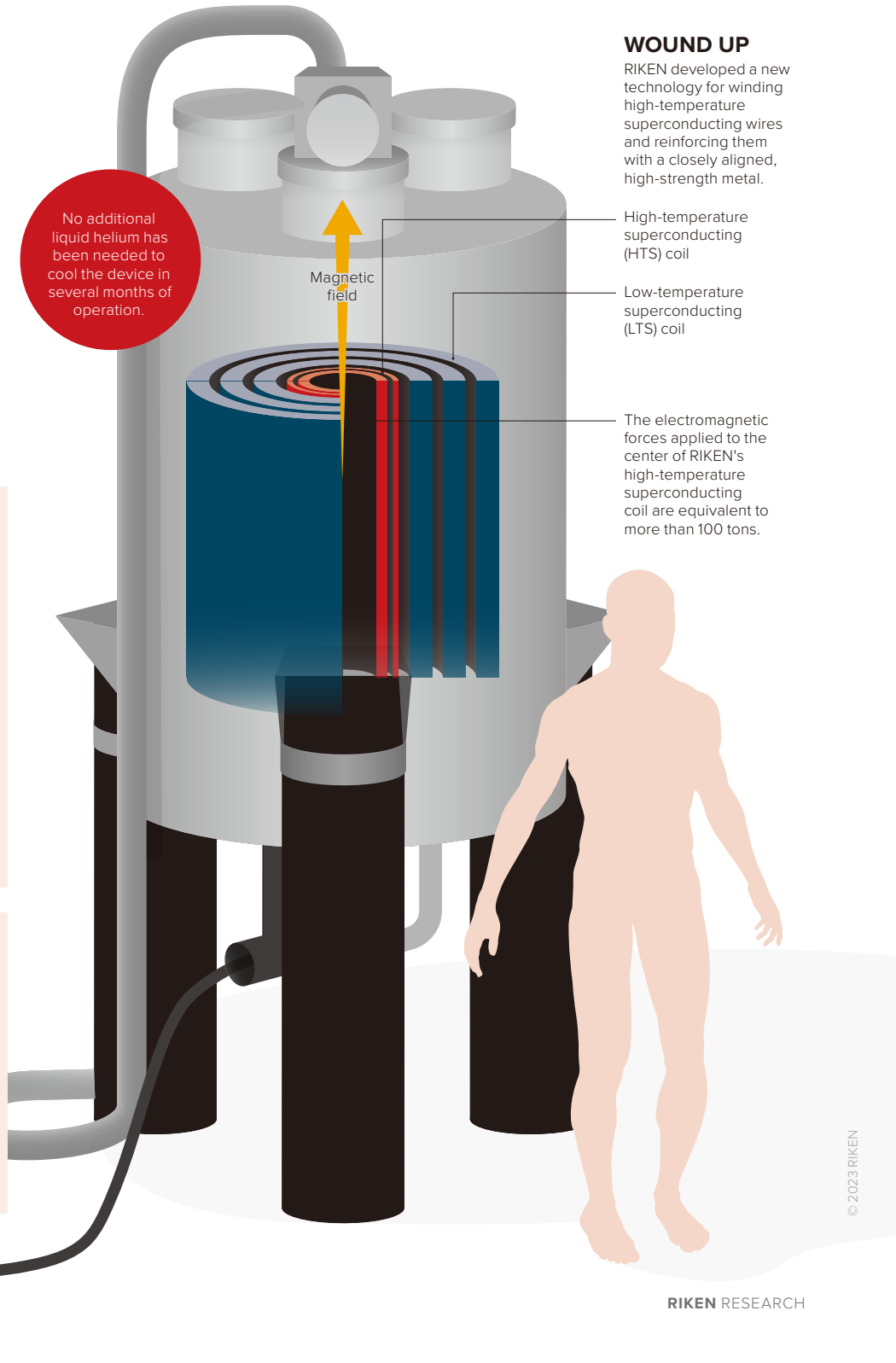
SMALL, BUT MIGHTY

A joint research team led by Yoshinori Yanagisawa at the RIKEN Center for Biosystems Dynamics Research has developed the world's lightest and most compact nuclear magnetic resonance (NMR) system (see more on page 8).

WHAT IS AN NMR SYSTEM?

Nuclear magnetic resonance (NMR) systems are used to analyze the molecular structure and physical properties of materials and biological samples. To do this, the subject is placed in a strong constant magnetic field perturbed by a weak oscillating magnetic field. Scientists can then measure the resulting electromagnetic signal frequencies produced by nuclei of the subject. Larger magnetic fields tend to provide better measurements, but the sizable magnets required to generate these are expensive and controlling their heat consumes rare and expensive liquid helium—limiting their use.

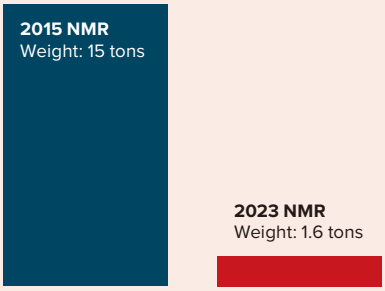


WOUND UP

RIKEN developed a new technology for winding high-temperature superconducting wires and reinforcing them with a closely aligned, high-strength metal.

ONE-TENTH THE WEIGHT

The new device provides high frequencies for analysis (>1 GHz), but it has a weight close to one-tenth that of existing systems.



TIGHTLY COILED

The team has increased the current density of their NMR system's high-temperature superconducting coils (HTS) by a factor of 1.5 to concentrate a larger current in a smaller space. The rest is handled by the low-temperature superconducting coil.

HTS share of magnetic current

2015 **15% HTS**

2023 **53% HTS**

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across Japan and around the world

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- ◆ SPring-8
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- ▼ RIKEN Information R&D and Strategy Headquarters (R-IH)

KEIHANNA

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- ● Center for Advanced Intelligence Project (AIP)
- ▼ Guardian Robot Project (R-IH)

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

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