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FALL 2022

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THE EYES HAVE IT

Self-driving cars could take lessons from human vision

ROBO-BOOST
AI exoskeleton helps users stand up

SLEEP ON IT
How snoozing benefits learning

COSMIC MUSIC
Merging black holes ring like bells

Foot on the accelerator
The 2014 and 2020 fuel stack design for the Toyota Mirai (internals pictured), which was one of the world's first hydrogen fuel cell electric vehicles, was aided by SPring-8 studies that examined efficient chemical bonding and electronic states at the surfaces of different types of core-shell cathodes, and studies on efficient water discharge.

RIKEN RESEARCH

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

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

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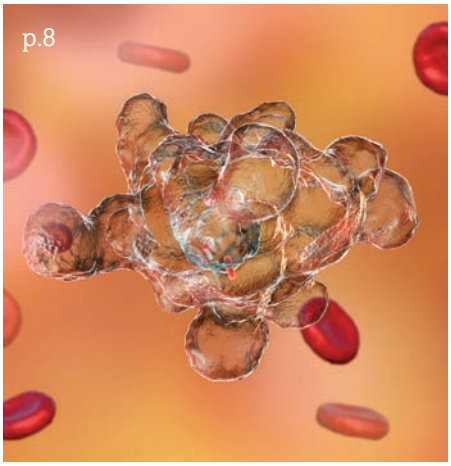
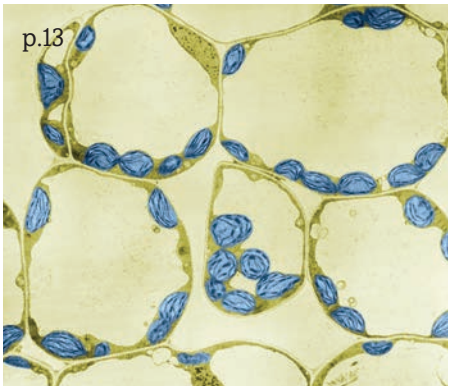
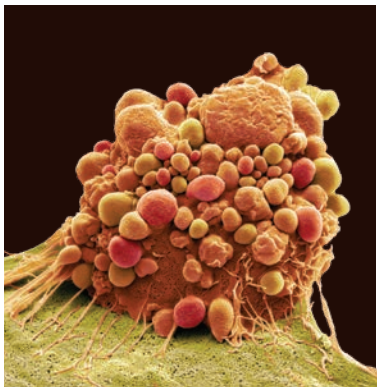
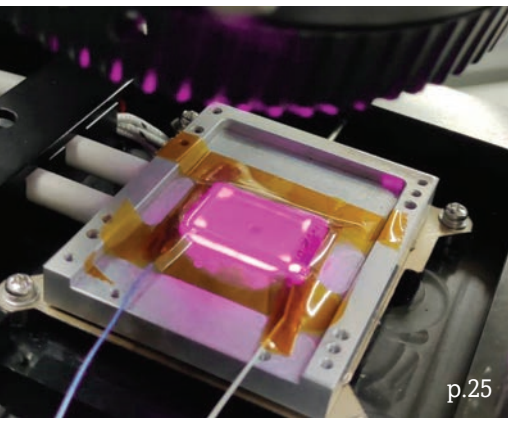
ISSN 1883-3519
www.riken.jp/en









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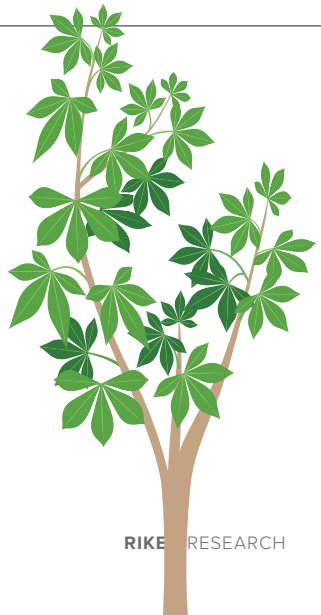

A minority among minorities

Makiko Naka
RIKEN Executive Director

In April this year, I was happy to join RIKEN as executive director in charge of international affairs and diversity.

Before this, I specialized in developmental psychology and studied interview methods for children that are the alleged victims of abuse and crimes. My attention is thus naturally focused on minorities and the vulnerable. I myself am a minority here, as I am a researcher in social science among natural scientists, and a woman in academia. In Japan, roughly 30% of social scientists are women and just 25% of natural scientists are women.

At RIKEN, though not enough, I found the diversity numbers to be encouraging. The proportion of woman researchers is about 25%, the same level as the national figure cited above. And the percent of international researchers is high, at 27%. Furthermore, we accept 300–500 young people every year—undergraduates, graduate students in master and doctoral courses, and postdoctoral researchers, which promotes diversity as well.

Of course, there are things that need to be improved. The proportion of women among principal investigators is only 10%, meaning that fewer women are advancing into higher positions. We need to provide further support, so both women and men can engage in research even when they have busy personal lives.

For international researchers, there are language and cultural difficulties that need to be overcome. We already provide Japanese language classes and translation of documents, but I think we need to go further, for example, further encouraging Japanese staff to use clear 'simple Japanese' so non-native speakers can understand them using emerging AI devices. We will also put more effort into helping diverse young researchers fulfill their goals at RIKEN, expecting that they will return in the future to play a central role as full-time researchers.

These are all lofty goals, but achievable with focus and perseverance. I look forward to interacting more with the readers of *RIKEN Research*.

COVER STORY:
Training neural networks so that they make visual copies, in the same way as the human eye, will help stabilize machine vision. *Page 22*

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Growing kidney organoids

Olena Trush
Research Scientist, Laboratory for Human Organogenesis, RIKEN Center for Biosystems Dynamics Research

Please describe your research
Each human kidney is made up of about a million filtering units called nephrons. I aim to reveal the mechanisms behind a key stage of nephron development during which a structure known as an S-shaped body (SSB) is formed. SSBs are characterized by a unique S-like folding and are critical to further looping of nephron tubules. Unfortunately, SSB structures are not easy to establish in cell cultures and we aim to improve this. I also work on another project that is trying to make pluripotent stem cell-derived kidney organoids—tiny, self-organized three-dimensional tissue cultures—for hamsters. Hamsters are short-term hibernators and we would like to induce this torpor state in the organoids and examine its unique mechanisms.

What do you think has been the most interesting discovery in your field in the last few years?
In my opinion, one important recent discovery has been how to reproduce kidney formation in the lab using human pluripotent stem cells. This advance was pioneered by our team leader Minoru Takasato. We are broadly using his core kidney organoid induction protocol for our research today.

"My research is important for sustainable development or society because…"
It is aiming to reduce the use of experimental animals by improving stem cell-derived cell cultures that can be used in their place. We also want to provide better patient-derived organoids to help with developing better personalized medicine, and for material to aid in organ regeneration and transplantation. The latter might also help eliminate organ rejection if it is generated by the patients' own cells.

How and when did you join RIKEN?
I found information about my current position using a government research-career support website called the Japan Research Career Information Network (JREC-IN) Portal. I immediately contacted Takasato-sensei to discuss the opportunity. Prior to submitting the application, I had a short visit to the lab to introduce myself to the team, and then I submitted the application and went through the selection process.

> *Each kidney is made up of about a million filtering units called nephrons. I aim to reveal a stage of nephron development in which a structure known as an S-shaped body (SSB) is formed.*

What has been your most memorable experience at RIKEN?
I think the most memorable part of my RIKEN experience was learning how to use the lab. I changed from developmental neuroscience to kidney development, so most of the relevant research techniques were new to me. It was an unforgettable experience to induce my first nephron-like structures from human stem cells and I had tremendous support from my colleagues during the transition.

How has being at RIKEN helped your research?
There are many reasons, but one is that we have steady and efficient access to animal material through the RIKEN LARGE (Laboratory for Animal Resources and Genetic Engineering). ■

Searching for buckwheat's origin

Jeffrey Fawcett
Senior Scientist, the Interdisciplinary Theoretical and Mathematical Sciences (iTHEMS) program

Please briefly describe your current research
One of my current projects is to understand the origin of common, domesticated buckwheat (from which soba noodles are made) and its dispersal to Japan. The results should lead to identifying important genes that can be useful to improve the breeding of buckwheat. More generally, I aim to understand the genetic and evolutionary processes that are responsible for creating diversity on earth through large-scale genomic data analysis.

"My research is important for society because…."
Improving the yield and productivity of minor, underutilized crops is thought to be essential to future food security. We believe that the genomic approach we are using should help advance the breeding of buckwheat and serve as an example of what can be achieved with other minor crops.

We are identifying important genes that could be useful to improve the breeding of buckwheat.

Please describe your role at RIKEN
Apart from conducting my own research projects, I interact with other iTHEMS scientists from different backgrounds, such as theoretical physics or mathematics, with the aim of facilitating interdisciplinary research and developing new projects.

What are some technologies that you use to conduct your research?
I have been using RIKEN's HOKUSAI BigWaterfall (HBW) supercomputer, which is essential for analyzing large-scale genomic data. In addition, I collaborate with researchers that use the Radioactive Isotope Beam Factory (RIBF) at the RIKEN Nishina Center to generate mutants with chromosome rearrangements in the hope of uncovering new genomic functions.

How did you become interested in your current field of research?
I was fascinated by the genomes of biological organisms. On one hand, there are some common principles that apply across plants, animals and fungi, while on the other, it is so dynamic that there is a huge amount of diversity even between individuals of the same species.

What has been the most interesting discovery in your field in the last few years?
Continued advances in DNA sequencing technology over the past 10–20 years has been very important. As a result, I am now able to use the genome sequence data of a large number of species and individuals, which is very important when studying evolution.

What has been a memorable experience at RIKEN?
Interacting with pure mathematicians and theoretical physicists. Being a biologist, I never imagined I would be able to learn and even enjoy (at least some aspects of) mathematics and physics.

What do you wish you had known before you came to RIKEN and/or Japan?
That RIKEN's Wako Campus is actually quite close to the center of Tokyo, with easy access by road, bus or train. ■

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RIKEN and Fujitsu's supercomputer Fugaku, based in Kobe, Japan, is number one on the High Performance Conjugate Gradient (HPCG) and Graph500 rankings.

Fugaku's fifth term at the top

The supercomputer Fugaku has taken the number one spot for the fifth consecutive term on the High Performance Conjugate Gradient (HPCG) and Graph500 rankings. It also ranked second in the TOP500 and HPL-AI rankings based on the Fugaku's full specifications (432 racks, 158,976 nodes). These results were announced on May 30 at ISC 2022, an international conference on high-performance computing held at the Congress Center Hamburg in Hamburg, Germany, and online.

According to R-CCS Director Satoshi Matsuoka: "This shows that it is still at the top of the world in terms of performance."

Fugaku began full operation in March 2021, and is now being used for projects including those under MEXT's 'Program for Promoting Research on the supercomputer Fugaku', researcher proposals that have been selected after public call outs for submissions, industrial agreements, and as part of important national policy needs.

"[Fugaku] will be able to play a key role in the development of Society 5.0, through which the Japanese government is aiming to create a super-smart society that can bring new value," said Matsuoka.

"[These rankings] make it clear that Fugaku is functioning fully as a High-Performance Computing infrastructure that will help accelerate the development of technologies for solving social issues through simulations, the development of artificial intelligence, and information distribution and processing."

www.riken.jp/en/news_pubs/news/2022/20220530_3

Agreement on joint nuclear science

On June 12, 2022, a ceremony was held in Germany to commemorate the signing of an agreement on collaborative nuclear physics research (a Memorandum of Understanding) between Japan's RIKEN Cluster for Pioneering Research (CPR), Germany's GSI Helmholtz Centre for Heavy Ion Research (GSI) and the international Facility for Antiproton and Ion Research (FAIR).

Chief Scientist Takehiko Saito of RIKEN CPR has had ongoing collaborations with GSI/FAIR, and the group have taken this partnership further with the establishment of a joint laboratory. The joint laboratory will be headed by Saito and Professor Christoph Scheidenberger of GSI/FAIR, with the aim of promoting collaborative research and expanding researcher and student exchanges.

The agreement also provides for the initiation of new collaborations between RIKEN and GSI/FAIR, which will be carried out by researchers from three CPR laboratories, the Atomic, Molecular & Optical Physics Laboratory led by Chief Scientist Toshiyuki Azuma, the Meson Science Laboratory led by Chief Scientist Masahiko Iwasaki, and the High Energy Nuclear Physics Laboratory led by Saito.

The agreement was signed both on-site at GSI/FAIR and online. From GSI and FAIR, Paolo Giubellino, scientific managing director of GSI and FAIR, and Jörg Blaurock, technical managing director of FAIR, participated. From RIKEN, Shigeo Koyasu, Director of CPR participated. Additionally, Keitaro Ohno, State Minister for Cabinet Affairs in charge of Science and Technology Policy and Economic Security, visited GSI and FAIR on the day and witnessed the signing, expressing his strong support for the cooperative relationship.

A co-operation agreement on nuclear physics research was signed at the GSI/FAIR joint campus in Germany.

www.riken.jp/en/news_pubs/news/2022/20220627_1

The center is at the University of California, Berkeley.

The RIKEN–Berkeley Center opened

RIKEN iTHEMS and N3AS Physics Frontier Center have opened a joint research center, the RIKEN-Berkeley Center (RBC), located on the 3rd floor of the physics building at the University of California, Berkeley. This new center aims to enhance nuclear astrophysics and quantum information science collaborations between the two institutions.

On May 27–29, 2022, the first annual meeting of N3AS was held at Berkeley together with their international partners, RIKEN iTHEMS and CNRS Centre Pierre Binetruy. iTHEMS members are encouraged to use RBC as a base to interact with researchers at Berkeley.

https://ithems.riken.jp/en/news/riken-berkeley-center-was-opened

Postscript

In the 'RIKEN-Max Planck Society symposium' article in the briefs of the Summer 2022 issue, Kazuki Saito, director the RIKEN Center for Sustainable Resource Science, was incorrectly called Takashi Saito.

PROTOZOAN PARASITES

Compound snatches iron from parasitic amoeba

A better drug for a parasitic amoeba could come from a new approach that exploits its need for iron

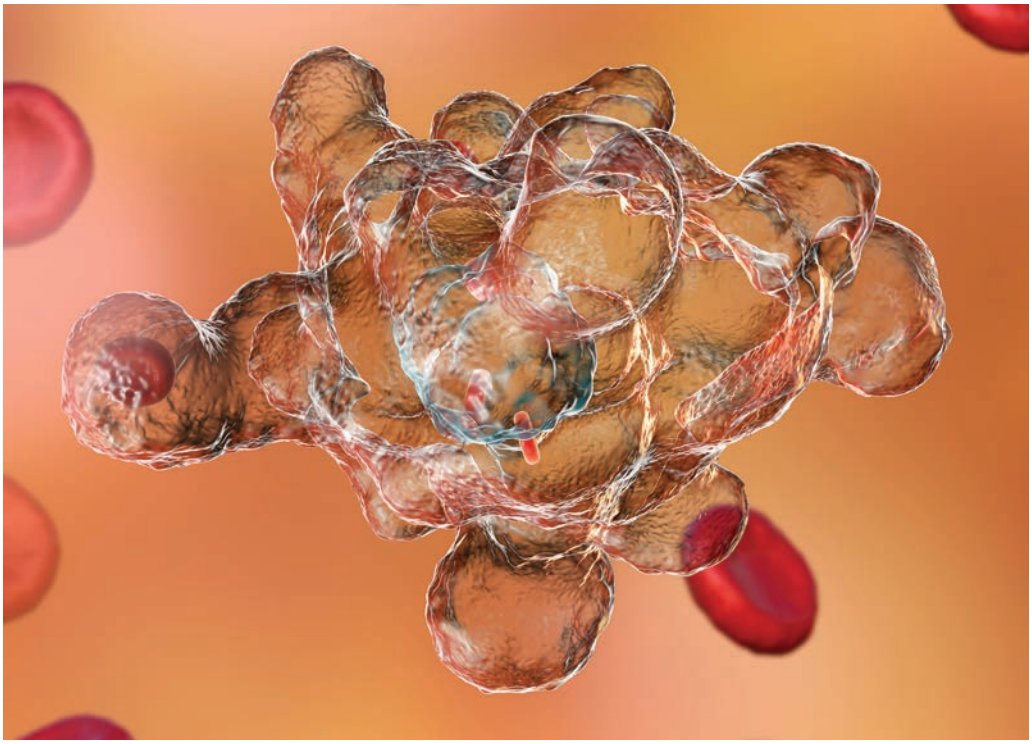
Next-generation drugs against the sometimes fatal disease amebiasis could result from a RIKEN researcher's new strategy targeting a source of iron that an infectious single-cell parasite needs to proliferate[1].

The parasitic amoeba *Entamoeba histolytica* (see image) infects about 50 million people a year, mostly in developing countries. It causes amebiasis, which has symptoms such as diarrhea, dysentery and colitis and is fatal in just over one in ten cases. The disease spreads via fecal contamination of food and water and is most common where sanitation is poor. *E. histolytica* initially invades the intestinal mucosa, but it may spread to other tissues such as the liver and lungs.

Amebiasis is usually treated with metronidazole, an anti-protozoal, but this drug is beset with various problems. "Metronidazole is a potential carcinogen, and there have been several issues with its use during pregnancy and lactation," explains Akira Wada of the RIKEN Center for Biosystems Dynamics Research. "Furthermore, long-term administration of the drug is needed to completely eliminate the pathogen and prevent recurrence."

There is thus a pressing need to develop safer drugs for treating amebiasis.

Now, Wada, along with Yumiko Saito-Nakano of the National Institute of Infectious Diseases and two other collaborators, has identified a new approach for combating *E. histolytica* infection that uses a compound that targets iron ions in the amoeba.



A computer-generated illustration of the parasitic amoeba *Entamoeba histolytica* engulfing red blood cells, which are an important source of iron for the parasite. A RIKEN researcher and collaborators have exploited the protozoan's need for iron to develop a promising iron-targeting compound for combating it.

"Metal ions are essential for maintaining the life activities of microorganisms," says Wada. "Recent studies have revealed that *E. histolytica* takes in a lot of iron ions, so it struck me that compounds with iron-targeting ability could curb the proliferation of the protozoan."

Importantly, the iron-targeting polypyridine compound did not appear to affect human cells much and so it is not expected to have significant side effects. "Most metal-binding compounds show some toxicity against human cells because they can capture metal ions inside mammalian cells as well as parasites," says Wada. "But we've succeeded in identifying an anti-amebic compound with no cytotoxicity against human liver cells."

When the team investigated the effectiveness of this strategy by using it to treat hamsters infected with *E. histolytica*, they found that it could completely cure liver abscesses in them without causing any serious side effects.

The researchers consider that the approach could be used against other parasites. "This metal-targeting strategy could inhibit the growth of other parasites," says Wada. "For example, we have already found several metal-targeting compounds with *in vitro* and *in vivo* activity against malaria."

The team is now looking at ways to enhance their iron-targeting compound. "Our ultimate aim is to develop next-generation drugs for treating amebiasis," says Wada.

Reference

1. Wada, A., Umeki, Y., Annoura, T. & Saito-Nakano, Y. *In vitro* and *in vivo* antiamebic activity of iron-targeting polypyridine compounds against enteric protozoan parasite *Entamoeba histolytica*. *ACS Infectious Diseases* **8,** 457–462 (2022).

Sometimes taking a nap is the best way to learn. A study by a RIKEN researcher has revealed the mechanism behind the consolidation of learning that occurs during sleep.

SLEEP RESEARCH

How we learn in our sleep

Learning gains while we sleep stem from the learning process

The consolidation of learning that occurs during sleep is a result of the learning process and not merely because certain brain regions get used a lot during learning, a RIKEN researcher and her collaborator have shown[1]. This finding resolves a long-standing debate among sleep researchers.

In Japan, many school students stay up very late to cram for exams, but that is a self-defeating strategy according to Masako Tamaki of the RIKEN Center for Brain Science. "When you want to learn something, you should go to bed at a regular time," she recommends. "Students study very late, but a lot of that knowledge will be lost if they don't get enough sleep."

That's because new knowledge and skills that we acquire while awake are consolidated through neural processing that occurs when we sleep.

But there has been much debate about how this consolidation occurs. Is it simply because neurons that get used a lot when learning are downregulated for renormalization during sleep? Or is there something inherent in the learning process that causes this consolidation to occur?

Now, strong evidence for the latter—known as the learning-dependent model—has been found by Yuka Sasaki at Brown University in the United States and Tamaki, who first became interested in sleep research after a sleep-paralysis episode during which she thought she was being strangled by a stranger.

Two groups of young volunteers each underwent two sessions of training with a visual exercise. For the first group, the two training sessions were identical and they got better at the exercise. In contrast, the second training session for the second group was designed to nullify the learning achieved in the first session, and consequently they showed very little overall improvement.

The two groups then slept, and their performances on the visual exercise were measured on waking. This allowed the team to test whether learning or just using the brain was responsible for consolidating memory. The results provided strong support for the learning-dependent model. First, the behavioral results indicated that the first group showed substantial improvements after sleeping, whereas the second group showed almost none despite having been trained for the same amount of time. Second, the brain-signal monitoring during sleeping revealed that two kinds of activities consistent with that model were involved in processing, namely theta activity during rapid eye movement (REM) sleep and sigma activity during non-REM sleep. However, the study found no involvement of slow-wave activity during non-REM sleep, which has been shown to be associated with use-dependent processes.

These results confirmed the pair's suspicions: learning, and not just brain usage, is critical for consolidation during sleep. "Previous studies we had done were more consistent with the learning-dependent model," notes Tamaki.

Reference

1. Tamaki, M. & Sasaki, Y. Sleep-dependent facilitation of visual perceptual learning is consistent with a learning-dependent model. *The Journal of Neuroscience* **42,** 1777–1790 (2022).

BLACK HOLES

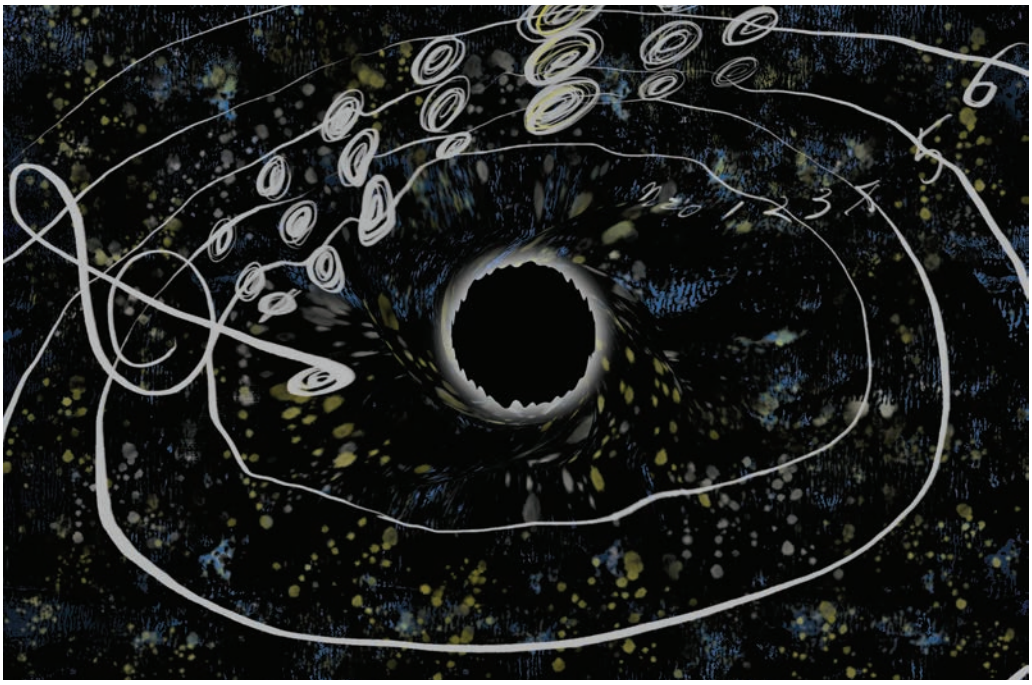
Ringing black holes could put Einstein to the test

Gravitational waves could reveal whether general relativity must be modified at the edges of black holes

Typical overtone chords in the gravitational waves produced when black holes collide could be used to test general relativity, a mathematical analysis by a RIKEN physicist has shown[1].

When black holes merge, they generate gravitational waves, which ripple outward like sound waves from a ringing bell. In theory, these gravitational waves can be broken down into tones and overtones—like in music—based on their different frequencies and the rate at which they dampen and die out. But in practice, gravitational-wave detectors are not yet sensitive enough to definitively pick up the overtones.

However, cosmologists are keen to measure the precise oscillation pattern because it can tell them more about a black hole's properties. In particular, the mass of the black hole and the rate at which it is spinning can be calculated from the damping rate and frequency.



When two black holes collide and merge, the new bigger black hole rings like a bell, generating gravitational waves that eventually dampen.

"One of the biggest reasons to study black-hole ringing is to test if general relativity is correct"

"It's like when you hear an instrument, you can understand if it is a guitar or a piano," says Naritaka Oshita of the RIKEN Interdisciplinary Theoretical and Mathematical Sciences Program (iTHEMS).

This is important for better understanding what happens to Einstein's theory of general relativity in the vicinity of black holes, which remain mysterious. Black holes famously swallow all objects that cross their surface, or event horizon. According to general relativity, these hapless objects are then drawn towards the black hole's core, or singularity.

But general relativity cannot describe what happens at this singularity, since Einstein's laws break down there. Importantly, general relativity states that black holes are completely characterized by their mass and the rate at which they spin. They have no other interesting features, or 'hair', that could affect the ringing.

But some physicists have posited that general relativity breaks down before the core, perhaps at the event horizon. In some alternative models, the surface of a black hole could reflect gravitational waves and produce 'echoes' of the gravitational-wave signal. These echoes may drastically alter the typical oscillation pattern of black holes.

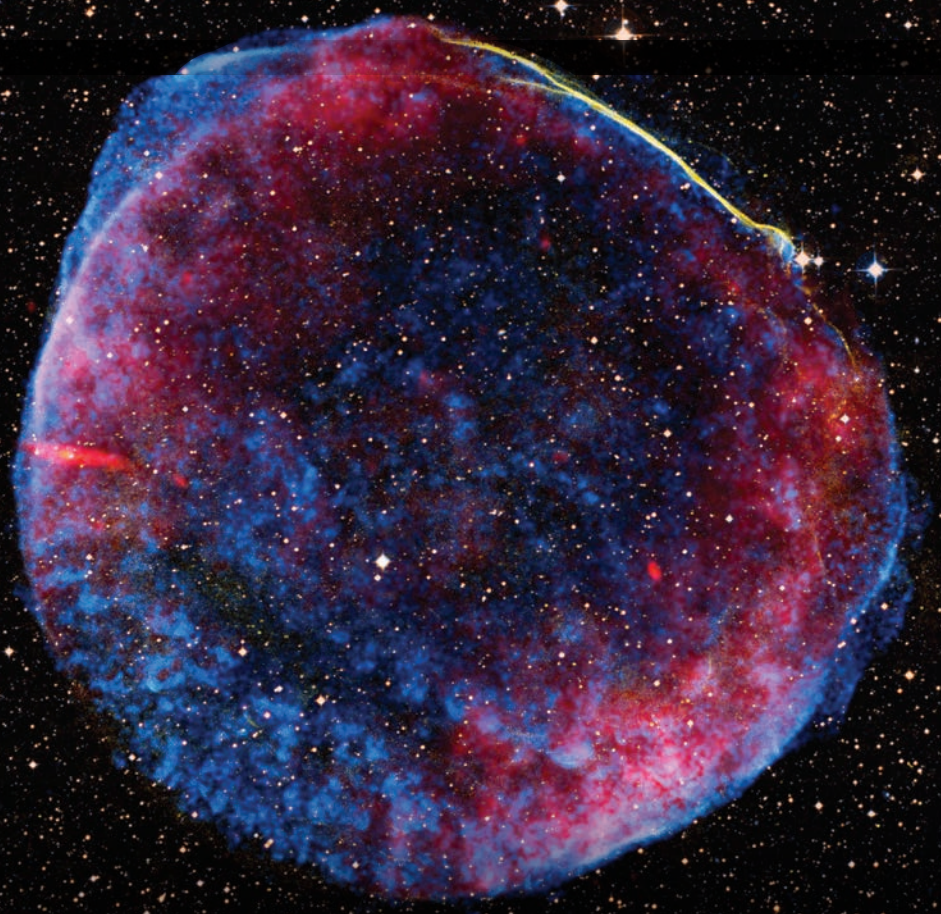
"One of the biggest reasons to study black-hole ringing is to test if general relativity is correct," explains Oshita.

With this in mind, Oshita analyzed the oscillation pattern predicted by general relativity. Previous studies by other groups had analyzed the gravitational-wave waveforms produced by computer simulations and had empirically found that of the many subtle overtones, the fourth and fifth overtones were dominant. Oshita's calculations have confirmed this, and they explain mathematically why it arises from Einstein's theory.

"If future data collected by gravitational-wave observatories agrees with this prediction, then general relativity will become stronger," says Oshita. ●

Reference

1. Oshita, N. Ease of excitation of black hole ringing: Quantifying the importance of overtones by the excitation factors. *Physical Review D* **104,** 124032 (2021).



The remnant of supernova SN 1006, the light of which first reached us more than 1,000 years ago. A computer model developed by RIKEN astrophysicists based on a hypothesized mechanism for type Ia supernovae can predict how the supernova remnant would evolve over thousands of years.

X-ray: NASA/CXC/Rutgers/G.Cassam-Chenai, J.Hughes et al.; Radio: NRAO/AUI/NSF/GBT/VLA/Dyer, Maddalena & Cornwell; Optical: Middlebury College/F.Winkler, NOAO/AURA/NSF/CTIO Schmidt & DSS

SUPERNOVAE

Modeling the shapes of supernova remnants

Predictions about the shapes of remnants left by supernova will help inform astronomers' observations

Computer modeling by RIKEN astrophysicists has predicted how a hypothesized type of supernova would evolve over thousands of years, providing astronomers with telltale signs for this type of supernova[1].

Type Ia supernovae are generally thought to be created by the explosion of white dwarfs—stars that have consumed all their hydrogen and have shrunk to a size not much bigger than the Earth. They are critical for cosmology since they are used as 'standard candles' to measure cosmic distances. Type Ia supernovae were used in measurements that unexpectedly revealed that the expansion of the Universe is accelerating.

Various mechanisms for the explosions that form type Ia supernovae have been proposed. One such mechanism, dubbed D6, has received a boost by the recent discovery of extremely rapidly moving white dwarfs. In this scenario, one of two white dwarfs in a binary system undergoes a double detonation: a surface layer of helium explodes, igniting a larger explosion in the carbon–oxygen core of the star, which obliterates the star. Suddenly freed from the gravitational pull of the exploding star, the companion is flung out at enormous velocity.

However, little is known about the shape of the remnant long after the initial explosion.

To explore this, the team simulated the evolution of a supernova remnant for thousands of years after the explosion. They found some features in the progenitor system, including a 'shadow' or dark patch surrounded by a bright ring, that would be specific to the D6 scenario. These features thus offer a way to probe the physics of supernovae. The researchers also concluded that the remnants of type Ia explosions are not necessarily symmetric, as commonly believed.

"We found that the D6 supernova explosion has a specific shape, and that there is a specific signature that we can still see thousands of years after the explosion," says Gilles Ferrand of the RIKEN Astrophysical Big Bang Laboratory. "We hope this will give observers new ideas of what to look for in supernova remnants."

"This is a very important finding, because it could have an impact on the use of Ia supernovae as cosmic yardsticks," says Shigehiro Nagataki, the leader of the RIKEN Astrophysical Big Bang Laboratory. "They were once believed to originate from a single phenomenon, but if they are diverse, then it might require a re-evaluation of how we use them."

The team now intends to extend their simulations. "We plan to more precisely compute the x-ray emission, taking into account the composition and state of the shocked plasma, in order to make direct comparisons with observations," says Ferrand.

Reference

1. Ferrand, G., Tanikawa, A., Warren, D. C., Nagataki, S., Safi-Harb, S. & Decourchelle, A. The double detonation of a double-degenerate system, from type Ia supernova explosion to its supernova remnant. *The Astrophysical Journal* **930,** 92 (2022).

PALAEONTOLOGY

Placing an ancient enigma in the evolutionary tree

One of the world's most powerful synchrotrons sheds light on an ancient ancestor of tetrapods

The mysterious, fish-like vertebrate *Palaeospondylus* was one of the earliest ancestors of four-limbed animals, or tetrapods, evidence found by a RIKEN-led team suggests[1].

About 5 centimeters long, *Palaeospondylus* had an eel-like body and lived about 390 million years ago in the Devonian period. Despite the abundance of its fossils, it has been difficult to place *Palaeospondylus* in the evolutionary tree due to its small size and the poor quality of cranial reconstructions from wax models and computed tomography (CT) scans. The body of *Palaeospondylus* has puzzled evolutionary scientists and has been thought to share features with both jawed and jawless fish. The most perplexing feature is the lack of teeth or dermal bones in the fossil record.

The most perplexing feature is the lack of teeth or dermal bones in the fossil record

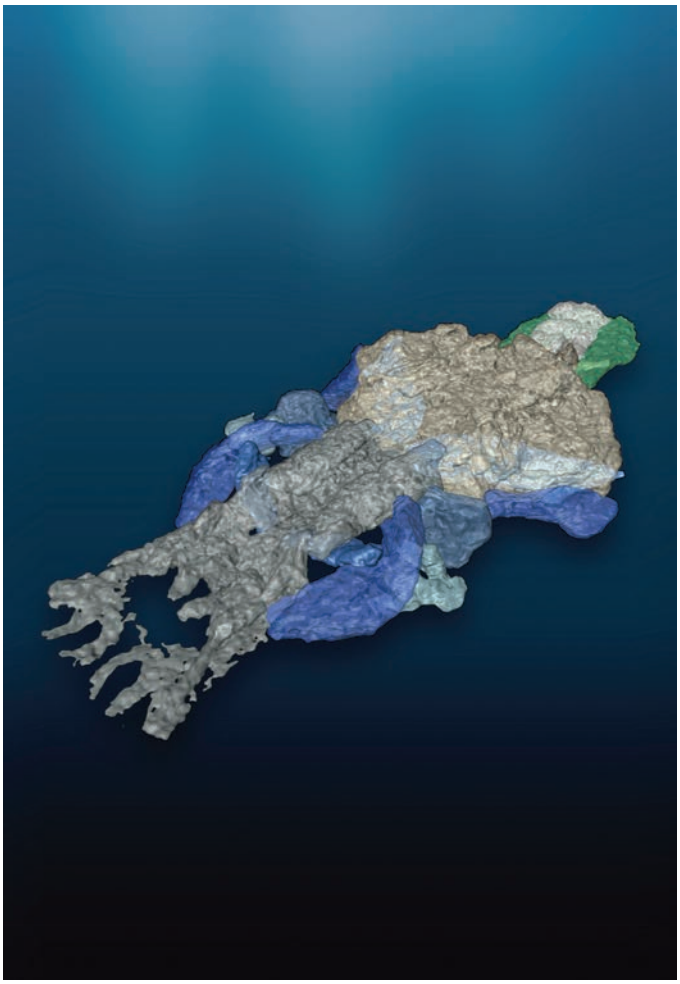
Now, a team led by Shigeru Kuratani of the RIKEN Evolutionary Morphology Laboratory has generated high-resolution micro-CT scans using x-rays from the extremely powerful RIKEN SPring-8 synchrotron.

The high-resolution scans revealed three semicircular canals, clearly indicating an inner-ear morphology of jawed vertebrates. This resolved an issue because previous studies had suggested that *Palaeospondylus* is related to primitive jawless vertebrates.

The scans also showed key cranial features that indicate *Palaeospondylus* belongs to tetrapodomorphs, a category consisting of four-limbed animals and their closest ancient relatives. Several analyses revealed that *Palaeospondylus* was more closely related to limbed tetrapods than to many other known tetrapodomorphs that retained fins.

However, unlike fossils of many other tetrapodomorphs, *Palaeospondylus* fossils lack teeth, dermal bones and paired appendages, despite these features being present in fossils of other animals that lived around the same time and in the same place. Their absence can be explained by the splitting of a set of developmental features, resulting in a larvae-like body. "Whether these features were evolutionarily lost or whether normal development froze half-way in fossils might never be known," says Tatsuya Hirasawa, also of the RIKEN Evolutionary Morphology Laboratory.

Unlike most previous studies, which used excavated fossil heads, the team selected fossils in which the heads were completely embedded in rock. "Choosing the best specimens for the micro-CT scans and carefully trimming away the rock surrounding the fossilized skull allowed us to improve the resolution of the scans," explains Hirasawa. "Although not quite cutting-edge technology, these preparations were certainly key to our achievement."



A three-dimensional reconstruction of a fossil of the fish-like vertebrate *Palaeospondylus*. The image was generated using x-rays from the RIKEN SPring-8 synchrotron.

Kuratani's team is also using molecular biology and genetics to study developing embryos of key modern vertebrates. "The strange morphology of *Palaeospondylus*, which is comparable to that of tetrapod larvae, is very interesting from a developmental genetics point of view," says Hirasawa. "We will continue to study the developmental genetics that brought about this and other morphological changes that occurred at the water-to-land transition in vertebrate history." ●

Reference

1. Hirasawa, T., Hu, Y., Uesugi, K., Hoshino, M., Manabe, M. & Kuratani, S. Morphology of *Palaeospondylus* shows affinity to tetrapod ancestors. *Nature* **606,** 109–112 (2022).

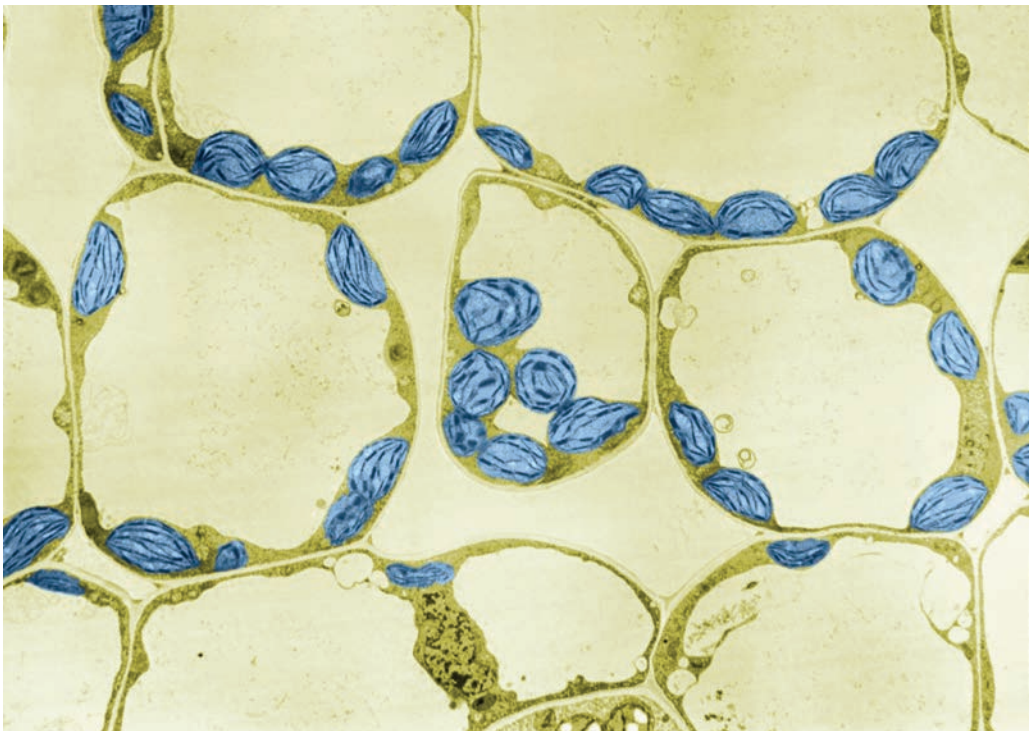
PLANT IMAGING

Lighting up plant cells with fluorescence

Specific components in plant cells can be easily imaged thanks to a series of new fluorescent dyes

Tailor-made fluorescent dyes produced by RIKEN chemists and plant scientists make the structures and activities of specific parts of living plant cells readily visible[1]. They promise to help advance our understanding of basic plant cell biology, which will ultimately benefit agriculture and environmental management.

Although life depends on plants for oxygen and food, many aspects of plant science lag behind biomedical science, including the use of molecular probes for imaging the internal structure and activities of cells. Shuhei Kusano of the RIKEN Center for Sustainable Resource Science (CSRS) and his co-workers are seeking to close this gap by developing a new range of fluorescent dyes with impressive abilities to visualize key parts of plant cells.



A color-enhanced transmission electron micrograph of spinach leaf mesophyll. The cell walls of plants makes it challenging to use fluorescent dyes to stain organelles inside plant cells such as chloroplasts (blue). Now, RIKEN researchers have developed fluorescent dyes that accumulate in specific parts of living plant cells, making cellular structures and activities readily visible.

One approach to making cell structures visible to microscopy involves using genetic engineering to create fluorescent proteins in structures of interest. But this is very time consuming for plant cells as it usually takes at least six months to establish stable genetically modified versions of even the most easily manipulated plants.

Another approach is to expose cells to fluorescent dyes that will selectively accumulate in regions of interest, such as the various membrane-bound components of cells called organelles. But this has proved more challenging in plants than in animals, partly because the plant cell wall, which largely consists of cellulose, poses a much greater barrier than the cell membrane in animals.

Now, Kusano and three colleagues, all at CSRS, have tackled this challenge by exploring chemical modifications to strongly fluorescent dyes based on molecules called 1,8-naphthalimides.

"We discovered that a series of 1,8-naphthalimide dyes could be chemically functionalized to visualize various membrane-bound compartments," says Kusano. "To our surprise, the probes could permeate across the cell wall and into the target membrane within ten minutes."

These non-toxic dyes allowed the team to light up and clearly reveal the structure and locations of several compartments inside living cells. The targeted regions included the membranes of organelles called chloroplasts, where photosynthesis occurs, and vacuoles, which store nutrients and other key molecules and host the degradation and removal of waste products.

The team demonstrated practical uses of their dyes by exploring the degradation of chloroplasts in the autophagy process—a crucial part of cell maintenance and turnover.

The team is now working on extending the inventory of dyes. "We're continuously developing new probes in the hope of visualizing every organelle and a wider range of plant-derived biomolecules," says Kusano.

Kusano believes that the knowledge gleaned using the dyes will help to improve our use of plants, including as crops and sources of materials, and in the bioremediation of pollutants. ●

Reference

1. Kusano, S., Nakamura, S., Izumi, M. & Hagihara, S. Development of 1,8-naphthalimide dyes for rapid imaging of subcellular compartments in plants *Chemical Communications* **58,** 1685–1688 (2021).

MOLECULAR DESIGN

Simplifying the search for new molecules

Six fluorescent compounds have been uncovered using a novel strategy for designing molecules that combines machine learning and quantum chemistry calculations

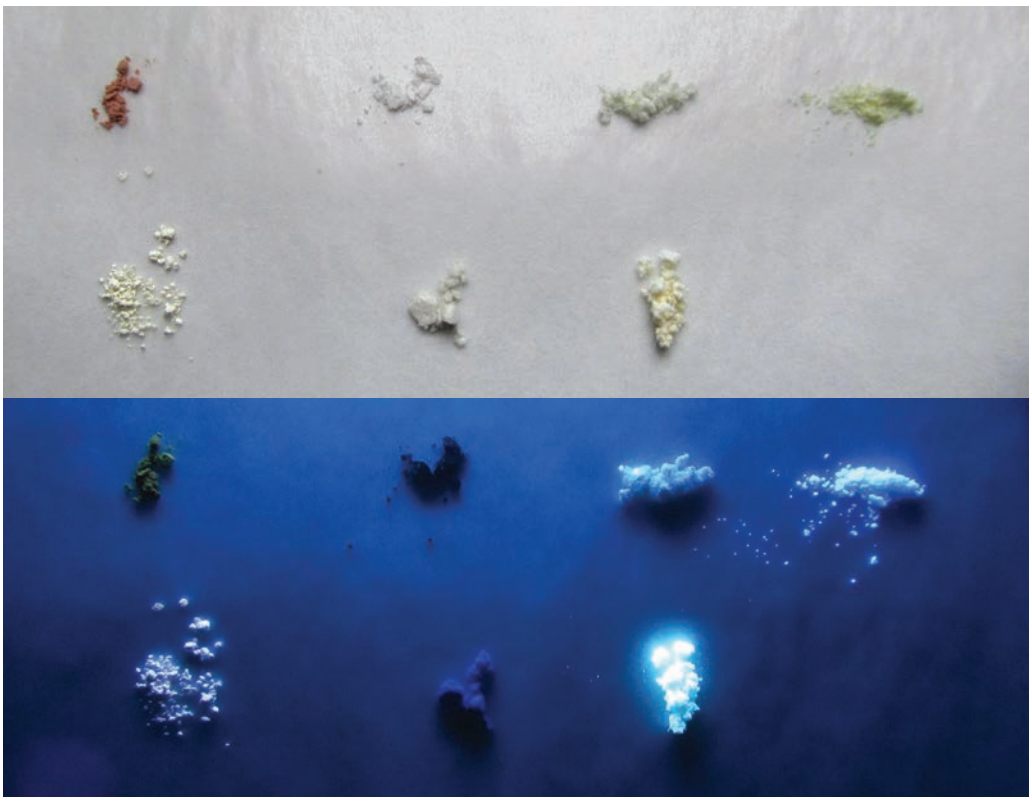
RIKEN chemists have demonstrated a powerful way of designing molecules to satisfy predefined specifications by using it to create six fluorescent compounds[1]. This method, which combines machine learning and quantum chemistry, promises to save chemists a lot of time making and testing compounds in the lab.

The conventional approach to molecular design is to start with a molecule that has properties close to the desired ones and then to try to improve on it through trial and error. This can be a time-consuming and hit-and-miss affair, as there is no guarantee that the final molecule is the best one.

Chemists have long wanted to reverse the situation so that they start with desired properties and then search all possible molecules for one that fits the bill. But a limitation has been that data only exists for a tiny fraction of all molecules.

Now, Masato Sumita of the RIKEN Center for Advanced Intelligence Project and his co-workers have demonstrated a new strategy that makes it possible to search the universe of molecules without having to make each compound individually.

They used a de novo molecule generator, which employs machine learning to suggest a molecule based on the desired properties. A simulator that performs quantum chemical calculations was then used to predict the molecule's properties. The cycle was repeated up to a specified computational time.



Eight compounds were predicted to fluoresce by a new method for designing molecules. Of the eight, six were found to fluoresce under ultraviolet light (five shown), including one compound that hadn't been previously reported (not shown).

To demonstrate the power of this approach, the team used their method to search for molecules that give off fluorescent light at wavelengths visible to the human eye. After five days of number crunching, the computer came up with more than 3,600 candidate molecules. The team picked eight of them to synthesize and found that six of them were fluorescent—including one compound that had never been reported before.

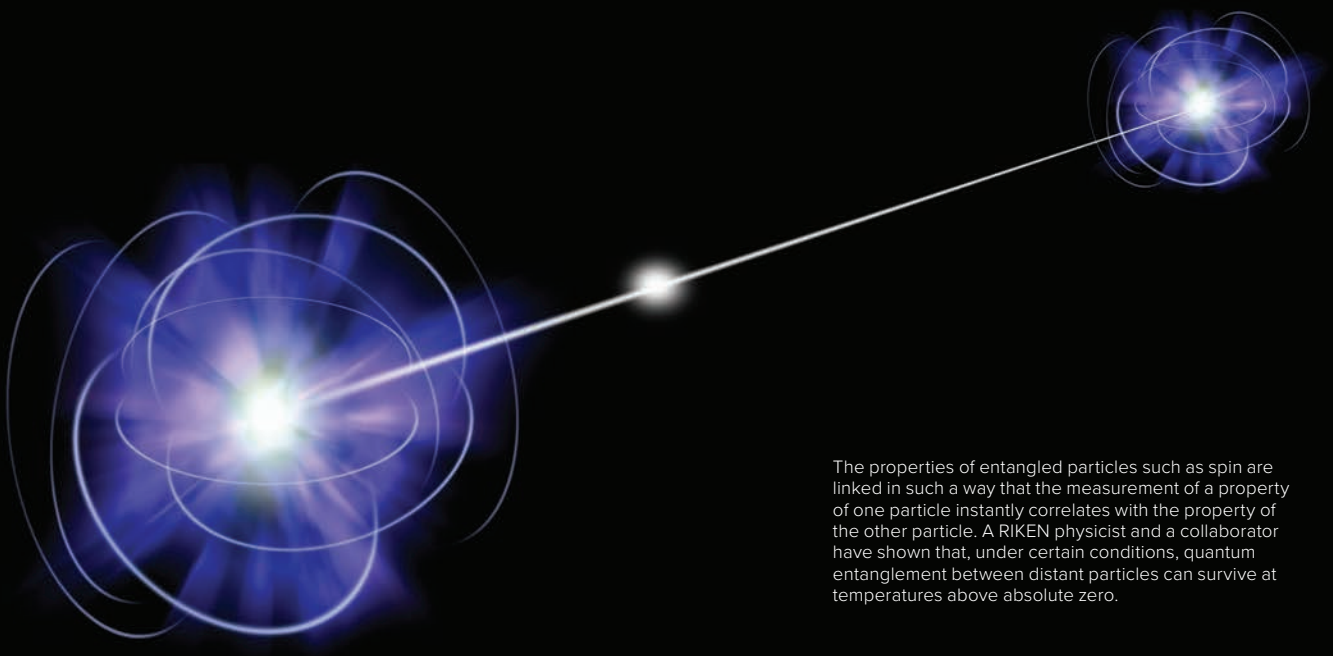
"This is the first time a de novo molecule generator combined with quantum-chemistry calculations has been used to discover fluorescent molecules," says Sumita. "I was very surprised at the high success rate of the method—75% of the eight candidate molecules fluoresced when we made them in the lab."

The search for a fluorescent molecule was a rigorous test for the method since, unlike simpler molecular properties such as light absorption, fluorescence is a multi-step process, making it tough to predict from molecular structure.

Sumita and his team now intend to apply their method to other chemical properties and to try to use it to optimize more than one property simultaneously. ●

Reference

1. Sumita, M., Terayama, K., Suzuki, N., Ishihara, S., Tamura, R., Chahal, M. K., Payne, D. T., Yoshizoe, K. & Tsuda, K. De novo creation of a naked eye–detectable fluorescent molecule based on quantum chemical computation and machine learning. *Science Advances* **8,** abj3906 (2022).



The properties of entangled particles such as spin are linked in such a way that the measurement of a property of one particle instantly correlates with the property of the other particle. A RIKEN physicist and a collaborator have shown that, under certain conditions, quantum entanglement between distant particles can survive at temperatures above absolute zero.

QUANTUM ENTANGLEMENT

It takes three to tangle

Quantum entanglement between particles separated by long distances can survive at temperatures above absolute zero under certain conditions

The types of long-range quantum entanglement that survive at non-zero temperatures have been revealed by a theoretical study by a RIKEN researcher and his colleague[1]. This finding will help to design quantum-computing devices that are stable at room temperature.

The weird and wonderful laws of quantum physics take over when things become very small. Large-scale or 'macroscopic' quantum effects are critical for developing quantum computers, which are the next revolutionary step in computing. However, current quantum-computing systems are only practically stable at temperatures slightly above absolute zero (–273 degrees Celsius).

'Quantumness' can be observed and measured at this scale in certain systems with the help of long-range quantum entanglement—famously described by Einstein as "spooky action at a distance." It occurs when a group of particles cannot be described independently from each other. This means that their properties are linked: if you can fully describe one particle, you also know everything about the particles it is entangled with.

Long-range entanglement is central to quantum-information theory, and understanding it better could lead to breakthroughs in quantum-computing technologies. Long-range quantum entanglement is stable at specific conditions, such as between three or more objects and at temperatures close to absolute zero, but it is not known what happens to two-body entangled systems at non-zero temperatures.

To answer this question, Tomotaka Kuwahara of the RIKEN Center for Advanced Intelligence Project and Keiji Saito of Keio University theoretically explored long-range entanglement at temperatures above absolute zero in two-body systems.

"We provide simple no-go theorems that show what kinds of long-range entanglement can survive at non-zero temperatures," explains Kuwahara. "At temperatures above absolute zero, particles in a material vibrate and move due to thermal energy, which acts against quantum entanglement. At arbitrary non-zero temperatures, no long-range entanglement can persist between only two subsystems."

The pair's findings are consistent with previous observations that long-range entanglement survives at a non-zero temperature only when three or more subsystems are involved. Their results suggest this is a fundamental aspect of macroscopic quantum phenomena at room temperature, and that quantum devices need to have entangled states between at least three objects.

"This result has opened the door to a deeper understanding of quantum entanglement over large distances, so this is just the beginning," states Saito. "We aim to deepen our understanding of the relationship between quantum entanglement and temperature in the future. This knowledge will spark and drive the development of future quantum devices that work at room temperatures, making them practical."

Reference

1. Kuwahara, T. & Saito, K. Exponential clustering of bipartite quantum entanglement at arbitrary temperatures. *Physical Review X* **12,** 021022 (2022).

ROBOTICS

Intelligent exoskeleton provides lower-limb lift

Artificial intelligence allows a robotic exoskeleton to surmise when its wearer is trying to stand up

An exoskeleton robot incorporating artificial intelligence technology that allows it to guess the user's intentions has been developed by RIKEN engineers[1]. In the future, the robot could help people with impaired mobility.

Robotic exoskeletons promise to play a key role in supporting an aging population. They are suits that give wearers the strength to perform tasks when their bodies are too weak to do them unaided.

However, exoskeletons developed to date tend to be heavy, and, if not properly controlled, they can hinder rather than assist users. It is thus critical to develop lightweight exoskeletons that do not hinder users' efforts.

The team used artificial intelligence to predict how the user wanted to move.

Now, a team led by Jun Morimoto of the RIKEN Guardian Robot Project has developed an exoskeleton that goes a long way to meeting these requirements.

The team developed a lightweight, carbon-fiber exoskeleton for the lower body that attaches to the thighs and lower legs of users. The exoskeleton was equipped with highly back-drivable actuators, which ensured that the exoskeleton did not impede the user's movements even when the actuators were not activated.

The team used artificial intelligence to predict how the user wanted to move. Specifically, they used a method known as positive and unlabeled learning to enable the exoskeleton to learn to correctly surmise the user's intentions based on readings of the user's muscle activities. Since it combines positively labeled data that the machine knows is correct with unlabeled data that might be positive or negative, this learning method can draw from ambiguous data that includes unlabeled data.

In an experiment, participants performed various movements that can begin in the same way: standing up, crossing their legs, leaning forward, and repositioning themselves in a chair. The exoskeleton used machine learning to guess when they were trying to stand up and then provided assistance for the movement.

The experiment was successful. "The results were better than conventional systems that use fully labeled data for situations when other user behaviors besides the target sit-to-stand motion can occur," says Jun-ichiro Furukawa, also of the RIKEN Guardian Robot Project. "This indicates that the method could be expanded to other movements as well."

"The key element of our research is that when controlling a robot to assist human movement, it is important to develop it based on the assumption that humans will behave in ways that are not in the learning data," explains Morimoto. ●

An exoskeleton robot developed by RIKEN engineers uses artificial intelligence technology to predict the movement the wearer is making.

Reference

1. Furukawa, J., Okajima, S., An, Q., Nakamura, Y. & Morimoto, J. Selective assist strategy by using lightweight carbon frame exoskeleton robot. *IEEE Robotics and Automation Letters* **7,** 3890–3897 (2022).

ORGANIC SYNTHESIS

Being selective when it comes to isomers

A roof-like ligand permits the selective synthesis of one of the three possible isomers of a key class of aromatic chemicals

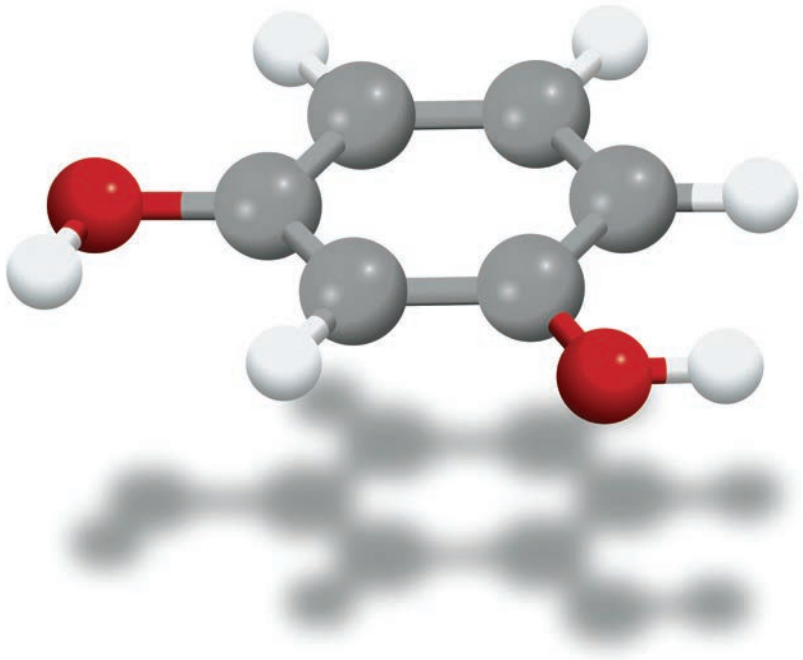
Four RIKEN organic chemists have come up with a way to selectively synthesize isomers—compounds made up of the same atoms, but in different arrangements—of an important group of aromatic compounds[1]. This promises to make it possible to manufacture chemicals for drugs, fertilizers and polymers without the need to perform costly separation procedures.

When making chemical compounds, placing a chemical group at the wrong position on a benzene ring can have dire consequences. "People can die if the position is wrong," asserts Laurean Ilies of the RIKEN Center for Sustainable Resource Science (CSRS). "For example, one form of vanillin is the chemical that gives vanilla its flavor, while another is quite toxic."

The benzene ring is hexagonal with a carbon atom at each of its six vertices. Since all the carbon atoms are identical, it makes no difference which one accepts the first chemical group to be added to the ring.

"one form of vanillin is the chemical that gives vanilla its flavor, while another is quite toxic"

Complexity arises when you add a second group because it can attach to any of five carbon atoms: the two neighboring the first group (to give the *ortho* isomer), the one diametrically opposite it (the *para* isomer), or the two carbons in between these two (the *meta* isomer; see image). The resulting isomers have identical chemical formulae, but often undergo very different biochemical reactions.



A molecular model of 1,3-dihydroxybenzene (gray spheres: carbon atoms; red spheres: oxygen atoms; white spheres: hydrogen atoms), the meta isomer of dihydroxybenzene. A team at RIKEN has developed a ligand that enables the selective synthesis of the *meta* isomers of arenes such as dihydroxybenzene.

It is relatively easy to block the two sites neighboring the first group, but organic chemists have struggled to devise general strategies to selectively synthesize the *meta* isomer.

Now, Ilies, Sobi Asako and two co-workers, all from CSRS, have produced an iridium catalyst bearing a ligand that blocks both the adjacent and opposite sites so that only the *meta* isomer is produced in significant amounts. This method can be used to add groups to benzene rings and produce compounds that are used for fertilizers, polymers and fine chemicals as well as drugs.

The team demonstrated the potential of their catalyst by using it to functionalize various pharmaceutical molecules at very high selectivities. "We were surprised at how well it worked," says Ilies. "It's very gratifying as it took us about three years of research to develop this approach."

The approach is very general and can be used on a wide variety of substrates. "We found out that quite a large variety of substrates can be functionalized using this method," says Ilies. "Maybe this was the best news."

The roof-like ligand is inspired by nature since it mimics the action of enzymes that have pockets to guide the synthesis of biomolecules of the right isomer.

The team now intends to expand this strategy to a larger variety of molecules and different selectivities. ●

Reference

1. Ramadoss, B., Jin, Y., Asako, S. & Ilies, L. Remote steric control for undirected *meta*-selective C–H activation of arenes. *Science* **375,** 658–663 (2022).

METAGENOMICS

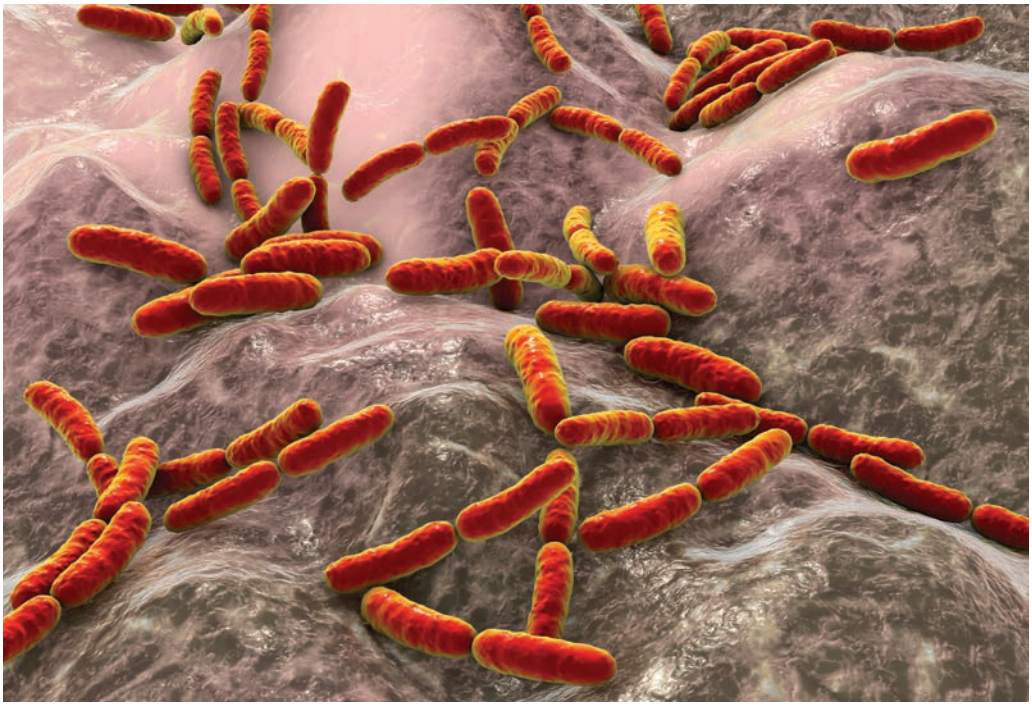
Accurate method to count single gut bacteria cells

A new technique for single cells can rapidly determine the make-up of bacterial communities

A single-cell method developed by RIKEN biophysicists, that can rapidly classify hundreds of thousands of bacteria according to species, promises to be an invaluable tool for discovering how gut, skin, ocean and soil microbes vary with changing conditions[1].

There has been an explosion in awareness of the various critical roles that bacteria in our guts play in health and disease. Biologists want to explore how the make-up of the gut microbiota affects their hosts, but methods for classifying bacteria according to species provide only very rough results.

Now, Katsuyuki Shiroguchi of the RIKEN Center for Biosystems Dynamics Research and his co-workers have devised a truly single-cell method that can accurately and rapidly characterize communities consisting of hundreds of thousands of bacteria.



A computer-generated image of *Lactobacillus* bacteria, the main component of the human small intestine microbiome. RIKEN researchers have used a high-throughput, single-cell technique for determining the species that make up microbiota such as the human microbiome.

"This tells us that our method can detect changes in just one species of bacteria."

Their method involves encasing individual bacteria in water-in-oil droplets and then labeling a stretch of bacterial DNA coding 16S ribosomal RNA (rRNA) with a unique DNA barcode. This barcode is 'read' during sequencing, allowing individual bacteria to be identified. And since each species of bacteria has basically its own 16S rRNA, the method can determine the number of bacteria of a particular species.

The team demonstrated the power of their technique by using it to see how diets deficient in vitamin A affected the gut microbiota of mice. They counted the bacteria at a distal location in the cecum—the entrance to the large intestine—of mice that had been fed a vitamin-A-deficient diet and control mice that had been fed a normal diet. The results revealed that only one species of gut bacteria was significantly affected. "We counted more than 200 different bacterial species in the cecum, but the amount of only one species changed significantly," says Shiroguchi. "This tells us that our method can detect changes in just one species of bacteria."

He is excited about the potential of the method to access the effects of recently developed bacterial therapies on the gut microbiome. "If we knew that this bacterial species is useful for addressing a specific health problem, doctors could prescribe it, but it hasn't been possible to accurately measure the change in the number of cells in the gut microbiome until now," explains Shiroguchi. "We want to contribute to such medical applications by accurately measuring the number of cells before and after a bacterial therapy."

The team now plans to apply their method to other communities of bacteria besides those in the gut. "We can use it to measure the microbiotas from the soil, sea, atmosphere and skin," he notes. ●

Reference

1. Jin, J., Yamamoto, R., Takeuchi, T., Cui, G., Miyauchi, E., Hojo, N., Ikuta, K., Ohno, H. & Shiroguchi, K. High-throughput identification and quantification of single bacterial cells in the microbiota. *Nature Communications* **13,** 863 (2022).

RIKEN researchers have identified genes critical for the healthy development of mouse fetuses.

GENOMIC IMPRINTING

Addressing an epigenetic cause of miscarriages in mice

A specific gene involved in epigenetic-related miscarriages in mice has been identified

In a finding with implications for understanding infertility and developing treatments, RIKEN researchers have discovered a gene responsible for prenatal death when mouse egg cells lack critical transgenerational instructions[1].

For embryos to develop normally, egg and sperm cells need to receive crucial biological instructions before they meet up. Once an egg is fertilized, some of these instructions tell genes to turn on or off depending on whether they came from the mother or father. This process is called genomic imprinting.

When modifications in gene expression are passed on to the next generation, they are called transgenerational epigenetic changes because they are inheritable even though the DNA code remains unchanged.

Researchers led by Azusa Inoue at the RIKEN Center for Integrative Medical Sciences have been studying a specific set of transgenerational epigenetic instructions given to egg cells called histone H3 lysine 27 (H3K27) trimethylation. They had previously found that preventing these instructions led to prenatal death in mice, particularly for male embryos, and to enlarged placentas in mothers.

Now, the team has demonstrated that these outcomes are directly related to failed imprinting.

Because the male offspring tended to die, the researchers suspected that the culprit was a gene on the sex chromosome. Of the nine maternal genes known to be suppressed in embryos in favor of the ones with paternal origins, only one, Xist, is on the X-chromosome.

To prevent transgenerational instructions from being given, the team knocked out a gene required for H3K27 trimethylation in eggs. They then added a knockout of the Xist gene to these eggs.

The results were almost as they had anticipated. Prenatal death was greatly reduced, and the high death rate for males disappeared after knocking out Xist. This demonstrated that failed Xist imprinting was causing prenatal death.

However, placentas were still enlarged. Reasoning that this was probably related to excess expression of the other eight genes that failed to imprint, the team created eight deletion mutants in the double-knockout embryos. Three of the eight genes resulted in normal-sized placentas.

"This study identified genes critical for fetal development whose expression is controlled by histone modifications transmitted from eggs to the next generation," says Inoue. "We succeeded in curing developmental defects in a mouse model that otherwise suffers from prenatal lethality and placental malformation due to the lack of transgenerational epigenetic instructions from mothers."

The researchers plan to conduct experiments to determine how these specific biological instructions are established when egg cells are created, and whether environmental factors can influence the process.

Reference

1. Matoba, S., Kozuka, C., Miura, K., Inoue, K., Kumon, M., Hayashi, R., Ohhata, T., Ogura, A. & Inoue, A. Noncanonical imprinting sustains embryonic development and restrains placental overgrowth. *Genes & Development* **36,** 483–494 (2022).

PLACENTA DEVELOPMENT

Uncovering the secrets of placental programming

Insights into the chromosomal features of precursor cells to the placenta could benefit reproductive research

RIKEN biologists have mapped out key features of the chromosomal landscape that lock in the identity of stem cells that give rise to the mouse placenta[1]. This could aid research into placental function and reproductive medicine.

The placenta is a unique organ in many ways. It is only found in mammals, forms only during pregnancy, and is discarded after serving its purpose. This distinctiveness can be traced backed to the stem cells that it develops from. Known as trophoblast stem cells (TSCs), they exhibit very different characteristics from those that form the embryo.

Indeed, TSCs are one of very few cell types that cannot be employed for somatic cell nuclear transfer—a standard procedure for generating clones by implanting the nucleus from a donor cell into an immature egg cell whose own nucleus has been removed.

"I've long been interested in the process that gives rise to TSCs," says Atsuo Ogura of the RIKEN BioResource Research Center. "They diverge from embryonic lineage cells as early as a few days after fertilization, develop independently, and terminate their role at birth."

Chromosomal DNA is wrapped around complexes of histone proteins, forming material known as chromatin. The organization and chemical properties of this chromatin can profoundly affect gene expression. Ogura and colleagues therefore set out to examine whether the features of TSC chromatin might contribute to these cells' distinctive identity and their incompatibility with somatic cell nuclear transfer.

The researchers performed a comparative analysis of chromatin in embryonic stem cells and TSCs of mice. They looked at the distribution of chromatin structures as well as at the patterns of histone methylation, a chemical modification with a particularly important influence on local transcriptional activity.

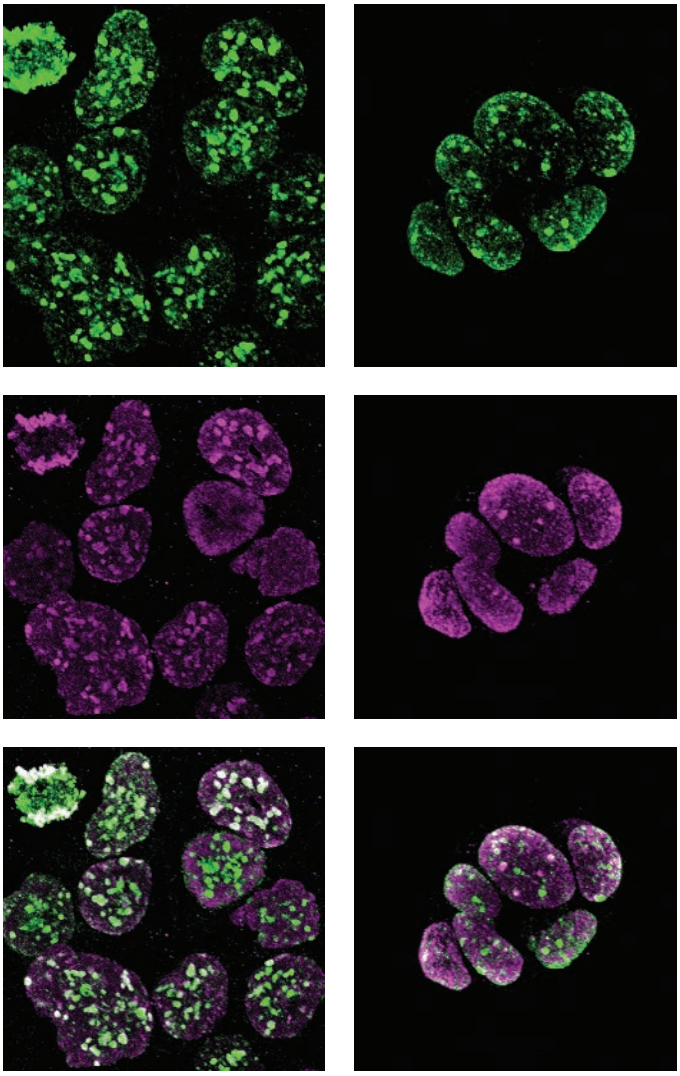
Intriguingly, the team noted that the chromosomes of both early embryonic and trophoblastic precursors are initially enriched with heterochromatin, a densely-packed form of chromatin, and exhibit a distinctive methylation profile.

But whereas TSCs retain these characteristics, Ogura notes "embryonic lineage cells reprogram these regions after implantation to enable diverse differentiation."

His team also confirmed that chromatin patterns observed in TSCs directly interfere with cloning.

However, when the researchers subjected TSCs to an epigenetic manipulation that altered their histone methylation profile, the nuclei from these cells suddenly proved amenable to somatic cell nuclear transfer. These results thus confirm the importance of these chromosomal modifications as a determinant of TSC identity.

There is considerable interest in developing better strategies for cultivating TSCs, both in research and reproductive medicine. By better understanding the features that define these cells during natural embryonic development, Ogura anticipates the possibility of generating lab-grown TSCs that can seamlessly integrate into functional placental tissue. ●



Trophoblast stem cells with fluorescent labels indicating heterochromatin (purple) and histone methylation (green).

Reference

1. Hada, M., Miura, H., Tanigawa, A., Matoba, S., Inoue, K., Ogonuki, N., Hirose, M., Watanabe, N., Nakato, R., Fujiki, K. *et al.* Highly rigid H3.1/H3.2–H3K9me3 domains set a barrier for cell fate reprogramming in trophoblast stem cells. *Genes & Development* **36,** 84–102 (2022).

EMBRYO DEVELOPMENT

Mouse stem cells for yolk sac established

The third type of stem cells that make up the precursors of mouse embryos has been established

Stem cells that give rise to the mouse yolk sac have been isolated and cultured in the lab for the first time by RIKEN researchers, raising the possibility of artificially creating mouse embryos from stem cells in the future[1].

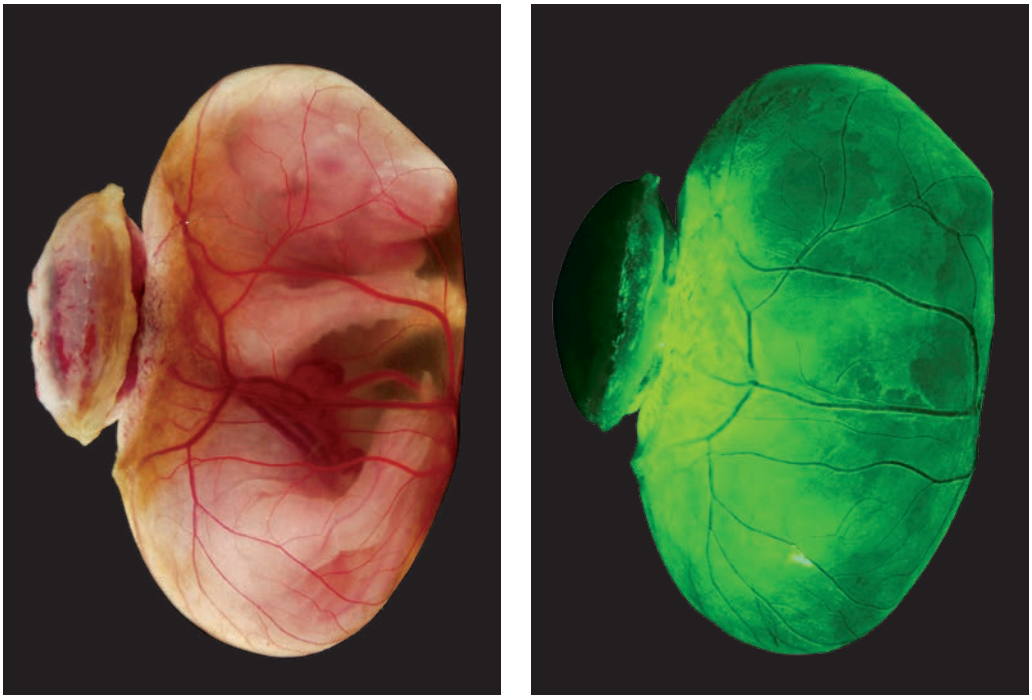
After fusing with a sperm, an egg develops into an early embryo called a blastocyst. It consists of dozens of cells of just three types: epiblast cells (forming the embryo), trophoblast cells (forming the placenta) and primitive endoderm cells (producing major parts of the yolk sac).

Stem cells have been isolated for both epiblast and trophoblast cells, but until now no-one had succeeded in producing stem cells for primitive endoderm cells.

Now, Yasuhide Ohinata of the RIKEN Center for Integrative Medical Sciences and co-workers have established primitive endoderm stem cells in mice, which form the yolk sac that sustains the developing blastocyst until the placenta takes over this role.

They achieved this by placing mouse blastocysts in various cultures and determining the conditions under which primitive endoderm stem cells flourished. Specifically, they perturbed key functional signaling pathways in the blastocysts by using recombinant proteins and small molecules, then observed the resulting cells.

The researchers confirmed that these cells fully complement fetal development of primitive-endoderm-cells-depleted blastocysts in chimeras. These blastocysts developed into normal offspring after transfer into uteri.



Bright-field microscopy image (left) and fluorescence microscopy image (right) of an E18.5 embryo with a yolk sac. When blastocysts that were depleted in primitive endoderm cells and injected with primitive endoderm stem cells were implanted in the uteri, they developed living offspring with yolk sacs (structure encasing the embryo), just like wild-type blastocysts.

This demonstration in living mice wasn't a trivial step. "There's a big leap between *in vitro* culture and *in vivo* function, as it's impossible to know whether established stem cells will function *in vivo* without transplanting them," says Ohinata. "We were fortunate in that we were able to achieve the expected results *in vivo*."

The team eventually hopes to artificially create embryos. "Our ultimate goal is to reconstitute embryos that can develop from stem cells alone," says Ohinata. "Primitive endoderm stem cells are essential for this, which is why we devoted so much effort to establishing a generally overlooked stem-cell type."

The researchers combined the three types of stem cells to generate embryo-like structures *in vitro*. When they implanted these in uteri, they formed descendants with yolk-sac-like structures but didn't develop into normal embryos. "While these results represent a major step forward in artificial embryo reconstitution, we will continue to pursue research to mimic embryos more precisely using stem cells," says Ohinata.

Ohinata notes that this achievement may not be directly applicable to people because of the differences between embryonic development in mice and humans, but he adds: "To understand human and mouse development in an integrated manner, we're conducting research using pigs, which are thought to retain human-type developmental mechanisms."

Reference

1. Ohinata, Y., Endo, T. A., Sugishita, H., Watanabe, T., Iizuka, Y., Kawamoto, Y., Saraya, A., Kumon, M., Koseki, Y., Kondo, T. *et al.* Establishment of mouse stem cells that can recapitulate the developmental potential of primitive endoderm. *Science* **375,** 574–578 (2022).

SENSORY PERCEPTION

Neural network adjusts for eye movement

The way the brain compensates for eye and head movement could help to improve machine vision

A RIKEN neuroscientist has developed a way to create artificial neural networks that learn to recognize objects faster and more accurately[1]. It can be applied to machine vision, facilitating self-driving cars to learn how to recognize important features on the road, for example.

Despite constantly moving our heads and eyes so that the input to our retinas is always changing, we don't perceive objects as blurred or unrecognizable. This perceptual stability is thought to be realized through neural copies of the movement commands, which are sent throughout the brain each time we move, allowing the brain to account for our own movements and keep perception stable. Some evidence suggests that eye movements and their motor copies may also help us to stably recognize objects, but how this happens was a mystery.

A method that enables artificial neural networks to learn to recognize objects faster and more accurately could help self-driving cars learn how to recognize important features on the road.

"This advance will help avoid dangerous mistakes in machine vision"

Now, Andrea Benucci of the RIKEN Center for Brain Science has developed a convolutional neural network that sheds light on this enigma.

The network was designed to optimize the classification of objects in a visual scene while the eyes are moving. It was first trained to classify 60,000 black-and-white images into ten categories, which it performed well. But its performance dropped drastically to chance level when tested with shifted images that mimicked naturally altered visual input that would occur when the eyes move.

However, the network's classification improved significantly after it was trained with shifted images—provided the direction and size of the eye movements that resulted in the shift were also included. In particular, adding eye movements and their motor copies to the network model allowed the system to better cope with visual noise in the images.

"This advance will help avoid dangerous mistakes in machine vision," says Benucci. "With more efficient and robust machine vision, it is less likely that pixel alterations will cause, for example, self-driving cars to label a stop sign as a light pole, or military drones to misclassify a hospital building as an enemy target."

Bringing these results to real-world machine vision shouldn't be as difficult as it seems. The improvements that Benucci observed when mimicking eye movements and their motor copies imply "that 'forcing' a machine-vision sensor to have controlled movements, while informing the vision network in charge of processing the associated images of the self-generated movements, would make machine vision more robust, and akin to what is experienced in human vision," explains Benucci.

Benucci will now collaborate with colleagues working with neuromorphic technologies to implement silicon-based circuits based on the principles he uncovered and then test whether they improve machine-vision capabilities in real-world applications. ●

Reference

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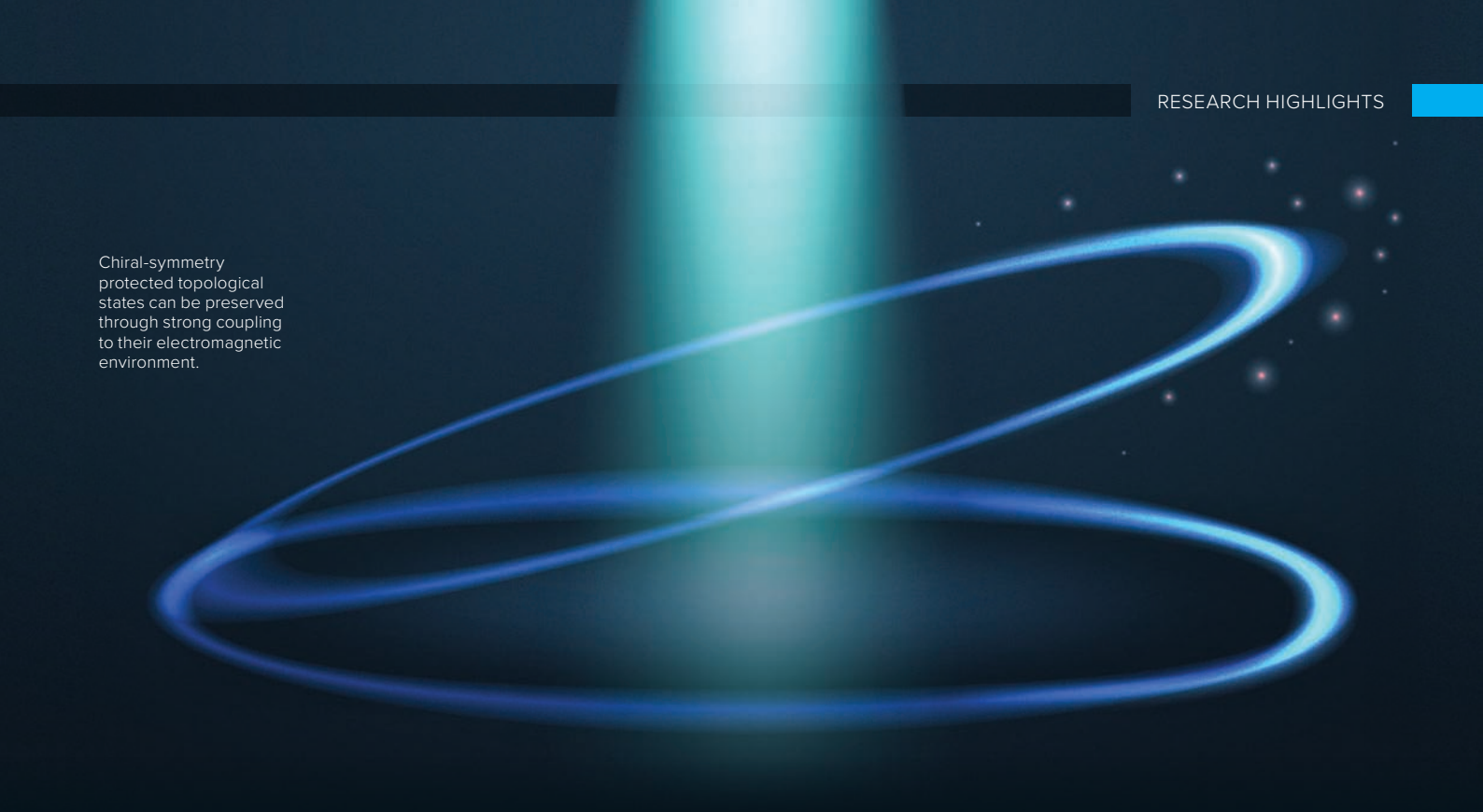

Chiral-symmetry protected topological states can be preserved through strong coupling to their electromagnetic environment.

QUANTUM MATERIALS

Protecting quantum matter with light

Quantum light can help create longer lasting quantum states useful for information processing

Quantum optics might offer a way to make a class of exotic materials known as topological materials even more robust against defects, theoretical physicists at RIKEN have shown[1]. This finding could benefit the development of quantum computers and other emerging quantum technologies.

Topological materials are exciting because local defects and imperfections in them don't affect their properties. But they are not immune to larger-scale, non-local disorder within the material.

Quantum optics is the study of how individual 'particles' of light, or photons, interact with matter. Its theory tells us that this interaction can be altered by controlling the electromagnetic properties of the matter's environment.

Coupling between light and matter has been employed to detect and manipulate topological matter. However, it is an open question how topological matter is modified by quantum light.

Now, in a theoretical study, Wei Nie and Franco Nori from the RIKEN Theoretical Quantum Physics Laboratory and their colleagues from France and China have discovered that the topology can be protected in vacuum electromagnetic fields.

"Our work pinpoints the novel properties of topological light–matter coupling," says Nori. "This may allow us to manipulate topological matter with quantum light."

By combining ideas from both condensed-matter physics and quantum optics, the researchers found that light emission from the topological electronic states changes with the strength of the light–matter coupling in a counterintuitive way. Light can be emitted in a weak-coupling regime, whereas strong light–matter coupling inhibits emission. It also increases the quantum coherence—the length of time the light can maintain its quantum state.

This is counterintuitive because stronger coupling to the environment usually reduces coherence: the symmetries protecting topological matter are supposed to be broken by the electromagnetic environment. "Instead, our work shows that for a topological emitter array coupling to a one-dimensional electromagnetic environment, the chiral symmetry that protects the system can be preserved," explains Nori.

This suggests an approach to tune quantum coherence without fiddling with the coupling between the system and the environment. Topological matter's robustness to local disorder makes it of great interest for quantum computation. However, non-local disorder remains a problem and limits the quantum coherence that is vital for all quantum technologies. The improved coherence offered by taking advantage of strong coupling can therefore be employed for better quantum information storage.

"Our work shows that topological light–matter coupling is an important resource for quantum optics and condensed-matter physics," says Nie. "The topological features of matter give rise to novel quantum optical phenomena, which are useful for quantum computation and quantum technologies."

Reference

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CHLORIDE PUMPS

How microbes pump ions

Light-induced changes in shape enable a pump in a marine bacterium to suck in chloride ions from seawater

RIKEN biochemists have discovered how a miniscule pump in a marine microbe shuttles negative ions into the cell by changing shape when activated by light[1]. As well as providing insights into how these ion pumps work, the findings will be useful for improving light-based tools for brain research.

Many bacteria and single-cell algae ferry ions into and out of their cells using pumps that are driven by light. By expelling or accepting ions, these pumps allow cells to regulate their contents relative to their environment. They work by altering their shape when activated by light.

The pump had an intriguing mechanism for preventing chloride ions from returning the way they came

Such light-driven pumps are not just of interest to biochemists; neuroscientists use them to probe brain circuits in animals by turning neurons on and off in response to light. Learning about how these pumps work will enable brain researchers to tailor them for this application.

Light-driven pumps that ferry positive ions across the cell membrane have been extensively studied, but much less is known about the workings of pumps that convey negative chloride ions.

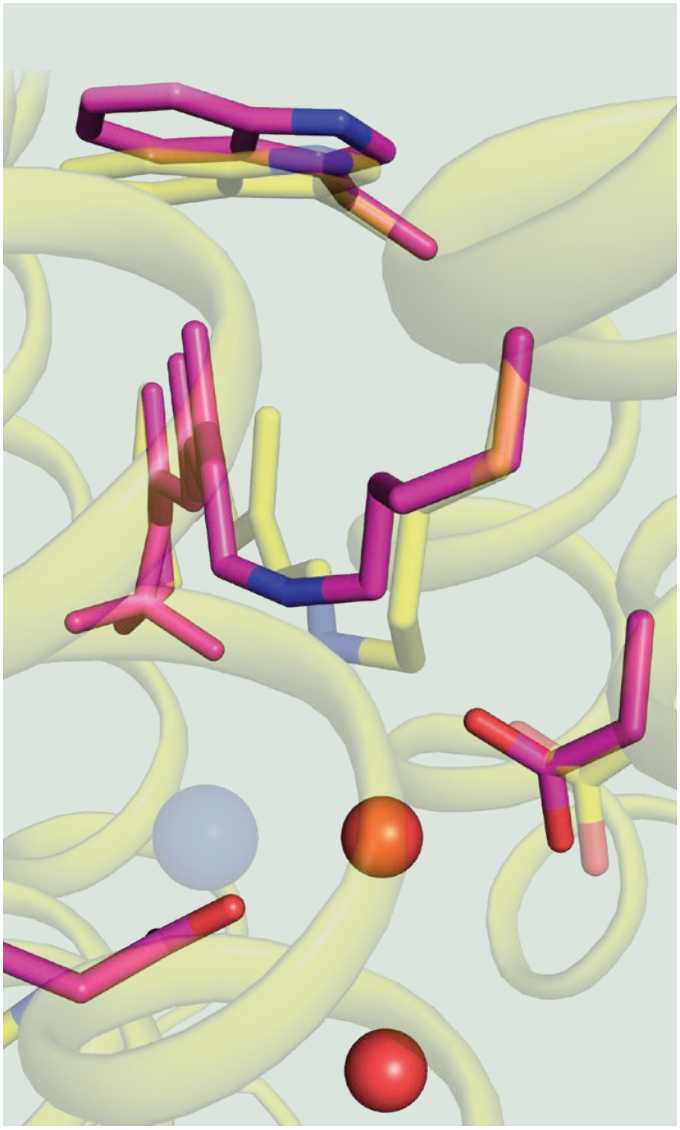
Now, Mikako Shirouzu and Toshiaki Hosaka at the RIKEN Center for Biosystems Dynamics Research, Eriko Nango at the RIKEN SPring-8 Center, and their co-workers have used a powerful x-ray laser—of which there are just a handful in the world—to visualize how the shape of a light-driven pump of chloride ions changes during operation (see image).

They looked at a chlorine pump from a marine bacterium that is based on the light-sensitive protein rhodopsin—a biological pigment similar to that in the light receptors of the human eye. The team used larger bromide and iodide ions rather than chloride ions because they are more detectable by x-rays.

The researchers discovered that the pump had an intriguing mechanism for preventing chloride ions from returning the way they came. "We were surprised to find that the amino-acid residue Asn98, which interacts with the anion, prevents backflow of the ion after it has passed through," says Hosaka. "There is thus a simple mechanism to transport just one ion with a single change in shape."

The results indicate that chloride-pumping rhodopsins employ a common mechanism for moving ions around.

Hosaka and his team intend to study other proteins by first rendering them sensitive to light. "Most proteins aren't responsive to light, making them difficult to control," says Hosaka. "In the future, we would like to modify ordinary proteins to make them responsive to light and thereby study the shape changes of a wider range of proteins." ●



Light-induced changes in structure (pink rods) near a chloride ion (blue sphere) are superimposed on the resting-state structure of a pumping protein (yellow). Water molecules are depicted by red spheres.

Reference

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LIQUID CRYSTALS

Shining light on a fluid completely changes its dielectric permittivity

Simply illuminating a fluid can cause its interaction with an electric field to greatly vary

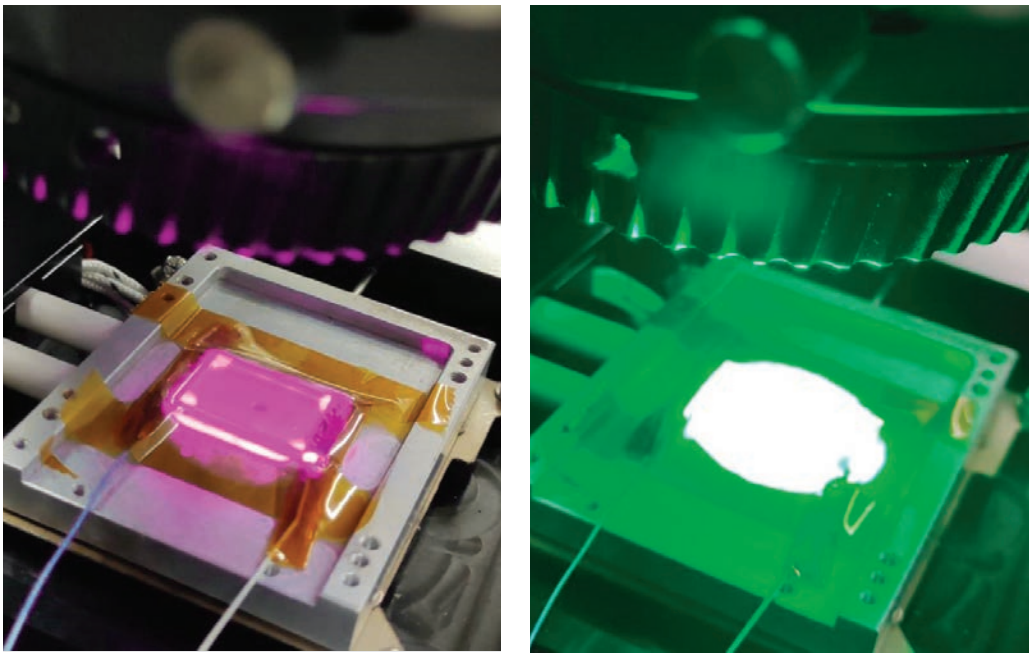
Three RIKEN researchers have created a liquid whose response to an electric field can be tuned over the largest range of any known material[1]. The fluid could find use in various applications including wearable electronics.

How materials respond to an electric field varies widely. Some ceramics, plastics and glasses show large responses because they are made of polar molecules, which have positive and negative parts. When an electric field is applied, the molecules align themselves with the electric field. In contrast, an electric field has very little effect on materials that have non-polar molecules such as air and most organic materials.

This response is measured by a number known as the dielectric permittivity—air has a dielectric permittivity very close to one, whereas materials with large responses have values in the thousands.

"We currently have no idea how this high dielectric permittivity is realized"

Now, Hiroya Nishikawa, Koki Sano and Fumito Araoka, all at the RIKEN Center for Emergent Matter Science, have developed a liquid whose dielectric permittivity can range from 200 to 18,000 in just half a minute when light is shone on it.



Shining blue light (left) on the fluid caused it to switch to a high dielectric permittivity phase, while shining green light on it (right) reversed the change.

The trio realized this by combining two molecules. The first molecule is a liquid crystal that has two phases: one with a low dielectric permittivity and the other with an extremely high one. The second molecule is light sensitive. When blue light was shone on the combined molecule, it switched from the low-dielectric-permittivity phase to the high one; when green light was shone on the fluid it reversed the situation, causing it to return to the low-dielectric-permittivity phase (see image).

Since a high dielectric permittivity is important for creating capacitors that store a lot of electric charge, the fluid could be used in applications that require variable capacitors. "If you wanted to get such a high capacitance, you would need a specially designed capacitor," says Araoka. "But we could realize a high capacitance by just sandwiching the material between electrodes because the fluid has such a high dielectric permittivity."

The team demonstrated an application of the fluid by coupling it with a sound generator and using it to change the sound's pitch over a wide range when they shone light on the fluid.

The mechanism behind the high dielectric permittivity is a mystery. "We currently have no idea how this high dielectric permittivity is realized," says Araoka. "So we'd like to discover the reason for it."

The team also wants to use the fluid to create flexible electronic devices. "In the current study, we used a glass substrate," says Nishikawa. "But we can replace it with a flexible film to create devices that can be worn on the skin." ●

Reference

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A CELL DEATH FIND CHANGES GUT PARADIGM

A new and unexpected cell death mechanism found in fly guts opens up big questions about how the digestive system really maintains its balance.

The new type of cell death found in the gut appears to be gradual, perhaps so the cells (pictured) can act as a protective barrier even as they break down.

STEVE GSCHMEISSNER / SCIENCE PHOTO LIBRARY

The discovery of a new form of cell death by RIKEN researchers challenges long-held beliefs about how old or damaged cells in the intestine of the fruit fly, *Drosophila*, are replaced[1]. If also found in mammals, the finding could have wide-ranging implications for the way we understand the gut and fight cancer.

In multicellular organisms, cell death is vital to maintaining tissue balance—homeostasis—by removing old, damaged and potentially harmful cells and replacing them with new ones. It has long been thought that gut cells die via a well-known type of cell death called apoptosis.

"Apoptosis is like cell suicide. It's very important during tissue development and also for preventing cancer," explains Sa Kan Yoo of the RIKEN Center for Biosystems Dynamics Research (BDR), who led the study.

The discovery of the new cell death mechanism—coined 'erebosis'—was made by chance. Researchers noticed that cells containing the angiotensin-converting enzyme (Ance), were missing many essential components (including the cell skeleton, DNA and other indispensable items). Conventional wisdom suggested it was impossible that the cells could still be alive.

A series of follow-up investigations revealed a number of surprising findings. "No matter how hard we tried, we couldn't find any role for apoptosis in normal fly gut physiology," says Yoo. "Even if we inhibit apoptosis, it doesn't prevent cell turnover or tissue homeostasis in fly guts."

The researchers also found that the erebotic cells were located near clusters of gut stem cells which produce new cells, indicating that the erebotic cells might be being replaced with new gut cells. This suggests that erebosis may not be an accidental form of cell death triggered by a trauma, but a normal part of gut function.

MECHANISM MYSTERY

After decades of research, the major cell death mechanisms were thought to be understood in detail.

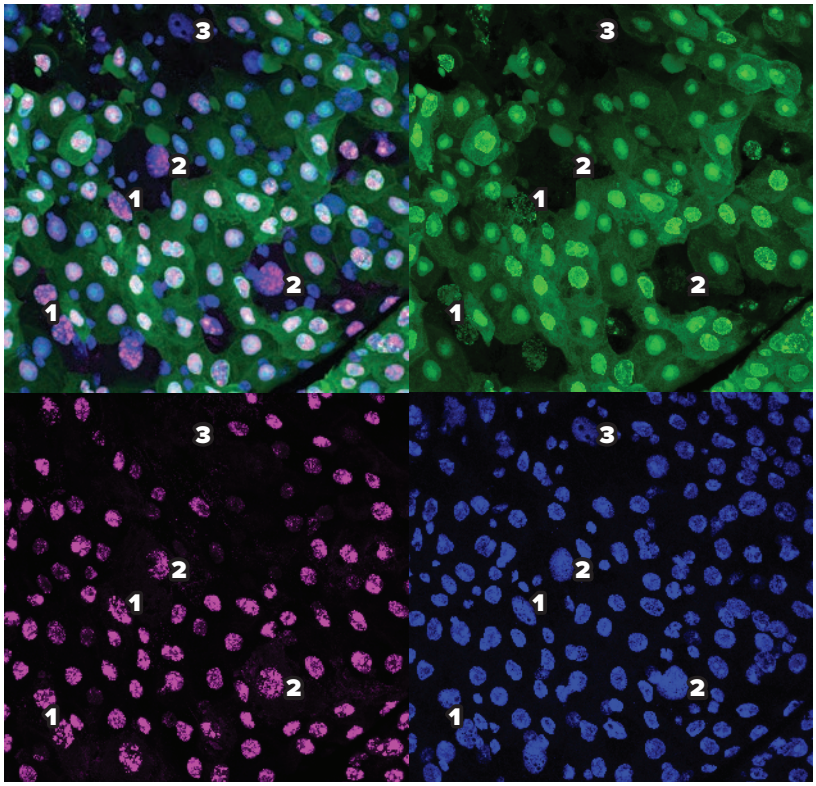
For instance, cells undergoing apoptosis undergo a series of well-defined molecular and morphological changes: they become rounder and smaller and activate an enzyme called caspase. This 'programmed cell death' plays an important role both during development and normal cell turnover.

Another type, called autophagic cell death, generally occurs during starvation. Autophagic cell death is characterized by the formation of large bubbles (or vacuoles) that destroy the contents of the cell. "Autophagy is a mechanism that can help cells to survive, but if it proceeds too much then it can lead to their death," explains Yoo.

Necrosis is more of an accidental process triggered by infection or injury. During necrosis, a cell will

This feature looks **at the work of**
SA KAN YOO

Yoo graduated in medicine from Kobe University. He worked on cell migration mechanisms at Dr Yasuhiro Minami's lab while he was not working on the wards. He later obtained his PhD on wound responses in zebrafish from Anna Huttenlocher's lab at the University of Wisconsin-Madison. Yoo then joined Iswar Hariharan's lab at the University of California, Berkeley as a postdoc and investigated mechanisms of tissue repair and oncogenic stress using *Drosophila* and zebrafish. At RIKEN, he was appointed an associate chief scientist in 2015, a chief scientist in 2017 and then a team leader in 2018. Yoo's laboratory focuses on mechanisms of tissue and organismal homeostasis such as cell death, cancer and aging.



These images using green fluorescent proteins (top right), red fluorescent proteins (bottom left) and DAPI (4′,6-diamidino-2-phenylindole) (bottom right) and a combination (top left) reveal the gradual process of a new type of cell death dubbed erebosis. At early-stage erebosis (1), cells lose cytoplasmic green fluorescent protein, but retain nuclear green fluorescent protein and red fluorescent protein. At intermediate erebosis (2), cells do not have signals of green fluorescent protein, but still retain nuclear red fluorescent protein. At late-stage erebosis (3), cells lose both green fluorescent protein and red fluorescent protein signals.

undergo swelling and then burst to release its contents.

While the exact mechanisms of erebosis are yet to be explored, the group noted via fluorescence studies that the new type of cell death appeared to be a gradual process. Because of this, they hypothesize that erebotic cells may be similar to skin cells, which act as a protective barrier even as they break down. This enables a continuous flux of gut tissue repair without allowing tissue integrity to be breached or arousing immune responses.

ACCIDENTAL CELL DEATH FINDING

Although most scientific breakthroughs take years of painstaking research, often serendipity provides a final push. Here, the researchers were actually studying Ance—the *Drosophila* equivalent of an enzyme in humans involved in controlling blood pressure—when they made their unexpected discovery.

"We found that Ance had a very interesting expression pattern in the fly gut," explains Yoo. "The cells that contained this enzyme were very unusual: they looked dark under the microscope."

After noticing that these dark cells were denuded, and making their hypothesis about seeing a new type of cell death, they named the phenomenon 'erebosis', based on the ancient Greek word 'erebos' meaning darkness or shadow.

The researchers also ruled out the possibility that they were dying through apoptosis, autophagic cell death or necrosis through a series of experiments. "The gut cells we found didn't have any of the striking features or characteristics of apoptosis, necrosis or autophagy," explains Yoo. "While there is no way to stop necrosis, there are many ways to experimentally stop apoptosis or autophagy from occurring. When we did this in the fly gut, erebosis still occurred."

"These results suggest that erebosis might play an important role in maintaining gut tissue homeostasis," says Yoo. "But we haven't proved that yet—it's still speculation."

The next critical step will be to identify specific molecular markers of erebosis and the genes involved in this process.

"If we can understand what's going on at the molecular level, we can then carry out experiments to find what happens when we stop this process from occurring in the fly gut," says Yoo. "That will then allow us to truly understand the function of erebosis."

Another huge unanswered question is whether erebosis also occurs in mammals, including humans. "In tissues like the skin, gut or blood, cell turnover is a very important process in our daily lives," Yoo points out. In many tissues, cell death is happening constantly and it is estimated that humans shed 10^{11} (100,000,000,000) cells from the small intestine every day[2].

Cell death is also a key player in tumor growth. During the development of colon cancer for instance, tumor cells are thought to become resistant to apoptosis. Defective apoptosis regulation has been linked to the extended lifespan and growth under stress conditions of cancerous cells, the accumulation of further genetic mutations, the formation of blood vessels in tumors and spread to different parts of the body. Insights into new forms of cell death my change our understanding of this process and lead to new treatments.

"I feel our results have the potential to be a seminal finding," Yoo says. "Personally, this work is the most ground-breaking I have ever done. We are keenly interested to find out whether erebosis exists in the human gut."

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A SPRING IN THE STEP OF SPring-8

Water discharge from the fuel stack of the Toyota Mirai, one of the world's first hydrogen fuel cell electric vehicles, was adapted using SPring-8 insights.

Plans for Japan's high-energy 4th generation synchrotron promise to accelerate green innovation along with electrons.

By Tetsuya Ishikawa, Director of the RIKEN SPring-8 Center

Synchrotron radiation is essential to nanoscience. As nanoscale production techniques improve, related insights are becoming increasingly crucial to produce a wide range of real-world innovations. For instance, recent nanoscale analyses have led to advances in carbon fiber technology, enabling more energy-efficient transport. New insights into the structures of catalysts have also spurred the creation of carbon capture technologies that reduce industry emissions.

Scientists use synchrotron radiation to better understand material interactions at the nanoscale level. These insights come from studying the light diffraction and scattering that results when a collision occurs between the atoms in a research sample and the X-ray light produced by the synchrotron. However, to achieve nanoscale level detail, the electron beam in the synchrotron must be accelerated over a 1.4 km

TETSUYA ISHIKAWA
Director, RIKEN
SPring-8 Center

Tetsuya Ishikawa has been the director of the SPring-8 Center at RIKEN since 2006. After graduating from the University of Tokyo and receiving his doctoral degree in 1982, he joined the Photon Factory at the High Energy Accelerator Research Organization (KEK), as a research associate, overseeing precision X-ray optics. After working at the University of Tokyo, in 1995 RIKEN appointed him Chief Scientist in charge of beamline development for SPring-8. He is now preparing the SPring-8 upgrade.

circular orbit to near the speed of light, while keeping it's spread very small — approximately the diameter of a human hair.

RIKEN's Super Photon Ring-8 GeV (SPring-8) is the world's largest 3rd generation facility and the only high-power synchrotron facility in Japan. To remain competitive on the international stage, SPring-8 has been planning to transition to a 4th generation facility since 2014. Construction will likely start in the second half of this decade, if funded.

This upgrade is necessary for the continued progression of nanoscience. When SPring-8 opened in 1997, we expected that scientific research would be the main focus of our users, with relatively few studies contributing to industry research. By 2018, approximately 2,300 projects had been conducted at SPring-8, and nearly 20% were industry-related. Today, synchrotron science worldwide regularly produces results that can be quickly adapted and used to produced socially beneficial innovations.

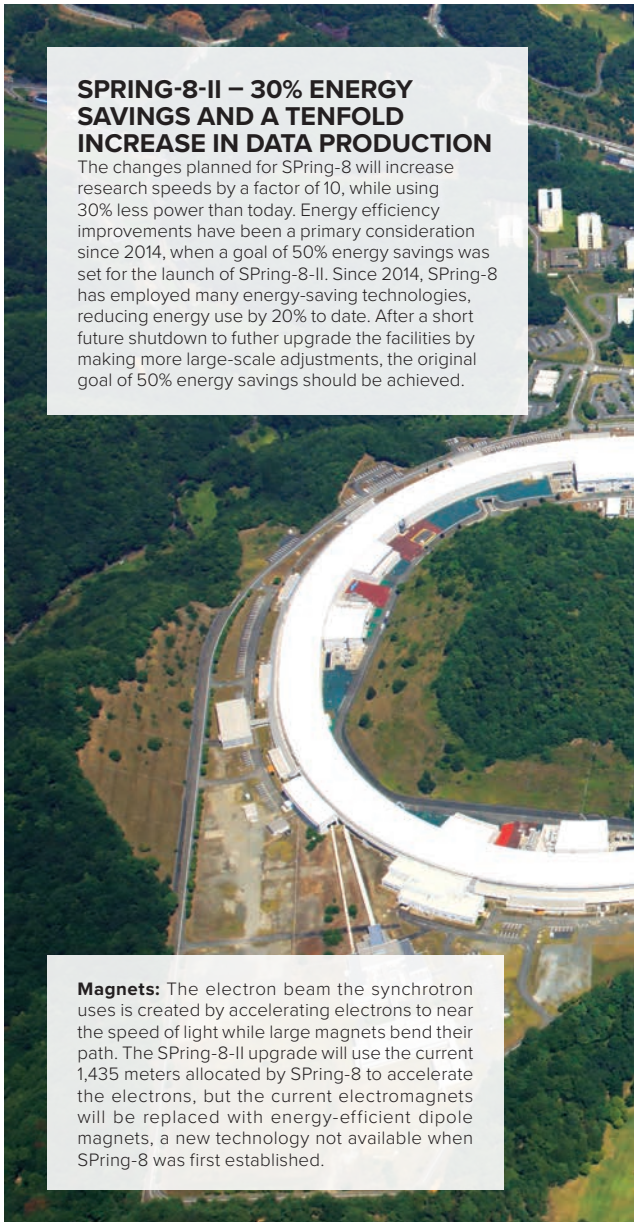
The facility's new design (see graphic) will significantly increase SPring-8's brilliance, speeding up data production by a factor of 10. It will also decrease the accelerator's power consumption by roughly 30%. Thus we will be able to provide less expensive, faster, and more detailed research, which will super-charge data collection.

ACCELERATING ELECTRIC VEHICLES

The four-door Toyota MIRAI is an example of the impact synchrotron research has on everday life. The MIRAI, launched in 2014, is one of the world's first commercial hydrogen fuel cell electric vehicles. The design for the fuel stack was aided by research insights obtained at SPring-8 by Toyota and Honda Motor Co., Ltd. between 2008 and 2010. This research focused on efficient chemical bonding and electronic states at the surfaces of different types of core-shell cathodes.

The findings were only possible because a collaboration between Toyota Motor Corporation and Toyota Central R&D Labs. Inc. had previously developed a unique analysis method at SPring-8, a technique for fast time-resolved X-ray absorption fine structure spectroscopy (XAFS). It allowed scientists to understand material structural changes in real-time by probing the electronic transitions of inner-shell electrons.

The first generation MIRAI had a fuel stack that uses hydrogen and oxygen to generate power, discharging water particles as a by-product. After the success of the MIRAI, the Toyota team returned to SPring-8 to observe the nano-sized particles of water discharged. These studies enabled the scientists to determine the most efficient shape for the discharged water, an insight enabling the development of an even more efficient fuel stack. The improved water drainage efficiency contributed to the design of a second generation MIRAI in 2019, which extended its driving range by 30%.



SPRING-8-II – 30% ENERGY SAVINGS AND A TENFOLD INCREASE IN DATA PRODUCTION

The changes planned for SPring-8 will increase research speeds by a factor of 10, while using 30% less power than today. Energy efficiency improvements have been a primary consideration since 2014, when a goal of 50% energy savings was set for the launch of SPring-8-II. Since 2014, SPring-8 has employed many energy-saving technologies, reducing energy use by 20% to date. After a short future shutdown to futher upgrade the facilities by making more large-scale adjustments, the original goal of 50% energy savings should be achieved.

Magnets: The electron beam the synchrotron uses is created by accelerating electrons to near the speed of light while large magnets bend their path. The SPring-8-II upgrade will use the current 1,435 meters allocated by SPring-8 to accelerate the electrons, but the current electromagnets will be replaced with energy-efficient dipole magnets, a new technology not available when SPring-8 was first established.

FUTURE GREEN INNOVATION

Insight into hydrogen energy catalysts is another great example of synchrotron data's capacity for impact.

Today, reducing greenhouse gas emissions is a global goal, and lowering dependence on fossil fuel energy represents a considerable portion of the challenge. If the energy created by reactions between hydrogen and oxygen were to replace the energy currently provided by fossil fuels, industry could vastly reduce its greenhouse gas emissions. Water is usually the only by-product of hydrogen energy catalysis. However, a catalytic conversion rate of 10% or more is needed for effective performance, and these reactions must then be adapted

Cooling system: SPring-8 currently requires energy-intensive water-cooling systems to control the temperature of the equipment as the electron beam is accelerated by the magnets. With the lower-energy beam and the new magnet technology, it is feasible to use air cooling for more energy-efficient temperature control.

A fourth generation comes of age: Today, only one 4th generation high-energy synchrotron is operational. It is located in France (est. 2020), and two more are currently under construction in the United States (to be completed in 2023) and in China (to be completed in 2026). SPring-8-II should debut before the end of the decade as Japan's first 4th generation high-energy synchrotron, with the unique advantage of being established from an already world-renowned facility.

Beam vacuum: With the introduction of a smaller beam, less energy is required to achieve an ultra-high-vacuum inside the accelerator, further increasing energy savings.

Injector: To produce such a small, brilliant beam requires a low-emittance, high-efficiency electron injector. The RIKEN SPring-8 Angstrom Compact Laser (SACLA), a linear X-ray free-electron laser, can efficiently inject a low-emittance electron beam into the storage ring. This will enable the removal of the current injector system comprised of a 1 GeV linear accelerator and an 8 GeV booster synchrotron.

Beam size: Currently, the electron beam at SPring-8 is about 0.4 mm wide. The upgrade will enable new X-ray mirror optics to reduce the beam to < 0.1 mm. The smaller beam size reduces photon loss, resulting in a brighter beam requiring lower energy input, which reduces radiation and energy loss. In addition, energy must be supplied to compensate for the synchrotron radiation loss caused by bending the path of the beam. This will be reduced by a factor of three. Furthermore, with a smaller beam, the accelerated light becomes more coherent and wavelike, facilitating increasingly straightforward observation of diffraction and scattering, providing a 10-fold improvement in data acquisition speeds.

for individual applications. In addition, it is theorized that even with this efficiency, the price of hydrogen production will not fall enough to be cost effective.

In April 2022, Kobe University published data obtained at SPring-8 that showed that by modifying the surface of their previously-developed hematite photocatalyst, it was feasible to inexpensively, safely, and stably produce hydrogen from sunlight and water, with hydrogen peroxide as a by-product. Hydrogen peroxide is used in everything from disinfectants and bleaches to soil treatments, so selling this by-product could help make hydrogen production more affordable.

This is only one of many examples of the possibilities facilitated by synchrotron research. Furthermore, industry demand is increasing both for solitary results and access to big synchrotron datasets for AI to analyze. To create these datasets, data production must be expedited faster than the timeline for the planned upgrades.

By building suitable datasets, engineers and scientists will have access to the information they need to design materials for more natural disaster resilient structures, lighter and more accessible transport, advanced medical devices and medications, and everything in between, well as the means to actualize green technology. ●

CREATING MORE SEMI-ARID CROPS

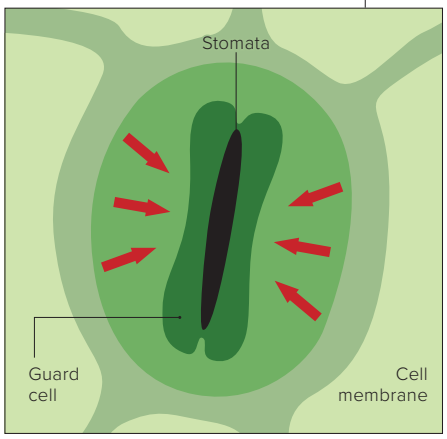
Rising temperatures were thought to be responsible for a 4% loss in cereal production between 1981 and 2010. A RIKEN devised treatment that increases the stress tolerance of crops—such as cassava, rice and wheat—opens up new farming possibilities.

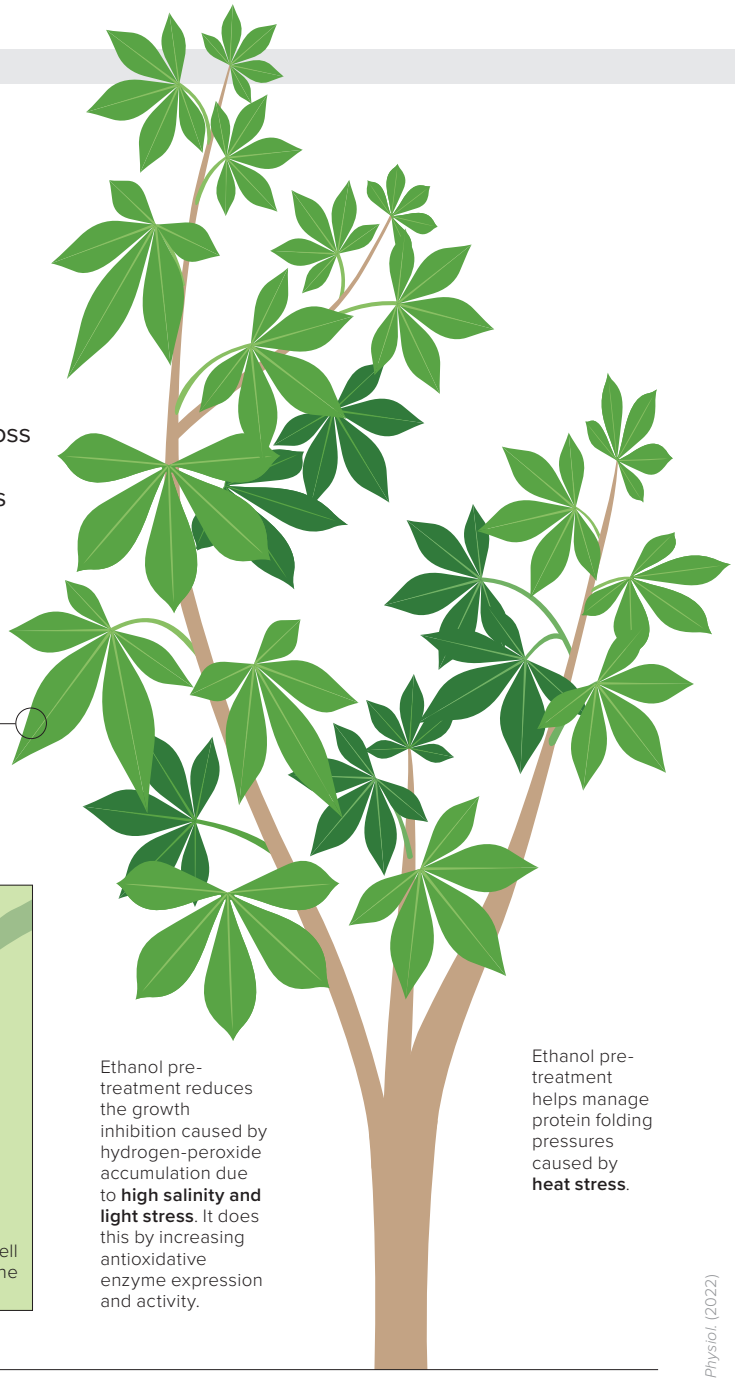
ETHANOL BOLSTERS STRESS TOLERANCE

Researchers from the RIKEN Center for Sustainable Resource Science have looked at how an ethanol pre-treatment can increase plant drought, salt and thermal tolerance. Here are some pathways annotated on a cassava plant.

Plants protect themselves from **water loss** by acting on kidney-shaped guard cells around plant pores, known as **stomata**. The plant hormone **abscisic acid (ABA) facilitates pore closure** via the guard cells during drought. Ethanol pre-treatment helps close the pores earlier, preserving water.

Ethanol pretreatment leads to an increase in **transitory starch** in the leaves, which is an important form of energy storage that can be depleted during plant stress.



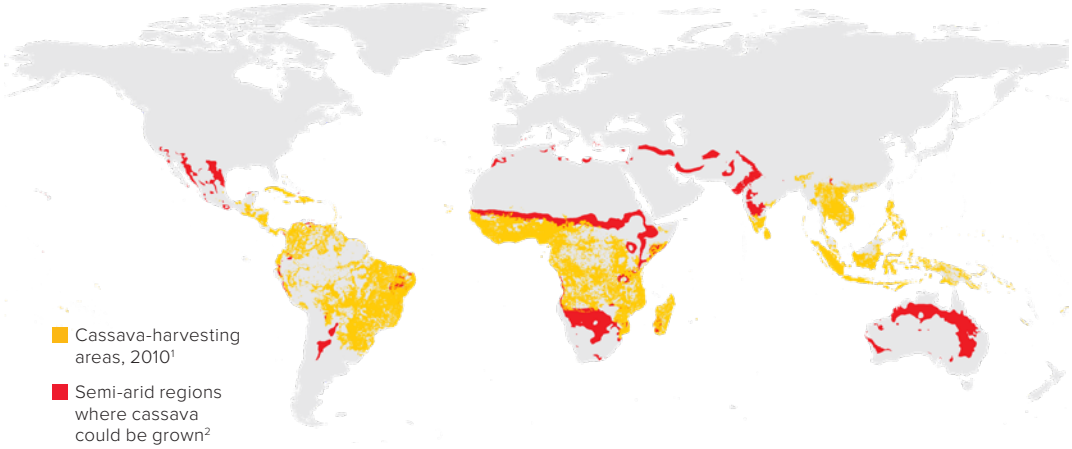


Ethanol pre-treatment reduces the growth inhibition caused by hydrogen-peroxide accumulation due to **high salinity and light stress**. It does this by increasing antioxidative enzyme expression and activity.

Ethanol pre-treatment helps manage protein folding pressures caused by **heat stress**.

NEW FARM LAND FOR CASSAVA?

Cassava is a major tropical starch crop that feeds up to one billion people. Its roots produce starch, known as tapioca which is used as a food, energy source, industrial material and livestock feed. It grows in poor soil, year-round. By pre-treating cassava plants with ethanol, production areas could potentially be extended to semi-arid regions, RIKEN researchers have suggested.



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