RIKEN RESEARCH

FALL 2018

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

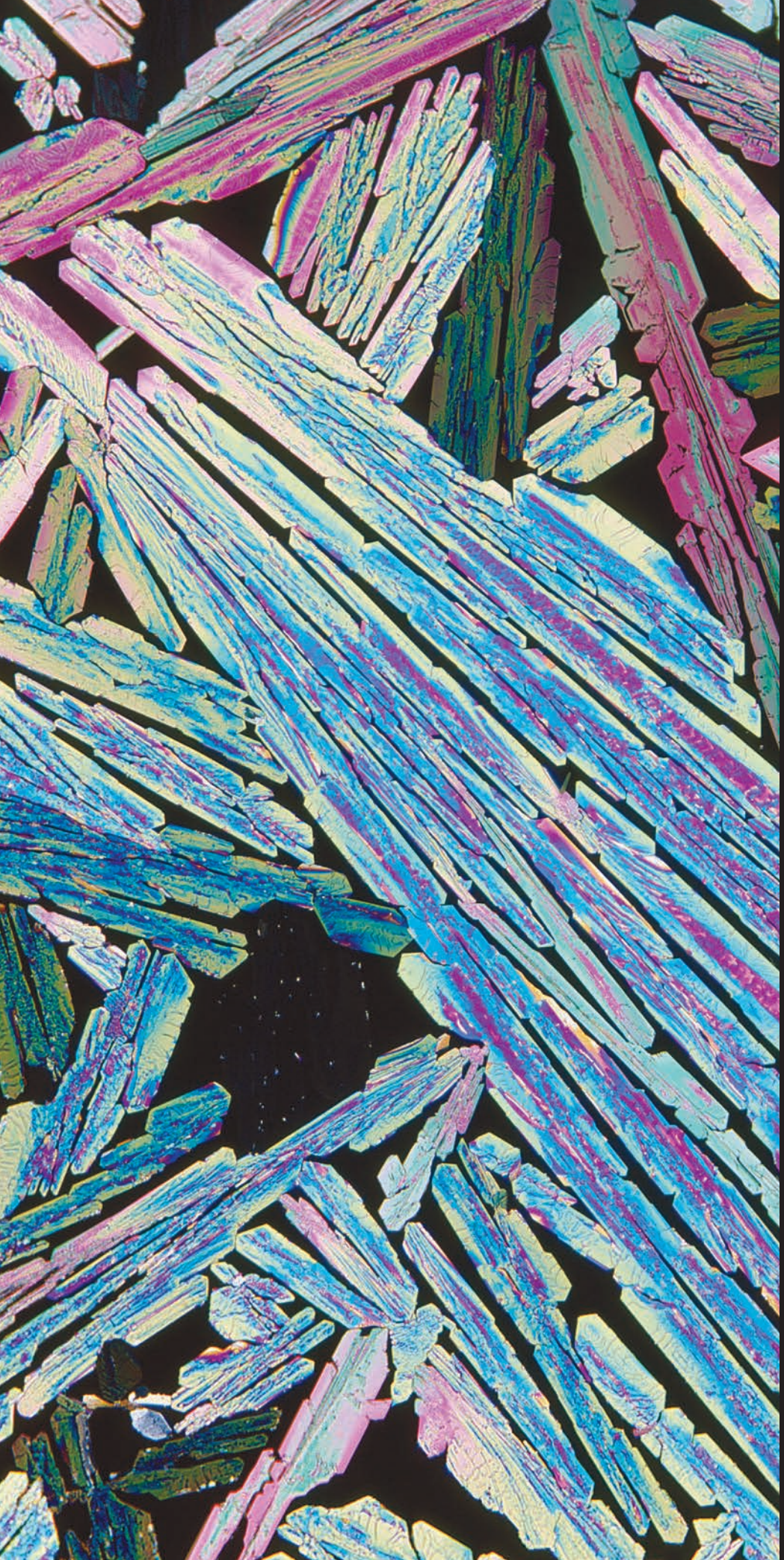
RECRUITING *E. COLI*

Harnessing bacteria to produce industrial chemicals

SALT AND PEPTIDE
Making plants resistant to salinity

PUTTING THE DIVISION IN MITOSIS
How mathematical modeling yields solutions across disciplines

STRANGE PREDICTIONS
Supercomputer suggests unusual six-quark particles



Cell Factory Research Team, RIKEN Center for Sustainable Resource Science.
Researchers have found a way to get modified bacteria to produce maleic acid from feedstock. Maleic acid is used to make drugs more stable and as an adhesion promoter for nylon and zinc, among other things.

RIKEN, Japan's flagship research institute, conducts basic and applied experimental research in a wide range of science and technology 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: www.riken.jp/en/research/rikenresearch Please visit the website for recent updates and related articles. Articles showcase RIKEN's groundbreaking results and are written for a non-specialist audience.

For further information on the research presented in this publication or to arrange an interview with a researcher, please contact:

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RIKEN RESEARCH

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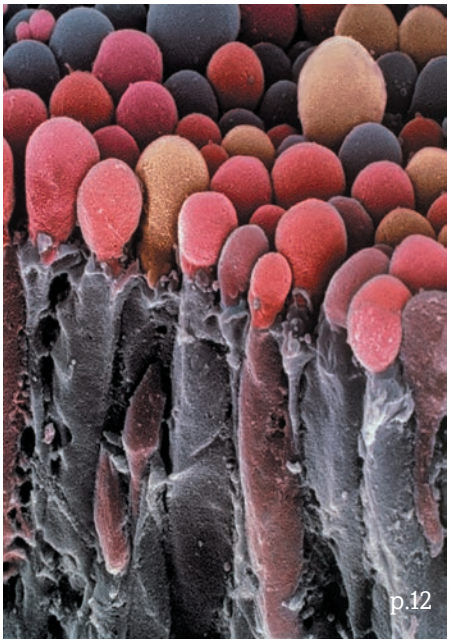

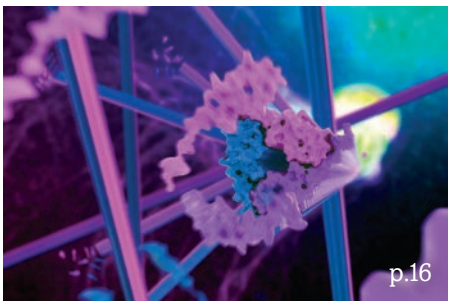

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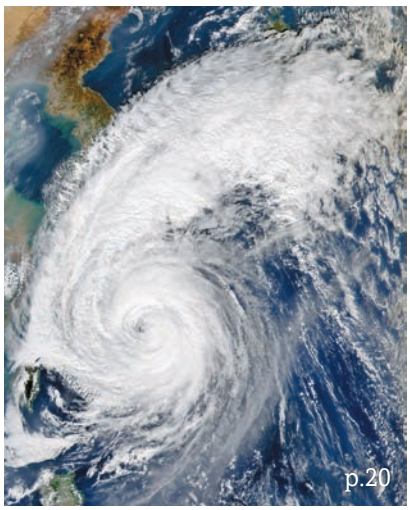
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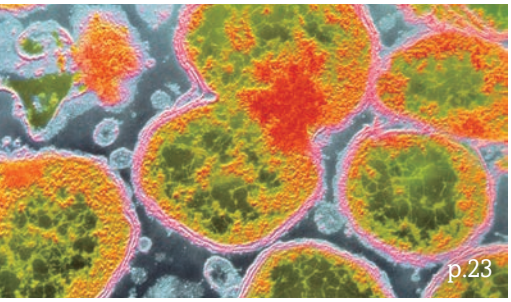
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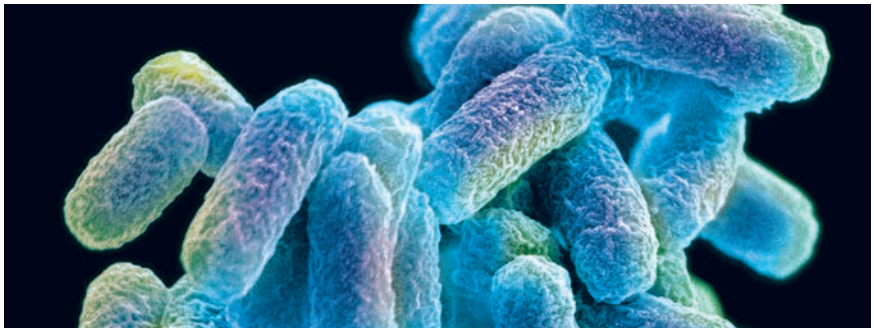
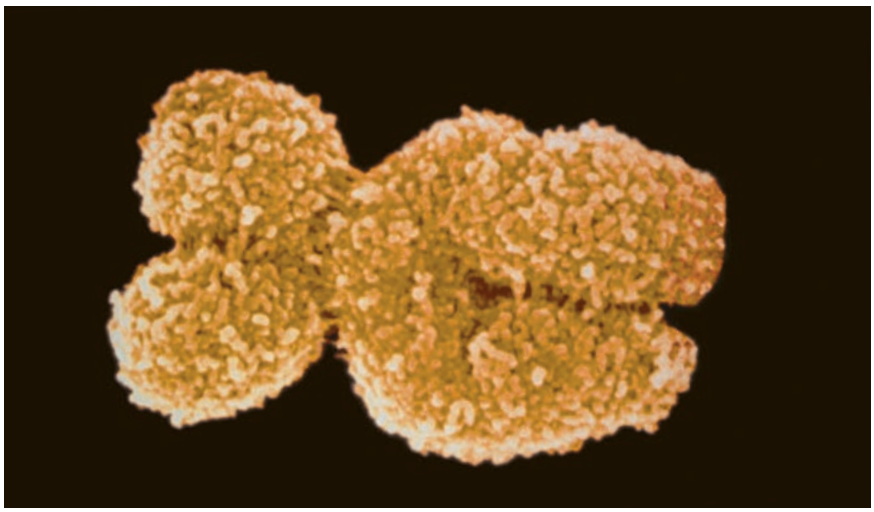


29 Perspectives COVER STORY



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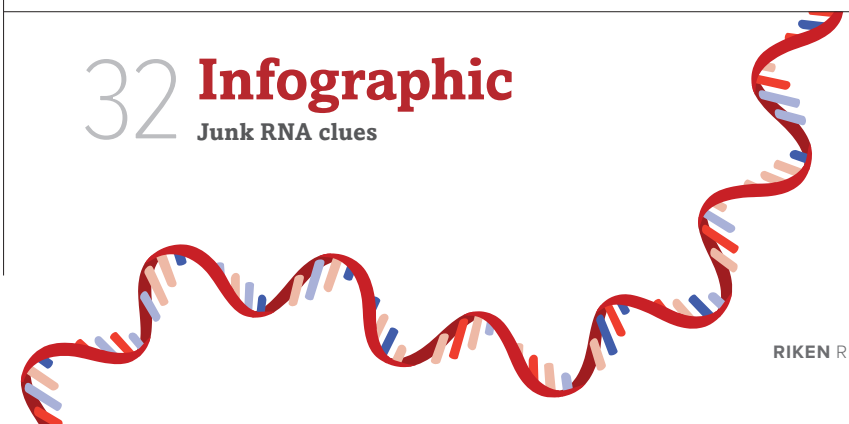

Working toward excellence in research administration

Shigeharu Kato
Executive Director, RIKEN

Though I'm sure that many readers of this quarterly are interested in its scientific content, I would like to take the opportunity to talk about RIKEN's administrative departments and how their staff support all this excellent research output.

There are some 500 full-time and 300 part-time administrative staff at RIKEN, supporting approximately 3,000 research staff. This 800-odd group work on strategic planning and resource allocation, organizational management, human resource management, procurement and accounting, relationship management with the government and other stakeholders, facility and energy management, safety measures, and many other tasks. Without them, no actual research could be carried out.

Drawing on my experience at other institutes, I think there are three attributes that distinguish RIKEN's support staff: their strong commitment to supporting scientists; close collaborative relationships with scientists; and the ability to translate scientific deliberation into language that is understandable and attractive to policymakers.

However, there are some fresh challenges ahead. Administrative staff are having to provide timely and effective administrative support as RIKEN rapidly expands and becomes a key science and technology hub. To cope with this, RIKEN's management has strengthened the administrative training program and are working toward the optimal allocation and training of existing staff, as well as the optimal recruitment of new graduates and mid-career staff.

We have also begun a program to exchange administrative knowledge with other large, important institutions. The first RIKEN-Max Planck Society Administrative Roundtable meeting was held in Munich last October, thanks to the support of the top tier of MPG's management. Participants report a quantum leap in their mindset about research administration. RIKEN will host the second meeting this fall. We are also very interested in networking in a similar manner with other institutes around the world so that we help each other to be as effective as we can be.

COVER STORY:
RIKEN researchers have genetically reprogrammed the bacterium *Escherichia coli* so that it produces the industrially important chemical maleic acid. *Page 26*

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Gut decisions

Todd Duane Taylor

Coordinator & Senior Research Scientist,
Office of the Center Director & Laboratory for Microbiome Sciences
RIKEN Center for Integrative Medical Sciences

What made you decide to become a scientist?
I started my undergraduate studies thinking I wanted to become an aeronautical engineer. But after working in the area for six months, during my second year of college, I decided it wasn't for me. In my final semester I took an introductory course in genetics and thought, "Wow, why didn't I discover this field a few years ago!" I eventually pursued a graduate degree in molecular genetics.

Describe your role
My main job is as an international coordinator, but I also research the microbiome.

What has been your most memorable experience at RIKEN?
My most memorable experience was working on the Human Genome Project with many of the world's top scientists on the most cutting-edge genomic science at the time. I played a very active role in the project and was the lead author for the paper on human chromosome 11.

Describe your research
I work in metagenomics, which is the study of genetic material recovered directly from environmental samples. It's still a relatively new field, and my lab has developed several tools for analyzing, classifying and visualizing the metagenomic sequence data that has been obtained in projects on the mouse and human gut, soil and so on.

What's most exciting about your current research?
There's still so much we don't know, not just about bacteria, but also other microbes such as viruses and small eukaryotes. Microbes account for most of life on Earth, and we're just scratching the surface in what we know about them and their effect on various environments.

Has being at RIKEN helped your research?
Immensely! I don't think there is another institute in Japan, or even the world, where I could have worked on such incredible projects to the same extent—these include the Human Genome Project, the chimpanzee genome, and many other genome and metagenome projects.

What has been the most interesting discovery in your field in the last few years?
Not very long ago the influence of microbes on a host or environment was mostly neglected because of how hard it was to study whole microbial environments, or microbiomes. Next-generation sequencing technologies now allow us to study complicated microbial mixtures in almost every type of environment. By comparing microbiomes and host genomes, scientists are beginning to clarify the interactions between them and identify the participating microbial metabolites and cellular components.

> *One personal goal is to share some of the exciting work we are doing on crowdsourced biocuration*

My research is important for sustainable development because…
We may be able to, for example, identify naturally occurring microbes or enzymes that can be used to biodegrade ocean pollutants, plastics, sewage and other types of waste. Some microbes can also be used to produce clean green fuels.

Tell us about your professional and personal goals
As an international coordinator, I want to focus on expanding our center's public relations activities using social media and other online resources, and promoting partnerships with international organizations. Across RIKEN, I aim to push for greater adoption of open-access concepts such as researcher digital identifiers, online digital repositories and publication preprint repositories. One personal goal is to share some of the exciting work we are doing on crowdsourced biocuration through channels such as TED Talks and by reaching out to high school and college students. ●

Laser links

Daniela Serien
Special Postdoctoral Researcher,
Advanced Laser Processing Research Team
RIKEN Center for Advanced Photonics

Please briefly describe your current research
As part of my research I use focused laser light to cross-link proteins. Specifically, I use computers to control the path of focused laser beams as they move through protein solutions. The lasers allow me to cross-link proteins along their path, fabricating proteinaceous microstructures using components that are smaller than a micrometer in thickness. Proteins are widely reported to retain their function after such fabrication, but in order to harness these creations we want to thoroughly understand why, as well as know how to make their function retention reliable even if they are very complex.

Why is this important?
If we understand how to cross-link naturally occurring and synthetic proteins by design, we may one day be able to use them to create biomimicking microenvironments that support organ-on-a-chip cell cultures, biochips, and drug-screening microfluidics. Proteins are also useful as environmentally friendly and biocompatible materials, as well as for pH-tunable optics, flexible optics and soft-matter actuators.

How did you become interested in your current field?
As a biophysics student, I was fascinated by the many amazing proteins we studied. Channelrhodopsins, for example, are light-gated ion channels that allow organisms such as single-cell algae to sense light. I also learned about tuning and engineering the tertiary structure of proteins and how the interplay of structure and function can have useful medical applications in areas such as optogenetics (in this field researchers use modified versions of channelrhodopsins and study neural and behavioral responses when they are stimulated with light). I then started to play with the idea of building devices from proteins. A couple of years later I had the chance to use a laser system in a laboratory developing microelectromechanical systems for biomedical applications. There, I created my first structures.

What has been the most interesting discovery in your field in the last few years?
The most interesting recent discoveries in my field have been regarding lasers and advances in the concepts around multiphoton fabrication, in which the fabrication process is confined to tiny volumes due to multiphoton processes and threshold conditions.

When did you join RIKEN?
In 2016, I joined RIKEN as a young postdoctoral researcher wanting to deepen my understanding of my research field, but also wanting to learn as much as I could about team management, fund management and research strategies.

How has being at RIKEN helped your research?
RIKEN has an amazing cooperative network of centers and teams and this encourages interdisciplinary work, which helps me better understand the wider questions around my own research. I also regularly use the fluorescence microscopy and electron scanning microscopy at RIKEN to study my microstructures and use Raman or Fourier-transform infrared spectroscopy to learn more about the nature of the cross-linking within the proteinaceous microstructures I have fabricated.

Lasers allow me to cross-link proteins along their path, fabricating proteinaceous microstructures

What excites you the most about your current research?
I really enjoy the challenge of creating something new and unknown—as well as the detail of fabrication, imaging interesting structures, and the vast possibilities for the applications of proteins. ●

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

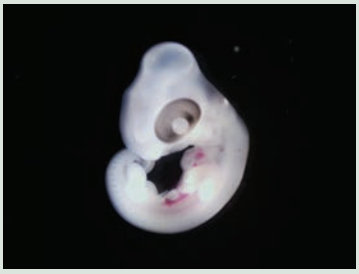
Artifical hair was grown by RIKEN's Takashi Tsuji at the Center for Biosystems Dynamics Research, opening up hopes for a cure to baldness.

Hopes for a hair regeneration treatment by 2020

More than 18 million people in Japan live with some form of baldness. Fortunately, RIKEN and Organ Technologies Inc. are working to commercially release a treatment for baldness, hopefully by 2020. The timeline of the project, led by Takashi Tsuji of the RIKEN Center for Biosystems Dynamics Research, has benefitted from changes to Japanese clinical trial laws that will speed up the process; clinical trials are planned for next year, while non-clinical safety tests are already underway. The treatment will entail taking the patient's own cells, multiplying them and transplanting them back into their own bald region. Previously, Tsuji's group at RIKEN succeeded in growing skin with functional hair follicles from iPS cells as an organ system, based on work demonstrating functional regeneration of multiple organs, including teeth, hair follicles, salivary glands and tear glands.

Why not use reptiles for genetic comparisons?

Mammals, including mice and humans, evolved from organisms resembling reptiles. But, reptiles are often ignored by the life sciences. To promote genetic comparisons using reptiles, researchers at the RIKEN Center for Biosystems Dynamics Research have decoded the whole genome of the ocelot gecko (*Paroedura picta*). This little gecko is deemed promising as a new study system for developmental biologists because of its high fecundity and the fact that it lays eggs with relatively young embryos inside, facilitating studies on early embryogenesis. Genome sequencing allowed the researchers to propose a new hypothesis on how vertebrates became more complex—they suggest vertebrates did this by using surplus gene copies. Ocelot geckos are currently supplied by RIKEN to scientists as research materials and the genome of the ocelot gecko has been released on an original online database (**http://transcriptome.cdb.riken.jp/reptiliomix/**). This research was published in *BMC Biology*: **https://doi.org/10.1186/s12915-018-0509-4**.



Not only individual ocelot geckos, but also fertilized eggs, are supplied by the Laboratory for Animal Resource Development, RIKEN BDR.

An adult of the ocelot gecko is providing a new study system for unbiased cross-species comparisons, now supported by its whole genome sequence.

SUMMER PROGRAM

#UntangleTheBrain at the Center for Brain Science summer program

This year's summer program at the Center for Brain Science (CBS) attracted young neuroscientists from countries as diverse as Singapore, Poland, China and the USA. This year, CBS also launched a 'social media takeover' with the students posting about their experiences on Facebook and Twitter using the hashtag #UntangleTheBrain. The participants worked on lab projects, attended a week of lectures by distinguished international researchers and presented posters on their research. Several current CBS group leaders were once participants of this summer program, which has been running for 19 years.

http://cbs.riken.jp/en/summer/

Young neuroscientists enjoy Japan while attending a Center for Brain Science program.

RIKEN researchers have looked into cleaning up palladium (Pd) (pictured). ^{107}Pd has a half-life of 6.5 million years and researchers have extracted it from radioactive waste, together with ^{105}Pd, using a method proposed by RIKEN that has won an award. Both isotopes were irradiated with neutrons, and converted to stable ^{106}Pd and ^{104}Pd.

Cleaning up radioactive waste

A research group, which includes RIKEN's Hideaki Otsu, has been awarded the 21st Century Invention Award for proposing a method for treating radioactive waste. The method uses a combination of laser and accelerator technology to extract, recycle and reduce long-lived fission products that are contained in high-level radioactive waste from nuclear power plants. The key to the invention is the selective extraction of long-lived nuclides with an odd atomic number using a polarized laser beam that exploits the fact that these nuclides have a nuclear spin. Then, to selectively convert the odd nuclides to stable ones, the researchers proposed to irradiate them with secondary neutrons generated by an accelerator. This concept was proposed jointly by RIKEN, Toshiba Energy Systems & Solutions Corp., the Japan Atomic Energy Research Agency and the Japan Science and Technology Agency (JST), as part of a project led by Reiko Fujita of JST under the umbrealla of the Impulsing Paradigm Change through Disruptive Technologies Program (ImPACT). The scientists hope to reduce radioactive waste by developing large-scale accelerators for processing and recycling rare metals.

19 receive new RIKEN awards

RIKEN has two new awards, the RIKEN EIHO Award and the RIKEN BAIHO Award. The EIHO awards are given to researchers whose achievements could have major impacts on society, while the BAIHO awards are bestowed on scientists who have done research that led to unique results. These awards, 19 of which were presented at an award ceremony on 5 June, are in honor of three famous RIKEN figures—Jokichi Takamine, who first proposed RIKEN be estabished; Eiichi Shibusawa, the force behind its early establishment; and Umetaro Suzuki, a chief scientist who did pioneering work on vitamins.

Representatives of the groups that won EIHO and BAIHO awards surround President Hiroshi Matsumoto.

BAIHO AWARDS

- **Hiroshi Imada (CPR)**
  Development and Application of a Single-Molecule Absorption/Emission Spectroscopy Based on a Novel Principle
- **Kenjiro Fukuda (CEMS)**
  Washable Ultrathin Organic Solar Cells
- **Kazuki Yoshizoe (AIP)**
  Implementation, Management, and Enhancement of an AI Purpose Computer System, RAIDEN
- **Michiel Jan Laurens de Hoon (IMS)**
  Creation of a Comprehensive Expression Atlas of miRNAs and Their Promoters in the FANTOM5 Project
- **Haru-hiko Ehara (BDR)**
  Structure of the Complete Elongation Complex of RNA Polymerase II with Basal Factors
- **Takashi Niwa (BDR)**
  Development of Molecular Renovation Strategy for Expeditious Preparation of Molecular Probes
- **Mitsuhiro Iwaki (BDR)**
  Development of World's Smallest Programmable Nanospring
- **Yu-Chiun Wang (BDR)**
  Discovery of a New Mechanism Driving Epithelial Morphogenesis
- **Tomoko Nishiyama (CBS)**
  Management of BSI 20th Anniversary Events
- **Kiminori Toyooka (CSRS)**
  Development of and Collaboration with Electron Microscopy Techniques
- **Daisuke Hashizume (CEMS)**
  Advanced Research Support Based on Structural Science
- **Daigo Miyajima (CEMS)**
  Development of Conceptually New Supramolecular Polymerization
- **Takemasa Miyoshi (R-CCS)**
  Research and Development for Research to Fuse Data Analysis with Simulations

EIHO AWARDS

- **Hideki Hirayama (CPR)**
  Achievement of Highest Record Efficiency Deep-UV LED
- **Shin-ichiro Fujii (IMS)**
  Development of New Cancer Vaccine and 'artificial Adjuvant Vector Cells (aAVC)' and Initiation of Phase I Clinical Trial
- **Naoshi Koide, Mitsuhiro Nishida, Noriko Sakai, Yumiko Shibata, and Motoki Terada (BDR)**
  Contribution to Cell Production, Quality Control, etc. in First iPSC-derived RPE Cell Transplantation in AMD Patient
- **Toshihiko Hosoya, Hisato Maruoka, Nao Nakagawa, and Taisuke Yoneda (CBS)**
  Discovery of Microcolumns as a Novel Organizational Module in the Neocortex
- **Xiuzhen Yu (CEMS)**
  Real Space Observation of Skyrmions and Their Dynamics
- **Yoshie Otake (RAP)**
  Research and Development of Novel Neutron Measurement Methods with RIKEN Accelerator-driven Compact Neutron Source, RANS

WHO DO THESE AWARDS HONOR?

- **Jokichi Takamine**
  The chemist was the first to isolate and purify adrenaline and patent a microbial enzyme.
- **Eiichi Shibusawa**
  The Japanese industrialist helped establish RIKEN.
- **Umetaro Suzuki**
  The agricultural chemist was a pioneer in vitamin research and the first to describe thiamine.

K computer tops Graph500 for seventh time

In June, for the seventh consecutive time, Japan's K computer was top ranked in the Graph500, a benchmark that assesses how well supercomputers handle data-intensive loads. Graph500 benchmarks computing that requires processing complex problems using big data, which is useful in areas such as cybersecurity, medical informatics, data enrichment, social networks, symbolic networks and modeling neural circuits in the brain. This ranking was the result of the collaborative efforts of RIKEN, Kyushu University, Tokyo Institute of Technology, the Barcelona Supercomputing Center, Fujitsu and Fixstars Corporation. The measurement was made by using 82,944 of the K computer's 88,128 computer nodes to solve a search of an extremely large graph made up of 1 trillion nodes and 16 trillion edges within 0.45 seconds. Two research projects funded by the Japan Science and Technology Agency CREST programs were utilized in the measurement: one looking into extremely large graphs on post peta-scale supercomputers and the other investigating big data and yottabyte processing. The group has published the program they used in this measurement as open-source code on the GitHub repository.

http://www.riken.jp/en/pr/topics/2018/20180629_1/

Ready to test: CPU prototype for the post-K supercomputer

The prototype CPU for the post-K computer—a supercomputer system being jointly developed by the RIKEN Center for Computational Science and Fujitsu—has begun being tested by Fujitsu. The new system is based on the widely used Arm® instruction set architecture, but has an expanded instruction set intended for supercomputer applications. The post-K computer is expected to begin full operation in 2021 and will be used for applications such as drug discovery, disaster prediction, climate prediction, producing energy-saving devices and artificial intelligence. The developers intend the new machine to be a world leader in terms of energy consumption, computational capability, usability and groundbreaking results.

http://www.riken.jp/en/pr/topics/2018/20180621_1/

NEUROSCIENCE

Extinguishing fear in the mind

Dopamine release in a specific brain region dissociates a stimulus from a sensation of fear

New ways for treating anxiety disorders could come as a result of RIKEN researchers discovering a brain circuit involved in unlearning fear[1].

People and animals develop fearful emotional responses, to sensory stimuli and situations that are associated with danger. Normally, fearful reactions will lessen over time as the sensory stimulus is dissociated from the fearful experience. This is called fear extinction. When this does not happen, it can lead to anxiety disorders, such as post-traumatic stress and phobias.

To understand how the brain regulates both normal and pathological situations, researchers at the RIKEN Center for Brain Science performed experiments in rats as they extinguished fearful associations. They reasoned that for fear to be extinguished, an animal first needs to recognize when an expected fearful event does not happen. As dopamine neurons in some brain regions are known to be active when expected unpleasant events do not happen, the team looked at dopamine neurons in a part of the brain called the ventral tegmental area (VTA).

After conditioning rats to associate a specific sound with a mild foot shock, the team began the extinction process. As expected, when the sound was played many times without a foot shock, rats stopped behaving as if they were afraid of the sound.

However, rats could not unlearn the fear response when VTA dopamine neurons were silenced just after playing the sound—exactly when the rats expected their feet to be shocked, but the shock did not occur.This showed that without VTA dopamine activity at that time, the mental link between the sound and the shock could not be removed.

This kitten will need dopamine release from the ventral tegmental area to get over this traumatic experience.

"Pharmacologically targeting the dopamine system may be an effective therapy"

But what does VTA dopamine activity do? This was difficult to answer because not all VTA dopamine neurons are connected to the same brain regions; some are connected to brain regions known for their role in storing extinction memories, while others are connected to areas related to reward learning.

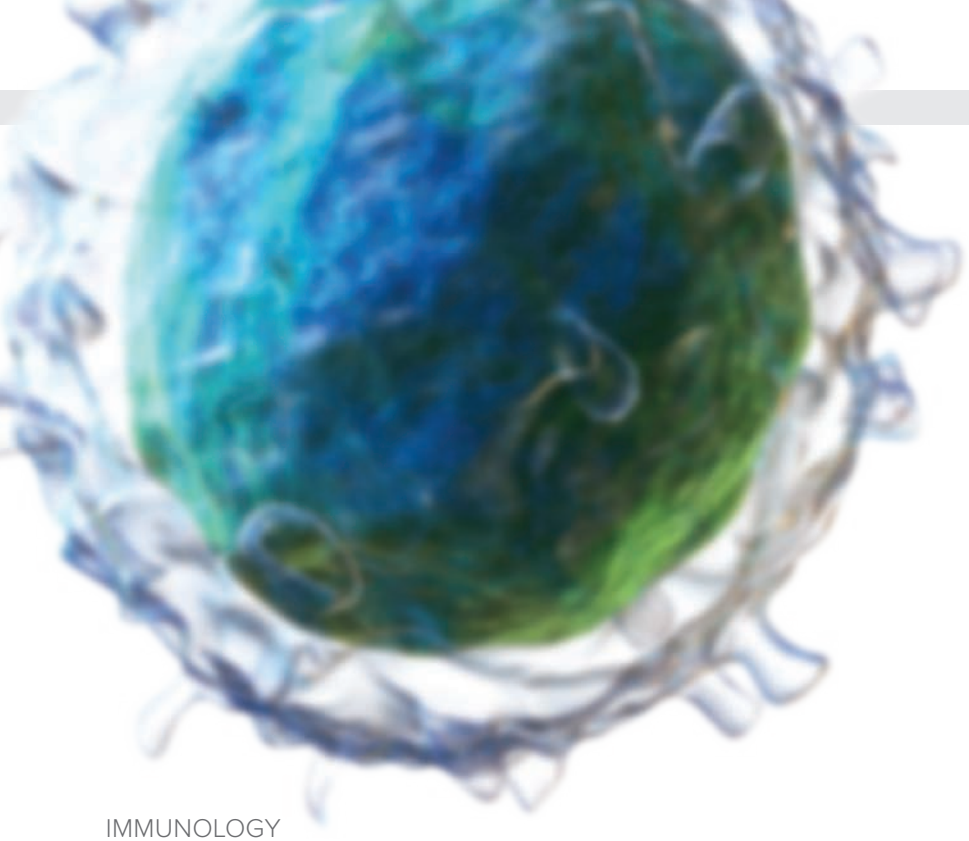
When the team blocked each of these pathways separately by using a laser beam to turn off specific neurons, they found that they both affected fear extinction, but in opposite ways: blocking the reward pathway prevented fear extinction, while blocking the other pathway enhanced fear extinction.

The team is now working on ways to target these neurons with drugs or molecular manipulations approaches rather than laser light.

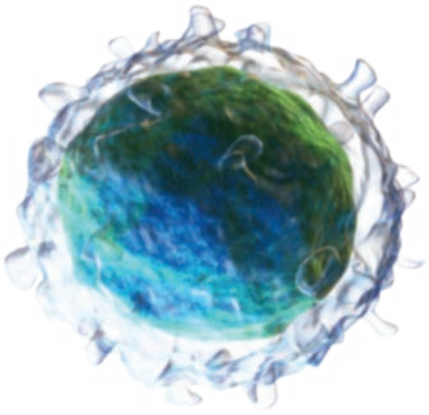
"Pharmacologically targeting the dopamine system may be an effective therapy for psychiatric conditions such as anxiety disorders when combined with clinically proven behavioral treatments such as exposure therapy," says Joshua Johansen. "To provide effective, mechanism-based treatments for these conditions, future preclinical work will need to use molecular strategies that can separately target these distinct dopamine cell populations." ●

Reference

1. Luo, R., Uematsu, A., Weitemier, A., Aquili, L., Koivumaa, J., McHugh, T. J. & Johansen, J. P. A dopaminergic switch for fear to safety transitions. *Nature Communications* **9,** 2483 (2018).



Artist's representation of plasma cells. RIKEN researchers have shed light on how their development is initiated.



IMMUNOLOGY

A fork in the road for baby immune cells

The origin of immune cells that attack viruses and other pathogens has been uncovered

Efforts to produce better vaccines will be assisted by RIKEN researchers determining the mechanism that determines which of two paths the precursors of a type of white blood cell will take[1].

Plasma cells (see image) move through the body releasing antibodies and are an important component of the body's defense against viruses and other invaders. Boosting the number of plasma cells is a major goal of vaccination.

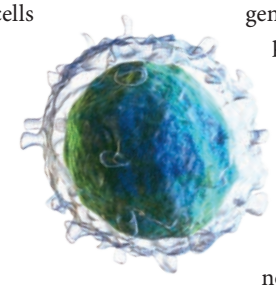
Plasma cells mature in germinal centers—groups of cells in lymph nodes and the spleen. Some remain there and undergo reprogramming to become more specific attackers of an infection, whereas others enter the body's fluids as plasma cells. Scientists do not fully understand what determines which of these two paths a precursor cell will take.

Now, researchers from RIKEN and Osaka University have discovered an important mechanism that governs how B cells are chosen to become plasma cells.

Plasma cells express transcription factor IRF4 but not transcription factor Bcl6. To assess whether the fate of the cells is determined while they are in the germinal centers, the team examined the expression of these two factors in B cells in germinal centers. They found that Bcl6 was expressed at low levels and IRF4 at high levels in a subset of cells and that these cells also express a cellular marker called CD69.

"[This] is important for creating more powerful vaccinations"

To determine whether these cells were precursors to plasma cells, the researchers compared them with germinal center-derived plasma cells. They found that the gene sequences of their B-cell receptors, which govern the antibodies they produce, were very similar, indicating that they were from the same cell group. These cells shared the same developmental features with germinal-center-derived plasma cells, suggesting that they were precursors.



The team then examined the relationship between these cells and T follicular helper cells, which are important for the maturation of B cells. Since T follicular helper cells stimulate B cells with a surface protein called CD40, the researchers created B cells that express CD40 at low levels, and found that the number of plasma cells dropped dramatically. Further experiments showed that the strength of the interaction between the plasma-cell precursors and the T follicular helper cells determines whether the B-cell precursors become plasma cells or remain in the germinal center to undergo further mutation.

"Understanding how the body generates high-affinity plasma cells, which are important in fighting viral infections such as influenza, is important for creating more powerful vaccinations," notes Tomohiro Kurosaki of the RIKEN Center for Integrative Medical Sciences. "Our work has given us important insights into how these cells are produced." ●

Reference

1. Ise, W., Fujii, K., Shiroguchi, K., Ito, A., Kometani, K., Takeda, K., Kawakami, E., Yamashita, K., Suzuki, K., Okada, T. *et al.* T follicular helper cell-germinal center B cell interaction strength regulates entry into plasma cell or recycling germinal center cell fate. *Immunity* **48,** 702–715 (2018).

CIRCADIAN RHYTHMS

Fine-tuning the body's rhythm

A peripheral part of the circadian system has been shown to influence the body clocks of mice

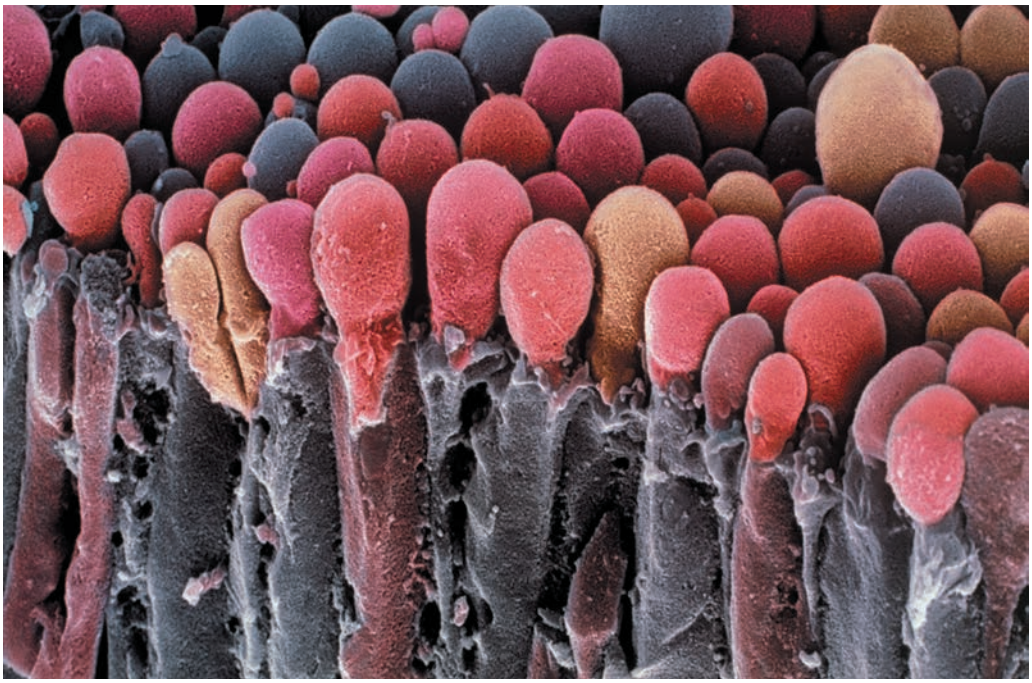
A hitherto underrated part of the circadian system affects the main driver of the circadian clock, a study led by RIKEN researchers has shown[1]. This discovery has important implications for our understanding of how the circadian clock is organized.

The mammalian body clock controls biological function in cycles of approximately 24 hours. Generated within the body, this circadian rhythm is modulated by external cues such as sunlight and food. The suprachiasmatic nucleus (SCN)—a tiny region of the brain in the hypothalamus—has long been regarded as the master clock of circadian rhythms.

In addition to the SCN, various other tissues and organs throughout the body can maintain autonomous circadian rhythmicity. These peripheral clocks are coupled to SCN rhythms, but until now it was unclear whether they could influence the SCN clock.

"Much to our surprise, and largely by chance, we found more robust rhythms in the choroid plexus"

One of these peripheral clocks is the choroid plexus, an organ that lines the brain ventricles and produces cerebrospinal fluid, a nutritive fluid that protects the brain and removes waste materials.



Choroid plexus cells that secrete cerebrospinal fluid. RIKEN scientists have shown that the choroid plexus plays an important role in regulating the circadian clock.

When Toru Takumi of the RIKEN Center for Brain Science and colleagues monitored the circadian rhythm in small pieces of brain tissue from mice, they were surprised to discover that the robust and persistent oscillation in the expression of clock genes in the choroid plexus exceeded that of the master SCN clock.

"We expected the SCN to be the strongest rhythm center," Takumi recalls. "But much to our surprise, and largely by chance, we found more robust rhythms in the choroid plexus."

Using tissue co-culture experiments and mice in which the clock gene *Bmal1* had been deleted in the choroid plexus, the team demonstrated that the choroid plexus could adjust the SCN clock to fine-tune circadian rhythms.

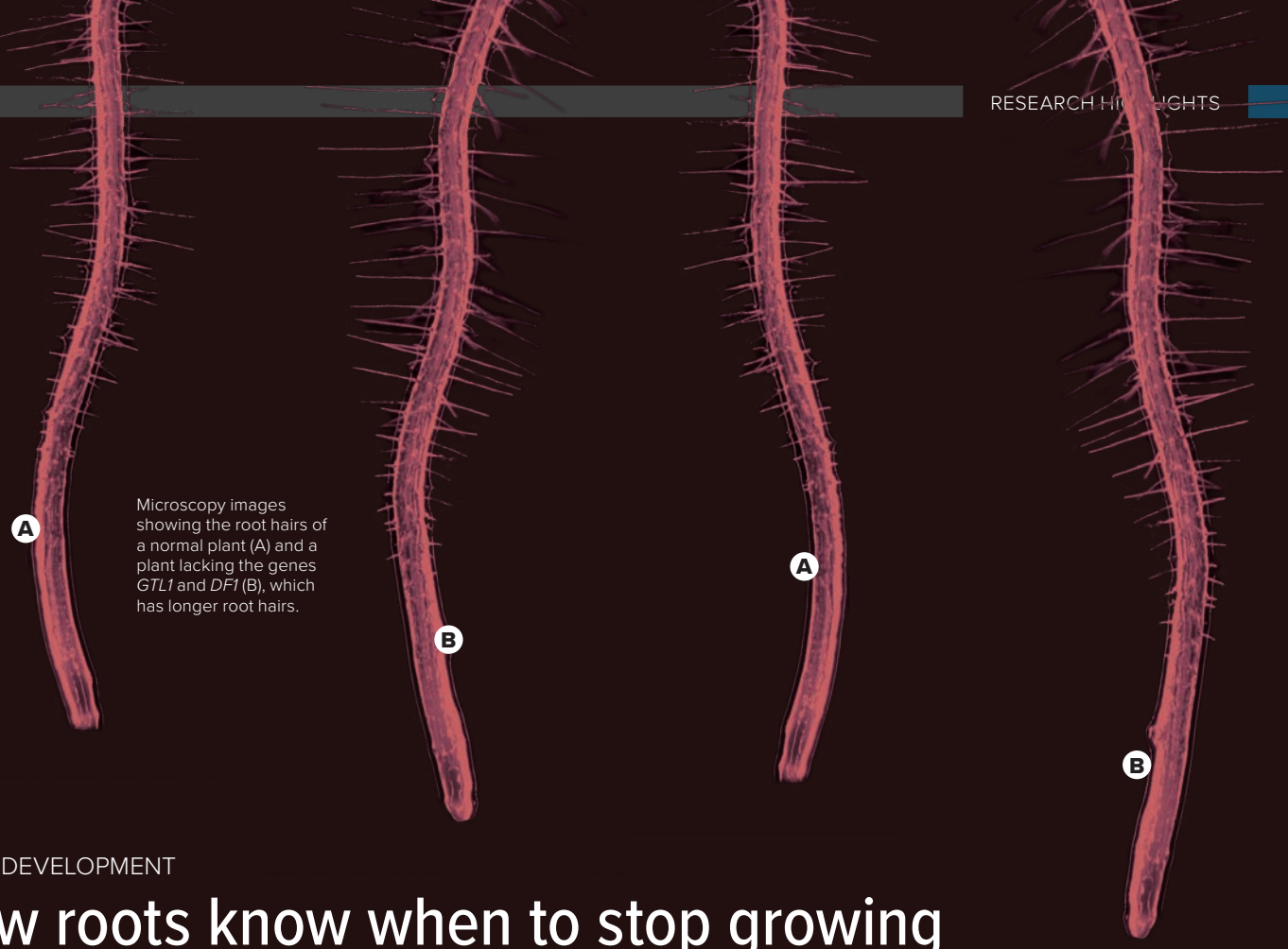
The researchers suggest that the choroid plexus may diffuse its clock signal to the SCN through ventricular circulation of the cerebrospinal fluid. The clearance of waste products in the brain such as beta-amyloid through the cerebrospinal fluid via the glymphatic clearance pathway has been shown to function mainly during sleep, raising the intriguing possibility that the choroid plexus clock regulates the daily variations in glymphatic clearance.

The results could have implications for sleep. "The interstitial space in the brain increases in volume during sleep, and faster clearance of waste products such as beta-amyloid is also observed during sleep," says Takumi. "Thus, the choroid plexus clock may be important for sleep too."

The study highlights the need both to further understand the physiological significance of the choroid plexus clock's robust rhythm and to re-evaluate the established hierarchical view of circadian clock organization. ●

Reference

1. Myung, J., Schmal, C., Hong, S., Tsukizawa, Y., Rose, P., Zhang, Y., Holtzman, M. J., De Schutter, E., Herzel, H., Bordyugov, G. *et al.* The choroid plexus is an important circadian clock component. *Nature Communications* **9,** 1062 (2018).



Microscopy images showing the root hairs of a normal plant (A) and a plant lacking the genes *GTL1* and *DF1* (B), which has longer root hairs.

PLANT DEVELOPMENT

How roots know when to stop growing

A trio of genes ensures that cells in plant roots grow to the optimal size

The interplay between three genes determines the size of key cells in plant roots, RIKEN scientists have discovered[1]. This finding may help researchers develop plants that can cope with droughts and nutrient-poor soils, and perhaps even boost crop yields.

How plants determine the final size of growing cells is an important unanswered question in plant development. Keiko Sugimoto's team at the RIKEN Center for Sustainable Resource Science is trying to find clues to this question by looking at the fine hairs on roots, since they consistently grow to the same size under similar environmental conditions. These hairs are crucial for the uptake of water and nutrients by the roots.

Scientists know that the gene *RSL4* promotes root hair growth, but, until now, they did not know the genes responsible for putting the brakes on hair growth.

Sugimoto's team suspected that *GTL1* might play a role, since it has been found to limit the growth of plant leaf hairs known as trichomes. However, since plants lacking *GTL1* have normal root hairs, other factors must be involved too.

These hairs are crucial for the uptake of water and nutrients by the roots

The team thought the missing factor might be *DF1*, the most closely related gene to *GTL1*. "Both genes are highly expressed in roots, and the single mutants have a phenotype in trichomes but not in roots," explains Michitaro Shibata, the study's lead author.

When the researchers knocked out both genes together, the plants developed much longer root hairs (see image). These root hairs did not grow faster than normal, but rather they continued growing when they should have stopped.

The team discovered that the gene *RSL4* was more strongly expressed in the double mutant. This implies that GTL1 and DF1 normally repress *RSL4* to stop root growth.

The researchers then compared the lists of genes regulated by RSL4, GTL1 and DF1 and found that they overlapped, with GTL1 and DF1 repressing a subset of RSL4 targets. RSL4 and GTL1 also regulate each other in a feedback loop, which stabilizes their expression to ensure consistent root hair size.

"The pathways overlapped more than I expected—that was a big surprise," says Sugimoto. "Of course, that also makes the regulatory network robust, so it makes sense looking back."

With these findings, the researchers have assembled the core network that fine-tunes the size of root hairs. They now aim to discover how environmental factors affect these genes and whether they can be used to breed stress-tolerant plants.

"Now that we have the tools to grow plants without root hairs, with lots of hairs, or with longer hairs, we can go and ask these kinds of questions," comments Sugimoto.

Reference

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PARTICLE PHYSICS

Most strange particle prediction

Scientists have predicted the existence of a new six-quark particle and have suggested ways to search for it

By performing complex simulations on the K computer, RIKEN researchers have predicted the existence of a new type of dibaryon—a particle that contains six quarks instead of the usual three[1]. Studying how these elements form could help scientists understand the interactions among elementary particles in extreme environments such as the interiors of neutron stars and the early Universe.

Particles known as baryons—principally protons and neutrons—consist of three quarks bound tightly together. A dibaryon is essentially a system with two baryons. There is only one known dibaryon in nature—deuteron, a deuterium (or heavy-hydrogen) nucleus that contains a proton and a neutron that are very lightly bound. Scientists have long wondered whether there could be other types of dibaryons but have not been able to find any so far.

"This work could give us hints for understanding the interaction among strange baryons"

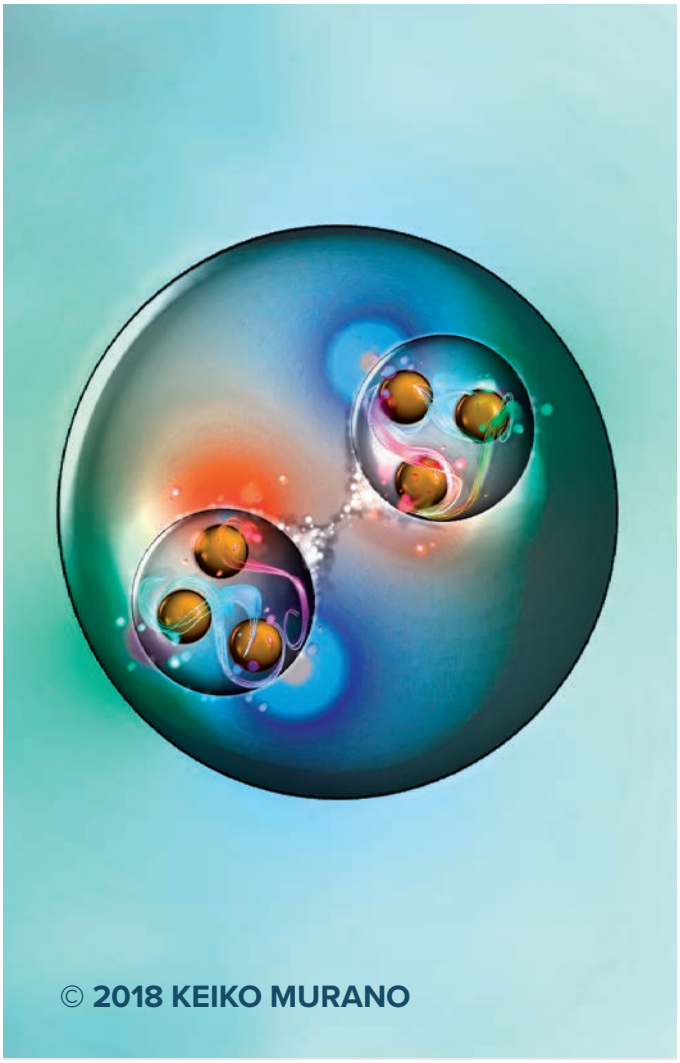
The researchers have now used powerful theoretical and computational tools to predict the existence of a 'most strange' dibaryon, made up of two 'Omega baryons' that contain three strange quarks each. They named it di-Omega (see image).

The prediction was made possible by better methods for performing quantum calculations, improved simulation algorithms and more-powerful supercomputers.

A new theoretical framework allowed researchers to extract the force acting between baryons from the large volume of numerical data obtained using the K computer. A new computational method enabled much more efficient calculation of a system with many quarks. Finally, the advent of powerful supercomputers gave the researchers the computing power they needed to do the calculations.

"We were very lucky to have been able to use the K computer to perform the calculations. It allowed fast calculations with a huge number of variables," says Shinya Gongyo from the RIKEN Nishina Center for Accelerator-Based Science. "Still, it took almost three years for us to reach our conclusion on di-Omega."

The team suggested a way to look for these particles experimentally. "We believe that these special particles could be generated by the experiments using heavy-ion collisions that are planned in Europe and in Japan, and we look forward to working with colleagues there to experimentally discover the first dibaryon system outside of deuteron," says Tetsuo Hatsuda of the RIKEN Interdisciplinary Theoretical and Mathematical Sciences Program. "This work could give us hints for understanding the interaction among strange baryons (called hyperons) and to understand how, under extreme conditions like those found in neutron stars, normal matter can transition to what is called hyperonic matter—made up of protons, neutrons and hyperons, and eventually to quark matter composed of up, down and strange quarks." ●



By performing calculations on the K computer, RIKEN researchers have predicted the existence of a new dibaryon—a particle that contains six quarks (gold spheres) instead of the usual three.

Reference

1. Gongyo, S., Sasaki, K., Aoki, S., Doi, T., Hatsuda, T., Ikeda, Y., Inoue, T., Iritani, T., Ishii, N., Miyamoto, T. *et al.* Most strange dibaryon from lattice QCD. *Physical Review Letters* **120,** 212001 (2018).

IMMUNOLOGY

The making of a B cell

Antibody-producing B cells pass through three gene expression networks on their way from stem cell to B cell

Future research into leukemia will benefit from a RIKEN analysis of thousands of genes, shedding light onto how a stem cell grows up to be a B cell in the immune system[1].

B cells are a type of white blood cell, and they help the body fight infections by producing antibodies. They start off life as hematopoietic stem cells (HSCs)—stem cells that go on to become blood cells.

Tomokatsu Ikawa of the RIKEN Center for Integrative Medical Sciences has long been interested in understanding the differentiation process that commits a stem cell to the fate of becoming a B cell. "Key transcription factors have been identified, but the underlying mechanisms remain to be revealed," he notes.

To discover how the expression of genes changes as an HSC becomes a B cell, Ikawa's team used a cell system they had previously developed: the induced leukocyte system. It consists of multipotent progenitor cells—stepping stones between stem cells and mature cells—that can be efficiently differentiated into B cells by triggering the expression of the protein E2A. This is a transcription factor essential for priming HSCs toward the B cell lineage. This cell system allowed Ikawa's team to synchronize the differentiation process and examine the cells' transcriptome at various time points.

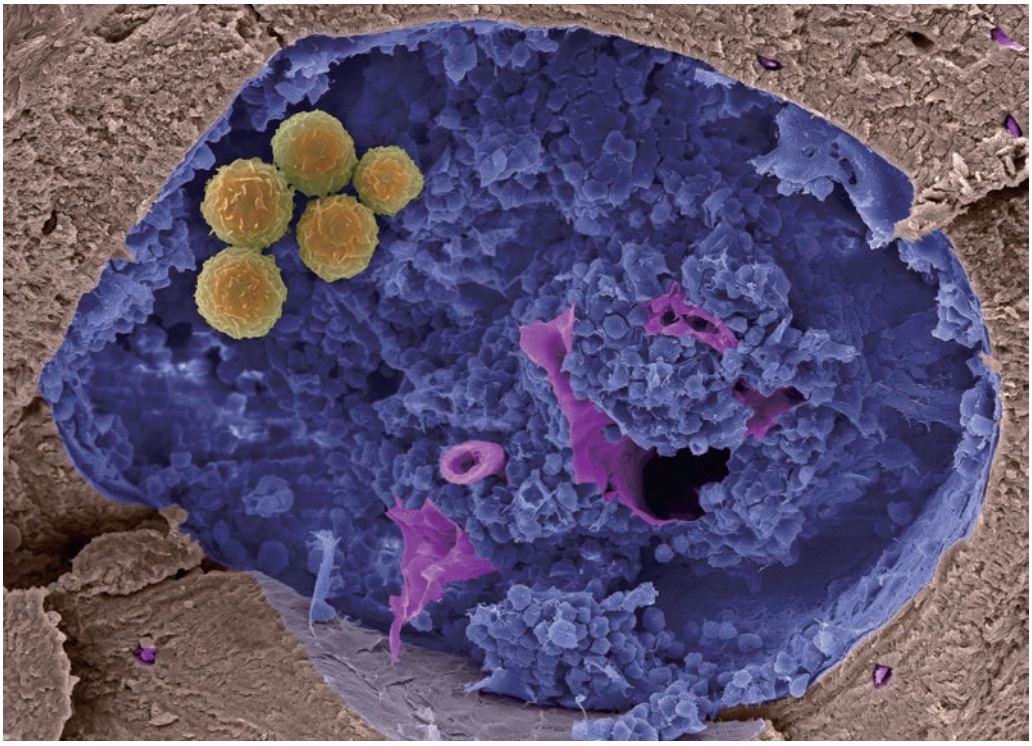
When the team analyzed the expression of thousands of genes, they saw distinct waves of expression as cells committed to the B cell lineage. They combined data on the transcription factors that were active in each wave and the genes they regulated with epigenetic data of histone marks—modifications to histone proteins made after translation of DNA. This allowed the researchers to construct three distinct networks: the early network of multipotent progenitor cells, a transitional state and the network of committed B cells.

While all these data were originally obtained from cells differentiated in a culture dish, the team saw the same expression patterns in B cell progenitors isolated directly from the bone marrow.

"We were surprised to find that the B cell lineage commitment process could be separated into three main stages based on messenger RNA expression profiles," recalls Ikawa.

Ikawa now wants to explore the metabolic pathways and non-coding RNA that underlie the development and function of immune cells; he is particularly interested in the role of long non-coding RNAs in the regulatory process.

Ikawa and his team are focusing on normal B cell development, but he predicts that this approach can also be used to study the mechanism by which B cell leukemia develops. "The more we understand this process, the more likely efficient points of intervention will be found," Ikawa comments.



Colored scanning electron micrograph of bone marrow cavity containing hematopoietic human stem cells (yellow spheres; the stems cells are shown at a higher magnification than the bone marrow cavity).

Reference

1. Miyai, T., Takano, J., Endo, T. A., Kawakami, E., Agata, Y., Motomura, Y., Kubo, M., Kashima, Y., Suzuki, Y., Kawamoto, H. *et al.* Three-step transcriptional priming that drives the commitment of multipotent progenitors toward B cells. *Genes & Development* **32,** 112–126 (2018).

ALZHEIMER'S DISEASE

Mutation protects against Alzheimer's in mice

The build-up of harmful plaques generated by Alzheimer's disease is lower in mice with a specific genetic mutation

A genetic mutation that can protect against Alzheimer's disease in mice has been discovered by an all-RIKEN team[1]. They found that the mutation can reduce the accumulation of fibrils made of a protein known as amyloid-beta peptide that characterizes the disease. This finding is expected to help researchers gain a deeper understanding of the mechanisms of Alzheimer's disease.

Alzheimer's disease afflicts tens of millions of people around the world, but despite decades of research, an effective treatment has yet to be developed. The progressive mental and behavioral changes that occur in people with Alzheimer's disease are accompanied by physical changes within the brain. In particular, one of the hallmarks of the disease is the progressive accumulation of plaques between neurons. These plaques are made from amyloid beta (see image), which is the part leftover from the amyloid precursor protein (APP) after enzymes cut it up.

The study demonstrates the usefulness of gene-editing targeted screening for the disease

While several genetic mutations have been found to increase the probability of getting Alzheimer's disease, so far only one mutation that offers protection against the disease has been identified in people. Previous research had indicated that an *App* gene with a single nucleotide change might reduce the build-up of amyloid beta.

To find a novel protective mutation, the team led by Takaomi Saido of the RIKEN Center for Brain Science created mice with a mutated *App*, the gene that codes for amyloid precursor protein (APP). They did this by using CRISPR/Cas9 technology—a powerful new tool for editing genes—to replace the normal gene with the mutated version. The researchers observed that the mouse model of the disease with this mutation exhibited less accumulation of amyloid beta than mice without the mutation.

This replacement process is a little messier than it sounds, and, as expected, sample mice varied in how much of the desired deletion was actually deleted. This was useful because the team was able to see that the most drastic reductions in amyloid-beta plaques occurred in the mice with the most compete deletions. Further analysis revealed that expression levels of the APP correlated with those of amyloid beta, which was also expected.

This process for finding beneficial mutations is powerful, since random screening of human populations is not easy if the frequency of the mutation is low, and it only works with naturally occurring mutations. Additionally, the study demonstrates the usefulness of gene-editing targeted screening for the disease. ●

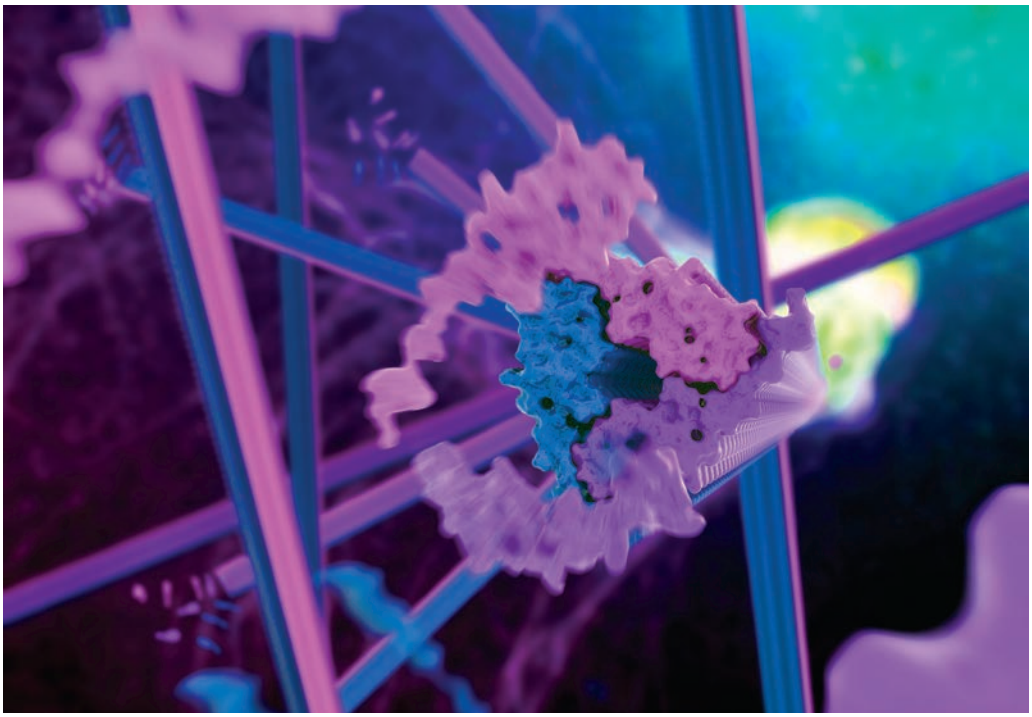


Illustration of human brain-derived beta-amyloid fibrils. These insoluble fibers resist degradation and so build up in brain tissue, forming the amyloid plaques found in the brains of Alzheimer's disease patients.

Reference

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Artist's impression of the X-ray Multi-Mirror Mission telescope, which collected x-ray data that reveals evidence of charge exchange.

ESA/XMM-Newton, CC BY-SA 3.0 IGO; NASA/JPL/MPS/DLR/IDA

STAR FORMATION

Electron theft in galaxy clusters revealed

X-ray data from galaxy clusters points to electron-stripping process at hot and cold galactic interface

Scientists' understanding of how stars form may be skewed by incorrect data, research by a RIKEN scientist and colleagues suggests. Their analysis of x-ray data from 21 galaxy clusters suggests the models may have overestimated some components by as much as 20 per cent.

Astronomers believe that when atoms in cold gas clouds smash into hot, ionized particles at the core of galaxy clusters, single electrons are stripped from the colder atoms and bind to the hot ions—a process known as charge exchange. The captured electrons initially have a high energy, which they rapidly lose by radiating characteristic x-rays. But these x-rays are hard to detect as they are usually swamped by much stronger heat signals from the cluster.

Hints of charge exchange appeared in 2014, when astronomers observed a bizarre x-ray signal emanating from the Perseus cluster. Some researchers proposed that this was caused by a new particle, but Liyi Gu at the RIKEN Nishina Center for Accelerator-Based Science and colleagues created a model that showed that it could be produced by charge exchange involving electrons captured by hot sulfur. However, independent analyses failed to confirm the presence of the signal.

Now, Gu's team has sifted through x-ray data from 21 galaxy clusters collected by the European Space Agency's X-ray Multi-Mirror Mission telescope for more convincing evidence (see image). They calculated that charge exchange involving oxygen ions should produce an x-ray signature at about a quarter of the energy of that for sulfur ions. After filtering out signals generated by heat, the researchers found this signature. Furthermore, its intensity matched that predicted by their model.

The analysis has implications for understanding how stars form and create elements such as oxygen. If Gu's team is correct, then astronomers may have overestimated the amount of oxygen in clusters by up to 20 per cent through not fully accounting for charge exchange, skewing their models of star formation.

The team's findings may not be corroborated until the launch of higher resolution x-ray telescopes, such as JAXA and NASA's X-ray Astronomy Recovery Mission (XARM), which is scheduled for 2021. XARM will enable astronomers to monitor charge exchange and to investigate why giant clouds of cold gas exist within otherwise hot clusters.

"The delicate balance between cooling and heating is one of the biggest mysteries of galaxy clusters," says Gu. His model could indicate the composition of the hot and cold regions and their collision speed. "It will be the first time we can remotely study an interface without seeing it in an image. It will for sure help to solve the mystery."

Reference

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PLANT RESILIENCE

The secret to plants' salt tolerance revealed

A plant peptide has been shown to make plants more tolerant to salty conditions

A hormone-like peptide that boosts plants' tolerance to excessive salt has been discovered by RIKEN researchers[1]. This will help scientists develop supplements that enable plants to grow in salty conditions.

Plants that grow in salty soil can become dehydrated and also absorb too much sodium, which can have toxic effects. Both effects can reduce crop yields. Plants react to physical stresses such as high salinity by mechanisms involving peptide hormones—small proteins that are not well understood.

Now, RIKEN researchers have found several genes that boost salt tolerance, the most effective one being a small gene that codes for the peptide AT13.

"We think that plants have many peptide hormones associated with physiological roles"

"We found the first functional evidence for improved salinity stress tolerance in plants in response to treatment with a small peptide," says Kentaro Nakaminami of the RIKEN Center for Sustainable Resource Science. "This is a first step toward the production of new agricultural supplements for plants growing in high-salinity conditions."

The researchers began looking for peptide hormones related to salt tolerance by using a microarray analysis to find small genes that were expressed more under high-salinity conditions. After finding 17 candidates, they created transgenic plant lines that each overexpressed one of the genes and then assessed how well they fared in a salinity stress test. Four of the plants showed better tolerance than control plants.

The team investigated the gene that induced the greatest tolerance, *AT13*, and discovered that levels of the AT13 peptide naturally increased when plants were subjected to salt stress. They then determined the exact portion of the peptide that was important. To do so, the team synthetically made pieces of the AtPep3 peptide and found that treating plants with one section (AT13-5) was just as effective in boosting tolerance as transgenic overexpression of the gene.

Further experiments showed that the AT13-5 peptide fragment did not affect how much water the plants lost. This means that it probably helps plants combat the excess sodium that accumulates inside them.

Using peptides to enhance plant resilience has key benefits. "Peptides are natural compounds that are safer than genetically modified plants," says Nakaminami. "Additionally, potential supplements made from synthetic peptide fragments will be easy to apply to different species of plants."

Peptide hormones could enable plants to grow in inhospitable places, such as highly saline soils.

Kousuke Hanada, who led the study, is hopeful that many more peptide hormones in plants will soon be discovered. "We think that plants have many peptide hormones associated with physiological roles," he says. "We strongly believe that analysis of small coding genes or peptide hormones may provide new targets for understanding plant biology and improving crop yields in environmentally stressful conditions." ●

Reference

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NEUROSCIENCE

Connecting the dots for bipolar disorder

A connection between a neurotransmitter and damaged mitochondria sheds light on their roles in bipolar disorder

Mutations in the gene *ANT1* may confer a risk for bipolar disorder—a major psychiatric disease characterized by manic and depressive episodes—through a complex interplay between the neurotransmitter serotonin and mitochondrial signaling in the brain, researchers at RIKEN have found[1]. This finding could lead to improved therapies for bipolar disorder.

Mitochondria are vital organelles that deliver energy to all cells. Damage to mitochondria has been linked to bipolar disorder—about one in five patients with mitochondrial disease also has bipolar disorder, and mitochondrial damage has been found in the brains of bipolar patients by brain imaging and post-mortem analysis.

Altered serotonin functioning also seems to be involved in bipolar disorder because drugs that target serotonin levels can effectively treat the condition.

"Our study suggests that mitochondrial dysfunction can alter the activity of serotonergic neurons in bipolar disorder"

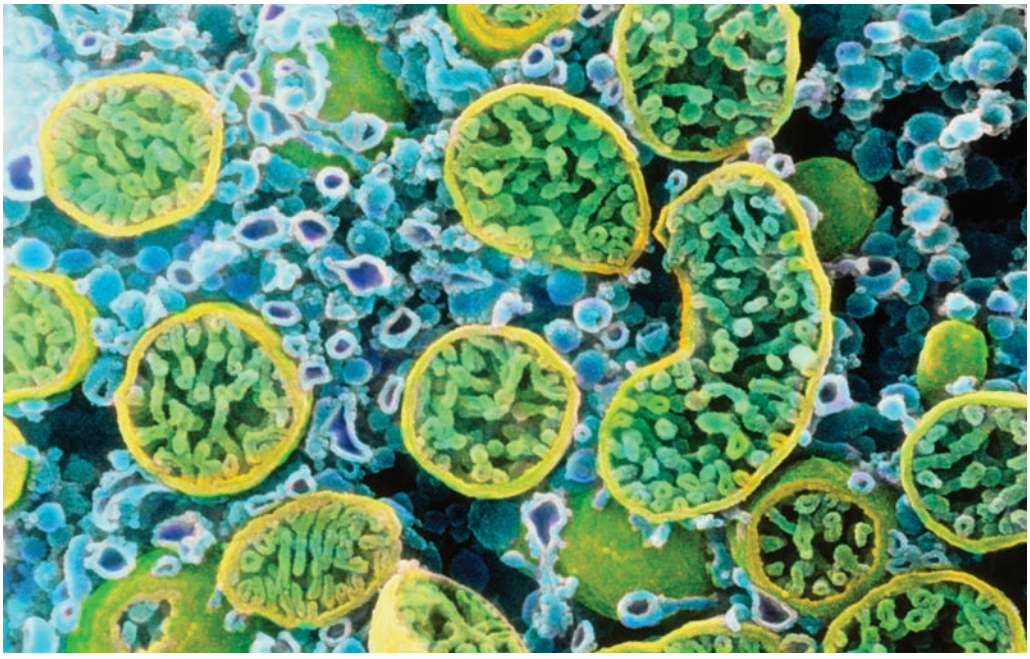
Now, Tadafumi Kato of the RIKEN Center for Brain Science and his co-workers have found that mitochondrial dysfunction affects the activity of serotonergic neurons in mice with mutations in the gene *ANT1*. This is the first time that a direct connection has been made between serotonin levels and mitochondrial dysfunction.

"Our study suggests that mitochondrial dysfunction can alter the activity of serotonergic neurons in bipolar disorder," says Kato. "This is the first time these two lines of evidence have been linked."

The researchers identified *ANT1* mutations in patients with bipolar disorder and then looked at mice lacking the *ANT1* gene in the brain only. Compared with non-mutant mice, the mitochondria in these knockout mice could not retain calcium and had leakier pores. The *ANT1*-mutant mice also showed lower impulsivity in behavior tests, and, consistent with this, their brains showed elevated serotonin turnover. This hyper-serotonergic state is likely to be a result of a cascade of changes that starts with the loss of the *ANT1* gene and the resulting dysfunctional mitochondria. Enhanced serotonergic activity may then further impair mitochondria, resulting in a vicious cycle.

Serotonergic neurons were found to deteriorate in a brain area called the dorsal raphe nucleus, a region that is also affected in Parkinson's disease, another condition that may have its roots in mitochondrial dysfunction. The *ANT1* mutation does not cause bipolar disorder, but it is associated with elevated risk.

The link found by Kato's team implies that emerging therapies for the underlying mitochondrial dysfunction could one day treat bipolar disorder more successfully than the serotonin-targeting drugs used today. ●



Colored scanning electron micrograph of mitochondria (green) in an ovarian granulosa-lutein cell.

Reference

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CLIMATE MODELING

Understanding regional climate more accurately

A new model demonstrates the importance of factoring in changes to tropical storms when modeling local climate

A more comprehensive approach to understanding changes to regional climate that includes aspects such as the frequency and paths of typhoons and cyclones has been developed by an all-RIKEN team of researchers[1]. It promises to help climatologists more accurately understand changes to local climates and also better distinguish between the various contributions to local climate change.

"We can evaluate the influences of dynamic changes as well as those of thermodynamic changes"

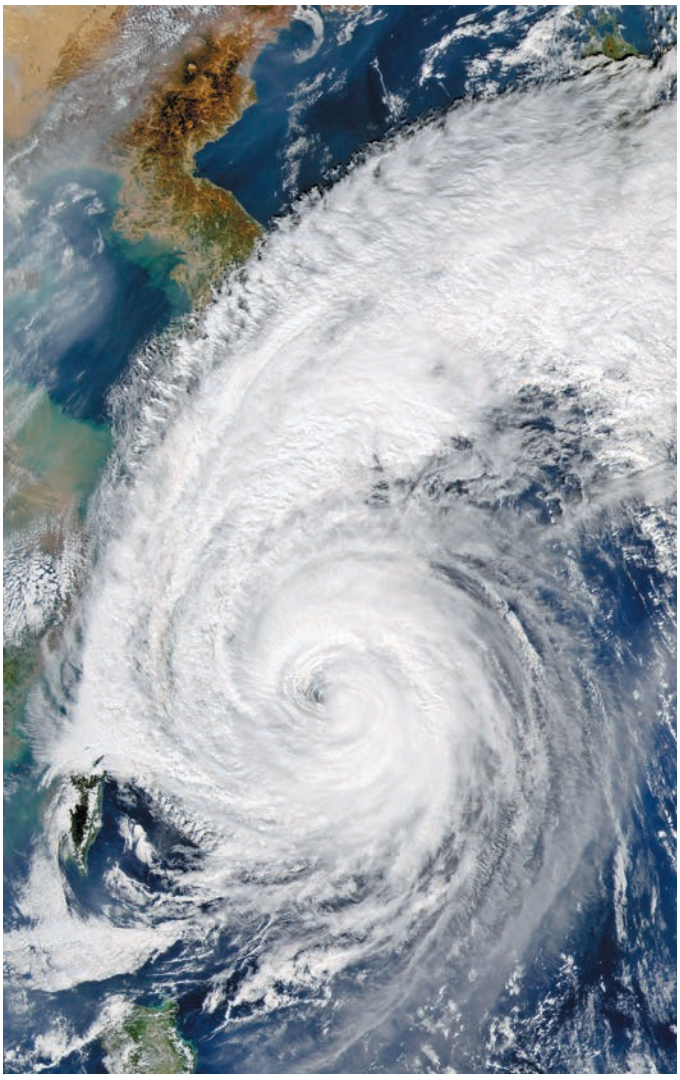
Global climate change is occurring as a result of increasing greenhouse gas levels in the atmosphere. But in order to be able to mitigate its effects, it is vital to be able to accurately predict changes to the climate on a local level. This is not easy to do, since the local climate is a complex mixture of three factors.

The first one is the warming of the atmosphere and the consequent rise in its water vapor content, which is a thermodynamic process. Another factor that needs to be considered is atmospheric dynamics; this includes things such as the path of a jet stream and the frequency and locations of major storms. A third factor is the resulting nonlinear changes to the local climate.

Now, Sachiho Adachi of the RIKEN Center for Computational Science and her colleagues have developed an elegant experimental method that distinguishes all three factors. It permits the effects of each factor to be assessed independently of the other two.

"Conventional methods for predicting changes to local climate have implicitly assumed that regional climate change will be controlled by global thermodynamic changes," explains Adachi. "Using our approach, we can evaluate the influences of dynamic changes as well as those of thermodynamic changes."

To demonstrate the usefulness of this approach, the team used their model to assess future changes to local rainfall in Japan. They then simulated two additional versions of the future climate, by holding either the thermodynamic or dynamic processes constant at present-day levels while allowing the other process to vary. The results they obtained revealed that all three factors affect precipitation, particularly extreme rainfall events, to a similar degree and thus are equally important when predicting local climate changes.



A new simulation method shows the importance of considering the paths and frequency of typhoons and cyclones when assessing local rainfall under future climate in Japan.

The study demonstrates that robust projections of local precipitation regimes demand reliable projections of atmospheric dynamics. Unfortunately, simulated dynamical changes tend to vary among climate models. The team's findings underline the importance of improving our understanding of dynamical processes in a warming climate.

"This study is a first step toward grasping meaningful information from future climate projections that include uncertainty," comments Adachi. ●

Reference

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NITROGEN CHEMISTRY

Taking steps to rebalance the nitrogen cycle

A catalyst with an unusual step-by-step mechanism could turn troublesome fertilizer runoff into harmless nitrogen gas

A catalyst inspired by nature may help bring the global nitrogen cycle back into balance, research by RIKEN scientists suggests[1]. It promises to offer a way to remove excess nitrogen from wastewater, which is currently upsetting the nutrient balance of natural ecosystems.

Nitrogen comes in many forms in nature—from biologically inert molecular nitrogen (N_2) in the air to ammonia and nitrates in soils and water, which plants depend on for growth. While various microbes in the soil convert nitrogen from one form to another, the industrial production of ammonia for fertilizer has overwhelmed nature's ability to cycle ammonia, nitrates and nitrites back into nitrogen gas. Algal blooms are one symptom of excess nitrites and nitrates in marine ecosystems (see image).

To rebalance the nitrogen cycle, researchers have been developing catalysts that turn nitrates into nitrogen gas. But it has proven very challenging to funnel the nitrogen through the series of electron- and proton-transfer steps required for this transformation without generating undesired by-products.

Now, inspired by nature's denitrification microbes, Ryuhei Nakamura of the RIKEN Center for Sustainable Resource Science and his team have developed an oxomolybdenum electrocatalyst with unusual reactivity that overcomes the selectivity problem.

Whereas proton and electron transfer occurs together for most denitrification catalysts, Nakamura's team realized their catalyst operated stepwise, via sequential proton–electron transfer (SPET).

The key observation was that the catalyst's activity depended highly on the pH, which would be expected only if proton transfer was a separate step. "SPET function is very rare, and so it came as a big surprise that our oxomolybdenum catalysts showed catalytic activity that clearly depended on the pH," says Nakamura.

The catalyst's pH sensitivity meant that the researchers could adjust the pH to maximize the rate of N_2 formation and minimize by-products. Using a technique called operando spectroscopy, they analyzed the pH dependence and verified that the catalyst operated via the SPET pathway.

The catalyst's selectivity needs to be enhanced even further before it can be used for wastewater treatment, Nakamura says. "We will try to improve the selectivity of nitrogen gas generation by regulating temperature and so on," he says. "In parallel, we will deepen our physicochemical understanding of SPET, as it has potential to broaden the horizon of catalytic chemistry," he adds. For example, reaction selectivity issues have hampered efforts to convert emissions of carbon dioxide, the main agent of climate change, back into useful chemicals and fuels. SPET catalysis could allow researchers to selectively turn carbon dioxide into products desired by the chemical industry.

Reference

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A beach in Brittany, France, covered by sea lettuce. Many beaches in Brittany are regularly affected by huge algal blooms due to fertilizers, primarily nitrates, leaching from farms into rivers. The algae pose a health hazard due to the poisonous fumes produced as they decay. A catalyst created by RIKEN researchers could be used to convert excess nitrates into benign nitrogen gas and hence reduce the occurrence of such algal blooms.

SPINTRONICS

Hall effects under control

Controlling the anomalous and topological Hall effects by applying an electric field could lead to new types of memory and logic devices

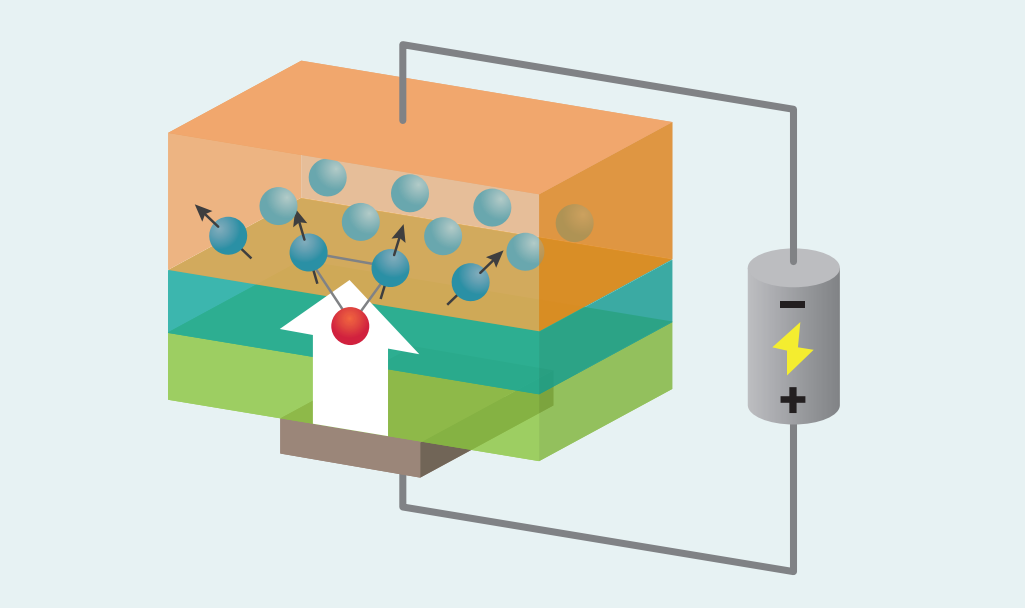
Two magnetic phenomena that could be harnessed for memory devices can be controlled by simply applying an electric field to suitably designed structures, RIKEN researchers have shown[1].

The Hall effect was discovered in 1879 by Edwin Hall, who realized that applying a magnetic field at right angles to an electric current causes the flowing electrons to veer in the direction perpendicular to both the applied magnetic field and the current, creating a voltage in that direction.

In ferromagnetic materials, the Hall effect can occur even without applying a magnetic field; in this case, it is called the anomalous Hall effect. Furthermore, in certain materials, local magnetic moments arrange themselves into stable vortex-like configurations known as skyrmions, and the 'fictitious' magnetic field produced by the skyrmions gives rise to an analogous phenomenon known as the topological Hall effect. Both the anomalous and topological Hall effects arise due to the strong coupling between the spin and orbital angular momenta of electrons in some materials.

Inspired by the recent observation of the topological Hall effect in structures consisting of $SrRuO_3$ and $SrIrO_3$, Jobu Matsuno from the RIKEN Center for Emergent Matter Science and his co-workers explored the effect of applying an electric field in mixed-composition structures composed of these materials.

"Despite the scientific importance of the anomalous and topological Hall effects, it has not been possible to control them so far," says Matsuno. "They are both transport properties that are electrically accessible inside devices."



Schematic drawing of one of the structures used in the study. The electric field (white arrow) modulates spin–orbit coupling, which affects the anomalous and topological Hall effects.

"We strongly believe that the strong spin–orbit coupling of electrons in iridium plays a significant role"

The team fabricated three heterostructures that had strontium titanate ($SrTiO_3$) as a substrate: in one, a non-magnetic $SrIrO_3$ layer was capped with ferromagnetic $SrRuO_3$; in the second, the two materials were inverted; and in the third, $SrIrO_3$ was not used.

The researchers then applied a voltage perpendicular to the layers in each heterostructure. In the first one, the voltage clearly influenced both the anomalous and topological Hall effects (see image), whereas no such effect was observed in the other two heterostructures.

The origin of this electric-field modulation has not yet been clarified, but Matsuno and co-workers have some ideas. "We strongly believe that the strong spin–orbit coupling of electrons in iridium plays a significant role," says Matsuno.

The researchers think it will be possible to control other magnetic properties, such as the magnetic anisotropy or the magnetic domain wall motion, by inserting thin layers of materials with strong spin–orbit coupling between a ferromagnetic layer and a gate dielectric. These phenomena could then potentially be used in memory devices and other applications. ●

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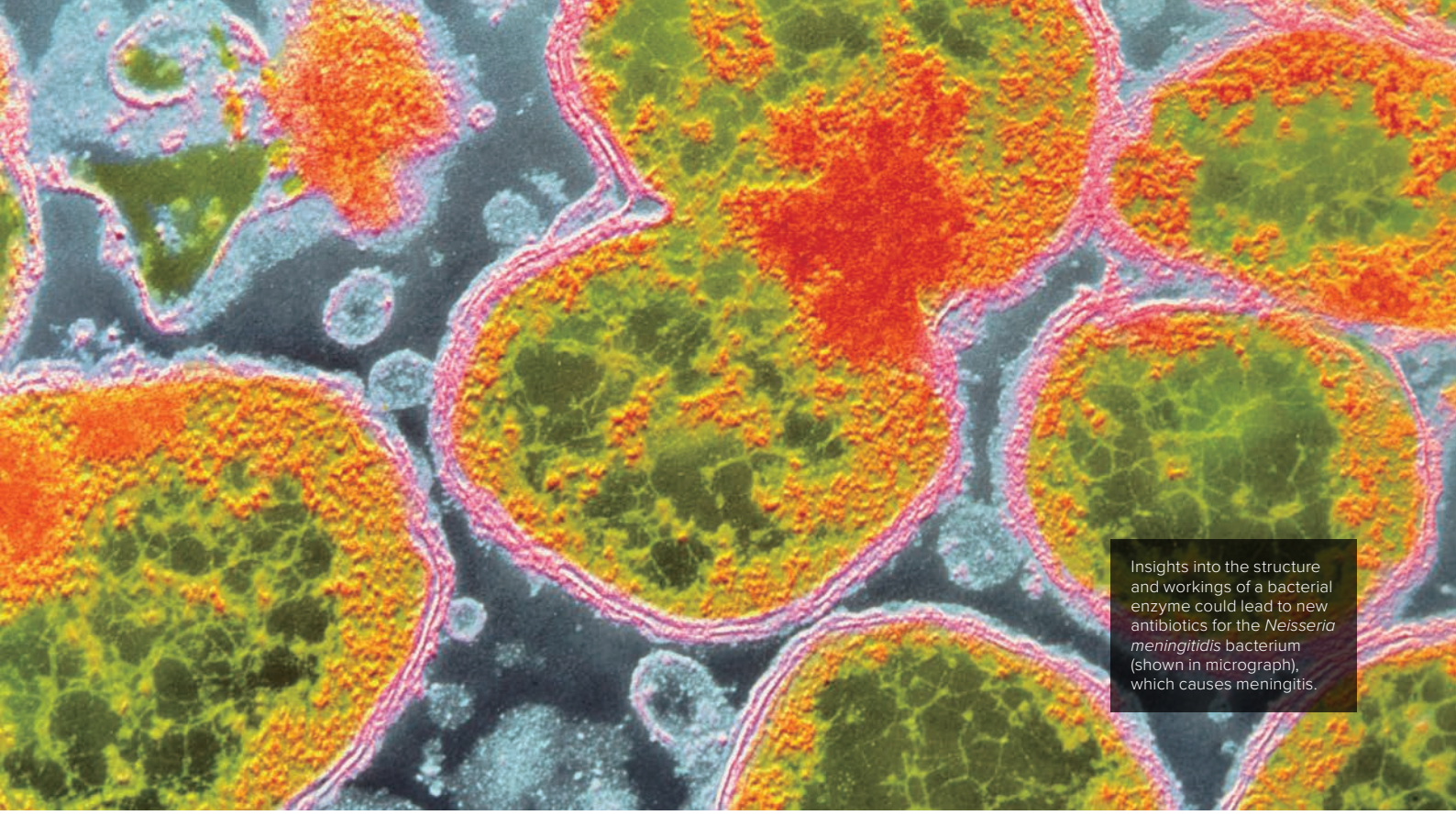

Insights into the structure and workings of a bacterial enzyme could lead to new antibiotics for the *Neisseria meningitidis* bacterium (shown in micrograph), which causes meningitis.

BIOCHEMISTRY

Sugar-activated virulence

The molecular structure of a bacterial enzyme reveals how a sugar is added to a protein that supports the growth of pathogenic bacteria

The molecular structure of an important enzyme in the disease-causing bacteria *Neisseria meningitidis* has been determined by a team of RIKEN researchers[1]. This information sheds light on how the enzyme works and also highlights targets for new antibiotics against several diseases, such as meningitis, gonorrhoea and pertussis.

The addition of sugar molecules to proteins regulates many cellular processes. Somewhat surprisingly, most enzymes that facilitate this addition (known as glycosyltransferases) can modify a variety of molecules. This is because their structures recognize the overall shape of protein domains and do not support the formation of many direct interactions with the protein's conserved amino acid residues.

An earlier study had revealed how the bacterial glycosyltransferase EarP transferred the naturally occurring sugar rhamnose to Arginine 32 of translation elongation factor P (EF-P). This unusual protein modification mechanism activates EF-P, which spurs on ribosomes that have stalled before protein synthesis is complete and stimulates the production of proteins that are toxic to the infected host.

To further understand how EF-P is activated, a team led by Shigeyuki Yokoyama and Tatsuo Yanagisawa of the RIKEN Structural Biology Laboratory analyzed the structure of *N. meningitidis* EarP. They showed with unprecedented detail how EarP recognizes its substrate protein (EF-P) and changes its shape, thereby allowing the sugar transfer reaction to occur.

Unlike other protein glycosyltransferases whose structures have been characterized, EarP binds to a particular region of EF-P, the β-sheet structure of EF-P domain I, through many interactions that recognize its conserved amino acid residues. In the absence of EF-P, EarP binds to a rhamnose donor in an inactive shape that does not allow the sugar to transfer to another protein. EF-P binding induces a shape change that allows the transfer of rhamnose to EF-P's Arginine 32 and the activation of EF-P.

"This novel and sophisticated mechanism ensures that EarP's only authentic substrate is rhamnosylated," explains Yokoyama.

Interestingly, most of the amino acid residues in EarP involved in the binding with EF-P and the rhamnose donor are conserved among EarP-containing bacteria. Mutating these residues in EarP significantly reduced its sugar transfer activity, which suggests that they could be a good starting point for developing EarP inhibitors.

The researchers anticipate their findings will help the development of new antibiotics. "A detailed understanding of the EarP structure and its unique reaction mechanism enables the rational, structure-based design of first-in-class drug candidates specific to a group of pathogenic bacteria," says Yokoyama.

Reference

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PLANT GENETICS

Blue light activates genes in plants

Exposure to sunlight affects which regions of RNA are translated in a developing plant

A process by which gene expression in plants is regulated by blue light has been discovered by RIKEN researchers[1]. This finding will give scientists more control over how plants produce proteins, both desirable and undesirable ones.

When a seedling emerges from the ground and is exposed to sunlight, the blue component of sunlight triggers the expression of certain genes that are normally silenced in the dark. The expression of these genes causes the seedling to undergo a series of physiological changes that allow it to grow and perform photosynthesis.

"We will be able to more efficiently control plant production of useful proteins"

Gene expression involves multiple steps. After a gene's DNA is transcribed to RNA, the RNA is read from one end to the other. Areas that are read first are 'upstream' of those read later. When a 'start' code is encountered, that RNA region is translated into a protein. A single gene can contain multiple start codes, with each one triggering the translation of different RNA portions.

The researchers adapted two new molecular biology techniques for use with plants. They discovered that, for certain genes, exposure to blue light changes which start code is used, ensuring that the main sequence is translated into a protein that can be used by the plant in light-related processes.

"We found that many mRNA transcription start sites in plants change in the presence of blue light," explains Minami Matsui of the RIKEN Center for Sustainable Resource Science. "Specifically, they change from the upstream site to the downstream site."

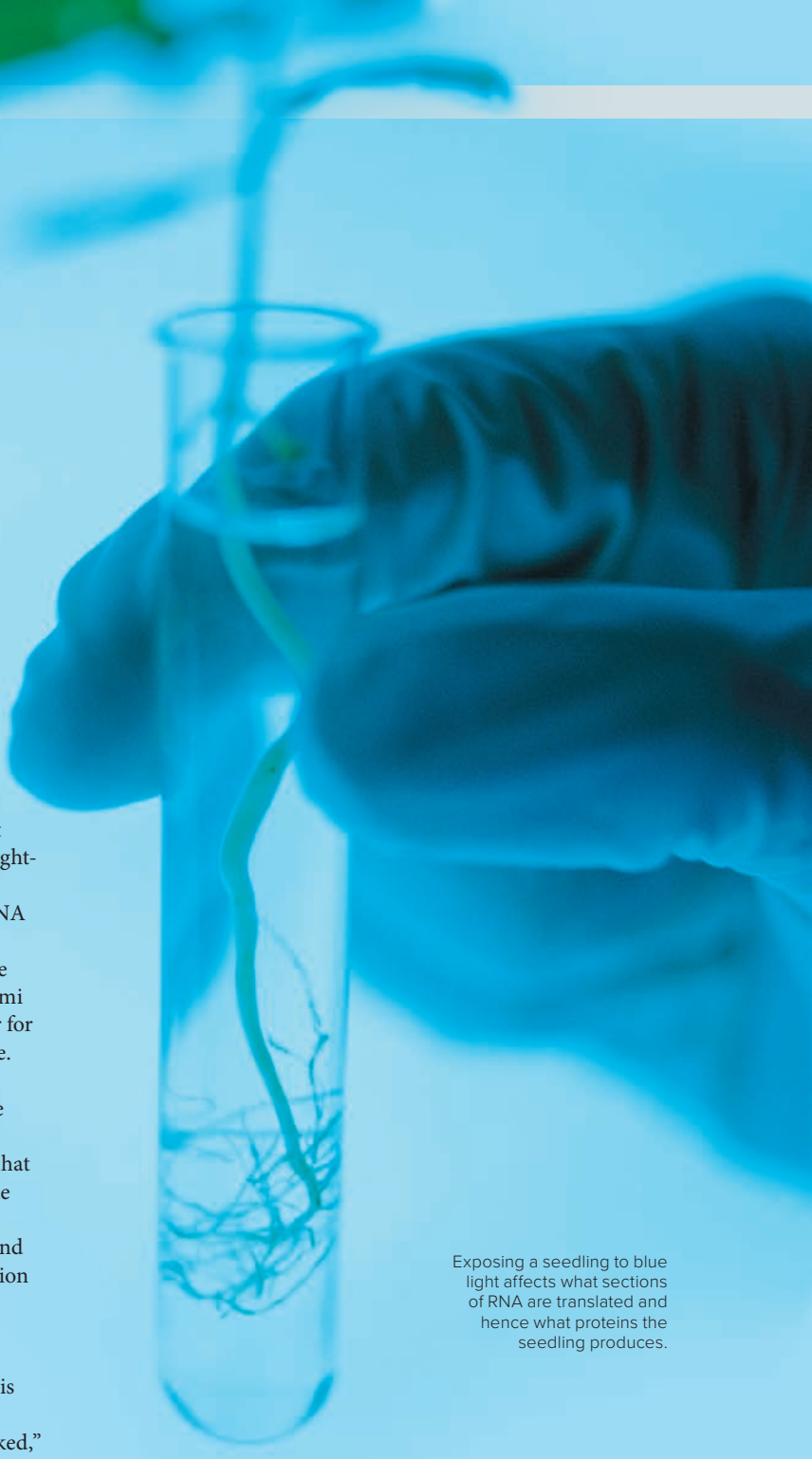
Matsui's team discovered that when the upstream start code is used, it inhibits the use of the downstream start code and could even lead to deterioration of the RNA.

"Without light, these mRNAs are doomed and unnecessary protein synthesis related to photosynthesis or photomorphogenesis is blocked," says Matsui.

The shift in start code means that when a seedling first encounters light, the RNA remains stable and the light-dependent processes can proceed with proper protein synthesis.

The finding may have implications beyond plants. Matsui believes that the underlying regulatory process—namely, the selection of start codes based on environmental factors—could apply to animals as well.

In terms of plants, knowing this process promises to be beneficial in several ways. "We can devise ways to tightly control the expression of proteins that can damage plants when expressed under improper physiological conditions," notes Matsui. "In the long run, we will be able to more efficiently control plant production of useful proteins and chemicals via synthetic pathways." ●



Exposing a seedling to blue light affects what sections of RNA are translated and hence what proteins the seedling produces.

Reference

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NEUROSCIENCE

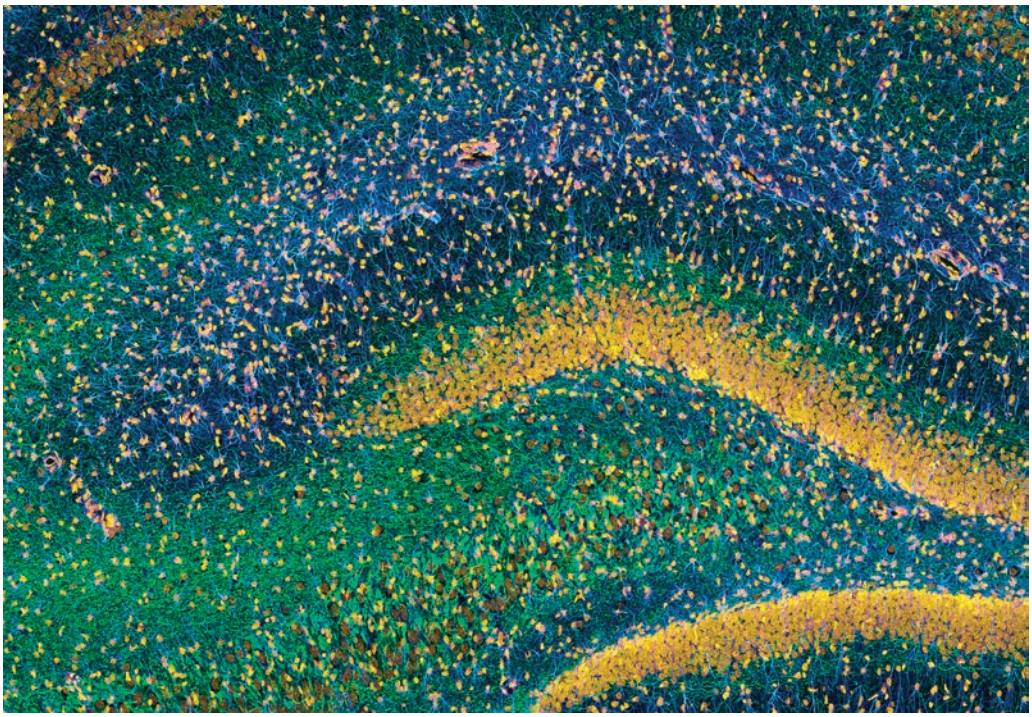
Less than total recall

Mice lacking a certain gene do not activate all neurons when consolidating memories by replaying past experiences

A gene that has been associated with human intellectual ability is also needed for normal memory formation in mice, RIKEN researchers have discovered[1]. This finding could have implications for human learning and memory impairments.

The brain reinforces memories by replaying past experiences. For example, when you go to a new place, neurons called place cells are activated in sequence. Later, while you are at rest or sleeping, these neurons are reactivated in the same sequence during episodes of electrical activity termed sharp-wave ripples. This replay mechanism allows you to recall the route the next time.

The team conjectured that this process might be abnormal in diseases that affect the hippocampus—the brain region where memory replay occurs. To test this, they used mice lacking one copy of the *Scn2a* gene.



Light micrograph of a section a rat's hippocampus. This is the brain region where memories get reinforced through a replay mechanism while resting or sleeping.

"The *Scn2a* gene is a site in the genome where mutations linked to neurological disorders can be frequently observed," explains Thomas McHugh of the RIKEN Center for Brain Science. "Changes that impair its function have been seen in patients with severe intellectual disability and autism spectrum disorder."

The mice with the deleted gene performed worse than control mice when required to find food using spatial memory. While the order in which place cells were reactivated during replay remained the same, fewer neurons participated in the replay than in the initial experience. In particular, neurons at the end of sequences were not reactivated, which explains why the mice lacking the *Scn2a* gene were unable to learn the food's location.

"These same hippocampal cells are responsible for encoding and retrieving episodic memories in general, not just spatial information," says first author Steven Middleton. Since mouse models are important for understanding human learning and memory impairments, this suggests that learning problems in people who have mutations to the *Scn2a* gene might also be due to similarly abnormal replay during sharp-wave ripples.

The *Scn2a* deletion model is one of many models of diseases that affect the hippocampus. In most models, place cells do not map locations normally, meaning that experiences cannot be encoded properly. The *Scn2a* deletion model is quite different. "We were surprised that the effects of *Scn2a* deletion were so specific to a single memory-specific process," says Middleton. "The *Scn2a* heterozygous deletion produced a very specific alteration to place-cell activity only when memories were replayed, but not during the initial experience."

The team will look at other disease models that display similar memory deficits to assess whether this truncation of replayed information is a common mechanism across diseases or whether each disease has its own way of disrupting ripple-related replay activity. ●

Reference

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GUT MICROBES

BECOME TINY INDUSTRIAL CHEMICAL FACTORIES

A schematic depiction of *Escherichia coli* bacteria. These bacteria usually dwell in the intestines of humans and other animals.

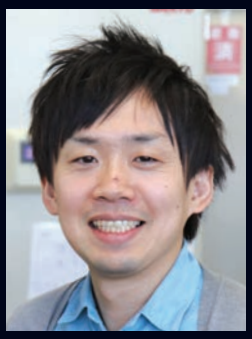
Researchers have developed an environmentally friendly way to make maleic acid, an industrially important chemical, from feedstock using genetically modified gut bacteria

Microbes are actually miniature chemical factories. They are constantly breaking down complex molecules and then using the components to make new compounds that they need to survive and thrive. People have been harnessing this quality in yeast microbes for millennia—yeast helps us produce alcoholic drinks and fermented foods, including cheese and yoghurt. But recent developments in genetic engineering mean biotechnologists can now tinker with the metabolic pathways of microbes so that they produce industrially important chemicals, cutting down on the energy-intensive conversion of petrochemicals. Metabolic engineering is an emerging field and it's only just beginning to have an impact on the commercial world, but some promising examples of widespread uptake exist. Bioethanol, for example, is a form of renewable energy and billions of liters are made each year from feedstock by yeast in both Brazil and the United States. Ajinomoto, a multinational Japanese food and beverage company, is also using the method to produce amino acids that can enhance the flavor and nutrition content of their products.

New research at RIKEN suggests that the production of an organic compound called maleic acid could be the next to benefit from engineered microbes. Over 1.8 million metric tons of maleic anhydride—the main derivative of maleic acid—was produced in 2007. While it's not much to look at (it's a colorless crystal that resembles sugar) maleic acid is important to a number of chemical processes and is essential to the production of everything from surface coatings and polyester resins, to lubricant additives and agricultural chemicals. At the moment, maleic acid is produced from benzene —a toxic, volatile, flammable liquid hydrocarbon byproduct of coal distillation that has to be processed at high pressures and temperatures.

ORGANIC AND ENVIRONMENTALLY FRIENDLY CHEMICAL PRODUCTION

Shuhei Noda and his colleagues at the RIKEN Center for Sustainable Resource Science are working on a more environmentally friendly production method



This feature looks at the work of SHUHEI NODA

Shuhei Noda earned his PhD in 2013 from the Department of Chemical Science and Engineering at Kobe University supported by a Research Fellowship for Young Scientists from the Japan Society for the Promotion of Science (DC2). Soon after, he began work with the Cell Factory Research Team at the RIKEN Center for Sustainable Resource Science. Noda moved on to became a research scientist in 2018. His research interests include metabolic engineering, synthetic biology, fermentation technology, enzyme engineering, among other things.

> In addition, by using microbes, maleic acid can be produced from renewable feedstocks such as sugar, glucose and other biomass sources

using a genetically modified *Escherichia coli*—a common bacterium that usually inhabits the intestines of people and other warm-blooded animals. While it's the first time microbes have been used to produce this substance, Noda's team has already been able to produce significant quantities in the laboratory[1].

Their microbe production method, says Noda, has some major advantages over the current process. "The reaction conditions for our process are very gentle," he points out. "In addition, by using microbes, maleic acid can also be produced from renewable feedstocks such as sugar, glucose and other biomass sources."

The researchers used genetic recombination, an engineered version of genetic material swapping that naturally helps bacteria adapt, to modify the DNA of *E. coli* so that it joined two metabolic pathways: one that breaks a ring of benzene molecules and another that produces a secondary metabolite. The team then incubated the genetically modified bacteria in one-liter fermenters and harvested maleic acid from the liquid at the top of the fermenters. Noda also points out that manipulating these genetic changes could be easier if they use a new technique called CRISPR-Cas9, which is currently taking the genetics world by storm.

OVERCOMING MALEIC ACID'S CHALLENGES

Other dicarboxylic acids have been made in commercial quantities by microbes—notably to help produce synthetic musk scents for perfumes in Japan—but Noda says that maleic acid was particularly challenging because it's the mirror image of another dicarboxylic acid that *E. coli* produces naturally. That might seem like an advantage to the uninitiated, but it's actually very difficult to turn mirror-image chemicals into one another and so the researchers had to do a lot of tinkering to get *E. coli* to produce maleic acid.

On a practical level, the yield levels of maleic acid were also an important consideration to the team. "After constructing this biosynthesis pathway, we had to enhance its productivity," Noda says. "That required making a lot of gene sets, which allowed us to identify a bottleneck in the synthesis pathway."

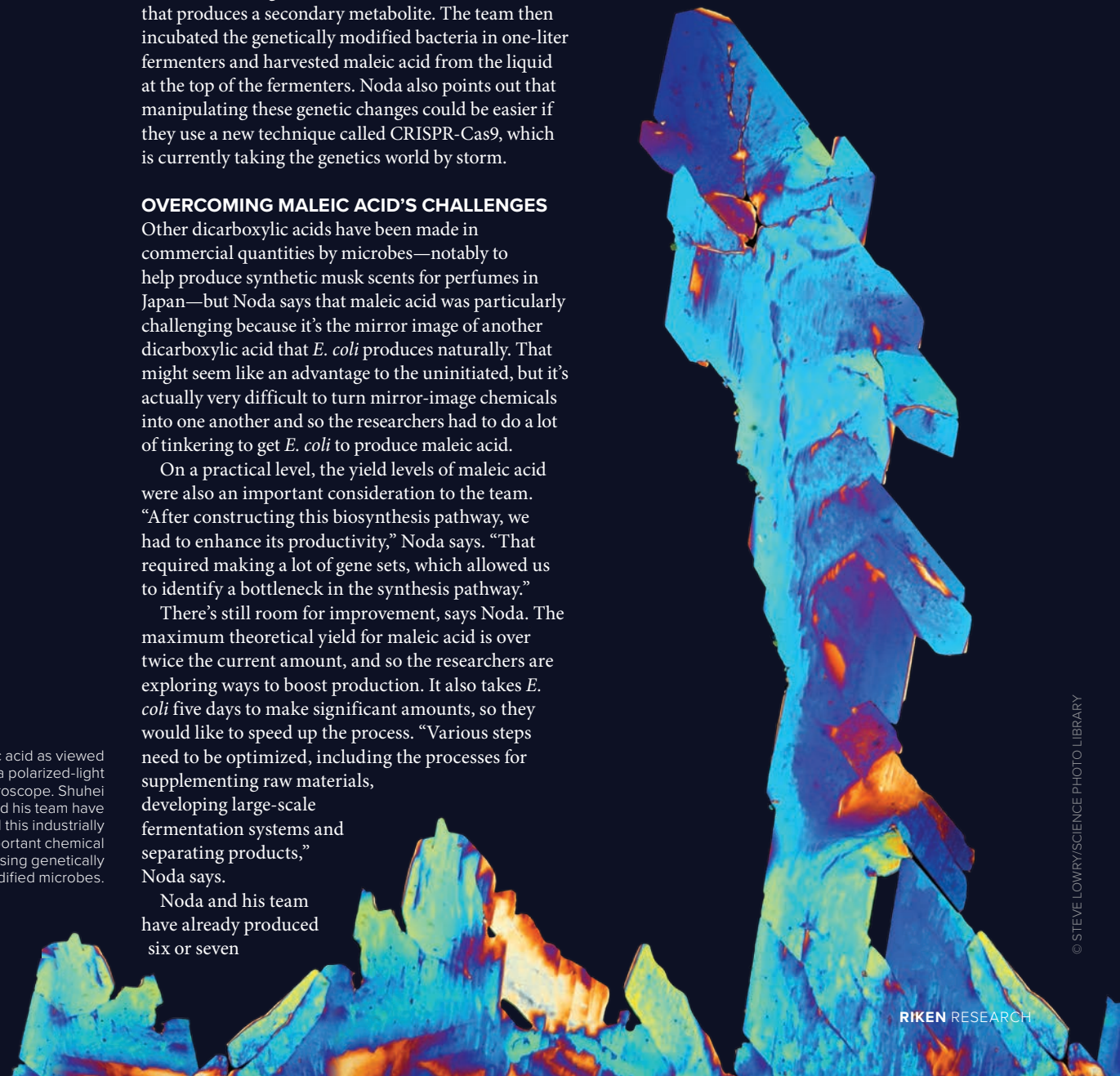
There's still room for improvement, says Noda. The maximum theoretical yield for maleic acid is over twice the current amount, and so the researchers are exploring ways to boost production. It also takes *E. coli* five days to make significant amounts, so they would like to speed up the process. "Various steps need to be optimized, including the processes for supplementing raw materials, developing large-scale fermentation systems and separating products," Noda says.

Noda and his team have already produced six or seven other compounds and are confident this method can be used to produce many other chemicals. "We want to use our method to produce more complex and valuable chemicals," Noda says. "For example, it could be used to make drug precursors and valuable compounds including aromatic moieties."

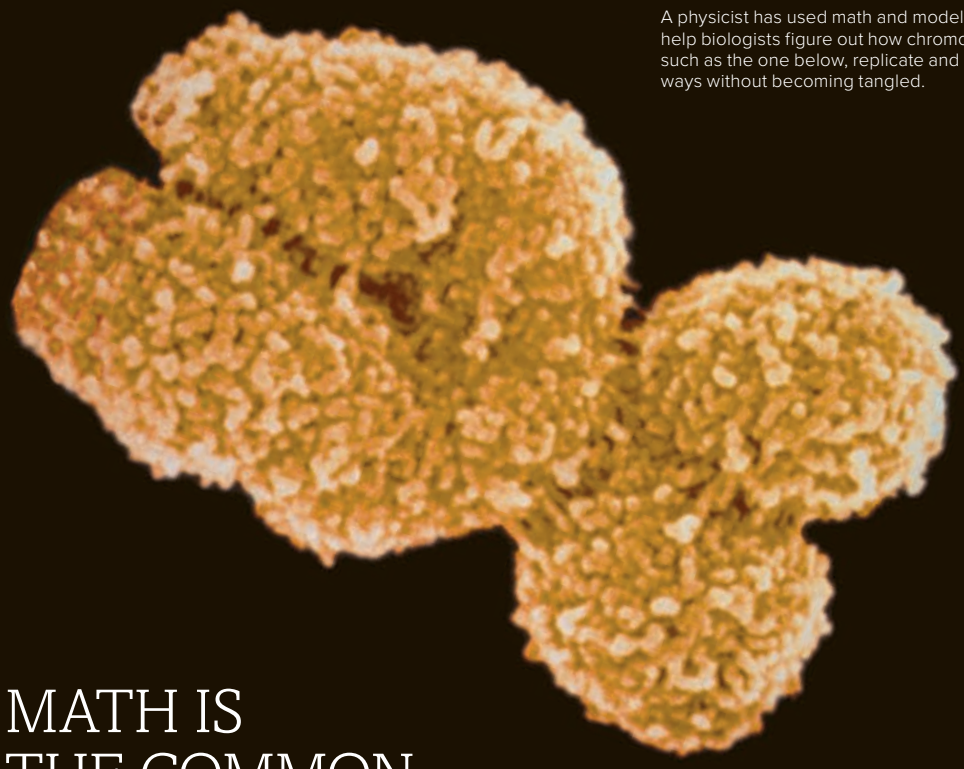
In addition to continuing their experiments, Noda is very keen to find industrial partners to collaborate with his team to help take their environmentally friendly production method from the lab to the world sooner.

REFERENCE

Noda, S., Shirai, T., Mori, Y., Oyama, S. & Kondo, A. Engineering a synthetic pathway for maleate in *Escherichia coli*. *Nature Communications* **8,** 1153 (2017).



Maleic acid as viewed under a polarized-light microscope. Shuhei Noda and his team have produced this industrially important chemical by using genetically modified microbes.



A physicist has used math and modeling to help biologists figure out how chromosomes, such as the one below, replicate and part ways without becoming tangled.

MATH IS THE COMMON DENOMINATOR

Engaging mathematicians is the key to accelerating the impact of interdisciplinary research

TETSUO HATSUDA
PROGRAM DIRECTOR,
RIKEN Interdisciplinary Theoretical and Mathematical Sciences Program (iTHEMS)

Theoretical physicist Tetsuo Hatsuda has spent more than 30 years working in particle and nuclear physics both in Japan and abroad. After 10 years at the University of Tokyo he joined the RIKEN Nishina Center for Accelerator-Based Science as a chief scientist in 2012. In 2013, he launched the Interdisciplinary Theoretical Science Research Group (iTHES), which became the Interdisciplinary Theoretical and Mathematical Sciences Program (iTHEMS) in 2016.

All theoretical approaches in the natural sciences are based on mathematics, but the truth is that most researchers are still using equations developed in the first half of the 20th century or earlier. In the intervening years, mathematics has become quite abstract and hard to understand. However, with increasing insights into genomics and huge advances in imaging, it's becoming obvious that the biological sciences have a lot to gain from newer developments in mathematical fields such as topology, algebraic geometry and stochastic analysis. Arguably, math is meeting the biosciences this century much as it met physics in the last.

As a result, math's growing relevance is being recognized worldwide. In April, a 68-page report chaired by computational mathematician Philip Bond, called *The Era of Mathematics—an Independent Review of Knowledge Exchange in the Mathematics,* was launched at the House of Lords in the UK. The authors focused on how the UK can support the expanding need for mathematics. Their recommendation—tripling funding for mathematics. The reasons cited include a Deloitte analysis that suggests the benefit-to-cost ratio of using mathematical science is 588:1, which dwarfs engineering's strong 88:1.

Linked to math's increasing sway is its ability to act as a bridge between interdisciplinary research teams tackling big questions. Theoretical science and math are a good starting point to try to talk across disciplines. The last few decades have seen concerted, if patchy, global efforts to boost interdisciplinary study, including incentives within the US's National Institutes of Health grants program from 2004 to 2012 and successful European Union policies on knowledge

exchange. Today, at least a third of cited papers point to other disciplines. Institutions in Asia are also becoming more conscious of the benefits of multidisciplinary teams to applied and large-scale projects. For example, prominent Chinese universities have recently set up interdisciplinary departments, and, in Japan, the quite recently established Okinawa Institute of Science and Technology Graduate University was designed specifically to support this type of work. Fortunately for RIKEN, one of Japan's most focused and long-standing interdisciplinary programs, the RIKEN Interdisciplinary Theoretical and Mathematical Sciences Program (iTHEMS), has already started work on integrating mathematicians into their agenda.

MATHEMATICS BRINGS DISCIPLINES CLOSER TOGETHER

The iTHEMS program was founded after I moved to the RIKEN Nishina Center for Accelerator-Based Science in 2012. After ten years at the University of Tokyo, I moved to RIKEN, in part because I wanted to work in a less-siloed environment. In 2013, I helped launch an interdisciplinary team of theoretical physicists, chemists and biologists who wanted to develop cross-disciplinary techniques that will accelerate work in all three fields. The team was called the Interdisciplinary Theoretical Science Research Group (iTHES).

We soon recognized that dedicated mathematicians could hugely accelerate this project. So, in 2016, iTHES was relaunched as the RIKEN Interdisciplinary Theoretical and Mathematical Sciences Program (iTHEMS), and we began recruiting mathematicians. Today, we boast nine mathematicians hailing from both pure and applied fields.

One of the reasons this works is because, while scientists are sometimes hampered by different terminology, theoretical biologists, chemists and physicists already use similar kinds of math. For example, all these areas delve into 'many-body systems' (physicists call this statistical mechanics). In physics, these systems could be composed of quarks and gluons, which group together to form protons and neutrons, while in biology they could be cells interacting together to form tissues. Consequently, some modeling techniques can be re-purposed for use across these fields.

> Sakai later showed that DNA INTERACTIONS can be studied using the same concepts as the macromolecules of polymer physics

Take, for instance, the Markovian lattice model, which I used in condensed-matter physics and elementary particle physics to study quantum questions. It turned out a similar method is used in biology. So, in 2017, we re-purposed the physics model and used it to show how a small deviation in fish-eye patterns leads to the formation of photoreceptor cells in fish retina. Our finding may have implications for the development of other organism structures, while our method could inform future interdisciplinary collaborations and the use of computer modeling across disciplines. With a bit of extra work, we can probably re-purpose a lot of physics-related modeling software for biologists.

Furthermore, as the detail on DNA comes into focus, both conceptually and under more powerful microscopes, its study is increasingly involving using mathematical fields such as knot theory—DNA is essentially a

iTHEMS'S UNIQUE STRUCTURE AND FINDING FORUMS TO TALK ACROSS DICIPLINES

Founded in November 2016, iTHEMS is made up of scientists who work in theoretical physics and astrophysics, theoretical biology, pure and applied mathematics, information science and computational science. iTHEMS has 'Research CELLs', groups designed to go beyond the boundaries of disciplines. Like biological cells, these groups interact and stimulate each other, and sometimes they may 'fuse' or 'divide'. There are currently four CELLS: Extreme Universe; Life and Evolution; Mathematics and AI; and Future Geometry.

Coffee meetings are also held every Friday, where researchers present their problems to a mixed crowd, and interdisciplinary workshops and lectures are frequent. Successes are hard to predict, but satisfyingly interesting. For example, after hearing a talk by a Google representative, one string theory researcher, Masato Taki, has become a popular author on machine learning and has already developed a well received code for breast cancer screening.

Frequent attempts to solve problems by harnessing the skills of other disciplines and mathematicians drives iTHEMS's research.

string of molecules that sometimes becomes entangled like a knot. Examples of how mathematical modeling can benefit the study of DNA have already been demonstrated by Yuji Sakai—but I'll discuss that below. Theoretical biologists and clinicians also want to make connections between the function of DNA and cells by examining topological, real-space structures using mathematical models. If this is successful, analysis might one day be performed using images and sophisticated mathematics-based modeling alone.

JUMPING INTERDISCIPLINARY BARRIERS

Nature reporter Heidi Ledford has noted that interdisciplinary collaboration faces some long-discussed social, publication and funding hurdles. For example, it's hard for researchers to know which area their work will be appreciated in—which journals to submit to; what departments to apply for jobs with; and, how to get grants. Because of this, some young scientists still feel the need to specialize in traditional subjects to get ahead. However, interdisciplinary complexity hasn't stopped some incredible successes at iTHES and iTHEMS—particularly when math has been re-purposed across disciplines.

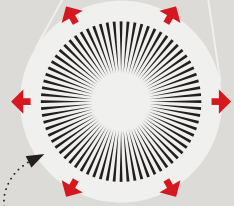
As mentioned above, one example is Yuji Sakai. He has used physics to explore chromosome formation and separation—a fundamental process that nonetheless remained a mystery to biologists for more than 100 years. Sakai was a post-doctoral researcher in nuclear physics. After coming to iTHES, he became fascinated with modeling how long DNA molecule chain copies tangle and then somehow separate during cell division, which occurs in tissue growth and regeneration. For example, in the mitotic phase of cell division, DNA that has been duplicated becomes quite tangled and condenses into characteristic rod-shaped chromosomes. Somehow these chromosomes separate into four chromatids and then rejoin in a different configuration to form two sets of identical chromosomes, which eventually become separate cells.

Sakai used his knowledge of simulations and physics to model this with researchers from RIKEN's Theoretical Biology Laboratory and Chromosome Dynamics Laboratory, and they found that a cut-and-paste mechanism likely untangles DNA during the separation process. Since DNA chains contain the macromolecule chromatin, Sakai later showed that DNA interactions can be studied using the same concepts as the macromolecules of polymer physics. Despite being trained as a nuclear physicist, Sakai is now an assistant professor working on modeling at the University of Tokyo's Graduate School of Medicine.

The second barrier I mentioned, journals, will pose a decreasing problem. Perhaps because of their heavily mathematical basis, many physics journals are already quite flexible in their subject matter. Sakai's study, for instance, was published in a specialized interdisciplinary journal, *Physical Review E*, which is published by the American Physical Society, the world's second largest organization of physicists. Established in 1993, the journal specifically covers interdisciplinary work in statistical, nonlinear, biological, and soft-matter physics, among other areas. New interdisciplinary journals are cropping up all the time.

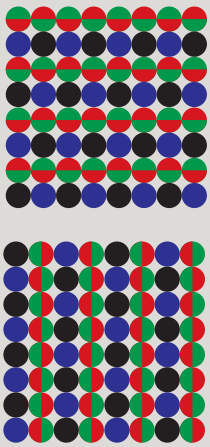
Finally, securing funding to support a culture of interdisciplinary work is still perhaps the biggest hurdle, although there are many reasons to be hopeful. Crossovers don't mean specialties will end. One of the biggest barriers to interdisciplinary work at iTHEMS is the huge amount of specific terminology that has arisen from the organic growth of biology as a field. No physicist can know everything about biology, or vice versa. I also strongly believe specialization is the key to meaningful outcomes. For this reason, iTHEMS is grouped into 'CELLs', a name derived from biology. The idea is that they can contain specialists, but that these groups can also evolve to become fused or separated like cells in the body. Several programs at iTHEMS are designed to support interaction between fields, researchers and these CELLs, so that this change and growth can happen naturally (see breakout).

Ledford notes that big problems often require interdisciplinary responses, while the authors of the *The Era of Mathematics* report also point out that disseminating mathematical solutions is still "largely about people and relationships, and that personal motivation for engagement in [knowledge exchange]". Thus, carefully thought-out academic programs like iTHEMS are key to supporting important interdisciplinary work. However, we're entering a phase in Japan and all over the world where science funding is very outcome oriented. A lot of what iTHEMS is doing is about building structures to support outcomes—we're building the capacity for young researchers to hop from one field to another. It will probably be five to seven years before we can harvest large-scale results. We see some hope in the fact that the world outside academia is beginning to acknowledge the need for complex computational mathematics, which is set to play a big role in industrial, biological, economic and environmental modeling. Banks, for example, often have access to big data without, perhaps, the knowledge of how to model it in very complex ways. Because of this, one possible avenue of support is to pursue some private funding for our core interdisciplinary facilitation work through industry collaborations. We welcome enquiries.



FISH RETINA PATTERN MYSTERY EXPLAINED

The retinas of fish and amphibians grow continuously by adding rings of new cone cells at the periphery, the ciliary marginal zone (CMZ, above). Zebrafish eyes have four different types of cone cells, which sense blue, ultraviolet and a combination of red and green in two different patterns (below). Biologists already know that these cells are added to the CMZ in a consistent radial pattern, but why they form this pattern and not an equally probable configuration that appears as if the radial pattern was turned 90 degrees (bottom), wasn't understood. Using a dynamic model from physics known as the Markovian lattice model, a group of researchers in iTHES and iTHEMS, including Tetsuo Hatsuda, were able to help a RIKEN team show that small flaws led to the consistent radial pattern in zebrafish retina.



JUNK RNA CLUES

Despite making up more than 98% of the RNA in a mammalian cell, non-coding RNAs were once thought to be extraneous 'junk' or 'noise'. Recently, however, studies show that most diseases can be linked to non-coding genes, although why is little-understood.

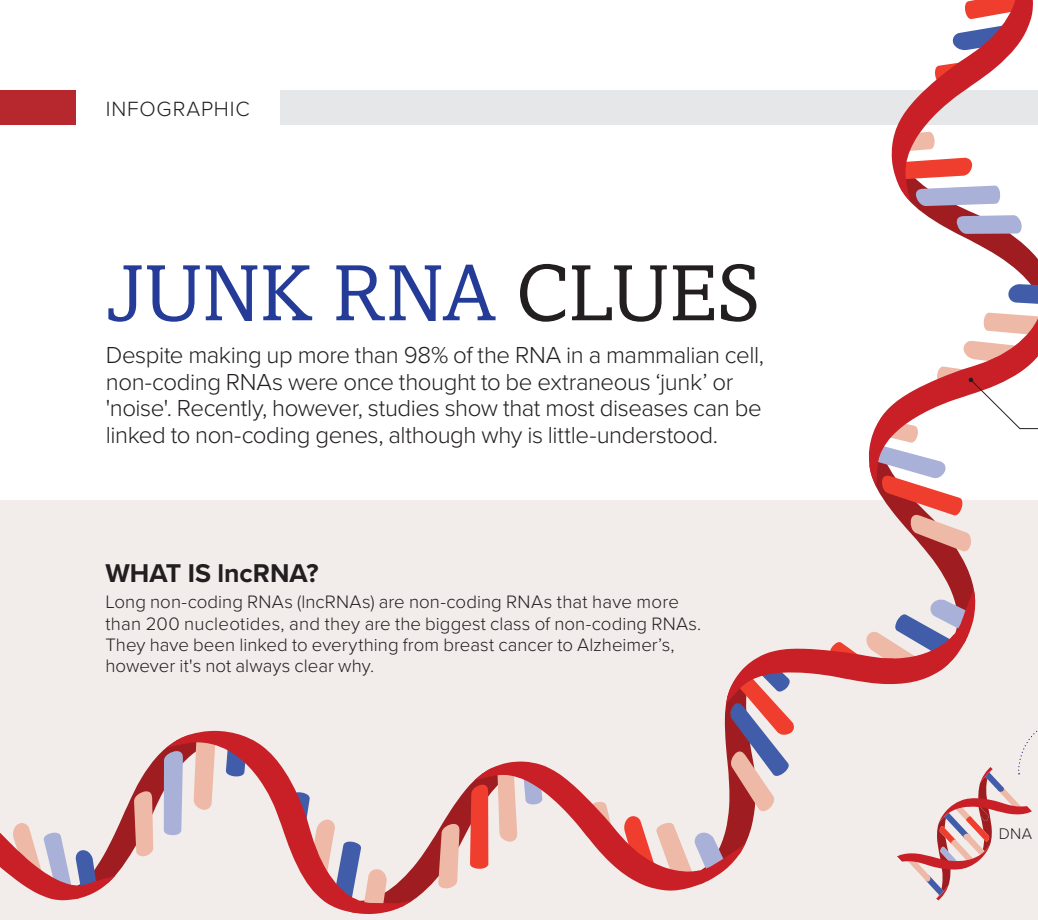
In 2017, FANTOM5 mapped out

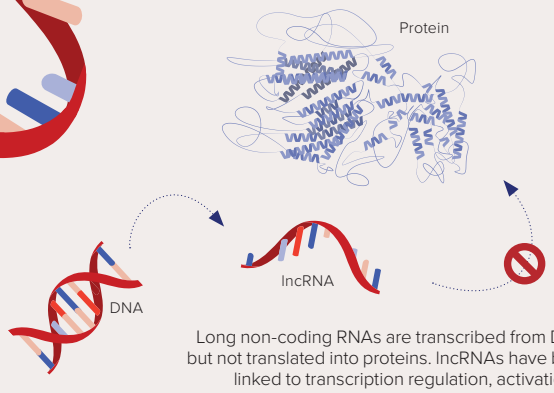
27,919 HUMAN lncRNAs

and found **69% of these** could be functional.

WHAT IS lncRNA?

Long non-coding RNAs (lncRNAs) are non-coding RNAs that have more than 200 nucleotides, and they are the biggest class of non-coding RNAs. They have been linked to everything from breast cancer to Alzheimer's, however it's not always clear why.

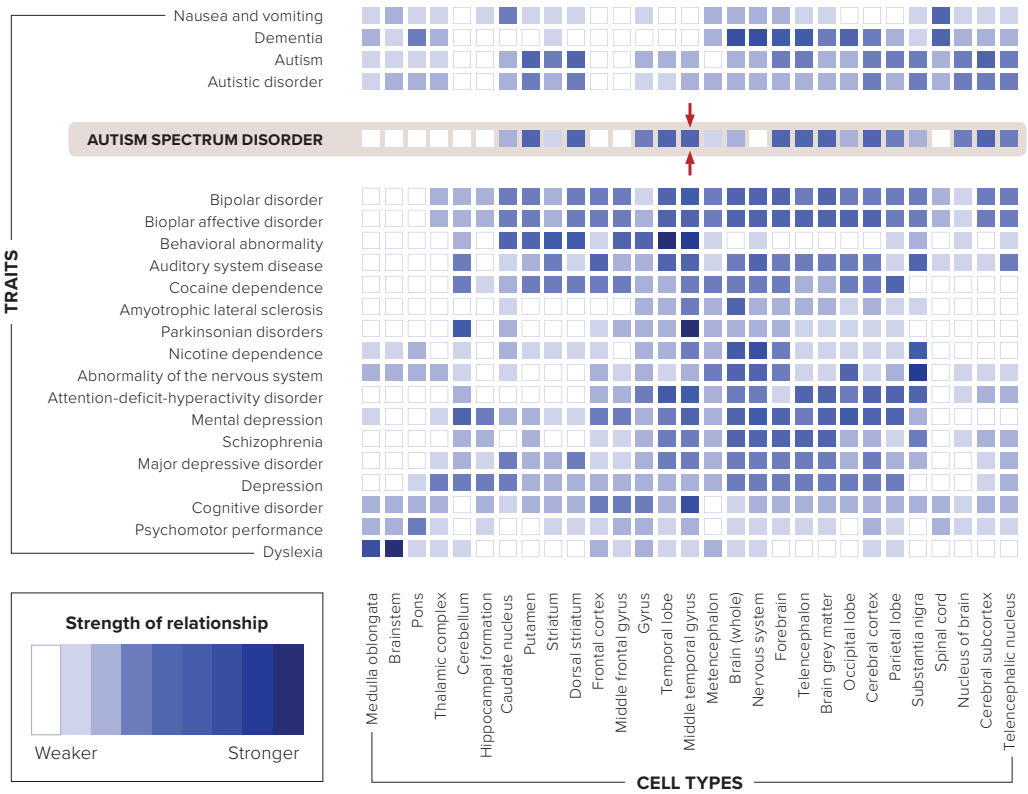


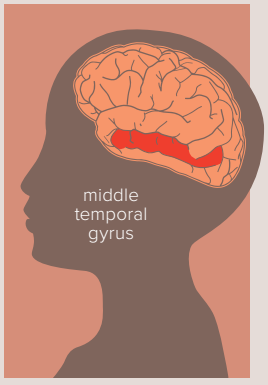


Long non-coding RNAs are transcribed from DNA, but not translated into proteins. lncRNAs have been linked to transcription regulation, activation of chromosomes and gene expression.

GUILTY BY ASSOCIATION

FANTOM5, an international project led by RIKEN, paired cells enriched in certain genes with traits exhibited by people with those genes. In doing this, FANTOM5 was able to imply that **1,970 lncRNAs may be related to particular traits,** which will help narrow the search when we look for the culprits in disease.





37%

Of the genes associated with the cells found in the middle temporal gyrus (part of the brain that has been linked to language processing) and also with autism spectrum disorder, 37% were lncRNAs.

Source: Hon, C.-C., Ramilowski, J. A., Harshbarger, J., Bertin, N., Rackham, O. J. L. *et al* An atlas of human long non-coding RNAs with accurate 5′ ends. *Nature* 543, 199–204 (2017)

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

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