RIKEN RESEARCH

SPRING 2020

SHOWCASING THE BEST OF JAPAN'S PREMIER RESEARCH ORGANIZATION • www.riken.jp/en

EARLY SCHIZOPHRENIA DETECTION

Biomarker found in hair

WHAT'S THE MATTER?

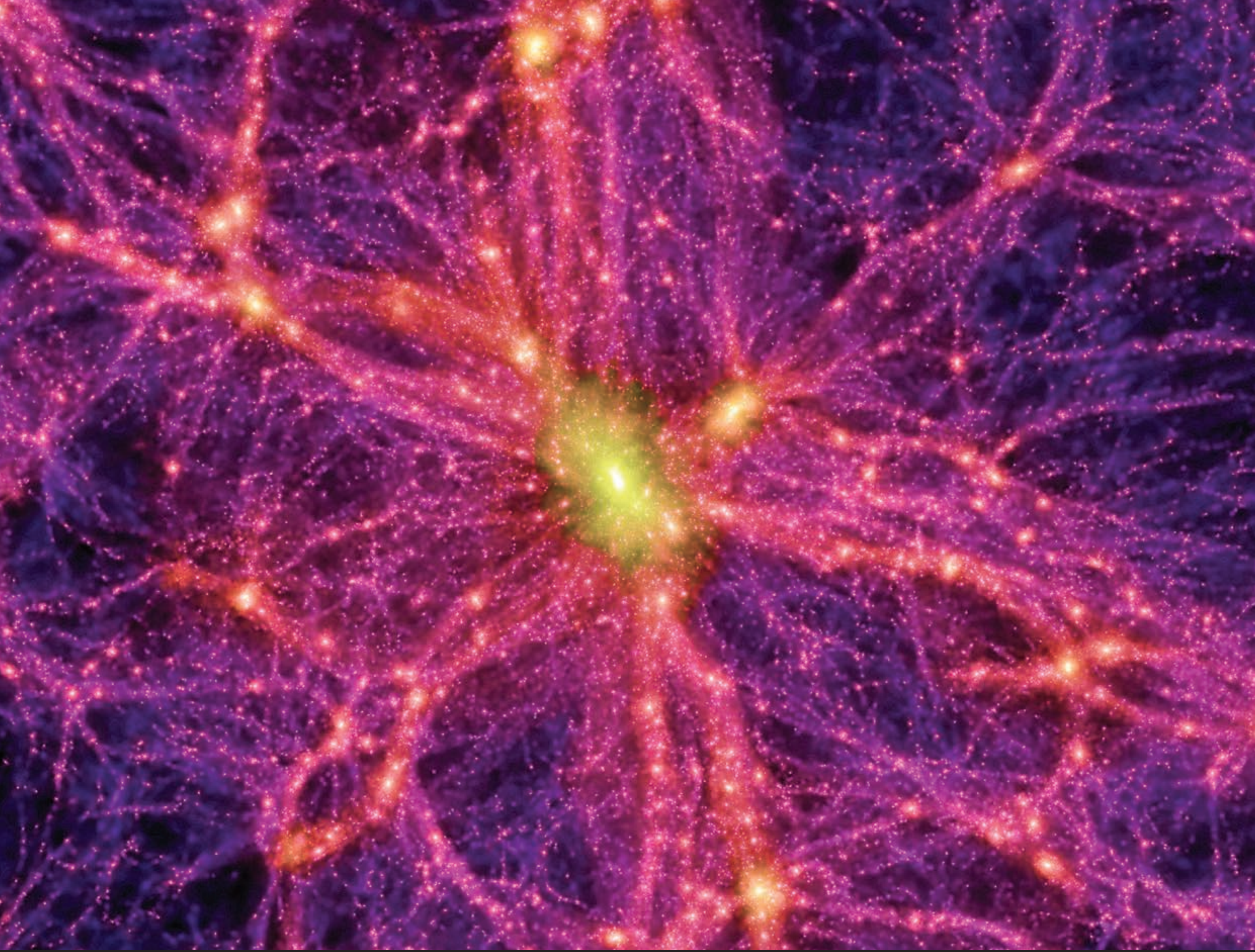
Possible link between two cosmic mysteries

LIVING UNTIL 110

Abundance of immune cell linked to longevity

READING THE MIND OF AI

Cancer prognosis method revealed



Web of dark matter
A supercomputer simulation showing the distribution of dark matter in the local universe. RIKEN astrophysicists have performed the first laboratory experiments to see whether the interaction between dark matter and antimatter differs from that between dark matter and normal matter. If such a difference exists, it could explain two cosmological mysteries: why there is so little antimatter in the Universe and what is the true nature of dark matter (see page 18).

RIKEN RESEARCH

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

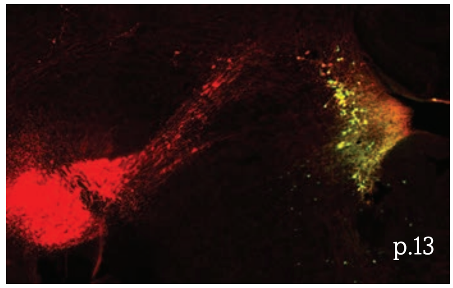
Initially established as a private research foundation in Tokyo in 1917, RIKEN became a national research and development institute in 2015.

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

RIKEN Research is published by RIKEN in collaboration with Nature Research Custom Media, a part of Springer Nature.

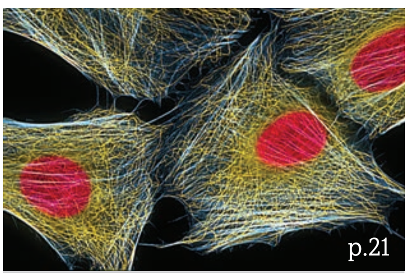
For further information on the research in this publication or to arrange an interview with a researcher, please contact:
RIKEN International Affairs Division
2-1, Hirosawa, Wako, Saitama, 351-0198, Japan
Tel: +81 48 462 1225
Fax: +81 48 463 3687
rikenresearch@riken.jp

ISSN 1883-3519
www.riken.jp/en

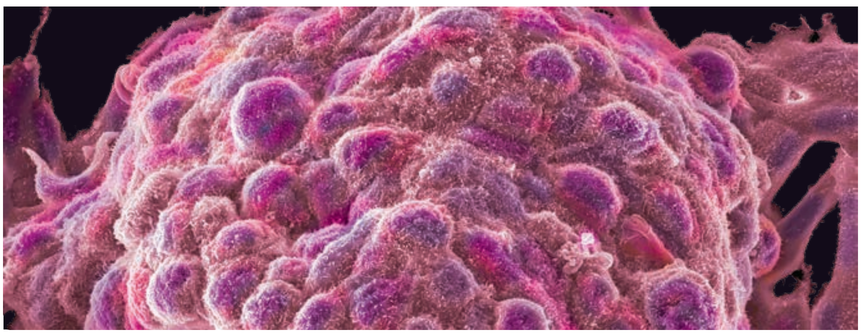

p.13


p.14


IYPT 2019
International Year of the Periodic Table of Chemical Elements
2019


p.21


p.23



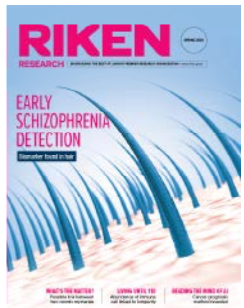
Data sharing, commercial strategies and performance

Hiroshi Matsumoto
President, RIKEN

Last year was an important one for us, as we went through our process of evaluation by external panels, culminating in the meeting of the RIKEN Advisory Council (RAC) at the end of November. For three very intensive days, we met with the panel, headed by the eminent neuroscientist, Sir Colin Blakemore. We gave the Council an overview of our current situation and goals, and received valuable advice from them. This system of receiving evaluations and recommendations by distinguished experts from around the world is unique among Japanese institutes. It allows us to maintain top-level research in the intensely competitive world of scientific research.

I am happy to report that their evaluation was largely positive, with strong support for new initiatives that we have made in recent years, such as the Hakubi Fellows and Kato Sechi programs for attracting talented young scientists and enhancing diversity, and for the establishment of the new company, RIKEN Innovation, to help use our research to the good of society. They also gave us recommendations for taking on some challenges that are common to research institutes around the world, such as making sure that we have the best performance indicators available, that we manage and share our data in the best possible way, and that we conduct our translational research based on a clear strategy. They asked us to explore an institutional policy on open access, for example, an issue that is being tackled by many of our partners around the world.

We are now carefully considering their recommendations and making changes accordingly, and I very much hope that you will see the fruits of these changes appear in the pages of future issues of *RIKEN Research*, both in terms of new initiatives and in research findings that have relevance to the society we live in. We also look forward to interacting with our partners around the world in addressing the many challenges facing the world of scientific research today. See a summary on page 7 for more details on the expert panel.



COVER STORY:
RIKEN researchers have found that the elevated expression of a gene called *MPST* in human hair could be an indicator of schizophrenia.
Page 10

Keep up to date

Online
www.riken.jp/en

Facebook
facebook.com/RIKEN.english

Twitter
twitter.com/RIKEN_en

LinkedIn
linkedin.com/company/riken

Observing the cosmic web

Hideki Umehata
Special Postdoctoral Researcher (SPDR)
Star and Planet Formation Laboratory, RIKEN Cluster for Pioneering Research

Please describe your role and current research.
I'm a Special Postdoctoral Researcher at RIKEN looking at galaxy formation and evolution in the early Universe. It has become clear that more than 12 billion years ago there were a number of cosmic 'monsters'—violent star-forming galaxies and rapidly growing super-massive black holes. I'm trying to understand the formation process of these monsters to help us understand cosmic history.

What excites you the most about your current research?
About four years ago, while visiting a collaborator in the United Kingdom, I analyzed an image taken by the Subaru Telescope in Japan and found the signatures of large extended gas filaments. These filaments (sometimes described as the cosmic web) had been assumed to exist in theory for many years, but no-one had directly observed them before. We published the finding in *Science* last October.

What do you think has been the most interesting recent discovery in your field?
In a broad context, the direct imaging of the black hole shadow of Messier 87 this year by the Event Horizon Telescope project was very impressive. It provided us with strong evidence of super-massive black holes. This is intrinsically important to me since super-massive black holes are one of my target cosmic objects.

How did you become interested in your current field of research?
During my childhood, I loved to gaze at the night sky. I was especially absorbed in astronomy when I was a high-school student after seeing the Leonid shooting stars created by debris left behind by the comet Tempel–Tuttle in 2001. Now, even after getting my PhD, I'm still captivated by the sky. Among the various fields within astronomy, the distant universe is the most attractive to me, partly due to its magnificence and vastness. And, personally, I also just enjoy the fun of an astronomical event. It would be great if we could see a supernova in the Milky Way with our naked eyes.

> *[Gas] filaments had been assumed to exist in theory for many years, but no-one had directly observed them.*

How and when did you join RIKEN?
I joined RIKEN about a year and a half ago. The team leader of the laboratory I work in, Dr. Nami Sakai, is an expert in using the ALMA Observatory telescopes in Chile, which is my favorite observatory and that's why I decided to join her team.

How has being at RIKEN helped your research?
RIKEN hosts several astronomy laboratories that cover theoretical fields, x-ray research, and our group studying the submillimeter/millimeter wavelengths of the electromagnetic spectrum, through which we can examine molecular clouds, looking at the process of star formation from earliest collapse to stellar birth, for instance. This wide variety of groups and high-level scientists helps stimulate ideas to further develop my research. I hope the opposite is also true. In fact, I would say that the environment here is the best thing to me. I really enjoy day-to-day life as a researcher here. ■

Computer-assisted disaster recovery

Bahareh Kalantar
Postdoctoral Researcher
Disaster Resilience Science Team, RIKEN Center for Advanced Intelligence Project

Tell me a little bit about yourself?

I grew up in Iran, in the city of Esfahan. I'm now a postdoc in the Disaster Resilience Science Laboratory at the RIKEN Center for Advanced Intelligence Project. The center is headquartered in central Tokyo, but my lab is located at the Keihanna campus, between Kyoto and Osaka.

How did you become interested in artificial intelligence?

When I was nine or ten, I used to play chess against a computer. Most of the time I lost. I was curious how a computer could be smarter than a human. Today, when we Google something or use Google Translate that's artificial intelligence (AI) too. It really is all around us.

> *AI could help quickly reveal if an area [hit by an earthquake] has been damaged and where help is needed.*

What is your research about?

I apply machine learning to natural disasters, such as landslides, earthquakes and floods. Earthquakes in particular destroy infrastructure in Japan, and AI could help quickly reveal if an area has been damaged and where help is needed.

Currently, I'm using aerial photographs from before and after the main shock to study the Kumamoto earthquakes of 2016. We plan to use a type of deep learning known as a convolutional neural networks (CNNs) to map which areas were damaged, slightly damaged or contained debris.

In the future, we could also use Light Detection and Ranging (LiDAR), which is a good tool for collecting data on building surface elevation. LiDAR uses its own light, so we could collect data at any time of day and under water.

Unmanned aerial vehicles (UAVs) could also be used more extensively to collect images in remote areas at a low cost compared to satellite images.

Others at the lab are using AI to better predict when earthquakes will occur.

Could you describe your work on landslides?

We are doing landslide susceptibility mapping, looking at conditioning factors such as slope, aspect, curvature, the stream power index (SPI) and terrain ruggedness index (TRI). Using the history of landslides in the area, an inventory map is produced. These conditioning factors and inventory map are used in machine learning algorithms to map landslide susceptibility. The results could be adapted for land-use planners and decision makers to improve landslide risk-assessments.

What is your aim as a scientist?

About one in three people is affected by natural disasters. I would like to contribute to creating better disaster resilience, particularly in vulnerable developing and undeveloped countries.

How did you come to RIKEN?

I was studying at the Universiti Putra Malaysia (UPM), and we had exchange programs with Japanese universities, so I met Japanese students or professors. As a result, I already knew I would like to work in Japan.

In 2017, when I learned there were openings for RIKEN postdocs, I noticed that Naonori Ueda (who is now my supervisor) is a widely recognised machine learning scientist. I felt it was a great opportunity for me.

Do you enjoy working at RIKEN?

Working with Japanese researchers is amazing. They encouraged me to focus on one specific thing and to do it perfectly. That's the way Japanese scientists work. ■

Careers at RIKEN
For further information, visit our Careers page:
Website: www.riken.jp/en/careers
E-mail: pr@riken.jp

Sixteen RIKEN researchers in the top 1% of their fields by citations

Clarivate Analytics selected 16 researchers from RIKEN among their highly cited researchers in 2019, a listing of the world's most influential scientists and social scientists, who, over the past 10 years, have shown considerable influence through highly cited published work. More than 6,000 scientists from 21 research fields were chosen to receive the citation, with 104 coming from Japan.

CLARIVATE ANALYTICS' HIGHLY CITED RESEARCHERS AT RIKEN

CROSS-FIELD

- **Yoshihiro Iwasa,** The University of Tokyo (UTokyo)/RIKEN
- **Takao Someya,** UTokyo/RIKEN

IMMUNOLOGY

- **Koji Atarashi*,** RIKEN
- **Kenya Honda,** Keio University/RIKEN

PHYSICS

- **Yoshinori Tokura*,** RIKEN/UTokyo
- **Naoto Nagaosa*,** RIKEN/UTokyo
- **Franco Nori*,** RIKEN/University of Michigan
- **Ryotaro Arita,** UTokyo/RIKEN

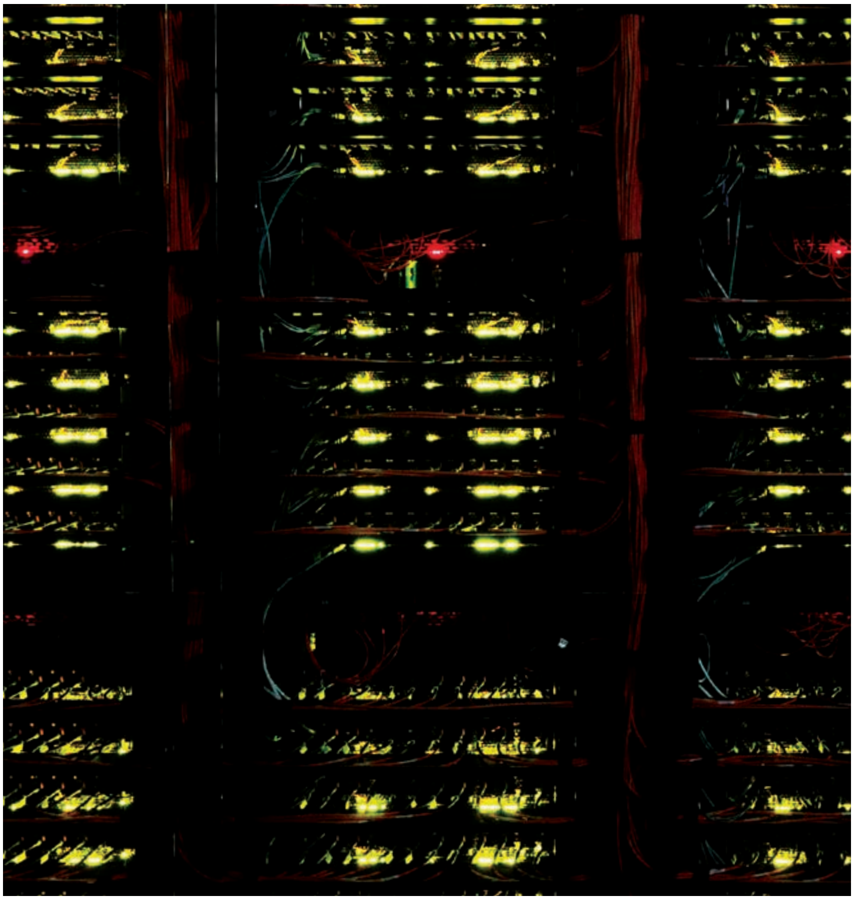
PLANT & ANIMAL SCIENCE

- **Kazuo Shinozaki*,** RIKEN/Nagoya University
- **Ken Shirasu*,** RIKEN
- **Yuji Kamiya*,** RIKEN
- **Motoaki Seki*,** RIKEN/Yokohama City University
- **Lam-Son Phan Tran*,** RIKEN
- **Kazuki Saito,** Chiba University/RIKEN
- **Hitoshi Sakakibara,** Nagoya University/RIKEN

NEUROSCIENCE & BEHAVIOR

- **Susumu Tonegawa,** Massachusetts Institute of Technology/RIKEN

**Asterisks indicate researchers whose primary affiliation is RIKEN.*



The supercomputer MDGRAPE-4A conducts molecular dynamics simulations for drug discovery. It was developed at the RIKEN BDR.

New supercomputer dedicated to drug discovery

The RIKEN Osaka campus is now host to a new supercomputer, MDGRAPE-4A. Designed to conduct molecular dynamics simulations for drug discovery, the computer was developed by the Laboratory for Computational Molecular Design at the RIKEN Center for Biosystems Dynamics Research (BDR).

In an aqueous solution, proteins change conformation—the spatial arrangements of atoms in a molecule as it rotates. In order to understand this, it's necessary to calculate the force of each atom and the surrounding water molecules, and to move the proteins inside a computer simulation. MDGRAPE-4A is designed for this purpose. It has an overall power of 1.3 petaflops, but is able to outperform faster general-purpose supercomputers due to its architecture. By modeling water molecules and the roughly 100,000 atoms that typically make up proteins, it can carry out a simulation of approximately 1.1 microseconds of molecular dynamics in a day. This allows it, in a realistic timeframe, to model the interactions between drugs and proteins in the body, which will help develop more effective targeted therapies.

The MDGRAPE-4A computer will be made available to academic and industry researchers globally. In the future, BDR plans to incorporate new elements such as artificial intelligence and hybrids of general-purpose and specific circuits to further improve the system. **www.riken.jp/en/news_pubs/news/2019/20191129_1/**

RIKEN Advisory Council 2019

■ Chair ■ Vice Chair

The 11th meeting of the RIKEN Advisory Council (RAC) was held in Tokyo in November 2019. Nineteen international experts from different scientific fields came together to examine RIKEN's initiatives and centers. They then presented a set of evaluations and recommendations. The panel was chaired by Sir Colin Blakemore from City University of Hong Kong. This system is a unique experiment pioneered in Japan by RIKEN. Prior to the meeting of the full council, individual centers hold their own advisory councils, and their reports are considered by the RAC in their discussions. **www.riken.jp/en/news_pubs/news/2020/20200122_1/index.html**

NAME	TITLE	INSTITUTION	FIELD OF RESEARCH	COUNTRY AFFILIATION
Blakemore, Colin	Chair Professor of Neuroscience and Senior Fellow (Former Chief Executive, Medical Research Council, UK)	Hong Kong Institute for Advanced Study, City University of Hong Kong	Neuroscience	Hong Kong
Bracco, Angela	Professor	University of Milan National Institute of Nuclear Physics, Italy	Nuclear Physics	Italy
Carpenter, Jean-François	Professor and Vice President	University of Rennes 1	Catalytic Chemistry	France
Chan, Tony F.	President	King Abdullah University of Science and Technology (KAUST)	Computer Science and Engineering	Saudi Arabia
Fujii, Kozo	Professor	Tokyo University of Science	Aerospace Engineering	Japan
Fukuyama, Hidetoshi	Advisor to President	Tokyo University of Science	Solid States Science	Japan
Hall, Wendy	Regius Professor (Former President of ACM)	University of Southampton	Computer Science	United Kingdom
Hara-Nishimura, Ikuko	Professor	Konan University	Plant Science	Japan
Hirano, Toshio	President (Former President, Osaka University)	National Institutes for Quatum and Radiological Science and Technology (QST)	Medicine, Immunology, Genetics	Japan
Howard, Jonathon	Professor	Yale University	Biochemisty, Biophysics	United States
Inan, Umran	President	Koc University	Physics Electromagnetic radiation	Turkey
Metternich, Rainer E.	1. Former Deputy Chairman of the Board and Acting CSO 2. Former Global Head of Small MoleculeReseach 3. Former Head of Basic Research and Site Head	1. Proteros biostructures GmbH, Germany 2. Hoffmann-La Roche, Switzerland 3. Merck & Co., USA	Drug Discovery, Medicinal Chemistry	Germany
Mishima, Yoshinao	SIP Sub Program Director (Former President, Tokyo Institute of Technology)	Cross Ministral Strategic Innovation Promotion Program (SIP)	Materials Engineering	Japan
Murray, Cherry A.	1. Professor 2. Director, Biosphere 2 (Former Director, USDOE Office of Science)	1. Harvard University 2. University of Arizona	Applied Physics	United States
Nagao, Makoto	Academic Advisor (Former President, Kyoto University)	International Institute for Advanced Studies	Information Technology	Japan
Oh, Se-Jung	Member of National Assembly of Republic of Korea (Former Professor of Physics, Seoul National University)	National Assembly, Republic of Korea	Applied Physics	South Korea
Smith, Austin	Professor	Wellcome Trust - Medical Research Council, Cambridge Stem Cell Institute	Embryo Stem Cell Biology	United Kingdom
Takeda, Haruo	1. Corporate Chief Engineer 2. Project Leader	1. Hitachi, LTD. 2. Science, Technology and Innovation for SDGs, EAJ	Mathematical Engineering, Innovation Studies	Japan
Tan, Chorh Chuan	Executive Director	MOH Office for Healthcare Transformation	Medicine: Renal Physiology	Singapore

Accelerating routes to innovation

RIKEN's first fully owned subsidiary, RIKEN Innovation, Co., Ltd., was established in September 2019. The company will work to improve communication with private industry, support collaborative projects and carry out work related to licensing technologies. This move was made possible by a new law passed in January 2019, which allows national research and development institutes to establish subsidiaries.

RIKEN Innovation will focus on four major areas: strategic management and transfer of intellectual property; support for start-ups working towards technology commercialization; support for large-scale collaborations, and co-creation with industry using RIKEN's knowledge and research.

"The image of RIKEN is that we are an institute focused on theoretical research," said President Hiroshi Matsumoto. "But the reality is that many of our breakthroughs are being used by industry, and our papers are frequently cited in patent applications.

"Thanks to the efforts of many people, a law was enacted giving us the ability to invest in an innovation company." Read more on page 26. **www.riken.jp/en/news_pubs/news/2019/20191217_3/**

Fugaku prototype is world's greenest supercomputer

The prototype for Fugaku, which is being developed by RIKEN and Fujitsu as a successor to the K computer, has recently been awarded the top spot on the Green500 list. This announcement demonstrates that the Fugaku prototype is the most energy-efficient of the world's 500 fastest computers as measured by the LINPACK benchmark.

Based at Fujitsu's plant in Numazu, Japan, the prototype achieved a mark of 16.876 gigaflops per watt of power. It also achieved a rating of 1.9995 petaflops on the LINPACK benchmark. The Supercomputer Fugaku, which will likely go into full operation in 2021, will be used in a variety of areas such as drug, natural disaster, and industrial simulations, and will become a platform for artificial intelligence and big data applications. **www.riken.jp/en/news_pubs/news/2019/20191118_1/**

CELEBRATIONS

Jean-Eric Paquet of the European Commission speaks at the event.

First anniversary of RIKEN's Europe Office

On 2 December 2019, a symposium in Brussels marked the first anniversary of the opening of RIKEN's Europe Office. More than 100 guests attended, including Takeshi Nakane, ambassador for Science and Technology of the Ministry of Foreign Affairs of Japan (MOFA), and Jean-Eric Paquet, Director General, DG Research and Innovation for the European Commission. In his welcoming address, RIKEN Executive Director Shigeo Koyasu said: "I hope today's symposium will be a trigger for further fruitful collaborations with European partners and beyond."

Representatives from RIKEN spoke about their respective centers and their partnerships with Europe, including director of the RIKEN Center for Sustainable Resource Science, Kazuo Shinozaki; director of the RIKEN Center for Integrative Medical Sciences, Tadashi Yamamoto; deputy director of the RIKEN Center for Emergent Matter Science, Seigo Tarucha, and director of the RIKEN Center for Computational Science, Satoshi Matsuoka.

The event also featured a panel discussion where policy specialists from Japan and the European Union, including Koshi Nitta, director of the International Science and Technology Affairs Division, part of the Science and Technology Bureau at the Ministry of Education, Culture, Sports, Science and Technology (MEXT), discussed trends in science and technology policy in Europe and Japan as well as the expansion of cooperation between RIKEN and research performing organizations in Europe. **www.riken.jp/en/news_pubs/news/2019/20191204_2/**

Front row at periodic table event

The closing ceremony of the International Year of the Periodic Table of Chemical Elements (IYPT) was held in Tokyo on 5 December 2019. The year 2019 marked 150 years since Russian chemist Dmitri Mendeleev arranged the 60 then-known elements into a periodic table, showing a pattern in chemical properties and hinting at undiscovered elements.

The IYPT was declared by the United Nations General Assembly and UNESCO and involved many events around the world. RIKEN has supported the IYPT and has been conducting educational outreach through public exhibitions and lectures.

The closing ceremony began with a greeting from Kohei Tamao, a RIKEN Honorary Science Advisor and chairman of the Executive Committee for IYPT2019 in Japan. Welcome addresses were also given by Natalia Tarasova, past president of the International Union of Pure and Applied Chemistry, who was co-chair of the Inter-Union Management Committee IYPT2019; Philippe Pypaert of the UNESCO Beijing Office; Grigory Trubnikov, First Deputy Minister of Science and Higher Education of the Russian Federation.

Kosuke Morita and Kouji Morimoto (top, front) represent nihonium. RIKEN President Hiroshi Matsumoto spoke.

RIKEN President Hiroshi Matsumoto also spoke, saying: "RIKEN is very lucky to have been able to contribute to the completion of the seventh period of the Periodic Table of the Elements. The periodic table is not only a driving force for chemistry and various scientific fields, but also a door that invites young people to science. I would like to thank everyone in the world who has contributed to this work for their great efforts."

The highlight was a session on recent international activities in the search for superheavy elements, chaired by Hideto Enyo, director of the RIKEN Nishina Center for Accelerator-Based Science. Fifteen scientists who were involved in creating and discovering superheavy elements appeared on stage to celebrate the completion of the 7th row of the periodic table, from the 104th element rutherfordium to the 118th element oganesson. From RIKEN, on behalf of the group who worked on element 113, nihonium, were Kosuke Morita and Kouji Morimoto of the Nishina Center.

A polarized light micrograph of a tangential section of human scalp showing sectioned hair follicles (round regions; dark ones still have hair intact). Levels of the enzyme Mpst in hair follicles could be a good biomarker for schizophrenia.

SCHIZOPHRENIA

Hair follicles could reveal sign of schizophrenia

Early diagnosis of a form of schizophrenia may be possible by measuring levels of a specific enzyme

A subtype of schizophrenia is related to abnormally high levels of hydrogen sulfide in the brain, RIKEN researchers have discovered[1]. This finding provides a new direction for exploring drug therapies and a biomarker for this type of schizophrenia.

Normally, we are not startled as much by a noise if it is preceded by a smaller burst—a phenomenon called prepulse inhibition (PPI). But people with schizophrenia generally have a lower PPI than people without the mental disorder.

Researchers at the RIKEN Center for Brain Science found that mice with low PPI expressed the enzyme Mpst in their brains more than mice with high PPI. This enzyme helps produce hydrogen sulfide, and the team found the low-PPI mice had higher hydrogen sulfide levels.

"Nobody has ever thought about a causal link between hydrogen sulfide and schizophrenia," says team leader Takeo Yoshikawa. "Once we discovered this, we had to figure out how it happens and if these findings in mice would hold true for people with schizophrenia."

To ensure that Mpst was the culprit, the researchers created an *Mpst*-knockout version of the low-PPI mice and found that they had a higher PPI than regular low-PPI mice. Thus, reducing the amount of Mpst helped the mice become more normal.

The researchers also found that *MPST* gene expression was higher in postmortem brains from people with schizophrenia than in those from unaffected people. Mpst protein levels in these brains also correlated well with the severity of schizophrenic symptoms.

The team then looked at *MPST* expression as a biomarker for schizophrenia. They examined hair follicles from more than 150 people with schizophrenia and found that expression of *MPST* mRNA was much higher than people without schizophrenia. Even though the results were not perfect—indicating that sulfide stress does not account for all cases of schizophrenia—*MPST* levels in hair could be a good biomarker for schizophrenia before other symptoms appear.

Because hydrogen sulfide can protect against inflammatory stress, the team hypothesized that inflammatory stress during early development might be the root cause. "We found that anti-oxidative markers—including the production of hydrogen sulfide—that compensate against oxidative stress and neuroinflammation during brain development were correlated with *MPST* levels in the brains of people with schizophrenia," says Yoshikawa.

Although current drugs for schizophrenia are not very effective and have side effects, pharmaceutical companies have stopped developing new drugs, Yoshikawa says. "A new paradigm is needed for the development of novel drugs," he explains. "Our results provide a new principle or paradigm for designing drugs, and we are currently testing whether inhibiting the synthesis of hydrogen sulfide can alleviate symptoms in mouse models of schizophrenia."

Reference

1. Ide, M., Ohnishi, T., Toyoshima, M., Balan, S., Maekawa, M., Shimamoto-Mitsuyama, C., Iwayama, Y., Ohba, H., Watanabe, A., Ishii, T. *et al.* Excess hydrogen sulfide and polysulfides production underlies a schizophrenia pathophysiology. *EMBO Molecular Medicine* **11,** e10695 (2019).

COMPUTATIONAL NEUROSCIENCE

Modeling a sense of responsibility

A simulation measures perception of action and outcome

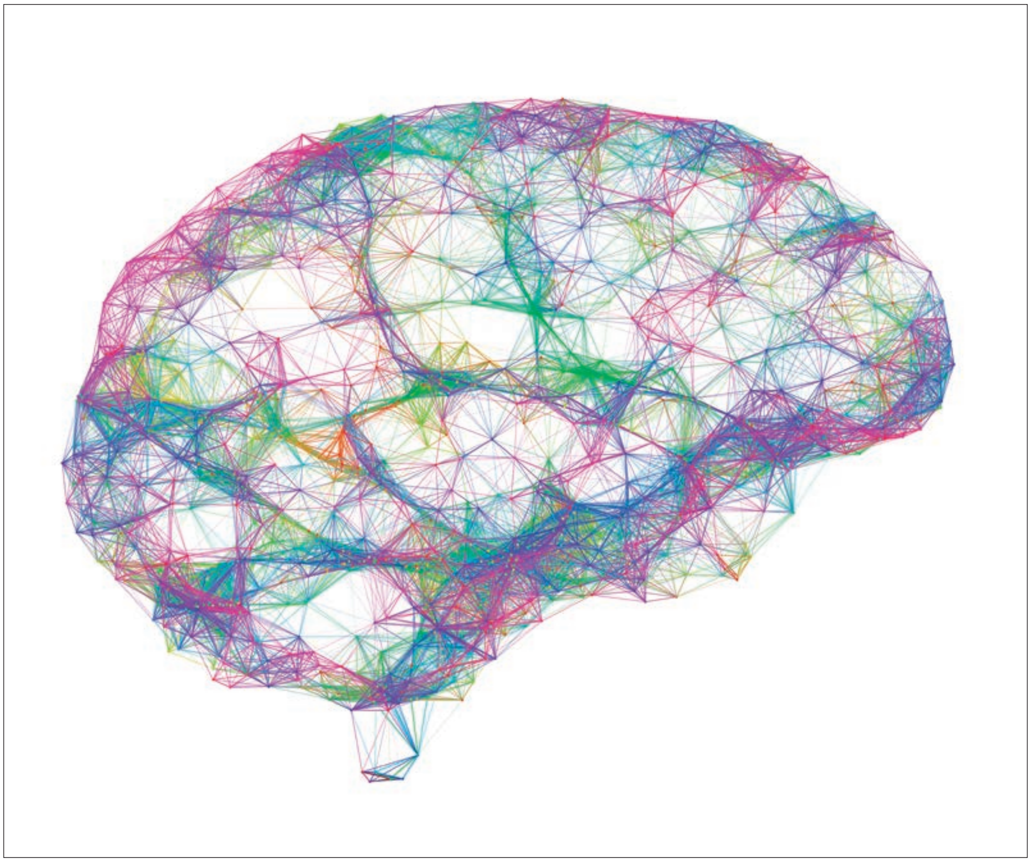
Two RIKEN neuroscientists have developed a model that helps to explain the sense people have that their actions cause events[1]. They have also proposed experiments for testing the model.

Our sense of agency is the feeling that we are responsible for our intended outcomes. As yet, scientists cannot explain how it arises in the brain.

"Understanding our sense of agency is fundamental to knowing ourselves," notes Taro Toyoizumi of the RIKEN Center for Brain Science (CBS), who devised the model together with CBS colleague Roberto Legaspi. It underpins the legal system, where people are held accountable for their deeds. It is also thought that people with schizophrenia and related disorders may wrongly think that their actions are caused by an external agent.

In a classic test of agency carried out in 2002, subjects pressed a button and would hear a sound. The subjects reported their estimates for the timings of their action and the sound. The results revealed that a person who believed that their action caused the sound would underestimate the delay between the two events, whereas someone who did not think they caused the outcome tended to overestimate the time delay. But there was no model to explain these perceptions.

Toyoizumi had previously worked on a model to explain the ventriloquism effect, in which a person is likely to mistakenly think that two spatially close events—a sound and a flash of light, for instance—originated from the same place, underestimating their true separation.



Two RIKEN neuroscientists have developed a model that helps to explain the sense people have that their actions cause events.

Legaspi and Toyoizumi adapted this model to describe the mistaken time-interval estimates seen in agency experiments. They performed computer simulations based on their model to investigate how people's perception of the time delay between action and outcome is related to their belief about whether they or something else caused the outcome. Their simulations matched the results of the classic experiment.

The model suggests that the person's perception that the outcome happened when they feel it should have occurred, underlies their sense of agency. "If our model is correct, human intention is not strictly needed to feel a sense of agency," explains Legaspi. "Reliable sensory inputs arriving at the predicted timing may be sufficient."

The two researchers say that their model can be tested with a fairly simple virtual-reality set up, in which the timings between action and outcome can be precisely controlled. If their predictions are correct, then follow-up brain-imaging tests could be used to monitor what happens when people believe they have caused an action, compared to when they do not feel responsible. ●

Reference

1. Legaspi, R. & Toyoizumi, T. A Bayesian psychophysics model of sense of agency. *Nature Communications* **10,** 4250 (2019).

NEUROSCIENCE

Brain waves vary with age of memory

The interaction between two brain regions differs for recent and distant memories

Recent and old memories can be distinguished based on the different brain activity signatures they produce, neuroscientists at RIKEN have found[1]. This finding has important implications for research into brain damage and memory loss.

Memory recall is considered to involve different neural circuits depending on when a memory was formed. Traditionally, scientists thought that memories are initially stored in the hippocampus and are transferred to the cortex over time. But there has been increasing evidence that the hippocampus is involved in the recall of old memories.

Now, a team led by Thomas McHugh of the RIKEN Center for Brain Science has explored the connection between the hippocampus and the anterior cingulate cortex (ACC) in the prefrontal brain at the level of signals from individual neurons.

Old and new memories in mice can be distinguished from the brain waves between a specific region in the hippocampus (red regions) and the anterior cingulate cortex.

"This suggests the hippocampus always plays a role in providing key details of an old experience."

They recorded activity in both brain areas before exposing mice to a foot shock and returned the mice to the same cage one day and one month later. If mice froze in the same context, it was a behavioral indication that they remembered the shock.

The neuronal recordings revealed that the ACC and hippocampus, specifically area CA1, were highly synchronized when mice recalled the fear memory. The interactions of the two brain areas changed over time, with ACC and CA1 activity becoming more correlated when an old or 'remote' memory was recalled compared to the recent, one-day memory.

"While memory is consolidated over time in frontal areas, we think in this case the ACC is facilitating the retrieval of contextual details back from the hippocampus," says McHugh.

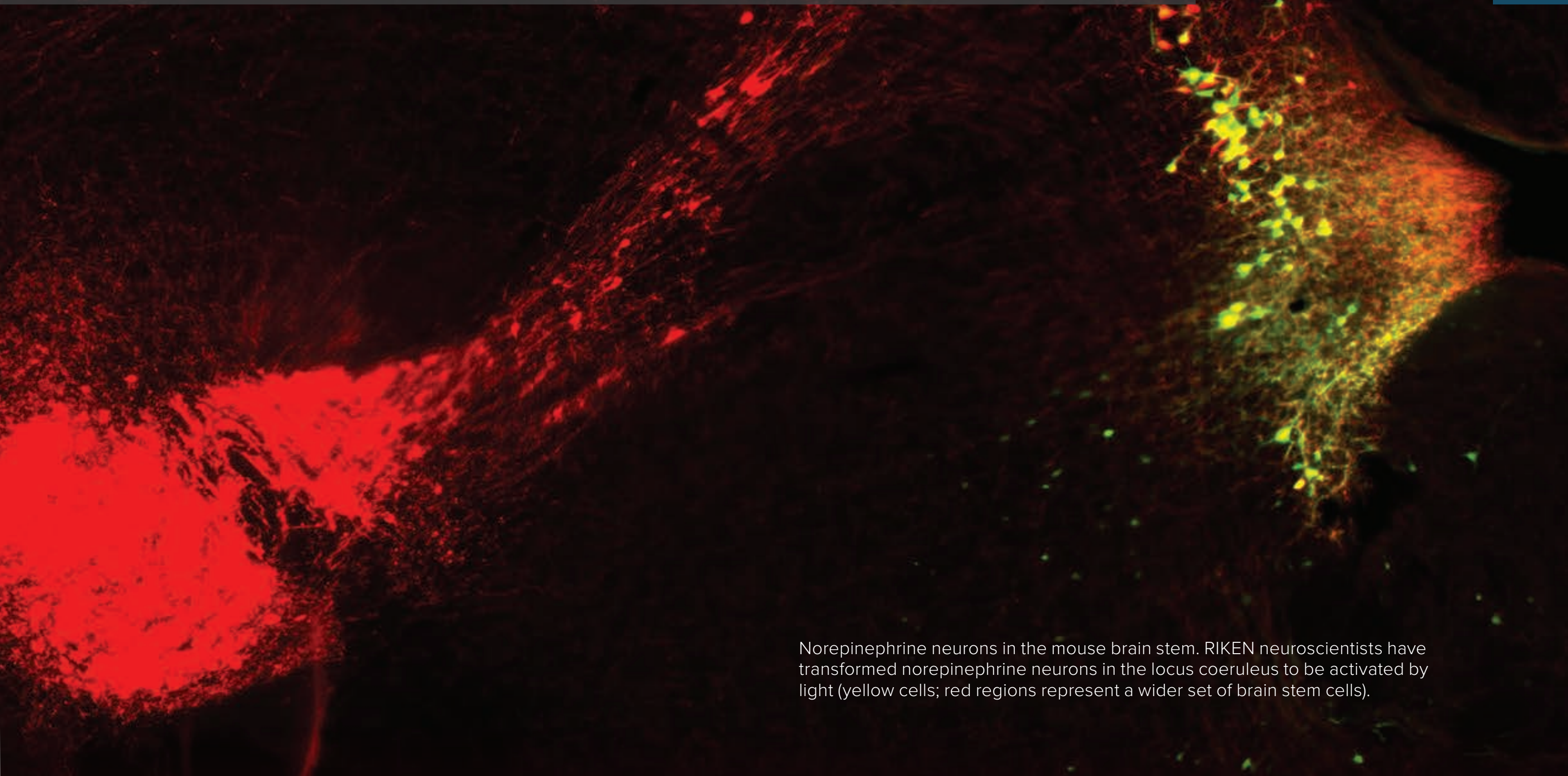
The evolving pattern of signals over time allowed the researchers to distinguish old and new memories in mice from the brain recordings alone. "We could decode whether a mouse was recalling a recent or remote memory by looking at the correlations in ACC–CA1 interactions," says McHugh. Moreover, the researchers suggest that a small group of CA1 neurons carries the information about memory age.

"While we have known for 20 years that the ACC is important for recalling older memories, how it contributes has remained a mystery," says McHugh. "We found that it plays an important role in organizing activity in the hippocampus, the part of the brain in which the memory was originally formed. This suggests the hippocampus always plays a role in providing key details of an old experience, at least in the healthy brain."

The team is now exploring how impairments in long-term memory that often accompany aging and disease impact activity in these brain circuits. ●

Reference

1. Makino, Y., Polygalov, D., Bolanos, F., Benucci, A. & McHugh, T. J. Physiological signature of memory age in the prefrontal-hippocampal circuit. *Cell Reports* **29,** 3835–3846 (2019).



Norepinephrine neurons in the mouse brain stem. RIKEN neuroscientists have transformed norepinephrine neurons in the locus coeruleus to be activated by light (yellow cells; red regions represent a wider set of brain stem cells).

NEUROSCIENCE

Thinking, fast and slow

Memories could be formed by different chemical pathways depending on whether a mouse is startled or in a state of heightened alert

A momentary startle releases a different signaling molecule in the mouse brain and generates a different type of memory from a sustained state of vigilance, RIKEN neuroscientists have found[1]. This finding provides new insights into how memories are formed and stored in the brain.

The release of the neurotransmitter norepinephrine (also called noradrenaline) is important for modifying the connections between neurons responsible for forming and consolidating memories. Brain cells called astrocytes are crucial mediators of these changes.

The RIKEN team wanted to observe in real time what happens in astrocytes when mice are learning. They induced brain cells in a brain region called the locus coeruleus (see image) to release norepinephrine by artificially stimulating them using laser light.

Norepinephrine release launched two chains of molecular events: one involving calcium activity and the other cyclic adenosine monophosphate (cAMP), an important signaling molecule. Calcium levels in astrocytes quickly became elevated after norepinephrine release, whereas cAMP levels exhibited a slower but more sustained increase.

"We think these fast and slow dynamics are significant because calcium elevation in astrocytes promotes synaptic plasticity, or the ability of cells to form new memory connections, while cAMP elevation mobilizes energy metabolism for memory consolidation," explains Hajime Hirase of the RIKEN Center for Brain Science (CBS).

To see how these fast and slow molecular responses are triggered naturally, mice were given random air puffs to the face to evoke startle responses. In this situation, cAMP levels did not go up at all, whereas calcium levels became elevated, as observed previously.

In a second experiment, mice were given a foot shock coupled with a sound to create a fear memory. When they heard the sound again, the mice would freeze in anticipation of a shock. This time, cAMP levels were noticeably higher, while calcium levels also rose but quickly tapered off.

"When mice are in this sustained state of vigilance, a lot of norepinephrine is released, coupled with gradually building cAMP," explains Yuki Oe, also at CBS. "This reflects how the astrocytes support the formation of fear memory."

Mice that had been given norepinephrine-blocking drugs did not exhibit calcium or cAMP responses, indicating that norepinephrine release triggers these changes.

The short- and long-term consequences of norepinephrine release in the brain thus depend on the situation and behavior. In particular, memory formation seems to be supported by cAMP level increases, whereas transient or low-vigilance states involve the short-term elevation of calcium levels.

"One of the effects of cAMP is to break down glycogen for quick energy in a fight-or-flight situation," comments Hirase. "This boosting of energy metabolism could help consolidate memories over longer time scales, while rapid calcium boosts could lower the threshold for synaptic plasticity." ●

Reference

1. Oe, Y., Wang, X., Patriarchi, T., Konno, A., Ozawa, K., Yahagi, K., Hirai, H., Tian, L., McHugh, T. J. & Hirase, H. Distinct temporal integration of noradrenaline signaling by astrocytic second messengers during vigilance. *Nature Communications* **11**, 471 (2020).

PLANT GENETICS

Roots of weed's parasitism run deep

Sequencing the genome of a parasitic plant offers a glimpse of its evolution and points the way toward improved control

The genome of the parasitic plant *Striga*, commonly known as witchweed, has been sequenced for the first time by RIKEN plant geneticists[1]. This genetic analysis both offers insights into how parasitic plants evolved and a tool for improving the monitoring and control of the costly weed.

A major agricultural pest, *Striga* (see image) causes billions of dollars of crop losses annually. It taps into the roots of host plants, depriving them of water and nutrients. Herbicides and mechanical removal can control the weed, but these methods are costly and do not remove seeds in the soil.

These findings open the door to further genetic and genomic analyses.

To improve our understanding of *Striga*'s evolution and biology, Ken Shirasu's team at the RIKEN Center for Sustainable Resource Science has sequenced the genome of a *Striga* species that invaded the US in the 1950s. They also sequenced the transcriptome of the most devastating *Striga* species.

The team identified roughly 35,000 protein-coding genes in the genome, and their analysis revealed evidence of two whole-genome duplication events in its evolution. More significantly, they found evidence that the *Striga* genome evolved in three phases, as suggested by theories of parasitic plant evolution.

First, *Striga* acquired genes to form its infectious root by repurposing genes normally involved in the regulation of lateral roots.

Next, the parasite lost certain functions in favor of getting a resource from the host. For example, gene families related to photosynthesis shrunk in *Striga* because it relies on carbon from its host. *Striga* also lost many genes responsible for hormonal response to environmental stimuli such as water loss.

Third, the relationship became more specialized on specific hosts. *Striga* seeds and seedlings sense their host by detecting hormones known as strigolactones. The strigolactone-sensing gene family was dramatically expanded in *Striga*, enabling the seedlings to recognize and colonize on a wide range of hosts.

"The expansion of the strigolactone-sensing gene family was surprising," says Shirasu. "We also found that many of these genes are expressed not in seeds but in roots, meaning that some of the gene family members are doing something other than controlling germination."

Finally, comparison of the *Striga* genome with other plant genomes revealed several transfers of large genomic fragments between species. This suggests that *Striga* can acquire genetic material from its hosts, which may have affected its evolution.

These findings open the door to further genetic and genomic analyses. "With this genomic data, we can also currently monitor *Striga* spreading in field at the genome level," says Shirasu. "This means that we can learn how *Striga* is adapting to infect current cultivars or to avoid agrochemicals, which could provide a strategy to select cultivars and chemicals."

The devastating parasitic plant *Striga hermonthica*.

Reference

1. Yoshida, S., Kim, S., Wafula, E. K., Tanskanen, J., Kim, Y.-M., Honaas, L., Yang, Z., Spallek, T., Conn, C. E., Ichihashi, Y. *et al.* Genome sequence of *Striga asiatica* provides insight into the evolution of plant parasitism. *Current Biology* **29,** 3041–3052 (2019).

PHOTORECEPTOR PROTEINS

First responder to light revealed

The protein component of a light-sensitive molecule in bacteria reacts first to light

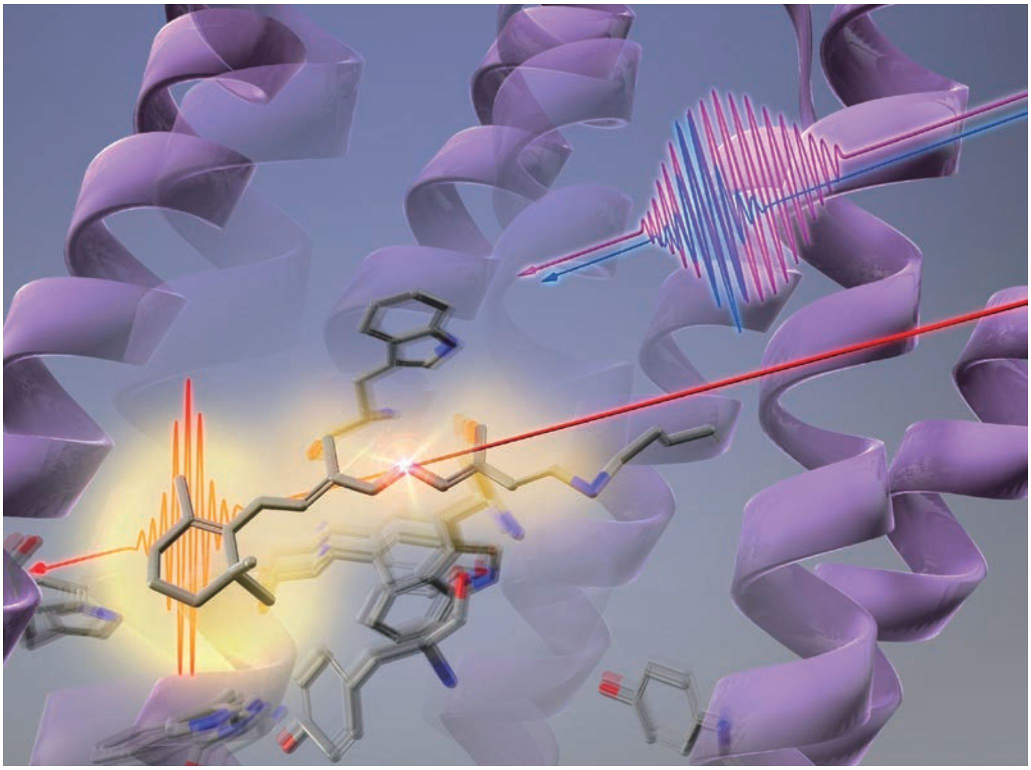
The sequence of changes that light triggers in a bacterial photoreceptor starts with its protein scaffolding rather than the light-absorbing chromophore, an all-RIKEN team has shown[1]. This finding goes against conventional wisdom and sheds new insight on how photoreceptors can convert light into chemical energy so efficiently.

Many bacteria use special light-sensitive molecules known as photoreceptor proteins to turn light into chemical energy, which they use to initiate various biological functions.

Scientists have long wanted to know how bacterial photoreceptors are so efficient in converting light. "One of the fundamental questions is how these biomolecules realize such high-efficiency, low-energy photoreactions," says Tahei Tahara. "This has been a long-standing question." One motivation for uncovering the mechanism of these photoreceptors is that it could inform efforts to develop artificial versions of these molecules.

The most well-studied bacterial photoreceptor, bacteriorhodopsin, contains a retinal chromophore, which changes shape when it absorbs a photon of yellow light. This configuration change sets off a series of structural changes in bacteriorhodopsin that enables it to pump protons.

Interestingly, when the retinal chromophore of bacteriorhodopsin is placed in solution, its light-conversion efficiency is three times lower than when it is nestled within the protein structure of bacteriorhodopsin. This clearly indicates that the protein plays an important role in aiding the conversion of light into chemical energy.



RIKEN researchers have found that light (long red line) first causes the shape of the protein (purple twirls) to change before the retinal chromophore (stick-like structure) in bacteriorhodopsin undergoes photoisomerization.

The conformational change of the retinal chromophore was assumed to be the first response of bacteriorhodopsin to light. But Tahara and his co-workers at the RIKEN Molecular Spectroscopy Laboratory and the RIKEN Center for Advanced Photonics have now discovered that there is a step that precedes it—the protein that cradles the retinal chromophore first alters its shape in response to light. This change in the protein could help the retinal chromophore use light efficiently.

The team took a spectroscopic technique known as femtosecond stimulated Raman spectroscopy, which can observe processes that occur faster than a picosecond (1 picosecond = 10^{-12} seconds), and extended it to the deep ultraviolet region. This allowed them to look at the protein part of bacteriorhodopsin (see image).

This discovery came as a surprise to Tahara. "I didn't expect that the protein would change shape before chromophore isomerization, but when I saw the experimental results I thought 'Wow, it's actually the case'," he says. "It was most surprising, and we were very excited."

While the team looked at bacteriorhodopsin in this study, they anticipate that the same effect could well occur in other rhodopsins. ●

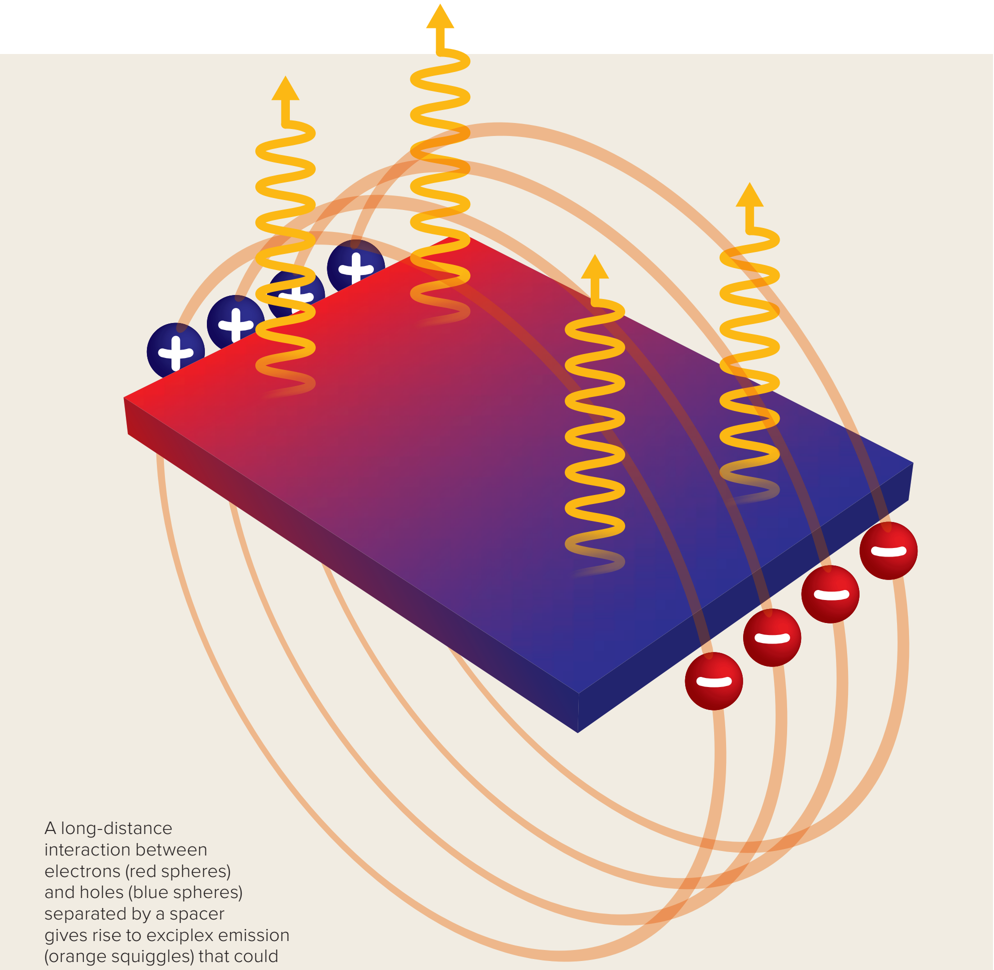
Reference

1. Tahara, S., Kuramochi, H., Takeuchi, S. & Tahara, T. Protein dynamics preceding photoisomerization of the retinal chromophore in bacteriorhodopsin revealed by deep-UV femtosecond stimulated Raman spectroscopy. *The Journal of Physical Chemistry Letters* **10,** 5422–5427 (2019).

EXCIPLEX EMISSION

Long-distance light sources

Light emission has been generated by two molecules separated by an exceptionally long distance



A long-distance interaction between electrons (red spheres) and holes (blue spheres) separated by a spacer gives rise to exciplex emission (orange squiggles) that could be used in efficient organic light-emitting diodes (OLEDs).

Highly sensitive sensors and photodetectors could result from RIKEN-led research that has shown that light-emitting complexes can form over far greater distances than ever suspected[1].

An exciplex is an excited-state complex formed between a molecule that donates electrons and one that accepts electrons. Exciplexes are generally of interest for their favorable light-emission properties. In particular, the excited state is readily able to undergo a process that enhances the efficiency of organic light-emitting diodes (OLEDs).

The two molecules usually have to be within a few nanometers of each other for an exciplex to form. However, by placing the electron donor and electron acceptor on either side of a spacer layer, Yong-Jin Pu from the RIKEN Center for Emergent Matter Science and his collaborators have created exciplexes when the donor and acceptor are up to 70 nanometers apart.

The team started with a spacer layer 10 nanometers thick, and then increased the thickness in increments of 10 nanometers. Remarkably, exciplex light emission was still seen even when the spacer thickness reached 70 nanometers.

"We tried to create a new and unique exciplex state, in which the electron-donor molecule and the electron-acceptor molecule are separated by a thick spacer layer," Pu explains. "The discovery was a big surprise—the spacer was much thicker than the 10-nanometer spacers previously reported. The exceptional thickness goes far beyond previous preconceptions."

The team used four different electron-donor molecules to demonstrate that the light emission really was from exciplex formation. "The type of donor molecule must influence the emission wavelength of the exciplex, due to the change of energy difference between the donor and acceptor," Pu explains. The emissions varied just as expected, confirming the formation of exciplexes.

Although the mechanism behind such long-distance exciplex formation is not yet well understood, the spacer layer plays an important role, Pu says. The spacer forms an exciplex state with the donor molecule and also with the acceptor molecule, the researchers suspect (see image). "The spacer molecule behaves as an acceptor to the donor molecule, and simultaneously behaves as a donor to the acceptor molecule," Pu says. "We're now trying to understand the mechanism and hidden physics of this long-distance exciplex formation and its emission."

The team is also considering possible applications of their surprising discovery, which may lie outside of the usual OLEDs. "We anticipate that this totally new exciplex could lead to highly sensitive sensors or photodetectors to external stimulus," Pu says. ●

Reference

1. Pu, Y.-J., Koyama, Y., Otsuki, D., Kim, M., Chubachi, H., Seino, Y., Enomoto, K. & Aizawa, N. Exciplex emissions derived from exceptionally long-distance donor and acceptor molecules. *Chemical Science* **10,** 9203–9208 (2019).

NEUROSCIENCE

A vital gene in the mating game

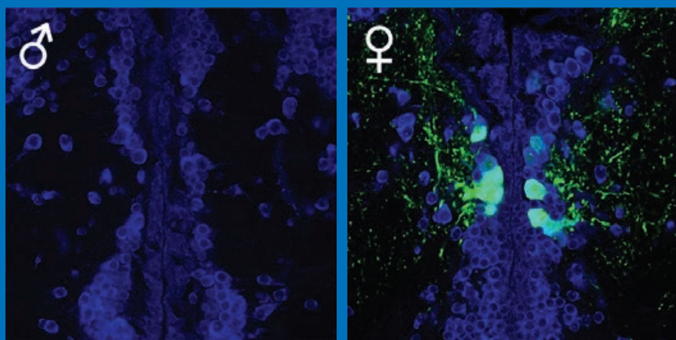
Eliminating genes for a neuropeptide can cause abnormalities in the sexual receptivity of female fish

A peptide expressed in the brains of fish helps to determine the different mating behaviors of the two sexes, RIKEN and University of Tokyo scientists have found[1]. This advances our understanding of the neurological processes that cause the sexes to behave differently in courtship.

For a long time, the sexual behavior of vertebrates, particularly mammals and birds, has been considered basically irreversible. The sex steroids produced early in life generally determine their sexual behavior.

But there are exceptions. Fish belonging to the teleost order, for example, can undergo physical and behavioral sex reversal in the wild. Researchers have even reversed the mating behaviors of such fish by manipulating their hormones. However, the genetic regions affected by hormones that govern vertebrate sexual reversibility have remained elusive.

Now, Towako Hiraki-Kajiyama at the RIKEN Center for Brain Science and her colleagues have examined the brains of medaka (see bottom image)—a teleost fish—for gene expression that depends on the sex of the fish.



Fluorescence micrographs of the brains of male (left) and female (right) medaka fish. They show that neuropeptide B (green regions) is expressed in this nucleus only in females.

"A big motivation behind our work was to uncover the sex differences in the brain that lead to sex differences in behavior," Hiraki-Kajiyama explains.

The team examined gene expression differences in medaka and found that a gene coding for neuropeptide B (NPB) is expressed exclusively in some nuclei in the female brain (see top image). Importantly, the brain region where Hiraki-Kajiyama's team discovered this female-specific NPB expression is the region most related to sexual behavior. Together, these findings suggested that expression of NPB might be the neurological difference between the mating behaviors of male and female medaka.

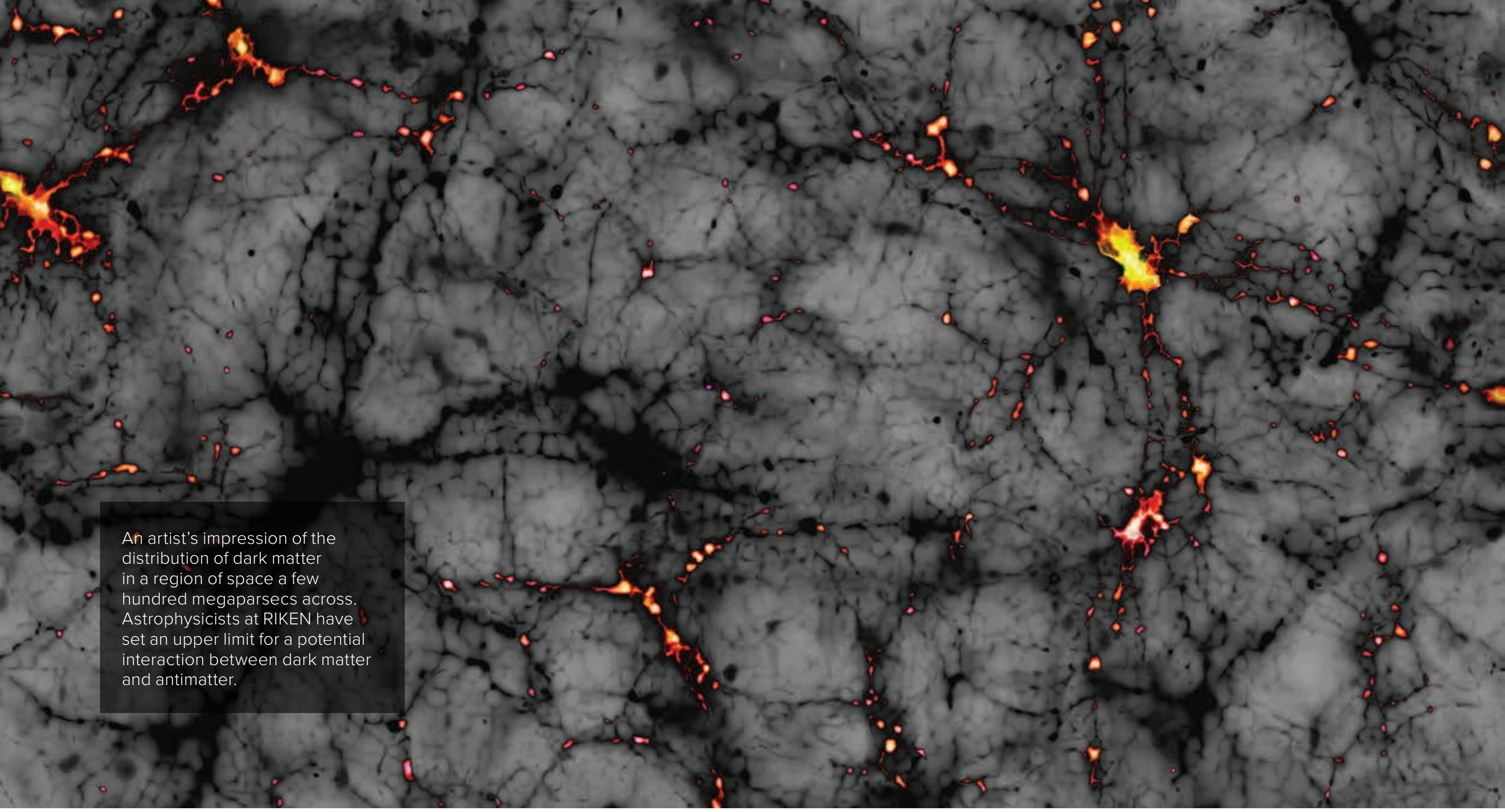
To confirm this, the team knocked out the *npb* genes and their protein receptors and found that female sexual behavior was altered when NPB was absent—a clear indicator that it is implicated in the genetic determination of sexual behavior.

The way in which the knockout affected sexual behavior surprised the researchers. "Most females spawn within a minute after viewing the courtship display of males, but many of the female knockout fish spawned without getting courtship display from males," Hiraki-Kajiyama says. "I would never have anticipated such a change, so I was surprised and very interested." This might mean that the NPB system enables females to select a suitable mate by mating only with males that show courtship display.

Since NPB is well conserved among vertebrates, including humans, it could affect sexual behavior in other species. "NPB is also expressed in mammals in brain regions thought to be homologous to the nuclei that have female-specific NPB expression, so NPB may be involved in female sexual receptivity in mammals," notes Hiraki-Kajiyama. ●

Reference

1. Hiraki-Kajiyama, T., Yamashita, J., Yokoyama, K., Kikuchi, Y., Nakajo, M., Miyazoe, D., Nishiike, Y., Ishikawa, K., Hosono, K., Kawabata-Sakata, Y. *et al.* Neuropeptide B mediates female sexual receptivity in medaka fish, acting in a female-specific but reversible manner. *eLife* **8**, e39495 (2019).



An artist's impression of the distribution of dark matter in a region of space a few hundred megaparsecs across. Astrophysicists at RIKEN have set an upper limit for a potential interaction between dark matter and antimatter.

COSMOLOGY

Killing two cosmic mysteries with one hypothetical particle

Experimentalists test whether the problems of antimatter and dark matter could be related

A RIKEN-led team has completed the first laboratory experiments to probe whether antimatter interacts slightly differently with dark matter than normal matter does[1]. If found, such an interaction could be the key to solve the mysteries of dark matter and antimatter—two of the biggest unsolved mysteries of modern physics.

The Big Bang should have created equal amounts of matter and antimatter, but the Universe we live in is made only of matter. Antimatter is created every day in experiments and even by natural processes such as lightning, but it is quickly annihilated when it collides with regular matter. Predictions based on our understanding of the matter content of the Universe are off by a factor of one billion, and no one knows why the asymmetry exists.

In the case of dark matter, astronomical observations indicate that some unknown mass is influencing the orbits of stars in galaxies, but the properties of dark-matter particles remain unknown. One theory is that they are a type of hypothetical particle known as an axion, which plays an important role in explaining the lack of symmetry violation in the strong interaction in the standard model of particle physics.

The researchers designed an experiment to test whether the lack of antimatter might be because antimatter interacts differently with dark matter than normal matter does. They used a specially designed device to magnetically trap a single antiproton, preventing it from contacting ordinary matter and being annihilated.

The team then measured a property of the antiproton called its spin precession frequency. Normally, this should be constant in a given magnetic field, and a modulation of this frequency could be accounted for by an effect mediated by axion-like particles, which are hypothetical candidates for dark matter.

While the experiment did not measure any variation in the spin precession frequency, the results are useful for theorists. "For the first time, we have explicitly searched for an interaction between dark matter and antimatter, and though we did not find a difference, we set a new upper limit for the potential interaction between dark matter and antimatter," says Christian Smorra, a member of the RIKEN Ulmer Fundamental Symmetries Laboratory.

The team intends to enhance the precision of their experiment. "We plan to further improve the accuracy of our measurements of the antiproton's spin precession frequency, allowing us to set more and more stringent constraints on the fundamental invariance of charge, parity, and time, and to make the search for dark matter even more sensitive," says Stefan Ulmer, who leads the laboratory. ●

Reference

1. Smorra, C., Stadnik, Y. V., Blessing, P. E., Bohman, M., Borchert, M. J., Devlin, J. A., Erlewein, S., Harrington, J. A., Higuchi, T., Mooser, A. *et al.* Direct limits on the interaction of antiprotons with axion-like dark matter. *Nature* **575,** 310–314 (2019).

QUANTUM PHYSICS

Kondo cloud spotted for the first time

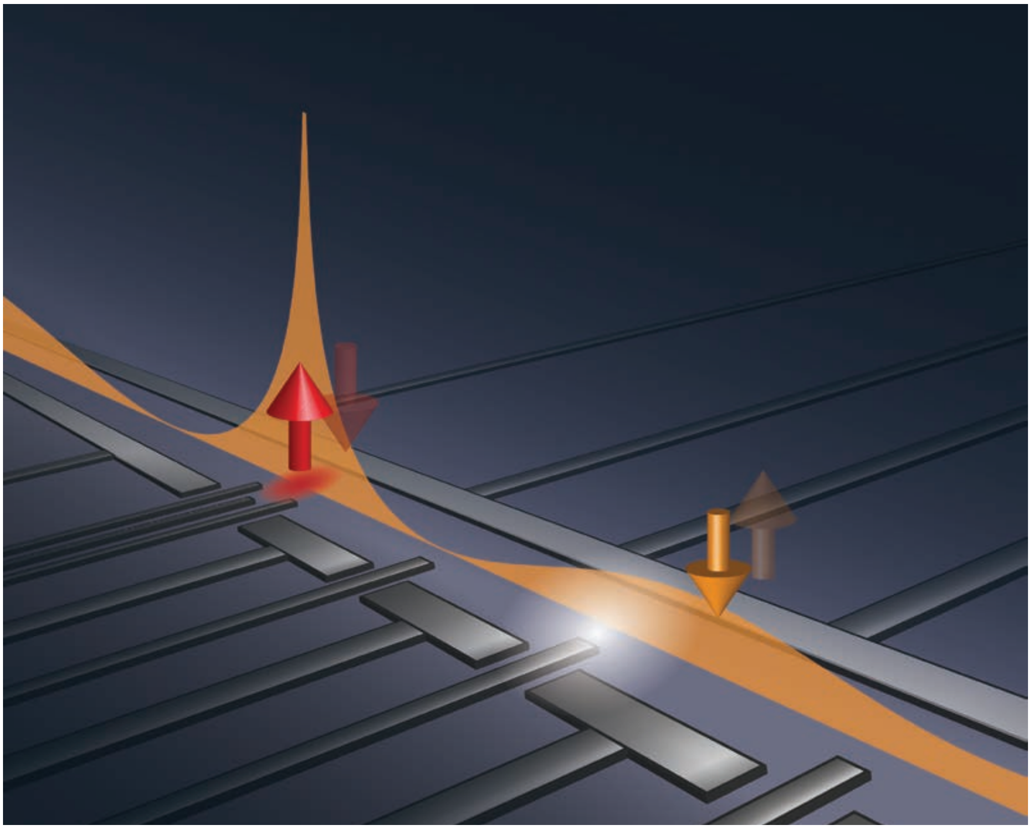
Predicted more than half a century ago, a quantum effect has now been directly observed

A quantum object known as the Kondo cloud has been directly observed by RIKEN experimentalists, ending a half-century quest[1]. This cloud is important for many physical systems including high-temperature superconductors and could provide physicists with new ways to manipulate such systems.

Magnetism arises from a property of electrons known as spin, which is essentially the angular momentum of an electron. The spins of electrons that flow freely in a material, known as conduction electrons, become entangled with a localized magnetic impurity and effectively screen it. This is called the Kondo effect after the Japanese theoretical physicist Jun Kondo who first revealed the effect in the mid-1960s, and its strength is known as the Kondo temperature.

The cloud size is another important parameter for materials that contain more than one magnetic impurity because the spins in the cloud couple with one another and mediate the coupling between magnetic impurities when the clouds overlap. This happens in various materials including high-temperature superconductors.

Although the Kondo effect for a single magnetic impurity is covered in textbooks on many-body physics, the Kondo cloud had not been directly detected until now despite many attempts over the past five decades. It was known to exist, but its spatial extension had never been observed, creating a controversy over whether such an extension actually existed.



Schematic depiction of the setup used to detect a Kondo cloud. (Image was created by Jeongmin Shim at KAIST based on his theoretical calculation of the Kondo cloud shape.)

Now, Michihisa Yamamoto of the RIKEN Center for Emergent Matter Science and his co-workers have observed a Kondo screening cloud formed by an impurity consisting of a localized electron spin in a quantum dot—a type of artificial atom—coupled to conduction electrons that are nearly aligned along a straight line (see image).

The researchers slightly perturbed conduction electrons far from the quantum dot using an electrostatic gate. The wave of conducting electrons scattered by this perturbation returned to the quantum dot and interfered with itself, similar to how a water wave forms striped ripples on being scattered by a barrier. The researchers measured changes in the Kondo temperature, allowing them to investigate the extent of the cloud at the location of the perturbation. They found that the size and shape of the cloud agreed well with theoretical calculations.

"It is very satisfying to have been able to obtain a real-space image of the Kondo cloud, as it is a real breakthrough for understanding various systems containing multiple magnetic impurities," says Yamamoto. "This achievement was only made possible by close collaboration with theorists. This opens up a novel way to engineer spin screening and entanglement." ●

Reference

1. Borzenets, I. V., Shim, J., Chen, J. C. H., Ludwig, A., Wieck, A. D., Tarucha, S., Sim, H.-S. & Yamamoto, M. Observation of the Kondo screening cloud. *Nature* in press. DOI: 10.1038/s41586-020-2058-6

SPIDER SILK

A new spin on spider webs

Two kinds of ions are shown to have opposite effects on spider silk protein

Artificial spider silk is a step closer to become a reality after an all-RIKEN team has revealed the role ions play in the production of spider silk[1].

Spider silk is one of nature's super materials, being light, flexible and biodegradable, while being stronger than steel on a weight-for-weight basis.

But spiders cannot be cultivated like silkworms. "We can't farm spiders because they kill each other," explains Nur Alia Oktaviani of the RIKEN Center for Sustainable Resource Science (CSRS). "In our lab, if we don't keep them in separate boxes, they start fighting to the death within seconds."

As a result, there is a strong desire to produce artificial spider silk. However, while many venture companies are making artificial silk fibers, the fibers lack the strength of natural spider silk. "We'd like to produce tougher artificial fibers that are more like natural spider silk," says Keiji Numata, also of CSRS.

Silk being secreted from the abdomen of a Golden Silk spider (*Nephila clavipes*). Chemists at RIKEN have shown the role that ions play in the formation of spider silk.

"We'd like to discover the secrets of natural spinning systems."

There are still many things scientists don't understand about how spiders produce silk. "We'd like to discover the secrets of natural spinning systems," comments Oktaviani. In particular, it is not clear how the liquid in the spider's abdomen solidifies into a fiber on being ejected from the spider's spinning duct.

Now, Oktaviani and Numata, with two co-workers, have used nuclear magnetic resonance (NMR) to see how ions affect the shape and dynamics of a highly pure form of spider silk protein produced by bacteria that had been genetically engineered to produce the protein.

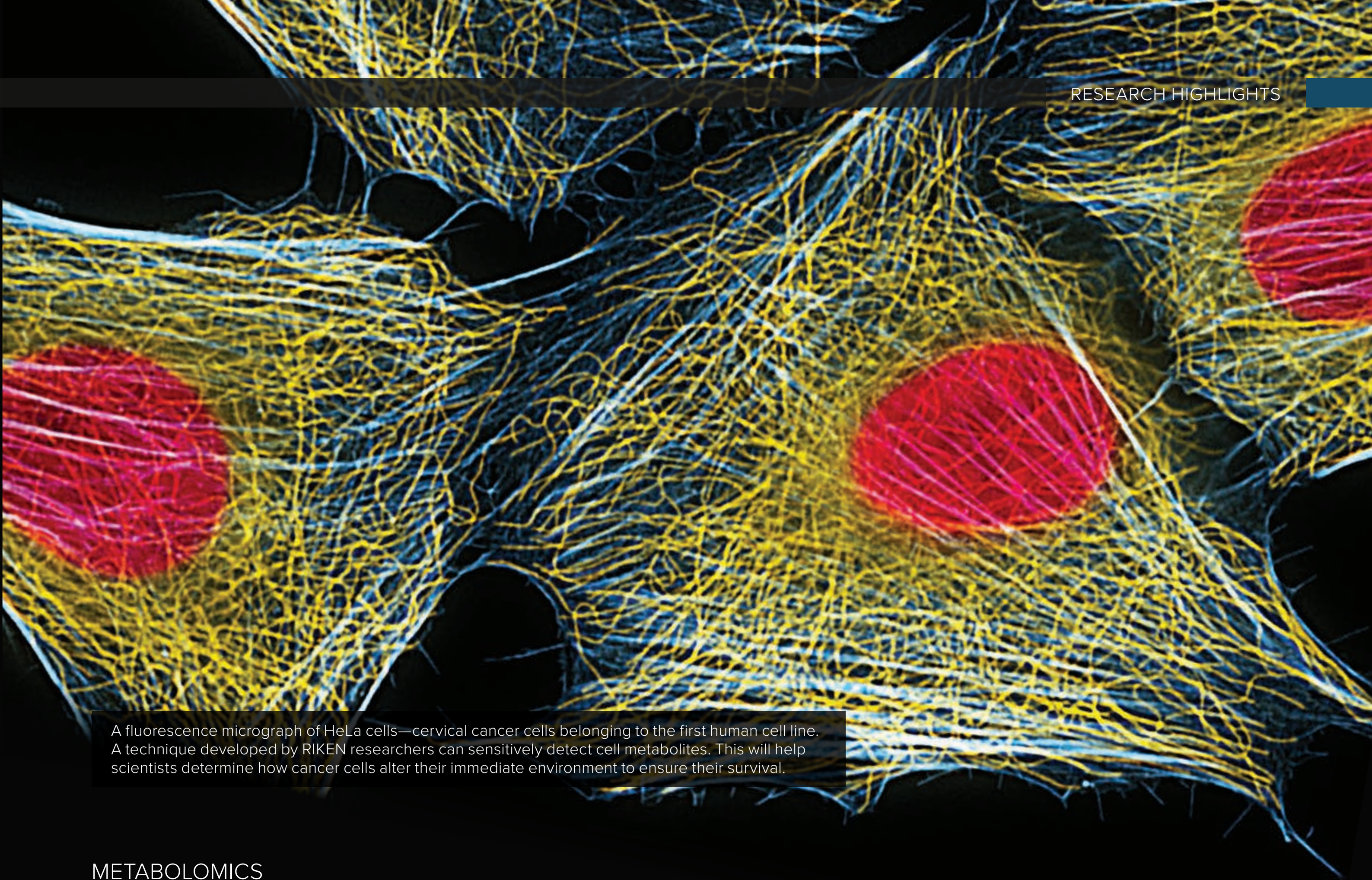
The researchers discovered that two types of ions in a spider's abdomen have different effects on spider silk protein. Ions of sodium and chlorine inhibit the formation of bonds between the molecules of spider silk protein and thus keep it in the liquid state. In contrast, ions of phosphate and sulfate promote the formation of hydrogen bonds between protein molecules and hence promote the solidification of spider silk.

The team was inspired to look at the effects of ions by previous studies that had found that an ion gradient exists inside a spider's abdomen: the concentration of the bond-inhibiting ions decreases toward the end of the spinning duct, whereas that of the bond-inducing ions increases. This gradient now makes perfect sense in light of the current results: the spider silk protein needs to be liquid in the spider's abdomen, but it needs to solidify on ejection from the spinning duct.

This finding will help inform efforts to produce artificial spider silk. "In the future, researchers should consider ion gradients if they want to make artificial spider silk," Numata says.

Reference

1. Oktaviani, N. A., Matsugami, A., Hayashi, F. & Numata, K. Ion effects on the conformation and dynamics of repetitive domains of a spider silk protein: implications for solubility and β-sheet formation. *Chemical Communications* **55,** 9761–9764 (2019).



A fluorescence micrograph of HeLa cells—cervical cancer cells belonging to the first human cell line. A technique developed by RIKEN researchers can sensitively detect cell metabolites. This will help scientists determine how cancer cells alter their immediate environment to ensure their survival.

METABOLOMICS

Detecting the metabolites of a single cell

An ultrasensitive analysis technique can detect the small molecules that a single cell makes

An analytical technique that is so sensitive it can identify the small molecules produced by a single cell has been made and demonstrated by an all-RIKEN team[1]. This opens up the possibility of analyzing the roles individual cancer cells play in tumor growth and survival.

Cells are tiny chemical factories, constantly manufacturing the compounds they need to survive and thrive. Their DNA contains instructions for how to make these compounds. Which compounds they produce at any particular time is determined in part by their environment.

Geneticists can currently determine the genetic makeup of a single cell and the messenger RNA that it produces. But there is no technique capable of reliably profiling the small molecules, or metabolites, that a single cell produces. Researchers would dearly love to be able to do this because it would provide a valuable window into how single cells react to their environment.

One area where such a technique is badly needed is cancer biology. "Cancer stem cells regulate their environment so that it is acidic and has low oxygen levels—this is a vital survival strategy for cancer cells," explains Takayuki Kawai of the RIKEN Center for Biosystems Dynamics Research. "But since this is a microscale phenomenon involving 10 to 100 cells, it is important to analyze microscale samples, even down to a single-cell level."

Now, Kawai and his co-workers have boosted the sensitivity of a conventional metabolomic analytic technique known as capillary electrophoresis–mass spectrometry (CE-MS) by up to 800 times, allowing them to profile the metabolites that a single cell produces.

The researchers improved CE-MS, which is typically used to analyze tens of thousands of cells, in two ways—they used a specially designed system to concentrate the sample before analysis and they used a thin-walled, tapered glass capillary tube to deliver the sample to the mass spectrometer.

The team demonstrated the sensitivity of their technique by using it to identify 40 metabolites from a single human cervical cancer cell. "This is the first time this level of analysis has been achieved," notes Kawai. "That's because our system is currently the most sensitive in the metabolomic analysis system in the world."

The team is looking for ways to apply their technique to areas of clinical interest. "This technique allows us to directly analyze metabolites from cellular micro-environments in humans such as tumors," says Kawai. "We're now searching for good target molecules for clinical applications, such as drug discovery and diagnosis." ●

Reference

1. Kawai, T., Ota, N., Okada, K., Imasato, A., Owa, Y., Morita, M., Tada, M. & Tanaka, Y. Ultrasensitive single cell metabolomics by capillary electrophoresis–mass spectrometry with a thin-walled tapered emitter and large-volume dual sample preconcentration. *Analytical Chemistry* **91,** 10564–10572 (2019).

WEARABLE ELECTRONICS

Wearing your heart monitor on your sleeve

Strong bonds between metal nanowires and polymer nanofibers enable a composite film to realize good electrical conductivity and high stretchability

RIKEN engineers have made a breathable material that is both highly stretchable and has good electrical conductivity, making it promising for on-skin electronics for people and wiring for robots[1].

To be suitable for use as wearable electronics, a material needs to be both stretchable and conductive. It should also be breathable and durable. Finding a material that satisfies all four criteria is not easy. One promising strategy is to combine elastic polymer nanofibers with a network of conductive metal nanowires, but it is challenging to get the two components to bond tightly to each other.

The film could find use as electrical wiring that can be used on the skin.

Now, Kenjiro Fukuda and Zhi Jiang of the RIKEN Thin-Film Device Laboratory and their co-workers have succeeded in producing a stretchable and conductive material by combining polyurethane nanofibers with silver nanowires.

Importantly, the two components bond strongly to each other. "There's very good adhesion between the silver nanowires and the polyurethane nanofibers," notes Fukuda. "This is why we simultaneously achieved a very good stretchability and conductivity." The team suspects that hydrogen bonds—the same bonds that hold pulp fibers together in a sheet of paper—are responsible for this good adhesion.

The film could find use as electrical wiring that can be used on the skin. Its flexibility allows it to stretch when a person bends their elbow or knee, and it can be stretched to three times its initial length. In the same way, it could also be used for wiring on robots.

Another potential use is as a sensor. Because its conductivity changes when it is stretched, it can be used to detect movement. The team demonstrated this by using their film to monitor the angle of a bent wrist and detect a person's pulse.

The film has other advantages besides good stretchability and conductivity. When the researchers tested their film by stretching and releasing it 1,000 times, they observed that its conductivity dropped off only moderately, indicating that it has good durability. Furthermore, it is easy to fabricate. "This film can be obtained by solution processes," says Fukuda. "That's very important for the mass production of the industrial product."

A photo of the film attached to a person's finger. It can be used as a wearable sensor to monitor heart rate and other movement.

Fukuda notes that his team resembles the material in that it combines researchers with different fields of expertise. Jiang brought his knowledge of stretchable nanowires to the project, while Fukuda and other team members supported the fabrication of the polymer nanomesh structures.

The team intends to improve the stretchability of the material by using longer silver nanowires. They also plan to experiment with other combinations of materials and pursue applications of these breathable conductors in real-time health monitoring systems and soft robotics. ●

Reference

1. Jiang, Z., Nayeem, M. O. G., Fukuda, K., Ding, S., Jin, H., Yokota, T., Inoue, D., Hashizume, D. & Someya, T. Highly stretchable metallic nanowire networks reinforced by the underlying randomly distributed elastic polymer nanofibers via interfacial adhesion improvement. *Advanced Materials* **31,** 1903446 (2019).

GENOME-WIDE ASSOCIATION STUDIES

Coffee habit could be genetically brewed

Certain genes make a person more predisposed to habitually consume a particular kind of food

Coffee drinking might be in your genes. RIKEN geneticists have found four genes that coffee drinkers often have.

Geneticists at RIKEN have found nine gene locations that are associated with the consumption of various foods and drinks such as meat, tofu, cheese, tea and coffee[1]. Among them, three were also related to having particular diseases such as cancer or diabetes.

Scientists usually conduct genome-wide association studies to determine whether a disease is related to a specific genetic variation. To do this, they group hundreds of thousands of people depending on whether or not they have the disease, and compare the genomes across groups. They scan the whole genome looking at variations in DNA called single nucleotide polymorphisms (SNPs). If they find one that is consistently associated with the disease group, they can say that people with that genetic variation might be at risk of the disease.

In the present study, rather than looking first at diseases, the RIKEN team looked at dietary habits since they wanted to determine whether any specific genetic variations make people 'at risk' of habitually eating certain foods.

"We know that what we eat defines what we are, but we found that what we are also defines what we eat," says Yukinori Okada, a visiting scientist at the RIKEN Center for Integrative Medical Sciences.

Using genetic data from more than 160,000 Japanese people who had filled out a food-frequency questionnaire, the team found nine genetic loci—positions on chromosomes—that were associated with consuming coffee, tea, alcohol, yogurt, cheese, *natto* (fermented soy beans), tofu, fish, vegetables or meat. Initial diet-genome associations showed that the ingredients mattered. For example, they found positive genetic correlations between eating cheese and eating yogurt.

The team discovered ten diet–genome associations that have never been reported before. Four of them were related to coffee and three to alcohol. One SNP already known to be associated with coffee and alcohol was found to be related to almost all the dietary items that were examined.

"We found that this particular variation in a single DNA nucleotide at the *ALDH2* gene was related to consuming less alcohol, *natto*, tofu and fish, and, at the same time, related to consuming more coffee, green tea, milk and yogurt," says Okada.

The researchers discovered that six of the SNPs were related to at least one disease phenotype, including several types of cancer as well as type 2 diabetes.

As with genome-wide association studies for diseases, the current results can benefit society in the long run.

"By estimating individual differences in dietary habits from genetics, especially the 'risk' of being an alcohol drinker, we can help create a healthier society," Okada explains. ●

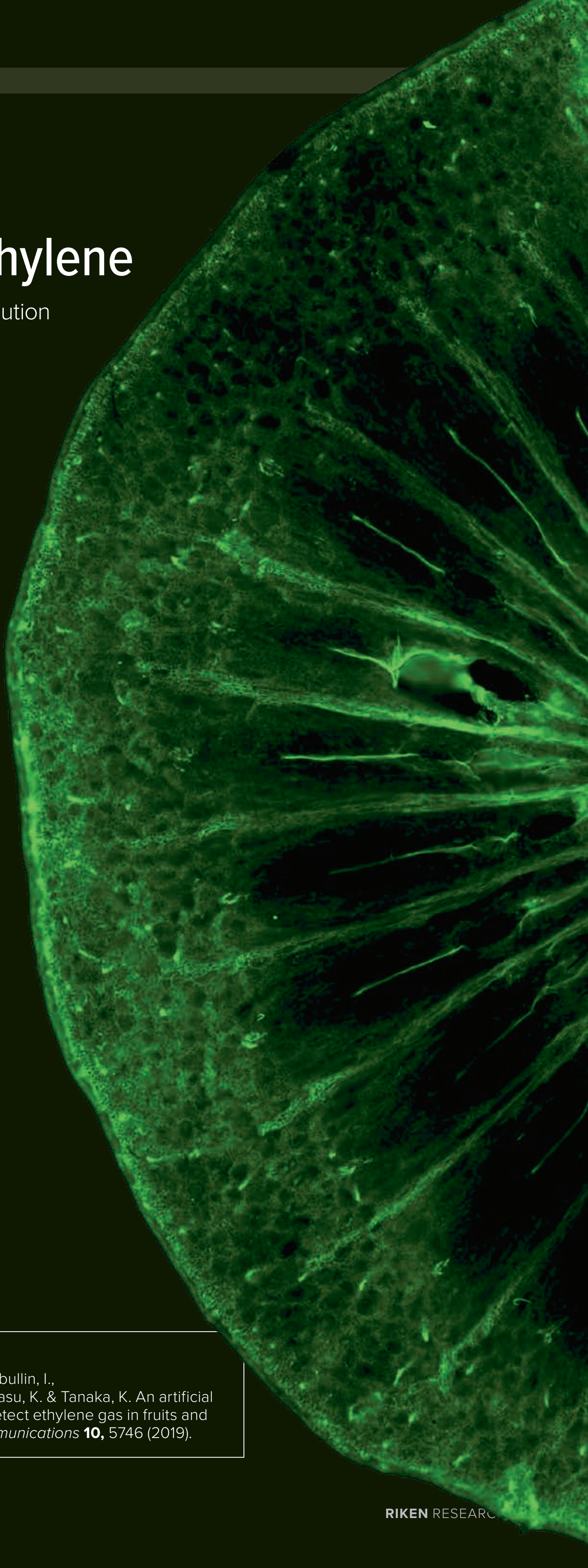
Reference

1. Matoba, N., Akiyama, M., Ishigaki, K., Kanai, M., Takahashi, A., Momozawa, Y., Ikegawa, S., Ikeda, M., Iwata, N., Hirata, M. *et al.* GWAS of 165,084 Japanese individuals identified nine loci associated with dietary habits. *Nature Human Behaviour* (2020).

PLANT HORMONES

Shining a new light on ethylene

A specially designed biosensor can detect the distribution of an important hormone in plants



A simple way to monitor the level of ethylene, an important hormone in plants, has been developed by chemists at RIKEN[1]. This development will help researchers probe in more detail than ever before the roles this hormone plays in plants.

Ethylene is involved in many processes in plants, including the ripening of fruit and the shedding of leaves in the fall. It is commonly used to induce fruit to ripen. But ethylene is a tiny molecule (C_2H_4) that readily diffuses across membranes, making it difficult to detect at the point where it is produced in a plant.

Metal catalysts encased in proteins known as artificial metalloenzymes are promising as sensors because scientists can design them to detect molecules of interest.

Now, a team led by Katsunori Tanaka of the RIKEN Biofunctional Synthetic Chemistry Laboratory has developed a biosensor based on an artificial metalloenzyme that can detect ethylene gas in fruits and leaves.

The team designed an artificial metalloenzyme, which consisted of a ruthenium-containing complex encased in an albumin scaffold, such that it fluoresces in the presence of ethylene. Specifically, the ruthenium complex has two components: one that fluoresces and one that quenches the fluorescence. When ethylene reacts with the artificial metalloenzyme, the fluorescence-quenching molecule is released and the complex starts to fluoresce. The protein casing both makes the metal complex soluble and protects it.

Tanaka and his team tested their metalloenzyme on various fruits and vegetables and found that it could detect ethylene in fruits as they ripened. Unlike previous ethylene biosensors, it could show the distribution of the ethylene over the fruit, providing a detailed spatial and temporal map of how ethylene spreads.

The researchers then used the experimental plant model *Arabidopsis thaliana* to examine the release of ethylene in response to stresses such as pathogens. They found that the biosensor accurately detected the presence of ethylene.

"Our work has two important implications," says Tanaka. "One is in the field of artificial metalloenzymes, where we have been able to use a principle of nature to produce something that does not exist in nature. And secondly, our work will contribute to understanding how ethylene is produced in plants, as we can measure the concentration of ethylene when it is still within cells."

The team now intends to improve the biosensor by making its reactivity faster so that it can measure ethylene before it becomes gaseous. They also plan to enhance its ability to enter cells rather than remaining in the extracellular environment.

Reference

1. Vong, K., Eda, S., Kadota, Y., Nasibullin, I., Wakatake, T., Yokoshima, S., Shirasu, K. & Tanaka, K. An artificial metalloenzyme biosensor can detect ethylene gas in fruits and Arabidopsis leaves. *Nature Communications* **10,** 5746 (2019).

IMMUNOLOGY

The killer cells for a ripe old age

A certain kind of immune cell may hold the secret to a long life

People over the age of 110 have high levels of a certain type of immune cell, RIKEN researchers have discovered[1]. This finding could provide important clues about how to enhance the body's immune system to fight diseases like cancer.

Supercentenarians, or people over 110, are extremely rare. For example, in 2015, Japan had more than 61,000 centenarians, but just 146 supercentenarians.

"We were especially interested in studying this group of people, because we consider them to be a good model of healthy aging, and this is important in societies like Japan where aging is proceeding rapidly," comments Kosuke Hashimoto of the RIKEN Center for Integrative Medical Science (IMS).

Supercentenarians are relatively immune to illnesses such as infections and cancer during their lifetimes, suggesting that their immune systems may be particularly strong. To explore this idea, the researchers looked at circulating immune cells from two groups: supercentenarians and younger controls. They found that the supercentenarians had fewer B-cells than the younger controls, but the two groups had about the same number of T-cells.

However, the supercentenarians had more of one subset of T-cells. Analysis of these cells revealed that the supercentenarians had very high levels of cells that are cytotoxic, meaning that they can kill other cells, sometimes amounting to 80% of all T-cells (compared to just 10% or 20% in the controls).

Normally, T-cells with markers known as CD8 are cytotoxic, while those with the CD4 marker are not. But the CD4-positive cells of the supercentenarians had become cytotoxic. Intriguingly, young donors had relatively few CD4-positive cytotoxic cells in their blood, indicating that this was not a marker of youth but a characteristic of the supercentenarians. The team speculates that the cells might be an adaptation to the late stage of aging.

To look at how these special cells were produced, the team examined the blood cells of two supercentenarians in detail and found that many of the cells were the progeny of a single ancestor cell.

"This research shows how single-cell transcription analysis can help us to understand how individuals are more or less susceptible to diseases. CD4-positive cells generally work by generating cytokines, while CD8-positive cells are cytotoxic, and it may be that the combination of these two features allows these individuals to be especially healthy," says Piero Carninci, also of IMS. "We believe that these types of cells, which are relatively uncommon in most individuals, even young people, are useful for fighting against established tumors, and could be important for immunosurveillance. This is exciting as it has given us new insights into how people who live very long lives are able to protect themselves from conditions such as infections and cancer." ●

RIKEN researchers found that supercentenarians had higher levels of cytotoxic CD4-positive cells—a kind of immune cell—than a younger control group.

Reference

1. Hashimoto, K., Kouno, T., Ikawa, T., Hayatsu, N., Miyajima, Y., Yabukami, H., Terooatea, T., Sasaki, T., Suzuki, T., Valentine, M. *et al.* Single-cell transcriptomics reveals expansion of cytotoxic CD4 T cells in supercentenarians. *Proceedings of the National Academy of Sciences USA* **116,** 24242–24251 (2019).

Building a roadmap to real world outcomes

With the launch of a new company, the deepening integration of industry and RIKEN researchers is poised to create a suite of new patent-winning products, says Hidetoshi Kotera.

As scientists, there is nothing more rewarding than seeing years' worth of relentless research effort make an impact in the real world. If inventing products from academic labs were simple, industry collaborations would be a clear win-win for everyone. The reality, however, is that the path is fraught with obstacles—and more often than not it's human factors, such as emotions and motivations, that impede progress. RIKEN is now working on ways to support researchers in their efforts to develop innovative products. A new RIKEN-funded corporation is yet another leap forward in making industry–academia partnerships fruitful.

Businesses, I should add, are also keen on having academics on board. Until a product is ready for the market, there are almost always small modifications—adjustments to engineering specs or tweaks to computational formulas—best done by the innovators already deeply involved in its development. However, Japanese academics consider the time it takes to do this detailed work as drawing them away the next big discovery. In the past, the researchers who collaborated to do this have been the outliers.

BATON ZONE

Baton Zone is RIKEN's flagship program bridging research and business. Within this program, we designate project leaders from industry and sub-leaders from RIKEN to form a joint team on one of RIKEN's campuses. The attraction for RIKEN researchers here is the potential to discover new ideas for research through the repeated trial and error of developing a product. During this time, researchers may begin to see their work in a different light—I'm told it gives them inspiration for new studies, which could evolve into yet more products worth developing.

Since its launch 16 years ago, the program has brought together businesses and RIKEN research labs in 36 mid- to long-term projects. We've seen incredible cases of success; an example from the field of medicine is DuraBeam, an artificial dura mater (a membrane that surrounds the brain and spinal cord) that is pasted onto a patient's skull during surgery. Using a RIKEN-developed polymer resin processing technology, DuraBeam overcomes the difficulties that other products have had with adhesion, minimizing the time it takes for surgery and thus reducing the risk of infections. With its high biocompatibility, it also overcomes the risk of adhesion to other organs, which becomes an issue in the long term.

In spring 2019, we moved from a funding system in which costs are shared equally by RIKEN and a partner company, to a new structure in which RIKEN funds a quarter of total research costs. This, I believe, is a healthier funding balance, as profits from commercialized products go to the business. RIKEN continues to partially fund the program thereafter, as we see value in the seeds of ideas born from collaborations.

While the Baton Zone is designed for projects close to the commercialization stage, the Industrial Co-creation Program (ICoP) facilitates open innovation for research concepts in an earlier stage of development. The objective is for upper-level management and researchers from industry to join RIKEN in brainstorming ideas for projects that tackle societal issues. The ideas emerging from ICoP tend to be for basic research, and these eventually mature into collaborative research projects like the ones undertaken in the Baton Zone program. As of spring 2019, we have 11 business partners working with RIKEN research centers—Toyota, Olympus, and Kao, to name a few.

Interest in collaborations for artificial intelligence (AI) has also soared over the past few years, with four partners joining forces with the RIKEN Center for Advanced Intelligence Project (AIP). One of these is a partnership with Toshiba that seeks to develop self-learning AI software to facilitate next-generation manufacturing and social infrastructure projects. One potential application, for example, is to control robots involved in routine infrastructure inspections—at present, these robots don't function well in changing environmental conditions, including rain and wind.

As of spring 2019, we have 11 business partners working with RIKEN research centers—Toyota, Olympus, and Kao, to name a few.

NEWCOMER TO COMMERCIALIZATION

A newcomer to RIKEN's industry collaboration ecosystem is RIKEN Innovation Co., Ltd., an external corporation established in September 2019 to bolster support for collaborations with industry. Concerningly, the conversation about industry–academia collaboration in Japan is heavily skewed towards initiating a partnership and tends to overlook providing support throughout the lifetime of a project. At the moment, collaborative teams are generally left to their own devices after partnerships kick off; given the aforementioned cultural disparities in academia and industry, it's an invitation for failure. One of the main

HIDETOSHI KOTERA
Executive Director

Hidetoshi Kotera was appointed an executive director at RIKEN in April 2018. He is also program director of the RIKEN Industrial Co-creation Program (ICoP), which supports joint research with industry, and the RIKEN Baton Zone Program, which helps transfer RIKEN's scientific achievements so that they can be used in commercial products through partnerships with private companies. Additionally he serves as the director of the RIKEN Cluster for Science, Technology and Innovation Hub, which aims to create and strengthen networks for research and development.

A FEW OF RIKEN'S TANGIBLE CONTRIBUTIONS

RIKEN partners have commercialized many of its findings and RIKEN will soon have a greater hand in this process.

1925
RIKEN scientists invent almite, which is used to coat aluminum for strong kitchenware.

1936
The predecessor of today's Ricoh (known now for photocopiers) is formed to sell positive sensitized paper.

1987
Kao Corporation launches Attack, a laundry detergent produced using alkaliphilic bacteria discovered by RIKEN's Koki Horikoshi.

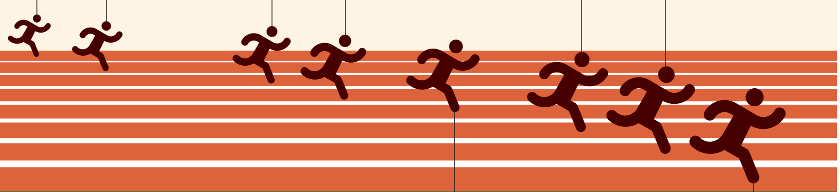
1990
Hitoshi Ohmori and Takeo Nakagawa develop a highly efficient process for grinding ceramics (ELID technique). This technology is now in use in processing automobile components.

2004
Launch of the Baton Zone program to support the transformation of RIKEN's scientific achievements into commercial products through partnerships with private companies.

2015
The PASESA Blood Pressure Monitor is released. The monitor includes the AVI Index, co-developed by RIKEN to analyze the central condition of the central arteries near the heart.

2017
DuraBeam, an artificial dura mater developed at RIKEN, is approved for production and distribution.

2019
Establishment of RIKEN Innovation Co., Ltd., an external corporation to support collaborations with industry.



functions of the new company is to provide ongoing project management, based on the personalities and work styles of the teams.

Thanks to a revision in the law in 2019, RIKEN is now able to invest in businesses that profit from RIKEN's research output. As a result, the RIKEN Innovation Company is, and will be, wholly funded by RIKEN. In addition to research coordination, the company provides multifaceted support, notably, in applying for technology licensing and venture capital. Patents are key to launching start-ups and protecting high-profile projects; there is now a stronger need than ever before to strategically foster patent-winning work years in advance of commercialization. To make sure this happens, RIKEN's new company will work in tandem with research teams. Its employees will start with market research on intellectual property strategies, help collecting supporting data to strengthen patents, and ultimately help to organize appropriate and nuanced contracts, for instance, flexible types of contracts for emerging areas such as artificial intelligence.

The company will also assist in developing ideas for startups derived from RIKEN research. This new capacity will especially be useful to the large number of projects where the market size for a promising product is viable, but relatively small, as projects like these tend to fly under the radar at large corporations. The new company will also help advise RIKEN on its funding distribution strategy among its existing startups and provide business management support.

RIKEN'S BIG INVESTMENT

With the RIKEN Innovation Company, we're piloting—for the first time in Japan—a scheme that brings together, in an external entity, support for technology licensing and for startups. We absolutely need the company to grow, since we expect it to channel significant output from RIKEN's basic research into society. A handful of unforeseen challenges will come our way, and that's okay; it's part of our intention to adapt the scheme as we go along.

One criticism I anticipate is this: Why establish an external corporation when the same tasks can be undertaken internally? My answer is that it is for the sake of customer satisfaction. If the organization were part of RIKEN, the services it provides would be RIKEN-centric, following rigid institutional rules for budgeting and staffing. On the other hand, with an external organization, RIKEN and industry partners both become clients. The organization's priority is to offer a solution that maximizes the benefits for both parties. That makes it much easier to identify priorities on actionable items. At the end of the day, it's the soft skills like a service-oriented business mindset and a fast-paced company culture that make or break a project. The bureaucratic, first-in first-out work style of traditional academic institutions simply will not work for securing patents in a fast-paced environment. An additional plus is that being a corporation lowers the barriers for other businesses reaching out for collaboration opportunities.

We've analyzed a wealth of data and are confident that RIKEN Innovation will be able to carry industry–academia collaborations forward. Now, it's a matter of making a success of the new strategy. The staff at the new company come from various backgrounds in academia and business; I anticipate three years for the company's culture to meld with RIKEN's, and five years until it is fully operating. At this point, micromanagement and nit-picking will kill the program. For the five years it takes until this new arm is at full throttle, I'd like to ask you all to provide only constructive feedback that will help the project to improve.

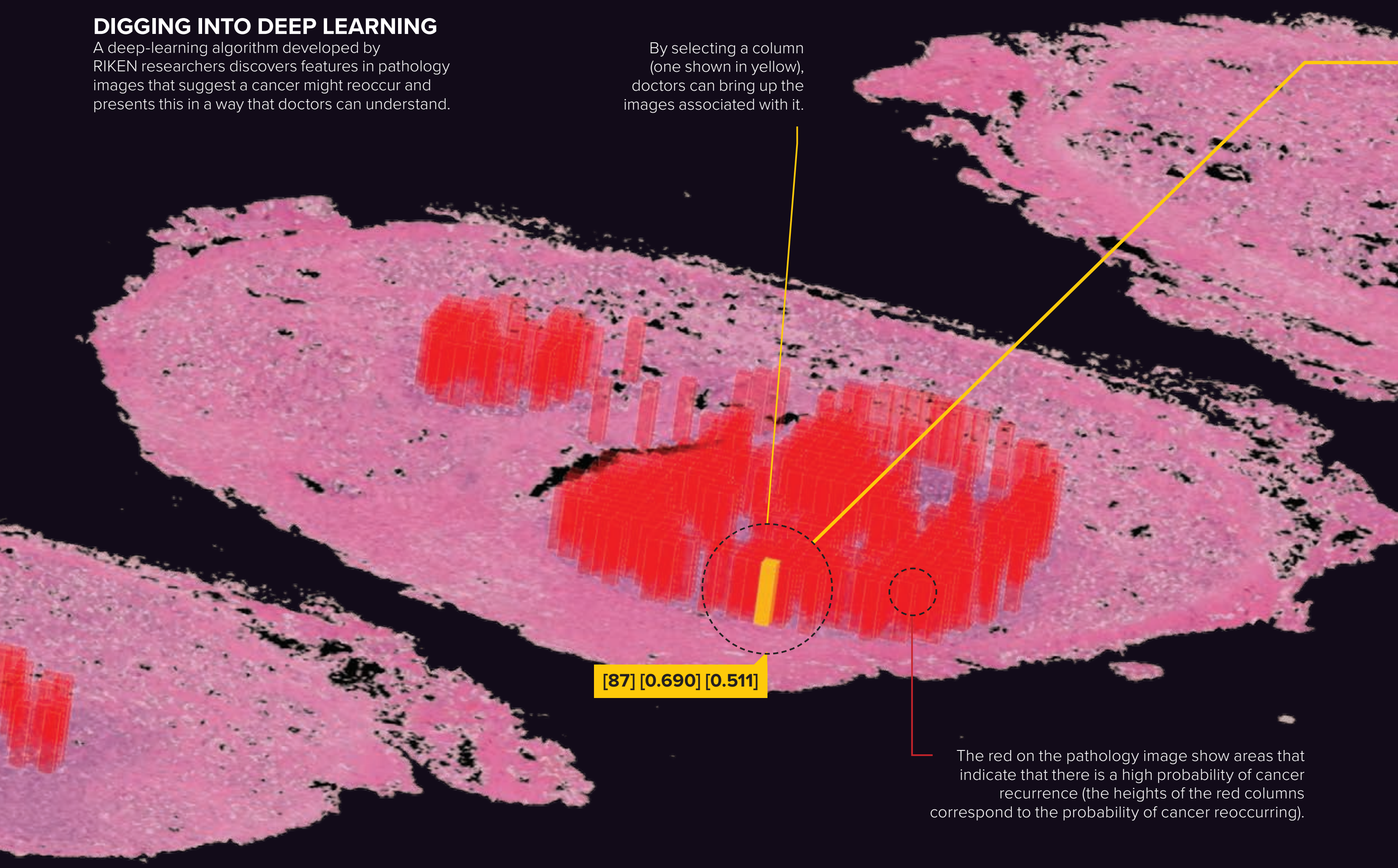
NEW CLUES IN AI CANCER PROGNOSES

Understanding artificial intelligence's reasoning has taken it from cancer prognosis tool to a means to understand why cancers reoccur

© ANNE WESTON, FRANCIS CRICK INSTITUTE / SCIENCE PHOTO LIBRARY

DIGGING INTO DEEP LEARNING

A deep-learning algorithm developed by RIKEN researchers discovers features in pathology images that suggest a cancer might reoccur and presents this in a way that doctors can understand.



Artificial intelligence (AI) is quickly changing the way medical diagnoses and prognoses are made. For example, machine learning systems can already diagnose Alzheimer's disease from pathology images with greater accuracy than human experts.

But AI suffers from a major limitation: the reasons it makes a prediction are so complicated that it is effectively a black box to human experts. The AI deep learning systems used in medical research often rely on algorithms in which correlations are reinforced (backpropagation), forming complex networks to provide suggested prognoses or diagnoses. But it can be a bit like looking up the answer to a math problem at the back of a text book—it might give you the right answer, but if you don't delve into the process of how it was derived, you're none the wiser when confronted with a different problem.

This issue was acknowledged by the guidelines drawn up by the G20 summit held in Osaka in June 2019, which call for AI to be developed in a fair and accountable manner with transparent decision-making processes and appropriate safeguards.

OPENING THE BLACK BOX

Now, Yoichiro Yamamoto of the RIKEN Center for Advanced Intelligence Project and his co-workers in Japan are lifting the lid on this black box.

Yamamoto's team has developed a deep-learning system that can surpass human pathology experts in accurately predicting the probability that prostate cancer will reoccur within one year[1].

They trained their system by using a portion of more than 13,000 pathological images of whole prostates acquired from a hospital in Tokyo. The researchers then evaluated its performance by letting it loose on the remaining images and seeing how well its predictions matched actual outcomes.

In the study, human pathologists scored an accuracy, as AUC (area under the curve), of 0.744 on a scale between 0 and 1 (where a score of 1 indicates perfect accuracy), while the machine achieved an

impressive 0.820. In the clinic, this could help doctors decide whether a patient needs additional treatments or merely to be monitored.

But Yamamoto's system goes further and shows what image features the AI has correlated positively or negatively with recurrence, so that pathologists can try to better understand why.

One example of a novel insight that the team's deep-learning technology has uncovered is that it sometimes highlights images that don't include any cancer cells. "AI says these images are very important for predicting cancer recurrence, but you won't find them in pathology books produced by humans," says Yamamoto. "This is new knowledge." More research is required to find out what is important in these images.

"Most AI techniques have only been used for classification, so they essentially mimic human pathologists," explains Yamamoto. "But our deep-learning technology goes beyond that—it can glean new insights."

The technology is therefore more than just a tool for helping pathologists to enhance the accuracy of their prognoses; it is also a powerful research assistant that can uncover new areas for human researchers to explore. "This is breaking new ground for AI," notes Yamamoto.

BETTER WORKING AND LEARNING TOGETHER

While the deep-learning system was more accurate than human pathologists, the highest accuracy was achieved when both AI and humans cooperated in making prognoses (a score of 0.842). Yamamoto thinks this is because humans and machines complement each other. "Humans and AI have different strengths when evaluating pathology images: humans tend to be better at focusing on the small areas that contain cancer cells, whereas AI is better at getting an overall view based on the entire image." So Yamamoto doesn't anticipate that AI will replace human pathologists any time soon. Indeed, he sees a two-way interaction in which humans will learn from machines and machines from humans.

ROBUST ACROSS HOSPITALS

Another critical point is that the deep-learning system had similar accuracies when it was used in two other hospitals in different prefectures in Japan. "This is a very significant result," says Yamamoto. He says it reveals the potential for very broad use of their system.

This robustness in different settings is the result of the use of our unsupervised learning-based algorithm, says Yamamoto. In this type of learning, a computer is fed unlabeled images and the outcome and has to figure out the relationship between the two on its own. In contrast, supervised deep learning involves spoon-feeding the machine with data that has been labeled with various output parameters. This makes it easier to implement, but its accuracy sometimes reduces markedly when it is used in environments different from the one in which it was trained, in which labeling or imaging might be slightly different. In contrast, unsupervised learning was much more stable in their dataset.

Yamamoto thinks that unsupervised learning should be highlighted in medicine more often and he says th e technique is not restricted to prostate cancer. Yamamoto and his team are now applying it to breast cancer and other rare cancers. They may also extend it to other, non-medical fields that involve large amounts of images. ●

REFERENCE

1. Yamamoto, Y., Tsuzuki, T., Akatsuka, J., Ueki, M., Morikawa, H., Numata, Y., Takahara, T., Tsuyuki, T., Tsutsumi, K., Nakazawa, R., Shimizu, A., Maeda, I., Tsuchiya, S, Kanno, H., Kondo, Y., Fukumoto, M., Tamiya, G., Ueda, N. & Kimura, G. Automated acquisition of explainable knowledge from unannotated histopathology images. *Nature Communications* **10,** 5642 (2019).

This feature looks at the work of YOICHIRO YAMAMOTO

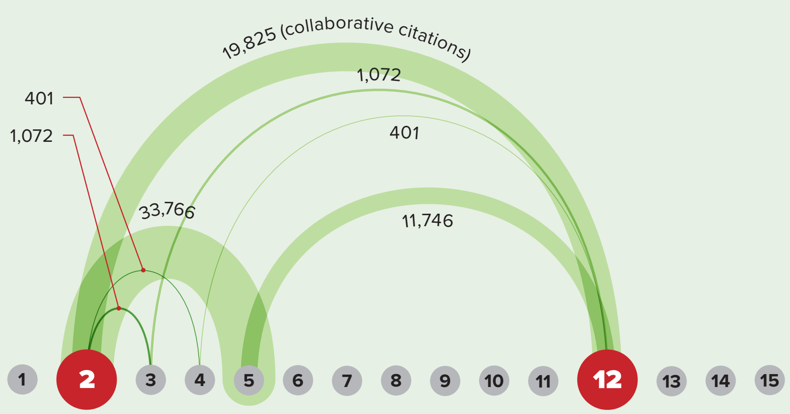
Yoichiro Yamamoto received his Doctor of Medicine and PhD degrees from Tohoku University. His PhD thesis focused on the cell dynamics in the carcinogenesis process. From 2012 onwards, he focused on mathematical modeling of cancer cell dynamics at the Mayo Clinic and Harvard University. This led to his current interest in artificial intelligence (AI). In 2014–2015, his research at Heidelberg University in Germany focused on computer science, and he succeeded in developing a new way to combine pathology and machine learning. In 2017, he moved to the RIKEN Center for Advanced Intelligence Project (AIP) to start his own lab. His lab's mission is to discover disease mechanisms and new therapies through state-of-the-art AI technologies and medical big data.

CREAM OF THE CROP

The RIKEN Center for Sustainable Resource Science (CSRS) is led by a number of researchers listed among 2019's top 1% in plant and animal science by citations. Two are at the center of an influential group of long-term collaborators that currently lead the world's top 15 plant science researchers by citations (below). Their findings are improving crops and cultivation knowlege around the globe.

TOP 15 RESEARCHERS BY CITATIONS IN PLANT SCIENCE GLOBALLY (1980–2019)

Primary RIKEN affilation   Unaffiliated with RIKEN



Kazuo Shinozaki

Director, RIKEN Center for Sustainable Resource Science (CSRS)

51,982 plant science citations (74,276 total citations)

PAPER HIGHLIGHT:
A 1998 *Plant Cell* paper on the importance of DREBs transcription factors in drought and cold stress responsive gene expression.

- **1,788 citations**
- **55 patent citations**
  One involved improving the drought resistance of rice by overexpressing an Arabidopsis gene.

Motoaki Seki

Team Leader, Plant Genomic Network Research Team, CSRS

21,572 plant science citations (26,551 total citations)

PAPER HIGHLIGHT:
A 2002 paper on the transcriptome analysis of Arabidopsis genes under drought, cold and high-salinity stresses.

- **1,330 citations**
- **27 patent citations**
  One on a method to increase stress tolerance in plants.

ALSO IN THE TOP 1% OF RESEARCHERS IN PLANT AND ANIMAL SCIENCE GLOBALLY

Kazuki Saito

Group Director, Metabolomics Research Group, CSRS

24,142 total citations

PAPER HIGHLIGHT:
A 2010 paper on a repository of mass spectra of small natural compounds for metabolomics study.

- **820 citations**
- **4 patent citations**
  One to produce plant compounds to defend against pathogenic microbes and herbivores.

Ken Shirasu

Group Director, Plant Immunity Research Group, CSRS

12,295 total citations

PAPER HIGHLIGHT:
A 2008 *Nature* paper on the inhibition of shoot branching by new terpenoid plant hormones. It's among the top 5% of all research outputs scored by Altmetric.

- **992 citations**
- **6 patent citations**
  One on a method for controlling root parasitic plants.

Lam-Son P. Tran

Unit Leader, Stress Adaptation Research Unit, CSRS

12,025 total citations

PAPER HIGHLIGHT:
A 2004 *Plant Cell* paper that also involved Kazuo Shinozaki on how NAC transcription factors regulate drought tolerance.

- **751 citations**
- **6 patent citations**
  One on a method to increase grain protein content and delay deterioration.

Hitoshi Sakakibara

Senior Visiting Scientist, Mass Spectrometry and Microscopy Unit

15,308 total citations

PAPER HIGHLIGHT:
A 2007 *Nature* paper on a pathway critical to rice size and branching.

- **449 citations**

Yuji Kamiya

Research consultant

19,802 total citations

PAPER HIGHLIGHT:
A 2011 *PNAS* paper on a key auxin (plant hormone) biosynthesis pathway indispensable to growth and development.

- **391 citations**

INTERNATIONAL YEAR OF
PLANT HEALTH
2020

Source: InCites; *All papers can be found online at www.riken.jp/en

RIKEN'S CENTERS AND FACILITIES
across Japan and around the world

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

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

SENDAI
- ● Center for Advanced Photonics (RAP)

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

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

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

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

NAGOYA

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

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

OSAKA
- ● Center for Biosystems Dynamics Research (BDR)

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

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

RIKEN RESEARCH

www.riken.jp/en

Science Blog
itaintmagic.riken.jp

Find us on Facebook
www.facebook.com/RIKEN.english

www.riken.jp/en

@riken_en
www.twitter.com/riken_en

LinkedIn
www.linkedin.com/company/riken

RIKEN 2020-016