SUMMER 2016

RIKEN RESEARCH

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ON THE FIGHT CIRCUIT
How fish are wired to win or lose

HOP AND STEP
Exciting times for carbon monoxide

INTO THE LIGHT
Optical stimulation retrieves memories

JAW-DROPPING DISCOVERY

Fish brain study turns vertebrate theory on its head

RIKEN Center for Sustainable Resource Science
Researchers in a greenhouse at the RIKEN Center for Sustainable Resource Science in Yokohama are growing wild rice to improve agriculture productivity.

RIKEN, Japan's flagship research institute, conducts basic and applied experimental research in a wide range of science and technology 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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ISSN 1883-3519

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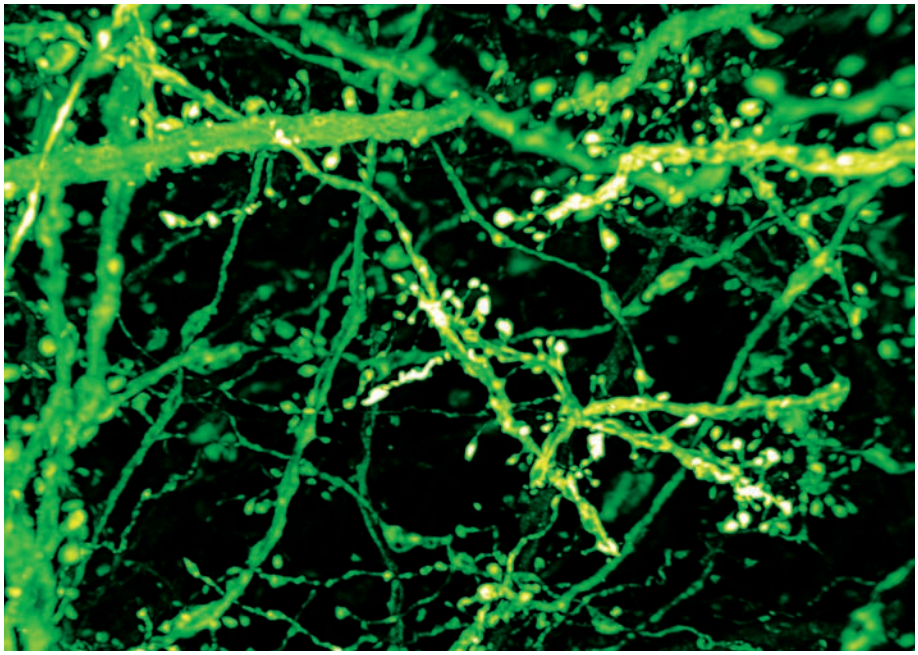

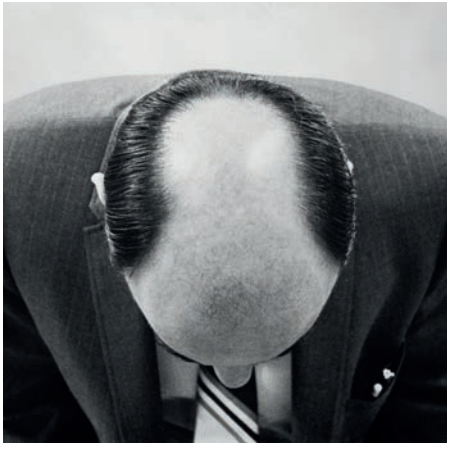

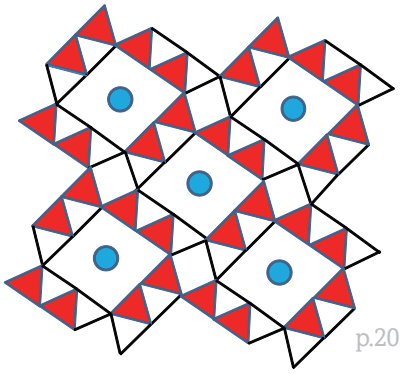

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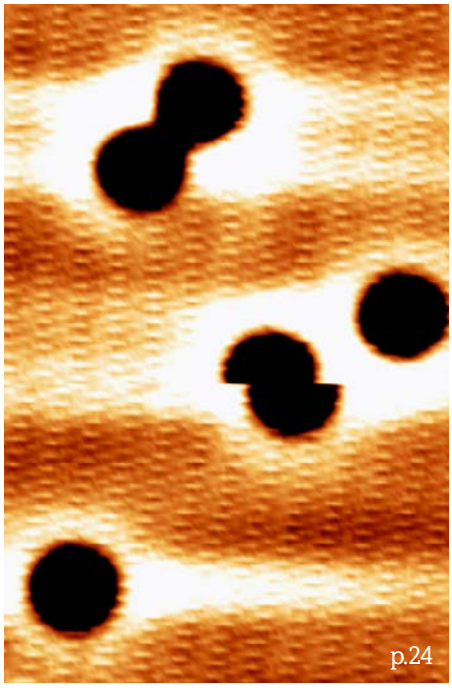

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Global science agenda

Cover story: Jawed and jawless vertebrates share a common ancestor. **Page 19**

This year is shaping up to be an important year for science in Japan. Science and technology ministers from the Group of Seven member states gathered in Tsukuba on 15–17 May to discuss ways to strengthen cooperation in science and technology and resolve global challenges, such as healthcare, gender inequality, clean energy and ocean management. The gathering included a special symposium and exhibition on the future of science and cutting-edge research in Japan, which was attended by government ministers, renowned scientists and the general public. Among the more than 30 leading research institutes invited to showcase their technologies, RIKEN presented its work in the area of global health, from the use of induced pluripotent stem (iPS) cells for regenerative medicine to using the power of the K computer to simulate a heart.

2017 promises to be an even bigger year for RIKEN. Founded in 1917, RIKEN will celebrate its 100th anniversary next year. The "Impact" article in this issue highlights an important research achievement from RIKEN's early days, which brought social and economic benefits to the institute and the world—the purification and commercialization of vitamin A by Katsumi Takahashi and Umetaro Suzuki.

The "Feature highlight" presents research led by Takashi Tsuji of the RIKEN Center for Developmental Biology into the development of artificial skin using reprogrammed iPS cells. And our "Research highlights" report on lots of breakthroughs, including the world's first nuclear physics study of long-lived fission products at the Radioactive Isotope Beam Factory and the use of light stimulation to recover memories in mouse models of Alzheimer's disease.

In "Perspectives", Tadashi Yamamoto, director of the RIKEN Center for Integrative Medical Sciences, stresses the importance of studying the internal and external triggers of disease to maintain a healthy aging population.

Our "People" section features interviews with Fumitaka Kagawa, who is laying the foundation for a new class of non-volatile memories, and David Priest, who moved from Adelaide to Osaka to explore cellular 'noise'.

Listening to the noise

David Priest

Foreign Postdoctoral Researcher

Laboratory for Single Cell Gene Dynamics
RIKEN Quantitative Biology Center

Please describe your role at RIKEN.
I work in Yuichi Taniguchi's laboratory, where I help to develop a deeper understanding of the inherent randomness, or 'noise', in biological systems. Living organisms exist far from equilibrium and are engaged in a constant battle against the randomizing and homogenizing forces of nature. While every cell in a clonal population shares the exact same genetic make-up, stochastic events such as transcriptional initiation give rise to large variations between cells and over time. To maintain homeostasis, cells often seek to rein in these stochastic events. We use model organisms to understand the causes and consequences of noisy cellular processes, which will ultimately lead to cures for diseases.

What excites you about your current research?
I was introduced to quantitative biology during my PhD in Keith Shearwin's laboratory in my hometown of Adelaide, Australia. I have since developed an insatiable appetite for genetics and biochemistry where it intersects with physics and engineering.

During my PhD, I studied my favorite organism, *Escherichia coli*, using bulk assays, which can measure average gene expression in a cell population. Although convenient and valuable, these types of assays overlook important details, such as cellular heterogeneity and differences between subpopulations, which can only be obtained using single-cell techniques like microscopy. Joining Taniguchi's lab gave me the chance to learn fluorescence microscopy. I am endlessly excited about using this technique to obtain high-throughput imaging data and then writing computer scripts to analyze the images.

What has been the most interesting discovery in your field in recent years?
The most stunning discovery in the field of noise biology has been that gene expression is not simply a random arrival process (one that follows a Poisson distribution), but that many genes are expressed in 'bursts'. This bursty transcription causes more variability than a Poisson process, which might be an unavoidable side-effect of controlling genes via binding of transcription factor proteins to their promoter DNA. Increased control might therefore come at the expense of increased noise.

If I'd known how rich life is in Japan, I would have tried to come here earlier.

When did you join RIKEN?
I joined RIKEN in the summer of 2014, after applying for a position directly with Taniguchi. I would encourage interested doctorate students to contact lab heads about possible opportunities. Get your foot in the door! If I'd known how rich life is in Japan, I would have tried to come here earlier.

What is the best thing about working at RIKEN?
Putting aside the exceptional facilities, funding and collaboration opportunities, the best thing about RIKEN is the casual atmosphere. One of my mottos is: "the best way to succeed is the relaxed way," and I've found this to be true time and time again. A stress-free working environment gives me the mental space to think deeply about my research and obtain ideas and insights that could save months of misdirected efforts by a stressed-out scientist.

What are your professional and personal goals?
I want to continue developing my skills in high-throughput data acquisition and analysis. Further down the track, I would like to help coordinate other researchers and teach university students. Personally, I seek to maintain a good work–life balance, enjoy precious time with friends, further my yoga practice and perhaps, one day, start a family. ■

Switching states in solids

Fumitaka Kagawa

Unit Leader

Dynamic Emergent Phenomena Research Unit
RIKEN Center for Emergent Matter Science

Please briefly describe your current research.
My work involves developing solid materials that can switch from one state to another —for example, from an insulator to a metal or from a non-magnetic phase to a magnetic one. This is an important area of research from a basic science point of view.

It could also form the basis for a new class of non-volatile memories that can store information even without a power connection. Today's computers mostly rely on volatile memories, which require a constant supply of power to retain information. Replacing volatile memory technologies with high-speed, non-volatile memories would lead to substantial energy savings.

> *It's like trying to identify the murderer in a mystery novel.*

How did you become interested in your current field of research?
The materials that I study, known as strongly correlated electron systems, maintain a delicate energy balance, with many electronic and magnetic states competing with each other. As a result, their physical properties often change dramatically—sometimes even unexpectedly—following a slight change in the temperature, pressure or magnetic field. These dramatic changes are quite interesting in and of themselves, but what I enjoy most about my research is trying to figure out why they occur—it's like trying to identify the murderer in a mystery novel. Understanding physical properties at a microscopic level is not easy, and we often have to deduce possible mechanisms from the many plausible options based on our experimental results.

What excites you the most about your current research?
I recently found that I can change the electronic and magnetic states of solid materials simply by applying a laser or electric pulse. The change is reversible and persists even without a power connection. Typically, researchers introduce such phase changes by altering a material's environmental parameters, such as the temperature, magnetic field or pressure. For example, some metals turn into superconductors when the temperature is lowered. My approach, on the other hand, does not involve altering the environmental parameters, thus opening up a new way to control physical properties.

What has been the most interesting discovery in your field?
One of the most exciting developments in my field has been the observation of a single skyrmion—a particle-like vortex found in magnetic materials. Because skyrmions can have radii as small as 10 nanometers and can be controlled by applying a weak electric current, they have become an emerging candidate for the next generation of magnetic memory devices, which will have high storage densities and require low power. To realize such applications, it was important to establish a method for creating and annihilating skyrmions under a given environmental condition. To this end, I applied my earlier developed method and succeeded in creating and annihilating many skyrmions at once using a single electric pulse.

How has being at RIKEN helped your research?
The RIKEN Center for Emergent Matter Science has many distinguished scientists with diverse expertise and backgrounds. Through discussions with my colleagues, I have gained new insights into my ongoing research and come up with interdisciplinary research plans. Moreover, at RIKEN I can easily consult with specialists on the use of highly sophisticated techniques and equipment for measuring physical properties. ■

Careers at RIKEN

For further information, visit our Careers page:
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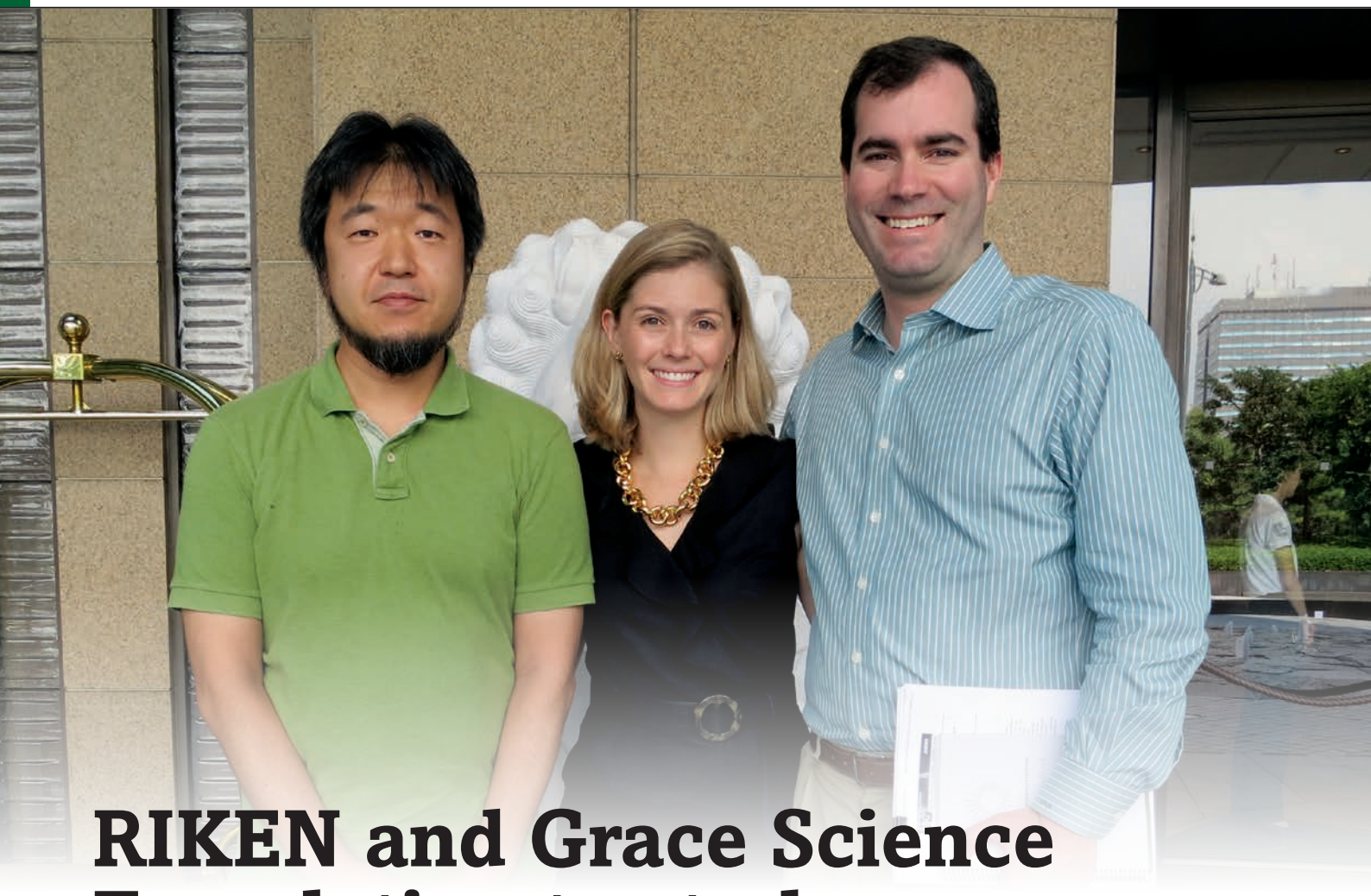

RIKEN and Grace Science Foundation to study rare genetic disorder

RIKEN is collaborating with the Grace Science Foundation to advance our understanding of a rare genetic disorder, discovered by American doctors only in 2012. NGLY1 deficiency is thought to be caused by mutations in the *NGLY1* gene, which encodes the enzyme N-glycanase-1 responsible for recycling misfolded glycoproteins. The disorder is characterized by a variety of symptoms, including global developmental delay, impaired movement, seizures and an inability to produce tears. It is extremely rare, with fewer than 50 known cases.

Under the collaboration, the Grace Science Fund at the San Francisco Foundation will provide support and funding to RIKEN to advance our limited knowledge of NGLY1 deficiency and look for potential therapeutic targets. Tadashi Suzuki (see image, left) will spearhead the research efforts at the RIKEN–Max Planck Joint Research Center for Systems Chemical Biology in Japan. Suzuki first identified N-glycanase-1 in mammals two decades ago and has recently discovered that a second enzyme, endo-β-N-acetylglucosaminidase (ENGase), might also be a potential therapeutic target. The project is further supported by Hiroshi Mikitani, president and CEO of Rakuten, a large e-commerce and Internet services company.

Matt Wilsey (right), president and co-founder of the Grace Science Foundation with wife Kristen Wilsey (center), applauded Suzuki's work over the last two decades, adding: "I believe this collaboration with the Suzuki lab and RIKEN will bring us closer to a cure for NGLY1 and other metabolic diseases." Suzuki appreciated the foundation's acknowledgement and support: "It is a privilege that my work has been recognized as being important for the potential cure of a serious genetic condition."

www.riken.jp/en/pr/topics/2016/20160615_1/
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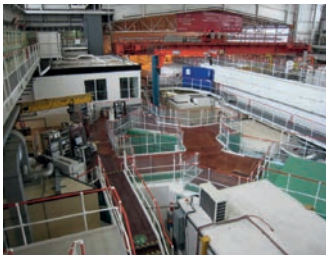
A quarter century of muon science



RIKEN celebrated 25 years of research into muons—unstable, heavy elementary particles—in a ceremony in Tokyo on 16–17 February 2016. The event was attended by more than 150 collaborators on previous muon experiments and included a lively session with 88 posters as well as congratulatory statements by RIKEN directors and the British Ambassador to Japan, Tim Hitchens.

In 1990, RIKEN signed an agreement with an agency in the United Kingdom formerly known as the Science and Engineering Research Council to conduct joint research into muon science. The following year, the two institutes began constructing the world's most intense experimental source of pulsed muons at the Rutherford Appleton Laboratory (RAL) in Oxfordshire.

The RIKEN–RAL Muon Facility was completed in 1996 and has since been used by more than 900 researchers from all over the world, resulting in over 400 papers being published in international journals. Notable examples include research into the properties of quantum spin liquid and the direct observation of muons 'sticking' to alpha particles produced during nuclear fusion, which limits the application of muon-catalyzed fusion.

Today, experimenters at the facility use the pulsed muon beam to measure and analyze the structure of internal magnetic fields in matter and elucidate the mechanisms between the emergence of superconductivity, magnetism, conductivity and insulation in innovative functional materials.

www.riken.jp/en/pr/topics/2016/20160304_1

Mathematicians, theoretical physicists and theoretical biologists met to celebrate the establishment of the Interdisciplinary Mathematical Sciences Team at RIKEN.

Visit from Malaysia

On 23 February 2016, a delegation led by Vice-Chancellor of Universiti Sains Malaysia (USM) Omar Osman visited RIKEN's Wako campus to discuss areas of mutual interest. During the visit, Osman met with RIKEN President Hiroshi Matsumoto, and researchers from both institutions exchanged ideas on potential projects to set up under the joint research center established at USM in February 2015. The USM–RIKEN International Center for Aging Science is the first international research center dedicated to advancing the science of aging. More than a quarter of Japan's population is above 65 years old, making it the most-aged society in the world. And Malaysia's elderly community is also on the rise.

The two institutions have a long history of research agreements, including a Comprehensive Agreement signed in April 2012 and a Strategic International Program Associate Agreement inked in November 2008 to host graduate students from USM at RIKEN.

www.riken.jp/en/pr/topics/2016/20160225_1

Back to basics

In April 2016, RIKEN inaugurated a new center that will carry out fundamental theoretical research and develop innovative technologies in areas related to informatics. The Center for Advanced Integrated Intelligence Research will aim not only to carry out academic research but also to promote innovations that will contribute to the development of society. Masashi Sugiyama of the University of Tokyo is scheduled to be the center's director.

A new interdisciplinary team on mathematics was also set up as part of the Interdisciplinary Theoretical Science Research Group (iTHES), which was launched in 2013. On 28 April 2016, RIKEN ran a symposium dedicated to celebrating the establishment of the Interdisciplinary Mathematical Sciences Team at iTHES. The symposium, jointly organized with the Advanced Institute for Materials Research (AIMR) at Tohoku University and the Institute of Industrial Science (IIS) at the University of Tokyo, was attended by scientists from all branches of mathematics, from pure to applied, as well as theoretical physicists and biologists.

In a keynote address titled 'Math is everywhere', mathematician Reiko Miyaoka from Tohoku University presented numerous examples of the application of mathematics to everyday life. She also discussed the importance of education in helping young people overcome their hesitation toward studying mathematics. In addition to research presentations, the symposium included an engaging panel discussion between seven researchers working in different fields on the future of mathematics and its relevance to different disciplines.

ithes.science-server.com

Genetic variation in Kawasaki disease

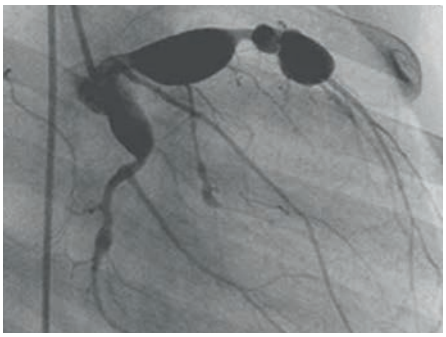
Variations in a calcium-channel gene could explain why children of Asian descent are more susceptible to Kawasaki disease, a condition characterized by inflamed blood vessels and redness of the eyes, lips and tongue.

The origins of Kawasaki disease remain a mystery. It appears seasonally—hinting at an infectious or other environmental cause—but is more prevalent among individuals of East Asian ancestry—suggesting that genetic factors could be behind it.

A team led by researchers at the RIKEN Center for Integrative Medical Sciences (IMS) screened the genomes of more than 2,500 people with Kawasaki disease and 2,400 healthy adults to identify genetic variations associated with the disease. Previous studies had linked the disease to a key pathway that regulates immune function in response to calcium signals. The team investigated the *ORAI1* gene involved in activating this calcium-mediated pathway and found a strong association between a single-nucleotide variation in the gene and Kawasaki disease. Intriguingly, this variation was 20 times more prevalent in Japanese than Europeans.

"It was interesting—and makes a lot of sense—that the common variation we discovered is common in East Asia," says Yoshihiro Onouchi at the IMS, first author of the study. "We hope that it could lead to treatments for the disease, which can have devastating consequences in some cases."

www.riken.jp/en/pr/press/2016/20160121_1



Kawasaki disease can cause massive swelling in the arteries that supply the heart.

Stem cells take time to recover

A DNA-binding protein rejuvenates shortened telomeres in mouse embryonic stem cells during long periods of cell division of more than 20 hours, according to a study by two scientists at the RIKEN Center for Developmental Biology. Prior to the investigation, researchers erroneously believed that the protein, known as Zinc finger and SCAN domain containing 4 (Zscan4), was involved in maintaining the stem cells' ability to give rise to any cell in the body—a power known as pluripotency.

"Unexpectedly, we found that there was no correlation between the two," says Yoko Nakai-Futatsugi, first author of the study. "Instead, we were surprised to find that the stem cells have different cell cycle lengths, and that intriguingly, the expression of Zscan4 is linked to the length of the cell cycle. It tends to be expressed in cells with longer cell cycles."

The researchers also found that high levels of Zscan4 expression led to shorter cycles in the next generation of cells, adding weight to the hypothesis that the cells slow down their cycle to allow for telomere recovery, and then speed it up again when the repair is complete. The findings could help to ensure the safety of induced pluripotent stem cells, which are currently moving into clinical use.

www.riken.jp/en/pr/press/2016/20160318_1

Mixing hard and soft x-rays

RIKEN's SPring-8 Angstrom Compact free electron Laser (SACLA) has become the only facility in the world capable of producing hard and soft x-rays simultaneously.

X-ray lasers are important tools for analyzing molecules and atoms in structures as small as viruses or nanoparticles. Soft x-ray lasers, which produce x-rays with slightly longer wavelengths than the more well-known hard x-ray lasers, are particularly suited for analyzing the function of gas-purifying catalysts and for producing electronic circuits using a patterning technology known as extreme ultraviolet lithography.

When SACLA first opened to the public in 2012, it had three beamlines: two for hard x-rays and one for soft x-rays. But since the hard and soft x-ray beams could not be produced at the same time, the less-popular soft x-rays were often taken off-line.

To solve the dilemma, RIKEN remodeled a retired piece of equipment known as the SPring-8 Compact SASE Source (SCSS) into an independent beamline for producing soft x-ray laser light. The new device accelerates electrons and passes them through undulators—magnets that change the path of the electrons—to make them emit a sharp beam of light.

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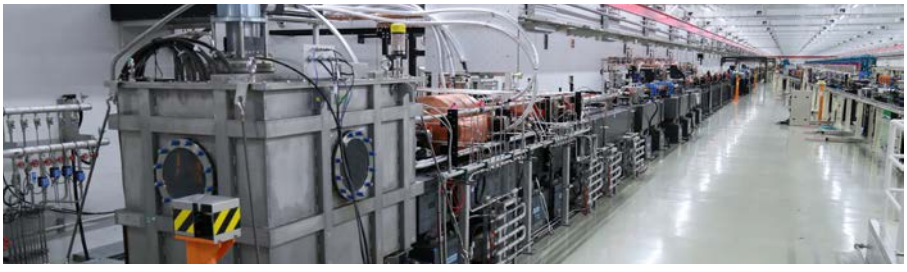
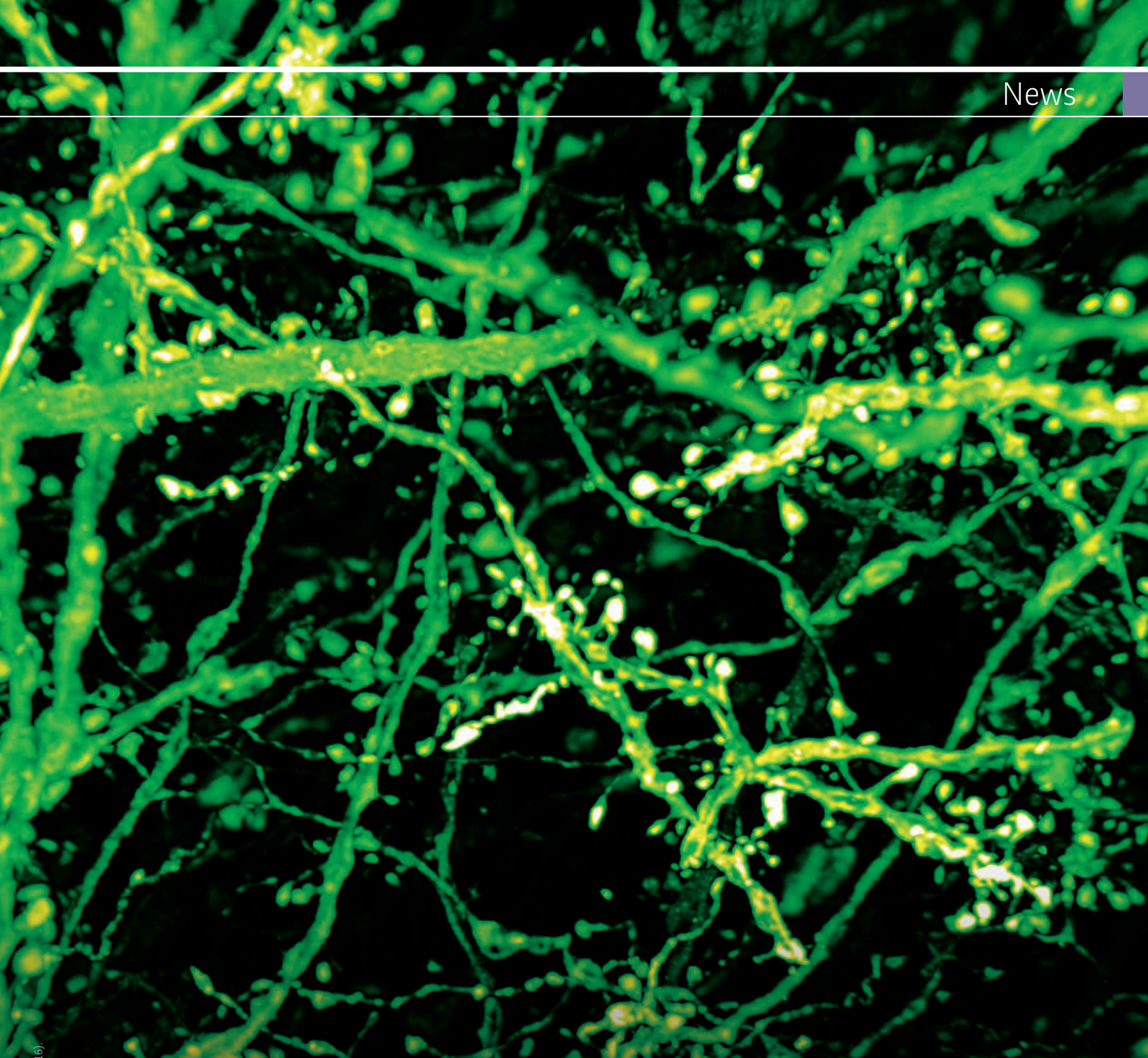




This image was published in *Cell Reports*, 14, M.-T. Ke *et al.*. Copyright Elsevier (2016).

Super-clear synapses

Researchers at the RIKEN Center for Developmental Biology (CDB) have found a way to probe the delicate neural circuitry deep inside the brain.

Many aspects of learning and behavior are accompanied by structural changes at points of communication between neurons, known as synapses. Synaptic abnormalities have been found in a host of cognitive and mental disorders.

To differentiate between normal and malfunctioning connections associated with healthy and pathological states, researchers need to be able to see these structural changes in three dimensions. The RIKEN researchers developed a special tissue-clearing agent called SeeDB2 that can make mouse and fruit fly brains transparent. The see-through brains allow fluorescence microscopy to obtain super-resolution, three-dimensional images of neural networks ten times deeper than before.

The researchers tested their optical clearing technique for imaging tiny filaments that protrude from neurons, called dendritic spines. Using SeeDB2, they were able to see that neurons lacking an important subunit of an excitatory glutamate receptor had larger dendritic spines and accumulated more inhibitory neurotransmitters at the synapse.

"We expect that super-resolution imaging of deep tissue neural circuitry will continue to be a powerful strategy for studying the 'connectome' at the synaptic level, and that SeeDB2 will have an important role in making these studies possible," says Takeshi Imai, who led the study at the CDB, which was published in *Cell Reports* in March 2016.

www.riken.jp/en/pr/press/2016/20160311_1

Research highlights

Nuclear power plants generate long-lived radioactive isotopes that are difficult to treat. Bombarding such isotopes with protons and deuterons produced stable isotopes or much shorter-lived isotopes.

PHYSICS | PRESS RELEASE

Cutting the life expectancy of nuclear waste

A promising method has been investigated for converting major long-lived isotopes produced by nuclear facilities into safer ones

Two hazardous radioactive isotopes found in nuclear waste can be converted into more easily managed isotopes, RIKEN scientists have shown[1]. Using the Radioactive Isotope Beam Factory (RIBF), they collided the isotopes into protons and deuterons (particles containing one proton and one neutron), which caused the isotopes to become stable isotopes or shorter-lived isotopes that quickly decay into stable ones.

Treating nuclear waste generated by nuclear power plants and other facilities is a major global problem. Isotopes such as cesium 137 and strontium 90 are particularly problematic as they are responsible for much of the radiotoxicity of nuclear waste and are long lived, having half-lives of around 30 years. Furthermore, they are difficult to treat. A promising way for treating these isotopes is to transmute (convert) them into stable isotopes or short-half-life isotopes that decay rapidly. Because these isotopes do not capture low-energy neutrons effectively, the group explored a new approach for this conversion, where energetic protons or deuterons collide with the isotopes.

The group investigated the approach's effectiveness by assessing the probability of isotopes produced in the collisions. They opted to collide the cesium and strontium ions with the protons

and deuterons rather than vice versa. "We decided to do this because it is easy to identify reaction products with a high speed, and the RIBF is the world's best facility for such study," explains He Wang of the RIKEN Nishina Center for Accelerator-Based Science (RNC).

The team created a beam of uranium 238—the most common natural isotope of uranium—and accelerated it to about 70 per cent of the speed of light. The beam was smashed into a beryllium target, causing it to break into isotopes such as cesium 137 and strontium 90, which were then separated. Finally, the isotope beams were collided with proton and deuteron targets. This experiment revealed that the approach transmuted the two isotopes much more efficiently than collisions involving neutrons, achieving a conversion probability 4 times higher for cesium 137 and 100 times higher for strontium 90.

"We were happy to find that 89 per cent of cesium 137 atoms and 96 per cent of strontium 90 isotopes were transmuted to either stable nuclei or short-lived species with half-lives less than one year," says Wang.

"We plan to continue experiments with the RIBF using a variety of reactions to find the most efficient ways to transmute problematic long-lived isotopes into other nuclei," says Hiroyoshi Sakurai, who is also at the RNC. "We hope that this will lead to practical ways to deal with the problem of disposing nuclear waste."

Reference

1. Wang, H., Otsu, H., Sakurai, H., Ahn, D. S., Aikawa, M., Doornenbal, P., Fukuda, N., Isobe, T., Kawakami, S., Koyama, S. *et al.* Spallation reaction study for fission products in nuclear waste: Cross section measurements for ^{137}Cs and ^{90}Sr on proton and deuteron. *Physics Letters B* **754,** 104–108 (2016).

BIOLOGY

Good neighbors make good defenses

A tight physical association between gut bacteria and the intestinal wall helps establish robust immune defenses

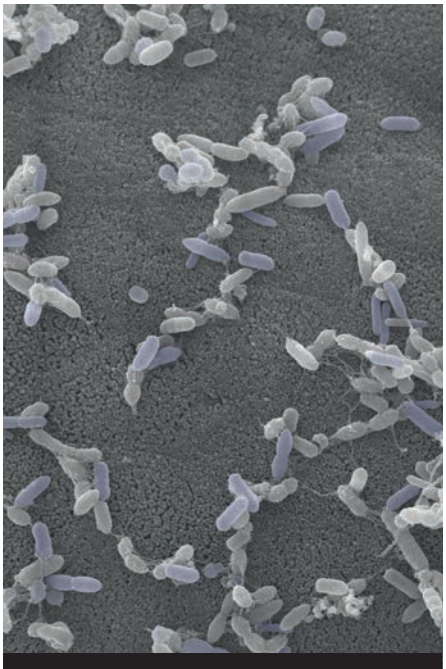
A recent study by RIKEN researchers has shed light on the conundrum of how microbes in the gut can influence the host's immune system, despite being separated by the gut lining[1].

The intestinal wall is a major entry point for infection, and immune cells known as T_H17 cells reinforce this barrier and fend off pathogens. Certain 'commensal' bacteria in the guts of mammals stimulate the proliferation of T_H17 cells.

In rodents, one subset of gut bacteria plays a particularly strong role in this process. "We had previously identified segmented filamentous bacteria (SFB) as one of the most potent inducers of T_H17 cells," explains Takeshi Tanoue, a member of the team, which was led by Kenya Honda of the RIKEN Center for Integrative Medical Sciences. "Tight adhesion to intestinal epithelial cells is a remarkable characteristic of these microbes."

The researchers explored whether this adhesion plays a major role in activating immunity in the gut. They began by exploiting the strikingly distinct SFB populations in rats and mice. "About 5–10 per cent of the genes are specific to each strain," notes Tanoue. Although rat-derived SFBs could proliferate in the mouse intestine and vice versa, neither population was able to adhere tightly to the intestinal wall after transplantation. This reduced adhesion correlated with a sharp decrease in T_H17 induction, indicating that the mere presence of these commensals is insufficient—a tight epithelial interaction is essential. Indeed, pathogenic bacteria that bind to the surface of the intestinal wall during infection also stimulate T_H17 proliferation, apparently via a similar mechanism.

These results offer only limited insights into humans, however. "SFBs haven't been found in the human intestine, and the counterpart T_H17-inducing bacteria have not yet been identified," says Tanoue. The researchers therefore collected fecal samples from human subjects and examined which specimens could act on T_H17 cells when transplanted into mice. The results enabled them to identify 20 bacterial strains that appear to play a similar role to mouse SFBs (see image).



Electron micrograph showing T_H17-inducing bacteria isolated from the human intestine.

Abnormalities in T_H17 activation can contribute to inflammatory bowel disease, and hence a detailed bacterial census may help to diagnose or treat this disorder.

Since the human commensals isolated in the present study came from a patient with inflammatory bowel disease, further experiments are needed to identify the 'optimal' gut bacterial community. "We don't know if these bacteria are pathogenic or beneficial to the host," explains Tanoue. "We're now trying to isolate T_H17-inducing bacteria from healthy human samples." In principle, such bacteria could be delivered clinically as 'probiotics' to help normalize disease-associated disruptions of gut immunity. ■

Reference

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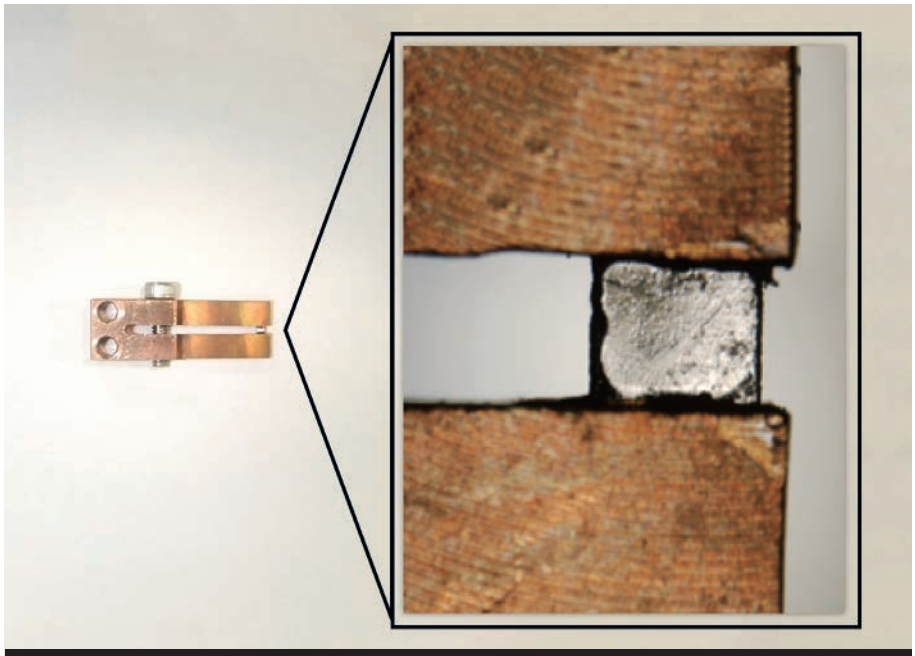
PHYSICS | PRESS RELEASE

A delicate dance in a new superconductor

Using x-rays to investigate atomic motion gives scientists insights into the microscopic interactions between magnetism and lattice vibrations

Scientists at RIKEN have clarified the role of magnetism in a new type of high-temperature superconductor, providing a better understanding of the atomic-scale behavior of these emerging materials[1]. By discovering how such materials superconduct at relatively high temperatures, physicists hope that they will eventually be able to fabricate new materials that superconduct close to room temperature and hence open up a whole new range of applications.

Some materials become superconducting when they are cooled below a certain temperature. That is, they conduct electricity without resistance. This phenomenon arises when pairs of electrons become coupled together or 'paired'. In conventional superconductors, this pairing arises due to vibrations of the ions in the structure. But in newer types of superconductors, such as cuprate superconductors and iron-pnictide superconductors, magnetism is suspected to give rise to the pairing mechanism.



Photograph showing a superconductor sample between two copper prongs of the sample holder.

"The question we addressed was how the atomic vibrations in the iron pnictides are affected by magnetism," says Alfred Baron, the leader of the Materials Dynamics Laboratory at the RIKEN SPring-8 Center. "This was especially interesting because atomic vibrations are understood to be the driving force of the older type of low-temperature superconductors, while magnetism is considered to be the probable driving mechanism of the new, high-temperature, superconductivity. Thus, it was, in some sense, an overlap of the old with the new."

The group, which included scientists from the RIKEN SPring-8 Center, Osaka University, the Japan Atomic Energy Agency, and the Japan Synchrotron Radiation Research Institute, measured the dynamics in specially prepared single-domain samples of an iron pnictide (see image) using a technique known as inelastic x-ray scattering. To achieve this they used two beamlines of the powerful SPring-8 synchrotron facility in Harima, Japan.

When the scientists compared their measurements with the results of calculations they had performed, they found evidence that magnetic fluctuations play an important role in the atomic vibrations. Naoki Murai, the graduate student who led the measurement, explains: "By very gently pressing the material in the correct direction, we were able to observe effects due to the onset of magnetic order."

"One of the nice things about this work is that it provides a basis for describing atomic vibrations in this whole class of materials, namely do calculations with magnetism and then add fluctuations," comments Baron.

Baron says the collaboration will continue to investigate the properties of these fascinating materials, and also, more generally, the interaction between magnetism and atomic vibrations.

Reference

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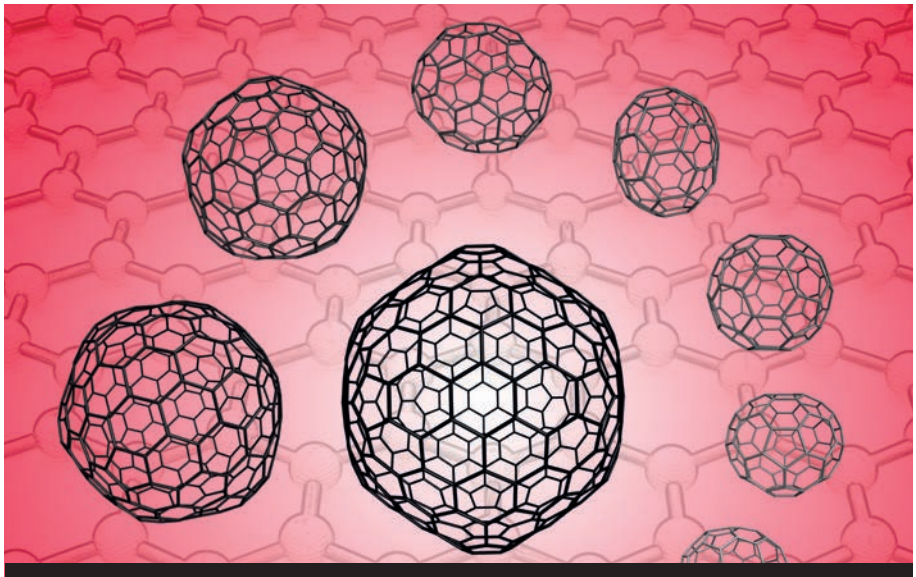
CHEMISTRY

Bridging the gap between buckyballs and graphene

Quantum simulations reveal what it takes to form large spherical carbon nanostructures with unique materials science applications

The discovery of the soccer-ball-shaped molecule 'buckminsterfullerene' (or buckyball) in 1985 kick-started a revolution in carbon nanomaterials that continues today with research into extremely conductive graphene. Now, an all-RIKEN team has used the institution's K computer to predict the stability of structures that bridge the gap between these two extremes, namely individual fullerenes and infinite sheets of carbon[1].

The heat of formation is a fundamental property used by chemists to gauge the energy released or consumed during a reaction. For small compounds, it can be determined quite accurately using calorimeters. However, measurement errors generally increase with increasing molecular size, making it challenging to quantify the energy required to make fullerene (C_{60}) from 60 carbon atoms.



A computational method can be used to determine the stability of carbon nanostructures lying between fullerene and infinite sheets of graphene.

State-of-the-art theoretical calculations have helped refine estimates of C_{60}'s heat of formation, but questions exist about the uncertainties of these methods. Furthermore, analyzing more-complex fullerenes requires supercomputers hundreds of times more powerful than those commonly available.

Kimihiko Hirao and colleagues from the RIKEN Advanced Institute for Computational Science realized that a change of approach might help crack this problem.

"Chemists consider a single molecule with hundreds of atoms very large," says Hirao. "But to materials scientists, it would be one of the smallest known nanomaterials. Finding a way to bridge the molecular and materials worlds required us to step out of our usual mindset."

The researchers first devised a series of model chemical reactions describing how the gradual build-up of carbon atoms into larger complexes can be represented by the formation of simple benzene rings. Similarly, they modeled the formation of oversized fullerenes in terms of a smaller, C_{20}-based ring

system. To develop procedures for rapidly analyzing large molecules, they used high-level supercomputer algorithms to evaluate the resulting heats of formation, as well as less computationally intense methods.

The quantum calculations determined the heat of formation of C_{60} with an uncertainty five times better than typical experiments. Additionally, the team saw that the per-atom heats of formation converged to a simple equation—enabling them to predict the existence of new fullerenes many times larger than C_{60}. Intriguingly, this equation estimates that at least 10,000 carbons are needed to reduce bond strain in fullerenes and impart them with graphene-like properties.

"The number of differently sized fullerenes that exist between the extremes of C_{60} and graphene suggests potential for a vast range of applications," says Hirao. "And the chemical and computational frameworks we developed can be easily used to compute other types of properties for large, but finite, molecules." ■

Reference

1. Chan, B., Kawashima, Y., Katouda, M., Nakajima, T. & Hirao, K. From C_{60} to infinity: Large-scale quantum chemistry calculations of the heats of formation of higher fullerenes. *Journal of the American Chemical Society* **138,** 1420–1429 (2016).

BIOLOGY | PRESS RELEASE

Illuminating memory loss in Alzheimer's

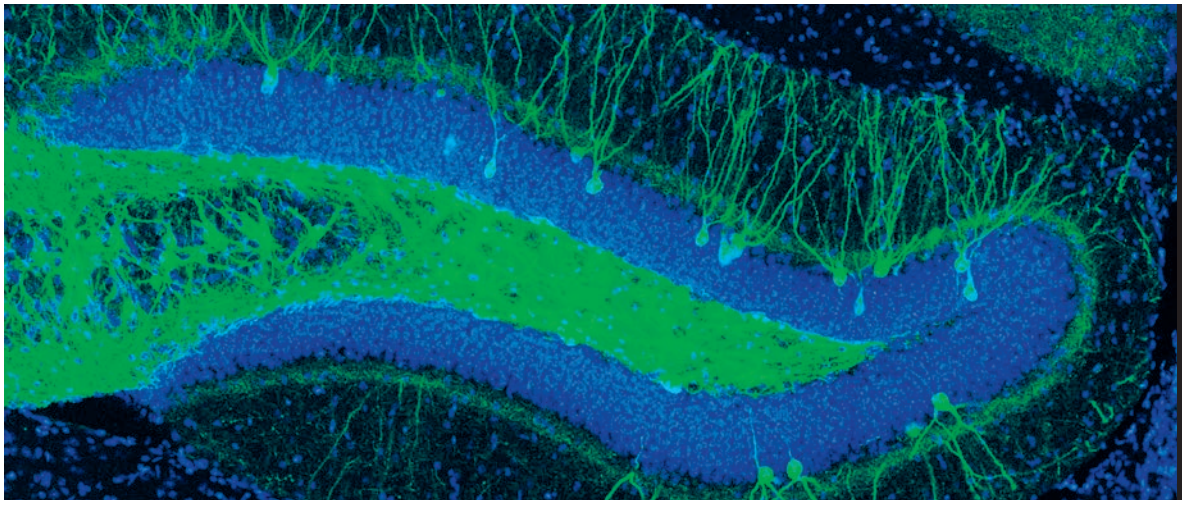
Memories lost to Alzheimer's disease in mice can be recovered by shining a light on specific cells in the brain

Light stimulation of brain cells can recover memories in mice with Alzheimer's-like memory loss, RIKEN scientists find[1]. This discovery suggests that impaired retrieval of memories, rather than poor storage or encoding of memories, might underlie this symptom of early Alzheimer's disease (AD).

Early AD is characterized by long-term memory loss of experiences in humans, as well as in mice genetically engineered to develop AD-like symptoms. Researchers led by the director of the RIKEN-MIT Center for Neural Circuit Genetics, Susumu Tonegawa, have shown that small spines on brain-cell dendrites (see image), through which synaptic connections are formed, are essential for memory retrieval in these AD mice. Moreover, light stimulation can regrow lost spines, helping mice recover the memory of a previous experience.

Mouse memory is often inferred from learned behavior, in this case associating an unpleasant footshock with a particular cage. Remembering and anticipating shocks causes mice to freeze in this enclosure but not in a neutral one. Compared with normal mice, AD mice exhibited amnesia and reduced freezing behavior, indicating progressive memory loss.

The engrams, or memory traces, of this particular experience are known to be located in the dentate gyrus of the hippocampus, a key brain area for memory processing. During fear conditioning, researchers used a virus to label active engram cells by delivering a gene to the



Tiny spines on brain-cell dendrites, through which synaptic connections are formed, are critical for memory retrieval in mice with Alzheimer's disease-like symptoms.

dentate gyrus. This allowed them to visually identify neurons that made up the engram for that fear memory. A second virus contained a gene making only these engram neurons sensitive to light. When the engram cells were reactivated with light in the AD mice, memory of the footshock experience became retrievable and the freezing behavior was restored.

"We have shown for the first time that increasing synaptic connectivity within engram cell circuits can be used to treat memory loss in mouse models of early AD," says lead author Dheeraj Roy.

In normal mice, light stimulation did not boost the number of spines or strengthen the fear memory, nor did indiscriminately shining light in the dentate gyrus result in any long-term memory improvement. Only the precise stimulation of engram cells increased the number of spines and improved the memory of AD mice. "The successful retrieval of memories in AD mice by increasing the number of spines for normal memory processing only in the memory cells, rather than in a broad population of cells, highlights the importance of highly targeted manipulation of neurons and their circuits for future therapies," says Tonegawa. "This level of specificity has not yet been accomplished in current deep brain stimulation therapies." ■

Reference

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MATERIALS

Single-atom lasers change gears

Single-atom lasers that emit one light particle at a time are predicted to be switchable between two activity regimes

The light emission from single-atom lasers will exhibit two stable states with low and high emission rates, predicts a theoretical study by RIKEN researchers[1]. This prediction is expected to be experimentally testable and will have important consequences for controlling the output of such lasers in experiments.

At the heart of every laser is a laser medium that emits light when excited. The atoms or molecules that make up the lasing medium emit particles of light, or photons, in concert, which gives rise to intense light beams in which all the photons travel in phase—a property known as coherence.

Many commercial lasers are so compact that they can be fabricated on silicon chips. But at the extreme of miniaturization, lasers have been made in which the laser medium consists of a single artificial 'atom'.

"Single-atom lasers are the quantum limit of normal lasers," explains Franco Nori of the RIKEN Center for Emergent Matter Science. "Instead of a large ensemble of atoms cooperating to produce a coherent laser beam, a single-quantum system emits individual photons over time."

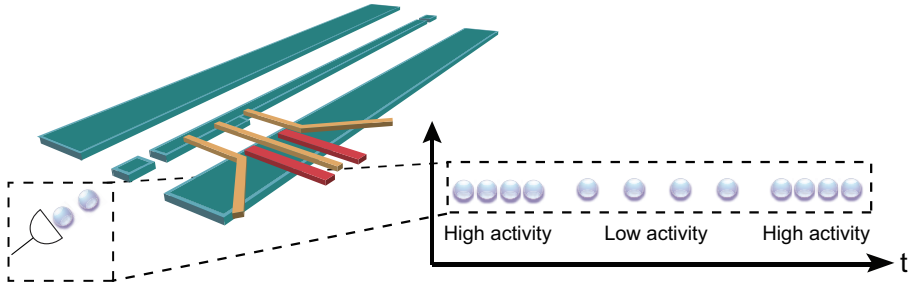
This ability to emit one photon at a time makes single-atom lasers valuable for fundamental investigations of quantum effects and also for applications that exploit quantum effects, such as quantum communication systems.

Now, Nori and his colleagues Neill Lambert and Christian Flindt have explored the properties of single-atom lasers by performing detailed theoretical calculations. They investigated a single-atom laser in which the 'atom' is a pair of quantum dots—tiny gate-defined regions of a semiconductor containing just a few electrons.

Their calculations revealed a hitherto unsuspected property of single-atom lasers. "Our calculations predict that such devices should exhibit dynamic bistability, switching between high- and low-activity regimes," says Lambert. The two stable lasing regimes are predicted to emit photons at low and high rates (see image).

This bistability is normally hidden because light detectors average the light collected over time, but it should be measurable in experiments using current technology. The bistability is expected to manifest itself in the statistics of the electric current used to deliver energy to the laser. By modulating this electric current, it should be possible to attain unprecedented control of photon emission from such lasers.

This prediction provides a glimpse into the fascinating world of quantum effects in lasers and has important implications for new applications. The team intends to look at ways to control this bistability using quantum feedback. ■



A theoretical study predicts that single-atom lasers (schematically depicted on the top left) will emit in two regimes: one with a high activity and another with a low activity. The 'pearls' represent individual photons.

Reference

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Feature highlight

Biology

Growing a thick skin

Lab-grown skin sprouts hair and grows glands, paving the way for burn, scar and hair-loss therapies

It looks like skin. It feels like skin. It functions like skin. But the skin created at RIKEN is no ordinary outer-body tissue. Scientists at RIKEN bioengineered this skin from mouse stem cells, carefully cultivating the cells into hair, oil-producing glands and many of the other appendages found in skin[1]. What's more, the elaborate organ system forms proper connections with surrounding muscles, nerve fibers and other tissues, all without yielding tumors.

The lab-made skin could one day assist in the treatment of severe burns, scars and hair-loss disorders. It may also allow drug and cosmetic companies to test the safety and efficacy of new products without relying on animals.

"We successfully regenerated a transplantable whole skin including skin appendages in mice, and confirmed their functions," says Takashi Tsuji of the RIKEN Center for Developmental Biology, who led the study. "We think that further studies could lead to clinical applications for badly burned patients and people with severe hair loss."

Skin in the game

For more than a decade, Tsuji and his colleagues have been experimenting on ways to grow small organs in the lab from stem cells. They have succeeded in making teeth, hair follicles and various glands of the eye and the mouth, but until now no-one had been able to regenerate a whole organ system that combines many of these components in a single working, complex tissue.

So, Tsuji and collaborators from several Japanese institutions—including RIKEN, Tokyo University of Science, Kitasato University and Tohoku University—developed a totally new method for constructing an entire 'integumentary' organ, as the skin and its accessory structures are collectively known. The researchers introduced viruses into cells taken from the gums of mice. The viruses express 'reprogramming factors' and created induced pluripotent stem cells that, like embryonic stem cells, can form any cell type in the body. They then cultured these stem cells in the lab for 7 days so that they formed small clumps, known as embryoid bodies.

The researchers gathered dozens of these developing aggregates in a collagen gel (Fig. 1) and transplanted the gooey cellular bundles under the kidneys of mice, where they formed several types of specialized cells found in the skin. The number of hair follicles in these structures depended on exposure to a special protein that activates a signaling pathway involved in the development of hair and other organs.

After a month, Tsuji's team extracted the cells to find three-dimensional skin, complete with shiny, black hairs and various accessory organs, including sebaceous glands that secrete an oily substance to lubricate and waterproof the skin and hair.

Takashi Tsuji

Takashi Tsuji received his master's degree from Niigata University in 1986. After working in the pharmaceuticals industry for three years, he returned to the university to complete his doctorate degree in 1992 and continue working as a researcher. Tsuji joined Japan Tobacco Inc. in 1994 and moved to Tokyo University of Science in 2001, where he was appointed a full professor in 2007. In 2014, Tsuji joined the RIKEN Center for Developmental Biology, where he leads a team working to gain a more complete understanding of the role of epithelial–mesenchymal interaction in organ induction, development and morphogenesis. His team seeks to apply their research toward the development of technologies for use in therapeutic organ regeneration.

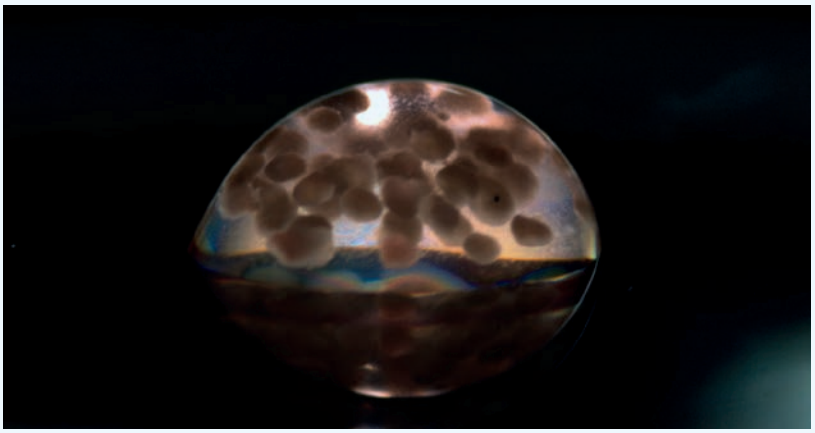

Figure 1: Clumps grown from stem cells in a collagen gel prior to being transplanted to form specialized skin cells.

Just like natural hair

The researchers cut out tiny skin specimens, each about the size of a grain of salt and containing about one to two dozen hair follicles, and transplanted them onto the backs of hairless mice. Within a few weeks, the scientists saw hair shafts sprouting (Fig. 2). And over the course of the three-month experiment, the hairs behaved normally, cycling through their phases with no signs of problems. "It was just like natural hair," Tsuji says. Furthermore, anatomical analysis revealed that the tissue had correctly linked up with the underlying muscles and nerves.

The team repeated the entire experimental protocol with induced pluripotent stem cells made from stomach cells. These stem cells were engineered to glow green to allow the scientists to track them (Fig. 3). Repeating the study with stem cells reprogrammed from a different part of the body confirmed that the generation of the bioengineered integumentary organ does not depend on the origin of the cell clones.

Figure 2: Stem-cell-derived skin and hair follicles transplanted onto the back of a mouse.

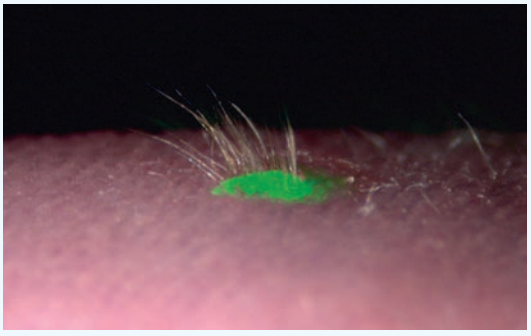

Figure 3: Transplanted bioengineered skin created using mouse stem cells labeled to glow green.

To eliminate the risk of tissue rejection, Tsuji and his colleagues transplanted the bioengineered skin onto the backs of mice that had been genetically engineered to lack a functioning immune system. In people, however, this kind of transplant would require recipients to take immune-suppressing drugs—unless the tissue could be perfectly immune matched. This would require finding just the right donor or, by using reprogrammed stem cells, growing tailor-made skin from a patient's own biopsied tissue.

Path to the clinic

The team says their next step is to adapt the approach for clinical applications. Currently available skin grafts made by tissue engineering are generally only one or two cell layers thick and lack the support structures involved in fat secretion, moisturizing and waste excretion. They also do not aesthetically look like normal skin. A three-dimensional, complete integumentary organ offers a better alternative.

But Tsuji and his colleagues first have to ensure that the system they demonstrated with mouse cells also works with human cells. This may be more complex than it might appear, because it is not just a matter of finding the recipe for coaxing human reprogrammed stem cells to form the various appendage organs of the skin—the researchers also have to find a way to make the bioengineered skin entirely in a lab dish without relying on living animals for any step of the process.

Despite the challenges, Tsuji thinks that it is only a matter of time before he will achieve his many objectives. "We hope to begin clinical testing in humans within the next decade," he says.

In 2008, Tsuji founded a Tokyo-based company called Organ Technologies to develop and commercialize organ replacement regenerative therapies. The Japanese drug maker Meiji Seika Pharma also recently inked a three-year deal with RIKEN to advance Tsuji's research for human applications.

Reference

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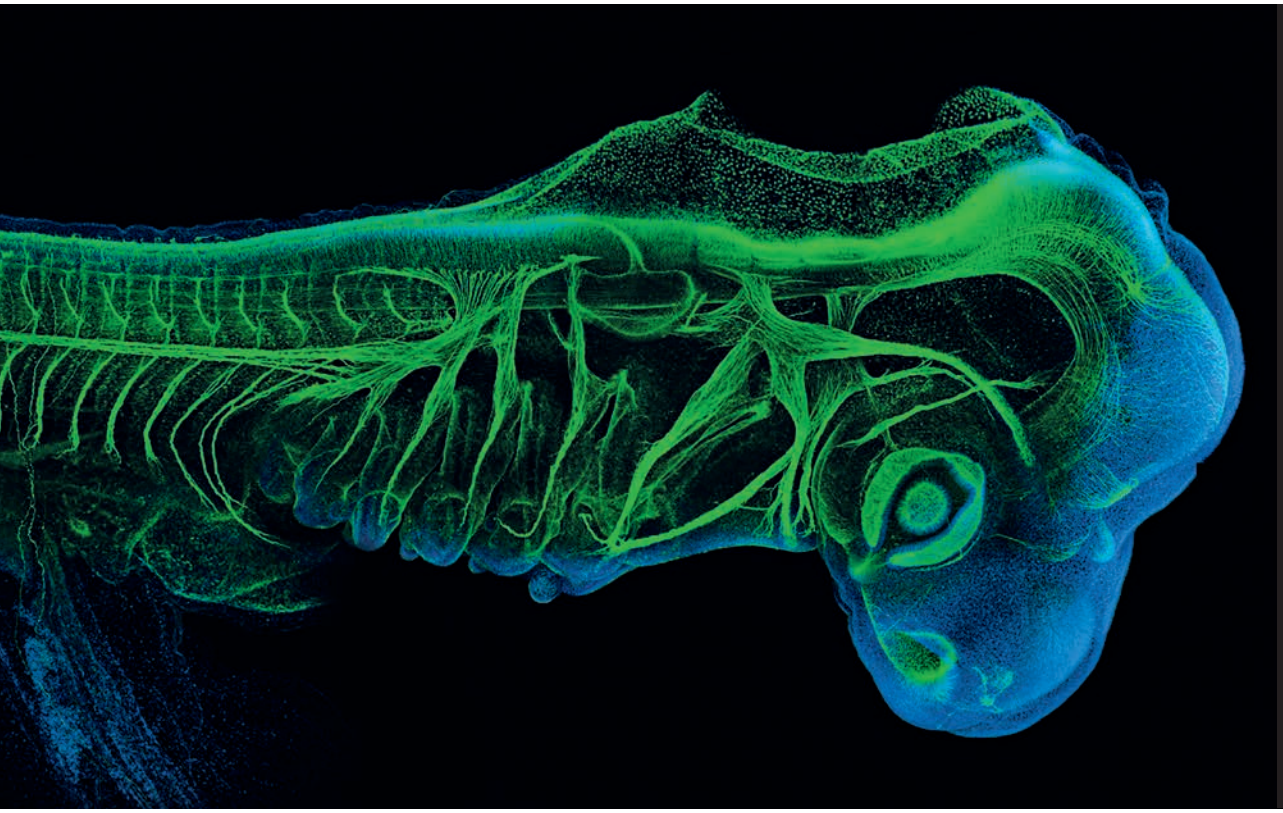

An embryo of a catshark (*Scyliorhinus torazame*), which was compared with those of the only jawless fish alive today—the lamprey and hagfish.

BIOLOGY | PRESS RELEASE

Brain complexity preceded jaw development

Scientists had long thought that complexity in vertebrate brains developed after jaws appeared, but new evidence suggests that this is not the case

Complex divisions in the vertebrate brain appeared before the evolution of jaws, more than 500 million years ago, RIKEN researchers have found. They discovered that two aspects of the brain thought to be unique to jawed vertebrates actually exist in two jawless fish[1].

Most living vertebrate species have jaws, a development thought to have occurred sometime in the Paleozoic era (about 542 to 251 million years ago).

In vertebrates, the brain develops from a neural tube that is divided into sections, whose development is controlled by the expression of particular genes at very precise times and specific locations. In particular, in jawed vertebrates, the medial ganglionic eminence (MGE) develops from a forward section of the neural tube that expresses *Nkx2.1* and *Hedgehog* genes, while the cerebellum develops from a region called the rhombic lip that expresses *Pax6*.

Because the brains of lampreys and hagfish—the only jawless fish alive today—seemed to lack these two brain regions, many scientists thought that the brain's basic developmental plan reached completion in jawed vertebrates.

Now, Shigeru Kuratani of the RIKEN Evolutionary Morphology Laboratory and co-workers have discovered a region in the hagfish brain in the correct location that expresses both *Nkx2.1* and *Hedgehog* genes, indicating that the hagfish brain does have an MGE. And while hagfish lack a true cerebellum, the team identified a clear rhombic lip region that expresses *Pax6*.

Confident that the brains of both hagfish and jawed vertebrates have similar developmental patterning, the researchers needed to show that this characteristic was not unique to lamprey and find evidence that the changes had not occurred independently in jawed and jawless lineages after they had split.

So the scientists reinvestigated the lamprey and discovered several new *Nkx2.1* genes expressed in the correct location. But they did not find any *Hedgehog* expression, indicating that the lamprey MGE differs slightly from the MGE in jawed vertebrates. They looked at lamprey larvae and found a rhombic-lip-like region that expresses *Pax6B*, albeit slightly differently than in hagfish and jawed vertebrates.

"We found that jawed-vertebrate patterning was more similar to the hagfish than to lampreys and the evidence indicates that this is likely due to secondary evolutionary changes in lamprey evolution, rather than changes unique to jawed vertebrates," says Kuratani. "We have shown that both extant jawless-fish species have a rhombic lip and an MGE. This firmly places the development of these patterns back to a common ancestor shared by jawless and jawed vertebrates." ■

Reference

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MATERIALS

Cooling an unusual magnetic material

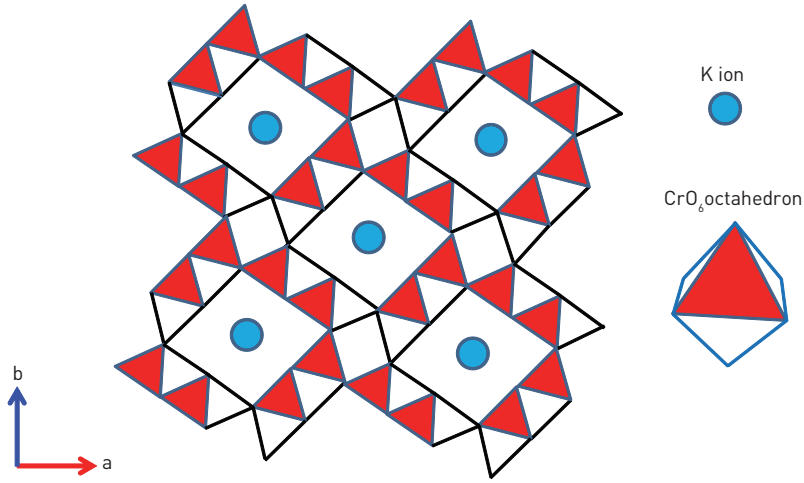
An experimental and theoretical study reveals how the interplay of electronic and structural effects leads to intriguing magnetic and electrical properties

The properties of typical ferromagnets like iron and nickel have been widely studied and are relatively well understood. However, a few rare magnetic materials exhibit complicated behaviors that are difficult to explain. In an experimental and theoretical investigation of one of these complex materials, RIKEN scientists, with collaborators in India, Germany and Japan, have uncovered how the interplay between electronic and structural effects gives rise to fascinating magnetic and electrical properties[1].

Ferromagnets consist of regions, or domains, in which all the magnetic spins are aligned in the same direction. The ordering of the magnetic spins is related to the arrangement of atoms in the crystal structure. It also depends on the valency of the magnetic atoms, namely the number of electrons in the outermost shell per atom. This parameter does not usually change across the ferromagnetic transition as a function of temperature.

One exception is $K_2Cr_8O_{16}$, a close relative of CrO_2, the magnetic compound used in recording tapes. As the temperature drops below 95 kelvin, $K_2Cr_8O_{16}$ changes from being electrically conducting to insulating, but unusually, it remains ferromagnetic. "A transition from a ferromagnetic metal to a ferromagnetic insulating ground state is quite rare, with only a few known examples," explains Ashish Chainani of the RIKEN SPring-8 Center, who led the study.

This surprising property of $K_2Cr_8O_{16}$ has been linked to its crystal structure (see image), which consists of a framework of octahedra



The interaction between electronic and structural effects in the complex crystal structure of $K_2Cr_8O_{16}$ causes its unusual magnetic and electrical properties.

made of chromium and oxygen atoms. The chromium atoms, which determine the magnetic properties, exist in a mixture of +3 and +4 valence states.

By performing spectroscopic measurements, the researchers tracked those valence states as the material transitioned from a conductor to an insulator. They found the distribution of +3 and +4 valence states changed as it was cooled to 95 kelvin. "These fluctuations have been totally missed in previous work," says Chainani. Once the material becomes insulating, the distribution of valence states is frozen in, with on average three in four chromium atoms having +4 states and one having a +3 state.

Theoretical calculations revealed that the structural changes in the crystal alone cannot explain such complex ferromagnetic properties. Rather, the unusual properties of this material stem from interactions between the electrons—known as strong correlations—along with small distortions in the crystal structure.

These findings highlight the importance of comprehensively studying the electronic and structural properties of complex materials, in which subtle effects can significantly alter the material properties. ■

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BIOLOGY | PRESS RELEASE

Victory is all in the mind

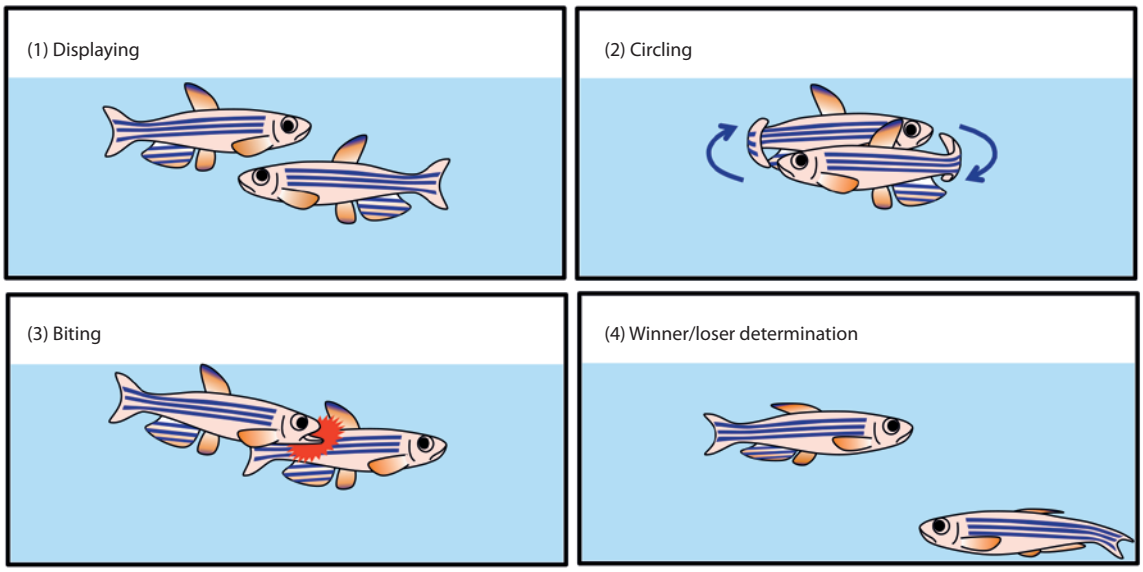
Two neural circuits in the zebrafish brain play a crucial role in deciding whether fish will win or lose a fight

In humans and other social animals, fighting is important in determining a group's social structure. RIKEN researchers have discovered that how such aggression is regulated depends more on the brain than brawn, at least for zebrafish. In particular, they found that two neural circuits in a deep-brain structure called the habenula interact in complex ways to influence the outcome of a fight[1].

The circuits originate in the habenula, pass through the interpeduncular nucleus (IPN) and terminate in the part of the fish brain thought to correspond to the region in mammals' brains that regulates fight-and-flight behaviors. This potential correspondence prompted the team to investigate whether the habenula is also involved in freezing, fleeing and fighting behaviors.

Hitoshi Okamoto of the RIKEN Brain Science Institute and co-workers investigated the circuits by documenting the signaling, circling, biting and surrender behaviors in zebrafish clashes and then measuring *in vivo* the summed electric current from a small group of neurons in the IPN of the winning and losing fish.

When subregions in the upstream dorsal habenula (dHb) were stimulated, activity in the dorsal IPN, but not the ventral IPN, was reduced in the defeated fish. This was confirmed by fluorescence signals linked to neural activity in brain slices, which showed that a defeated state is associated with reduced signaling from the lateral



Stereotypical steps in a fight between two male zebrafish: displaying, circling, biting and determination of the winner and loser.

subregion of the dHb to the dorsal IPN, whereas the signal from the medial subregion of the dHb to the ventral IPN was enhanced.

Thus, the IPN weighs the habenular inputs, essentially acting like a calculator of the outcome of the fight behavior. The case was clinched by transgenic fish, in which these circuits were selectively silenced with a nerve toxin. Fish with no activity in the lateral-dHb-to-dorsal-IPN circuit were much more likely to lose, whereas silencing medial dHb activity disposed a fish to win. Since these transgenic fish were developmentally and physically the same as their wild-type counterparts, transmission in the habenula–IPN circuits must be decisive in determining the outcomes of fights.

"We think the activity in the habenular circuits may be dynamic during a fight, with competition between the lateral and medial subregions," explains Okamoto. "When a threshold in activity is reached, it may push the fish into a winner or loser state, so that it either continues the aggression or surrenders."

"These same circuits exist in all vertebrates, including humans, with possibly the same bistable mechanism," says Okamoto. Devising an equation to describe the activity would allow scientists to predict fight outcomes purely from neural data. ■

Reference

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CHEMISTRY

Tuning in to soft vibrations

Details about the structure and properties of metal cluster complexes have been revealed thanks to a new spectroscopy method

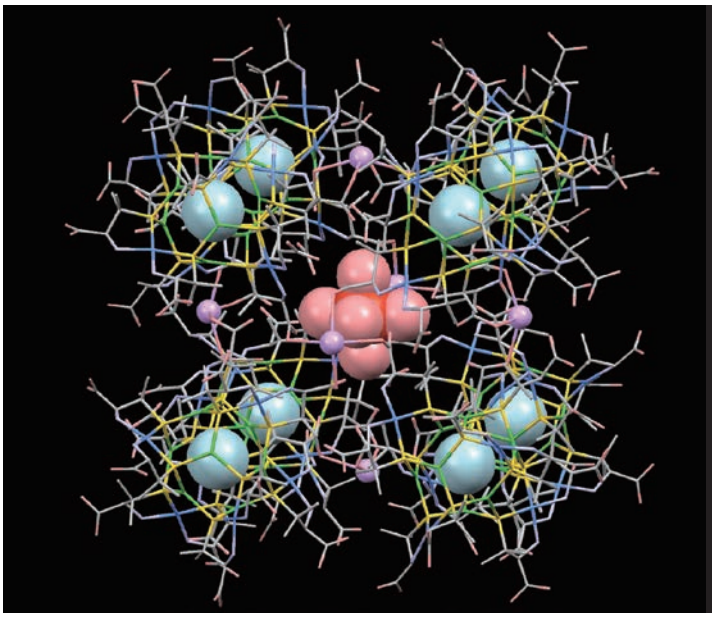
Useful structural information can be teased from metal cluster complexes by tickling them with terahertz radiation, RIKEN researchers have shown. By applying the recently developed technique of terahertz absorption spectroscopy to analyze a copper-rich metal cluster complex, they showed that the technique can deepen our understanding of the structure and behavior of metal cluster complexes[1].

Metal cluster complexes are important molecules in nature and industry alike: they help plant leaves capture energy from sunlight as a key cog in the machinery of photosynthesis and are used as powerful catalysts in industry.

But to fully understand each cluster's mode of action, better information is needed about the structure of these clusters and their aggregates, says Hal Suzuki of the RIKEN Center for Advanced Photonics. "Most structural studies of these substances have used x-ray diffraction, but it has a weak point—the target material must be a crystal," he says. Since terahertz spectroscopy does not require crystals, it is expected to become a powerful analytical tool.

As its name suggests, terahertz spectroscopy probes compounds using terahertz radiation, which has shorter wavelengths than microwaves but longer wavelengths than infrared. It is similar to infrared spectroscopy in that it extracts structural information by picking up characteristic vibrations in the molecule being analyzed. But whereas infrared spectroscopy detects high-frequency vibrations between individual atoms in a structure, terahertz spectroscopy listens for low-frequency 'soft' vibrations, such as those of metal clusters in an aggregate.

To demonstrate the technique's potential for studying these structures, Suzuki and another RIKEN researcher, Chiko Otani, collaborated with two researchers from Osaka University to analyze a recently discovered metal cluster complex that contains 14 copper ions (see image). These complexes form large, porous aggregates whose voids are filled with water molecules. "By slightly tweaking its synthesis conditions, this cluster



Copper-rich metal clusters can form several different aggregates, including this cubic structure, which was analyzed using the technique of terahertz absorption spectroscopy.

complex can be aggregated into different crystal structures," Suzuki explains. "It can thus be used as a model substance to reveal the general rules behind aggregation of cluster complexes."

Using terahertz spectroscopy, the researchers were able to track structural changes in each aggregate as it was heated to drive out the water molecules. The technique revealed that the aggregates became disordered as the component clusters became distorted by the loss of water molecules.

"There is still more that terahertz spectroscopy, in combination with other techniques, can tell us about these complexes," Suzuki says. "The next step is to reveal the role of water molecules in building up the cluster complexes as well as the crystalline forms." ■

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PHYSICS | PRESS RELEASE

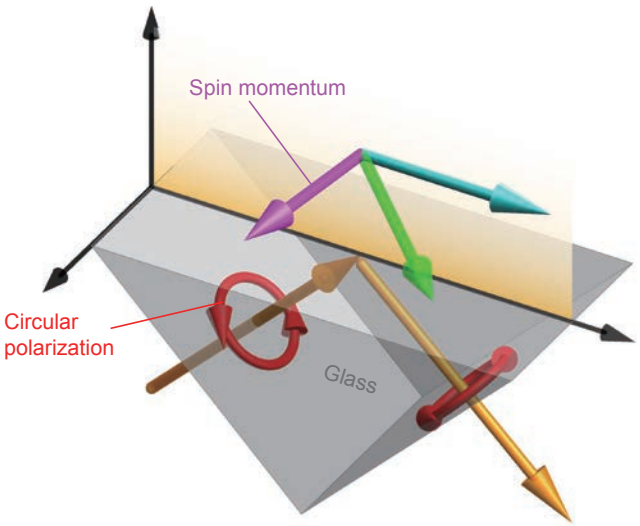
Enigmatic spin momentum of light detected

Extremely sensitive measurements show that light has a mysterious momentum perpendicular to its direction of travel

Ever since Kepler's observation in the 17th century that the Sun's radiation is one of the reasons why comet tails always face away from the Sun, light has been known to exert a pressure in the direction that it travels in. This so-called radiation pressure is produced by the momentum carried by light, and it plays a crucial role in a variety of systems, from atomic to astronomical scales.

Now, RIKEN scientists have measured for the first time a new type of pressure associated with light, which acts perpendicular to the direction light travels in[1].

In an earlier theoretical study, a group from the RIKEN Center for Emergent Matter Science (CEMS) had showed that momentum density in non-uniform optical fields has an unusual component. Unlike the momentum associated with conventional radiation pressure, this new component is directed at right angles to the propagation direction of light and its magnitude is proportional to the optical spin (namely, the degree of circular polarization). The researchers predicted that this spin momentum would produce a transverse spin-dependent optical force that is a few tens of times weaker than the usual radiation pressure.



Highly sensitive measurements reveal that circularly polarized laser light bouncing off the surface of a glass slide generates momentum that points perpendicular to the direction that the light is traveling in.

Based on that study, a group of researchers from CEMS, together with scientists from the United Kingdom, the Czech Republic and Ukraine, has used an extremely precise technique to experimentally verify that light does in fact exert the extraordinary perpendicular force, which is determined by the polarization of the light.

The scientists used an extremely sensitive nano-cantilever to measure this new type of optical momentum and force. This instrument had a femtonewton resolution, meaning that it could measure a force even smaller than the weight of a single bacterium. In the measurements, the nano-cantilever was positioned in the intense, but very thin, electromagnetic field above a glass slide; this field was produced by red laser light being totally internally reflected by a glass surface (see image).

"Our findings revisit the fundamental momentum properties of light and, by

revealing a new type of optical force, enrich the field of optomechanics," says Konstantin Bliokh at CEMS.

"Our group's investigations integrate relativistic-field-theoretical, quantum-mechanical, and optical aspects of the dynamical properties of light," says Franco Nori, who led the team. Looking to the future, he adds, "they offer a new paradigm, which could provide insights into a variety of phenomena, from applied optics to high-energy physics." ■

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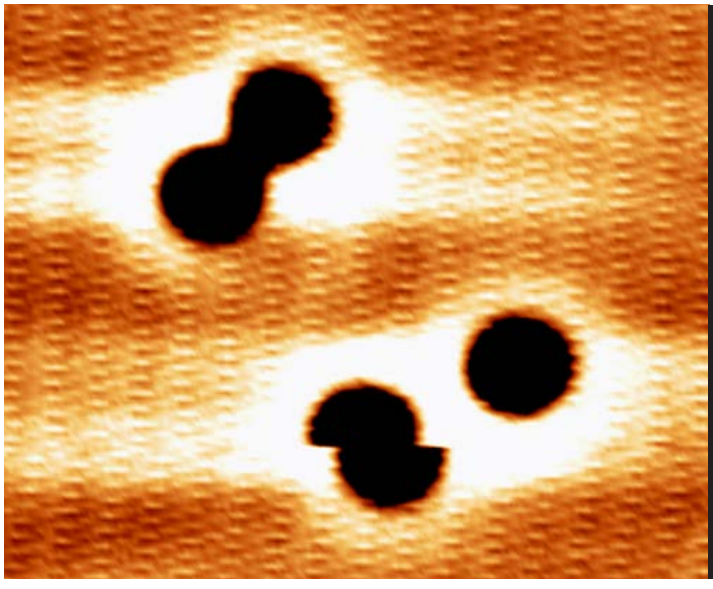
PHYSICS

Catalysts hitting the right overtones

A new method for inducing carbon monoxide molecules to 'hop' on a catalyst surface could lead to more efficient catalysts

RIKEN researchers have discovered a novel way to cause carbon monoxide molecules to move on a catalyst surface. While studying the excitation mechanisms of carbon monoxide molecules on a silver surface (see image), they found that a carbon monoxide molecule can be induced to move by exciting vibrations of the chemical bond between its carbon atom and a surface silver atom[1]. Since the atomic movement on the surface can be excited by electrons with energies even below those of the catalytic energy barrier, the revelation could lead to more efficient catalysis.



Topographic image showing five molecules of carbon monoxide on a silver surface. The molecule that appears sliced in half near the center of the figure is 'hopping' to a neighboring site.

The catalytic reactions of carbon monoxide have been widely studied for commercial applications, such as the manufacture of liquid fuels and the catalytic conversion of toxic carbon monoxide in car exhaust into carbon dioxide. In such catalytic reactions, carbon monoxide molecules are adsorbed onto a metal surface and then 'hop' on the surface until they encounter a reagent molecule.

To study this hopping of carbon monoxide molecules, Yousoo Kim, head of the RIKEN Surface and Interface Science Laboratory, and his collaborators at other institutions in Japan and Korea used an action spectroscopy technique that employs a scanning tunneling microscope to reveal energy excitations on a molecular level. Recently developed at RIKEN, this method uses electrons from the microscope tip to excite molecules at different energies and then analyzes their induced surface motion and reactions.

"This spectroscopy technique enables us to not only assign vibrational modes, but also to discover the dynamics of the underlying reaction mechanism," comments Kim.

The researchers observed that the hopping of carbon monoxide on silver surfaces could be incited in two ways: by exciting vibrations of the carbon–oxygen bond within carbon monoxide and by exciting vibrations between the carbon atom in carbon monoxide and a surface silver atom.

In the latter case, the hopping of carbon monoxide on the surface can be excited through overtones, in which multiple electrons contribute to induce movement. In this way, the energy an individual electron needs to induce motion is reduced. For example, for a second-order overtone, excitation occurs in two steps, each providing half the total energy needed to excite the chemical bond.

This is the first time that pure overtone excitations have been observed for this process at energies below the catalytic activation energy, and it could have profound implications for catalysis. "These results open new opportunities to utilize higher adsorbate overtone modes for triggering elementary surface chemistry processes," says Kim. They will also stimulate further spectroscopic and theoretical investigations using this experimental approach. ■

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Integrative medical science

A healthy balance

By 2030, a quarter of the Japanese population could be over 85 years old. This major shift in population dynamics will make it even more difficult to keep people happy and functioning as they age. The RIKEN Center for Integrative Medical Sciences is addressing this challenge through a clearer understanding of the delicate equilibrium maintained by the body in times of health, and the internal and external triggers of disease.

Tadashi Yamamoto is director of the RIKEN Center for Integrative Medical Sciences
Yamamoto is interested in the intracellular signaling pathways and gene expression activated in response to extracellular signals. His current research focuses more specifically on the coordinated mechanisms controlling mRNA stability.

The Ancient Greek physician Hippocrates was one of the first to associate homeostasis—a condition of internal stability—with health. A state of well-being, he explained, consists of a balance between the four 'humors' produced by the body: blood, phlegm, yellow bile and black bile. Any excess, deficiency or change in the quality of these fluids results in disease.

While our description of homeostasis has changed over the past millennia, the concept remains central to our understanding of life and death. The body constantly makes adjustments to maintain a stable internal environment, such as dropping blood sugar levels after a candy binge or generating heat in response to cold temperatures. These internal stabilizing systems keep the body in check, preventing disease and ultimately death.

Both environmental and genetic factors can disrupt the body's ability to maintain stability and fight disease. The common skin disorder atopic dermatitis, for example, has long been known to run in families. However, while many genes may contribute to a child's risk of developing the condition, exposure to toxins, irritants and pollutants are equally important in triggering a reaction.

The RIKEN Center for Integrative Medical Sciences (IMS) is advancing our understanding of the internal and external factors that contribute to disease to help people maintain homeostasis and good health. Established in 2013, through a merger between the former RIKEN Research Center for Allergy and Immunology and the RIKEN Center for Genomic Medicine, the IMS combines a long history of research into the body's critical artillery for protecting itself against foreign threats, the immune system, with the development of large-scale genome studies to uncover the sources of instability that lie within.

DNA banks

Significant technological advances over the past decade have led to deeper insights into the agents underpinning or upsetting homeostasis. The IMS has been developing and utilizing state-of-the-art technologies for the analysis of information within the human genome.

Following the success of the Human Genome Project in sequencing the entire human genome in 2003, it became possible to study genomic variations within and between entire populations. Scientists hypothesized that differences in the code could explain observable differences in physical traits, and even offer clinically relevant information about disease susceptibility. The development of faster, cheaper and more accurate genome sequencing technologies made these studies possible.

In 2002, researchers at RIKEN published one of the first genome-wide association studies (GWAS) looking for single-nucleotide differences between the genomes of a group of people. This study compared the genomes of about 100 Japanese heart-attack patients and around 650 healthy individuals. Since then, close to 2,500 GWAS studies have associated more than 16,000 variations in DNA lettering with diseases ranging from macular degeneration to type 2 diabetes and multiple sclerosis.

In 2003, the former RIKEN Center for Genomic Medicine joined a national BioBank project to collect hundreds of thousands of blood samples from Japanese citizens for further genome studies. Analyses of these samples have since identified more than 34 billion single-nucleotide variations and 170 genes associated with specific diseases, 20 of which respond to drugs.

Kazuhiko Yamamoto at the IMS has been using the BioBank's genome data for the past decade to search for the genetic basis of rheumatoid arthritis, a complex autoimmune disease characterized by swelling and pain in the joints. In 2014, he collaborated with a large international research team in a GWAS of 100,000 individuals of European and Asian descent[1]. The team connected 101 nucleotide links in the DNA chain with a risk of developing rheumatoid arthritis—every single-letter switch representing a lead for a potential treatment. An extensive drug search found that approved drugs for rheumatoid arthritis already target proteins expressed by 27 genes linked with an increased risk of the disease, and approved cancer drugs overlap with 2 genes. The approach taken by Yamamoto is a powerful, unbiased and data-driven route to drug discovery.

Annotated DNA

While sequencing the genome is an important first step to understanding many diseases, scientists still have a lot to learn. Every cell in the body contains an identical copy of DNA, but a neuron's interpretation of the genetic code varies considerably from that of a cardiac muscle cell, for example. One of the keys to this diversity lies in how DNA is packaged.

Advanced sequencing technologies can now observe the hustle and bustle around the genome coordinating genetic expression at specific moments in time. In 2012, IMS researcher Katsuyuki Shiroguchi improved on the accuracy of an RNA sequencing technique by developing a digital barcode method for counting the RNA in a sample, and has been refining

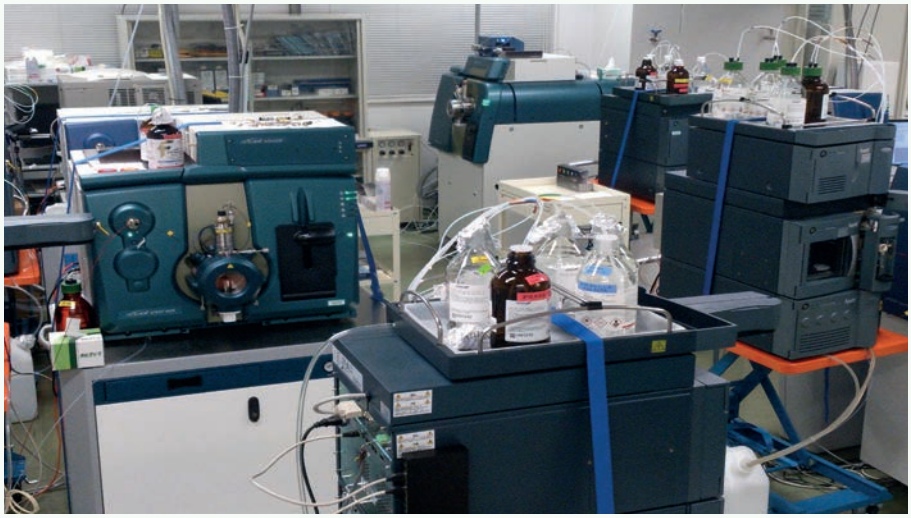

Figure 1: Makoto Arita's laboratory at the RIKEN Center for Integrative Medical Sciences uses advanced mass spectrometry to characterize the metabolites present in a cell, tissue or organism.

the technique at the IMS for single-cell analysis. Systematic tools have also been developed for characterizing and quantifying the proteins (proteomics) and small-molecule chemicals (metabolomics) present in a sample. Makoto Arita's laboratory, for example, uses advanced mass spectrometry to analyze the structure and function of many types of lipids synthesized and degraded by the body (Fig. 1). These lipid metabolites play an important role in regulating inflammation and maintaining tissue homeostasis.

Supercomputers and advanced computational systems have also allowed vast amounts of information to be stored and processed within manageable time frames. And live cell and *in vivo* imaging tools can capture the vibrant detail of life in motion, even in full color.

Functional analysis

To observe how genetic and environmental factors control homeostasis at a systemic level, researchers rely on another well-known experimental tool—the model organism. Animal models have been used to study the effects of knocking out crucial genes, to analyze disease pathogenesis, and to test the therapeutic or toxic effects of various compounds. To investigate the role of environmental factors, researchers at the IMS frequently use germ-free organisms, which are born and maintained in sterile, isolated chambers.

But animal models can be poor representations of human biology and disease. To address this problem, Fumihiko Ishikawa at the IMS has developed a method for studying the behavior of human cells, tissues and organisms in 'humanized' mice. The technique involves transplanting human cells into mouse models with weak immune systems to ensure that the foreign cells are not rejected, instead growing and differentiating in their host.

Using this method, Ishikawa has differentiated human stem cells isolated from umbilical cord blood and introduced to germ-free mice into mature blood cells, including cell types essential to the immune system such as dendritic cells and lymphocytes. Humanized mice facilitate the study of human immunity *in vivo*, from examining our response to pathogens and tumors to testing vaccines against infectious diseases and cancers.

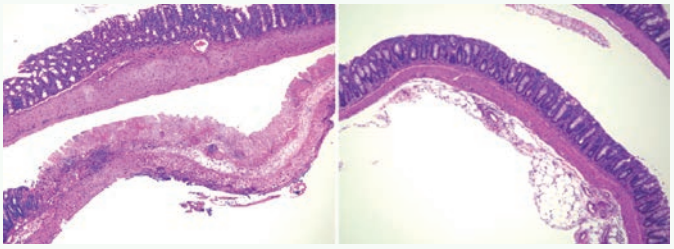

Figure 2: Mouse models of colon inflammation treated with a mixture of 17 bacterial strains had healthier guts (right) than those who did not receive the treatment (left).

Environmental factors

From genomics and its many '-omics' derivatives to computational science and animal experiments, researchers at the IMS have become adept at consolidating the latest tools and techniques to trace the origins of stability in the human body.

This integrated approach is particularly relevant in the field of immunology. Shohei Hori, for example, has clarified the mechanism by which regulatory T cells prevent other lymphocytes from attacking themselves, a suicidal behavior that if unsuppressed can cause a range of autoimmune diseases such as type 1 diabetes, thyroiditis and inflammatory bowel disease.

IMS researchers, including Hiroshi Ohno, Sidonia Fagarasan and Kenya Honda have further identified how the self-protective function of regulatory T cells is shaped by microbes living in the gut. Their research has revealed the critical role of interactions between the body and its gut microbes in maintaining immune homeostasis; any breakdown in communication could cause inflammation.

Honda took this research a step further by colonizing the guts of germ-free mice with bacterial strains taken from either a healthy human or patients of ulcerative colitis. Seventeen of the introduced bacterial strains from the healthy individuals were found to induce anti-inflammatory molecules and T regulatory cell activity[2], while a cocktail of bacterial strains from patients of ulcerative colitis induced pro-inflammatory immune cells in the mouse guts. The bacterial strains from the healthy humans were subsequently fed to mouse models of colon inflammation. The diet-treated diseased mice showed milder symptoms, such as less severe diarrhea and reduced colon shortening, and lower mortality rates (Fig. 2).

Clinical harvest

Modern medicine and research is one of the main reasons people today live longer than any generation before them. But the challenge for society will be to ensure that longevity progresses alongside physical, mental and social well-being. This will require more research into homeostasis and its role in human health and disease, an endeavor that will require collaboration between researchers and clinicians.

In 2016, RIKEN launched a project called the Innovation Hub, led by Kazuhiro Sakurada together with Hiroaki Kitano, Tatsuhiko Tsunoda and Haruhiko Koseki at the IMS, to bring these two groups closer together. In partnership with four hospitals across Japan, it will collect and analyze blood samples from patients with rheumatoid arthritis and atopic dermatitis. Using machine-learning and artificial intelligence to process the incoming data, the project will hopefully lead to new markers for diagnosing and eventually even predicting the onset of disease. The IMS is expected to play a pivotal role in this project.

A fragmented approach to medical science is no longer sustainable. The IMS's model of integrating research follows in the footsteps of the great father of modern medicine, Hippocrates. ■

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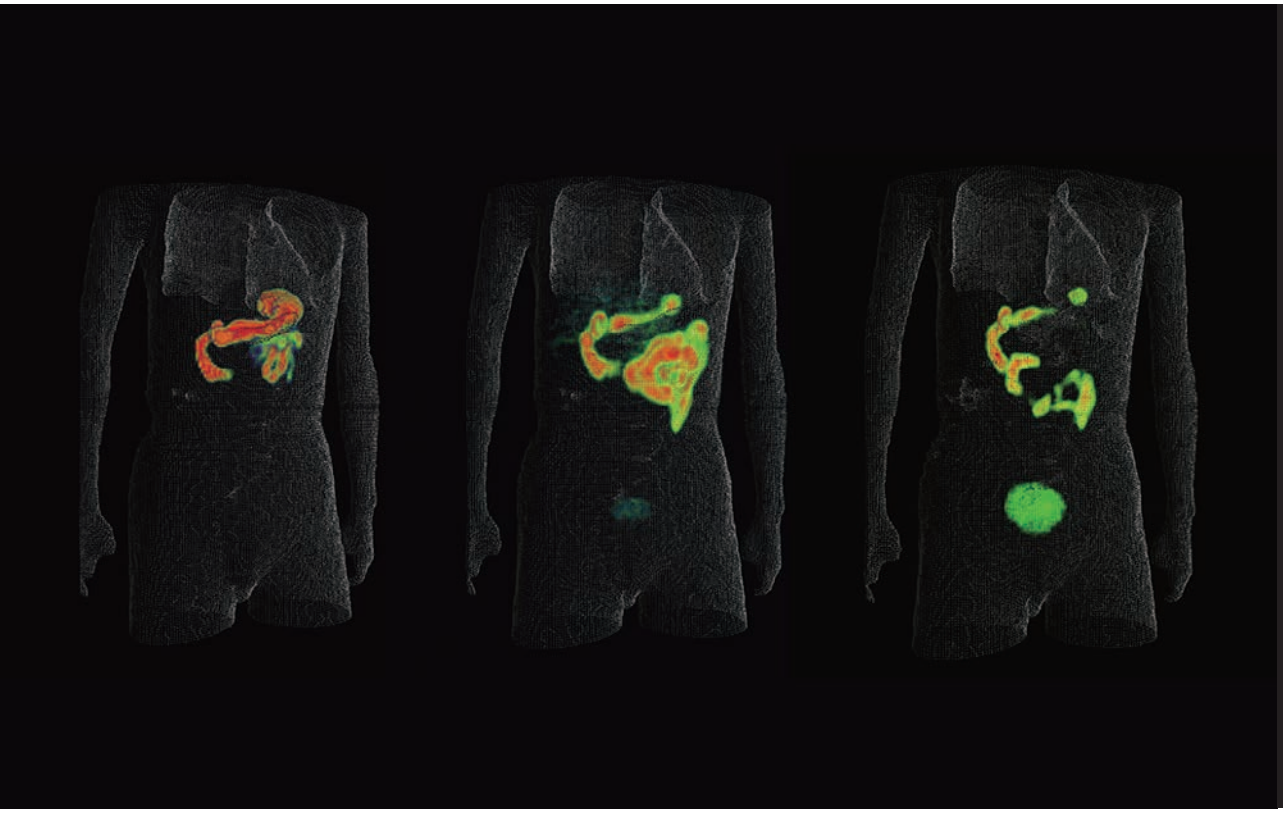
For additional references, visit the online version of this article at:

www.riken.jp/en/research/rikenresearch/perspectives/8192

Research highlights



Positron emission tomography (PET) probes can be used to pinpoint the location of tumors in the body. RIKEN researchers have found a straightforward way to produce PET probes containing radioactive fluorine.

CHEMISTRY

Breaking bonds for probes and drugs

A method for transforming carbon–fluorine bonds offers new opportunities in drug research and medical imaging

A chemical procedure developed by an all-RIKEN research team has the potential to enhance the usefulness of positron emission tomography (PET) for discovering new drugs and diagnosing diseases.

Many promising candidate drugs have to be abandoned when they enter clinical trials because they give rise to adverse side effects. Such side effects could be detected earlier by using improved methods to assess the metabolism of a drug candidate after administration. Incorporating suitable radioactive atoms—radioisotopes—into prospective drugs allows researchers to follow how a molecule is processed in the body. For example, PET scanning detects gamma-rays generated by the release of positrons when radioisotopes spontaneously decay.

"As the number of fluorine-containing drugs is increasing," says Takamitsu Hosoya of the RIKEN Center for Life Science Technologies, "it is vital to find ways to incorporate radioactive fluorine atoms into a wide range of molecules."

Compounds known as fluoroarenes are suitable starting materials for making fluorine-containing probes. But to transform

them into useful probes requires breaking one of the strongest bonds in nature—the carbon–fluorine bond.

This is the key process that Hosoya and his colleagues have now achieved. They used a nickel–copper catalyst to break the carbon–fluorine bond in a way that permits non-radioactive fluorine-19 atoms to be swapped with radioactive counterparts, fluorine-18 atoms[1]. This also permitted the researchers to transform the initial fluoroarenes into a range of other potentially useful compounds, including some that do not contain fluorine.

The reaction schemes involve creating an organoboron compound, in which the original fluorine atom is replaced with a boron atom, prior to further chemical transformation. Organoboron compounds are widely used intermediates in chemical synthesis. Appreciating the details requires a deep knowledge of chemistry, but the key consequence is that fluoroarenes have now become a much more versatile source of many kinds of useful molecules.

"We anticipate that our method will be applied to make new PET probes that can help the early diagnosis of diseases," Hosoya explains. Such PET probes are chemicals that are selectively taken up by diseased tissues, such as tumors, and thus reveal the location of such tissue in PET images (see image). The researchers plan to build on this work by linking it to existing collaborations with clinical teams that can use it in applied research in humans. "By developing our innovative chemical methods, we hope to contribute to the advance of life science and drug discovery," says Hosoya. ■

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PHYSICS | PRESS RELEASE

Electrons lose weight

Modeling electrons in materials that move from a metal to an insulator phase sheds new light on the transition

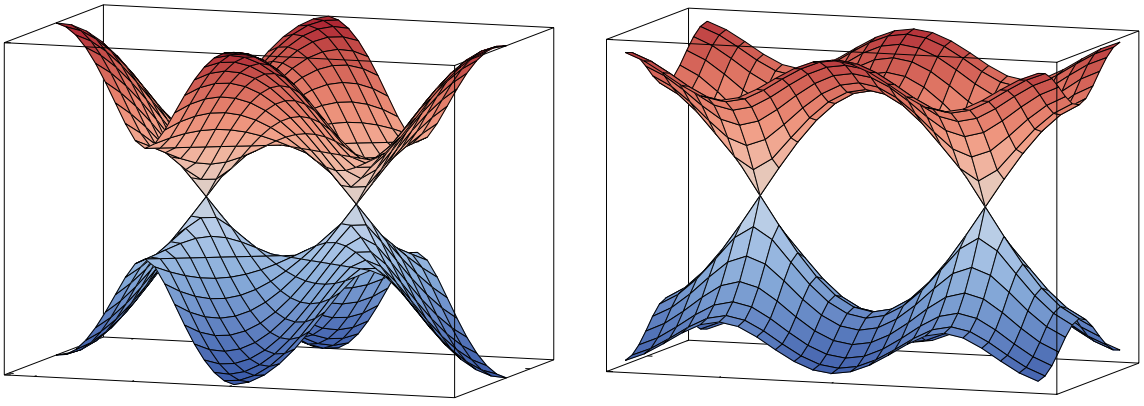
Using the powerful K computer, three RIKEN researchers have performed a large-scale analysis of the behavior of electrons in a material transitioning from a metal to an insulator phase[1]. Their analysis confirmed that the transition is direct—that is, no transitional phase exists between the two phases. Furthermore, it showed that the behavior is tied to the electrons in the material—called Dirac electrons—losing identity as they become correlated with one another.

Most materials are either conducting or insulating depending on their composition. However, some materials can transition between the two states through either environmental changes, such as pressure or magnetic field, or doping with other atoms. How this transition happens has long been a mystery.

Hints came from the fact that band theory, which explains the properties of materials by looking at the energy bands occupied by electrons, gave wrong predictions for certain classes of materials. This discrepancy was due to the correlation between electrons in these materials, which are affected by the repulsive Coulomb interactions between them.

To shed new light on this problem, Yuichi Otsuka, Seiji Yunoki and Sandro Sorella from the RIKEN Advanced Institute for Computational Science modeled large numbers of electrons on two lattices with about 100 to 3,000 sites, using variations of a model that has been successful in describing such materials.

They found that the systems transitioned directly from a metal to an insulator as the correlation between the electrons increased, which goes against theories that predict there is a transitional phase. The large scale of their simulations allowed the researchers to predict



Two models of electrons in materials that undergo a transition from a metal phase to an insulator phase shed new light on this transition.

when and how the transition will occur with greater accuracy than before.

They also discovered that the key factor was the loss of spectral weight of the Dirac electrons and not the speed at which they traveled, which seemed unrelated to the transition.

Surprisingly, this metal–insulator transition, which is expected to arise in graphene-like materials, can be understood in terms of the language of particle physics, despite electrons in graphene having much lower energies than the elementary particles of particle physics.

"Our study determines for the first time the universality class of the metal–insulator transition of interacting Dirac electrons," explains Otsuka. "We expect that our findings will be relevant not only to condensed-matter systems but also to Dirac fermions in particle physics. There are still many things we do not understand about interaction-driven insulators, and research in this area may help us elucidate those mysteries." ■

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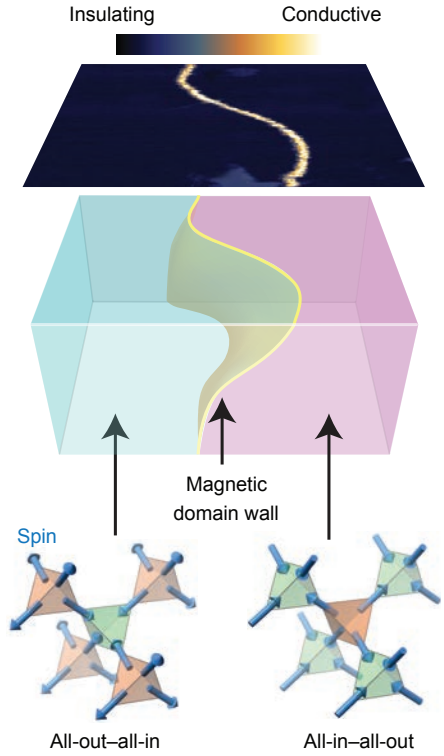
PHYSICS

A better foundation for 3D memory

The discovery of metal-like domain walls in magnetic insulators may help realize energy-efficient memory devices with massive storage capacities



Scanning probe experiments reveal that metal-like domain walls emerge at the nanoscale when two insulating, 'all-in–all-out' magnetic phases come into contact.

Efforts to shrink memory devices beyond the limits imposed by conventional lithography have focused on nanoscale regions, known as magnetic domain walls, which can be manipulated in three dimensions. Now, RIKEN researchers and international collaborators have detected a new type of domain wall with highly conductive, mobile metallic states that promises to make three-dimensional memory systems easier to control and miniaturize[1].

Magnetic materials contain distinct regions, known as domains, in which electrons with the same spin configuration—normally spin-up or spin-down states—are separated by domain wall boundaries. Recent theoretical studies have suggested that domain walls adopt different electronic states and become electrically active in certain magnetic insulators. But detecting metallic behavior in insulating crystals, where grains are often smaller than the width of a human hair, is experimentally challenging.

Kentaro Ueda from the RIKEN Center for Emergent Matter Science and colleagues investigated neodymium iridate pyrochlore ($Nd_2Ir_2O_7$), a rare-earth-based magnetic insulator with unusual properties. Spins in this material are arranged tetrahedrally and alternately point 'all-in' toward the center of the tetrahedron, or face 'all-out'. Two types of magnetic domains form in $Nd_2Ir_2O_7$—'all-in–all-out' or 'all-out–all-in' (see image)—and some large-scale studies have hinted at abnormal conductivity occurring at the barriers between them.

The team used a technique called microwave impedance microscopy to obtain direct nanoscale information on the domain walls of $Nd_2Ir_2O_7$. Samples were cooled to close to absolute zero and their surfaces were then scanned by an ultrasharp and highly conductive probe that senses variations in electrical resistance. The resulting images revealed the presence of narrow, curvilinear features, roughly 100 nanometers wide, that were hundreds of times more conductive than surrounding regions.

"The emergence of metallic domain walls, in spite of the fully insulating bulk state, provoked a lot of discussion in our team," says Ueda. "Where does this behavior originate? And why is this material so special?"

The strong response of the nanoscale regions to thermal and magnetic fields provided some clues to these questions. "In conventional metals, resistivity usually depends on temperature," explains Ueda. "The domain walls show virtually temperature-independent ohmic behavior,

indicating an anomalous metallic defect or edge state."

One potential application of this technology is magnetic random access memory (MRAM), in which data is stored by altering the electrical resistance of the recording medium. Currently, resistance changes of several tens of per cent are used in MRAM. In contrast, metallic domains can change the resistance by factors of several hundred, which should enable much more compact MRAM devices to be fabricated. ■

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CHEMISTRY | PRESS RELEASE

Brain calcium controls how long we sleep

Researchers identify seven genes that strongly affect length of sleep and find that they are all related to calcium changes in neurons

As well as making our bones stronger, calcium could also be the key to a good night's sleep. Researchers at RIKEN have unveiled a new theory of how sleep works, which suggests that slow-wave sleep depends on the activity of calcium in neurons[1].

"Although sleep is a fundamental physiologic function, its mechanism is still a mystery," says Hiroki Ueda of the RIKEN Quantitative Biology Center (QBiC).

The multidisciplinary team used various scientific techniques, including conducting computational modeling and studying knockout mice (see image), to search for the fundamental mechanism underlying sleep.

The team created a computational neural model to predict which currents in a neuron are critical for maintaining the type of neural activity associated with slow-wave sleep. "Our model made four predictions, which provided us with four starting points to search for critical genes involved in sleep," explains Fumiya Tatsuki of the University of Tokyo. "Each prediction was tested and proven correct in experiments with knockout mice or by pharmacological inhibition, and we were ultimately able to identify seven genes that work in the same calcium-related pathway to control sleep duration."

The researchers created 21 knockout mice using recently developed CRISPR technology, which Ueda's team has refined into a highly accurate and efficient *in vitro* system. Additionally, Genshiro Sunagawa, also from QBiC, developed an automated sleep monitoring system that continuously collected the necessary behavioral data.

Knockout mice lacking target genes were observed *in vivo* for changes in sleep duration. By identifying mice with abnormal sleep patterns, the team was able to pinpoint seven genes that critically affected sleep duration in the mouse models.

All seven genes allow calcium-dependent changes in neurons that caused them to resist becoming active. As predicted by the model, down-regulating six of these genes reduced sleep duration in knockout mice, whereas down-regulating the final gene led to longer sessions of sleep.

Seven genes have been identified that critically affect how long mouse models sleep.

"Our study revealed that sleep is regulated by calcium-related pathways," says Shoi Shi, who is also at the University of Tokyo.

"These findings should contribute to the understanding and treatment of sleep disorders and neurologic diseases that have been associated with them," notes Ueda. "In addition to becoming new molecular targets for sleep drugs, the genes we have identified could also become targets for drugs that treat certain psychiatric disorders that occur with sleep dysfunction."

Sunagawa cautions that much work is still needed. "Although our study reveals a mechanism for sleep regulation, the molecular details of the mechanism are still unknown, as is the real relationship between sleep dysfunction and psychiatric disorders." ■

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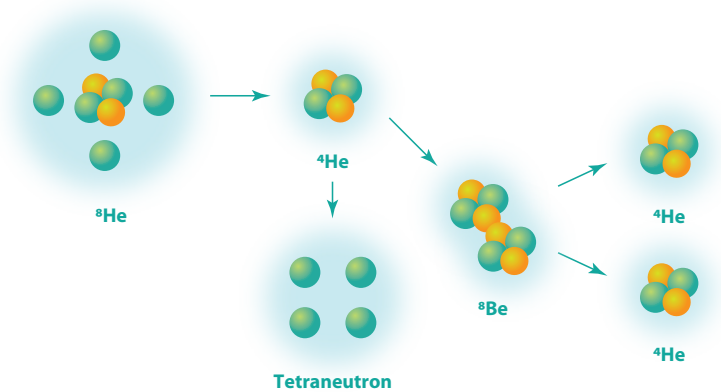
PHYSICS

Mythical nuclear beast spotted?

Highly compelling evidence for the much-debated existence of the four-neutron system has been obtained by colliding helium nuclei

Among nuclear physicists, a system consisting of four neutrons—aptly named the tetraneutron—has assumed the mythical status of the Loch Ness Monster. Several experimental sightings have been reported in the literature, but they have failed to convince the nuclear physics community, which remains skeptical about the particle's existence. RIKEN scientists have recently found the most tantalizing evidence yet that the beast actually does exist.

Since neutrons are electrically neutral and do not repel each other, the tetraneutron might naively be assumed to be even more stable than its extremely stable cousin, the helium nucleus (two positively charged protons and two neutrons). But quantum physics prohibits two identical 'fermions' (elementary particles that include neutrons and protons) from occupying the same quantum state simultaneously. Consequently, nuclei consisting of approximately equal mixtures of protons and neutrons (such as helium nuclei) are the most stable, whereas the all-neutron tetraneutron is predicted to be too energetically unstable to exist.



By firing a beam of neutron-rich helium nuclei (^{8}He) at a target of normal helium nuclei (^{4}He) and analyzing the collision products, researchers have found compelling evidence for the fleeting existence of the four-neutron system, the tetraneutron.

Now, a 51-member team led by Keiichi Kisamori at the RIKEN Nishina Center for Accelerator-Based Science and Susumu Shimoura of the University of Tokyo has obtained strong experimental evidence that the tetraneutron exists, albeit in an unstable resonance form rather than as a stable bound nucleus[1].

They fired a beam of unstable neutron-rich helium nuclei (two protons and six neutrons) at normal helium nuclei (two protons and two neutrons). On four occasions, they obtained an unstable form of beryllium (four protons and four neutrons), which promptly decayed into two helium nuclei (see image). That leaves four neutrons unaccounted for. The researchers strongly suspect that these four neutrons briefly formed a tetraneutron.

The existence of the tetraneutron would be far too fleeting (it probably lasted for just 10^{-21} seconds) to observe directly. But by considering the energies of all the particles involved, it could be inferred at a 4.9-sigma significance level—just shy of the 5-sigma level that is the gold standard for establishing something statistically.

The finding has generated much excitement. "The nuclear physics community is very surprised," says Kisamori. He notes that the finding has both inspired

theoreticians to conduct new calculations and emboldened experimentalists to renew their search for the tetraneutron.

"We have paved the way to a firmer understanding not only of the fundamental properties of nuclear forces, but also of the structure of neutron stars," says Kisamori, referring to the incredibly dense remnants left after supernova explosions that consist entirely of neutrons.

The scientists intend to conduct experiments on other nuclear reactions to improve the statistics and to explore new aspects of tetraneutron physics. ■

Reference

1. Kisamori, K., Shimoura, S., Miya, H., Michimasa, S., Ota, S., Assie, M., Baba, H., Baba, T., Beaumel, D. & Dozono, M. Candidate resonant tetraneutron state populated by the ^{4}He (^{8}He, ^{8}Be) reaction. *Physical Review Letters* **116,** 052501 (2016).

BIOLOGY | PRESS RELEASE

Calcium waves make mice happier

Electrical stimulation of the brain reduces depressive symptoms in mice through generating surges in calcium levels in star-shaped brain cells

The benefits of stimulating the mouse brain with a direct current come from its effects on astrocytes—not neurons, find RIKEN researchers[1]. They discovered that applying a direct current to the head releases synchronized waves of calcium from astrocytes that can reduce depressive symptoms and also boost neural plasticity. Transcranial direct-current stimulation (tDCS) involves targeting specific brain areas by applying a weak electric current through the head. It has been used for decades to clinically treat major depression and has also been shown to enhance learning and synaptic plasticity in humans and animals.

"While we have known the clinical benefits of this kind of stimulation for quite some time, our research is aimed at understanding the cellular mechanisms through which its effects are made possible," notes Hajime Hirase of the RIKEN Brain Science Institute (BSI).

Hirase's team decided to use calcium imaging to examine brain activity during tDCS, because calcium levels in astrocytes—star-shaped glial cells in the brain—have recently been shown to be important for transmitting signals that help neurons strengthen connections with each other.

They made a transgenic mouse that expresses a fluorescent calcium-indicator protein in astrocytes and some neurons, which allowed them to image brain-wide calcium activity using a standard fluorescence microscope.

The researchers found that tDCS caused large-amplitude calcium surges. "Surprisingly, the calcium surges occurred very quickly after stimulation onset and appeared synchronized all over the cortex, not only near the stimulated location," explains lead author Hiromu Monai, also at the BSI.

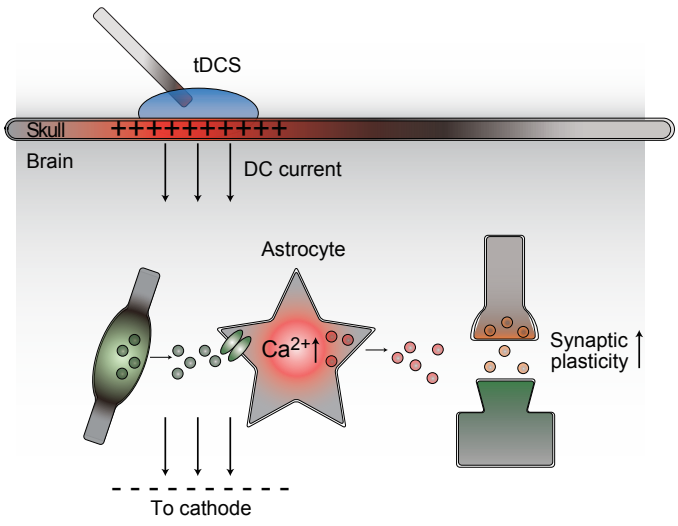
No calcium surges were observed when the same experiment was performed on mice in which rising calcium levels in astrocytes were prevented, demonstrating that astrocytes, not neurons, were the source of the waves.

The researchers next examined the importance of the calcium surges using a mouse model for stress-induced depression. While tDCS can normally reduce depression-like behavior in these mice, it failed when they blocked the astrocytic calcium surges.

"This suggests that the positive effects of tDCS on depression lie in these widespread calcium surges," says Monai. "But we also wanted to investigate their effects on neural plasticity in general."

To examine this effect of astrocytic calcium surges, the team looked at changes in sensory responses after tDCS. They measured the responses to flashes of light and whisker stimulation, and found that they were more than 50 per cent greater after stimulation—an effect that lasted for 2 hours after stimulation.

"That this mechanism is mediated by astrocytic activity is exciting and hints that astrocytes could be a major therapeutic target for neuropsychiatric diseases," notes Hirase. ■



Surges in the calcium levels of astrocytes in mouse brains reduce depressive symptoms and boost neural plasticity.

Reference

1. Monai, H., Ohkura, M., Tanaka, M., Oe, Y., Konno, A., Hirai, H., Mikoshiba, K., Itohara, S., Nakai, J., Iwai, Y. & Hirase, H. Calcium imaging reveals glial involvement in transcranial direct current stimulation-induced plasticity in mouse brain. *Nature Communications* **7,** 11100 (2016).

Chemists at the front of RIKEN elixir of health and wealth

The pioneering research of two RIKEN chemists in the early twentieth century had a major impact on the organization's success

Profits from selling bottles of RIKEN Vitamin sustained half of RIKEN's entire research budget during the years between World War One and World War Two.

Until Umetaro Suzuki isolated the first vitamin in 1911, no one had seen one of these miracle molecules that could prevent vitamin-deficiency diseases such as rickets, scurvy and beriberi.

Suzuki was born in Shizuoka in 1874. He studied agricultural chemistry at a prestigious university in Tokyo. Like many of his Japanese contemporaries in the natural sciences, he then moved to Europe to continue his postdoctoral research. In Germany, he worked under the Nobel-winning chemist, Emil Fischer, who urged him to focus on research pertinent to Japan, warning that competing with Western scientists would be a losing game.

Suzuki took Fischer's advice and returned home in 1906, thinking about rice. He had heard of beriberi, a life-threatening nerve disease characterized by wobbly knees and paralysis. Many sailors in the Imperial Japanese Navy who lived on a diet of white rice had developed the affliction. In the late nineteenth century, Christiaan Eijkman, a Dutch physician living in Java discovered that chicks fed brown rice instead of milled and polished rice did not develop beriberi. Suzuki wondered what was hidden in the bran. While working as a researcher at the University of Tokyo, he found out that the vital nutrient was thiamin, or vitamin B1, which he named aberic acid.

Umetaro Suzuki (left) and Katsumi Takahashi (right).

Several years after Suzuki's discovery of the first vitamin, he joined the newly established Institute of Physical and Chemical Research, now known as RIKEN. In 1918, a sharp increase in the price of rice caused riots throughout Japan. Suzuki was concerned that the country's staple food was being wasted on sake, and was determined to produce a synthetic version of the traditional liquor. He mixed succinic acid, lactic acid, some amino acids and sugars in a watered-down ethanol solution to create the same flavor and effects of fermented rice wine.

Masatoshi Okochi, an enterprising president of RIKEN, supported the large-scale production of RIKEN-*shu*, which was

sold under the name RIKYU—a brand still stocked in liquor stores today, under new owners and with refined ingredients.

Ample vitamins

It was not long before Suzuki hit on an even bigger commercial blockbuster, through the diligence of Katsumi Takahashi, a student who joined Suzuki's laboratory at RIKEN after graduating from the University of Tokyo. By then, researchers in the United States had discovered another vitamin, known as vitamin A, in animal fats, and doctors were using it to treat the contagious and deadly disease, tuberculosis. Difficulty in extracting the vitamin meant production could not keep up with global demand. Suzuki, who had become director of RIKEN's chemistry division, set Takahashi the task of purifying and clarifying the chemical structure of vitamin A. This would enable its production on a large scale.

It did not take much time for Takahashi, well trained in handling lipids, to purify vitamin A from cod liver oil in 1922. He transformed the oil into soap, treated the unsaponified portion with a series of chemicals and distilled it. 20 kilograms of cod liver oil yielded approximately 10 grams of transparent, viscous 'biosterin', or pure vitamin A. The substance was bitter but odorless, and had a yellowish-red tinge.

"With an ample amount of the substance thus obtained, the authors have been able to make a thorough study on its physical and chemical properties, and its physiological effects," describes a paper Takahashi published in 1925, the same year that he died of typhus when only 32. The paper went on to present the first evidence of the toxic and potentially lethal effects of a vitamin overdose. It was a prescient finding considering the prevalence of vitamin deficiencies around the world at the time.

Windfall profits

Takahashi's vitamin A research was a financial windfall for RIKEN. Its success was driven by President Okochi's revolutionary strategy to commercialize inventions to generate revenue—he called it 'science-driven industry'. "Looking back, it may well be called the frontrunner of innovation today," says Tomoya Ogawa, science adviser to RIKEN, who considers himself an "academic grandchild of Suzuki".

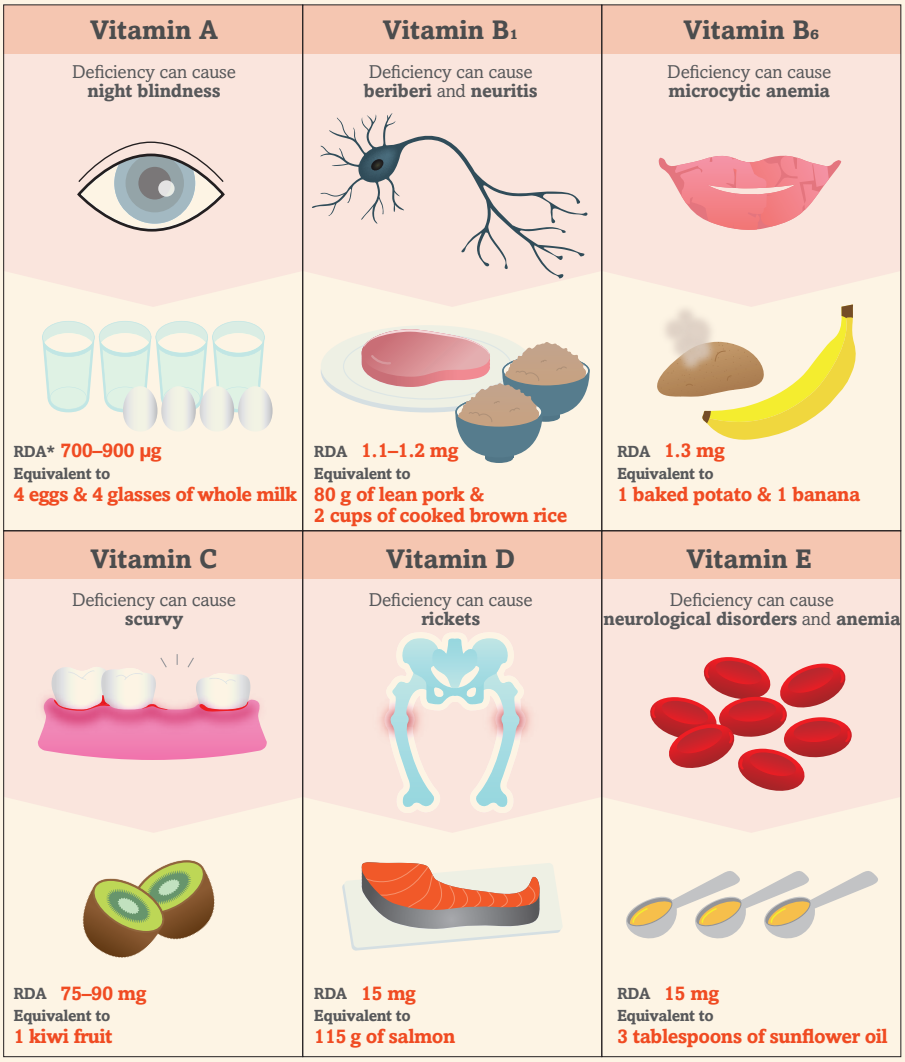
Okochi invested in a venture called Rikagaku Kogyo in 1927, which sold vitamin A in copper-colored glass bottles under the brand name RIKEN Vitamin. During the interwar period, sales of RIKEN Vitamin raised profits worth JPY 600,000 a year, enough to cover half of RIKEN's entire research budget. Almost 70 ventures were born during Okochi's presidency.

In 1949, the vitamin business spun off from RIKEN, with the establishment of an independent company named RIKEN Vitamin Oil, known today as RIKEN Vitamin. The company took advantage of molecular distillation techniques developed by nuclear physicists at RIKEN to scale up industrial production. In 1958 alone, it produced 120 trillion international units (IU) of vitamin A, fulfilling 60 per cent of global consumption—the recommended daily intake for a healthy adult ranges from 2,000 to 3,000 IU.

By the 1950s, Japan's booming vitamin industry was facing stiff competition from abroad, as chemists from the European pharmaceutical giant, Hoffmann-La Roche, discovered how to manufacture synthetic vitamins. Artificial vitamins are easier to mass-produce than those extracted from natural sources.

Suzuki continued his research into vitamins, including vitamins B6, C, D and E, until his death in 1943. That year, he was awarded the Culture Order and the First Class Order of the Sacred Treasure. To this day, researchers like Ogawa remember him as a scientist who "pursued strategic basic research mainly from the viewpoint of nutrition and good health for the Japanese people". ■

Umetaro Suzuki's research has spanned many essential vitamins, including vitamins A, B1, B6, C, D and E.



*Recommended Dietary Allowance (RDA): Average daily intake required to meet the nutrient needs of a healthy adult
Source: Linus Pauling Institute

Junior Research Associate program

The Junior Research Associate (JRA) program provides part-time positions at RIKEN for energetic and open-minded young researchers enrolled in PhD programs at Japanese universities to give them the opportunity to carry out research alongside RIKEN scientists, while enhancing RIKEN's creative and basic research capabilities and strengthening ties between RIKEN and Japanese universities.

From 2011, RIKEN has been making special efforts to foster the development of basic research in medical fields. Recent graduates of medical and dental universities who have acquired their medical or dental licenses are welcome to apply.

Applications are publicly solicited every year (usually in autumn). A committee consisting of RIKEN scientists working in the relevant field screens each applicant on the basis of submitted documents.

For more details please visit the URL below or send an email to jra@riken.jp
www.riken.jp/en/careers/programs/jra/

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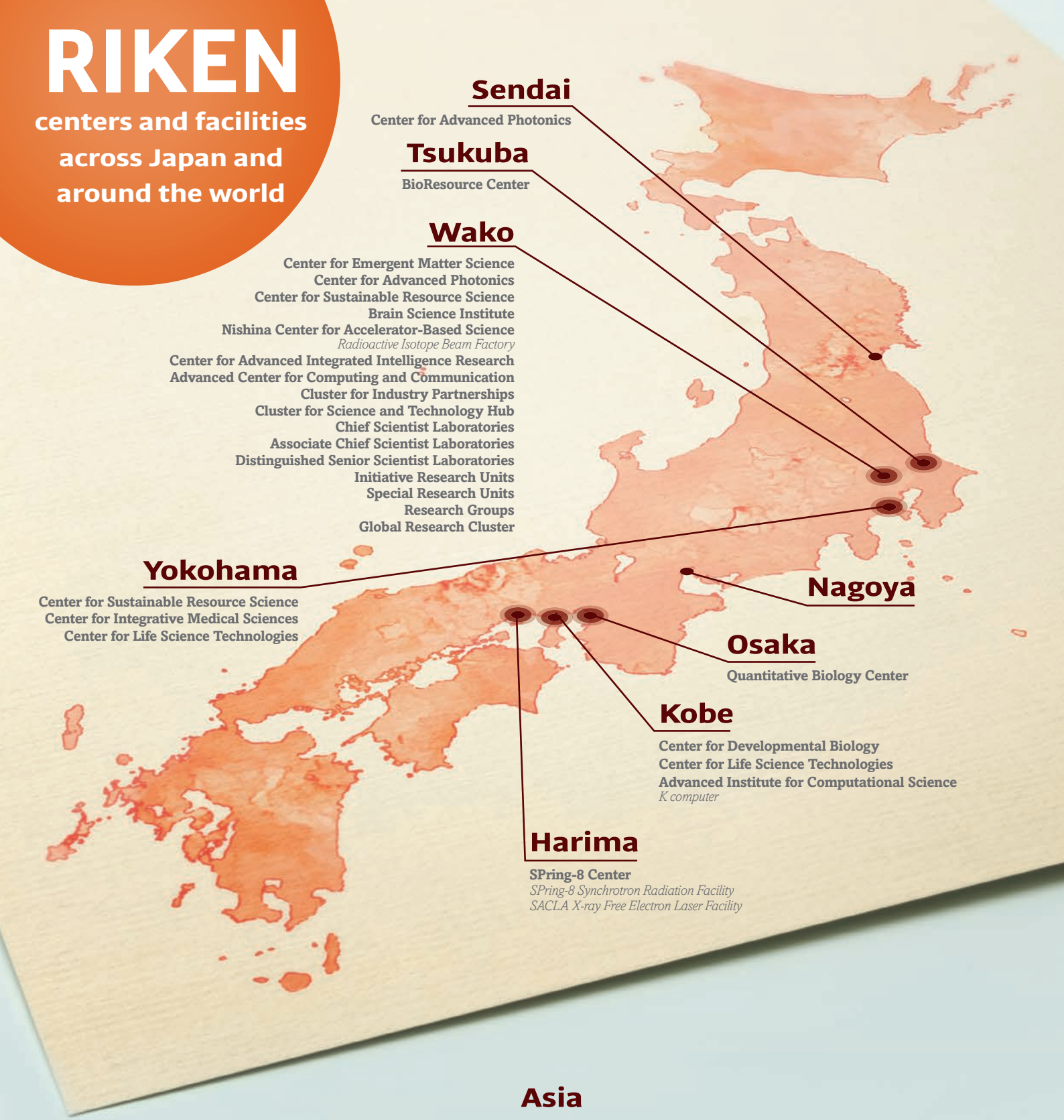

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