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WINTER 2020
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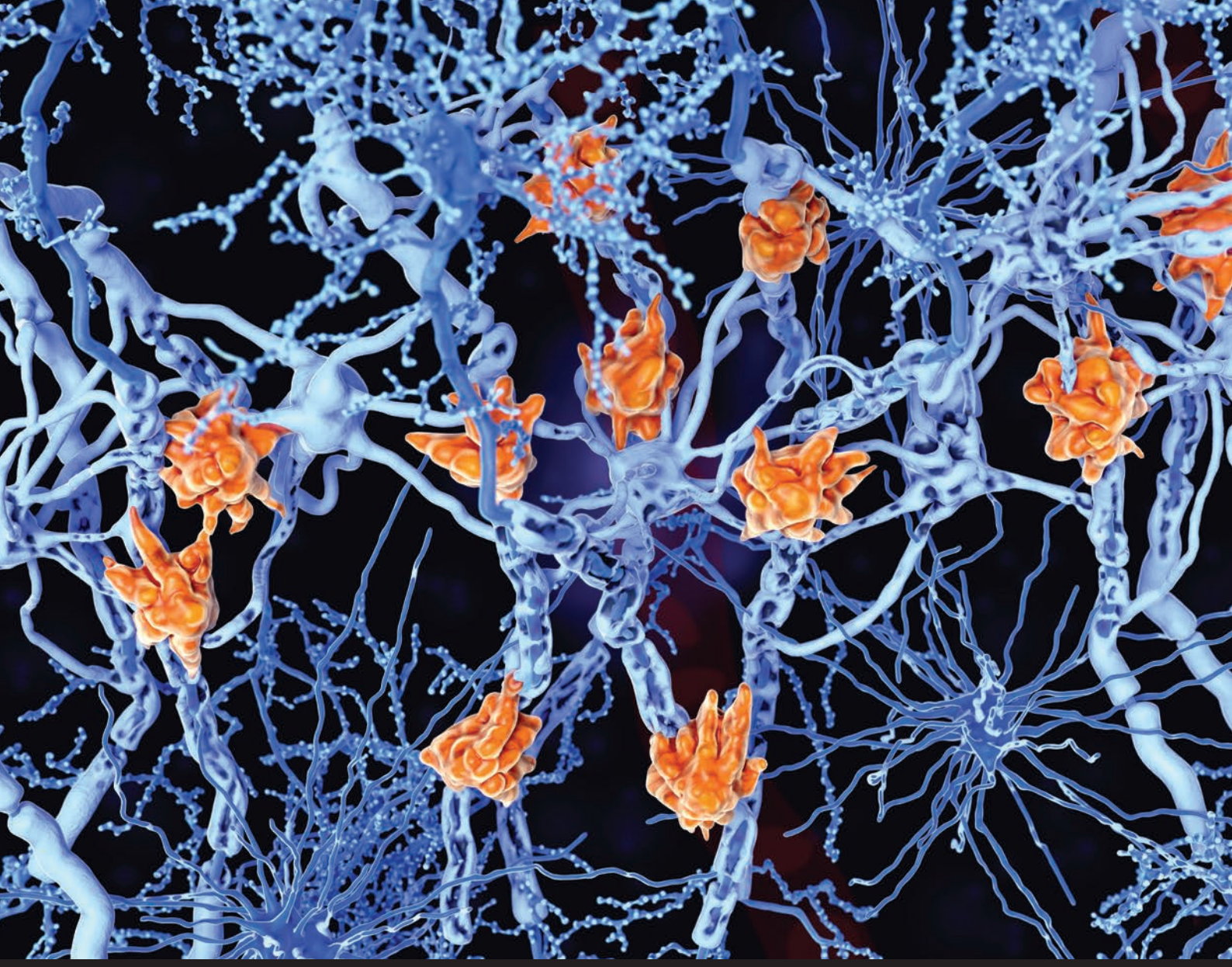
HUMAN HIBERNATION?
Mouse studies hint at possibilities

CURRENT THINKING
Low-energy skyrmion control

MULTIPLE SCLEROSIS
Bacteria pair worsen symptoms

ONE DIRECTION
How magnets manipulate sound

DESIGNER THREADS
Bacteria yield spider silk



▲ **Problematic pair**
Multiple sclerosis (MS) is caused by MS-microglia cells (red) that damage the myelin sheath of neuron axons (blue). In an article published in *Nature* in September 2020, researchers from the RIKEN Center for Integrative Medical Sciences (IMS) looked at how two gut bacteria working together worsened MS.

RIKEN RESEARCH

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

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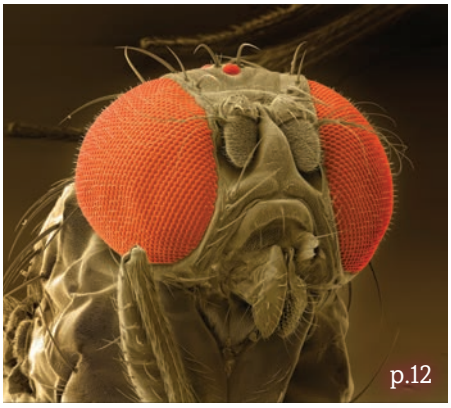
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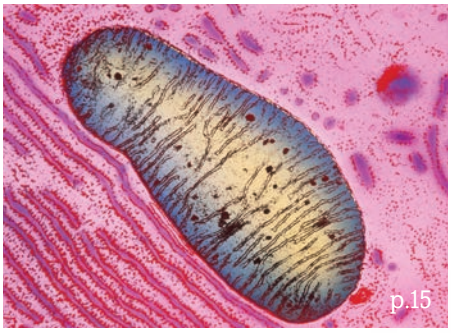
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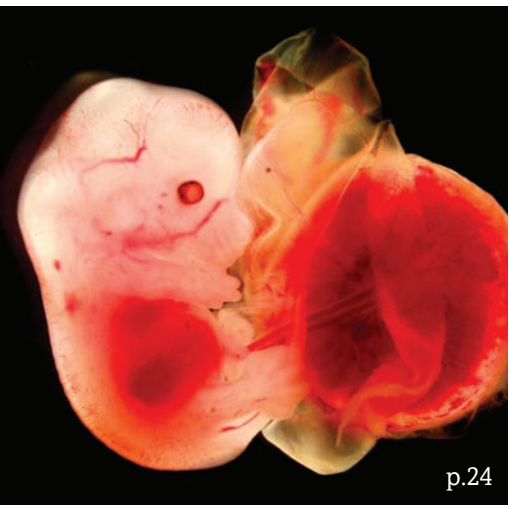
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COVER STORY

Hijacking hibernation: In the last few years, scientists have been able to clarify the energy-saving mechanisms at work in hibernation, culminating in two important papers published in June 2020. But what does this mean for human hibernation?

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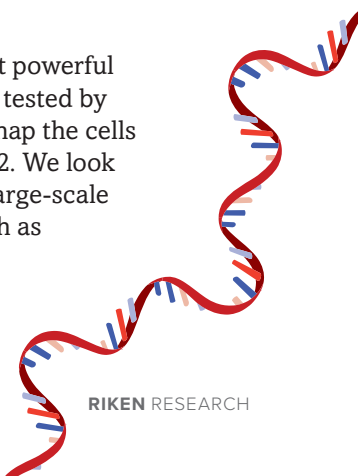

Supporting serendipity in a post-COVID-19 world

Yuko Harayama
Executive Director

In early October we hosted the Global Summit of Research Institute Leaders, a roundtable on academic management that is held annually as part of the Science and Technology in Society Forum. This year, of course, was special, as the summit was held as an online event.

We are learning a great deal about living and working in a world with COVID-19. It's a bit ironic that while we have realized that cooperation is more important than ever, we have also found that collaboration has become more complex.

We have found many tools to help us work together, which is encouraging. However, I think there is something missing. I feel that one important element of meetings and events is the chance for informal communication. These discussions can not only be a wonderful source of inspiration, but can also lead to new research collaborations, even years later. It's a chance to run into people and to maintain friendships. However, our new working style makes those kinds of contact more difficult, and conversations tend to be much more focused. This can make it hard to experience 'serendipity', which is important to science, as it allows us to encounter new ideas beyond the sphere of the scientific community to which we belong.

When thinking about this missing piece, I contemplate diversity, which is part of my responsibility at RIKEN. We often think of diversity in terms of gender or ethnicity, but I think that we should think of it in a broader way, in terms of ways of thinking, feeling and acting. In this new era, we will be required to act more intentionally to compensate for the lack of spaces for serendipity and casual interactions between different types of people and scientific communities. I hope that we can think of ways to promote informal communication among people both within, and among, different institutes. I believe that talking among ourselves will give us fresh ideas on how to move forward and to design new spaces for serendipity.

We would love to hear any ideas from our partners both inside and outside Japan on this and other issues related to our work in this new era.

COVER STORY:
A RIKEN team have produced very strong and lightweight spider silk using photosynthetic bacteria. *Page 22*

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Searching for the secrets of spin

Xiuzhen Yu
Team Leader
Electronic States Microscopy Research Team,
RIKEN Center for Emergent Matter Science

Describe your role at RIKEN.
I lead a team focused on microscopic phenomena, including tiny magnetic vortices called skyrmions and antiskyrmions. These phenomena are found in substances in their solid state, also known as condensed matter materials.

Please briefly describe your current research.
We are using atomic resolution Lorentz transmission electron microscopy to directly observe emergent phenomena in strongly correlated electron systems, including the realization of different topological spin textures.

My research is important to society because…
The ability to manipulate nanometer-scale spin textures is a key to the development of spintronics (next-generation electronic devices that consume very little power). We believe that these spin textures could be used to transmit data and logic in a similar way to the bits in standard computing. The secret to the low power consumption of spin textures is that it can be stimulated using minimal electric charge.

What excites you about your current research?
Our Lorentz transmission electron microscope allows us to study crystal structures and magnetic domain structures that correlate with novel physical properties. It has allowed us to prove that when external stimuli trigger a structural transition in crystals of topological spin textures between tetragonal and hexagonal lattices, there is an effect on these topological spin-textures; they transform between the meron and skyrmion spin states.

How did you join RIKEN?
The director of the Center for Emergent Matter Science, Tokura Yoshinori, is a pioneer of condensed matter physics and I had always wanted to join Tokura's RIKEN group. Luckily, I became part of the Tokura FIRST program as a postdoctoral fellow in 2010. The FIRST program funded young PhD candidates to train with world-leading researchers to encourage them to direct research and development with practical applications.

> *My team was the first to observe skyrmions in a helimagnet and recently observed its antiparticle in real time.*

What do you think has been the most interesting discovery in your field in the last few years?
Although researchers have been hypothesizing about skyrmions for several decades, they were only experimentally proven for the first time in 2009. After that finding, there was a boom in worldwide skyrmion research. In 2010, my team was the first to observe skyrmions in a helimagnet using improved Lorentz transmission electron microscopy under external magnetic fields. We also recently observed its antiparticle, the antiskyrmion, in real time. These findings pave the way for more work toward real-world applications. We are now developing a 3D imaging technique to directly visualize minute topological spin textures for further investigation. ■

Helping regenerative ideas flourish

Cody Kime
Special Postdoctoral Researcher/Cell Reprogramming Team Lead
Laboratory for Retinal Regeneration,
RIKEN Center for Biosystems Dynamics Research

Describe your role at RIKEN.
I have assembled a team focused on creating new cell reprogramming systems to practically address retinal disease and vision loss. I am also a young investigator in the Organoid Project at the RIKEN Center for Biosystems Dynamics Research (BDR). I specialize in the emerging field of synthetic embryogenesis; we are working to generate early embryo-like structures and cells from reprogrammed stem cells.

How did you become interested in your field?
I fell in love with cell reprogramming when I was asked to review Shinya Yamanaka's seminal 2006 and 2007 papers on iPS cells while at university in the United States.

How and when did you join RIKEN?
I joined Masayo Takahashi's Lab for Retinal Regeneration (the Retina Lab) in 2015 as an International Program Associate while enrolled for medical science at the Kyoto University Graduate School of Medicine. Dr Takahashi is doing some of the world's most cutting-edge work on retinal regeneration with iPS cells in collaboration with Dr Yamanaka. I wanted to join RIKEN to work in the developmental biology environment from which my field originated, so I proposed a new cell reprogramming method to treat retinal disease, and the Retina Lab agreed to develop it with me.

What has been your most memorable experience at RIKEN?
The moment that I had concrete evidence that my synthetic embryos could implant and grow in the uterus of a fertile mouse mother was, by far, the most life-changing moment for me at RIKEN. I was shaking and crying as the importance of that fact became real to me.

How has being at RIKEN helped your research?
RIKEN, Dr Takahashi and the Retina Lab have supported my research with funds and enthusiasm for more than five years. The Retina Lab's doctors provide critical medical insight and incredibly rare retina transplant skills. I also performed my most critical embryo transplant tests with Dr Hiroshi Kiyonari of BDR's Lab for Animal Resources and Genetic Engineering (LARGE). Recently, I started working with the Takasato and Kuraku labs at the BDR to expand my skills in single cell RNA sequencing through advanced Next Generation Sequencing/bioinformatics. In Yokohama, Piero Carninci, Erik Arner and their associates at the RIKEN Center for Integrative Medical Sciences have been key collaborators, helping me to train and experiment with completely new bioinformatics and analytical technologies developed at RIKEN.

What do you wish you had known before you came to Japan?
I wish I had known more about the quality of day-to-day life in Japan. Living in Japan has its pros and cons, but it feels very safe and has the highest level of convenience (transportation, food, school, finance, etc.) that I have ever seen. I have a family, so those qualities are incredibly valuable. Also, the quality of raw and prepared foods here is so high that nearly everything is really a treat to eat. ■

Careers at RIKEN
For further information, visit our Careers page:
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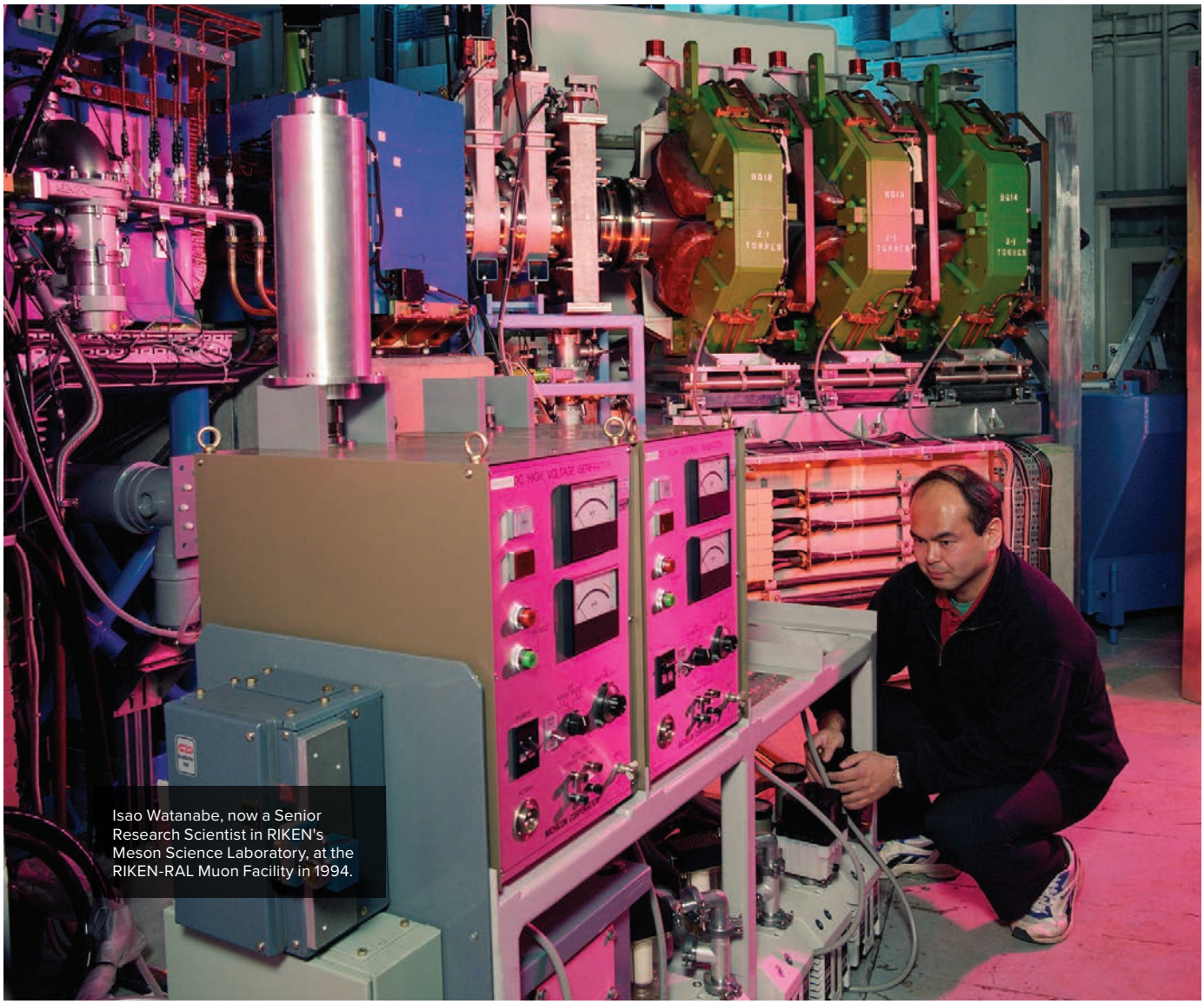


Isao Watanabe, now a Senior Research Scientist in RIKEN's Meson Science Laboratory, at the RIKEN-RAL Muon Facility in 1994.

Celebrating 30 years of RIKEN-RAL

The RIKEN-RAL Muon Facility is one of the largest and longest-standing international science collaborations at the ISIS Neutron and Muon Source, which is located at the Rutherford Appleton Laboratory in Oxfordshire in the United Kingdom. The facility, used for fundamental and applied studies on or using muons, was owned and operated by RIKEN until 2018, after which the operators of the base facility took over. Since then the Oxfordshire-based facility and RIKEN have been collaborating on a significant refurbishment, while a number of users from Japan and the UK continue research partnership work.

September marked 30 years since the first agreement for the facility was signed in 1990. The facility produced first muons in 1994, and was officially inaugurated in April 1995. Since then it has produced more than 500 papers, had researchers from over 90 Japanese institutions come to use it, and stimulated collaborations with a further 40 institutions around the world including agreements between RIKEN and universities in Indonesia, Malaysia and South Korea.

As it is 30 years since the partnership began, and there are 30 days in September, the RIKEN-RAL Muon Facility released one video message of congratulations and one highlight each day during September 2020. "We've created and sustained a very strong international partnership that has produced excellent science over three decades," says Phillip King, Director, RIKEN Facility Office at RAL. "It is an achievement that RIKEN and ISIS can be rightly proud of."

https://www.isis.stfc.ac.uk/Pages/30-years-RIKEN-ISIS.aspx

RIKEN to launch new quantum computing center

By 2021, RIKEN will establish a quantum technology research center, tentatively dubbed the 'Quantum Computer Center' as part of the Japanese government's 'Quantum Technology Innovation Strategy'. At the new center, RIKEN will bring together researchers who study quantum electronics and quantum computers, currently at the RIKEN Center for Emergent Matter Science (CEMS).

With this organizational change, RIKEN will further strengthen the work on the research and development of quantum computers and related basic science, basic technology, hardware and software.

A newly established 'Planning Office for the Quantum Computing Center' is working to develop a management system based on an integrated approach that takes advantage of RIKEN's strengths, as well as promoting cooperation with other research and development agencies and private companies. The office is also working to develop an international platform for quantum computing research that carries out everything from basic research to technology validation, open innovation, intellectual property management, and human resource development with top-class researchers and engineers from Japan and overseas.

Yasunobu Nakamura, Director of the Planning Office for the Quantum Computing Center.

A JAXA supercomputer combined with nowcasting is producing highly accurate rain predictions up to five days in advance.

RIKEN and JAXA collaborate on real-time rainfall forecasts

Researchers from RIKEN, Chiba University, the University of Tokyo and the Japan Aerospace Exploration Agency (JAXA) have used a combination of satellite data and supercomputer simulations to offer five-day rainfall forecasts over the Internet covering the globe. The new system combines a variety of techniques, particularly precipitation nowcasting and numerical weather prediction, to come up with predictions that are accurate on a variety of time scales.

For the project, which began in 2013, the group of researchers began experimenting with ways to make more accurate rainfall forecasts. They began by developing a system—using data assimilation—to incorporate observational data, from weather satellites, into a type of forecasting called nowcasting—where the most recent data is used to predict what will happen in several hours based on a motion tracking technique, without relying on sophisticated computer models. Forecasts of this system for up to 12 hours were made available starting in 2017.

The next step of the group's research was to develop a sophisticated numerical weather prediction model, known as NICAM, and a data assimilation method, called LETKF, which could assimilate the satellite-based precipitation data called GSMaP. This new numerical weather prediction system, running on the JAXA Supercomputer System Generation 2 (JSS2) allows forecasts up to five days in advance.

The latest advance was to combine the forecasts made on the supercomputer with the nowcasting, to create a sophisticated system that relies heavily on nowcasting for the first few hours and then gradually shifting to the supercomputer simulations for forecasts further in the future.

According to Takemasa Miyoshi of the RIKEN Center for Computational Science (R-CCS), who has been leading the project, "Climate change is leading to changes in weather patterns, and it is very important to create more accurate forecasts of rainfall to mitigate damage. We hope that our research using satellite data will be helpful in preventing losses from heavy rain and drought, particularly in the areas where we have limited observing capability."

https://www.riken.jp/en/news_pubs/news/2020/20200820_2

Forecasts are available from RIKEN at: https://weather.riken.jp/index_en.html or from JAXA at https://sharaku.eorc.jaxa.jp/GSMaPxNEXRA/index.htm

Senior Scientist Oleg Gusev from the Laboratory for Transcriptome Technology carried out a live discussion on the mechanisms of the sleeping chironomid.

Yokohama campus holds its annual open day online

Once a year in the early fall, RIKEN's Yokohama Campus opens its doors to members of the public with tours, seminars, hands-on experiences and other special programs designed to increase knowledge of the life sciences and the research work done onsite. Activities are developed, organized and run by RIKEN Yokohama and Yokohama City University Tsurumi Campus, which are situated on the same site.

The 2020 Open Day was held online for the first time in the interest of preventing the spread of COVID-19. Twenty-three different programs took place, with some taking advantage of the unique opportunity to try something new, such as a virtual reality lab tour with a 360-degree camera or live experiment broadcasts via YouTube. In a normal year, RIKEN Yokohama and Yokohama City University Tsurumi Campus Open Day activities bring some 3,000 visitors, mostly from the local community in Yokohama and Kawasaki. The online format attracted more than 3,000 viewers from around Japan, since participants did not need to be physically present to take part.

The Yokohama Campus is home to many foreign researchers. Allen Yi-Lun Tsai, a Special Postdoctoral Researcher in the Dormancy and Adaptation Research Unit at the RIKEN Center for Sustainable Resource Science gave a seminar entitled 'A Canadian researcher in the Far East and the globalization of academia', while Oleg Gusev, a Senior Scientist in the Laboratory for Transcriptome Technology at the RIKEN Center for Integrative Medical Sciences, carried out a live program on the mechanisms of the sleeping chironomid.

The year 2020 also marked the 20th anniversary of the RIKEN Yokohama Campus. In commemoration of this milestone, Kazuo Shinozaki, Special Advisor and Group Director at RIKEN's Center for Sustainable Resource Science, gave a lecture on life science development over the last two decades. A special retrospective website also allows participants to look at the Yokohama Campus and its research results over the past 20 years.

https://www.riken.jp/pr/news/2020/20200907_3

Global Summit of Research Institute Leaders

Multilateral collaboration during the COVID-19 pandemic was the focus of this year's Ninth Global Summit of Research Institute Leaders, held in conjunction with the STS Forum's Annual Meeting. Twenty-six national research institutes leaders from around the world attended online.

Among the issues raised was the fact that the global pandemic represents a 'moment for science' and there is a need to mobilize scientific resources on a global scale both to combat the current epidemic and to prepare for future ones. Participants stressed the need to maintain transparency and trust in science, and to have flexible funding and other mechanisms to ensure that research organizations can swiftly set up multilateral projects and share resources to combat crises. It was resolved the institutes would explore new modes of multilateral collaboration, enabling use of human and other resources most effectively in this unique situation.

RIKEN and the National Institute of Advanced Industrial Science and Technology (AIST) co-hosted the meeting which was co-chaired by RIKEN's President, Hiroshi Matsumoto, and President Matthias Kleiner of the Leibniz Association.

Secondary and tertiary students participate in Fugaku Challenge

Due to the coronavirus, the final round of the annual Supercomputing Contest (SuperCon), a programming competition for high school and technical college students, was cancelled. Instead an event called the 'Fugaku Challenge' was held between September 13 to 20, 2020. At this event, 16 teams from throughout Japan were able to stretch their skills and use the new supercomputer Fugaku to complete a challenge, with every participant receiving a prize.

STEREO PROJECTION OF HIGH RESOLUTION CLOUD SIMULATION
Toshiki Matsushima, RIKEN R-CCS

CHRISTMAS LIGHTS
Thomas Chater, RIKEN CBS

RIKEN IMAGE/VIDEO COMPETITION WINNERS

RIKEN held its first institute-wide image and video competition to find the best images/videos of RIKEN's campuses, facilities and research. Over 90 entries were received from 13 centers/divisions from throughout RIKEN. These entries will be featured in future promotional material.

NUCLEAR PHYSICS

Mystery of particle generation in proton collisions deepened

A consensus among nuclear physicists is challenged by measurements of collisions between protons

A team of RIKEN researchers has challenged the previous consensus regarding particle generation in measurements of collisions between protons, shedding light on the cascade of particles produced when particles from outer space enter the Earth's atmosphere[1].

The Earth is constantly being bombarded by high-energy particles from outer space. These so-called cosmic rays are mostly hydrogen nuclei (that is, protons), but a small percentage of them are nuclei of heavier elements. They collide with nuclei in the upper atmosphere and produce cascades of particles that fall towards the Earth. Since most high-energy particles originate outside our Solar System, such showers provide a valuable window on extreme astrophysical phenomena such as supernova.

"This result necessitates a reexamination of previous theoretical interpretations."

However, it is difficult to study how particles are created, since the force that binds protons in the nucleus and that bind quarks and gluons into protons—the strong nuclear force—is much stronger than the other three fundamental forces. One avenue for exploring these important challenges has involved an attribute of protons called spin. The spin of protons can be artificially aligned by a process called polarization.

Accelerator experiments in the 1970s revealed that subatomic particles known as pions generated near the front of collisions involving polarized protons were not evenly distributed but were strongly skewed in the left–right plane. Experiments using even more energetic protons showed that this left–right asymmetry persisted even at higher energies. A consensus emerged that this asymmetry was caused by direct interactions among the quarks and gluons in the protons.

Now, a team led by Yuji Goto at the RIKEN Nishina Center for Accelerator-Based Science (RNC) has found evidence that challenges this consensus. By looking at gamma rays generated by pion decays at the very forward region of the collision, they found that the left–right asymmetry in neutral pions persists even in that very narrow area, where quarks and gluons do not directly interact.

"We found that the asymmetry continues to exist at a very narrow angle from right in front of the collision, and in fact increases as the angle moves away from zero," says Goto.

An artist's impression of cosmic rays. High-energy particles and radiation from a star in deep space generate a cascade of subatomic particles when they hit the atmosphere. Measurements of collisions between protons by RIKEN researchers shed new light on these cascades of particles

"This result necessitates a reexamination of previous theoretical interpretations."

"We plan to continue our work to understand the mechanism that generates the left–right asymmetry," says Minho Kim, also at RNC. "This is sure to give us insights into cosmic-ray showers and thus help us to understand phenomena that take place in the extreme environment of the Universe." ●

Reference

1. Kim, M. H., Adriani, O., Berti, E., Bonechi, L., D'Alessandro, R., Goto, Y., Hong, B., Itow, Y., Kasahara, K., Lee, J. H. *et al.* Transverse single-spin asymmetry for very forward neutral pion production in polarized $p + p$ collisions at $\sqrt{s}$ = 510 GeV. *Physical Review Letters* **124,** 252501 (2020).

TRANSCRIPTOMICS

Unlocking the key to cell identity and health

RNA plays critical roles in defining cell types and regulating cell functions

Two RIKEN-led studies have identified a core regulatory network that governs cell types in different vertebrate species and uncovered the role that RNA plays in regulating cell identity and function[1,2].

Understanding RNA (the transcriptome) is crucial for advancing biology because although the cells in our bodies share the same DNA, their diversity depends on their RNA make-up. Thus, understanding how RNA is expressed is critical for grasping how each cell type establishes its distinctive function, morphology and behavior by activating specific transcriptional programs.

RIKEN is spearheading research in this area through the FANTOM Consortium, which was established two decades ago.

The first study[1] compared transcriptome data from matching primary cell types in human, mouse, rat, dog and chicken. The team used CAGE, a RIKEN-developed technology based on next-generation sequencing, to profile the transcriptome. Although the transcriptome differed markedly between species for the same cell type, a core regulatory network that defined each cell type was common between species. In general, the genes encoding products involved in RNA biology in the cell nucleus were activated consistently in the same cell type regardless of species.

"We identified genes acting within the nucleus whose usage was conserved for hundreds of millions of years of evolution," says Michiel de Hoon of the RIKEN Center for Integrative Medical Sciences (IMS). "On the other hand, genes that primarily act in communication between cells had diverged and were being used differently in different species."

Using an automated screening platform (shown in this photograph) and CAGE, a RIKEN-developed technology based on next-generation sequencing, RIKEN researchers have profiled the transcriptome of human cells.

The second study[2] looked at human long non-coding RNAs, whose function is poorly understood. Using an automated robotics system, the researchers suppressed nearly 300 long non-coding RNAs in human fibroblast cells. They then used live cell imaging with CAGE to observe how the cells responded at cellular and molecular levels.

"This allowed us to perform a functional analysis of long non-coding RNAs at an unprecedented level," says Jordan Ramilowski of the IMS. "It provides a valuable resource for investigating RNA biology in detail and its potential application to enhancing human health."

The team found that more than 25% of long non-coding RNAs affected cell growth and morphology, as well as cell migration, which is important in cancer. Surprisingly, targeting different isoforms (variants) of the same long non-coding RNA led to profoundly different cellular and molecular phenotypes, giving rise to the enticing conjecture that each isoform produced by a cell might have its own specific regulatory function.

"We're excited to see that long non-coding RNAs, often considered 'junk' when discovered some 15 years ago, are often proven to be functional," says Piero Carninci, also of the IMS. ●

Reference

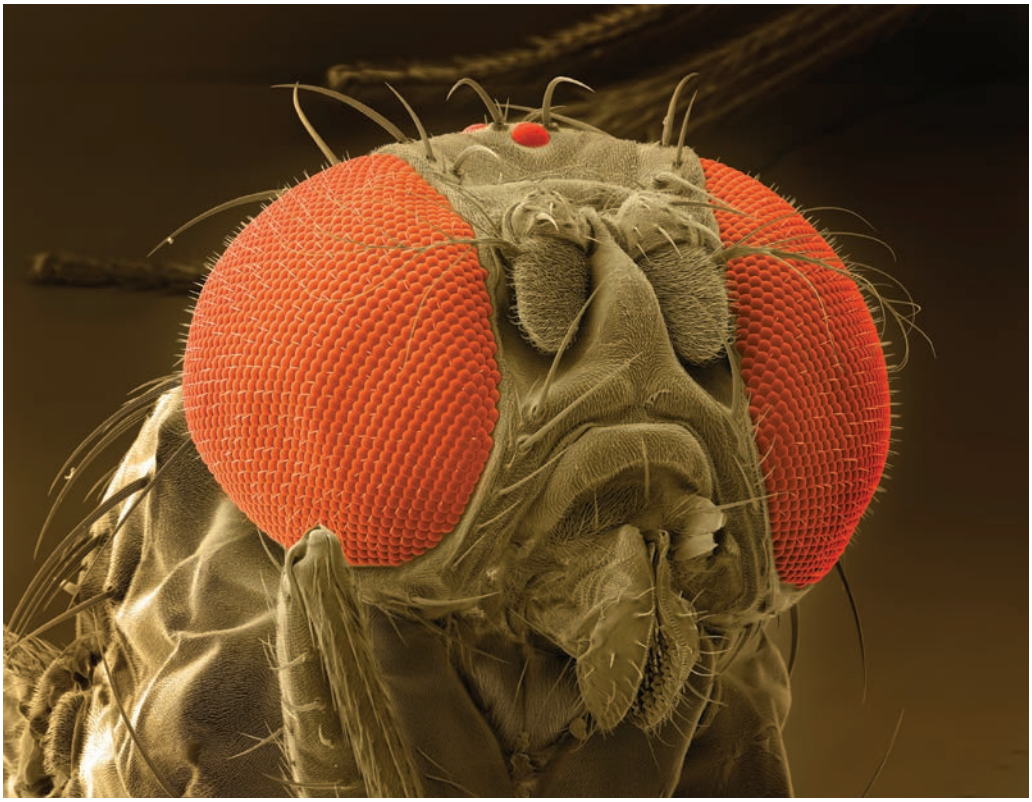
1. Alam, T., Agrawal, S., Severin, J., Young, R. S., Andersson, R., Arner, E., Hasegawa, A., Lizio, M., Ramilowski, J. A., Abugessaisa, I. *et al.* Comparative transcriptomics of primary cells in vertebrates. *Genome Research* **30,** 951–961 (2020).

2. Ramilowski, J. A., Yip, C. W., Agrawal, S., Chang, J.-C., Ciani, Y., Kulakovskiy, I. V., Mendez, M., Ooi, J. L. C., Ouyang, J. F., Parkinson, N. *et al.* Functional annotation of human long noncoding RNAs via molecular phenotyping. *Genome Research* **30,** 1060–1072 (2020).

OLFACTION

How the brain sorts smells

A fly study uncovers how the brain classifies mixtures of odors into broad categories



Colored scanning electron micrograph of the head of a fruit fly. RIKEN neuroscientists have discovered how the fruit fly brain classifies smells into categories.

Three RIKEN neuroscientists have discovered how the fruit fly brain classifies smells into categories[1]. This finding explains how different individuals perceive varying odors similarly.

Animals use their sense of smell to recognize food sources, predators, potential mates and family. Despite odors generally being a mixture of volatile molecules, animals do not recognize each molecule one by one, but rather the entire mixture as a single smell. However, it is not well understood how the brain generates common categories of odors from these mixtures.

The common fruit fly, whose olfactory system has been very well mapped on the neuron level, can recognize and generalize odors. In the fly brain, odor information travels from the primary olfactory center, called the antennal lobe, to the secondary center, called the mushroom body.

The team investigated differences between these two brain regions in the sensory pathway, which required simultaneously measuring the responses from many more neurons than has been done previously. "Characterizing the activity of all 2,000 cells of the mushroom body at once was the biggest technical hurdle," explains Hokto Kazama of the RIKEN Center for Brain Science. "Previous studies had only recorded from less than 5% of them, which was not enough for our purposes." They overcame this problem by developing an algorithm that automatically locates and tracks all the cells over an hour of recording.

Different flies had similar neural expressions of unitary odors in their mushroom bodies

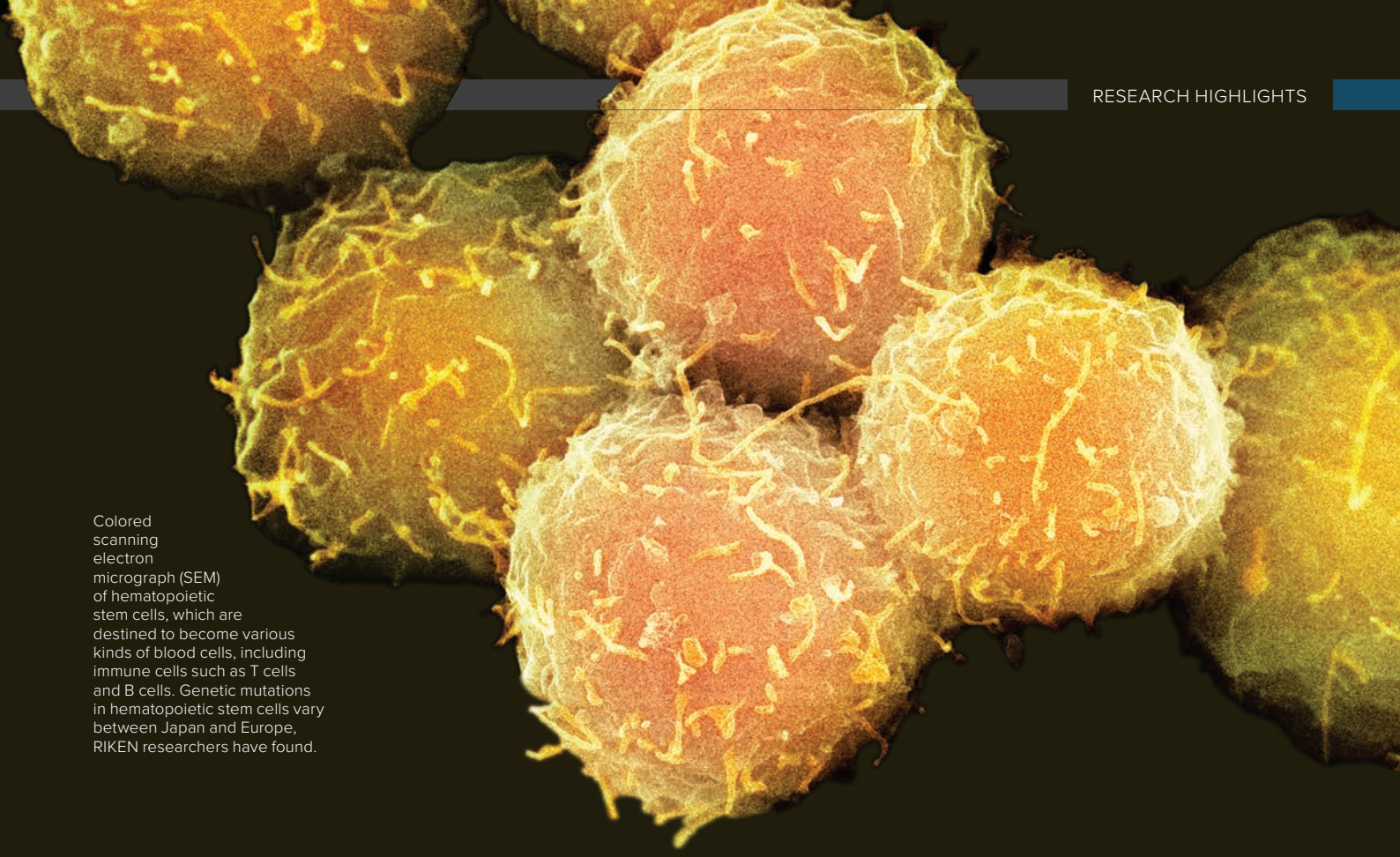
The researchers presented flies with 15 different odors, both individually and in mixtures, and recorded their neuronal responses by imaging the calcium released by activated neurons. They found that clusters of neurons in the mushroom body responded selectively to individual odors, mixtures, or groups of odors. In contrast, neurons in the antennal lobe responded much less selectively. These results imply that the mushroom body integrates input from the antennal lobe and creates distinct odor representations.

The trio was able to reproduce their experimental results using a mathematical model of neural information processing. From this, they discovered that different flies had similar neural expressions of unitary odors in their mushroom bodies, which can explain why different individuals recognize odors similarly.

"The most surprising finding was that the same computation in the olfactory circuit can generate unitary representations for individual odors as well as groups and mixtures of odors," says Kazama. "Because the basic wiring pattern of the olfactory circuit is highly conserved across phyla, we believe that the type of computations we have discovered here may also be found in other more complex animals, such as humans. We are curious to know if these odor object representations remain stable or flexibly change over time as animals experience various odors in their environment." ●

Reference

1. Endo, K., Tsuchimoto, Y. & Kazama, H. Synthesis of conserved odor object representations in a random, divergent-convergent network. *Neuron* **108,** 367–381 (2020).



Colored scanning electron micrograph (SEM) of hematopoietic stem cells, which are destined to become various kinds of blood cells, including immune cells such as T cells and B cells. Genetic mutations in hematopoietic stem cells vary between Japan and Europe, RIKEN researchers have found.

CANCER EPIDEMIOLOGY

Blood cell mutations linked to leukemias are inevitable as we age

Links between blood cell mutations and leukemias have been clarified in a comparison study

Differences in blood cell mutations between Japanese and European populations can explain why the rates of different kinds of leukemias vary between Europe and Japan, a RIKEN-led study has found[1].

Our blood cells are continuously being renewed from a stock of blood stem cells in the bone marrow. These stem cells, called hematopoietic stem cells (HSCs), produce progenitor cells that in turn give rise to the many different kinds of blood cells, including immune cells such as T cells and B cells.

Blood cells that come from the same stem cell or progenitor can be identified from their DNA. For example, all T cells derived from a particular HSC are clones of each other. If the HSC had a mutation, all the T cells in that lineage will possess that mutation, but T cells from different HSCs won't have it.

These types of clonal mutations have been studied in European populations, but Chikashi Terao and his team at the RIKEN Center for Integrative Medical Sciences suspected they might get different results in their older Japanese population of almost 180,000 individuals.

They found that more than 35% of people over 90 years old had clonal mutations. "Our findings strongly suggest that chromosomal alterations in hematopoietic clones are an inevitable event in the very old," says Terao.

Comparisons with data from the UK Biobank revealed that more than 80% of mutations in T-cell lineages occurred in the Japanese population, whereas more than 90% of B-cell lineage mutations occurred in the European sample. These data are consistent with reported cases of leukemia—T-cell leukemia occurs 10 times more often in Japanese people than in Europeans, whereas chronic lymphocytic leukemia, a B-cell-related leukemia, is five times more prevalent in Europeans.

This doesn't imply that mutations selectively occurred in different genes depending on the population. The data only included clonal mutations that survived and replicated enough to be detectable. "We can infer that the advantage of a particular chromosomal mutation differs depending on the genetic and environmental context," Terao explains.

The researchers found genetic components related to the risk of having clonal HSC mutations. The likelihood of a person having one of the critical mutations now or in the future can be estimated by looking for these variations in their DNA.

"Not everyone with these mutations gets cancer," emphasizes Terao. "A simple blood test that you can get at any regular health checkup will be able to identify people at risk of leukemia by checking for clonal HSC mutations. A DNA test based on the blood sample can also identify those at high risk of developing the critical HSC mutations in the future."

Reference

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Machine learning can predict the properties of new materials, thereby saving scientists a lot of time synthesizing them in the laboratory. RIKEN researchers have developed an algorithm that can discover special materials that go against the trend set by other materials.

MATERIALS DISCOVERY

Finding materials that buck the trend

A new algorithm can roam the material landscape looking for materials that offer the best of both worlds

A machine-learning algorithm that can predict the compositions of trend-defying new materials has been developed by RIKEN chemists[1]. It will be useful for finding materials for applications where there is a trade-off between two or more desirable properties.

Artificial intelligence has great potential to help scientists find new materials with desirable properties. A machine-learning algorithm that has been trained with the compositions and properties of known materials can predict the properties of unknown materials, saving much time in the lab.

But discovering new materials for applications can be tricky because there is often a trade-off between two or more material properties. One example is organic materials for organic solar cells, where it is desired to maximize both the voltage and current, notes Kei Terayama, who was at the RIKEN Center for Advanced Intelligence Project and is now at Yokohama City University. "There's a trade-off between voltage and current: a material that exhibits a high voltage will have a low current, whereas one with a high current will have a low voltage."

Material scientists thus frequently want to find 'out-of-trend' materials that buck the usual trade-off. But unfortunately conventional machine-learning algorithms fare much better at spotting trends than discovering materials that go against them.

Now, Terayama and his co-workers have developed a machine-learning algorithm, BLOX (BoundLess Objective free eXploration), that can locate out-of-trend materials.

The team demonstrated the algorithm's power by using it to identify eight out-of-trend molecules with a high degree of photoactivity from a drug-discovery database. The properties of these molecules exhibited good agreement with those predicted by the algorithm. "We had concerns about the accuracy of the calculation but were delighted to see that the calculation was correct," says Terayama. "This shows the potential of computation-driven materials development."

BLOX uses machine learning to generate a prediction model for key material properties. It does this by combining data for materials randomly selected from a materials database with experimental or calculation results. BLOX then uses the model to predict the properties of a new set of materials. From these new materials, BLOX identifies the one that deviates the most from the overall distribution. The properties of that material are determined by experiment or calculations and then used to update the machine learning model, and the cycle is repeated.

Importantly, unlike many previous algorithms, BLOX imposes no restrictions on the range of material structures and compositions that can be explored. It can thus range far and wide in its search for outlying materials.

The team has made BLOX freely available online (http://github.com/tsudalab/BLOX). ●

Reference

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MITOPHAGY

Detecting the death of decrepit mitochondria

A probe that works in both live and fixed cells can give key insights into neurodegenerative disorders

A versatile probe that can detect with pinpoint accuracy the programmed destruction of defective mitochondria—the powerhouses of cells—has been developed by RIKEN researchers[1]. They used it to show that damaged mitochondria in dopamine-producing neurons fail to be destroyed in mice with a condition resembling Parkinson's disease.

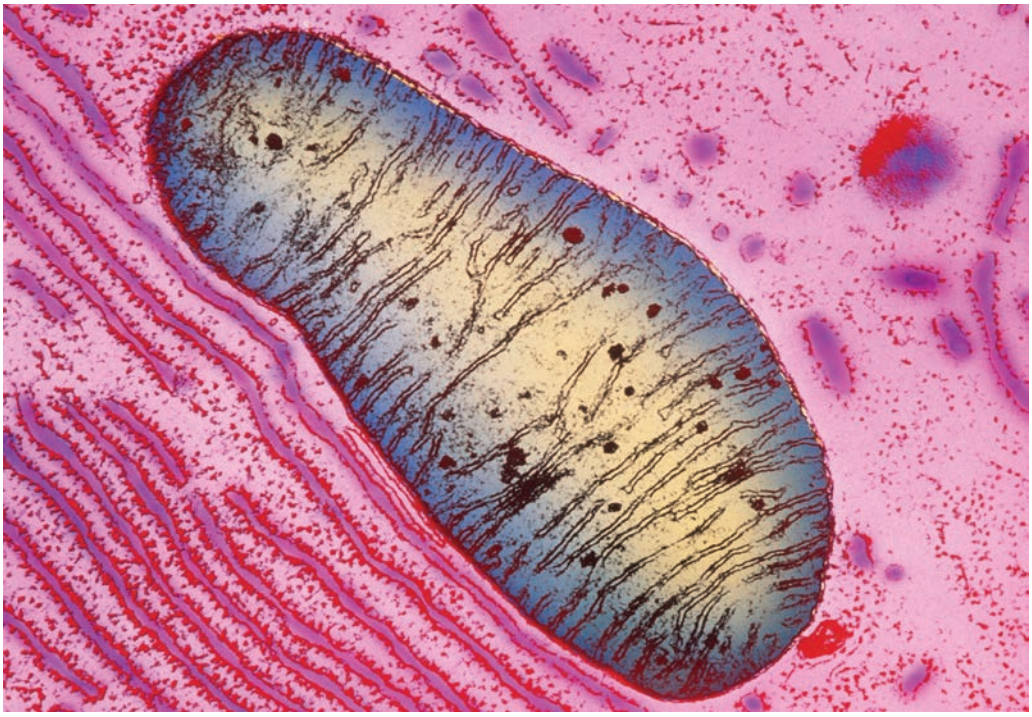
Mitochondria are organelles that generate most of the chemical energy our cells need to function. But when cells are stressed, mitochondria can malfunction and produce highly reactive oxygen radicals, which damage cells. Thus, cells routinely weed out and destroy defective mitochondria by assigning them to lysosomes, which function as the waste-disposal system of cells, breaking down unwanted components.

If this selective elimination of dysfunctional mitochondria—known as mitophagy—fails, it can lead to various diseases. There is thus much interest in monitoring mitophagy in cells.

Fluorescent probes have been developed that can detect mitophagy. But some can only be used in living cells, while others are vulnerable to destructive processes that do not involve lysosomes.

Now, Atsushi Miyawaki of the RIKEN Center for Brain Science and co-workers have developed a new fluorescent probe that can be used in both living and fixed cells and is highlighted specifically in lysosomes.

Their probe contains two parts: one that can withstand the enzymes in the lysosome and another that is destroyed by them. Thus, by monitoring the color of the probe's fluorescence, the researchers could detect when a mitochondrion had entered a lysosome. Unlike their previous mitophagy probe, the new probe is sensitive to the degrading enzymes in lysosomes and acidity, so it works even in fixed cells where lysosomes are no longer acidic.



Colored transmission electron micrograph of a single mitochondrion in a human pancreas cell. RIKEN researchers have developed a fluorescent probe that can detect the programmed death of defective mitochondria in the lysosomes.

The team used the probe to investigate Parkinson's disease—a neurodegenerative disease that causes shaking, muscle stiffness and progressive difficulties with movement.

Using a mouse model of Parkinson's disease, the researchers found that neurons that produced the neurotransmitter dopamine failed to eliminate defective mitochondria, but other neurons that did not produce dopamine did. Since Parkinson's disease is characterized by a dopamine deficiency in the brain, this suggests that the inability of dopamine-producing neurons to perform mitophagy could be a major factor in the disease.

By collaborating with researchers from the pharmaceutical company Takeda, Miyawaki's team identified a compound that can induce the destruction of damaged mitochondria. Such compounds could help to treat Parkinson's disease in the future.

The probe is promising for advancing research into other diseases. "Since many other neurodegenerative disorders involve mitophagy, our probe can contribute to their study," says Miyawaki. "Furthermore, diseases in other organs involve oxidative stress and hence mitophagy. We're currently using our probe to look at heart disease." ●

Reference

1. Katayama, H., Hama, H., Nagasawa, K., Kurokawa, H., Sugiyama, M., Ando, R., Funata, M., Yoshida, N., Homma, M., Nishimura, T. *et al.* Visualizing and modulating mitophagy for therapeutic studies of neurodegeneration. *Cell* **181,** 1176–1187.e16 (2020).

SOCIAL NEUROSCIENCE

Starved fish are hungry for victory

Hunger activates a pathway in the brain of a zebrafish that makes the fish less likely to give up in a fight against another zebrafish

Depriving a zebrafish of food for six days boosts its chances of winning a fight against a well-fed fish because starvation activates a certain pathway in its brain, neuroscientists at RIKEN have shown[1]. This finding could well have implications for other animals and humans since the neural pathway is conserved across species.

Social animals, including fish, cats and primates, often fight to establish the social hierarchy of a group and hence who gets first pick of limited resources such as food and mates. Neuroscientists are interested in uncovering how networks in the brain regulate such social behaviors. Zebrafish make good subjects for these studies because they display well-defined fighting behaviors.

If asked to bet on the outcome of a fight between a well-fed zebrafish and one that hadn't eaten in six days, most people would probably put their money on the well-nourished fish. But a study by a RIKEN-led team has found that in 75% of fights, the hungry zebrafish emerges as the victor.

In an earlier study, the team had discovered that a zebrafish would tend to win fights when a specific pathway originating in a brain structure called the habenula was activated, whereas it would have a propensity to lose fights if another pathway in the same region was activated.

Now, Haruna Nakajo and Hitoshi Okamoto of the RIKEN Center for Brain Science, together with their co-workers, have shown that starving zebrafish activate the 'winner pathway' in the habenula, making them less likely to give up during a contest with another fish.

There is logic to this finding. "Hungry fish are more motivated to obtain food," explains Nakajo. "And since winners of fights secure more resources such as food, it makes sense that starved fish try harder to win fights."

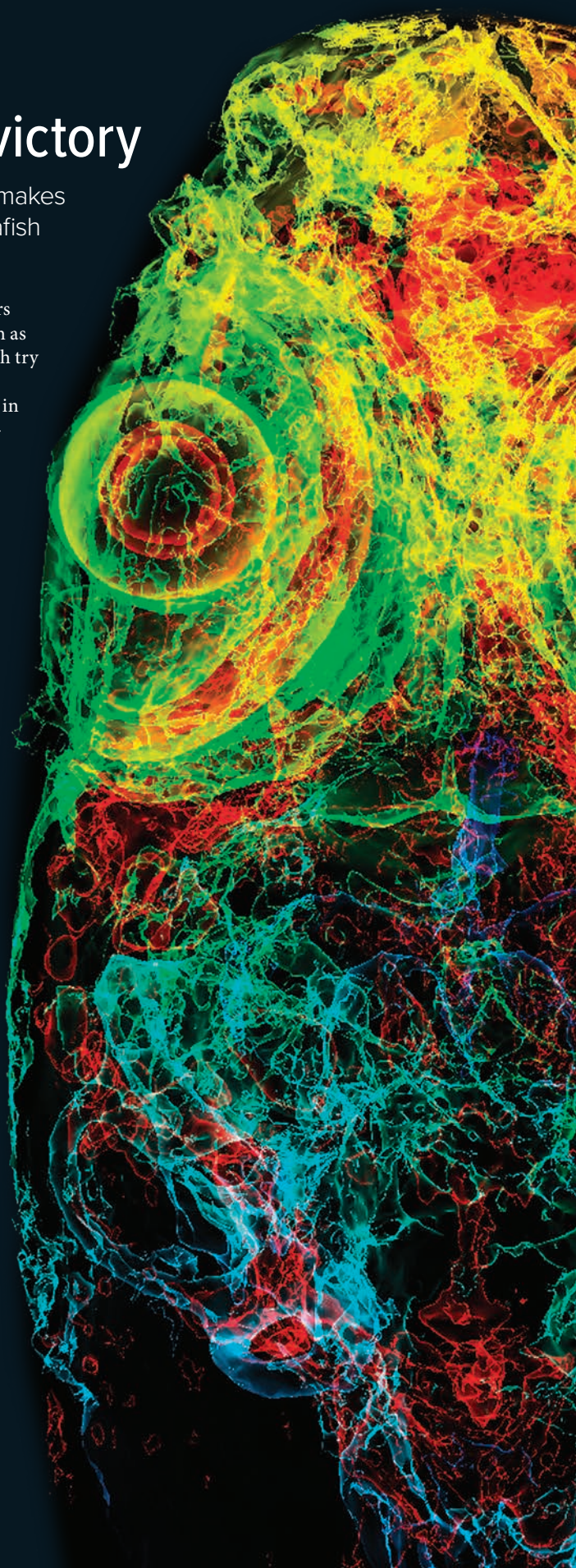
Hunger may cause similar effects in people too. "The habenula–interpeduncular pathway is evolutionary conserved from fish to humans," says Nakajo. "So we think that similar functions are conserved even in humans."

One surprise was that hunger activated the winner pathway in the habenula via a neuropeptide called orexin. Orexin is well known for its role in regulating sleep and appetite, but it had not previously been implicated with social behaviors such as fighting. It was also the first time that orexin has been shown to regulate the expression of specific genes, Nakajo says.

The team is now intending to investigate the molecular mechanisms behind this hunger-activated pathway.

Reference

1. Nakajo, H., Chou, M.-Y., Kinoshita, M., Appelbaum, L., Shimazaki, H., Tsuboi, T. & Okamoto, H. Hunger potentiates the habenular winner pathway for social conflict by orexin-promoted biased alternative splicing of the AMPA receptor gene. *Cell Reports* **31,** 107790 (2020).



Colored 3D reconstructed micro-computed tomography scan of the head of a zebrafish. RIKEN researchers have shown that hunger activates a neural pathway in the habenula that makes a fish less likely to give up in a conflict with another fish.

ATTOSECOND SCIENCE

Pulses that are short on time, but high on energy

Ultrashort, energetic pulses can now be generated by combining three highly controlled pulses

A way to reliably produce x-ray pulses that are both incredibly short and have high energies has been demonstrated by physicists at RIKEN[1]. This will allow researchers to investigate ultrashort phenomena that involve multiple photons.

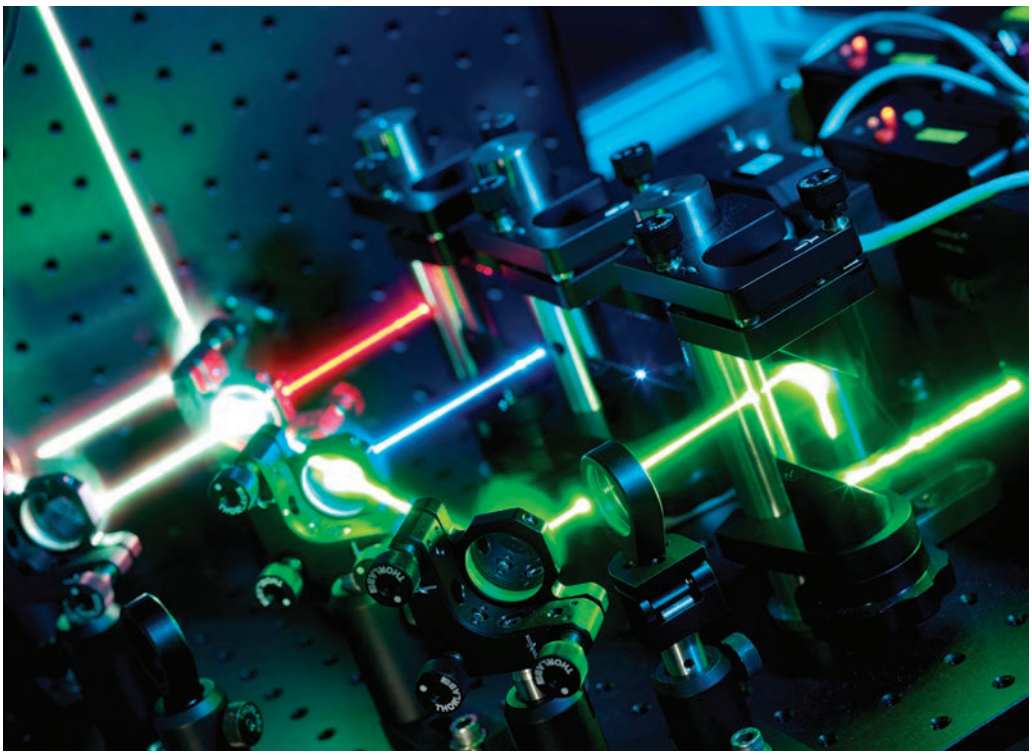
It is hard to appreciate how short an attosecond is. Each second is made up of a quintillion (10^{18}) attoseconds; the equivalent number of seconds would be more than twice the current age of the Universe. Light can travel from the Earth to the Moon in about 1.25 seconds, but it covers a mere 0.3 nanometers in an attosecond.

When scientists produced laser pulses on the timescale of several hundred attoseconds in 2001, they opened up new vistas to researchers. In particular, it became possible to probe and control the motion of electrons in molecules.

Pulse durations have dropped to a few tens of attoseconds today, but one limitation is that the pulses have low energies. Producing more-energetic attosecond pulses will allow researchers to explore nonlinear phenomena that involve two or more photons.

Now, Eiji Takahashi of the RIKEN Center for Advanced Photonics and his co-workers have produced high-energy pulses in the attosecond regime.

"To the best of our knowledge, the combination of the 240-nanojoule energy and 170-attosecond duration of our isolated attosecond pulses represents a new record for studies using synthesizers or other techniques. Moreover, despite being an attosecond pulse, its peak power exceeds a gigawatt," says Takahashi.



In a fluorescence microscopy experiment (shown here), white light is split into its component colors. RIKEN scientists have done the reverse—they have combined three laser pulses of different wavelengths using a high-energy waveform synthesizer to generate high-energy pulses in the attosecond regime.

The team produced these pulses by combining, or synthesizing, three pulses with wavelengths ranging from red light to infrared light. Importantly, they were able to achieve precise control over the timing and shape of these pulses, allowing the team to both optimize and accurately reproduce them. The researchers then used the combined pulse to produce an attosecond pulse using a nonlinear process known as high-order harmonic generation in argon gas.

To realize the stability they needed, the team developed a stabilized, high-energy amplifier for driving their synthesizer. This high-energy laser amplifier stretches a pulse in duration, amplifies it, and then compresses it with actively stabilizing carrier-envelope phases. "The development of this amplifier was one of the key achievements in this study," says Takahashi.

The team anticipates that their method will accelerate research in the attosecond regime. In particular, it will be useful for probing electrons using attosecond spectroscopy. "We're convinced our method will pave the way to realize nonlinear attosecond-science experiments in the near future," says Takahashi. "This will certainly catalyze research on ultrafast phenomena and nonlinear optics."

Reference

1. Xue, B., Tamaru, Y., Fu, Y., Yuan, H., Lan, P., Mücke, O. D., Suda, A., Midorikawa, K. & Takahashi, E. J. Fully stabilized multi-TW optical waveform synthesizer: Toward gigawatt isolated attosecond pulses. *Science Advances* **6,** eaay2802 (2020).

AUTOIMMUNITY

Tag team worsens multiple sclerosis symptoms

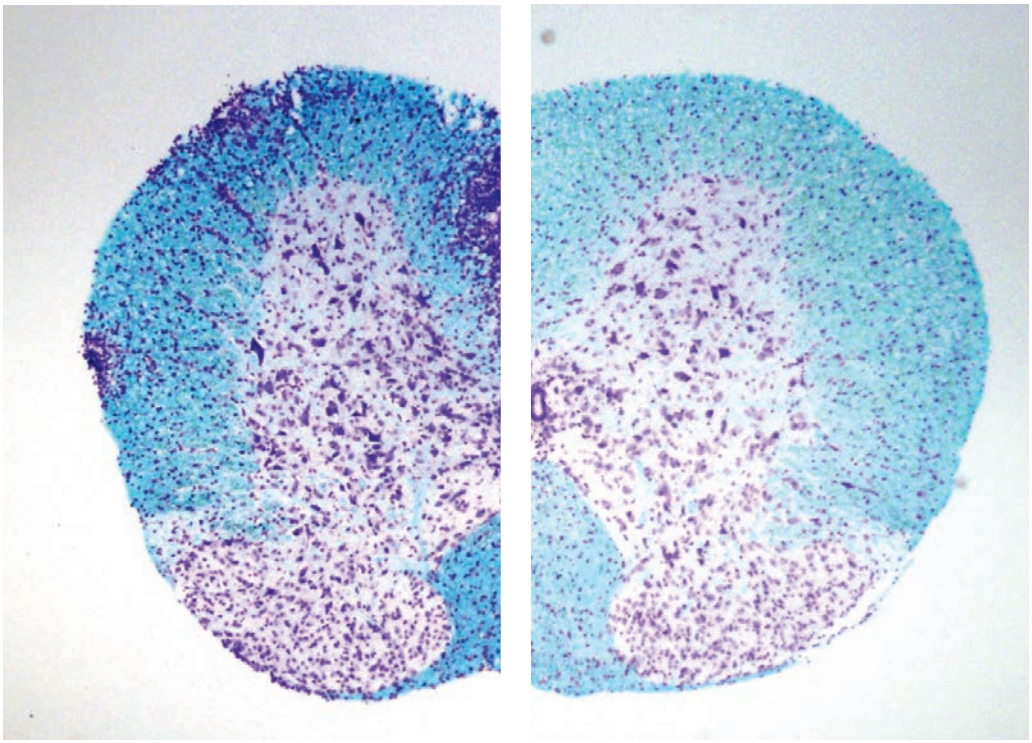
Two bacteria working in tandem intensify symptoms in mouse model of multiple sclerosis

The discovery by RIKEN researchers that two gut bacteria worsen symptoms in mice with a multiple-sclerosis-like condition could lead to new treatments for the debilitating disorder[1].

Multiple sclerosis is an autoimmune disease in which the immune system attacks the myelin membrane that protects nerve cells in the brain and spinal cord. This damage causes symptoms such as numbness, weak muscles, tremors, and the inability to walk. Gut microorganisms are known to affect the symptoms of multiple sclerosis, but just how bacteria in the intestines affect myelin in the brain and spinal cord has been a mystery.

Now, a team led by Hiroshi Ohno at the RIKEN Center for Integrative Medical Sciences (IMS) has investigated this connection using mice that experience similar demyelination of the spinal cord due to autoimmune attacks by T cells that produce a certain cytokine.

The antibiotic ampicillin both reduced demyelination in these mice (see image) and prevented the activation of a particular type of T cell that attacks a protein called myelin oligodendrocyte glycoprotein (MOG), which helps myelin stick to neurons. When the researchers took immune cells from the small intestines and other regions and measured their cytokine production in the presence of MOG, cytokine production was reduced only by ampicillin and only when the T cells came from the small intestine.



Stained spinal-cord sections from control (left) and ampicillin-treated (right) mice models of multiple sclerosis. The ampicillin-treated sample shows reduced demyelination.

The team next investigated which bacteria in the small intestine activate MOG-specific T cells, which then attack myelin. Because only ampicillin reduced symptoms in the model mice, they looked for gut microbes that were almost completely deleted only in ampicillin-treated mice. Just one bacterium fitted the bill—a strain called OTU002. The team found that mice lacking all bacteria except OTU002 had more severe symptoms than germ-free mice.

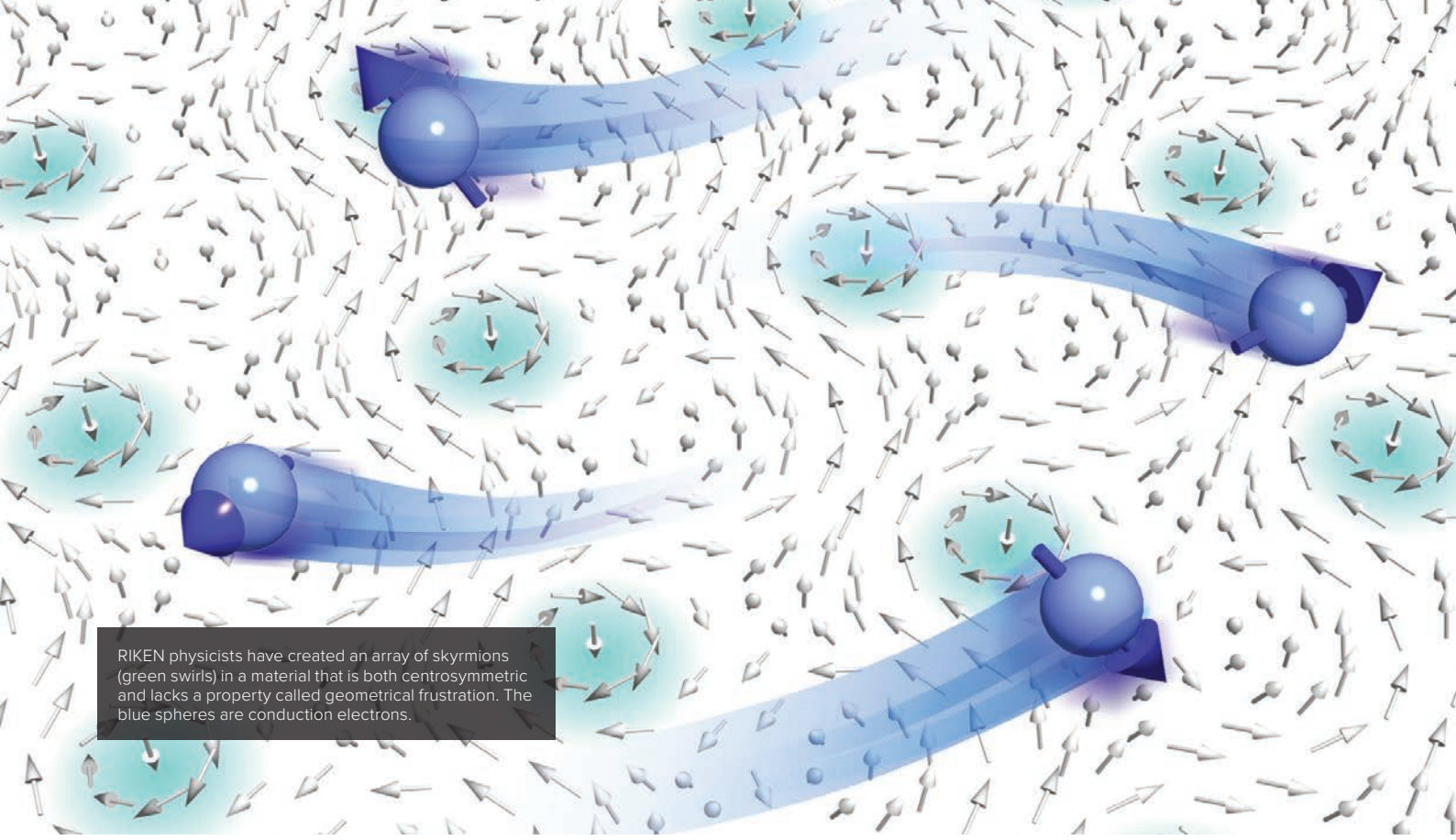
"But there was a problem," says Eiji Miyauchi, also of IMS. "Symptoms in the OTU002-only mice were not as bad as those in the regular model mice."

The team hypothesized that another bacterium was cross-reacting with MOG-specific T cells, mimicking the location on MOG that the T cells recognize. Shotgun genome sequencing revealed that a protein expressed by the bacterium *Lactobacillus reuteri* resembles a region of MOG, and when tested, it weakly activated MOG-specific T cells. Mice co-colonized with *L. reuteri* and OTU002 had more severe symptoms than OTU002-only mice and just as severe symptoms as the original model mice, indicating that the results are devastating when these two bacteria work together.

While these results provide fresh hope for effective treatments for multiple sclerosis, further studies on human microbes and autoreactive T cells are needed since humans have different gut microbes and T cell-binding locations on myelin than mice. ●

Reference

1. Miyauchi, E., Kim, S.-W., Suda, W., Kawasumi, M., Onawa, S., Taguchi-Atarashi, N., Morita, H., Taylor, T. D., Hattori, M. & Ohno, H. Gut microorganisms act together to exacerbate inflammation in spinal cords. *Nature* **585,** 102–106 (2020).



RIKEN physicists have created an array of skyrmions (green swirls) in a material that is both centrosymmetric and lacks a property called geometrical frustration. The blue spheres are conduction electrons.

SKYRMIONS

Skyrmions without the frustration

Tiny magnetic swirls can form in a broader range of materials than have been used in previous experiments

A restriction on the kind of materials that can host nanoscale magnetic whirlpools known as skyrmions has been lifted by experimentalists at RIKEN[1]. This will significantly expand the range of the materials skyrmions can be created in, making them even more attractive for use in low-power data-storage devices.

First discovered a little over a decade ago, skyrmions are highly promising for application in low-power, high-density storage and transfer of data. They are attracting increasing interest, and there are predictions that the first skyrmion-based commercial devices will start appearing in about ten years.

However, until recently, skyrmions had been observed only at interfaces and in a special class of materials whose crystal structures lacked a center of symmetry. Last year, a RIKEN-led team succeeded in creating them in a material that had a center of symmetry, increasing the range of materials that could host skyrmions. They were able to do this because their material possessed a property known as geometric frustration, where the geometry of a material prevents the system from adopting the lowest possible energy state at low temperatures.

Now, Shinichiro Seki and Nguyen Duy Khanh of the RIKEN Center for Emergent Matter Science and their co-workers have gone a step further and shown that skyrmions can be created even in centrosymmetric materials that lack geometric frustration. They created a square array of skyrmions that are less than 2 nanometers in diameter—the smallest skyrmions created to date in a single material—in the centrosymmetric tetragonal magnet $GdRu_2Si_2$.

This demonstration expands the range of materials that skyrmions can be hosted in even more. "Rare-earth intermetallic compounds are a very broad class of materials," says Nguyen. "Our finding means that skyrmions can be created in many compounds—they're no longer restricted to a very limited class of material."

Since geometric frustration kicks in only at very low temperatures, the finding that it is not needed for generating skyrmions raises the possibility that they could be formed at room temperature, which will be a huge boost for their use in applications. "We're now looking for a new system that has a magnetic ordering temperature at close to room temperature or even above," says Nguyen.

After a fortuitous encounter at a conference last year, the team has been collaborating with theorists at the University of Tokyo to uncover the mechanism that allows skyrmions to be created without geometric frustration. "We were very surprised to learn that they are working on the problem and that their theoretical results agree very well with our experimental results," Nguyen notes.

Reference

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SKYRMIONS

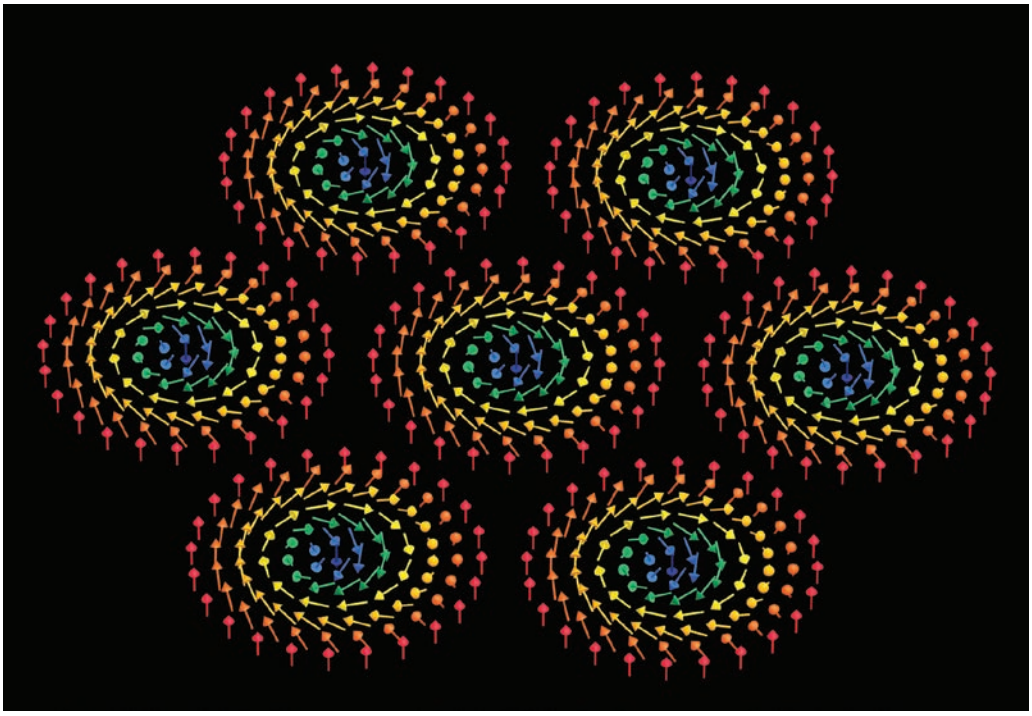
Gently nudging skyrmions along

A low electric current is all that is needed to manipulate tiny magnetic whirlpools

In a first step that could lead to the development of much more energy-efficient memory devices, a RIKEN team has manipulated and tracked the movement of individual skyrmions—tiny magnetic vortices—using electric currents that are about a 1,000 times weaker than those used in conventional hard disk drives[1].

Skyrmions are both tiny—generally tens of nanometers in diameter—and robust. It is thus possible to cram multitudes of them into a minuscule area, while it is difficult to accidentally erase them. Both properties make skyrmions highly attractive as building blocks for next-generation computer memories and logic devices.

However, their small size causes skyrmions to bunch together in crystalline lattices (see image), which require hefty electric currents to move around. These large currents would make devices less energy efficient as well as generate undesirable heat. Researchers have been trying to isolate individual skyrmions because they are much easier to manipulate, but this has proved difficult to achieve until now.



Skyrmions tend to group together and form lattices, which are difficult to move. RIKEN researchers have succeeded in developing a method that can move them using electrical currents.

"We hope that this will help the development of more energy-efficient racetrack memory"

A team led by Xiuzhen Yu of the RIKEN Center for Emergent Matter Science has now succeeded in using very small electric currents to isolate and manipulate individual skyrmions that were 80 nanometers in diameter.

"We have demonstrated that it is possible to manipulate and track individual skyrmions and its crystal using a relatively low electric current," says Yu. "We hope that this will help the development of more energy-efficient racetrack memory as well as neuromorphic computing."

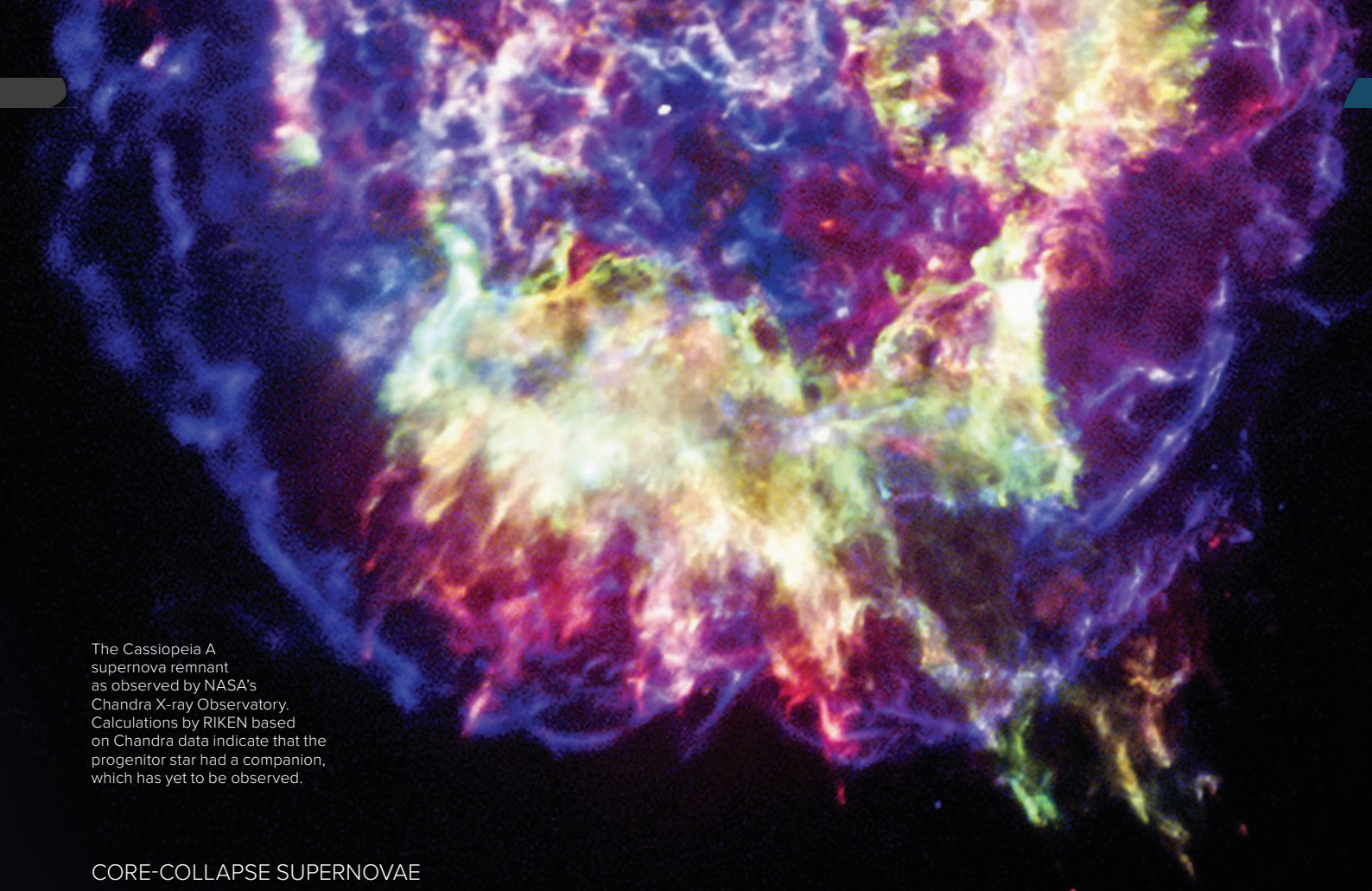
The researchers used a thin film of a magnetic material whose magnetic domains were organized in a spiral arrangement. This unusual magnetic structure facilitated the manipulation of skyrmions since their magnetic moments followed the helical patterns.

By adding a square notch to the film, the researchers were able to confine a spin current at a point near a corner of the notch. They then experimented with applying pulses of electric current in one direction and then the opposite direction while monitoring the results with a Lorentz transmission electron microscope. This allowed Yu and her team to locate a point on the film where they could isolate individual skyrmions. They recorded the skyrmion movement using an emergent phenomenon known as the topological Hall effect.

The team is now planning to enhance their device to make it more amenable to real-life applications. "By developing a bilayer system that can host combined skyrmions, we plan to further improve the device to enable it to be used in practical applications," says Yu. ●

Reference

1. Yu, X. Z., Morikawa, D., Nakajima, K., Shibata, K., Kanazawa, N., Arima, T., Nagaosa, N. & Tokura, Y. Motion tracking of 80-nm-size skyrmions upon directional current injections. *Science Advances* **6,** eaaz9744 (2020).



The Cassiopeia A supernova remnant as observed by NASA's Chandra X-ray Observatory. Calculations by RIKEN based on Chandra data indicate that the progenitor star had a companion, which has yet to be observed.

CORE-COLLAPSE SUPERNOVAE

Supernova had a missing companion star

A fresh analysis of x-ray data suggests that one of the best known supernovae had a companion star

The massive star that exploded to form the supernova known as Cassiopeia A most likely had a companion star that has yet to be spotted, a spectroscopic analysis by RIKEN astrophysicists suggests[1]. This will provide fresh impetus to efforts to locate the companion.

Supernovae are among the most violent events in the Universe. They occur when a massive star exhausts its supply of fuel and its core collapses under the huge gravitational pull of the star.

While theories have been put forward to explain the processes involved, they are yet to be corroborated by observations. "The explosion mechanisms of massive stars are a long-standing problem in astrophysics," notes Toshiki Sato of the RIKEN High Energy Astrophysics Laboratory. "We have theoretical scenarios, but we would like to confirm them by observations."

An important parameter in studying the evolution of stars is the ratio of heavier elements to the lightest element, hydrogen—a ratio known as the metallicity. Shortly after the Big Bang, there were only three elements: hydrogen, helium and lithium. But with each succeeding generation of stars, heavier elements have become increasingly abundant.

The starting metallicity of a star is an important factor in determining its fate. "The initial metallicity affects the way a star dies," says Sato. "So it is very important to investigate the initial metallicity to understand how a star exploded."

Now, Sato and his co-workers have determined the initial metallicity of Cassiopeia A for the first time. They did this by combining data from the 13 observations of the supernova by the Chandra X-ray Observatory over the past 18 years to find the ratio of the elements manganese to chromium at the time of the explosion. From this ratio, they estimated that the initial metallicity of Cassiopeia A was lower than that of the Sun.

Cassiopeia A is known as a stripped envelope supernova because its outer layer of hydrogen has been stripped away. But the low initial metallicity implies that the stellar wind would have been too weak to strip the hydrogen layer away. The only explanation that remains is that it was removed by a companion star—a surprising finding since no indication of a companion star has been found to date.

"The reason it hasn't been observed may be because it is a compact, faint object such as a black hole, a neutron star or a white dwarf," says Sato. "This finding thus provides a new direction for understanding the origin of Cassiopeia A. We hope it will lead to a significant advance in understanding the mechanism of supernova explosions."

Reference

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SPIDER SILK

Modified bacteria weave spider silk

Genetically modifying a bacterium that lives in seawater causes it to produce high-quality spider silk

A new era in which photosynthetic biofactories stably output spider silk could be realized as a result of a RIKEN team producing spider silk from photosynthetic bacteria[1].

Spiders produce amazingly strong and lightweight threads called draglines, which are made from silk proteins. In addition to being tough and lightweight, silks from arthropod species are biodegradable and biocompatible, making them attractive for various applications.

The fibers produced in the bacteria were very similar to those produced naturally by spiders

"Spider silk has the potential to be used in the manufacture of high-performance and durable materials such as tear-resistant clothing, automobile parts and aerospace components," says Choon Pin Foong of the RIKEN Center for Sustainable Resource Science (CSRS). "Its biocompatibility makes it safe for use in biomedical applications such as drug-delivery systems, implant devices and scaffolds for tissue engineering."

But getting enough of the protein is difficult because a single spider produces a small amount and it is difficult to breed large numbers of spiders. Consequently, attempts have been made to produce artificial spider silk in a variety of species.

A team led by Keiji Numata of the CSRS focused on the marine photosynthetic bacterium *Rhodovulum sulfidophilum*—an ideal bacterium for establishing a sustainable biofactory because it grows in seawater, requires carbon dioxide and nitrogen in the atmosphere, and uses solar energy, all of which are abundant and inexhaustible.

The researchers genetically engineered the bacterium to produce the protein MaSp1, the main component of the *Nephila* spider dragline, which is thought to be important for the strength of spider silk. By optimizing the gene sequence that was inserted into the bacterium's genome, the researchers were able to maximize the amount of silk produced.

They also found that a simple recipe—artificial seawater, bicarbonate salt, nitrogen gas, yeast extract, and irradiation with near-infrared light—allowed *R. sulfidophilum* to grow well and produce the silk protein efficiently. Further observations confirmed that the surface and internal structures of the fibers produced in the bacteria were very similar to those produced naturally by spiders.

"Our current study shows the initial proof of concept for producing spider silk in photosynthetic bacteria. We are now working to mass produce spider-silk dragline proteins at higher molecular weights in our photosynthetic system," Numata says. "The photosynthetic microbial cell factories, which produce bio-based and biodegradable materials via a carbon neutral bioprocess, could help us in accomplishing some of the Sustainable Development Goals adopted by the United Nations, such as Goal #12 'Responsible Production and Consumption' and Goal #13 'Climate Action'. Our results will help provide feasible solutions for energy, water and food crises, solid-waste problems and global warming." ●

By genetically engineering bacteria, RIKEN researchers have succeeded in getting it to produce MaSp1, the main component of the dragline of the *Nephila* spider (shown here).

Reference

1. Foong, C. P., Higuchi-Takeuchi, M., Malay, A. D., Oktaviani, N. A., Thagun, C. & Numata, K. A marine photosynthetic microbial cell factory as a platform for spider silk production. *Communications Biology* **3,** 357 (2020).

PARASITIC PLANTS

Plant defence provides opening for parasite

A parasitic plant exploits a molecular mechanism that plants use to keep bacteria out

New strategies for combating the beautiful but devastating crop parasite witchweed (Striga) could come from a link RIKEN researchers have discovered between the parasite and the defense responses in plants[1].

Annual global losses due to Striga parasites attacking crops such as maize, sugarcane and sorghum amount to well over a billion US dollars. All varieties of the parasite sense DMBQ, which belongs to a class of aromatic compounds widely found in plants known as quinones. Striga then forms appendage-like organs that it uses to invade the host and siphon off water and nutrients.

Ken Shirasu and his co-workers at the RIKEN Center for Sustainable Resource Science want to find ways to prevent crop losses from the parasite by developing treatments or Striga-resistant crops. This requires understanding the molecular events in the parasitic plant's response to quinones. "We needed to answer a more basic question: why are quinones in non-parasitic plants in the first place?" says Shirasu.

The researchers found that the model plant *Arabidopsis* produced a calcium signal in response to quinones. When they examined 50,000 mutagenized seedlings, they found 11 mutants lacking this response. All 11 mutants had mutations in the same gene, which the researchers dubbed *cannot respond to DMBQ 1 (card1)*.

A genetic analysis showed that a non-parasitic plant sets off a biological chain of events that involves responses to wounds and stress when it detects DMBQ and the quinone activates the CARD1 protein.

A photograph of asiatic witchweed (*Striga asiatica*), a red-flowered parasitic plant. RIKEN researchers have discovered a link between the parasite and the defense responses in plants.

The team tested whether quinone signaling is related to immune responses and found that the *card1* mutants were more easily infected by a common bacterium than wild-type plants. A typical immune response in plants is to close pores in their leaves to prevent pathogens from entering. Further analysis showed that these stomatal pores failed to close in the mutant plants because the plants could not respond to quinones. This likely led to the increased susceptibility to infection. Pretreating plants with DMBQ increased resistance to bacterial infection via the CARD1 signaling pathway.

Satisfied that the CARD1 protein is essential for immune-related responses to quinones in non-parasitic plants, the team investigated if quinone signaling in parasitic plants was related to a similar gene. They found CARD1-like proteins in a model parasitic plant, which were expressed in the roots and also involved in DMBQ-induced calcium increase.

Understanding plant quinone signaling should provide targets for combating parasitic plants and rule out other targets. "Our current research shows that if we simply target quinones, it will likely have the unwanted side effect of making crops more susceptible to bacterial infection," explains Shirasu. "Another approach could be to create crops that do not produce quinones, but can still initiate the downstream responses that provide protection from microbial infection, perhaps with treatment."

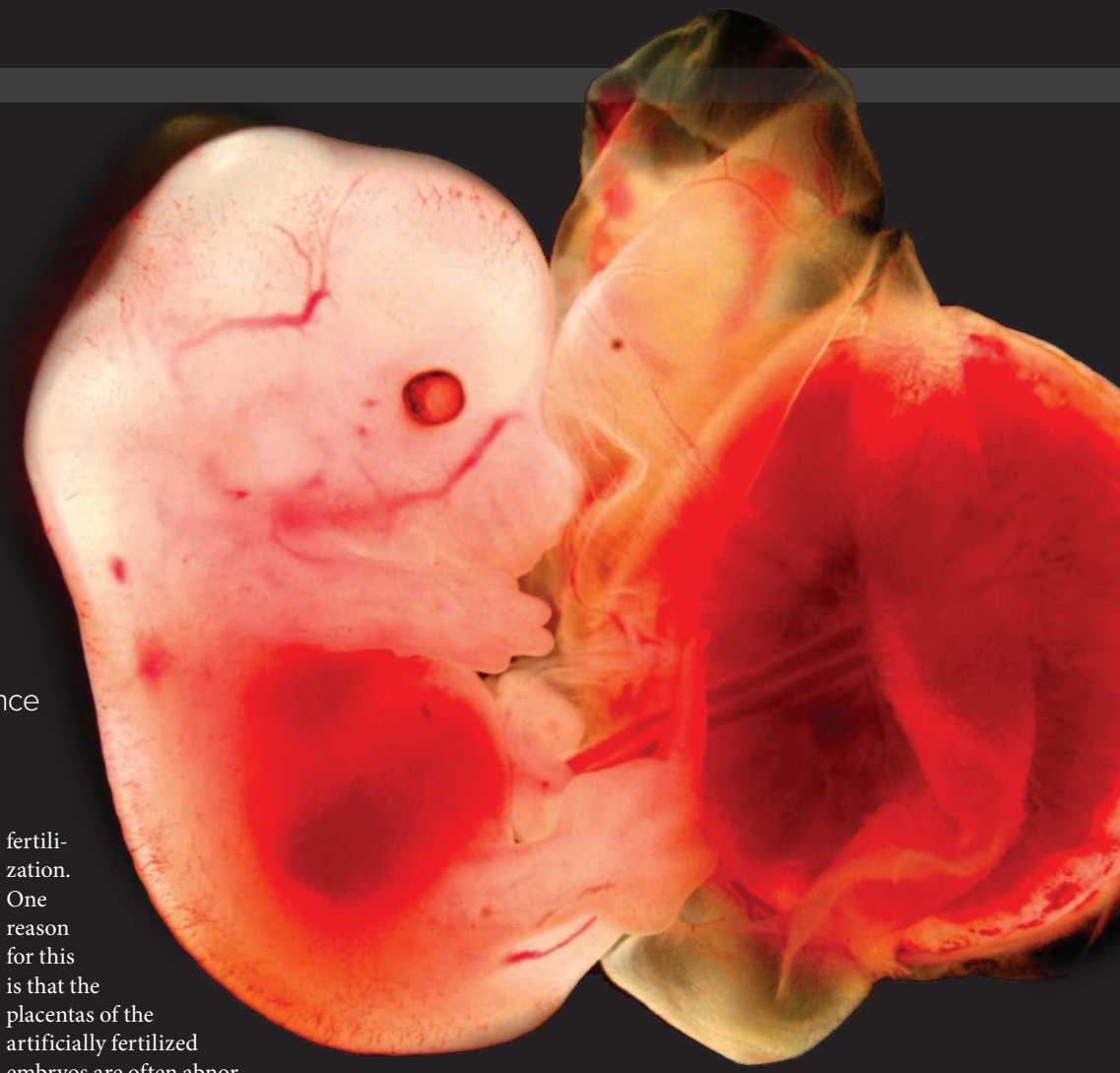
Reference

1. Laohavisit, A., Wakatake, T., Ishihama, N., Mulvey, H., Takizawa, K., Suzuki, T. & Shirasu, K. Quinone perception in plants via leucine-rich repeat receptor-like kinases. *Nature* **587,** 92–97 (2020).

SOMATIC CELL NUCLEAR TRANSFER

Mystery of oversized placentas solved

The birth rate of a cloning technique can be doubled by correcting for the absence of an epigenetic mark



A mouse embryo (left) produced by somatic cell nuclear transfer (SCNT) attached to a normalized placenta (right). RIKEN researchers have discovered why SCNT produces such large placentas.

One reason a technique for cloning animals often results in oversized placentas, and hence failed births, has been uncovered in mice by an all-RIKEN team[1]. This finding will help improve the success rate of the cloning method and could also shed light on fertility treatments for people.

The cloning method known as somatic cell nuclear transfer (SCNT) made headlines in 1997 when Dolly the sheep became the first mammal cloned from an adult cell. It involves swapping the nucleus of an egg cell from the mother with a nucleus from a normal somatic cell from the nuclear donor animal and then placing the egg into the uterus of a surrogate mother. SCNT is a powerful tool for basic research, medicine, agriculture and environmental science.

When they corrected for this, they were able to double the birth rate.

However, despite significant progress, SCNT's birth rate is still well below that of natural fertilization. One reason for this is that the placentas of the artificially fertilized embryos are often abnormally large, which frequently leads to developmental complications. But even after 20 years of research, the cause of this problem has remained a mystery.

Now, Kimiko Inoue, Atsuo Ogura and their co-workers, all at the RIKEN BioResource Research Center, have discovered that the overexpression of the largest imprinted microRNA clusters in mice is one of the main reasons why SCNT often produces placentas that are too large. When they corrected for this, they were able to double the birth rate.

A process known as genomic imprinting guides the early development of mammals by switching certain genes on and off as the embryo and placenta develop and grow. This can lead to the expression of genes from only one parent, depending on small molecules attached to the genetic sequence called epigenetic marks. The team found that SCNT placentas' lack of genomic imprinting based on the epigenetic mark histone methylation goes a long way to explaining their abnormal size.

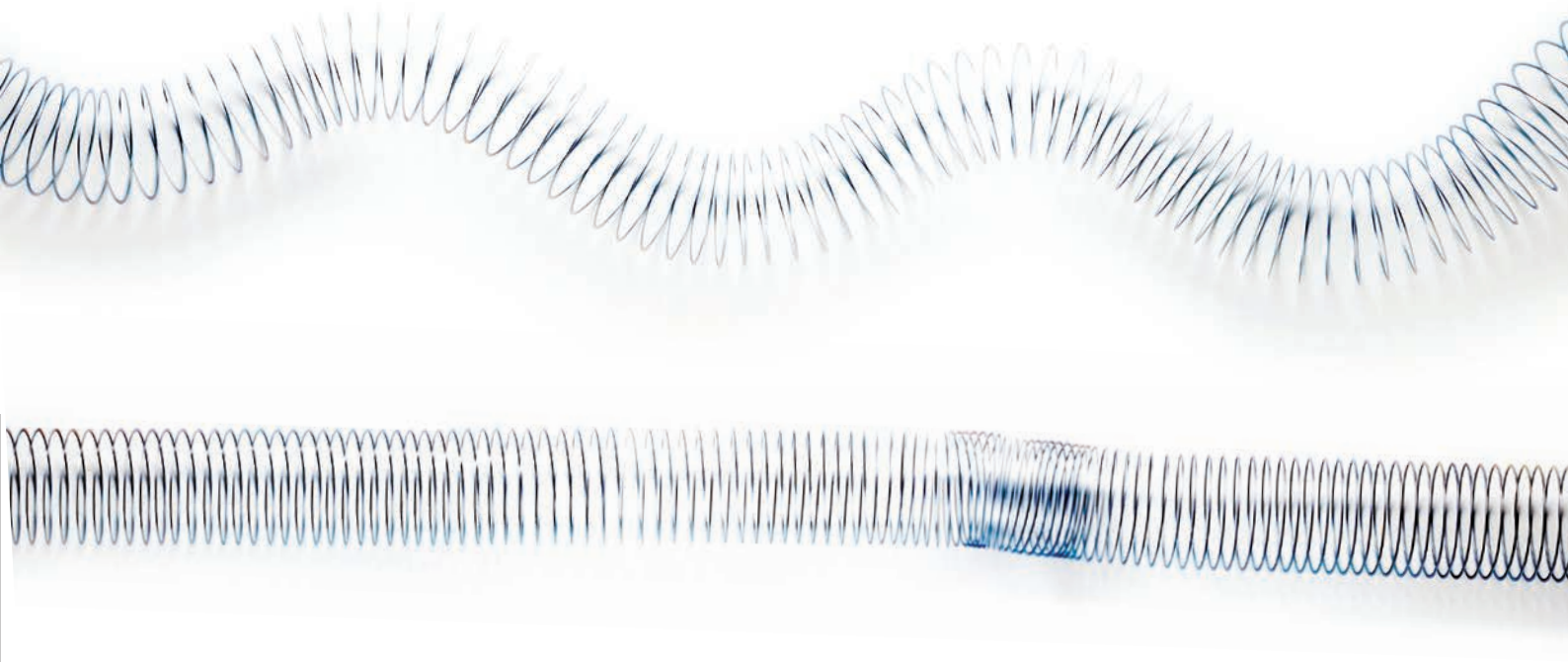
"DNA methylation is the main epigenetic mark that governs this expression system," says Inoue. "However, imprinting specific to the placenta is regulated by trimethylation at lysine 27 of histone H3 and this represses the expression of the mother's gene."

Inoue wasn't expecting to find that the culprit was a microRNA that didn't code for proteins. "I was surprised to discover that a non-protein-coding microRNA, and not a protein-coding gene, was the main cause of the oversized placentas produced by SCNT," she says.

The study has repercussions beyond SCNT. "We've demonstrated that non-coding microRNA plays an essential role in the healthy development of placentas," says Inoue. "I anticipate this will help us understand placental abnormalities and develop gene markers for assisted reproductive technologies for people."

Reference

1. Inoue, K., Ogonuki, N., Kamimura, S., Inoue, H., Matoba, S., Hirose, M., Honda, A., Miura, K., Hada, M., Hasegawa, A. *et al.* Loss of H3K27me3 imprinting in the Sfmbt2 miRNA cluster causes enlargement of cloned mouse placentas. *Nature Communications* **11,** 2150 (2020).



Most sound waves are longitudinal waves (bottom of image), but some are transverse (top of image) and cause the atoms or molecules of the material to oscillate perpendicular to their direction of travel. RIKEN researchers have succeeded in generating transverse sound waves in a thin flake of VTe_2.

PHOTOACOUSTIC WAVES

Light induces a different kind of sound wave

Ultrashort laser pulses induce unusual sound waves via a structural instability in a material

RIKEN physicists have initiated unusual sound waves in a flake of VTe_2 using ultrashort pulses of laser light and then created videos of their movement using electron microscopy[1]. This advance should help engineers to achieve higher precision control of heat flow and sound in nanodevices using light.

In 1880, Alexander Graham Bell, of telephone fame, reported that light can be converted into sound waves in some materials. Now, 140 years later, this effect is generating a lot of interest because it can be used to control the flow of heat and sound in nanomaterials.

"By utilizing this effect we can manage heat and sound on a nanometer scale," says Asuka Nakamura of the RIKEN Center for Emergent Matter Science. "This allows us to make novel functionality in very small devices."

Most sound waves compress and expand the material along the direction they travel in—these are known as longitudinal waves. But some sound waves are transverse and cause the atoms or molecules of the material to oscillate perpendicular to their direction of travel (see image).

In previous experiments that used light to induce sound waves in nanomaterials, the light heated the material, causing it to expand in all directions and thereby creating longitudinal sound waves. Now, Nakamura and his co-workers have used a different mechanism to produce transverse sound waves in a thin flake of VTe_2.

The researchers used ultrashort laser pulses to induce a structural instability, altering the crystal structure of the material and producing a transverse sound wave. They were able to detect this change in structure from electron diffraction measurements.

Transverse waves promise to give engineers greater versatility. "By utilizing this new mechanism, it may be possible to control the direction of atomic displacement in sound waves in the future," says Nakamura.

The team imaged the waves in the flake using a special electron microscope—one of only two in Japan. This was no mean feat because the flake was just 75 nanometers thick and the time resolution was on the order of picoseconds (1 picosecond = 10^{-12} second). "This ultrafast electron microscopy was one of the most important aspects of our study," says Nakamura. "It allowed us to take electron microscopy videos of the sound waves."

The researchers are excited by the potential of their microscope. "It will allow us to evaluate quantitatively the amplitude of acoustic waves by electron diffraction," says Nakamura. "Also, our system can visualize magnetic structures and waves."

Reference

1. Nakamura, A., Shimojima, T., Chiashi, Y., Kamitani, M., Sakai, H., Ishiwata, S., Li, H. & Ishizaka, K. Nanoscale imaging of unusual photoacoustic waves in thin flake VTe_2. *Nano Letters* **20,** 4932–4938 (2020).

HIJACKING HIBERNATION

In the last few years, scientists have been able to clarify the energy-saving mechanisms at work in hibernation, culminating in two important papers published in June 2020.

But what does this mean for **human hibernation?**

Humans aren't hibernators. However, we have very recently discovered how to induce hibernation in non-hibernators such as rats and mice, the latter of which normally only go into temporary torpors. Are humans next? Maybe. Another primate, the fat-tailed dwarf lemur native to Madagascar, enters this energy-saving state for up to seven months a year, and at least three other lemur species are known to hibernate. While tucked safely into a tree hollow, this lemur lowers its set body temperature and its metabolic activity plummets by nearly 90%[1]. Complex physiological adjustments mean that essentials, such as muscle cell activity, are maintained and the lemurs don't waste away. Studies on the transcriptomes of hibernating bears have revealed complex hibernation-related adjustments occur on the cellular level throughout the year[2], so long bouts of human hibernation are a little while off.

But hibernation still holds some exciting possibilities for medical science. For example, hibernating squirrels use melatonin to protect their cells when blood flow increases after months of inactivity. In the early 2000s, a University of Nebraska team used this as inspiration for a treatment to reduce tissue damage when blood suddenly returns after trauma-related hemorrhagic shock. After recent success in rats[3] and pigs[4], the Nebraska team is now looking at clinical trials. Short bouts of hibernation could also be helpful in limiting tissue damage in stroke victims or organ transplants.

On 11 June 2020, we took a step closer to this when our understanding of hibernation leapt forward. Two studies, both published in *Nature*[5,6], have identified several specific neuron subsets behind the end of the optic nerve that, when activated, lower set body temperatures in mice, inducing an energy-saving, hibernation-like state.

These studies, one of which I co-led, both support modifications to the previous model of thermoregulation activation in the brain. This change to the model has been brewing since 2016 due to a small flurry of studies on the genetic markers involved in the body's response to skin temperature changes. The studies revealed that the key neurons that cause the sudden drop in body temperature seen in hypothermia are not located in the hypothalamus' broader medial preoptic area, as previously thought, but in the much smaller median preoptic nucleus[7,8,9]. This greatly refined our understanding of the neurons and neuropeptides that might be involved in thermoregulation, which is the central mechanism of hibernation.

BURDENED BY BODY HEAT

Thermoregulation is key to energy consumption. Most mammals have a narrow body-temperature range around a set point of 37 degrees Celsius (98.6 degrees Fahrenheit). That's why even a one-degree rise in humans is our first clue to a fever. In shorter daily torpors, some animals can lower their body temperature closer to ambient air temperature, which is thought to achieve as much as a 70% reduction in energy use. However, in this daily torpor, the animal's set-point temperature remains the same, and the animals may be enduring a feeling of coldness for the energy-saving benefits[10]. Deeper hibernation states, most often seen in animals living in extreme environments, reduce an animal's set-point body temperature for longer, lowering energy use by 90% or more, but this requires much more sophisticated physiological adjustments.

Mice can go into short energy-conserving daily torpors in response to a lack of food. But the aspect of our June study that caused excitement was that by activating the small subset of neurons that express pyroglutamylated RF-amide peptide (QRFP) in mice, we were able to achieve a longer dormancy and a lowered set-point body-temperature, reminiscent of hibernation states[5]. The other study I mentioned was led by researchers at the Harvard Medical School in the United States, and it echoed our findings, observing shorter torpor states in mice after drug-induced activation of these same neurons[6]. While we genetically modified our mice to achieve the artificial activation and subsequent hibernation state, the hope is that we have found something that could eventually result in the development of hibernation state control in mammals, and ultimately humans.

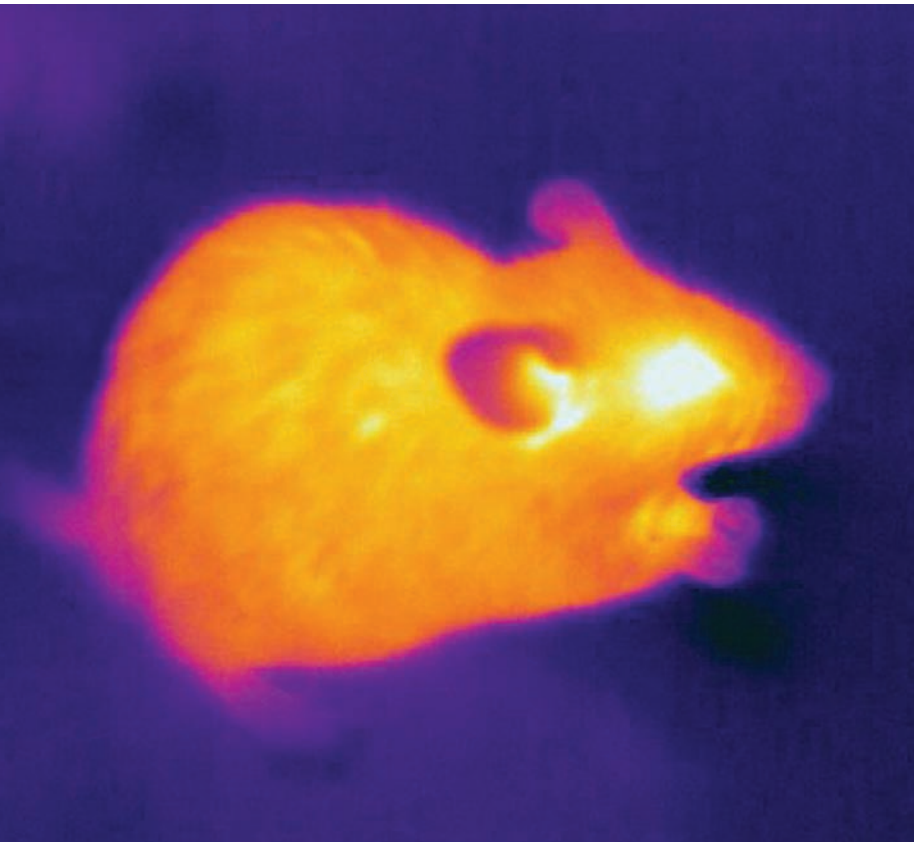
MEDICAL SYNTHETIC HIBERNATION?

The origins of our successful activation of hibernation-like state in mice lie in the long-time study of neuropeptides by wakefulness expert and the corresponding author on our paper, Takeshi Sakurai, and his group at the University of Tsukuba. Sakurai has long been examining functions in the brain of G-protein-coupled receptors, a diverse group of message carriers that are the targets of up to half of all marketed drugs. He observed that injecting QFRP into the brains of mice—QFRP has been linked to feeding and adrenal responses—made them very active. However, when his group tried exciting the neurons that express QRFP in 2017, their mice became still and their body temperature dropped.

Sakurai called me soon after, and my Kobe lab soon began recording the metabolism of the genetically

GENSHIRO SUNAGAWA
Senior Scientist, Laboratory for Molecular Biology of Aging and Laboratory for Retinal Regeneration, RIKEN Center for Biosystems Dynamics Research

Genshiro Sunagawa has been working in the Laboratory for Retinal Regeneration since 2015, where he focuses on active hypometabolism in mammals. He has been working as a clinician (pediatrician and anesthetist) since 2001. The discovery of hibernating tropical primates by Kathrin Dausmann in 2004, inspired him to take a step in the field of biomedical applications of natural phenomena such as hibernation. He hopes to develop safe human hibernation for use in clinical settings.



The researchers observed that QFRP-neuron-stimulated mice were comfortable below 30 degrees Celsius (86 degrees Fahrenheit), when normally they would be cold. This suggested that their set body temperature had been lowered in a manner reminiscent of a deep hibernation state.

modified mice with a special G protein-coupled receptor expressed on QRFP-neurons, which helped us to stimulate them. With these mice, we were able to induce more than 48 hours of a hibernation-like state within 30 minutes of injecting into the stomach compounds with ligands to the G protein-coupled receptor, a speed that bodes well for the possibilities of use in medical triage. For 48 hours or more, we observed the body temperature of our QFRP-neuron-stimulated mice lowered below 30 degrees Celsius (86 degrees Fahrenheit) and it even dropped to 24 degrees Celsius (75 degrees Fahrenheit) under cold conditions. Their heart rate, oxygen consumption and respiration rate were also all reduced. And we have also been able to replicate this in rats, a species that neither hibernates nor has daily torpor.

In the future, slowing metabolic processes like this might give stroke, heart attack and trauma victims more time before tissue damage becomes too severe to treat. Dormancy could also extend the viability of organ transplants. Currently, a waiting kidney or liver can be preserved in cold solutions for only 24 hours, while a heart or a lung is viable for a mere four to six hours. If we could slow the degradation rate by 90% that would be huge. With an eye to this, the next step for us at RIKEN is to try to induce hibernation in human iPS cell-derived tissues. If we can do this without modifying the genes involved, the possibilities of using short-term dormancy for medicine becomes more real.

LONG HUMAN HIBERNATION

In terms of longer hibernation states, things become more complex. The fat tissue of grizzly bears has been shown to be among the most affected by hibernation. A 2019 transcriptional analysis showed 900 differentially expressed genes in a hibernating grizzly's adipose tissue compared to an active season. Hibernation was also characterized by reduced expression of genes associated with insulin signaling, muscle protein degradation, and urea production, and increased expression within muscle protein anabolic pathways. It's thought that we contain the genes that make this possible, but activating these supporting processes in humans would likely be hugely complex.

However, grizzly bears also become resistant to insulin during hibernation, but they don't suffer from fluctuating blood sugar levels. Huge weight loss occurs as par for the course, but no bone loss or atrophied muscles have been observed. A human experiencing some of these conditions could easily end up with diabetes, obesity or worse. Will mimicking grizzly bear fat become a future treatment for diabetes? Is aging slowed by hibernation? Could we enter torpor for a few hours every night as part of a beauty or health regime? One theory suggests that deep meditation is designed to replicate hibernation. Can we achieve a hibernation or torpor state using only the mind? These are some of the many questions that will be fascinating to explore now that we can induce hibernation states in one of our main mammalian research models.

Eventually, it's possible that long-term hibernation in humans could be a game changer for space travel, healthcare and even climate change. And like genomic medicine, which once seemed so far away, there will be ethical considerations. What does consent look like to a hibernating human? Will hibernators pay taxes? And when are you really terminally ill? We need to start exploring these questions, as the last year has shown us that the science in this area can rapidly jump forward. If long-term hibernation is possible, it could change our concept of time entirely: could we hibernate through a pandemic, or hit pause and wait for the planet to repair itself? These are questions that our children may have to answer, which is an exciting thought.

REFERENCE

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

A ONE-WAY STREET FOR SOUND WAVES

A new way for sound waves to interact with magnetic film could lead to 80% more directional control

We are one step closer to devices that can control the direction and power of sound waves. A team led by Yoshichika Otani at the RIKEN Center for Emergent Matter Science (CEMS) has fabricated a magnetic film in which sound waves interact with electron spins, so that the amplitude and direction of sound waves can be manipulated with a similar degree of control as electrical currents.

The interaction involves 'magneto-rotation coupling', which is when the rotational motion of surface sound waves causes the atomic lattice in a ferromagnetic material to move in a circular motion. The magnetism of a ferromagnet, the classic example of which is the bar magnet, derives from the spins of their electrons tending to align in the same direction. Coupling makes the magnetization precess, a wobbling motion that occurs when a spinning object is the subject of an external force. Depending on the direction of the sound waves, this precession can weaken the waves or leave them unaffected. An exciting finding is that when conditions are tweaked in accordance with theory, the sound waves travel in only one direction.

ONE DIRECTION TUNE

It was only during the review process of their research paper that the team realized that they had achieved 100% 'rectification'. Rectifiers are essentially one-way streets that allow energy to flow in a single direction. One of the reviewers noted theory predicted that complete rectification should be possible, and when the team re-examined their data, they found that their measurements did indeed show 100% rectification — a big increase over the previous record of 20%.

Importantly, the amount of rectification can be easily controlled. "The magnetic field controls how much you block the sound waves traveling in one direction," says Jorge Puebla, one of the co-authors from CEMS. "So you could have a knob on your device that adjusts how much sound comes in from the outside and how much you block, for example." Puebla notes that the sound waves used in this experiment are too high in frequency to be audible to people, so this will require further study for more conventional sound blocking uses. However, this finding could be more immediately useful in sound isolators for other types of experiments.

In addition, electrical rectifiers that permit electric currents to flow one direction but not the other are used extensively in the electronics industry. For example, they can be used to convert alternating electric currents into steady direct currents. Now, acoustic rectifiers based on magneto-rotation coupling are a possibility, and might be useful in devices such as sound isolators and specialized magnetic properties sensors, which could be applied to superconductivity research among other areas.

A FAMILIAR NAME

Ferromagnetism is an old technology, dating back at least two and a half millennia. But what has made this new control possible is the advancement of the emerging field of spintronics. The technology of spintronics uses the spins of electrons rather than their charges (as in conventional electronics) to convey information. It's seen as promising for creating devices that have ultralow power consumption, as spin can flow without electrons physically moving. One way to create and manipulate the flow of spins, or spin currents, is to use sound waves in ferromagnetic materials. Sound waves that travel as ripples along the surface of a ferromagnetic material displace the electron spins, giving rise to a spin current. Known as magnetoelastic coupling, this effect has been extensively studied for some time.

However, the team was surprised when they scoured the literature for the magneto-rotation

MINGRAN XU | Student Trainee, Quantum Nano-Scale Magnetism Research Team, RIKEN Center for Emergent Matter Science

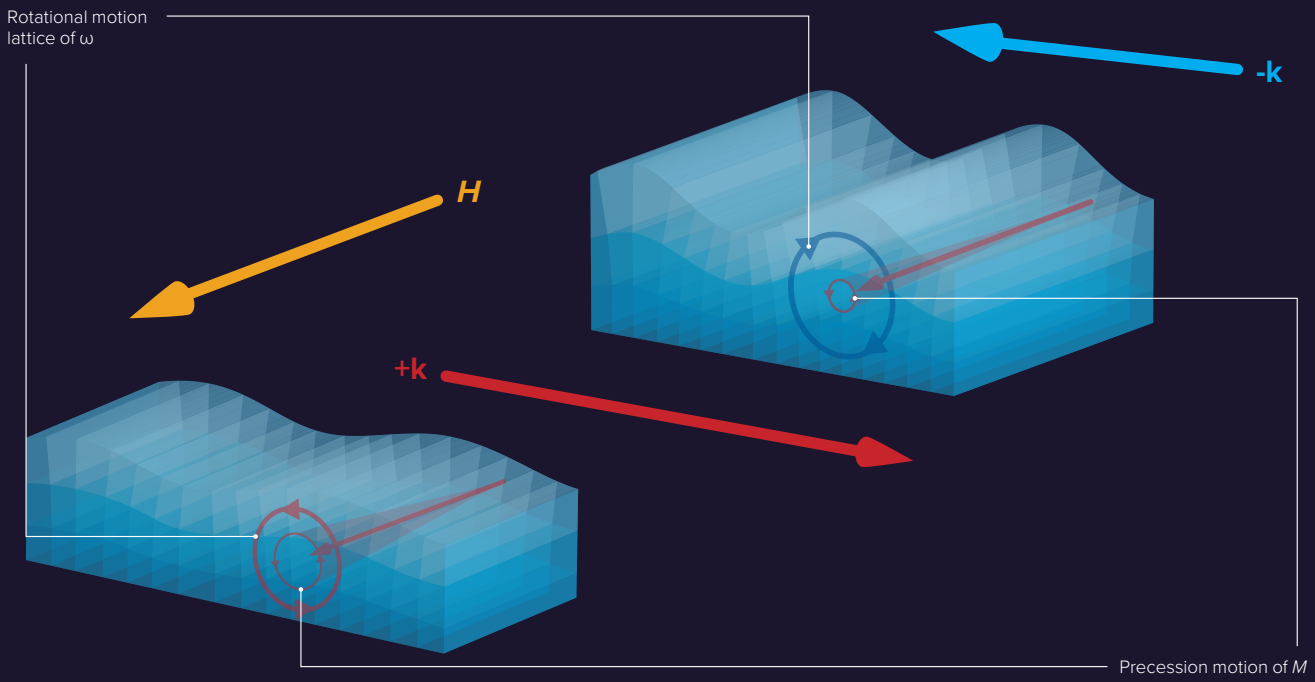
Mingran Xu is a PhD course student at Graduate School of Frontier Sciences at University of Tokyo and a research student at RIKEN. He was first supported by the RIKEN International Program Associate (IPA) Program, and later by a three-year Japan Society for the Promotion of Science fellowship (JSPS DC1). He has been working on a spin conversion project since began his masters. His research is focused on magnon–phonon coupling systems.

JORGE PUEBLA | Research scientist, Quantum Nano-Scale Magnetism Team, RIKEN Center for Emergent Matter Science

During his PhD Jorge Puebla studied spin phenomena in semiconductor nanostructures (quantum dots and wires) in the Department of Physics and Astronomy at the University of Sheffield in the United Kingdom. Later, he was the recipient of a Marie Curie Fellowship and worked as the project leader in technology developments in microscopy, interferometry and photovoltaics for the German company Attocube Systems. In 2015, he joined RIKEN, where he leads projects on photon coupling and phonons with spin systems.

NOISE CONTROL

Sound waves traveling on the surface of a magnetic film (blue) interact with the magnetism differently depending on which direction they travel in. This effect could be used to make acoustic rectifiers. Figure provided by Mari Ishida.



coupling they had observed. They uncovered a theoretical paper in the proceedings of a 1976 conference that predicted the effect, and the name of the first author of the paper, Sadamichi Maekawa, looked very familiar. In fact, he was a CEMS colleague who was working two floors below the team's lab. The experimental observation of an effect that he predicted more than 40 years ago was sweet vindication for Maekawa: "I had almost forgotten about my work, but I was very happy when Dr Puebla discovered my paper." Puebla concurs: "It was a very nice surprise to discover that we had someone to talk to who was so nearby."

One reason it had taken so long to observe the effect is that the experiment needed to be performed at high frequencies, which requires small structures. Recent advances in nanofabrication have made it possible to make devices small enough to perform the measurement. "If you want to analyze this effect you need a really high-frequency device," explains Mingran Xu, who did most of the experiments. "But you need extremely small structures to fabricate a high-frequency device. It was really quite challenging to make."

The team now intends to use magneto-rotation coupling to explore magnetism in exotic two-dimensional materials. "Two-dimensional materials with magnetism have been discovered and some of them have magnetism out of the plane," says Puebla. "But when you consider that these materials are just one or two atoms thick, it's not really clear where this anisotropy is coming from. We want to fabricate some devices and see if we can contribute to this important question in two-dimensional materials.

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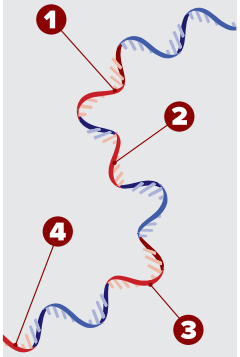
Xu, M., Yamamoto, K., Puebla, J., Baumgaertl, K., Rana, B., Miura, K., Takahashi, H., Grundler, D., Maekawa, S. & Otani, Y. Nonreciprocal surface acoustic wave propagation via magneto-rotation coupling. *Science Advances* **6,** eabb17242020 (2020).

HOW BEST TO MAP TISSUE CELLS

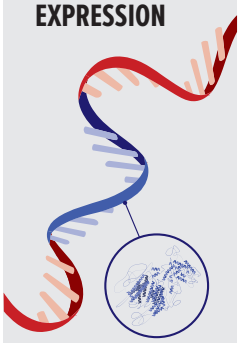
The most powerful of 13 single-cell RNA sequencing methods tested by an international group for their ability to map the cells in complex tissues is Quartz-Seq2. Developed by Itoshi Nikaido, Yohei Sasagawa and colleagues of the RIKEN Center for Biosystems Dynamics Research, Quartz-Seq2 best identified cell types and most finely distinguished between changing cell states via the measures listed below. The study was designed to help large-scale collaborative tissue mapping projects, such as the Human Cell Atlas, as they seek to standardize sequencing methods globally.

GENE DETECTION



The number of genes able to be detected, which relies on a method's sensitivity to gene markers and its gene library complexity. This will determine the detail in tissue profiles produced.

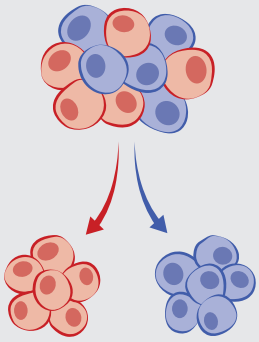
MARKER EXPRESSION



The expression levels of cell-type protein signatures produced, which also determines a method's ability to detect genes.

*Quartz-Seq2 has strong poly(A) tagging, which increases the amplified cDNA yield.

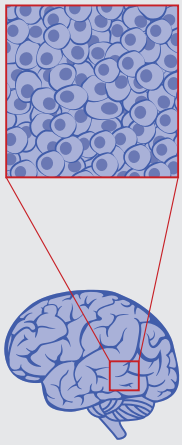
CLUSTERABILITY



This is the probability of cells being clustered with cells of the same type in analysis, in other words a method's ability to discriminate between cell types.

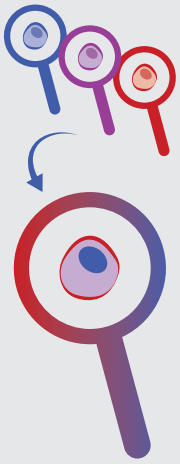
Integrated clusterabilty is clusterability when different methods are used and corrected for.

MAPPABILITY



The ability of a method to predict and produce a map of a tissue's cells in a way able to be used with a reference atlas.

MIXABILITY



This is the ability of protocols to be combined without a drop in their power to discriminate between cell types.

THE SCORE BOARD

Protocol name	Gene detection	Marker expression	Clusterability	Integrated clust.	Mappability	Mixability	Total score
Top 3 — **Quartz-seq2** Developed at RIKEN							
Top 3 — **Chromium**							
Top 3 — **Smart-seq2**							
CEL-seq2							
C1HT-medium							
C1HT-small							
ddSEQ							

Higher score — Lower score

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

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

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

NAGOYA

KEIHANNA
- ● Center for Advanced Intellegence Project (AIP)
- ■ BioResource Research Center (BRC)

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

OSAKA
- ● Center for Biosystems Dynamics Research (BDR)

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

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