SOMETHING SMELLS FISHY

Injured fish release warning compounds

JAPANESE ANCESTRY TWIST
A third lineage revealed?

TIME FLIES
New key to aging in insects

GREEN LIGHT
Jellyfish solve illumination issue
SPIDER SILK IN THE MAKING
A colored scanning electron micrograph of silk being extruded from glands on an Orb weaver spider. RIKEN researchers have produced artificial spider silk that has a similar structure to natural spider silk by using a microfluidics device (see page 12).

RIKEN RESEARCH

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The secrets of longevity: RIKEN scientists at the Center for Integrative Medical Sciences and the Center for Biosystems Dynamics Research have looked at longevity from many angles.
For this issue, I would like to tell our readers about some changes taking place at RIKEN Innovation, the company that RIKEN established to carry out innovative and commercial activities.

RIKEN Innovation was established in 2019, following a change in the laws governing scientific institutes that allowed us to invest into subsidiary companies. The company was tasked with a variety of activities including licensing intellectual property, supporting startups, and promoting joint research with industry. During the five years since then, the company operated, but we came to feel that the time had come to make some changes. This year I was appointed to take charge of it and implement these changes.

Prior to coming to RIKEN, I myself was at the helm of the company set up to handle innovation activities for the University of Tokyo. In fact, I was the first person in Japan who really made a business out of technology transfer from academia to industry. I spent time in the United States and learned a lot from the activities of Niels Reimer, who established innovation companies at Stanford University, MIT, UC Berkeley, and UC San Francisco, as well as through my activities in ATTP, an international society of innovation professionals.

Concretely, the current reforms will involve projecting a new image, based on a new logo that represents the wind to portray action, and changing job titles to fit with international standards, so that our partners abroad will more easily understand the functions of our staff. We have also changed the Japanese name, which used to incorporate a difficult Chinese character, into ‘RIKEN Innovation’, matching the English name. We are now considering how to appeal to partners overseas through videos that will feature some of our important technologies. And in order to make sure that we have a good grasp of the breadth of work at RIKEN, we have visited about 80 percent of the laboratories, talking with laboratory leaders about how their work could be turned into innovation.

We would be happy to hear from potential partners overseas. Some of the places I am looking at most closely now are technologies involving AI, in areas such as materials and pharmaceuticals, as well as quantum technologies, semiconductors, and also promising environmental technologies that could help us to attain the Sustainable Development Goals.
Briefly describe your current research
My objective is to understand why some species are the way they are and why they live where they live. These characteristics often correspond to how a group of organisms split off as a distinct group, a process known as speciation. Understanding this process is important to help us more clearly recognize what a distinct species is, which is necessary to help assign a value to biodiversity. It also allows us to understand the genetic changes that species undergo to become distinct. This can help generate new knowledge on the functions of certain genes.

What excites you the most about your research?
I joined RIKEN in April 2022 through the Special Postdoctoral Researchers Program and joined the Interdisciplinary Theoretical and Mathematical Sciences Program (iTHEMS).

When I applied, I had already been living in Japan for several years, because I also studied my master’s and doctoral courses in this country.

I decided to apply and join iTHEMS for two reasons. One is that I was compelled to follow a more computational and theoretical approach to see if I could answer questions that had been opened up by my postdoctoral research, such as—is speciation a process that follows universal rules? Or is speciation the sum of independent evolutionary events that vary across biological groups? Can we unify a theory of speciation? Secondly, I had already met some iTHEMS members and they were (and are) very kind and nice people.

At iTHEMS, I have been learning about how complex concepts can be represented as equations, and how those equations can sometimes then be applied to multiple phenomena.

This has helped me to identify ideas that are new to my field and to explore them further.

How did you become interested in your current field?
I always had a fascination with how an organism’s characteristics seem to correspond to the environment in which they live. I grew up in a city in a desert region of Mexico. There I observed plants that produce thick, succulent trunks, sharp thorns, or tiny leaves to avoid water loss.

These kind of observations made me want to learn more about how and why life always tries to persist, even in the most extreme environmental conditions.

What is the best thing about working at RIKEN?
RIKEN offers a great atmosphere within which to interact with many of the leading scientists in Japan.

There are also many opportunities to start new research projects, and RIKEN allows a working style that prioritizes intellectual freedom.

In addition, RIKEN is a very foreigner-friendly institution. Directors, researchers and administrative staff all pay attention to the issues that foreigners may encounter while constructing their careers and personal lives in Japan.
Detecting energy from exotic nuclei

Martha Liliana Cortes Sua
Special Postdoctoral Researcher, Radioactive Isotope Physics Group, RIKEN Nishina Center for Accelerator-Based Science

Describe your role at RIKEN.
I study the nuclear structure and shell evolution of exotic isotopes, which are usually produced in a laboratory.

The protons and neutrons forming the nuclei of these rare isotopes are arranged in different shells.

I investigate how energy levels and shells change when neutrons are added or removed from the isotopes, and I look at the gamma radiation that is emitted by nuclei when excited.

Understanding why and how this happens helps us to understand fundamental nuclear force.

Please describe your research
At the RIKEN Nishina Center for Accelerator-Based Science in Wako, Tokyo, I lead the testing and development of a new gamma-ray detector, which uses a recently developed scintillator material. The new detector will have a faster detection time and a better energy resolution than current detectors.

What excites you the most about your current research?
The new gamma-ray detector will allow us to measure properties such as excited states and transition probabilities in isotopes that are currently considered very hard to experiment on, because they are so short lived.

By measuring such properties, we will be able to understand the nuclear forces at work within the isotopes, the origin of nuclear deformation, and the interactions between nucleons inside the nucleus.

What do you wish you had known before you came to Japan?
I wish I had learned the Japanese written system for English words, katakana, before arriving. Most Japanese textbooks start by using the more traditional writing system, hiragana, but as a foreigner, reading English words in katakana is very useful.

Careers at RIKEN
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What interested you about your field?
During my undergraduate degree in my country of origin, Colombia, I became fascinated by the possibility of creating exotic isotopes, so I joined a nuclear physics group. Since then, I’ve always really enjoyed working on instrumentation related to the discovery of the properties of radioactive isotopes.

How did you come to join RIKEN?
I first started working at RIKEN in 2016 while on a scholarship from the Japanese Society for the Promotion of Science (JSPS).

On that occasion I stayed for two years and then moved to Europe to pursue further research. However, isotopes at the limits of existence can be better studied at RIKEN, so I submitted a research proposal and came back in 2022 as a Special Postdoctoral Researcher.

How has being at RIKEN helped your research?
The Radioactive Isotope Beam Factory at the RIKEN Nishina Center can produce some of the most exotic isotopes in the world. It is one of the few locations where cutting-edge research on nuclear structures can be performed.

What are some of the technologies that you use?
The Superconducting Ring Cyclotron (SRC) at the RIKEN Nishina Center produces some of the rarest isotopes that exist. We also use some of the latest developments in readout electronics, such as fast digitizers.
Immunologist Masaru Taniguchi passed away on April 8, 2024, at the age of 84. In the 1990s, Taniguchi opened up a new field in medical and immunology research when he discovered natural killer T cells, a subset of T lymphocyte immune cells. In particular, his findings on the immune rejection of cancers, which could be induced by NKT cell activation, have had a significant impact on basic and clinical cancer research worldwide.

Taniguchi also helped establish immunology centers at Chiba University in Japan and at RIKEN. In 2001, he became the founding director of the RIKEN Research Center for Allergy and Immunology, a position he held until 2013. After this, he continued to serve at the RIKEN Research Center for Integrative Medical Sciences as a lab leader and an IMS Honorary Research Fellow, inspiring many young researchers.

We would like to express our deepest condolences to all those who knew him.


RIKEN Advisory Council meeting

From December 13 to 16, 2023, the 12th meeting of the RIKEN Advisory Council (RAC) was held in Tokyo at RIKEN.

The council is a group of external experts from Japan and abroad who meet on a regular basis to review RIKEN’s management and research activities and make recommendations to RIKEN’s president.

In anticipation of the conclusion of RIKEN’s 4th Mid- to Long-Term Plan period, which ran from fiscal 2018 to 2024, RAC carried out an evaluation of RIKEN’s operations and initiatives in that time. There was a particular focus on new initiatives implemented since the financial year 2022 with an eye to their place in the 5th Mid- to Long-Term Plan period, which will run from fiscal years 2025 to 2031.

The council then gave advice on the draft policy for the coming plan period from an international perspective. The RAC brought together world-renowned domestic and international scientists as committee members, including Chairperson Tan Chorh Chuan, chairman of Singapore’s Agency for Science, Technology and Research (A*STAR).

RIKEN plans to address the recommendations of the RAC, and to quickly formulate measures to reflect them in RIKEN’s operations, research activities, and the 5th Mid- to Long-Term Plan.


In memoriam: Masaru Taniguchi, father of natural killer T cells

Immunologist Masaru Taniguchi passed away on April 8, 2024, at the age of 84. In the 1990s, Taniguchi opened up a new field in medical and immunology research when he discovered natural killer T cells, a subset of T lymphocyte immune cells. In particular, his findings on the immune rejection of cancers, which could be induced by NKT cell activation, have had a significant impact on basic and clinical cancer research worldwide.

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RIKEN symposium Europe 2024

In February, 2024, a symposium focused on organoid research was held in Brussels to celebrate the fifth anniversary of the opening of RIKEN’s Europe office in 2018.

The event featured a series of presentations on research into organoids—engineered tissues that approximate the structures and functions of actual human organs.

Eventually, it is hoped that scientists will be able to develop organoids that can be used in regenerative medicine, but today they are being used as experimental models to advance areas such as drug discovery.

The event featured RIKEN researchers and scientists from collaborating institutes in Europe, including Imec in Belgium, Freie Universität Berlin in Germany, INSERM in France, St. Anna Children’s Cancer Research Institute in Austria, The National Research Council in Italy, and the Joint Research Center, which is headquartered in Italy and Spain.

The symposium also featured addresses by RIKEN Executive Director Makiko Naka and Kazutoshi Aikawa, ambassador extraordinary and plenipotentiary to the European Union at the Mission of Japan.

On April 5, 2024, RIKEN and Argonne National Laboratory (ANL) in the United States signed an agreement to carry out joint research on ‘AI for science’—AI models that are designed to aid researchers and are trained on specific datasets related to the area of interest.

The use of these curated datasets to train AIs results in more-reliable outputs tailored to the needs of specific fields, such as the life sciences or materials sciences.

The two organizations will also work on fundamental technologies, including: those for data generation; automation and acceleration of experiments and simulations; evaluating the performance of models; system software development; data management; and computing system operation.

They will also share ideas and provide in kind use of their world-class computing resources and datasets, including the use of RIKEN’s supercomputer Fugaku and the Argonne National Laboratory’s supercomputer, Aurora.

“Generative AI is creating many changes in our society,” noted RIKEN President Makoto Gonokami. ANL Director Paul Kearns added that their models will address “some of the most complex challenges facing society”.

RIKEN will collaborate with ANL as part of the Transformative Research Innovation Platform of RIKEN Platforms (TRIP) project, which aims to link RIKEN’s platforms across a number of fields.

Gonokami and Kearns signed the agreement in an online ceremony attended by ANL Associate Director Rick Stevens, RIKEN Executive Director Makiko Naka, RIKEN Center for Computational Science Director Satoshi Matsuoka, and Makoto Taiji, the program director of the Advanced General Intelligence for Science Program (AGIS) based at the TRIP headquarters.

A few days after the ceremony, Japan’s Ministry of Education, Culture, Sports, Science and Technology and the United States’s Department of Energy chose to include the idea of AI for science in a collaboration framework between the Japanese and US governments.

The US’s Department of Energy has also launched a new project that is focused on AI for science, with ANL playing a leading role.

Meanwhile, RIKEN’s AGIS has recently launched the TRIP-AGIS project, which also aims to develop generative AI models to aid scientific research.

President of the Max Planck Society, Patrick Cramer, visits RIKEN

On April 9, 2024, a delegation led by Patrick Cramer, president of the Max Planck Society in Germany, visited RIKEN’s Tokyo and Wako campuses.

The delegation toured the Tokyo area as well as the RIKEN Cluster for Pioneering Research, which is based in the Wako area. During this time, they were briefed on some of RIKEN’s work by Masashi Sugiyama, director of the RIKEN Center for Advanced Intelligence Project and Mihoko Otake, team leader of the Cognitive Behavior Support Technology Team at the RIKEN Center for Advanced Intelligence Project.

In the evening, a reception was held at the residence of the Ambassador of the Federal Republic of Germany to Japan to commemorate the 40th anniversary of research collaboration between the Max Planck Society and RIKEN, jointly hosted by the German Embassy in Tokyo and the Max Planck Society. The reception was attended by a large number of people, and congratulatory speeches were delivered by Cramer, and H.E. Clemens von Goetze, Ambassador of the Federal Republic of Germany to Japan, and Misako Kaji, Ambassador for Science and Technology Cooperation of the Ministry of Foreign Affairs of Japan.


Indian Ambassador to Japan visits Wako Campus

On February 28, 2024, H. E. Sibi George, Ambassador of India to Japan, visited the RIKEN Wako Campus to meet with President Makoto Gonokami and discuss cooperation between RIKEN and research institutes in India.

The visit began with tours of the RI Beam Factory (RIBF)—a heavy-ion accelerator facility—and other RIKEN Nishina Center for Accelerator-Based Science facilities, as well as tours of the superconducting quantum computer ‘A’ and other facilities at the RIKEN Center for Quantum Computing.

At the visit were Center Director Hiroyoshi Sakurai, Team Leader Laurean Ilies from the Advanced Organic Synthesis Research Team at the RIKEN Center for Sustainable Resource Science, Unit Leader Eisuke Abe from the Superconducting Quantum Electronics Joint Research Unit at the RIKEN Center for Quantum Computing and a number of RIKEN researchers from India.

The tour was followed by addresses from President Gonokami and Ambassador George, and by an introduction to RIKEN from Executive Director Makiko Naka.

H. E. Sibi George (left), Ambassador of India to Japan, and Hiroyoshi Sakurai, director at the RIKEN Nishina Center for Accelerator-Based Science.
A new method offers a global view of the proteins responsible for cellular uptake of small extracellular vesicles (EVs). As well as offering insights into how healthy cells communicate, it could also reveal how cancer cells spread.

One way that cells communicate with each other is through the secretion and uptake of extracellular vesicles. EVs convey a multitude of cargoes, including proteins, lipids and nucleic acids. Their uptake affects the function of recipient cells by influencing signaling processes and gene expression.

However, despite extensive study of EVs, little is known about their cell-specific uptake by recipient cells. “Understanding how recipient cells take up EVs is critical for deciphering the broader mechanisms governing cell-to-cell communication in cellular processes in both health and disease,” explains Koshi Imami of the RIKEN Center for Integrative Medical Sciences.

Imami and colleagues have now developed a novel method to track the interaction between EVs and recipient cells. The TurboID-EV system works by labeling recipient cellular proteins close to EVs with biotin (vitamin B7).

“Unlike traditional techniques that tag EVs with fluorescent proteins or use microscopy, our method provides a global view of proteins involved in the uptake of EVs,” says Imami.

By identifying the biotin-tagged proteins using biochemical enrichment and mass spectrometry, researchers can glean clues into the molecular mechanisms underlying EV uptake.

Imami and colleagues expressed a biotin ligase that is engineered to fuse with EV membranes in human embryonic kidney cells without interfering with EV secretion. By collecting secreted TurboID-EVs and incubating them with recipient cells labeled with heavy amino acids and supplemented with biotin, they could examine biotinylation events that occur during the uptake of EVs.

The researchers identified more than 450 biotinylated recipient proteins. They included well-known ones involved in the process by which cells engulf external substances to bring them in. The team also found proteins involved in intracellular transport and membrane-associated proteins, which could be key for EV uptake in this model.

The method can be adapted for different EV subtypes and cell types. “The versatility of our system allows researchers to investigate the specificity of EV uptake mechanisms in many biological contexts,” Imami says.

Discovering the proteins involved in EV uptake could further our understanding of how cancer cells spread and help develop EV-based drug-delivery systems that target specific cell types.

Imami’s team is now trying to apply the TurboID-EV system to a mouse model to understand how cancer spreads between organs. “Tumor-derived EVs are known to be taken up by organ-specific cells to prepare for cancer to spread to new organs,” Imami explains. “We want to characterize the function of these EVs.”

Reference
Electronic states that resemble molecules and are promising for use in future quantum computers have been created in superconducting circuits by physicists at RIKEN\(^1\).

The most obvious advantage of superconductors—materials that offer no electrical resistance to the flow of electrons—in electronic circuits is that they don’t produce any wasteful heating, which limits the energy efficiency of conventional circuitry.

But they also have another big advantage. Superconductivity arises due to quantum-mechanical interactions between electrons. These exotic effects could be harnessed in devices, providing them with a wide range of functionality not available in conventional devices.

Now, Sadashige Matsuo of the RIKEN Center for Emergent Matter Science and co-workers have investigated just such an effect. Known as an Andreev molecule, it could be used for quantum information technologies in future quantum computers.

The basic building block of superconducting circuits is the Josephson junction: a device made by sandwiching a normal material between two superconductors, which can control the flow of the supercurrent.

Where the normal material interfaces the superconductors, an electron in the normal material is reflected as a hole, and a pair of electrons is generated in the superconductor. This reflection forms bound states in the normal material of the Josephson junction, so-called Andreev bound states.

If two Josephson junctions are close enough, they can form an Andreev molecule by linking to one another. Matsuo and his co-workers focused on the two Josephson junctions that shared one short superconducting electrode. In the structure, the Andreev bound states in the different junctions are expected to link to one another through the shared electrode.

“When these Andreev molecules exist, one Josephson junction can control another Josephson junction,” explains Matsuo. “And then exotic and useful superconducting transport phenomena emerge, such as the Josephson diode effect—an effect that could lead to less dissipative rectifiers in superconducting circuits.”

Matsuo and his co-workers made two Josephson junctions with a thin layer of indium arsenide. They then coupled them together through a shared superconducting electrode made of aluminum, which is superconducting at very low temperatures.

The team studied the electronic properties of this structure by measuring the tunneling current to the junctions at various applied voltages and magnetic-field strengths, a technique called tunneling spectroscopy. This enabled them to observe the energy levels in the Josephson junctions corresponding to Andreev molecules.

“Researchers had previously reported the spectroscopic characterization of Andreev molecules in the different device structures,” says Matsuo. “But we have now succeeded in observing them in coupled Josephson junctions and demonstrating their controllability for the first time.”

“Our work provides fundamental information about the Andreev molecule,” adds Matsuo. “And it will pave the way for engineering exotic superconducting transport phenomena in coupled Josephson junctions in the future.”

**Reference**

In a discovery that could help to develop crops that are more resistant to pathogens, RIKEN researchers have traced the origin and evolutionary trajectory of immune receptors in plants.1

Similar to animals, plants have immune responses that help them fight pathogens such as viruses, bacteria and fungi. Plants detect pathogens by using pattern-recognition receptors on the surfaces of their cells. The ability of these receptors to detect molecular patterns associated with pathogens depends on two types of proteins, called receptor-like proteins (RLPs) and receptor-like kinases (RLKs), both of which can contain leucine-rich repeats—sections in which the amino acid leucine appears multiple times.

To trace the evolution of plant immunity, a team led by Ken Shirasu and Yasuhiro Kadota at the RIKEN Center for Sustainable Resource Science (CSRS) examined the numbers and patterns of receptors. Using publicly available data from 350 plant species, they analyzed more than 170,000 genes encoding RLKs and about 40,000 genes encoding RLPs.

The team discovered that RLKs and RLPs with leucine-rich repeats were the most abundant receptor types among all 350 plant species, making up nearly half of RLKs and 70% of RLPs.

RLPs, and some RLKs, contain a special island region that is crucial for recognizing parts of pathogens. The team discovered that among RLPs containing leucine-rich repeats, this special region was almost always located in the same place—between the fourth and fifth leucine-rich repeats. These RLPs were found to be associated with immune responses.

The team also discovered that the island region was located at the same position in some RLKs, nearly all of which belong to a functional group that regulates growth and development.

The sequence of the four repeats below the island region was very similar between the two types of protein detectors, suggesting that they have a common evolutionary ancestry. In particular, these four sets of leucine repeats contained sections needed for bonding to the same co-receptor, called BAK1. This means that immunity-related RLPs and growth-related RLKs inherited the ability to bind to BAK1 from a common ancestor.

“Intriguingly, we found that exchanging the four regions of leucine-rich repeats among these receptors did not disrupt their functionality,” says Bruno Pok Man Ngou, also of CSRS.

Creating a hybrid receptor by combining a growth-related RLK with an immunity-related RLP resulted in a hybrid receptor that recognized pathogens and induced both immune and growth-related responses. This implies that scientists should be able to engineer receptors with new functions by swapping those modules.

“We’re currently isolating immune receptors from various plants using this information, aiming for practical applications such as developing disease-resistant crops in the future,” says Shirasu.

Reference
RIKEN researchers have developed a device that spins artificial spider silk that closely matches its natural counterpart. This ecofriendly innovation could impact industries as diverse as textile manufacturing and biomedicine.

Renowned for its strength, flexibility and light weight, spider silk is also biodegradable and biocompatible. Since large-scale harvesting of silk from spiders has proven impractical, scientists are keen to develop a way to produce it in the lab.

Spider silk is a biopolymer fiber made from large proteins with highly repetitive sequences, called spidroins. Spider silk fibers contain molecular substructures known as beta sheets, which must be properly aligned for the fibers to have their unique mechanical properties. Recreating this complex molecular architecture has confounded scientists for years.

Rather than trying to devise the process from scratch, RIKEN scientists took a biomimicry approach. “We attempted to mimic natural spider-silk production using microfluidics, which involves the flow and manipulation of small amounts of fluids through narrow channels,” explains Keiji Numata of the RIKEN Center for Sustainable Resource Science (CSRS). “Indeed, one could say that the spider’s silk gland functions as a sort of natural microfluidic device.”

They developed a small, rectangular microfluidic device with tiny channels in it. Precursor spidroin solution is placed at one end and then pulled toward the other end by negative pressure. As the spidroins flow through the channels, they are exposed to precise changes in the chemical and physical environment, which are made possible by the design of the microfluidic system. Under the correct conditions, the proteins self-assembled into silk fibers with their characteristic complex structure.

“The researchers optimized the interactions between the different regions of the microfluidic system. They discovered that using force to push the proteins through did not work; only when they used negative pressure to pull the spidroin solution could continuous silk fibers with the correct alignment of beta sheets be assembled.”

“It was surprising how robust the microfluidic system was, once the different conditions were established and optimized,” says Ali Malay, also of CSRS. “Fiber assembly was spontaneous, extremely rapid, and highly reproducible. Importantly, the fibers exhibited the distinct hierarchical structure that is found in natural silk fiber.”

The ability to artificially produce silk fibers using this method could have numerous benefits. For example, it could help reduce the environmental impact of textile manufacturing and it could be used for biomedical applications, such as sutures and artificial ligaments.

“We want to have a real-world impact,” says Numata. “For this to occur, we will need to scale up our fiber-production methodology and make it a continuous process.”

Reference
Two compounds—rather than one—alert fish of danger when their shoal-mates are injured, RIKEN scientists have found\(^1\). This finding could have implications for other communications via smell.

In 1938, Nobel-laureate Karl von Frisch discovered that a shoal of minnows behaved as if a predator was nearby when an injured minnow was placed in their tank. This defense mechanism allows fish to avoid danger even when they have not directly detected a predator themselves. Von Frisch surmised that the injured minnow’s skin released some alarm substance, which its shoal-mates detect through their sense of smell, called olfaction.

Scientists have since found that fish in the superorder Ostariophysi, to which roughly 75% of freshwater fish belong, behave similarly—but only when the injured fish is of the same species. However, the identity of the alarm substance had been a mystery.

“Many researchers have attempted to purify and identify alarm substances using skin extracts from various fish species,” says Yoshihiro Yoshihara of the RIKEN Center for Brain Science. “What sets our study apart, and the reason for our success, was that we chose a completely different type of screening method.”

Yoshihara’s team screened for substances based on brain activity. They dropped damaged zebrafish skin into a tank of zebrafish and detected which parts of the olfactory brain region reacted. They repeated the experiment using damaged skin from two other fish species: goldfish, which are in the same Ostariophysi superorder, and medaka, which are not.

The team found that three olfactory brain regions reacted to the damaged skin: one was non-specific, responding to all three types of damaged skin; one was superorder specific; and one was zebrafish specific.

As medaka do not have alarm responses, and zebrafish did not react much to damaged goldfish skin, the researchers reasoned that two chemical signals were needed for the behavior to occur: a superorder-specific smell signaling ‘danger!’ and a species-specific smell signaling ‘for us’.

The researchers biochemically purified the molecule responsible for the zebrafish-specific brain response, which they named daniol sulphate, and they identified the molecule behind the Ostariophysi-specific olfactory response, which they named ostariopterin.

When the team examined the skin of many fish species, they found that, consistent with their hypothesis, Daniol sulphate was unique to zebrafish, whereas Ostariopterin was observed in many fish species in the Ostariophysi superorder.

The researchers repeated their experiments using these compounds instead of damaged skin. Zebrafish showed the characteristic robust fear response, but as predicted, only when both daniol sulphate and ostariopterin were put into the water.

“This type of biological two-factor messaging system could be a common theme underlying many types of social communication through olfaction,” notes Yoshihara.

Reference
**Modeling the blood–brain barrier using a cube system**

A new model of the protective barrier between the bloodstream and the brain developed by RIKEN researchers could aid drug discovery by replacing animal models in preclinical studies.1

The blood–brain barrier protects the brain by preventing foreign substances in the blood from entering it. But when developing drugs for brain diseases, it is crucial to confirm that potential drugs can pass through the barrier.

Drug-development methods conventionally rely on animal testing in the early stages, but it can be difficult to predict how effective and safe a drug will be in humans based on them. This problem is spurring researchers to develop new methods that do not rely on animal testing.

With this in mind, Isabel Koh and Masaya Hagiwara, both at the RIKEN Center for Biosystems Dynamics Research, have developed a new model of the blood–brain barrier using a cube-based system they recently created for modularizing different human tissues.

Reconstructing multiple tissues simultaneously and analyzing their interactions is vital. But it is extremely challenging because drugs have to traverse different types of tissues before reaching the target area. In the case of the blood–brain barrier, drugs must pass through vascular endothelial cells, astrocytes and pericytes before they can enter the brain.

To construct the blood–brain barrier model, Koh and Hagiwara created 5-millimeter CUBE frames, filled them with a hydrogel embedded with astrocytes and pericytes derived from the human brain, and seeded vascular endothelial cells differentiated from human stem cells onto the surface to form cell sheets.

The results of testing the device were encouraging. “We were happy to find that it accurately mimicked the real blood–brain barrier in terms of structure and function,” says Hagiwara. “And like the real barrier, it only allowed limited substances to pass through.”

Importantly, the CUBE frame can be easily manipulated with forceps, allowing convenient handling of the blood–brain barrier model.

To demonstrate the usefulness of the system for drug development, the pair conducted drug-screening experiments. Brain tumor cells were cultured in the CUBE container to prepare a brain tumor module. The blood–brain barrier and brain tumor modules were then transferred into a fluidic chip and connected. This setup allowed the researchers to verify how much of an anticancer drug could pass through the barrier and reach the brain tumor.

“This innovative approach offers a promising alternative to animal testing for essential drug development tests, involving the understanding of drug behavior, effectiveness, and safety,” says Hagiwara. “Our modularized platform could be adapted for various diseases, including age-related neurodegenerative diseases such as Alzheimer’s and Parkinson’s diseases.”

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**Reference**

1. Koh, I. & Hagiwara, M. Modular tissue-in-a-CUBE platform to model blood-brain barrier (BBB) and brain interaction. *Communications Biology* 7, 177 (2024).

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Confocal light micrograph of a section through a blood vessel in the brain, showing the blood–brain barrier. RIKEN researchers have developed a new model of the blood–brain barrier that uses a cube system they had developed previously.
A more appetizing avenue to longevity

Flies that cut back on a certain amino acid during early adulthood outlive those who don’t, raising the possibility that the same effect may apply to people.

Fruit flies live consider-
ably longer when fed a diet that limits consumption of a certain amino acid during early adulthood, RIKEN biologists have found. If a similar effect occurs in humans, it could allow people to live longer by eating restricted diets during certain stages of life.

Many studies have suggested that the life expectancy of animals can be extended by a lifelong diet of calorie restriction, but for many people this road to longevity is unpalatable. However, similar benefits may be possible by a much more targeted dietary intervention, research by Fumiaki Obata of the RIKEN Center for Biosystems Dynamics Research and co-workers now suggests.

The advantages of caloric restriction are mainly associated with reduced protein consumption. In past experiments with female fruit flies, Obata and others have specifically linked these gains in lifespan to reduced intake of methionine, an amino acid that needs to be sourced from food since the body doesn’t produce enough of it to maintain good health.

“But nobody actually knew at what life stage this amino acid affects the lifespan of animals,” says Obata.

To address this question, Obata and co-workers compared the survival and health of female flies exclusively fed a methionine-reduced diet in early versus late adulthood.

Remarkably, flies fed the restricted diet for the first four weeks of adulthood experienced nearly the same longevity gains as flies that consumed reduced methionine throughout their entire lives—as much as 10% longer than flies on a standard diet. In contrast, the diet seemingly conferred little benefit when administered solely in late adulthood.

The researchers were also able to link diet-associated gains in longevity with boosted expression of an enzyme that biochemically ‘repairs’ damaged byproducts of methionine, thereby boosting available reserves of this amino acid.

For reasons that remain unclear, male flies do not exhibit equivalent gains from methionine restriction, although it may have to do with the greater reproductive burden borne by females.

“Evolution is usually a friend of faster growth and greater reproductive activity at the cost of aging,” says Obata. Higher protein and/or amino acid intake may favor the former processes, while restriction may shift the balance to slower aging.

It remains to be seen whether a similar pattern occurs in mammals, something that Obata and his team now intend to further examine.

Obata is intrigued by the possibility of an easier avenue to healthier aging for humans. “It’s clearly much more preferable if we can shorten the length of dietary restriction and still reap the full benefit,” says Obata. He is keen to further explore opportunities to achieve extended lifespan through targeted metabolic interventions delivered at earlier ages.

Beef is a rich source of the amino acid methionine. Data from fruit flies suggest that the longevity benefits of a methionine-restricted diet could be achieved with a more targeted intervention in early adulthood.

Reference
Using heat to swap between skyrmions and antiskyrmions

Waste heat could be harnessed to flip between miniscule magnetic vortices and their antivortices

In a finding that could help realize ultralow-energy devices, RIKEN researchers have converted tiny magnetic vortices (skyrmions) into antivortices (antiskyrmions) using heat and magnetic fields. Nanoscale magnetic whirlpools, skyrmions, and their counterparts, antiskyrmions, are an active area of research, as they could be used for next-generation memory devices.

Previously, scientists have used electric currents to move skyrmions and antiskyrmions and to create transformations between them. But because electronic devices consume electrical power and produce waste heat, a team led by Xiuzhen Yu of the RIKEN Center for Emergent Matter Science (CEMS) wanted to see if they could use heat gradients to create transformations.

“As approximately two-thirds of the energy produced by power plants, automobiles, incinerators and factories is wasted as heat, we thought it would be important to try to create transformations between skyrmions and antiskyrmions—which has previously been done using electric current—using heat,” says Yu.

The researchers used an extremely precise fabrication system to create a microdevice from a single-crystal magnet. They then examined its magnetic properties at very small scales.

When a temperature gradient and a magnetic field were simultaneously applied to the crystal at room temperature, the antiskyrmions within it transformed into non-topological bubbles—a sort of transition state between skyrmions and antiskyrmions—and then into skyrmions, as the temperature gradient was raised. They remained in a stable configuration as skyrmions even when the thermal gradient was removed.

While this finding is consistent with theoretical expectations, a second finding amazed the team. “We were surprised to also find that when the magnetic field was not applied, the thermal gradient led to a transformation from skyrmions to antiskyrmions, which also remained stable within the material,” says Fehmi Sami Yasin, also of CEMS.

“What is very exciting about this is that this means we could use a thermal gradient—basically using waste heat—to drive a transformation between skyrmions and antiskyrmions, depending on whether a magnetic field is applied or not,” says Yasin. “It is particularly significant that we were able to do this at room temperature. This could open the way to a new type of information-storage device such as nonvolatile memory devices using waste heat.”

“We are very excited about this finding, and plan to continue our work to manipulate skyrmions and antiskyrmions in new and more efficient ways,” says Yu. “Our goal is to build spintronic devices that could be used in our everyday lives.”

Reference
fuses,” explains Miyawaki. “For example, it may result in cross-linked experimental artifacts in some host proteins.”

To overcome this limitation, the team determined the green fluorescent protein’s crystal structure to identify structural features that may drive the formation of dimers. They then used directed evolution to modify the protein’s structure at these key points. Their goal was to suppress dimer formation without impairing the green fluorescent protein’s brightness or stability.

Remarkably, the monomer-forming variant that the researchers developed turned out to be even brighter and more photostable than the first generation of StayGold.

The researchers demonstrated the potential of their monomeric variant in several live fluorescence imaging studies.

“We used the monomer to label filaments of actin and the inner membranes of mitochondria,” says Miyawaki. “It enabled us to successfully image these structures with an enhanced spatiotemporal resolution and over an extended observation period.”

The team is now seeking to elucidate the molecular basis of the outstanding photostability of the variant. They are also striving to develop a photostable, red-emitting fluorescent protein that could be used in combination with StayGold or its monomer for live fluorescence imaging.

Delicate cellular structures and dynamic processes within cells that were hitherto unseen could be revealed by the next generation of a green fluorescent protein developed by chemists at RIKEN.

Green fluorescent proteins are widely used in biological research for lighting up structures of interest in fluorescence microscopy. They emit green light when illuminated by blue or ultraviolet light.

Previously, Atsushi Miyawaki of the RIKEN Center for Brain Science and his co-workers had derived a green fluorescent protein from a naturally occurring fluorescent protein made by a tiny Japanese jellyfish (see image). It overcame a common problem with green fluorescent proteins, namely they become dimmer under the powerful or long illumination used in fluorescence imaging of live cells.

Cellular proteins labelled with the green fluorescent protein, which the team named StayGold, could be tracked within live cells over extended time frames.

“It’s a highly bright and photostable green fluorescent protein,” says Miyawaki. “That makes it useful for imaging a variety of components in cells with an enhanced resolution and over long times.”

One limitation with the original StayGold, however, was its propensity to pair up and form dimers—molecules made up of two identical building blocks, or monomers. This can cause problems with some proteins.

“The formation of dimers may interfere with the functions of the host proteins to which StayGold

Reference
**Research Highlights**

**New insights into how the human immunodeficiency virus (HIV) curates and assembles its lipid envelope have been gleaned by RIKEN biologists.** These findings into HIV biology could help to inform the search for new treatments.

A well-chosen outfit can open doors in the human world. The same holds true for HIV, which wraps itself in a coat of specialized lipids that greatly affects its ability to gain an entry into—and subsequently exit—host cells.

Like most viruses, HIV has only a bare-bones set of essential genes and lacks virtually all of the metabolic functions present in cells.

"Since viruses cannot synthesize lipids, HIV 'steals' lipids from the plasma membrane of host cells," explains Toshihide Kobayashi of the RIKEN Pioneering Project on Integrated Lipidology.

However, the biochemical composition of this membrane differs notably from that of the viral envelope, which is heavily enriched for two subtypes of lipids: cholesterol and sphingomyelin.

A viral protein called Gag facilitates the gathering of these lipids as newly replicated viruses 'bud' from the membranes of infected cells, but the underlying mechanism was unclear.

To fathom the depths of this mystery, Kobayashi teamed up with researchers at the University of Strasbourg in France, where he also maintains a lab.

The expression of the HIV Gag protein is sufficient to drive plasma membrane budding in cultured human cells, and the team used a sophisticated multipronged imaging strategy to observe this process.

"Our lab has been developing and characterizing proteins that bind to specific lipids," says Kobayashi. The team labeled sphingomyelin- and cholesterol-binding proteins with fluorescent dyes. They then observed how these lipids behave during Gag-induced budding with cutting-edge microscopy methods that can resolve single molecules.

The plasma membrane consists of two layers: the inner and outer leaflets (named based on their position relative to the cellular interior).

The researchers observed that when Gag attached to the inner leaflet, it overlapped with islands of cholesterol and sphingomyelin on the outer leaflet, physically isolating these lipids. As more Gag proteins bound the leaflet and interacted with each other, sphingomyelin accumulation continued to increase.

As a consequence, the nearby surface of the membrane began to curve, further concentrating these lipid domains as a prelude to the final stages of the budding process.

These findings represent an important step forward to understanding HIV biology, but key questions remain. "We've shown that the inner leaflet protein reorganizes outer leaflet lipids, but we do not know how," says Kobayashi. "Our priority is to clarify this mechanism."

**Reference**

In a massive genetic analysis of autism spectrum disorder (ASD), RIKEN researchers have discovered that some mutations affect neighboring genes, thus explaining how ASD can occur even though there are no mutations to ASD-related genes\(^1\). This finding could affect the diagnosis and treatment of the disorder.

A developmental disorder that often gives rise to repetitive behaviors and difficulties in social interaction, ASD runs in families. But the genetics of its heritability are complex and only partially understood.

ASD’s high heritability cannot be explained by genes that code for proteins. Rather, the answer could lie in the non-coding regions of the genome, particularly in promoters—parts of the genome that ultimately control whether proteins are produced.

Now, a team led by Atsushi Takata of the RIKEN Center for Brain Science has examined de novo gene variants—new mutations that are not inherited from parents—in these parts of the genome. They analyzed an extensive dataset of over 5,000 families, making this one of the world’s largest genome-wide studies of ASD to date. The team focused on topologically associating domains (TADs)—3D structures in the genome that allow interactions between different nearby genes and their regulatory elements.

They found that de novo mutations in promoters heightened the risk of ASD only when the promoters were in TADs that contained ASD-related genes. Because they are nearby and in the same TAD, these de novo mutations can affect the expression of ASD-related genes.

This finding explains how mutations can increase the risk of ASD even when they aren’t located in protein-coding regions or in the promoters that directly control the expression of ASD-related genes.

“Our most important discovery was that de novo mutations in promoter regions of TADs containing known ASD genes are associated with ASD risk,” says Takata. “And this is likely mediated through interactions in the 3D structure of the genome.”

The team confirmed this by making mutations in specific promoters by editing the DNA of stem cells. They observed that a single genetic change in a promoter caused alterations in an ASD-associated gene within the same TAD.

This finding has implications for diagnosis of the condition, Takata believes. “At the very least, when assessing an individual’s risk for ASD, we now know that we need to look beyond ASD-related genes when doing genetic risk assessment, and focus on whole TADs that contain ASD-related genes,” says Takata.

It could also lead to new ways of treating the disorder. “Further, an intervention that corrects aberrant promoter-enhancer interactions caused by a promoter mutation may also have therapeutic effects on ASD,” adds Tanaka.

AUTISM SPECTRUM DISORDER

Neighboring genes can lead to autism spectrum disorder

Mutations in genes that are not directly related to autism spectrum disorder can play a role in the development of the condition

Reference

A RIKEN-developed mouse model of an enigmatic lung disease promises to unlock new biological insights and catalyze the development of treatments for millions affected globally1.

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease in which scarring of the lungs makes breathing increasingly difficult. The cause is unknown with no cure, and it often leads to eventual death.

About a decade ago, Kazuyo Moro of the RIKEN Center for Integrative Medical Sciences and her colleagues investigated the role that a special population of immune cells, known as group 2 innate lymphoid cells (ILC2s), play in the body’s response to lung infections. As part of that effort, they created mice lacking two key immune-related genes. Without these genes, the mice exhibited defective signaling of a critical immune-modulating molecule called interferon-gamma, leading to enhanced activity of ILC2s and the associated inflammation that can spur allergic reactions.

But intriguingly, these same mice tended to develop fibrotic lesions in their lungs as they aged.

Now, Moro’s team has shown that these mice mimic the progression of IPF more closely than other mouse models of the lung disease. In particular, unlike traditional mice models—where lung damage originates within the airways—these mice exhibit scarring on the lung’s lining (pleural side), mirroring the pathology observed in IPF patients.

This unique aspect of the model offers unprecedented insights into IPF’s external triggers and progression. “This is important for understanding why fibrosis begins in IPF patients,” says Moro. “Many basic researchers and pharma companies can now use this mouse model for drug development.”

Moro’s team showed that the lack of interferon-gamma signaling in these mice results in over-activation of ILC2s. These cells, in turn, express a receptor on their surface that promotes interactions with fibroblast cells on the outside of the lungs, leading to excess collagen production that can spur lung stiffness and tissue thickening.

Supporting evidence for the mouse data came from an interrogation of ILC2s isolated from the blood of IPF patients. As with mice, the patient-derived ILC2s exhibited elevated expression of the receptor needed to engage fibroblasts, along with decreased levels of a protein implicated in interferon-gamma signaling.

The researchers also showed that ILC2-activated fibroblasts initiate the production of IL-33, thereby reactivating ILC2s and setting up a positive feedback loop.

While these mice aren’t the perfect stand-in for IPF, they are more reflective of IPF than any commonly used model today, Moro says.

The main drawback is that mice take about 15 weeks to develop signs of fibrosis, longer than other models. Nonetheless, the benefits of biological accuracy far outweigh the convenience of speed, Moro contends. ●

IDIOPATHIC PULMONARY FIBROSIS
Unlocking the secrets of lung fibrosis with a new mouse model

Genetically modified mice have a lung condition that closely mirrors one in humans, opening up the potential to better understand the mysterious disease.

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Reference
Turning up the intensity of x-ray beams used to probe the atomic structures of materials can actually reduce the intensity of x-rays scattered from the material, a RIKEN-led team has found. This rather counterintuitive result could be harnessed to produce ultrashort pulses of x-rays. Scientists have been using x-rays to reveal the structure of crystalline materials for more than a century now. X-ray diffraction has played a large role in determining the structures of many key compounds, including DNA and cellulose.

The past decade has seen the development of massive x-ray laser facilities known as x-ray free-electron lasers (XFELs) that can deliver extremely intense, ultrashort pulses of x-rays. The pulses are so intense that they destroy samples. But because they are so short, the diffraction pattern can be recorded before a sample blows apart.

Recent advances in XFEL technology have allowed a more than 10^20-fold increase in the intensity of x-ray beams at the sample surface compared with x-ray tubes used for medical applications, allowing diffraction patterns to be obtained from smaller crystals than was previously possible. But some simulations have predicted that the intensity of diffraction patterns will fall off at such high irradiation intensities.

Now, Ichiro Inoue of the RIKEN SPring-8 Center and co-workers have shown experimentally that this is indeed the case. The team used SACLA in Hyogo prefecture, Japan— one of about five XFELs globally—to measure the diffraction patterns of thin slices of silicon over a range of x-ray intensities. They observed a sharp reduction of nearly 50% above a certain intensity.

The reduction was so great that the team picked up on it while performing the experiments, even before analyzing the data. “We could clearly see the drop in diffraction intensity while increasing the x-ray intensity,” recalls Inoue. “That was really surprising.”

Simulations performed by the team indicated that above a certain x-ray intensity, the first x-rays to hit the silicon sample knock out electrons lying close to the nuclei of the silicon atoms. As a result of this, subsequent x-rays are scattered much less than usual.

This effect will mean that x-ray diffraction patterns obtained at such high intensities will need to be analyzed differently from those obtained at lower intensities.

But the effect could be harnessed to create even shorter x-ray pulses. Since the intensity drops off in the latter half of the pulse, silicon could be used as a filter that trims pulses. “We now want to try to demonstrate power shortening based on this phenomenon,” says Inoue.

Reference
A model developed by RIKEN researchers incorporates species that change sex during their life cycles for the first time, promising new insights into genes affecting the reproductive success of males and females differently.

Some genes that boost the reproductive success of females can be detrimental to that of males, and vice versa—a phenomenon dubbed ‘sexual antagonism’. Sometimes such genes can be silenced in individuals of the sex they are detrimental to. However, it may take a long time for these sexually antagonistic genes to be turned off, and so they may remain active in both sexes for generations.

“Researchers have long been interested in how sexual antagonism may maintain genetic variation in populations, and whether variants favoring one sex are systematically preferred,” says Thomas Hitchcock of the RIKEN Interdisciplinary Theoretical and Mathematical Sciences.

Most models of sexual antagonism assume a simple life cycle, where individuals produce offspring and then die. Scientists are now adding greater realism to these models by considering factors such as inbreeding and overlap between generations.

Some species, including some fish, plants and crustaceans, have the ability to change sex throughout their life cycles. They are known as sequential hermaphrodites, and individuals can reproduce as both male and female at different ages.

Since sexual antagonism may be particularly acute in these species, they could prove useful for testing theories of sexually antagonistic selection.

“Sequential hermaphrodites are interesting to model because they blend problems of age and sex,” notes Hitchcock. Now, Hitchcock and Andy Gardner at the University of St Andrews, UK, have included sequential hermaphrodites in models of sexual antagonism for the first time.

Their model allows for arbitrary patterns of sex change, including species that change sex from male to female and from female to male. The model also includes species that alternate between male and female reproductive strategies, such as certain corals.

Genetic variants that are beneficial when young may be favored over those that are beneficial when older. In sequential hermaphrodites, a similar pattern would generate a bias toward one sex, and this bias would depend on the direction of sex change.

“Our model shows how different sex-change systems predict distinct consequences for sexual antagonism, and how this varies across different portions of the genome,” says Hitchcock.

The pair found that, for species that change from female to male, it is generally easier for female-beneficial genetic variants to increase in frequency in the next generation. The opposite trend holds for species that change from male to female.

However, further research is needed given the complexities of sex change, age and external influences. “This is intriguing, and we’re keen to collaborate with others to pursue these investigations,” says Hitchcock.

Reference
Chemists at RIKEN have developed a method for making synthetic derivatives of the natural dye indigo that doesn’t require harsh conditions. This discovery could inspire advances in electronic devices, including light-responsive gadgets and stretchy biomedical sensors.  

Organic molecules also have the advantage of realizing a broad range of structures. "Organic semiconductors have flexibility in molecular design, enabling them to adopt new functionalities," says Keisuke Tajima of the RIKEN Center for Emergent Matter Science, who led the research.  

To explore this potential for enhanced electronic function through molecular design, Tajima and his team investigated a molecule related to indigo, called 3,3-dihydroxy-2,2-diindan-1,1-dione (BIT). "This project started with a simple question: can protons and electrons move in concert in the solid state?" says Tajima.  

Proton-coupled electron transfer—in which the motion of electrons is linked to that of protons—is often considered critical for realizing efficient electron transfer in biological systems. If it can be incorporated in organic solid-state materials, it could lead to semiconductors with unique dynamic properties. Until now, however, no solid-state material displaying proton-coupled electron transfer has been demonstrated.  

Tajima and his team have now found that BIT and its derivatives undergo unusual rearrangements in their structures involving double-proton transfer, which may lend them unique capabilities as electronic functional materials.  

Tajima identified BIT and its derivatives as promising materials for solid-state proton-coupled electron transfer, because the molecule incorporates two protons that appear ideally positioned to hop from one position to another during electron transfer.  

Until now, making BIT required harsh conditions that severely restricted the range of derivatives that could be made. Members of the team developed a room-temperature approach that enabled the synthesis of several BIT derivatives under much milder conditions.  

With BIT derivatives in hand, the team explored the molecules’ properties. "The most difficult part was to prove that the protons in BIT undergo proton transfer between molecules in the solid state," says Tajima. In collaboration with RIKEN experts in x-ray crystallography and solid-state nuclear magnetic resonance (NMR), the team demonstrated that the two protons do rapidly exchange their positions.  

Calculations suggest that proton transfer is indeed coupled with charge transport; the team’s next target is to confirm this coupling experimentally. "We don’t know if the presence of a proton will enhance charge transport, but as fundamental physics it could open interesting avenues," says Tajima.

Reference  
A flexible solar cell that survives the washing machine

New organic films that convert sunlight into electricity are waterproof without sacrificing flexibility.

An organic film that converts light into electricity and is both waterproof and flexible has been developed by RIKEN researchers. This opens up the possibility of realizing wearable solar cells that still function after being worn in the rain or even washed.

One potential use of organic photovoltaic films—films that convert light into electricity—is powering wearable electronics. For example, they could be attached to clothing and used to power biomedical devices, eliminating the need for batteries.

However, it has been difficult to make organic photovoltaic films waterproof without adding extra layers, which has the undesirable effect of reducing their flexibility.

Now, a team led by Kenjiro Fukuda of the RIKEN Center for Emergent Matter Science (CEMS) has overcome this key limitation of previous organic photovoltaic films and produced a film that is both waterproof and flexible.

Photovoltaic films typically consist of several layers. An active layer captures energy of a certain wavelength from sunlight and uses it to separate electrons and 'electron holes'. The electrons and holes can then reconnect through a circuit, generating electricity.

In previous devices, the layer transporting the electron holes was generally created by sequentially producing layers. In contrast, Fukuda and his team deposited a silver anode layer directly onto the active layers, resulting in better adhesion between the layers. They did this by heating the film at 85 degrees Celsius in air for 24 hours.

"It was challenging to form the layer, but we were happy to have accomplished it," says Sixing Xiong, also of CEMS. "We were able to create a film that was just 3 micrometers thick."

The results of putting the film through its paces were very encouraging. When the team tested the film by immersing it in water for four hours, they found that it still had 89% of its initial performance. They then stretched a film underwater 300 times by 30%. Even after that punishment, the film retained 96% of its performance. Finally, the team ran a film through a washing-machine cycle, and it survived the ordeal—something that had never been achieved before.

“We have created a method that can be used more generally,” says Fukuda. "Looking to the future, by improving the stability of devices in other areas, such as exposure to air, strong light, and mechanical stress, we plan to further develop our ultrathin organic solar cells so that they can be used for really practical wearable devices.”

Reference
SELF-HEALING POLYMERS

A self-healing polymer that glows

A new self-healing polymer that fluoresces could lead to more durable organic solar cells and other devices

A self-healing polymer developed by a RIKEN team emits high amounts of fluorescence when light is shone on it. This demonstration could lead the way to the creation of new devices such as organic solar cells that are more durable than current ones.

Solar cells and light-emitting diodes are conventionally made from hard semiconductors such as silicon. But making them from organic polymers offers many advantages, including being thinner and more flexible and lightweight, though they tend to be less robust than their silicon-based counterparts.

“Fluorescent polymers are very useful as they can be used for organic light-emitting diodes, organic field-effect transistors and solar cells,” says Masayoshi Nishiura of the RIKEN Center for Sustainable Resource Science (CSRS). “One of the main problems of these materials, however, is their short lifetime during usage.”

Polymers that have the ability to self-heal after being damaged have attracted a lot of interest in recent years because they are anticipated to extend device lifetimes as well as improve their safety.

In 2019, Zhaomin Hou, also of the CSRS, and his team created a polymer that displayed remarkable self-healing properties when damaged. Building upon this success, they have now incorporated a light-emitting component into the polymer and formed a self-healing polymer that also emits fluorescence.

The resulting polymer was both tough and healed itself without any external stimulus or energy. Its tensile strength fully recovered within 24 hours, demonstrating a high self-healing speed compared to other binary copolymers. The polymer could self-heal in water, acidic and alkaline solutions, giving it potential uses in a variety of environments.

“Our new material can be expected to afford longer lifetime of products and increased reliability,” says Nishiura.

The material could find application in data storage. The team used laser light to write a 2D image onto the fluorescent self-healing film. Although the image was invisible under natural light, it became recognizable under ultraviolet light, suggesting potential applications for the film as a data-storage device. The film maintained its excellent self-healing properties and elasticity even with the images.

“Our new material can be expected to afford longer lifetime of products and increased reliability.”

“The material we synthesized through a one-step reaction gave us the ability to control its optical and mechanical properties by adjusting the composition of the monomer,” says Hou. “We think it could contribute significantly to the development of novel functional materials with high self-healing capabilities in various practical environments.”

Reference
More than 100 YEARS of collaboration

Chemist Setsuro Tamaru helped design RIKEN’s first building, the Institute of Physical and Chemical Research, which was based on what is now known as the MPG Fritz Haber Institute.
Two leading research institutes located far from each other, but formed in the early 20th century along similar lines, continue to make breakthroughs together.

On April 9, 2024, a ceremony was held at the German embassy in Tokyo to celebrate 40 years of formal research collaboration and a much longer special relationship between RIKEN and the Max Planck Institute.

Historically, the Max Planck Society (MPG), Germany’s premier cluster of research institutes, was a prominent model for the founders of RIKEN. MPG, which was then known as the Kaiser Wilhelm Society, was founded in 1911, six years before RIKEN.

In many countries, there was a perception among the academics and politicians that the rapid pace of industrialization had demonstrated that many new technical problems could only be solved with greater knowledge of chemical or physical principles. The scientific communities in both Germany and Japan felt institutions dedicated to basic research would be needed to make that possible.

Max Planck came about as an attempt to create a system of specialized, independent, non-governmental research institutes that would exist alongside universities, a move that has molded the modern-day research environment within Germany.

RIKEN, for its part, was founded when a similar idea was put forward by a number of prominent scientists, including chemist Jokichi Takamine—who was the first to isolate the human hormone adrenaline in a way that could be used for medicine. Today, adrenaline is used to treat heart and respiratory problems, and severe allergic reactions.

Takamine, who was already involved in successful collaborations with overseas scientists, argued that Japan needed its own national scientific research center, in line with its international standing and to help other Japanese academics develop similar collaborations.

When RIKEN was founded in 1917, it was conceived as a specialized institute. Its model was similar in form to the Kaiser Wilhelm Society—which in turn echoed the Rockefeller Institute for Medical Research (1901) and the Carnegie Institution for Science (1902) in the United States, and the Institut Pasteur (1887) in France. But RIKEN’s relationship with the Kaiser Wilhelm Society was special.

Even RIKEN’s first building, erected in the Komagome area of Tokyo, was based on what is now known as the MPG Fritz Haber Institute. The building was conceived by chemist Setsuro Tamaru, who became one of RIKEN’s first chief scientists.

Tamaru based the design on the imposing Kaiser Wilhelm Society structure where he had worked in the years prior with Fritz Haber, whose work on the Haber-Bosch process of ammonia synthesis would win him a Nobel Prize in Chemistry in 1918.

**MODERN MODELS**

This year marks the 40th anniversary of a more formalized relationship between MPG and RIKEN that began in 1984, RIKEN and MPG signed their first official research cooperation agreement.

From this agreement has sprung many prominent research initiatives. In 2011 the Max Planck-RIKEN Center for Systems Chemical Biology formed as a collaboration between the Max Planck Institute of Molecular Physiology, the Max Planck Institute of Colloids and Interfaces and the RIKEN Advanced Science Institute.

While the joint center wound up in 2022, the partnership was a fruitful one. For example, one group—led by Peter Seeberger of the Max Planck Institute of Colloids and Interfaces and Naoyuki Taniguchi, formerly of the Systems Glycobiology Research Group at RIKEN—identified a new drug target for the treatment of Alzheimer’s disease.

They showed that the removal of the GntT-III gene in mice resulted in a marked decrease in the formation of amyloid-beta peptide plaques, leading to an improvement in cognitive function. Many groups globally are now working on targeting the expression of this gene to treat Alzheimer’s disease.

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**RIKEN in Europe**

About one third of RIKEN’s collaborative research agreements involve institutions in Europe and roughly one quarter of non-Japanese personnel at RIKEN are from Europe. To support these important relationships and further promote collaborative research and innovation, RIKEN established a Europe Office in November 2018, following offices that opened in Singapore in 2006 and Beijing in 2010.

The Europe Office is responsible for all of Europe and its surrounding regions, with a mission that includes promoting the enhancement of RIKEN’s research capacity and visibility through collaborative research, fostering brain circulation through personnel exchanges, and tackling global challenges together with European partners.

Located in the heart of the EU quarter in Brussels, the RIKEN Europe Office interacts with research organizations, higher education institutions, funding agencies, research intensive industries, policymakers and individual researchers and managers, including RIKEN alumni. Recent events held by the Europe Office include the RIKEN Europe Symposium 2024, which focused on organoid models for clinical research. —Toshiyasu Ichioka, Director, RIKEN Europe Office

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Toshiyasu Ichioka is the director of the RIKEN Europe Office, which opened in 2018 in Brussels.
In 2019, another joint center was established between RIKEN and partners at the Max Planck Institute for nuclear physics, the Max Planck Institute for quantum optics, and the National Metrology Institute of Germany (PTB). Together the parent institutes involved have funded the MPG-PTB-RIKEN Center for Time, Constants, and Fundamental Symmetries to the tune of US$9.5 million (¥1,489 million) over five years.

The center is dedicated to developing incredibly sensitive instruments—and RIKEN-led sub-projects have ranged from developing clocks that are more precise than the world’s most accurate timepieces, to building cutting-edge antimatter detectors at the European Organization for Nuclear Research (CERN) in Switzerland, the largest particle physics laboratory in the world.

These powerful tools and others aim to investigate whether the fundamental constants really are constant or if they change in time by tiny amounts; to detect subtle differences in the properties of matter and antimatter; and to test of fundamental symmetries in the search for physics beyond the Standard Model.

In other words, they explore the very limits of existence in order to understand the world better.

Today, MPG is among RIKEN’s top collaborators internationally. And the partnership is only becoming more important as we look to solve large-scale social issues, a challenge that demands robust international collaboration as well as cutting-edge tools such as RIKEN’s high-performance computing facilities.

The problems we hope to tackle include not only global warming, but aging societies, food security, and the rise of generative artificial intelligence.

At celebrations for the 40th anniversary of the formal research co-operation agreement signed by the two institutions in 1984, delegates discussed these issues and talked about expanding their collaborations as a result.

We would like to add to our joint work in the fields of physics and chemistry—which have been the mainstay until now—new projects in the life sciences, such as neuroscience, and in artificial intelligence. These areas will hopefully present bold new chances to make important breakthroughs with our old friends.
A genetic study led by researchers from RIKEN’s Center for Integrative Medical Sciences has uncovered evidence that people in Japan descend from three ancestral groups.

The findings, published in *Science Advances* in April 2024, challenge the longstanding belief that there were two main ancestral groups in Japan: the indigenous Jomon hunter–gatherer–fishers and the rice-farming migrants from east Asia.

Instead, the researchers identified a third group with potential ties to north-east Asia—the so-called Emishi people, thus lending further credence to a ‘tripartite origins’ theory first suggested in 2021.

The Japanese population isn’t as genetically homogeneous as everyone thinks, says RIKEN’s Chikashi Terao, who led the study. “Our analysis revealed Japan’s subpopulation structure on a fine scale, which is very beautifully classified according to geographical locations in the country.”

**COMBING FOR CLUES**

Terao’s team arrived at their conclusions after sequencing the DNA of more than 3,200 people across seven
regions of Japan, running the length of the country from Hokkaido in the north to Okinawa in the south. It is one of the largest genetic analyses of a non-European population to date.

The researchers used a technique called whole-genome sequencing, which reveals an individual’s complete genetic makeup—all three billion DNA base-pairs. It provides roughly 3,000 times more information than the DNA microarray method, which up until now has been used more widely. “Whole-genome sequencing gives us the chance to look at more data, which helps us find more interesting things,” says Terao.

To further enhance the data’s usefulness and examine the potential links between genes and certain diseases, he and his collaborators combined the DNA information obtained with relevant clinical data, including disease diagnoses, test results and information on both medical and family history. They collated all of this into a database know as the Japanese Encyclopedia of Whole-Genome/Exome Sequencing Library (JEWEL).

One topic of particular interest to Terao’s was the study of rare gene variants. “We reasoned that rare variants can sometimes be traced back to specific ancestral populations, and could be informative in revealing fine-scale migration patterns within Japan,” he explains.

Their hunch proved right, helping to reveal the geographic distribution of Japanese ancestry. Jomon ancestry, for instance, is most dominant in the southern, subtropical shores of Okinawa (found in 28.5% of samples) while lowest in the west (just 13.4% of samples). By contrast, people living in western Japan have more genetic affinity with Han Chinese people—which Terao’s team believes is likely associated with the influx of migrants from east Asia between the year 250 and year 794, and is also reflected in the comprehensive historical adoption of Chinese-style legislation, language and educational systems in this region.

Emishi ancestry, on the other hand, is most common in northeastern Japan, decreasing to the west of the country.

**TRACES OF THE PAST**

The researchers also examined JEWEL for genes inherited from Neanderthals and Denisovans, two groups of archaic humans that interbred with *Homo sapiens*. “We are interested in why ancient genomes are integrated and kept in modern human DNA sequences,” says Terao, who explains that such genes are sometimes associated with certain traits or conditions.

For instance, other researchers have shown that people in Tibet have Denisovan-derived DNA within a gene called *EPAS1*, which is believed to have aided their colonization of high-altitude environments. More
recently, scientists discovered that a cluster of Neanderthal-inherited genes on chromosome 3—a trait that is present in roughly half of all south Asians—is linked to a higher risk of respiratory failure and other severe symptoms of Covid-19.

The analysis by Terao’s team shed light on 44 ancient DNA regions present in Japanese people today, most of which are unique to East Asians. These include a Denisovan-derived one, located within the \( NKX6-1 \) gene, known to be associated with type 2 diabetes, which the researchers say could affect a person’s sensitivity to semaglutide, an oral medication used to treat the disease. They also identified 11 Neanderthal-derived segments linked to coronary artery disease, prostate cancer, rheumatoid arthritis and four other conditions.

**TOWARD PERSONALIZED MEDICINE**

The RIKEN-led team also used data on rare genetic variants to uncover the potential causes of diseases. For example, they found that one variant of a gene called \( PTPRD \) has the potential to be “highly damaging” because it could be linked with hypertension, kidney failure and myocardial infarction, says Xiaoxi Liu, a senior scientist in Terao’s lab and the study’s first author.

Additionally, the team noted significant incidence of variants—also called loss-of-function variants—in the \( GJB2 \) and \( ABCC2 \) genes, which are associated with hearing loss and chronic liver disease, respectively.

Teasing out the relationship between genes, their variants, and how these impact traits, including disease predisposition, could one day play a role in helping scientists develop personalized medicine, says Terao. “What we’ve tried to do is to find and catalog loss-of-function gene variants that are very specific to Japanese people, and to understand why they are more likely to have some specific traits and diseases,” he says. “We’d like to connect population differences with differences in genetics.”

In the future, he hopes to expand JEWEL and include even more DNA samples in the dataset. For the longest time, large-scale genomic studies have focused on analyzing data from people of European descent. But Terao says it’s “quite important to expand this to the Asian population so that in the long run, the results can benefit us too.”

**REFERENCES**

The Secrets of Longevity

Scientists at RIKEN have shown that the gut and immune system play a vital role in determining the longevity of humans, fruit flies, nematodes and mice. The rate of aging in each of these species appears to be affected by elements ranging from gut bacteria, bile acids and amino acids, to immune and intestinal cells.

**Human Studies**

**Centenarian Bile Acids**
Japanese people who had lived to more than 100 years of age were found to have higher levels of some secondary bile acids in their guts. Bile acids help the body eliminate or absorb lipids, cholesterol and fat-soluble vitamins. The researchers who made this finding in 2021 hypothesized that the bile acids may be protecting the centenarians against the inflammatory effects of harmful gut bacteria.

**Supercentenarian Immunity**
In a 2019 study, people aged 110 years or more were found to have an excess of a type of immune cell, called a cytotoxic CD4 T-cell. These were found to be made via a cloning process. The researchers hypothesized that this cloning process may be a useful adaptation to late-stage aging in a small number of long-lived people.

**Mouse Studies**

**Over Protective**
A 2023 study in mice described a mechanism that causes the immune system’s T cells to produce inflammatory cytokines and chemokines that are protective in the short term, even when no pathogens are present. In the long term this process induces various age-related diseases.

**Nematode Studies**

**Growth Mindset**
A 2021 study on nematodes showed that communication between brain and intestinal cells linked to cell division and muscle growth activates genes associated with longevity.

**References**

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

For more information, please visit:
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