

RIKEN

WINTER 2022

RESEARCH

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

REMOTE-CONTROLLED ROACHES

Solar-powered reconnaissance bugs



AI TO EYE

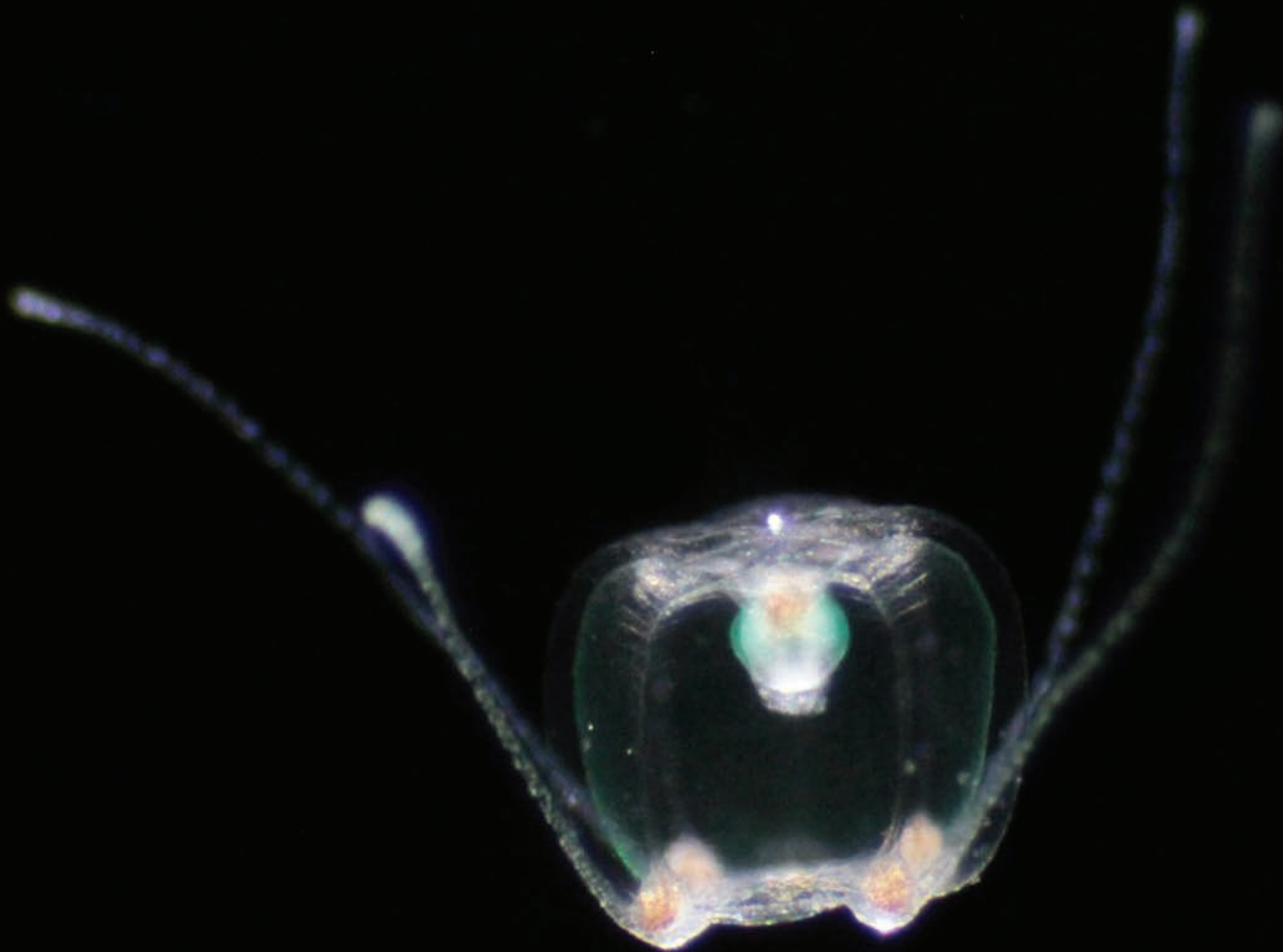
Robots help restore retinas

PARCHED CROPS

Alcohol helps build drought resistance

LAB-GROWN ORGANS

The potential of regenerative medicine



▲ **Glowing in the dark**

The diminutive jellyfish *Cytaeis uchidae* is found off the Japanese coast. RIKEN chemists have succeeded in producing a green fluorescent protein that is both bright and stable to light from a fluorescent compound found in the jellyfish.

RIKEN RESEARCH

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

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

RIKEN Research is an online and print publication that highlights the best research published by RIKEN. This

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

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

For further information on the research in this publication or to arrange an interview with a researcher, please contact: RIKEN International Affairs Division
2-1, Hirosawa, Wako, Saitama, 351-0198, Japan
Tel: +81 50 3500 5438
rikenresearch@riken.jp

ISSN 1883-3519
www.riken.jp/en



ADVISORY BOARD

BIOLOGY

- Kuniya Abe (BRC)
- Makoto Hayashi (CSRS)
- Shigeo Hayashi (BDR)
- Joshua Johansen (CBS)
- Atsuo Ogura (BRC)
- Yasushi Okada (BDR)
- Hitoshi Okamoto (CBS)
- Kensaku Sakamoto (BDR)
- Kazuhiro Sakurada (R-IH)
- Harukazu Suzuki (IMS)
- Toshitada Takemori (IMS)
- Koji Yonekura (RSC)

COMPUTER / COMPUTATIONAL SCIENCE

- Toshiaki Iitaka (R-CCS)
- Takahito Nakajima (R-CCS)
- Hirofumi Tomita (R-CCS)

CHEMISTRY

- Hideki Abe (CSRS)
- Keisuke Tajima (CEMS)
- Katsunori Tanaka (CPR)

ARTIFICIAL INTELLIGENCE

- Hiroshi Nakagawa (AIP)
- Satoshi Sekine (AIP)

PHYSICS

- Akira Furusaki (CEMS)
- Erika Kawakami (RQC)
- Hiroaki Minamide (RAP)
- Yasuo Nabekawa (RAP)
- Shigehiro Nagataki (CPR)
- Atsushi Noguchi (RQC)
- Masaki Oura (RSC)
- Toru Tamagawa (RNC)
- Tomohiro Uesaka (RNC)
- Yasunori Yamazaki (CPR)

3 Editorial

Our plan going forward

4 People

How do young star clusters form?

Nadia M. Murillo Mejias
Special Postdoctoral Researcher, Star and Planet Formation Laboratory, RIKEN Cluster for Pioneering Research

Looking for rules within quantum complexity

Tomotaka Kuwahara
Team Leader, Analytical Quantum Complexity, RIKEN Hakubi Research Team, RIKEN Center for Quantum Computing

8 Research highlights

8 Eye development works well under mechanical force

9 Error correction achieved in a silicon qubit system

COVER STORY

10 Accelerating regenerative medicine using AI-assisted robots

11 Where the brain weighs information for decisions

12 Alzheimer's model shows plaque deposition

13 An IVF workaround for male infertility

14 Helium nuclei found lurking inside carbon nuclei

15 A modern analysis of an ancient herbal treatment



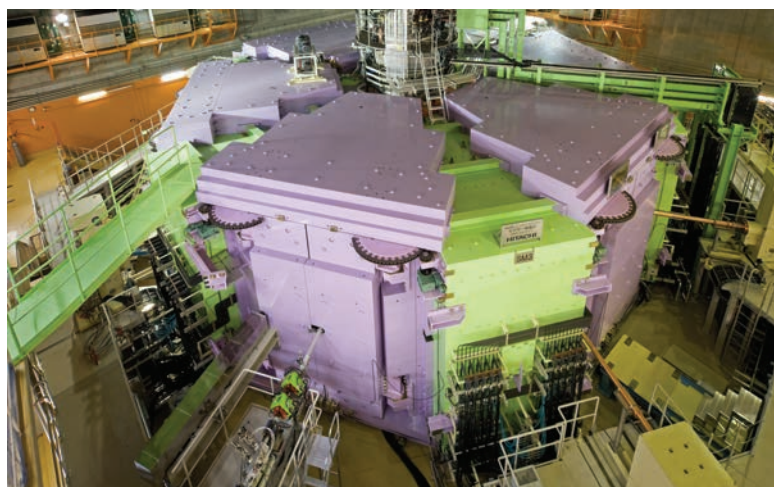
6 Briefs

GUINNESS WORLD RECORDS®:
Highest beam energy cyclotron

Eleventh Global Summit of Research Institute Leaders

Japan and France extend agreement for collaborative research

Crown Prince Akishino visits AOI-PARC



16 Research highlights

16 Far-ultraviolet LED designed to tackle pandemics

COVER STORY

17 A solar-powered cyber-roach

18 Genetic recombinations turn up everywhere

19 Harnessing marsupials' heart regeneration ability

20 Hitting the bull's eye at an angle

21 Jellyfish yields bright and photostable fluorescent protein

22 How to calm crying babies

23 'Cuddle hormone' strongly affects male mice

24 Applying quantum speed limits to macroscopic systems

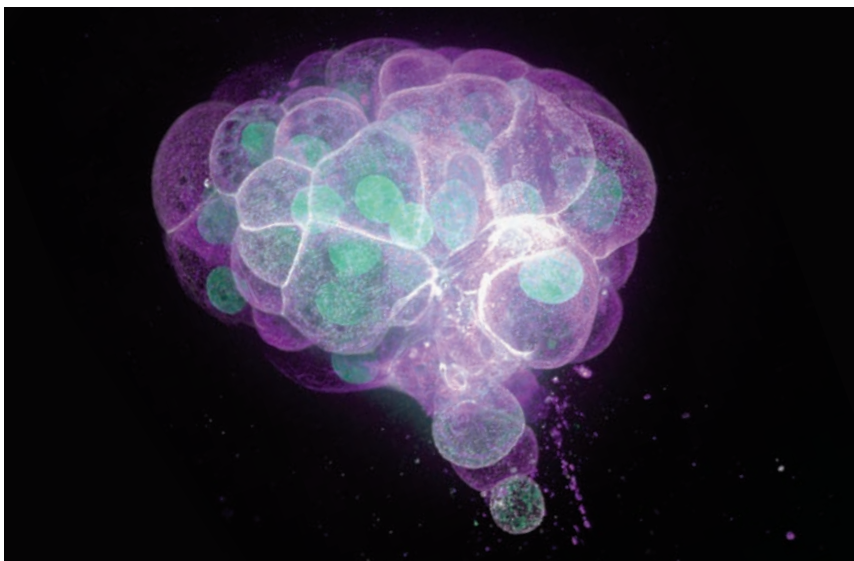
25 Discovering how heavy elements are made



p.24

26 Perspectives **COVER STORY**

The next milestones in generating artificial organs: RIKEN's Organoid Project tackles the latest challenges in this highly promising field for regenerative medicine and drug discovery.



29 Feature **COVER STORY**

Ethanol preps rice and wheat for drought: A cost-effective soil treatment could increase the survival rate of water-stressed crops more than ten-fold by reducing water loss and increasing sugar production in the aftermath.



Our plan going forward



Kohei Miyazono
RIKEN Executive Director

I have some important news to report in this issue of *RIKEN Research* concerning the direction we intend to go as an organization. Since taking office on April 1, 2022, the new RIKEN leadership has been focusing on the direction that our research will take, and on September 30, we issued a plan for implementing some new personnel policies. Along with that, we have a plan for transforming the way we conduct research, including a number of ideas related to digital transformation.

Under that plan, known as the Transformative Research Innovation Platform of RIKEN platforms (TRIP), we will first aim to encourage new progress in science by integrating high-quality data that will connect our cutting-edge platforms in areas such as biosources and synchrotron radiation. We will do this by introducing a hybrid model of classical supercomputers and quantum computing, and introducing tools of mathematical science, including artificial intelligence—all fields in which

RIKEN already has a strong presence. The ultimate goal of this plan is to pioneer a new science to ‘predict and control the future’, and to provide an engine for social change for the domestic and international community. Some of the fields in which we will implement the plan include the prediction and control of elemental transmutation, functionalities of many-electron systems, and green digital transformation.

We are looking forward to continuing to act as a promoter of international knowledge exchange through our ‘Brains Without Borders’ strategy—an important approach to progress science and technology, and to promote interdisciplinary collaboration both inside and outside of RIKEN. I look forward to hearing ideas from our readers as we launch this transformation.

宮園浩平



COVER STORY:

Cockroaches equipped with a specially designed solar-powered backpack that allows them to be controlled remotely could be used to inspect hazardous sites or locate trapped people. *Page 17*

© 2022 RIKEN

Keep up to date



Online
www.riken.jp/en



Facebook
facebook.com/RIKENHQ



Twitter
twitter.com/RIKEN_en



LinkedIn
linkedin.com/company/riken

How do young star clusters form?

Nadia M. Murillo Mejias

Special Postdoctoral Researcher, Star and Planet Formation Laboratory, RIKEN Cluster for Pioneering Research

▣ Describe your role at RIKEN.

I'm currently a special postdoctoral researcher (SPDR) focused on studying the formation and evolution of low-mass multiple protostellar systems. Protostars are the objects from which stars, like our Sun, form. When two or more protostars are in a system, these are called multiple protostellar systems. I apply observational, numerical and

experimental techniques to study the physical and chemical structure of these systems.

▣ Briefly describe your current research.

I'm currently leading a project to study the relationships between parameters—such as gas temperature, mass, density and kinematics—in multiple protostellar systems by observing a range of molecular species. Multiple stars are key to many phenomena, from gravitational waves to stellar physics. Observations of star-forming regions have shown that multiple protostellar systems are common, indicating that multiple stars are born as a system rather than created during stellar evolution. Hence, discovering how these systems form and evolve is relevant to understanding a key aspect of stellar physics and evolution.

▣ How did you become interested in your current field of research?

My interest in star formation arose during a winter school on star formation in my sophomore year of university, while I was watching how multi-epoch observations of a molecular outflow could show

the motion of these objects. I quickly became interested in multiple protostars, how they were a crucial, but often ignored part of star formation, and the physico-chemical structure of protostars in general.

▣ What do you think has been the most interesting discovery in your field in the last few years?

The last two decades have seen a vast and wonderful increase in our knowledge of star formation at all scales thanks to developments in telescopes, numerical techniques and experiments. Surveys of large regions have shown the physical and chemical properties of star-forming regions. Detailed high-resolution observations have revealed gaps and rings in disks, mass needed for planet formation, inflowing material from cloud to disk scales, amazing outflows and complex chemical structures. All this new knowledge provides context within which I try to make sense of the star-formation process.

“*The last two decades have seen a vast and wonderful increase in our knowledge of star formation at all scales*”

▣ What has been your most memorable experience at RIKEN?

I've enjoyed the chance to learn how to use different facilities, such as the scanning electron microscope and the infrared instruments at SPring-8.

▣ Tell us about your goals.

I aim to keep doing research on the formation and evolution of multiple protostellar systems. One of my long-term goals is to find a way to connect these systems from the stages of formation through to the end of stellar life-cycle. It would be interesting to explore how the characteristics set during the early stages of star formation transfer (or not) to the other parts of the stellar life-cycle. ■



Looking for rules within quantum complexity

Tomotaka Kuwahara

Team Leader, Analytical Quantum Complexity RIKEN
Hakubi Research Team, RIKEN Center for Quantum Computing

▣ Please briefly describe your current research.

My team aims to solve the most important unsolved problems in the field of quantum information.

To do this, I look at Hamiltonian complexity. The Hamiltonian of a system is the sum of its kinetic energy (energy of motion) and its potential energy (energy of position). Hamiltonian complexity is the study of the universal structural constraints of a system of many interacting quantum particles—quantum many-body systems—due to these energies.

Currently, my aim is to characterize via an information-theoretic lens the intrinsic complexity of quantum many-body systems and apply these understandings to the quantification, storage and communication of digital information.

▣ What excites you the most about your current research?

Well, statements on Hamiltonian complexity are universal and can be written in mathematically precise ways. These laws may resolve great mysteries about how the world works.

Physicists are also very keen to figure out how to solve quantum many-body problems using quantum/classical hybrid computers. However, understanding the computational complexity of a quantum many-body system is equivalent to completely clarifying the information-theoretic structure of the quantum many-body system.

▣ How did you become interested in your current field of research?

I was initially puzzled about why our living world is so complicated despite having such simple fundamental laws. This, I discovered, may boil down to the essential difference between one-body and many-body problems. However, realistic quantum many-body systems are thought to be ‘not too complicated’. That is, realistic many-body systems are much simpler than typical theoretical ones. So I became interested in why our world has a moderate level of complexity in terms of physics.

▣ What do you think has been the most interesting discovery in the last few years?

Recently, the ‘no low energy trivial state conjecture’, a previously unproven idea posed in 2014, has been solved. It had been a fundamental unresolved obstacle to applying a theorem, called the PCP theorem, to the quantum realm. The PCP theorem is a cornerstone of conventional computing, helping us to understand algorithmic complexity and the conditions of near-optimal solutions for optimization. This finding inspired me to work towards solving famous unsolved conjectures.

▣ What other goals do you have at RIKEN and in your life?

I aim to lead a team that will increase the presence of Japanese researchers at the world’s most prestigious international conferences on quantum physics, such as the Quantum Information Processing conference and the Theory of Quantum Computation, Communication and Cryptography conference. Since I am a Christian, my ultimate goal is to follow in the footsteps of great Christian physicist predecessors like Isaac Newton, Michael Faraday, and Blaise Pascal. This always encourages me: “For I can do everything through Christ, who gives me strength” (Philippians 4:13). ■

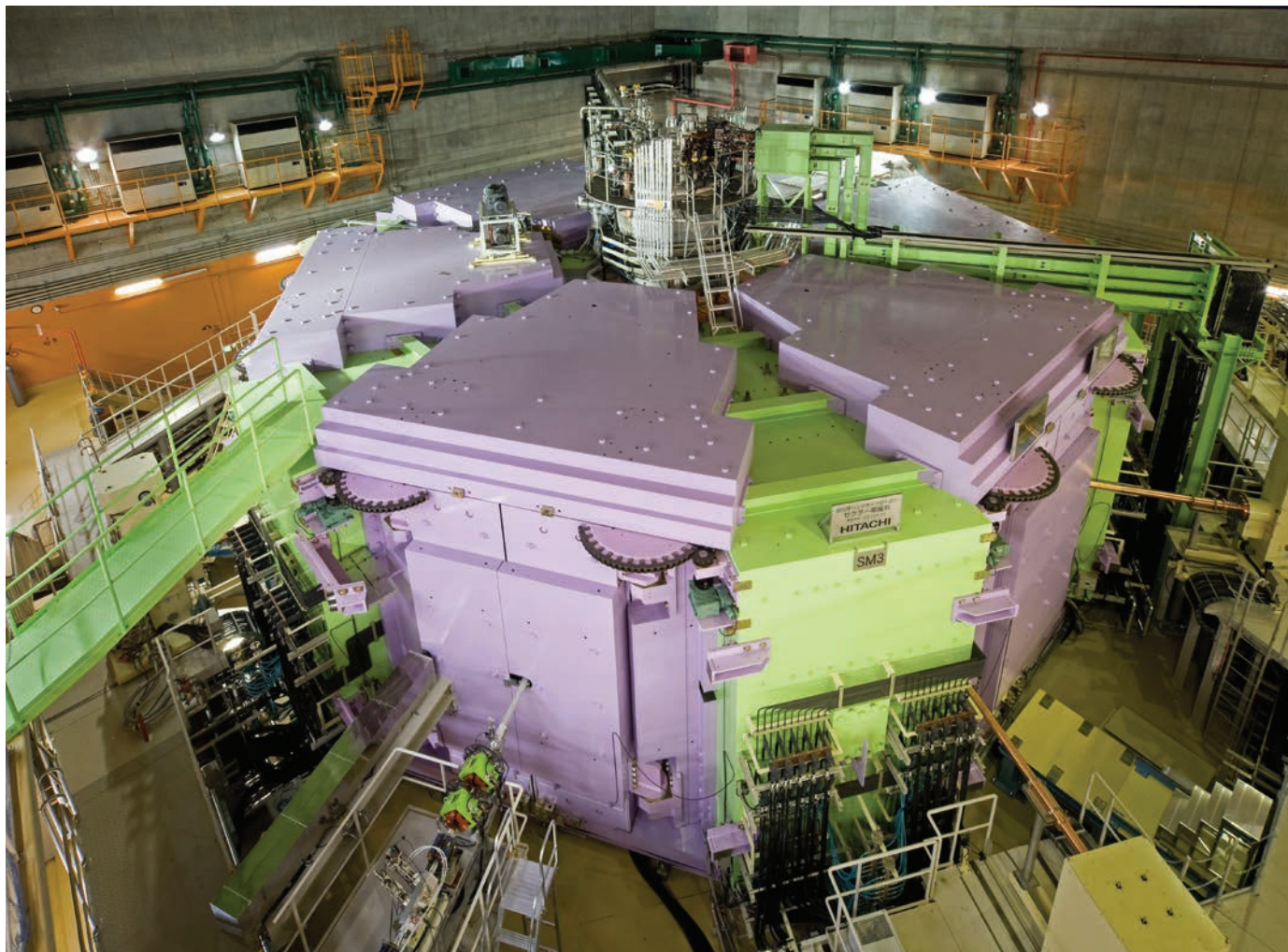
Careers at RIKEN

For further information, visit our Careers page:

Website: www.riken.jp/en/careers

E-mail: pr@riken.jp





The world-record-breaking Superconducting Ring Cyclotron is located at the RIKEN Nishina Center for Accelerator-Based Science RI Beam Factory on the Wako campus.

GUINNESS WORLD RECORDS®

Highest beam energy cyclotron

A total of 82,400 mega-electronvolts was achieved by RIKEN's Superconducting Ring Cyclotron (SRC) on March 28, 2022. According to Guinness World Records, it was the "highest intensity beam energy cyclotron" in the world at the time.

Cyclotrons are a type of particle accelerator that continuously accelerate charged particles along a spiral path between large magnetic poles and high-frequency electric fields.

These beams are used to generate unstable nuclei to study their properties, among other things.

The SRC's construction started in 1995 at the RIKEN Nishina Center for Accelerator-Based Science RI Beam Factory at RIKEN's Wako campus in Saitama. Its first beam was extracted at the end of 2006. Various improvements have since increased the beam's intensity, particularly of heavy-element

ions such as uranium, by a factor of more than 1,000. The SRC was also the world's first ring cyclotron to generate a high magnetic field by introducing superconductivity into the electromagnet that is the heart of the machine. It has contributed to the discovery of more than 150 new isotopes and anomalies in magic numbers, among other things.

www.guinnessworldrecords.jp/world-records/675272-highest-beam-energy-cyclotron

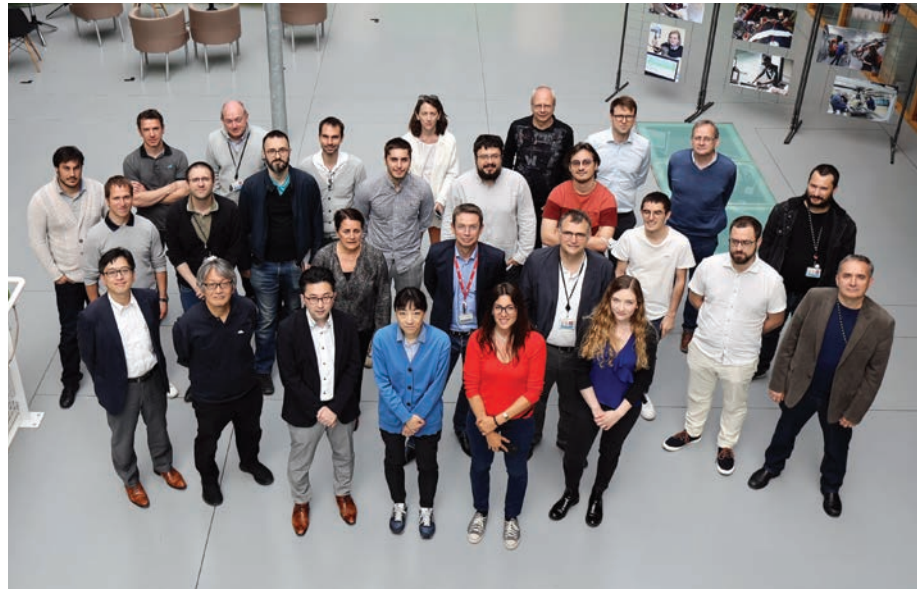
Eleventh Global Summit of Research Institute Leaders

On October 1, 2022, leaders of national research institutes from around the world gathered for the Eleventh Global Summit of Research Institute Leaders, which was held in conjunction with the Nineteenth Annual Meeting of the Science and Technology in Society forum (STS *forum*), which aims to provide a mechanism for scientists and global leaders to resolve problems stemming from the application of science and technology. For the first time in three years, the meeting was held in person, in Kyoto, Japan.

At the event, chaired by RIKEN President, Makoto Gonokami, participants discussed why funding diversity is important and how to achieve it. This discussion started with a short presentation by Iain Stewart, president of the National Research Council (NRC) of Canada. Participants then discussed the benefits and drawbacks of various funding sources. In closing, the group adopted a statement in which they agreed that in addition to a diversity of funding, international collaboration was also important to help stabilize the funding of public research institutes, in order to expand our knowledge base and promote brain power circulation.

The meeting was co-hosted by RIKEN and the National Institute of Advanced Industrial Science and Technology (AIST). It was also moderated by Stefan Noreen, a former Swedish Ambassador to Japan. The meeting's participants came from 13 institutes around the globe.

www.riken.jp/en/news_pubs/news/2022/20221114_2/



Representatives from RIKEN and the French Alternative Energies and Atomic Energy Commission agreed to continue collaborating in the area of high-performance computing for at least the next five years.

Japan and France extend agreement on collaborative research

On January 11, 2017, RIKEN and the French Alternative Energies and Atomic Energy Commission (CEA) signed the CEA-RIKEN High Performance Computing and Computational Science agreement. The five-year arrangement strengthened their partnership in the areas of high-performance computing and computational science.

A little more than five years on, in July 2022, both sides elected to extend this agreement after holding the CEA-RIKEN bi-annual High Performance Computing and Artificial Intelligence workshop. They also added quantum computing to their collaborative research fields.

Under this agreement, the two organizations will enhance their collaboration in a broad range of areas including high-performance computing applications, development

of system software, and exchanges of personnel. Through this agreement, RIKEN aims to nurture future generations of talented researchers and contribute to the expansion of Japanese-French science and technology.

Research and development centered on next generation supercomputers has also been ranked as a national project by both Japan and France. The addition of quantum computing to the fields of collaboration on July 28, 2022, will further strengthen research collaboration between the two nations.

The new agreement will be for five years, until January 10, 2027, with the possibility of extension for an additional five years if both sides consent.

www.riken.jp/en/news_pubs/news/2022/20220802_1

Crown Prince Akishino visits AOI-PARC

On July 20, 2022, His Imperial Highness Crown Prince Akishino visited the Agri Open Innovation Practical and Applied Research Center (AOI-PARC) in Shizuoka, a few hours

south-east of Tokyo. The AOI-PARC is an innovation center for research institutes and companies from Shizuoka and other prefectures. They all bring their technological capabilities and ideas and work together to innovate on agricultural productivity. The RIKEN Center for Advanced Photonics (RAP) contributes to AOI-PARC by developing practical applications. During the visit,

RIKEN Executive Director Shigeo Koyasu introduced the latest research results from AOI-PARC, and following that, Team Leader Satoshi Wada of the Photonics Control Technology Team at RAP showed the visitors the Next Generation Cultivation System and explained the details of his group's research.

www.riken.jp/en/news_pubs/news/2022/20220728_1

DEVELOPMENTAL BIOLOGY

Eye development works well under mechanical force

The normal, symmetric formation of the vertebrate eyes is coordinated by a molecular sensor that responds to mechanical force

In a surprising discovery with important implications for developmental biology and regenerative medicine, RIKEN biologists have learned how mechanical forces guide the formation of the eyes in chick embryos¹.

Healthy embryonic development is guided through the complex interplay of diverse genetic, chemical and physical ‘instructions’. In vertebrate embryos, the visual system originates from a structure called the optic vesicle. This forms at one end of the neural tube, which is the progenitor of the entire nervous system.

To their surprise, the team learned that SHH signaling regulates sensing and response to physical force

During normal development, the optic vesicle extends laterally in both directions, and two eyes ultimately form at the ends of those projections. When this process goes awry, the left and right optic vesicles fail to elongate. Instead, their tips fuse in the center of the face, forming a single eye.

Five researchers, all at the

RIKEN Center for Biosystems Dynamics Research, set out to discover how malfunctions in a gene called *sonic hedgehog* (*SHH*) contribute to this ‘cyclopia’ birth defect.

Team Leader Yoshihiro Morishita notes that hundreds of papers have delineated SHH’s role in regulating cell proliferation and differentiation during the development of a wide range of organs, including the eyes. But it is unclear precisely how SHH helps orchestrate dynamic tissue deformation to form organ-specific morphologies.

To investigate this, the team compared the pattern of collective cell motion and its contribution to tissue dynamics during eye development in healthy chick embryos with that in embryos treated with an SHH inhibitor.

To their surprise, the team learned that SHH signaling regulates sensing and response to physical force, guiding the direction of cell rearrangement and motion under the given stress environment within the forebrain tissue.

“The direction of stress differs depending on the location within the tissue, which in turn changes the direction and degree of elongation and shrinkage, resulting in the creation of the desired shape,” explains Morishita.



A light micrograph of a chick embryo. The normal developmental process that yields a working pair of symmetrically-positioned eyes in vertebrates requires a gene called *SHH*.

When this sensing and response capability is disrupted by the SHH inhibitor, the optic vesicle cells no longer know where to go, and fail to undergo the lateral branching required to produce a pair of functional eyes.

This discovery is exciting for several reasons. Given the prominent role SHH plays in development of many organs, mechanical sensing and response may be a far more important driver of tissue organization and formation than previously recognized. By extension, “randomized cellular behaviors due to loss of mechanosensation might be a common cause of different

congenital malformations,” Morishita notes.

A deeper understanding of this mechanism could also benefit researchers trying to recapitulate organ formation in the lab as a tool for disease research or the development of transplantable tissues. ●

Reference

- Ohtsuka, D., Kida, N., Lee, S.-W., Kawahira, N. & Morishita, Y. Cell disorientation by loss of SHH-dependent mechanosensation causes cyclopia. *Science Advances* **8**, eabn2330 (2022).

QUANTUM COMPUTING

Error correction achieved in a silicon qubit system

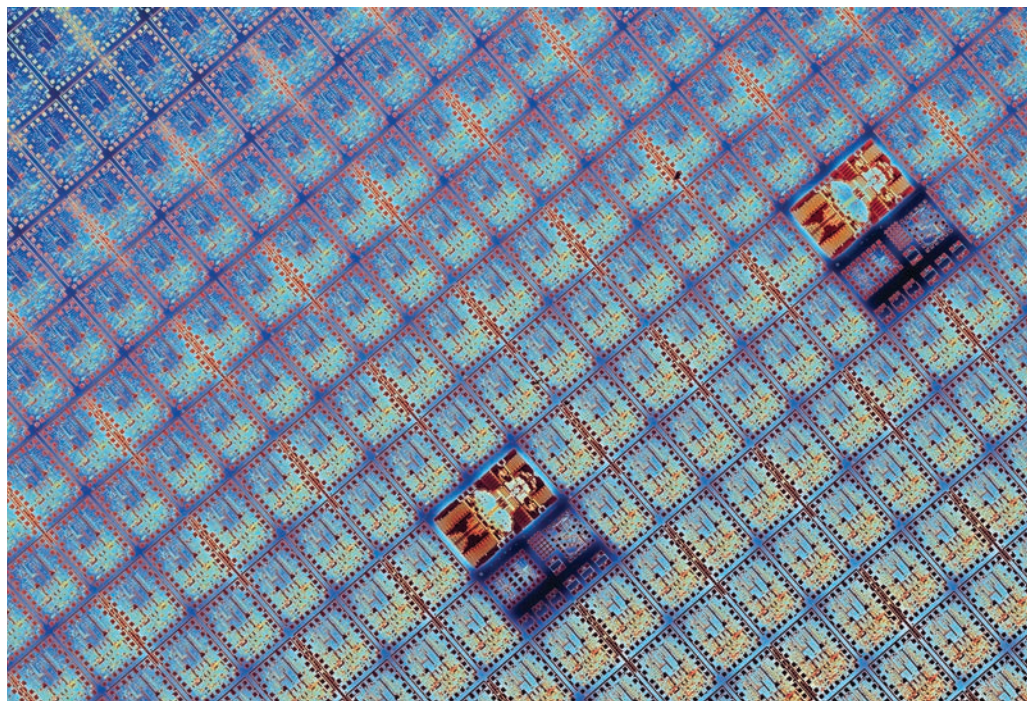
For the first time, a way to correct errors in a silicon-based quantum-computing system with three qubits has been realized

A major step toward large-scale quantum computing has been demonstrated by RIKEN researchers involving an error correction in a three-qubit, silicon-based quantum-computing system¹. This work could pave the way toward realizing practical quantum computers.

Quantum computers are a hot area of research today, as they promise to make it possible to solve certain important problems that are intractable using conventional computers. They have a completely different internal architecture, using a superposition of states found in quantum physics rather than the simple 1 or 0 binary bits used in conventional computers. However, they are very sensitive to environmental noise and other problems, and hence require error correction to do precise calculations.

A key challenge is choosing the best system for ‘qubits’—the basic units used to perform quantum calculations. Different candidate systems have their own strengths and weaknesses. A popular one uses superconducting circuits and ions. It has the advantage that some form of error correction has been demonstrated, allowing it to be put into actual use, albeit on a small scale.

Silicon-based quantum technology, which has only begun to be developed over the past decade, has an advantage in that it utilizes a semiconductor nanostructure similar to what is commonly used to integrate billions of transistors in a



A computer-enhanced image of part of a semiconductor wafer. By demonstrating error correction in a silicon qubit system, RIKEN researchers have brought the realization of quantum computing in silicon closer to reality, which can exploit existing semiconductor fabrication techniques.

small chip, and thus could take advantage of current production technology.

“Our next step will be to scale up the system”

However, a major problem with silicon-based technology is the lack of a technique for error correction. Researchers have previously demonstrated control of two qubits, but that is not enough for error correction, which requires a three-qubit system.

Now, a team led by Seigo Tarucha of the RIKEN Center for Emergent Matter Science (CEMS) has demonstrated full control of a three-qubit system (one of the largest qubit systems in silicon), thus providing the first prototype for quantum error correction in silicon.

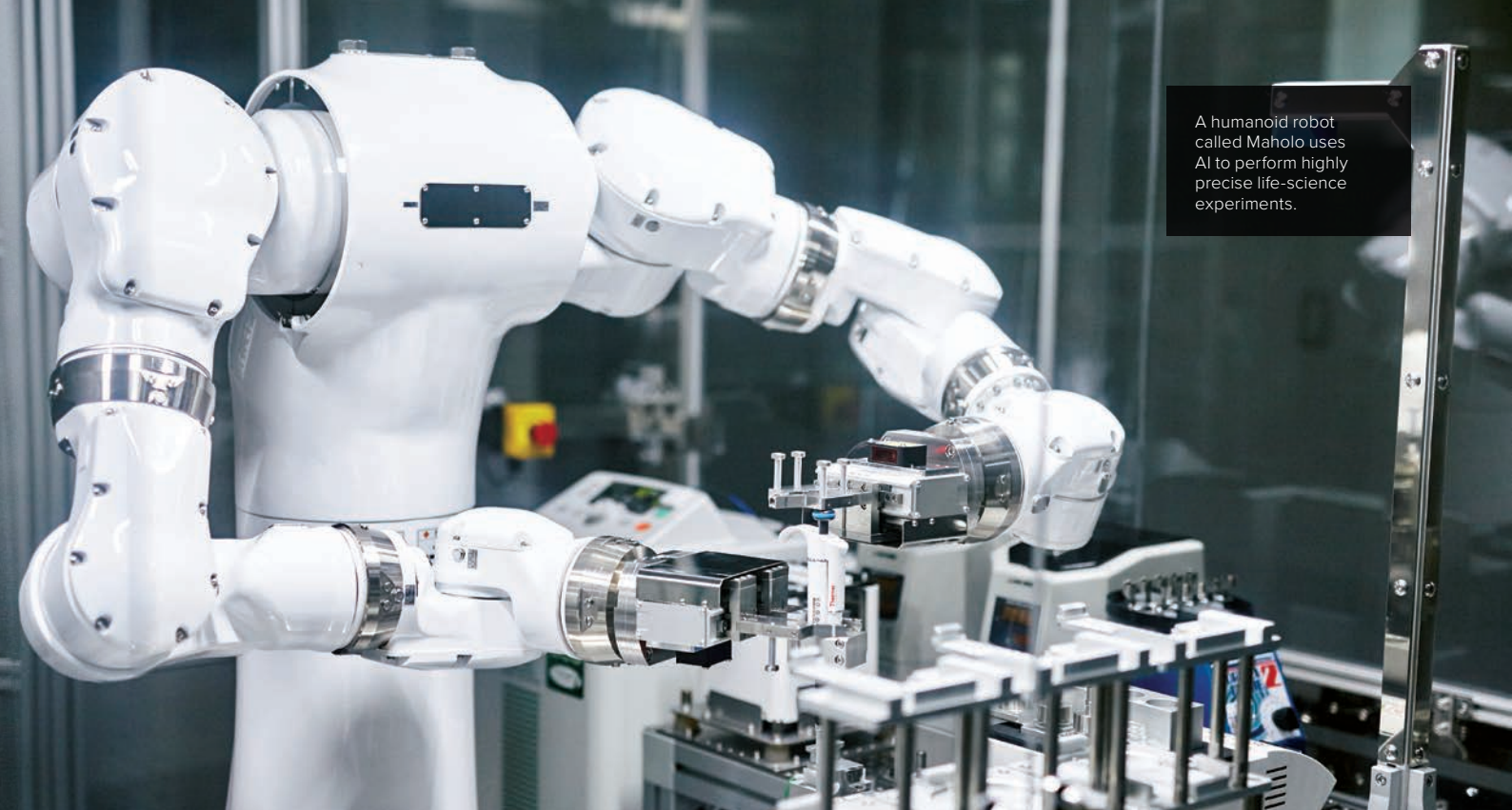
“The idea of implementing a quantum error-correcting code in quantum dots was proposed about a decade ago, so it is not an entirely new concept, but a series of improvements in materials, device fabrication and measurement techniques allowed us to succeed in this endeavor,” says Kenta Takeda, also of CEMS. “We are very happy to

have achieved this.”

The team plans to follow up this demonstration by creating a larger system. “Our next step will be to scale up the system,” says Tarucha. “For that, it would be nice to work with semiconductor industry groups capable of manufacturing silicon-based quantum devices at a large scale.” ●

Reference

1. Takeda, K., Noiri, A., Nakajima, T., Kobayashi, T. & Tarucha, S. Quantum error correction with silicon spin qubits. *Nature* **608**, 682–686 (2022).



A humanoid robot called Maholo uses AI to perform highly precise life-science experiments.

AUTOMATED SYSTEMS

Accelerating regenerative medicine using AI-assisted robots

A robot employing AI takes the drudgery out of stem-cell experiments

A robotic artificial-intelligence (AI) system that can determine the optimal conditions for growing replacement retina layers has been developed by RIKEN researchers¹. This demonstrates the potential of the automated design and execution of experiments to enhance the efficiency and speed of life-science research.

Regenerative medicine research often requires performing numerous time-consuming and labor-intensive experiments. In particular, creating specific tissue from stem cells—a process called induced cell differentiation—involves months of work. Determining the optimal type, dose and timing of reagents and optimal physical variables is difficult, requiring an enormous amount of trial and error.

To make this process more efficient and practical, a team led by Genki Kanda at the RIKEN Center for Biosystems Dynamics Research has developed an autonomous experimental system that can determine the optimal conditions and grow functional retinal pigment layers from stem cells.

They chose retinal pigment epithelium (RPE) cells because their degeneration causes a common age-related disorder that leaves people unable to see. Also, transplanting RPE retinal layers has had some clinical success.

For autonomous experiments to be successful, the robot must repeatedly perform the same series of precise movements and manipulations, and the AI must evaluate the results and formulate the next experiment.

The new system accomplishes these goals using a general-purpose humanoid robot named Maholo, which is capable of performing highly precise life-science experiments. Maholo is controlled by AI software that uses a newly designed optimization algorithm to determine which parameters should be changed and by how much in order to improve the differentiation efficiency in the next round of experiments.

Researchers inputted the necessary protocols for generating RPE cells from stem cells into Maholo. While RPE cells were successfully generated in all experiments, the initial efficiency was only 50%.

After establishing this baseline, the AI initiated the optimization process to determine the best

conditions among all chemical and physical parameters. Maholo achieved a differentiation efficiency of 90% in less than a fifth of the 2.5 years that it would have taken humans to achieve that goal. The cells displayed many of the typical biological markers that would make them suitable for transplant into an eye with a damaged RPE cell layer.

The goal is not to replace human lab workers with robots, however. “Using robots and AI for carrying out experiments will be of great interest to the public. However, it’s a mistake to see them as replacements,” says Kanda. “Our vision is for people to do what they are good at, which is being creative. We can use robots and AI for the trial-and-error parts of experiments.” ●

Reference

1. Kanda, G. N., Tsuzuki, T., Terada, M., Sakai, N., Motozawa, N., Masuda, T., Nishida, M., Watanabe, C. T., Higashi, T., Horiguchi, S. A. *et al.* Robotic search for optimal cell culture in regenerative medicine. *eLife* **11**, e77007 (2022).

METACOGNITION

Where the brain weighs information for decisions

A previously unsuspected brain region is found to play a crucial role in weighing information from different sources when making decisions

Three RIKEN neuroscientists have found a region of the brain in macaques that is responsible for integrating information from different sources during decision making¹. This finding will help inform research into psychiatric disorders that interfere with introspection.

Sometimes when making decisions, we have to draw on both our memories and the facts in front of us. One example is attempting to decipher a hastily scribbled note while simultaneously trying to recall what we were writing about. To arrive at a decision, our brains assign levels of confidence to the two sources of information and then combine them.

Known as metacognition, this ability to self-evaluate thoughts and memories underpins many behaviors. But it hasn't been clear where the brain integrates this information when making decisions.

Now, by conducting experiments on macaque monkeys, Kentaro Miyamoto, Rieko Setsuie and Yasushi Miyashita, all at the RIKEN Center for Brain Science, have shown that a brain region known as the posterior inferior parietal lobe (pIPL) performs this integration.

Monkeys were shown an image, and had to decide whether they had seen it before or not. To assess their confidence in their decision, the monkeys then had to bet on it by selecting between high-risk/high-reward or low-risk/low-reward options.

Perhaps unsurprisingly, the



Card games that involve remembering previous cards played while assessing the current hand require integrating information from various sources through metacognition processing. RIKEN researchers have found that the posterior inferior parietal lobe in macaques plays a key role in this ability.

monkeys selected the high-risk option more often when they had answered the question correctly than when they had answered it incorrectly. This showed that the monkeys were employing effective metacognition processes.

Functional magnetic resonance imaging during these experiments revealed that the pIPL was active while the monkeys were weighing their betting options based on the memory test.

Miyamoto was surprised by this. “The prefrontal cortex is thought to be the key region for overseeing behavior and making decisions based on rules; some

believe it's where ‘the intelligence of the soul’ resides,” he explains. “So I was very surprised that the whole-brain mapping indicated that a region at the back of the brain was active during metacognition.”

The pIPL drew on information from three brain regions in the prefrontal cortex that Miyamoto's and Miyashita's team had previously found are involved in determining confidence in memories. “The memory system itself is not found in the prefrontal cortex, but the prefrontal cortex is important for reading out the confidence in memories,” says Miyamoto.

The pIPL then sent a signal to another region, the dorsal anterior cingulate cortex, to implement the betting decision.

Miyamoto intends to explore metacognition processing at the neuronal level and investigate its connection with psychiatric disorders in which people compulsively behave in ways they don't want to. ●

Reference

1. Miyamoto, K., Setsuie, R. & Miyashita, Y. Conversion of concept-specific decision confidence into integrative introspection in primates. *Cell Reports* **38**, 110581 (2022).

ALZHEIMER'S DISEASE

Alzheimer's model shows plaque deposition

A new model mouse for the disease responsible for most cases of dementia also exhibits a common condition that accompanies Alzheimer's in people

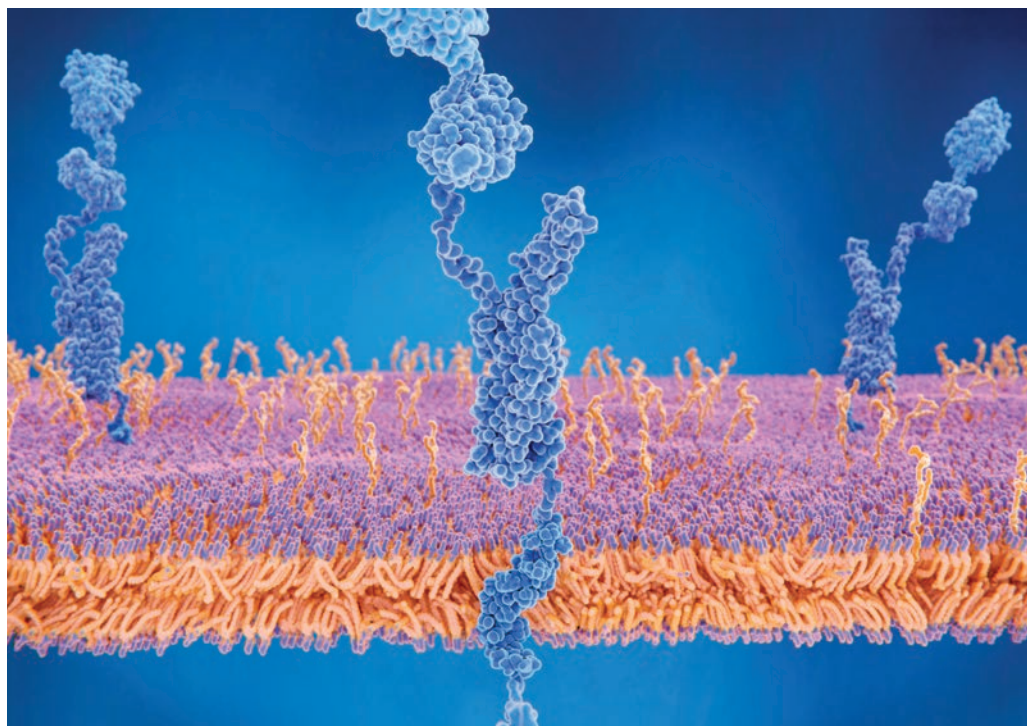
For the first time, RIKEN biologists have produced a mouse that both approximates Alzheimer's disease in humans and exhibits significant buildup of a peptide called amyloid beta in blood vessels in the brain, which often goes hand-in-hand with Alzheimer's in humans¹. This will help researchers to explore the connection between the two conditions.

Despite being the most common form of dementia, affecting tens of millions of people globally, and the focus of extensive research over decades, Alzheimer's disease still lacks an effective treatment.

A plethora of genetically engineered mice with Alzheimer-like conditions has been developed to investigate the neurodegenerative disorder, but none of them perfectly reproduces Alzheimer's in humans. In the past, several potential drugs showed a lot of promise in mice only to flop when they underwent clinical trials in human patients.

Mouse models produced to date exhibit very little buildup of amyloid beta in blood vessels in the brain—a common occurrence in people with Alzheimer's, the buildup often starting decades before symptoms appear. This has made it difficult to explore the connection between Alzheimer's disease and the deposition of amyloid beta in the blood vessels of the brain.

"Vascular amyloid deposition is a key pathology for Alzheimer's disease, with most patients exhibiting it," says Shinobu Kitazume from the RIKEN Center for Brain Science. "But



An illustration depicting the amyloid precursor protein at a cell membrane. Shinobu Kitazume and her team produced mice that expressed the protein in their endothelial cells and then crossed them with a model mouse for Alzheimer's disease.

most Alzheimer's model mice show very limited vascular amyloid deposition."

Now, Kitazume, who is also at the Fukushima Medical University School of Medicine, and her co-workers have succeeded in producing a model mouse for Alzheimer's that has significant amyloid beta accumulation in the brain blood vessels.

Kitazume, who is a biochemist by background, discovered that mice and rats had much lower levels of the soluble precursor protein for amyloid in their bloodstream than humans. She speculated that was because their endothelial cells—cells that line blood vessels—produced

low levels of the precursor.

Yuriko Tachida in Kitazume's team then produced mice that expressed the human version of the amyloid precursor protein in their endothelial cells. When they crossed these mice with conventional Alzheimer model mice produced by colleagues at RIKEN, the resulting mice exhibited both Alzheimer-like characteristics and high amyloid beta deposition in their brain blood vessels.

Kitazume sees a lot of potential to use the mice to both explore the buildup of amyloid beta in brain blood vessels as well as how it interacts with Alzheimer's disease. "There are several

interesting ways to use these mice," says Kitazume. "And already several pharmaceutical companies have expressed interest in using them." ●

Reference

1. Tachida, Y., Miura, S., Muto, Y., Takuwa, H., Sahara, N., Shindo, A., Matsuba, Y., Saito, T., Taniguchi, N., Kawaguchi, Y. *et al.* Endothelial expression of human amyloid precursor protein leads to amyloid β in the blood and induces cerebral amyloid angiopathy in knock-in mice. *Journal of Biological Chemistry* **298**, 101880 (2022).



In conventional *in vitro* fertilization (IVF) procedure, sperm are injected into an egg (oocyte). RIKEN researchers have discovered that using oocytes that are half their usual size can enhance IVF outcomes when sperm production is faulty and immature sperm (spermatocytes) are used as substitutes.

REPRODUCTIVE MEDICINE

An IVF workaround for male infertility

Using half-sized eggs provides an avenue for childbearing in mice

A new approach for assisting reproduction in mice when sperm production is faulty has been demonstrated by researchers at RIKEN¹. It could eventually help human couples who are struggling to conceive by traditional *in vitro* fertilization (IVF) techniques.

In a typical IVF procedure, doctors collect a woman's eggs (mature oocytes) and a man's sperm and combine them in a laboratory dish to make embryos for implantation. The sperm and egg normally each contain a single copy of all 23 human chromosomes.

But owing to errors in cell division, some men cannot make mature sperm with the proper chromosome count. Immature sperm cells, known as spermatocytes, can get stuck part way through the

chromosomal-sorting process called meiosis. The faulty cells degenerate in the testes, and so men fail to produce any measurable sperm in their semen.

The new method addresses this cause of male infertility in mice. Through a simple tweak to developing egg cells, RIKEN researchers have found a way to restore these abnormal spermatocytes and produce viable offspring.

All they did was halve the volume of the immature oocytes. "We have successfully overcome the technical difficulty by reducing the oocyte size," says Atsuo Ogura of the RIKEN BioResource Research Center, who led the study.

Ogura's method builds on a recent discovery by Tomoya Kitajima and Hirohisa Kyogoku at the RIKEN Center for Biosystems Dynamics Research.

In 2017, they reported that the large size of oocytes—the biggest cells in the mammalian body—made them more prone to chromosome-distribution errors.

All that fluid cytoplasm sloshing around inside the oocyte seemed to encumber the ability of chromosomes to divvy themselves up properly. Maybe, thought Ogura, this same problem was undermining the success of IVF techniques that rely on spermatocytes as well.

So, Ogura's group, in collaboration with Kitajima's, decided to put the oocyte size-reduction strategy to the test.

They cut the cytoplasm volume in half and found that this small change made a big difference. The rate of chromosome segregation errors dropped from 98% to 79%. What's more, the proportion of successful live births in

mice increased from 1% to 19%. The egg adjustment also allowed for the production of pups from mouse spermatocytes containing a genetic defect linked to male infertility in humans.

With further refinements and safety tests, the technique could eventually provide a new avenue for childbearing among couples unable to produce viable sperm for traditional IVF. ●

Reference

- Ogonuki, N., Kyogoku, H., Hino, T., Osawa, Y., Fujiwara, Y., Inoue, K., Kunieda, T., Mizuno, S., Tateno, H., Sugiyama, F., *et al.* Birth of mice from meiotically arrested spermatocytes following biparental meiosis in halved oocytes. *EMBO Reports* **23**, e54992 (2022).

NUCLEAR STRUCTURE

Helium nuclei found lurking inside carbon nuclei

Calculations provide a glimpse inside carbon nuclei, revealing the presence of three clusters resembling helium nuclei

In a result with implications for how carbon nuclei, the atomic building blocks of life, are birthed inside stars, calculations by a RIKEN-led team suggest that the dozen protons and neutrons that make up the carbon-12 nucleus are clustered into three groups of two protons and two neutrons—essentially three helium nuclei¹.

The sheer complexity of the many interactions between the protons and neutrons in atomic nuclei makes it impossible to precisely calculate their structures beyond the very smallest nuclei. Nuclear physicists thus rely on models to gain insights into the structures of nuclei.

“Our finding could contribute to a better understanding of nuclear synthesis”

One particularly compelling model, first proposed in the 1930s, posits that the neutrons and protons in large nuclei clump into groups of two protons and two neutrons. The helium nucleus is unusually stable, as evidenced by the fact that massive, unstable nuclei such as uranium often spit out helium nuclei when they decay into more-stable nuclei.

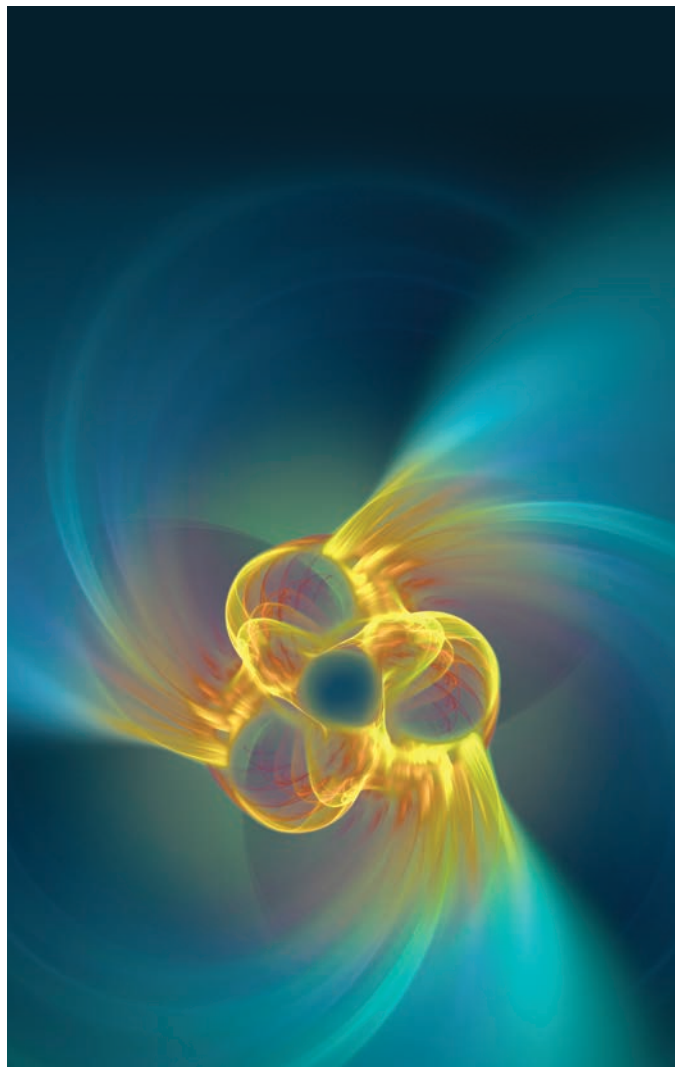
But attractive as this model

is, it hasn't yet been confirmed experimentally because of the difficulty of taking snapshots of nuclei whose protons and neutrons are constantly moving.

In the case of carbon-12, this question has ramifications for life on Earth. “Carbon makes up nearly a fifth of the human body and is critical for all life on Earth,” says Takaharu Otsuka of the RIKEN Nishina Center for Accelerator-Based Science. “But we still lack a complete picture as to where and how carbon was created in the Universe.” Having more accurate knowledge of the structure of the carbon nucleus would help astrophysicists improve their understanding of how carbon is made inside stars.

Now, supercomputer simulations performed by Otsuka, Takashi Abe and Hideki Ueno, all at the RIKEN Nishina Center for Accelerator-Based Science, and co-workers have revealed that the ground and Hoyle states (an unstable form of carbon-12 thought to be a key stepping stone toward stable carbon-12) of the carbon-12 nucleus consist of three helium nuclei that are arranged in surprising ways.

These calculations were performed on RIKEN's Fugaku, one of the world's most powerful supercomputers. Importantly, they were based on first principles, meaning that they didn't involve any assumptions about how nuclei should behave.



Calculations performed on RIKEN's Fugaku supercomputer have revealed that the carbon-12 nucleus consists of three clusters with the same make-up as three helium atoms.

Also, the results were consistent with experimental observations, inspiring confidence that they provide an accurate depiction of what is really going on inside nuclei.

The team also showed that clusters of helium nuclei are present in two isotopes of the element beryllium: beryllium-8 (four protons and four neutrons) and beryllium-10 (four protons and six neutrons). They suspect that they exist in larger nuclei too, although the calculations to show that would need more-advanced supercomputers.

This result will help inform models of how nuclei form. “Our finding could contribute to a better understanding of nuclear synthesis,” notes Otsuka. ●

Reference

- Otsuka, T., Abe, T., Yoshida, T., Tsunoda, Y., Shimizu, N., Itagaki, N., Utsuno, Y., Vary, J., Maris, P. & Ueno, H. α -Clustering in atomic nuclei from first principles with statistical learning and the Hoyle state character. *Nature Communications* **13**, 2234 (2022).

COLITIS

A modern analysis of an ancient herbal treatment

How a Japanese herbal medicine protects the gut against inflammatory bowel disease

A common herbal remedy reduces the severity of colitis—one of two conditions that comprise inflammatory bowel disease—in mice, RIKEN researchers have found¹. It does this by preventing an imbalance in gut microbes and by increasing levels of immune cells in the colon that fight inflammation, they report.

A kind of chronic inflammation of the colon, colitis is characterized by an imbalance in gut bacteria and an abnormal immune response. Its prevalence has doubled during the past 20 years, and it's currently a global health concern, particularly in Europe and North America. Treatments for it are only partially effective.

Some researchers are examining traditional Chinese herbal medicines that are also commonly used in Japan and other Asian countries. For example, daikenchuto (DKT) is a formula containing specific amounts of ginger, pepper, ginseng and maltose. Previous research has hinted that it might be useful for treating colitis, but evidence, particularly at the molecular level, has been lacking.

Now, Zhengzheng Shi and Naoko Satoh-Takayama, both at the RIKEN Center for Integrative Medical Sciences, and their co-workers have examined DKT's effects on a mouse model of colitis.

They induced colitis in mice using dextran sodium sulfate, which is toxic to the cells that line the colon. When these mice were given DKT, their body weights remained normal, and they had lower clinical scores for colitis.



RIKEN researchers have shown that the Japanese herbal medicine daikenchuto can alleviate intestinal diseases like colitis by rebalancing *Lactobacillus* (depicted) levels in the gut microbiome.

They also had much less damage to the cells lining the colon.

The researchers analyzed the gut microbiome of the mice and expression levels of anti-inflammatory immune cells, since colitis is associated with an imbalance in these gut microbiota. They found that a family of lactic acid bacteria and one of their metabolites, a short-chain fatty acid called propionate, were depleted in the colitic mice. Treating the model mice with DKT restored many of these missing bacteria—particularly those from the genus *Lactobacillus*—and propionate levels were normal.

Colitis is also associated with

an abnormal immune response that causes the characteristic intestinal inflammation. The team found that untreated colitic mice had lower levels of a type of intestinal immune cell called ILC3 than DKT-treated colonic mice. Also, mice engineered to lack ILC3 suffered more and did not benefit from DKT treatment. This indicates that ILC3s are critical for protecting against colitis and that DKT works by interacting with them.

“Daikenchuto is commonly prescribed to prevent and treat gastrointestinal diseases,” says Satoh-Takayama. “We have shown that it can also alleviate intestinal diseases like colitis by

rebalancing *Lactobacillus* levels in the gut microbiome. This likely helps reduce inflammatory immune responses by promoting the activity of type 3 innate lymphoid cells.” ●

Reference

1. Shi, Z., Takeuchi, T., Nakanishi, Y., Kato, T., Beck, K., Nagata, R., Kageyama, T., Ito, A., Ohno, H. & Satoh-Takayama, N. A Japanese herbal formula, daikenchuto, alleviates experimental colitis by reshaping microbial profiles and enhancing group 3 innate lymphoid cells. *Frontiers in Immunology* **13**, 903459 (2022).

GERMICIDAL LAMPS

Far-ultraviolet LED designed to tackle pandemics

A powerful LED can efficiently disinfect surfaces, while remaining safe for humans

A highly efficient LED that is deadly to microbes and viruses but safe for people has been engineered by three RIKEN physicists¹. It could one day help countries emerge from the shadows of pandemics by killing pathogens in rooms full of people.

Ultraviolet germicidal lamps are extremely effective at exterminating bacteria and viruses, and they are routinely used in hospitals to sterilize surfaces and medical instruments.

Such lamps can be made with LEDs, making them energy efficient. But these LEDs use ultraviolet light in a range that damages DNA and thus cannot be used around people. The hunt is on to develop efficient LEDs that shine light within a narrow band of far-ultraviolet light that appears to be both good at disinfecting and safe for people.

“We trust that our findings ... will be very useful for safeguarding society against this and future pandemics.”

Germicidal LED lamps that operate in the absence of humans are often made from aluminum,

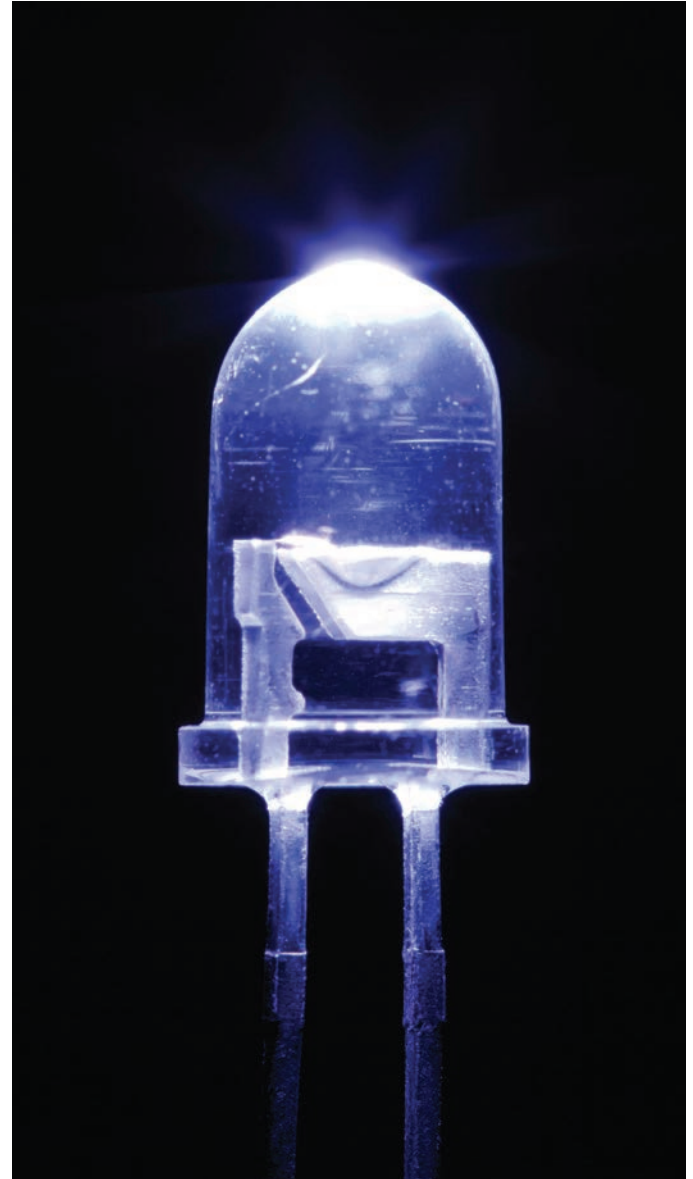
gallium and nitrogen. By increasing the amount of aluminum they contain, these LEDs can be modified to work in a wavelength region that is safe for humans. But traditionally this has dramatically reduced their power.

To get around this, Masafumi Jo, Yuri Itokazu and Hideki Hirayama, all at the RIKEN Quantum Optodevice Laboratory, created an LED with a more complex design. They sandwiched together multiple layers, each containing slightly different proportions of aluminum, while in some layers they also added tiny amounts of silicon or magnesium.

This effectively created an obstacle course for electrons, hampering their movement across the material and trapping them for longer in certain areas. This, in turn, increased the amount of light emitted by the device and reduced the amount it absorbed.

To help pin down the best design, the team used computer simulations to model all possible effects. “We then grew samples to see if it was effective or not,” Jo says. The biggest experimental challenge was precisely controlling the thickness of each layer. They created an LED operating in the far ultraviolet, with an output power almost ten times higher than their previous best.

The COVID-19 pandemic



Most LEDs emit visible light, but RIKEN physicists have created an LED that emits in a narrow region in the far ultraviolet that is safe for humans but deadly for viruses and bacteria.

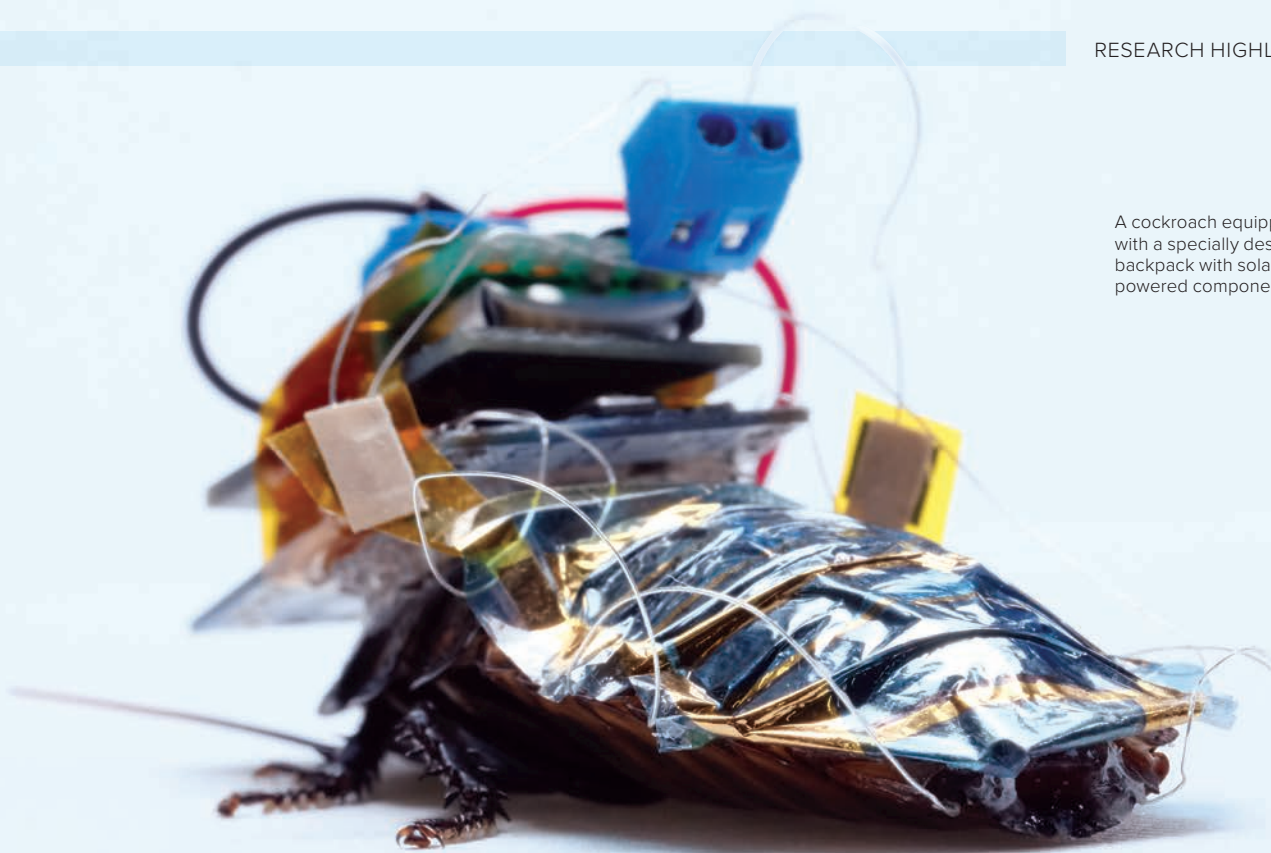
highlighted the importance of being able to destroy viruses and microbes on surfaces. “We trust that our findings and technologies will be very useful for safeguarding society against this and future pandemics,” says Jo.

Jo adds that the trio will strive to improve their LED’s performance even further. “There’s still much room for

improvement in the output power and the power efficiency,” he notes. ●

Reference

1. Jo, M., Itokazu, Y. & Hirayama, H. Milliwatt-power far-UVC AlGaN LEDs on sapphire substrates. *Applied Physics Letters* **120**, 211105 (2022).



A cockroach equipped with a specially designed backpack with solar-powered components.

CYBORG INSECTS

A solar-powered cyber-roach

Remote-controlled cockroaches powered by sunlight show promise for practical applications

Remote-controlled cyborg cockroaches—equipped with tiny wireless control modules powered by a rechargeable battery attached to a solar cell—have been demonstrated by RIKEN researchers¹. This could lead to cyborg insects being used to inspect hazardous sites or monitor the environment.

For cyborg insects to be put to practical uses, handlers need to be able to control them remotely for long stretches of time. This requires wireless control of their leg segments, powered by a tiny rechargeable battery. Keeping the battery adequately charged is critical, and the most practical way to achieve this is to use an onboard solar cell.

To integrate these devices into a cockroach, a team led by Kenjiro Fukuda of the RIKEN Thin-Film Device Laboratory developed a special backpack, ultrathin

organic solar-cell modules, and an adhesion system that keeps the machinery attached for a long time while also allowing natural movements.

The team experimented with Madagascar hissing cockroaches, which are about 6 centimeters long. Using the specially designed backpack, they attached the wireless leg-control module and lithium polymer battery to the top of the insect's thorax. The backpack, which was made by 3D printing an elastic polymer, conformed perfectly to the cockroach's curved surface, allowing the rigid electronic device to be stably mounted for more than a month.

Mounted on the dorsal side of the abdomen, the ultrathin, organic solar-cell module had a power output that was more than 50 times greater than that of current state-of-the-art

energy-harvesting devices on living insects.

The researchers found that the abdomen changes shape and portions of the exoskeleton overlap during natural cockroach movements. To accommodate this, they interleaved adhesive and non-adhesive sections onto the films, which allowed them to bend but also stay attached. When thicker solar-cell films were used or the films were uniformly attached, the cockroaches took twice as long to run the same distance and had difficulty righting themselves when on their backs.


The team tested the cyborgs by charging their battery with artificial sunlight for 30 minutes. They were able to make the cockroaches turn left and right using the wireless remote control.

“Considering the deformation of the thorax and abdomen

during basic locomotion, a hybrid electronic system of rigid and flexible elements in the thorax and ultrasoft devices in the abdomen appears to be an effective design for cyborg cockroaches,” notes Fukuda. “Moreover, since abdominal deformation is not unique to cockroaches, our strategy can be adapted to other insects like beetles, or perhaps even flying insects like cicadas in the future.” ●

Reference

1. Kakei, Y., Katayama, S., Lee, S., Takakuwa, M., Furusawa, K., Umezu, S., Sato, H., Fukuda, K. & Someya, T. Integration of body-mounted ultrasoft organic solar cell on cyborg insects with intact mobility. *npj Flexible Electronics* **6**, 78 (2022).



Using a new method they developed, RIKEN researchers have investigated two repeated genomic sequences, which are repeated millions of times in the genome of each cell.

GENETIC RECOMBINATION

Genetic recombinations turn up everywhere

Widespread in human genomes, DNA recombinations are implicated in both development and disease

Once considered ‘junk DNA’, recombinations of specific genomic sequences repeated millions of times in the genome of each of our cells are common in both healthy and sick people, RIKEN researchers have discovered¹. Identifying the mechanisms that lead to this myriad of recombinations could be crucial to understanding how our cells develop and what can make them unhealthy.

Following the discovery of DNA, it was long believed that all the cells in our body share the same genetic code, safely guarded within the nucleus. However, recent advances in DNA sequencing have challenged this view, by revealing that mutations accumulate in the genomes of single cells starting from the very early stages of development. But the magnitude of this phenomenon and how it contributes to disease have not

been well understood.

Now, RIKEN researchers have developed a method to study two repeated genomic sequences, called Alu and L1, which are repeated millions of times in the genome of each cell. They chose these two sequences because they recombine with each other, generating mutations often found in cancer and other genetic disorders.

By analyzing the DNA of people unaffected by disease, the researchers identified millions of DNA mutations caused by the recombination of these repeated sequences. They discovered that different tissues in the body are characterized by different recombination signatures.

The team also found that the differentiation of human stem cells into neuronal cells is accompanied by distinct changes of recombination of repeated sequences. This indicates that

this particular type of DNA mutation may be a physiological phenomenon involved in human development.

“We’ve shown that the recombination of repeated elements in the human genome is a widespread phenomenon that contributes to the complex constellation of genomic variants making up our genomes,” says Giovanni Pascarella of the RIKEN Center for Integrative Medical Sciences (CIMS).

Finally, the researchers looked at the recombination of repeated sequences in samples from people affected by Alzheimer’s and Parkinson’s diseases, the two most prominent neurodegenerative disorders in the developed world. They found signatures of recombination that are specific to each disease, suggesting that genomic recombinations caused by these repeated sequences may be involved in brain diseases.

“Random recombinations of Alu and L1 in somatic cells may occasionally prime the genome of individual cells at vulnerable sites and drive the transition from healthy to pathological states,” says Piero Carninci, also of CIMS. “However, it’s difficult to know at this point whether the recombinations in disease are truly causative or if they are effects of the disease state. Further studies are needed to address this important question.” ●

Reference

1. Pascarella, G., Hon, C. C., Hashimoto, K., Busch, A., Luginbühl, J., Parr, C., Yip, W. H., Abe, K., Kratz, A., Bonetti, A. *et al.* Recombination of repeat elements generates somatic complexity in human genomes. *Cell* **185**, P3025–3040 (2022).

HEART REGENERATION

Harnessing marsupials' heart regeneration ability

By applying a marsupial finding, researchers have induced heart regeneration in one-week-old mice

By discovering how the hearts of newborn marsupials — mammals that develop in their mother's pouch — retain the ability to regenerate for several weeks after birth, RIKEN biologists have repaired mouse hearts damaged a week after birth¹. The finding could help to develop regenerative heart therapies.

Heart disease is a leading cause of human death. Damaged heart muscle in humans and other mammals—such as after a heart attack—cannot be naturally repaired because mature heart muscle cells do not regenerate. Heart repair requires the birth of new cells, which only happens through cell division. In most mammals, heart muscle cells lose their ability to divide a couple of days after birth.

However, in contrast to most mammals, marsupials such as kangaroos, koalas and opossums are born in an underdeveloped state, and many of their internal organs, including their hearts, continue to develop after birth.

Conjecturing that heart growth after birth occurs because marsupial heart muscle cells retain the ability to divide, a team led by Wataru Kimura at the RIKEN Center for Biosystems Dynamics Research tested this in opossums.

They observed that opossum hearts continued to grow for several weeks after birth. The hearts of two-week-old opossums resembled those of one-day-old mice, and opossum heart-muscle cells continued dividing for weeks after birth. Experimentally induced heart



The muscle cells in the hearts of opossum pups retain the ability to divide for several weeks after birth. RIKEN researchers have discovered a protein that turns off the ability of heart muscles to regenerate.

damage at this age repaired itself within a month, indicating that the heart can be repaired provided heart cells continue to divide.

The team explored why this is possible in opossums but not mice. Gene expression in two-week-old opossums was similar to that in a few-day-old mice. Analysis of changes in gene expression in both animals around the time that heart regeneration ceased being possible revealed a common factor—a protein called AMPK. Further experiments showed that AMPK activation in mice and opossums coincided with the arrest of cell division in the heart muscle.

The researchers speculated that inhibiting AMPK or its ability to work could extend the period during which heart regeneration is possible. “If we could exploit the molecular pathway that determines the capacity for cardiac regeneration, we should be able to establish novel therapeutic approaches for treating cardiovascular disease,” says Kimura.

They confirmed this in opossums and mice. Specifically, injecting neo-natal mice with AMPK inhibitors allowed hearts that were experimentally damaged a week after birth to regenerate and regain normal function, with minimal scarring.

The team intends to investigate

what triggers AMPK expression at birth in mice but not in opossums. “One important and exciting question is how neonatal marsupials retain regenerative capacity in extra-uterine environments,” says Kimura. “The answers could lead to therapies that can induce heart regeneration in adults.” ●

Reference

1. Nishiyama, C., Saito, Y., Sakaguchi, A., Kaneko, M., Kiyonari, H., Xu, Y., Arima, Y., Uosaki, H. & Kimura, W. Prolonged myocardial regenerative capacity in neonatal opossum. *Circulation* **146**, 125–139 (2022).

TERAHERTZ TECHNOLOGY

Hitting the bull's eye at an angle

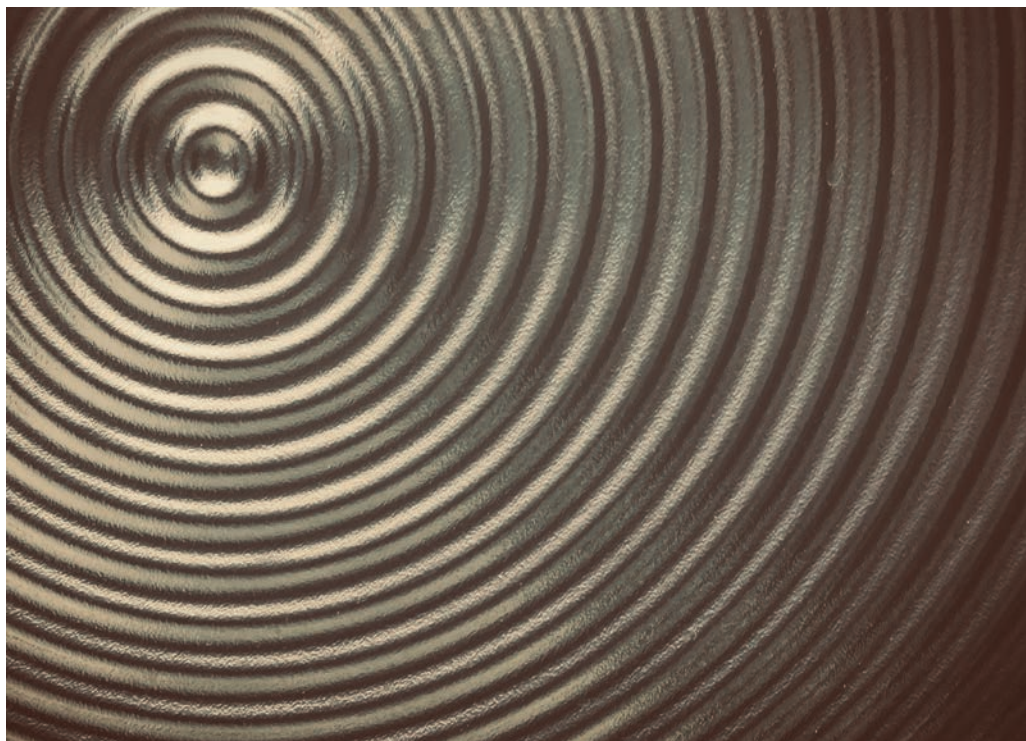
Researchers explore how terahertz waves, which are finding use in an expanding range of practical applications, interact with lenses with bull's-eye patterns

New terahertz devices such as biosensors and antennas in rapid communication systems stand to benefit from an analysis of a terahertz lens with a bull's-eye structure conducted by an all-RIKEN team¹.

Terahertz waves are so-called because they typically have frequencies between 0.1 and 10 terahertz (1 terahertz is a trillion cycles per second). They are sandwiched between the microwave and infrared regions on the electromagnetic spectrum. New technologies based on terahertz waves are taking off in areas such as imaging, wireless communication and sensors.

Lenses consisting of concentric grooves are commonly used to focus terahertz waves in applications such as high-resolution imaging and antennas for rapid wireless communication. These bull's-eye structures funnel propagating terahertz waves into apertures smaller than the wavelength of the terahertz radiation. But so far their focusing performance has been measured only for terahertz waves hitting them square on and not for waves that strike them obliquely.

"These lenses depend strongly on the angle of the impinging terahertz wave," says Yu Tokizane of the RIKEN Center for Advanced Photonics. "This angle dependence has been ignored in previous studies because measurements at oblique incidence are difficult due to the low signal intensity. However, many practical applications of the terahertz bull's-eye structure require various incident angles."



RIKEN researchers have investigated how terahertz waves behave when they pass through lenses with a bull's-eye structure at an oblique angle of incidence.

Now, Tokizane, Hiroaki Minamide and three co-workers, all at the RIKEN Center for Advanced Photonics, have measured the response of a bull's-eye structure lens to terahertz waves hitting it at angles between 0 and 8 degrees.

"Our results will be useful for optimizing the coupling efficiency of bull's-eye antennas, a type of device that could be used in spectroscopic and ranging applications," says Tokizane.

The team discovered that the lenses set up two resonances: a main resonance that varies with the incident angle and a side lobe

to the main resonance. These results could be well reproduced by a simple model.

"The measured spectra of the bull's-eye structure look complicated at first sight," notes Tokizane. "However, our model describes the experimental results including tiny peaks, which makes us confident that the experimental results are not artifacts. In this study, it was interesting to discover that apparently complicated results are correct and only consequences of simple physical phenomena without fancy assumptions."

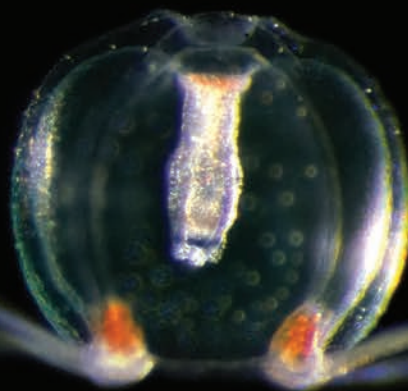
Tokizane, who has

subsequently taken up a post at Tokushima University, will be working on terahertz imaging and communication technologies. "Both research areas require resonating terahertz waves generated using devices such as bull's-eye structure lenses," he notes. ●

Reference

1. Tokizane, Y., Ohno, S., Takida, Y., Shikata, J. & Minamide, H. Incident-angle-dependent extraordinary transmission of the terahertz bull's-eye structure. *Physical Review Applied* **17**, 054020 (2022).

RIKEN researchers have derived a photostable and bright green fluorescent protein from the Japanese jellyfish *Cytaeis uchidae*.



GREEN FLUORESCENT PROTEINS

Jellyfish yields bright and photostable fluorescent protein

A bright fluorescent protein that stays bright under illumination will help researchers image subcellular structures

Fluorescence imaging of biological samples stands to benefit greatly by a RIKEN discovery of a fluorescent protein derived from a Japanese jellyfish that maintains its brightness even when illuminated by strong light¹.

Proteins that give off green light when illuminated are powerful tools for imaging fine structures within living cells. Researchers can attach such fluorescent proteins to target structures they are interested in, which then light up when blue light is shone on them.

However, researchers find themselves in a bind—they want to use as little fluorescent protein as possible so that it doesn't interfere with normal cellular processes, but that necessitates using strong illumination in

order to obtain high-quality images. The trouble is that when strong light is shone on a fluorescent protein, its brightness drops off rapidly due to a process known as photobleaching. To complicate matters, there is a trade-off relationship between brightness and photostability: increasing one will almost inevitably reduce the other.

Now, Atsushi Miyawaki of the RIKEN Center for Brain Science and his co-workers have discovered a fluorescent protein that flouts this trade-off relationship: it offers both high brightness while being roughly ten times more photostable than the best commercial fluorescent proteins.

Appropriately named StayGold, the fluorescent protein is derived from a naturally

occurring fluorescent protein found in *Cytaeis uchidae*, a tiny jellyfish found off the coast of Japan.

There was an element of serendipity in the discovery. “We noticed that the fluorescent protein from the jellyfish was photostable but very dim. And I wasn't optimistic about making the protein brighter while keeping that photostability, because I simply believed the tradeoff,” recalls Miyawaki. “However, to our surprise, we were able to increase both the protein's photostability and its brightness. So we could have our cake and eat it too.”

The team demonstrated the usefulness of StayGold by using it to image the endoplasmic reticulum network and

mitochondria in cells with enhanced spatiotemporal resolution and length of observation. They also used it to image the spike protein of SARS-CoV-2, the virus that causes COVID-19, in infected cells.

The intense interest generated by the study is reflected in the fact that it has been accessed more than 53,000 times since publication in late April. Researchers wanting to try the protein can obtain it from the RIKEN BioResource Research Center (web.brc.riken.jp/en/).

Since it remains unclear why StayGold can both be bright and stay bright under illumination, Miyawaki and his team intend to investigate the mechanism behind this. ●

Reference

1. Hirano, M., Ando, R., Shimozone, S., Sugiyama, M., Takeda, N., Kurokawa, H., Deguchi, R., Endo, K., Haga, K., Takai-Todaka, R. *et al.* A highly photostable and bright green fluorescent protein. *Nature Biotechnology* **40**, 1132–1142 (2022).

INFANT BEHAVIOR

How to calm crying babies

Carrying babies and then sitting with them increases the chance of getting them to sleep

The importance of carrying crying infants while walking, rather than simply holding them has been revealed by a study by RIKEN researchers into the physiological effects of holding, carrying, and laying down crying babies¹. The findings point to a simple and effective technique for boosting the chance of getting a crying infant to calm down and sleep in bed.

All parents know the frustration and discomfort of dealing with a crying baby.

Now, Kumi Kuroda of the RIKEN Center for Brain Science and her team have uncovered a ‘transport response’ that causes distressed mouse pups and human babies to calm down when carried by their mothers. It’s a complex series of parallel biological processes that result in reduced crying and lower heart rates.

Using a baby electrocardiogram and video cameras, the team systematically compared changes in infant heart rate and behavior as mothers performed common activities for calming infants, including carrying, being pushed in a stroller, and holding while sitting. Data during these activities were recorded from babies that were crying, awake and calm, or sleeping. At each heartbeat, behavior was assessed as ‘asleep’, ‘alert’ or ‘crying’, and scored accordingly. This allowed the researchers to track behavioral and physiological changes with sub-second precision.

“Walking for five minutes promoted sleep, but only for



Carrying crying babies and then sitting with them helps them to sleep more soundly.

crying infants,” says Kuroda. “Surprisingly, this effect was absent when babies were already calm beforehand.”

All babies stopped crying by the end of a five-minute walk and had lower heart rates, and about half were asleep. Sitting and holding crying babies was not calming; heart rates tended to go up and crying persisted.

The heartbeat measure allowed the researchers to investigate the effect of each micro-activity as infants were handled. The babies were extremely sensitive to all movements by their mothers. For example, heart rates went up when mothers turned or when they stopped walking. The most

significant event that disturbed the sleeping infants happened just when they became separated from their mothers.

Most parents have experienced the disappointment of having a finally sleeping baby wake up again after being put down. The researchers pinpointed the problem using the heartbeat data.

“Although we did not predict it, the key parameter for successful laydown of sleeping infants was the latency from sleep onset,” says Kuroda. Babies often woke up if they were put down before having about 8 minutes of sleep.

Thus, based on the data, Kuroda recommends that when

babies are crying too much and can’t sleep, parents should carry them steadily for about five minutes with few abrupt movements, followed by about eight minutes of sitting, before laying them down for sleep. ●

Reference

1. Ohmura, N., Okuma, L., Truzzi, A., Shinozuka, K., Saito, A., Yokota, S., Bizzeo, A., Miyazawa, E., Shimizu, M., Esposito, G. *et al.* A method to soothe and promote sleep in crying infants utilizing the transport response. *Current Biology* **32**, P4521–P4529. E4 (2022).

Childbirth and lactation unleash many physiological and endocrinological changes in female mice. Now, RIKEN researchers have found that male mice also exhibit neuro-endocrinological changes on becoming fathers.



PARENTAL BEHAVIOR

'Cuddle hormone' strongly affects male mice

Hormone causes male mice to change from being aggressive toward pups to caring for them

The radical flip in attitude of male mice toward pups on the birth of their own offspring—from aggressive to nurturing—stems from the hormone oxytocin, RIKEN neuroscientists have discovered¹. This surprising finding could also have implications for human fathers.

A mature male mouse that has never mated will often attack and even kill pups, but the same mouse can become a doting father on the birth of its own young. The neurological basis for this transformation, which is seen in many other animals, has been a mystery until now.

Kazunari Miyamichi at the RIKEN Center for Biosystems Dynamics Research is intrigued by this and other examples of rewiring in the brain. "One of the most fascinating aspects of the brain is its ability to change in

response to previous experience and the specific demands of a life stage," he says. "This neuroplasticity is caused by alterations in the strengths of synaptic connections, but it's generally tough to pinpoint which neurons or neural circuits undergo a plastic change upon any biological event."

Now, in a mouse study, Miyamichi and his co-workers have shown that neurons that secrete oxytocin in a brain region called the paraventricular nucleus in the hypothalamus are responsible for activating the paternal instincts of new fathers.

This discovery unlocked a slew of surprises for Miyamichi, who himself flipped from studying the neuroscience of smell to that of fatherhood on becoming a father.

For a start, he didn't anticipate that a single factor, oxytocin, would have such a strong effect

on fathers. "While females experience many physiological and endocrinological changes to their bodies on becoming mothers, any neuro-endocrinological changes in males were thought to be subtle or non-existent," he says. "But we found that oxytocin—a hormone associated with childbirth and lactation—exerts a strong effect in male mice."

Another totally unexpected aspect of the finding was the plasticity of neural circuits in the hypothalamus. "The functions of the hypothalamus are generally thought to be mediated by hard-wired neural circuits that never change once established," explains Miyamichi. "Our work is one of very few recent studies that show functional and structural plasticity in the hypothalamus."

There could be repercussions for human fathers. "One study

has reported that human fathers who experience more skin-to-skin contact with their children tend to have elevated levels of oxytocin in their blood," says Miyamichi. "And so we speculate that oxytocin plays significant roles in human fathers as well."

The team now intends to explore both the mechanisms that give rise to the neural plasticity of fathers and how oxytocin facilitates caregiving behaviors in fathers. ●

Reference

1. Inada, K., Hagihara, M., Tsujimoto, K., Abe, T., Konno, A., Hirai, H., Kiyonari, H. & Miyamichi, K. Plasticity of neural connections underlying oxytocin-mediated parental behaviors of male mice. *Neuron* **110**, 2009–2023 (2022).



A RIKEN researcher has derived a quantum speed limit for macroscopic transitions in non-equilibrium systems.

QUANTUM PHYSICS

Applying quantum speed limits to macroscopic systems

Speed limits for quantum phenomena have been extended to macro objects

An expression for the maximum speed at which changes in macroscopic systems can occur has been derived by a theoretical physicist at RIKEN¹. This will deepen our understanding of quantum phenomena in systems that are not in equilibrium.

One of the hardest aspects of quantum mechanics to grasp is the Heisenberg uncertainty principle that states that it is not possible to simultaneously pin down both the position and momentum of an object. In other words, the more precisely a particle's position is determined, the broader the range of its possible momentum becomes (and vice versa).

In 1945, two physicists, Leonid Mandelstam and Igor Tamm,

focused on another type of the uncertainty relation, namely one between time and energy fluctuation, and showed that transitions in quantum systems don't happen instantaneously; rather, the speed at which a transition occurs is capped by an amount determined by how much the energy of the system fluctuates.

Many other so-called quantum speed limits have subsequently been derived, which have helped better understand the physics of quantum systems and have been useful in various quantum applications.

But big problems arise when quantum speed limits are applied to macroscopic systems. "Previous quantum speed limits, which are useful for

small systems, typically become meaningless for macroscopic transitions," notes Ryusuke Hamazaki of the Nonequilibrium Quantum Statistical Mechanics RIKEN Hakubi Research Team. "For example, conventional quantum speed limits give an infinite upper bound for the speed of transitions in a gas made up of atoms."

Now, Hamazaki has succeeded in deriving a quantum speed limit for transitions in macroscopic systems.

"This new derivation provides fundamental limits that can be applied to various types of non-equilibrium quantum macroscopic phenomena," he says. "I hope that many fundamental laws and applications concerning

macroscopic quantum dynamics will appear based on the concepts introduced in this study."

Hamazaki derived the more stringent quantum speed limit by developing a general framework based on the conservation law of probability, a fundamental principle in physics.

One unexpected outcome for Hamazaki was the discovery of a new trade-off relationship. "Instead of a trade-off relationship between time and energy fluctuation, as in the Mandelstam–Tamm bound, I found one between time and the gradient of the quantum phase—a fundamental quantity in quantum physics."

Hamazaki now intends to extend his strategy to see whether it can be used to derive quantum speed limits for quantities like the growth of quantum entanglement. ●

Reference

1. Hamazaki, R. Speed limits for macroscopic transitions. *PRX Quantum* **3**, 020319 (2022).

NUCLEOSYNTHESIS

Discovering how heavy elements are made

A rapid way to measure masses of short-lived nuclei sheds light on how heavy elements are created

Nuclear physicists at RIKEN have measured the mass of a neutron-rich nucleus of the element palladium to a greater accuracy than ever before¹. When this mass is fed into models of merging neutron stars, it reproduces well the abundance of heavy nuclei found in the Solar System.

The Big Bang is thought to have only produced the three lightest elements: hydrogen, helium and lithium. The other 80 or so stable elements were formed through later processes such as supernovae, the death of low-mass stars, and nuclear fission induced by cosmic rays.

The mergers of neutron stars may have created a large proportion of heavy nuclei that contain 41 protons or more. They are conjectured to create new elements through nuclei capturing loose neutrons, followed by a neutron decaying

into a proton and an electron through beta decay.

A long-term aspiration of nuclear astrophysicists is to be able to reproduce the abundances of the elements that we see in the Universe today. But that requires precise knowledge of nuclear parameters including nuclear masses, which is challenging because many neutron-rich nuclei are highly unstable and have only fleeting existences.

“A big problem is that the abundances are very difficult to calculate because the nuclei involved in this process are unstable and so we don’t know much about them,” explains Sarah Naimi at the RIKEN Nishina Center for Accelerator-Based Science.

Now, Naimi and her co-workers have measured the mass of a palladium nucleus (46 protons) containing 77 neutrons to a

higher accuracy than before and have used their measured value to estimate the abundances of heavy nuclei in the Solar System.

Since the half-lives of some unstable nuclei could be shorter than 10 milliseconds, the researchers developed an ultrafast measuring technique that was about 100 times faster than the conventional method.

But measurement speed wasn’t the only advantage of the setup. “The uniqueness of our facility is that particles are pre-identified before being injected into the storage ring,” explains Naimi. “Since we always know what we inject into the storage ring, we could measure neutron-rich nuclei with very short half-lives.”

When the team dropped their measured value for the mass of the neutron-rich palladium nucleus into a model for element production via the neutron capture process, the

estimates given by the model for the abundances of nuclei with 122 and 123 protons and neutrons were very close to observed abundances. “We were really surprised at how well our result reproduced the solar abundances of these elements,” remarks Naimi.

The team now intends to use their method to measure the masses of nuclei with even shorter half-lives. ●

Reference

1. Li, H. F., Naimi, S., Sprouse, T. M., Mumpower, M. R., Abe, Y., Yamaguchi, Y., Nagae, D., Suzaki, F., Wakasugi, M., Arakawa, H. *et al.* First application of mass measurements with the rare-RI ring reveals the solar *r*-process abundance trend at $A = 122$ and $A = 123$. *Physical Review Letters* **128**, 152701 (2022).

Mergers of neutron stars are thought to have created many of the heavier elements in the Universe today.



THE NEXT MILESTONES IN GENERATING ARTIFICIAL ORGANS

RIKEN's Organoid Project tackles the latest challenges in this highly promising field for regenerative medicine and drug discovery, says Minoru Takasato

A 3D organoid culture of human colon cancer. These organoids could help researchers understand the molecules and mechanisms involved in tumor formation to fine tune the response of individual cancers to treatment..

© Science Photo Library / Alamy Stock Photo

What is the ultimate goal of research using human pluripotent stem cells? In the context of regenerative medicine, I think it's to recreate whole, replaceable organs in a laboratory setting. Transplanting these organoids could improve many treatment options. For instance, in the case of kidney damage, where patients must currently undergo dialysis for the remainder of their lives or until a donor organ is available.

Today, organoids are essentially miniature organs developed from stem cells and cultured on 3D frameworks, where they self-organize into functional tissue. These can partially replicate what cells within certain organs do. However, the largest organoids available today are only a few millimeters across. Once we discover how to grow them at scales comparable to real organs, we could create artificial organs derived from a patient's own stem cells.

The technology is also poised to accelerate drug discovery. Emerging 'organ-on-a-chip' devices—in which various cells are placed on a transparent microchip and connected through hollow channels—simulate the activities and cell interactions of an organ or organ system. Using these, it's possible to screen potential drugs using a cell system that more closely resembles the human body than 2D cell cultures or animal models. The enhanced efficiency should help cut costs in drug development, making treatments more accessible.

Historically speaking, RIKEN researchers were the first to demonstrate that cultured cells could self-organize into 3D tissues, first with cerebral cortical tissue in 2008, and then with cells from the optic cup, which is a part of the back of the eye, in 2011. We've continued to build on these groundbreaking findings at the RIKEN Center for Biosystems Dynamics Research (BDR), and are working to take the technology further through the Organoid Project.

THE ORGANOID PROJECT

We're entering an era where developmental biologists alone can't solve forthcoming organoid challenges. The Organoid Project is a consortium that brings together RIKEN researchers and external collaborators to tackle organoid challenges and find real-world applications. In addition to developmental biologists, the Organoid Project includes researchers and technicians with expertise in areas such as microdevices, 3D printing, biomaterials and bioinformatics. This positions us uniquely to become a world-class base for generating organs in 3D.

Research under the Organoid Project spans the four key phases that take us from basic research to real-world applications: research on the self-organization mechanisms in stem cells; designing organoids;

long-term culture and maturation; and optimization for applications.

Developmental biologist Mitsuru Morimoto and I work on the earlier phases of this process at RIKEN's Kobe campus. Here, Morimoto's team has succeeded in developing human lung alveoli organoids in the lab, which are now being used to model and develop treatments for lung diseases, such as pulmonary fibrosis, a scarring of the lungs.

His team has also elucidated the cell–cell communication signaling in the foregut, the top end of the esophagus, the stomach, and a portion of the duodenum, which is the embryonic origin of the trachea and esophagus. They have used these findings to develop tracheal cartilage tissue from human pluripotent cells. His group is now collaborating with the Center for Stem Cell and Organoid Medicine (CuSTOM) at Cincinnati Children's Hospital Medical Center in the United States to create a multiple organoid system that replicates the respiratory organs and esophagus.

Meanwhile, my team has established a method for generating kidney and bladder organoids from human induced pluripotent (iPS) cells. The kidney organoids have all the components of a nephron, the functional unit of the kidney. The bladder organoids exhibit a barrier function that holds urine in a way similar to the bladder, and we have also been able to replicate the muscle layers surrounding the bladder, which help hold and release urine.

However, a new frontier for organ regeneration is to replicate entire organ systems instead of standalone organs. From a surgical point of view, transplanting a whole urinary tract system instead of a kidney organoid alone could increase the likelihood of a transplant being successful. My team is working to connect organoids of the kidney, bladder and ureter, which connect the kidneys to the urinary bladder, to replicate the urinary system.

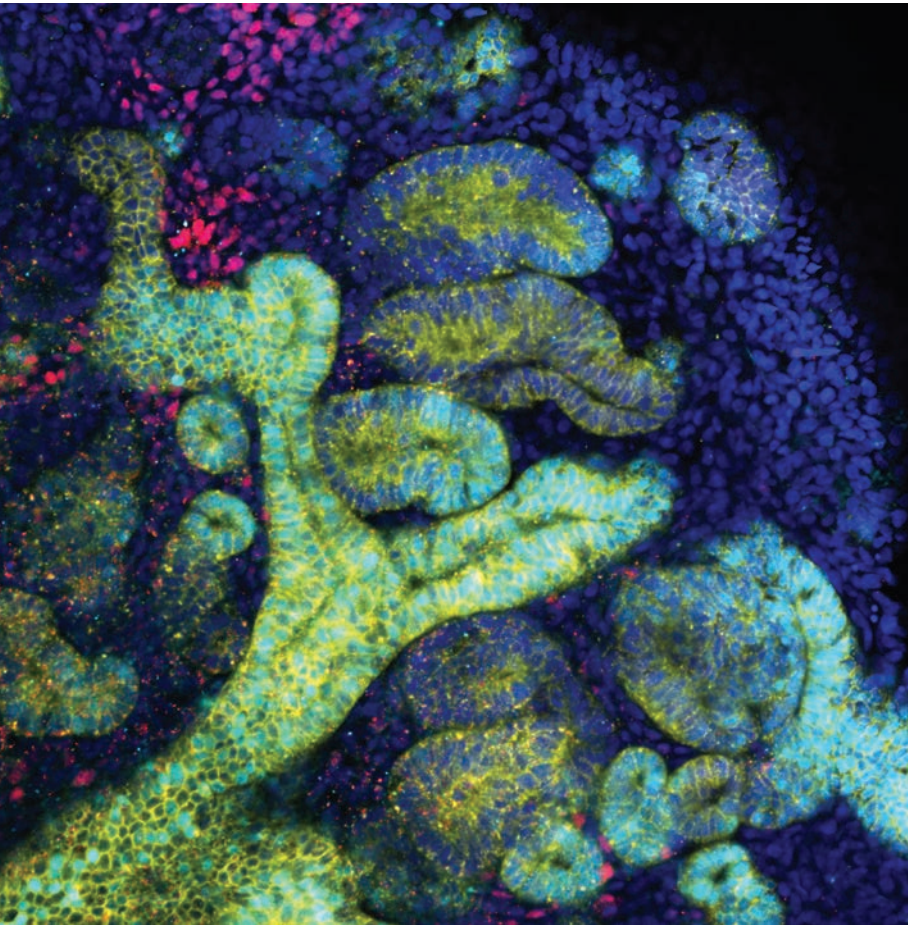
A challenge is that the urinary system connects organs, tissues and cells derived from two of three types of cell layers, called germ layers, formed in the third week of human embryonic development. The relevant cells here are from the endoderm—which develop into the inner linings of the body, such as the digestive system and bladder—and from the mesoderm, which develop into the kidney, muscles, and red and white blood cells, among other things. The connections at the kidneys and bladder are a rare point where these two types of tissues connect, and replicating this connection would be a major feat.

Research by Takashi Tsuji of RIKEN BDR and Masayo Takahashi—formerly at RIKEN and now an external collaborator at Kobe City Eye Hospital—is closer to real-world applications. Tsuji's team has developed a groundbreaking method, called the organ germ method, which uses organ-inducing



MINORU TAKASATO

Minoru Takasato completed his PhD in the study of mouse kidney development at the University of Tokyo, Japan, in 2008. He then began working as a postdoc at the Institute for Molecular Bioscience at the University of Queensland and Murdoch Children's Research Institute, both in Australia. During that period, he generated kidney organoids from induced pluripotent stem cells for use in drug screening and disease modeling. Takasato has been a team leader at the RIKEN Center for Biosystems Dynamics Research since 2016, where he heads the Organoid Project and conducts regenerative research for urinary-tract organs, including the kidney, bladder and prostate. He is an expert in the directed differentiation of human pluripotent stem cells to 3D organ-like tissues, which are commonly known as organoids. His work has drawn a great deal of international interest in the kidney development and stem cells research fields.



Minoru Takasato's team has established a method for using human induced pluripotent cells to generate kidney organoids (pictured) that have all the components of a nephron, the functional unit of the kidney.

epithelial and mesenchymal stem cells to replicate organogenesis, which is the growth and differentiation of tissues into organs during embryo development. In mice, his team has succeeded using this method to regenerate fully functional teeth, hair follicles and the salivary and lacrimal glands.

Using pluripotent stem cells, Tsuji's team has also generated organoids of the pituitary gland, salivary gland and 3D integumentary system, a skin system that includes hair follicles and sebaceous glands. He is now focusing on bringing the functional regeneration of teeth and hair follicles to world-first human clinical trials.

Meanwhile, Masayo Takahashi and her team at the Kobe Eye Center have begun clinical research on retina organoid transplants, in particular on optimizing organoids for transplant and assessing organoid quality. Retina organoids come as a flat sheet, and a challenge is to ensure that they include a robust layer of photoreceptors. Previously, Takahashi's team found that treating iPS cells with valproic acid helped yield retina organoids with sufficient photoreceptors. Achieving this, however, is dependent on the skill of

the technician. Currently, the quality of an organoid can only be assessed by slicing and examining a cross-section. Takahashi and her team are now developing a technique that combines robotics and AI to achieve consistent quality, and to monitor the quality in processing.

Early-career researchers working on the Organoid Project at RIKEN BDR have also been working on cutting edge discoveries. In Kobe, Hidetoshi Masumoto, for instance, has discovered a way of applying mechanical energy to iPS-derived heart tissue, which will hopefully make it behave in similar ways to real heart tissue; while working at RIKEN, Cody Kime developed synthetic embryos that should help us understand early development in the human body; and Hideya Sakaguchi, also based in Kobe, has generated organoids of the hippocampus, the area of the brain associated with memory.

CORE CHALLENGES

One of the challenges that remains is how to culture organoids for extended periods of time and to allow them to mature.

Organoids can be categorized into two major types: those made from adult stem cells, and those from embryonic stem (ES) cells/iPS cells. Adult stem cells are found in organs, such as the intestines or the stomach, where there is a high turnover of cells. They generate new cells throughout adult life and replace old ones in the lining of these organs. By extracting stem cells from a given organ, it's possible to generate organoids that resemble the functionality of adult organs.

In contrast, organoids made from ES/iPS cells replicate organs in the earliest stage of human development, in the embryo or fetus. In the real world, babies mature in the womb for nine months before being born, but the organoids we create are often comprised of cells at just a few weeks to several months into development.

This means that replicating the entire developmental process with ES/iPS-derived organoids would take just as long. And the question remains—how can we culture organoids in 3D for such an extended period of time? Establishing methods to run blood vessels through organoids could be a game-changer for this, as they would deliver essential nutrients and oxygen over long periods.

But how do we develop blood vessels on organoids? How do we control maturity level and size? How do we consistently create high-quality organoids that function the way they should? These questions must be overcome for organoid technology to be applied more widely. Today, organs have a sophisticated beauty that we can't yet capture in organoids, but modeling that complexity in its fullness is something the researchers behind the Organoid Project hope to achieve. ●

Ethanol preps rice and wheat for

DROUGHT

A cost-effective soil treatment could increase the survival rate of water-stressed crops more than ten-fold by reducing water loss and increasing sugar production in the aftermath

The northern hemisphere summer of 2022 has been a brutally hot one—China suffered its most severe heatwave in six decades, water in western Europe’s River Rhine dropped so low that big ships couldn’t pass through and the Horn of Africa experienced low rainfall for a fourth consecutive season.

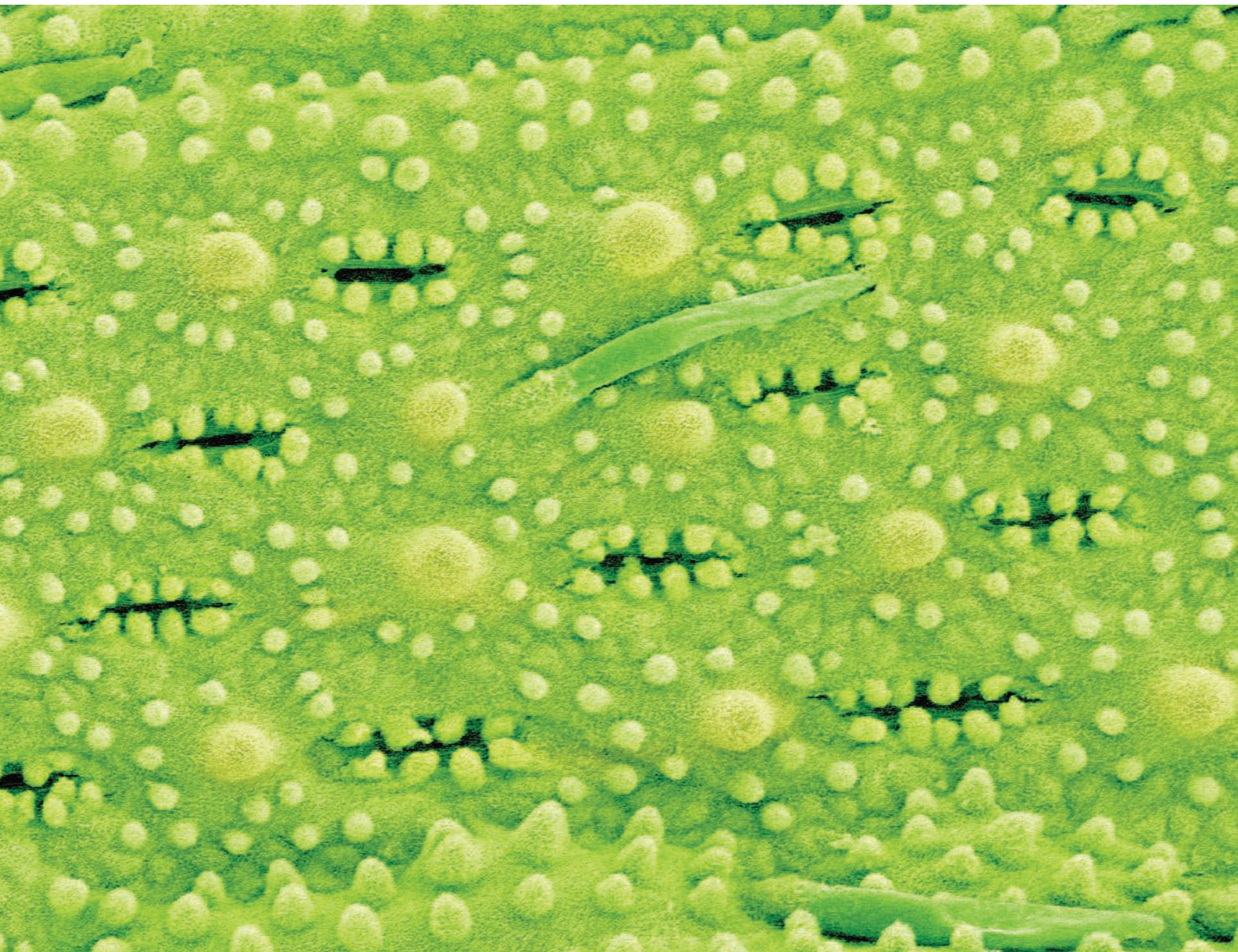
The events followed on the heels of a stark warning

issued by the United Nations in May: the world has experienced a 29% increase in the duration and frequency of drought since 2000. We must now, they urged, use “every tool we can” to halt its rise. Droughts spell disaster on many levels—not only is it the deadliest natural disaster (killing more than 650,000 people between 1970 and 2019), it is also a major threat to our food production.

“Water scarcity is a serious agricultural problem that causes significant losses to crop yield and quality,” says Motoaki Seki, a plant scientist at the RIKEN Center for Sustainable Resource Science. “Because droughts are happening more frequently, we need to find a way to prevent plants from dying when it’s extremely dry.”

At present, the main approach involves genetically modifying plants to ensure their stomata—tiny pores in leaves and stems—remain shut, thus minimizing water

Adding ethanol to soil helps to protect plants from the increasing incidence of drought conditions, which have risen globally by almost a third since 2000.



Both genetically modifying plants and applying ethanol treatments to the soils in which they grow help to ensure that plant stomata—tiny pores in leaves and stems (pictured)—remain shut, minimizing water loss.

loss. But this technique is time consuming, costly, and is not publicly accepted in many countries, says Seki.

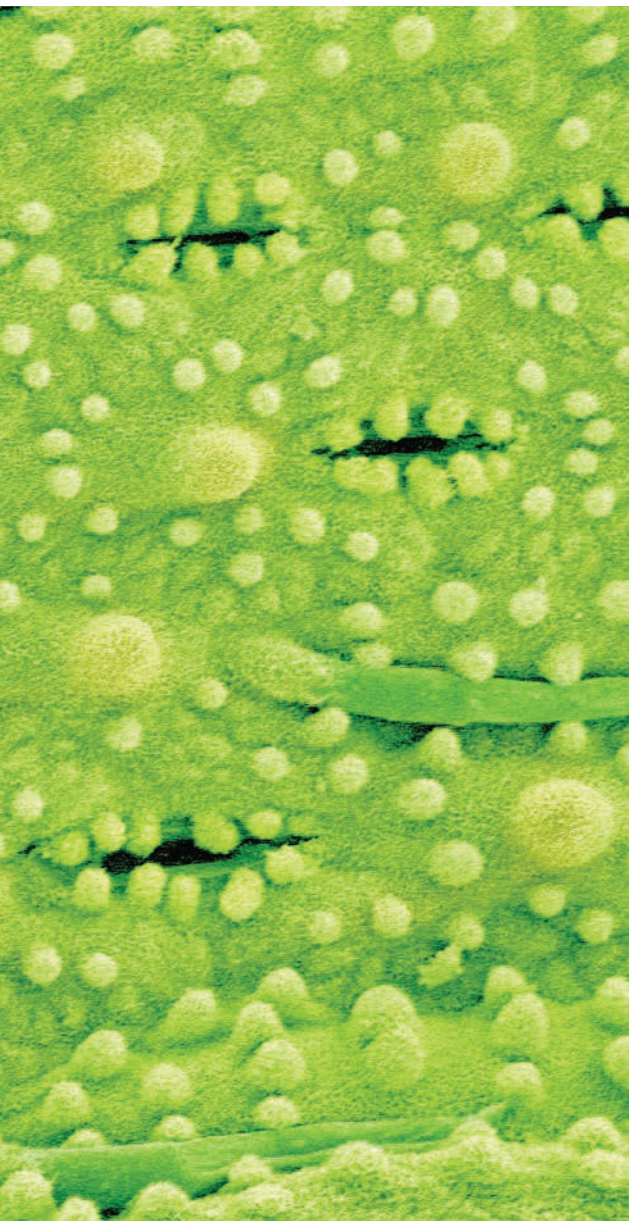
Instead, he and his team, alongside local and international collaborators, propose an alternative, novel solution: apply ethanol to the soil to protect plants from drought. The approach, they observed in a recent study, helped plants—including popular crops, rice and wheat—survive water-deficient conditions¹. “Ethanol is a simple and cheap compound, one that has been widely used as a disinfectant during COVID-19,” says Seki.

ETHANOL THE PROTECTOR

Seki and his team arrived at ethanol somewhat

serendipitously. “In searching for compounds that make plants resistant to stress, we were exploring the easy-to-access organic solvents that are commonly used to dissolve compounds during experiments,” he recalls.

Ethanol seemed a good bet, given that some plants naturally produce the colorless liquid in times of stress. Pine trees, for instance, are known to synthesize ethanol when damaged by wildfires, allowing them to continue breaking down sugars to produce energy. On the other end of the spectrum, rice seedlings have been observed producing ethanol when exposed to chilly temperatures, which helps improve their tolerance to the cold and possibly reduces membrane damage.



Seki's team began experimenting with ethanol, and, in 2017, they discovered that the compound, in situations of high salinity, helped to protect rice and *Arabidopsis thaliana*, a small flowering plant widely used as a model organism in plant biology. Could ethanol possibly do the same in conditions of drought, they wondered?

To test their hypothesis, the researchers first grew rice and wheat plants with ample water for two weeks. Next, they added ethanol to the soil for three days, before withdrawing water for the final four days and two weeks for rice and wheat, respectively. The results were unequivocal: approximately 75%

of ethanol-treated plants survived after rewatering following the drought. By comparison, fewer than 5% of untreated plants lived.

CHEMICAL PRIMING

To determine why this was the case, Seki and his team examined how the plants' physical attributes and gene expression changed with time, using the model plant *A. thaliana*.

"In ethanol-treated plants, there seems to be two phases of drought stress response," he explains.

In the early phase, genes related to drought tolerance are upregulated—even before water deprivation begins, giving plants a head start to deal with the dry conditions ahead. Leaf temperatures also increase, indicating the surface stomata were closing. Narrowed or closed stomata help reduce the rate of transpiration, the process through which a plant takes liquid water from the soil and releases it as water vapors into the air from their leaves. Reduced transpiration delays water loss, adds Seki. Indeed, ethanol-treated plants were observed to have higher water levels in their leaves after 11 days of water deprivation compared with their non-treated counterparts.

All this indicated that ethanol primes the cellular environment so that the plant is better prepared to withstand drought stress, Seki notes.

In the later stages of drought stress, drought-induced genes start to become downregulated. At the same time, those related to photosynthesis as well as sucrose and starch metabolism are ramped up. The result? The ethanol-treated plants began accumulating sugars, including some that are made from the excess ethanol, which provides these plants with extra energy to sustain their growth.

"We find that the external application of ethanol enhances drought tolerance in all plant species tested—*Arabidopsis*, rice, and wheat," concludes Seki. "Ethanol offers us a cheap and easy way to increase crop yield even when water is limited, without the need for genetic modification."

Next up, his team plans to examine the molecular mechanisms of ethanol-mediated stress tolerance in greater detail, in the hopes of "revealing undiscovered players" in the pathways involved.

The overall aim is to develop stress-tolerant plants by use of chemical compounds, says Seki. "Through our study of stress adaptation and resistance, we would like to contribute to solving the global food crisis brought about by climate change due to global warming and achieving the Sustainable Development Goals." ●

REFERENCE

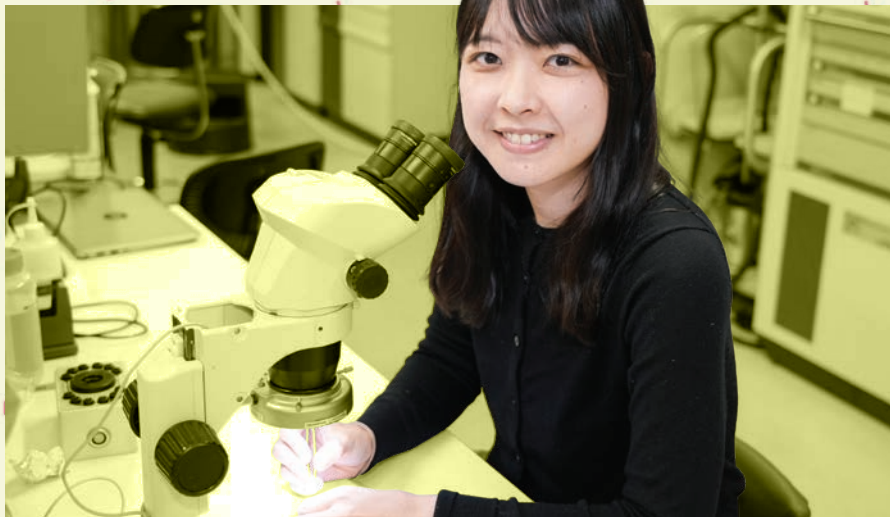
1. Bashir, K., Todaka, D., Rasheed, S., Matsui, A., Ahmad, Z. *et al.* Ethanol-mediated novel survival strategy against drought stress in plants. *Plant & Cell Physiology* **63**, 1181–1192 (2022)



This feature looks
at the work of
MOTOAKI SEKI

Motoaki Seki began his academic career with a degree from the Faculty of Agriculture at Kyoto University in Kyoto, Japan. He then obtained his PhD at Hiroshima University in 1994. Seki joined RIKEN in 1995 and started studying plant environmental stress adaptation under drought, heat, high-salinity and cold stresses. He has been leading the Plant Genomic Network Research Team at the RIKEN Center for Sustainable Resource Science (CSRS) (formerly, RIKEN Plant Science Center) since 2006. His research interests include the molecular mechanisms of plant environmental stress adaptation, the regulatory networks of tuberous root development in cassava and technology development for useful plants, such as enhanced stress tolerance and improved plant productivity. He has been a Clarivate Highly Cited Researcher in the field of Plant & Animal Science since 2014.

SCAN TO
LEARN
MORE!



PROGRAMS FOR

YOUNG RESEARCHERS



INTERNATIONAL PROGRAM ASSOCIATE

The International Program Associates (IPA) Program provides non-Japanese doctoral students the opportunity to carry out research for up to three years at RIKEN under a joint supervision scheme run by RIKEN scientists and researchers from partner graduate schools or research institutions both in Japan or overseas. Candidates must be enrolled in PhD programs at a university that has (or is expected to have) a Joint Graduate Program agreement with RIKEN by their arrival date.

FIELDS: Mathematical sciences, physics, chemistry, biology, medical science and engineering

SUPPORT: Living allowance of ¥5,200/day; rent-free use of on-campus housing or a housing allowance of up to ¥70,000/month for off-campus housing; and one round-trip travel fare to and from RIKEN.

APPLICATIONS: RIKEN researchers can apply to host a student in spring and autumn. Students should start by contacting the RIKEN researcher they would like to work with.

LEARN MORE: riken.jp/en/careers/programs/ipa

RIKEN HAKUBI FELLOWS PROGRAM

The RIKEN Hakubi Fellows Program provides junior principal investigator (PI) positions to exceptionally talented individuals, allowing them independent research at their own laboratories for up to seven years.

SUPPORT: Research budget of ¥10–40 million per year; salary of ¥910,000/month; commuting and housing allowances.

LEARN MORE: riken.jp/en/careers/programs/hakubi

SPECIAL POSTDOCTORAL RESEARCHERS PROGRAM

The Special Postdoctoral Researcher (SPDR) Program provides creative young scientists the opportunity to conduct autonomous and independent research that is in line with RIKEN objectives and research fields, for up to three years. Applicants must have a PhD awarded within five years of application or expect to be awarded a PhD by the date of hire.

FIELDS: Mathematical sciences, physics, chemistry, biology, medical science and engineering

ANNUAL RESEARCH BUDGET: ¥1,000,000

MONTHLY SALARY: ¥487,000 and commuting and housing allowances

APPLICATIONS: February to April

LEARN MORE: riken.jp/en/careers/programs/spdr

JUNIOR RESEARCH ASSOCIATES

The Junior Research Associates (JRA) Program provides part-time research positions for young researchers, giving them the opportunity to carry out research alongside RIKEN researchers, for up to three years (or four years in some cases). Candidates must be enrolled in PhD programs in Japanese universities that have collaborative agreements with RIKEN or are involved in joint research with RIKEN scientists by the date of hire.

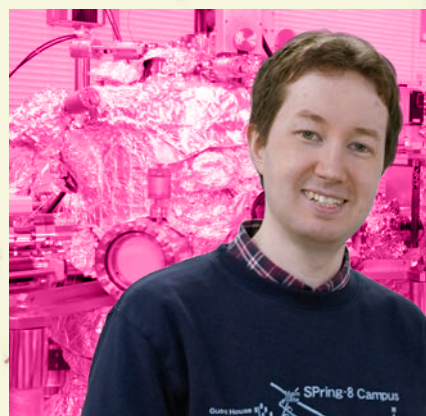
FIELDS: Mathematical sciences, physics, chemistry, biology, medical science and engineering

SUPPORT: ¥164,000/month (¥200,000/month from April 2023)

APPLICATIONS: October to November

PROGRAM START: April 1st or October 1st

LEARN MORE: riken.jp/en/careers/programs/jra



RIKEN'S CENTERS AND FACILITIES

across Japan and around the world



Since relocating its original campus from central Tokyo to Wako on the city's outskirts in 1967, RIKEN has rapidly expanded its domestic and international network. RIKEN now supports five main research campuses in Japan and has set up a number of research facilities overseas. In addition to its facilities in the United States and the United Kingdom, RIKEN has joint research centers or laboratories in Germany, China, South Korea, India, Malaysia, Singapore

and other countries. To expand our network, RIKEN works closely with researchers who have returned to their home countries or moved to another institute, with help from RIKEN's liaison offices in Singapore, Beijing and Brussels.

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



RIKEN RESEARCH

www.riken.jp/en



Science Blog

itaintmagic.riken.jp



Find us on
Facebook

www.facebook.com/RIKENHQ



www.riken.jp/en

 @riken_en

www.twitter.com/riken_en

LinkedIn

www.linkedin.com/company/riken