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SPRING 2022

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A STOMACH FOR SURVIVAL
Centenarian study reveals distinct gut bacteria

BETTER BUBBLE TEA
Tweaking tapioca for health benefits

THE BIG PICTURE
Framing a research renaissance

THE GOLDEN TOUCH

Glue-free technique improves flexible electronics

▲ **GABA immunity discovery**
A polarized-light micrograph of crystals of the neurotransmitter gamma-aminobutyric acid (GABA). Immunologists at RIKEN have shown that GABA from B cells helps regulate the immune response, which could lead to new strategies for attacking cancer (see page 9).

RIKEN RESEARCH

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

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

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

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ISSN 1883-3519
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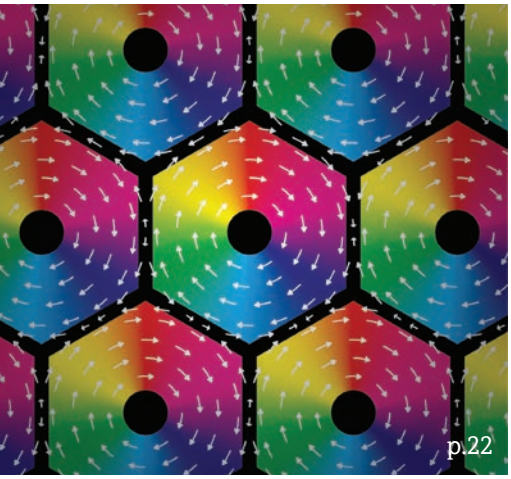
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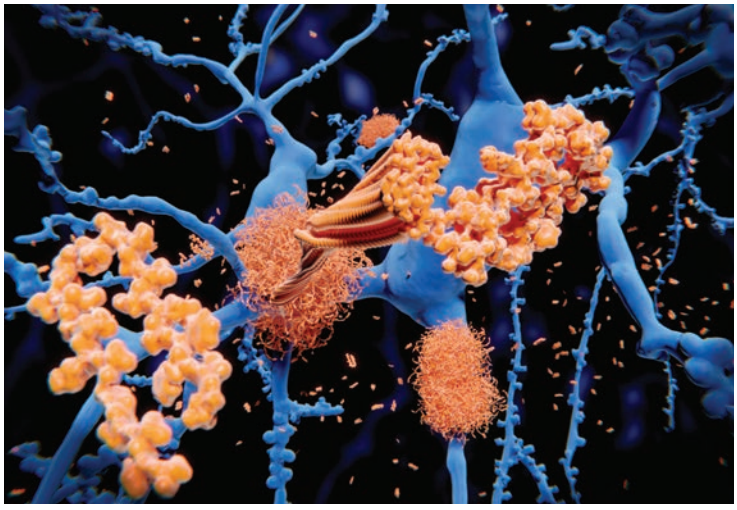

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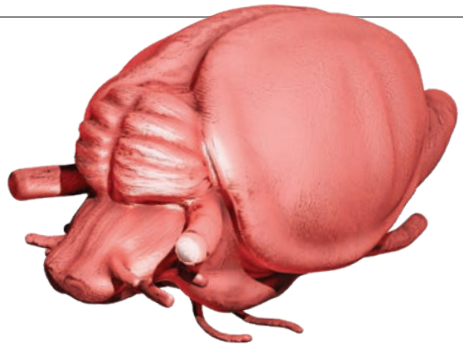

Seven years of streamlining science for social good

Hiroshi Matsumoto
RIKEN President

As I approach the end of my seven-year term as president of RIKEN, I would like to look back on what we have achieved. I have also given some of my views on the future of the scientific endeavor in the Perspectives article on page 29.

First, I am proud to say that I have been able to implement a number of reforms during the last seven years.

When RIKEN was founded in 1917, it became an important player in the progress of Japanese society. The early leaders believed that it was important to return the fruits of their research to society, and this idea was promoted in particular, by Masatoshi Okochi, who was director of RIKEN for 25 of its first 30 years. In 2019, a mechanism to swiftly return RIKEN's results to society was established in the form of RIKEN Innovation, a fully-owned subsidiary.

One of my major goals has been help to build what we call science and technology hubs to develop stronger relationships with Japan's national universities. In the coming years we are planning, as a world-class research institute, to strategically strengthen our relationships with universities and research institutes overseas. As part of that effort, we established an office in Brussels in 2018, which joins our existing offices in Beijing and Singapore.

We have also adopted a number of programs to nurture excellent human resources. For example, the RIKEN Hakubi program, established in 2016, which allows young researchers to gain practical experience as principal investigators. In terms of employment, we were also able to extend the employment term for fixed-term research personnel from five to seven years, giving them more time to concentrate on their research projects, and to open up a path for outstanding fixed-term researchers to move on to tenured positions.

I also need to mention that during my term we saw the arrival of the COVID-19 pandemic, which has had a huge impact on the scientific world. Though it has been a difficult and tragic experience, we must also see it as an opportunity to learn how to deal with similar shocks in future. The aim of science is to build a better future—so let us figure out how to tackle the future together.

COVER STORY:
RIKEN researchers developed a breakthrough method to secure flexible wiring connections. They used water-vapor plasma to create stable bonds between gold electrodes printed onto ultrathin polymer sheets. *Page 12*

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Foundational structures, from nano to human

Yuichiro Kato
Chief Scientist, Nanoscale Quantum Photonics Laboratory, RIKEN Cluster for Pioneering Research

Please describe your role at RIKEN.
I am the chief scientist for the Nanoscale Quantum Photonics Laboratory at the RIKEN Cluster for Pioneering Research and a team leader for the Quantum Optoelectronics Research Team at the RIKEN Center for Advanced Photonics.

Please describe your research.
We are working to build the foundations of atomically defined technology. We believe this will enable devices that make use of quantum effects at room temperature to process and transmit information with extremely high efficiency. Typical experiments involve integration of individual nanomaterials into device structures and testing using automated microspectroscopy systems.

More specifically, my group studies the quantum properties of nanomaterials and the quantum physics of nanoscale photonic devices. At the moment, the nanomaterials of interest are carbon nanotubes and layered two-dimensional materials, while devices of interest include photonic crystal cavities and electrostatically formed diodes. My research covers quantum phenomena within these systems, such as photon antibunching and the Purcell effect.

What excites you most currently?
By using automated microspectroscopy, we can identify carbon nanotubes with precise atomic arrangements. Recently, we developed a method to pick up and place the tubes on device structures, which means that we are now able to choose atomically defined nanomaterials and assemble them. Although we are still very far away from fabricating arbitrary structures with atomic precision, we are making exciting steps toward devices that utilize atomically defined components.

How has being at RIKEN helped your research?
RIKEN is different to other universities in Japan, as I'm able to hire postdocs from various fields such as physics, chemistry, materials engineering, mechanical engineering and electrical engineering. Building an interdisciplinary group is important in nanoscience, as we use both top-down and bottom-up techniques.

What is the best thing about working at RIKEN?
It's great to be able to work with the best scientists from different fields. I have served as the chair for the RIKEN Scientists' Assembly (RSA), which works to enhance interdisciplinary interactions within RIKEN. My aim was for its membership to encompass all of RIKEN. For historic reasons many research centers were not part of the RSA, but after I visited many center directors, all have joined.

> *We are making exciting steps toward devices that utilize atomically defined components.*

What was your most memorable RIKEN experience?
I'll never forget how helpful the administrative support was when I started my lab. I had to go back and forth between RIKEN and The University of Tokyo to design the lab and plan my move. They supported me by making schedules for the construction and moving processes, and by arranging meetings with the facilities people. The RIKEN office got quotes from the contractors to help expedite the process. They also guided me through all the necessary administrative processes for bringing students in, moving equipment and transferring funds. Everything went so smoothly, and it was a major change from being at a university where administrative support for research was minimal. ■

Skyrmion's the limit

Licong Peng

Special Postdoctoral Researcher, Electronic States Microscopy Research Team, RIKEN Center for Emergent Matter Science

Please describe your role at RIKEN.
I am a special postdoctoral researcher in the Electronics States Microscopy Research Team at RIKEN Center for Emergent Matter Science (CEMS), led by Xiuzhen Yu. I use Lorentz transmission electron microscopy to perform real-space observations of magnetic vortex-like particles and anti-particles, and then drive and control their dynamic behaviors in spintronic devices that we fabricate. This could be useful to energy-saving magnetic recording storage devices, for example, because their controllability can be enabled at an ultralow threshold electric current.

What excites you the most about your current research?
Recently, we have, for the first time, been able to directly drive and control the motion of a single nanometric skyrmion at room temperature, and have demonstrated the first experimental evidence to confirm the universal behaviors or skyrmion motion in chiral-lattice magnets. This is very exciting research since the controllability of a single skyrmion at room temperature is one of the keys to spintronic devices.

What do you think has been the most interesting discovery in the last few years?
In 2020, we directly controlled the topological nature of nanometric skyrmions ('particles') and anti-skyrmions ('anti-particles'), including controlling their topological numbers, helicity and lattice form. The transformations between skyrmions and anti-skyrmions could be used to transmit information in the same ways as bits, in which a skyrmion is a 1 bit and and antiskyrmion is a 0 bit, in magnetic recording devices. After this discovery, many researchers started to investigate the properties of anti-skyrmions, including their three-dimensional tomography, heating/current-induced dynamics and transport properties. Some also began to search for anti-skyrmion-hosting new materials (see page 10).

How and when did you join RIKEN?
Xiuzhen Yu, who leads the Electronics States Microscopy Research Team in RIKEN CEMS is the world's leading expert in real-space exploration of topological textures and novel emergent phenomena. I read a lot of high-impact research papers by Dr. Yu and Professor Yoshinori Tokura (the center director). I was keen to join Yu's team and also very curious about how they published such pioneering work. Hence, I applied for a position and luckily became the first postdoctoral researcher in her team in 2018.

CEMS is the world leader in real-space exploration of topological textures and novel emergent phenomena.

What has been your most memorable experience at RIKEN?
Sometimes, we will have research progress meetings every Monday, Tuesday and Wednesday to foster collaboration between teams. Such frequent discussions allow the PIs and professors to follow up on experimental details, and we can glean valuable suggestions.

Please tell us about your professional and personal goals.
I hope in future that skyrmion-based spintronic devices will be used in real life. A personal goal is to be an independent principal investigator at a top Chinese university and to set up my own research laboratory with both experimental and theoretical sections. I would also like to build advanced experimental platforms with equipment such as Lorentz transmission electron microscopes and nanofabrication systems. ■

View Licong Peng's article online: https://www.riken.jp/en/news_pubs/research_news/pr/2021/20211124_1/

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Hiroshi Matsumoto awarded the Grand Cordon of the Order of the Sacred Treasure

In 2021, recent RIKEN President Hiroshi Matsumoto was honored with Japan's Grand Cordon of the Order of the Sacred Treasure. This order is the highest rank and is awarded to individuals who have made advancements by dedicating themselves to public service. Upon receiving the award, Matsumoto said, "I have always believed that learning is a form of human relation that revolves around the truth. Learning is a vast truth-seeking activity, and there is only so much that one individual can do. We must learn from the wisdom of our predecessors, have discussions with those who share the present with us, and entrust our achievements to future generations. Connections with people have always been my support, and I would like to express my deepest gratitude to my family, my mentors, all my colleagues from the days when I was a laboratory researcher, my colleagues from Kyoto University and RIKEN, and all those who have been a part of my life."

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COVID-19: Fugaku wins Gordon Bell prize

In 2021, RIKEN researchers and their collaborators won the Association for Computing Machinery (ACM) Gordon Bell Special Prize for High Performance Computing-Based COVID-19 Research. Their work, 'Digital transformation of droplet/aerosol infection risk assessment realized on 'Fugaku' for the fight against COVID-19', models the spread of droplets and aerosols. It helped guide decisions in Japan on face mask requirements and social distancing, as well as whether certain public facilities and private businesses should be closed. In addition to Fugaku, the group used the Oakforest-PACS supercomputer system, which is operated by the University of Tokyo and the University of Tsukuba.

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Fugaku's reign continues

At the end of 2021, the supercomputer Fugaku (above) again established its place at the top of the high-performance computing world. Fugaku was awarded first place on the: TOP500 list, the best-known supercomputing benchmark; the HPCG list, a measure of supercomputer performance in real-world applications; the HPL-AI list, which ranks computers on artificial intelligence-related tasks; the Graph500 list, which gauges a computer's ability to handle data-intensive loads; and, for the first time, the MLPerf HPC benchmark on CosmoFlow, which is used to gauge a supercomputer's capability in the area of large-scale machine learning processing. Fugaku, which was jointly developed by RIKEN and Fujitsu Limited, was launched for shared use in March 2021.

In the TOP500 benchmark, it achieved a score of 442.01 petaFLOPS using 158,976 nodes. In the HPCG ranking, it achieved a score of 16.00 petaFLOPS, also using all 158,976 nodes. In the HPL-AI ranking, it had a score of 2.004 exaFLOPS, achieving an exascale rating for the forth time.

And its score in the Graph500, won via a collaboration involving RIKEN, Kyushu University, Fixstars Corporation, and Fujitsu, was 102,955 gigaTEPS.

Remarkably, the MLPerf HPC feat was achieved using just half of Fugaku's capability—the remaining resources being used simultaneously for other projects—and the system still achieved a score 1.77 times faster than its closest rival.

MLPerf HPC includes three separate benchmarks, each measuring a supercomputer's performance on different tasks. CosmoFlow involves calculating cosmological parameters based on three-dimensional simulations of the distribution of dark matter. Fugaku was able to train 637 deep learning models in eight hours and 16 minutes, a rate of about 1.29 deep learning models per minute.

Deep learning has become a key method for making conclusions based on large data sets. Essentially, a computer is fed data, and it tries to learn from the data by looking for patterns. For the MLPerf HPC benchmarks, supercomputers are asked to conduct a series of machine learning

tasks, and the score gauges how quickly it was able to perform the tasks. In addition to CosmoFlow, two other benchmarks measure a supercomputer's ability in identifying abnormal weather phenomena and how molecules react on a catalyst surface.

In the future, the researchers plan to make the libraries and AI frameworks they used open to researchers around the world, in order to encourage further advances in machine learning processing.

The announcements for all these rankings were made at SC21, a hybrid high-performance computing event held in the city of St. Louis in the United States and online. According to Satoshi Matsuoka, director of the RIKEN Center for Computational Science, "Fugaku is a crystallization of the world's most advanced IT technology, combining high performance, low power consumption, and user friendliness. In addition to topping the major benchmarks of simulations, big data, and AI for the fourth consecutive term, it has also made a major contribution to the establishment of COVID-19 safety guidelines for the government and private sector, and has helped lead a digital transformation in the area of infectious diseases. With this continued dominance we have shown that Fugaku is leading the world in a range of areas. We will continue to use it to contribute to the achievement of Society 5.0 and the SDGs in Japan."

According to Naoki Shinjo, Corporate Executive Officer of Fujitsu Limited, "I look forward to seeing many researchers take advantage of the world-leading performance of Fugaku, and to seeing it contribute to the further development of science and technology and the achievement of a safe and secure society. I would like to express my heartfelt gratitude to RIKEN and other parties for their cooperation and support. We ourselves are conducting research on high-performance computing and have used Fugaku for real-time predictions of tsunami flooding. We will continue to contribute to efforts for the achievement of Society 5.0."

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Finnish Ambassador to Japan visits RIKEN Center for Computational Science

On November 29, 2021, Finnish Ambassador to Japan, Pekka Orpana (below, at left), visited the RIKEN Center for Computational Science (R-CCS) in Kobe. The visit began with an overview of RIKEN by Kenichi Fujita, director of RIKEN's International Affairs Division. This was followed by an introduction to the R-CCS and supercomputer Fugaku by R-CCS Director, Satoshi Matsuoka (below, middle). The visit included an exchange on potential cooperation between Japan and Finland in information science and a visit to Fugaku.

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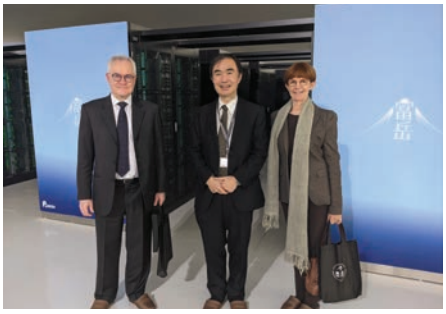

Joint workshop with the University of Strasbourg

On September 9, 2021, RIKEN and the University of Strasbourg held a joint workshop focused on presentations by mid-career researchers. The aim was to celebrate 25 years of partnership and encourage networks between the two institutions. The event began with opening remarks by RIKEN Executive Director Yuko Harayama and University of Strasbourg Vice-President for Research Remi Barillon, followed by eight presentations by researchers from the two institutes on subjects including immunology, sleep, disease transmission, artificial metalloenzymes, and image reconstruction in computer tomography.

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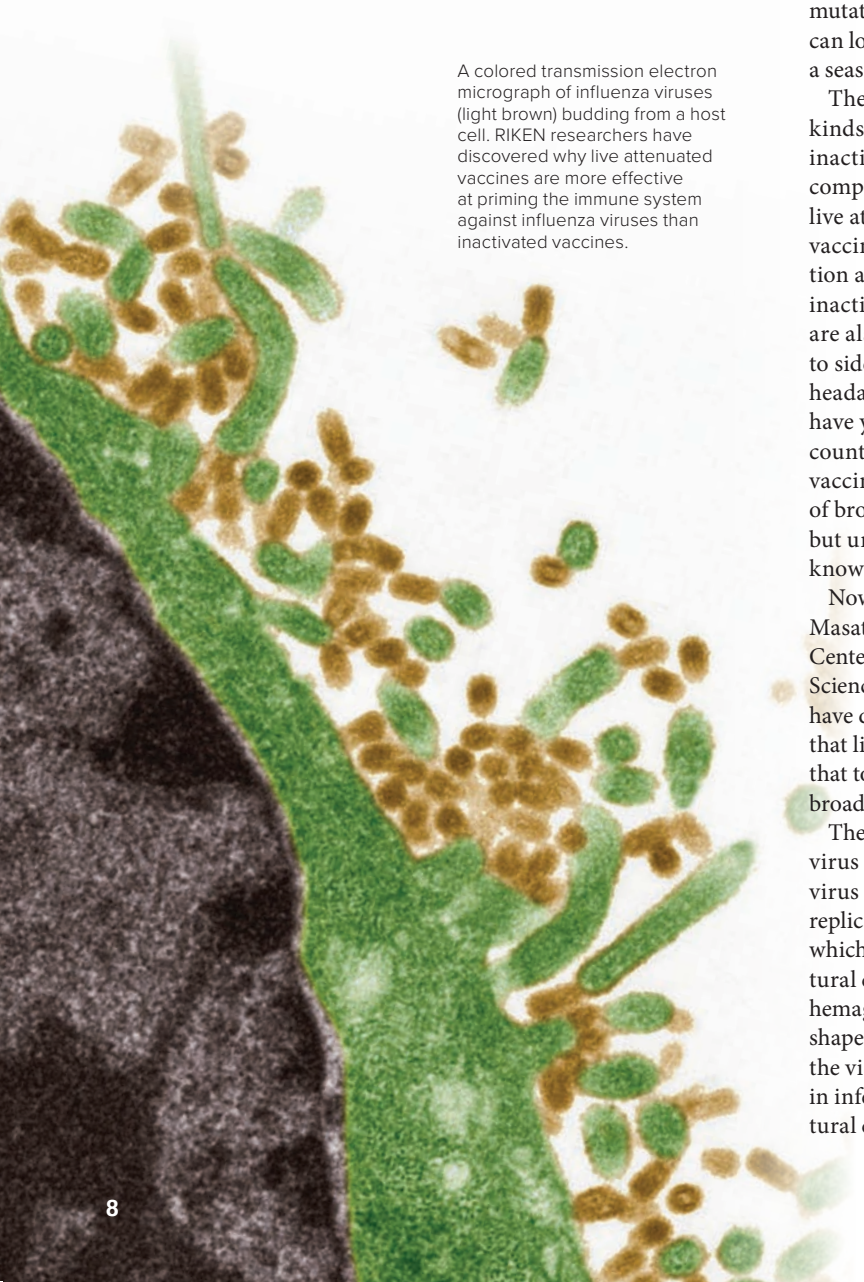
VACCINATION

The secret behind live flu vaccines' broad response

A mouse study reveals why some influenza vaccines offer a broader response against the virus than others



A colored transmission electron micrograph of influenza viruses (light brown) budding from a host cell. RIKEN researchers have discovered why live attenuated vaccines are more effective at priming the immune system against influenza viruses than inactivated vaccines.

In a finding that should help researchers develop vaccines that offer broad protection against viruses, a mouse study by RIKEN immunologists has shed light on why people vaccinated with an inactivated form of the influenza virus still sometimes contract the disease[1].

Influenza is a major global health burden, with the World Health Organization estimating that it causes one billion cases annually. Each year, vaccines are developed that offer some protection against infection. But the influenza virus is a moving target that is constantly mutating, and so vaccines can lose their effectiveness as a season progresses.

There are two common kinds of influenza vaccines: inactivated vaccines (including component vaccines) and live attenuated vaccines. Live vaccines offer broader protection against variants than inactivated vaccines, but they are also more likely to give rise to side effects such as fevers and headaches and as a result they have yet to be approved in some countries such as Japan[2]. Live vaccines induce the production of broadly reactive antibodies, but until now, scientists didn't know why.

Now, in a study on mice, Masato Kubo of the RIKEN Center for Integrative Medical Sciences and his co-workers have discovered two processes that live vaccines induce in mice that together account for their broader protection.

They found that, like the virus itself, the live vaccine virus causes the virus to replicate deep in the lungs, which in turn induces a structural change in the virus hemagglutinin—a mushroom-shaped protein on the surface of the virus that plays a major role in infecting cells. This structural change exposes regions of antigens that are recognizable by the immune system but are usually hidden from it. This is the first process.

The second process is the activation of germinal cells by interleukin 4 (IL-4), a cytokine that plays a major role in regulating antibody production. IL-4 is derived from special T cells known as follicular helper T cells. This activation causes a minor population of B cells to proliferate and it is these B cells that are responsible for generating broadly protective antibodies.

The role of IL-4 in inducing the broad immune response came as a surprise. "Until now there had been no direct evidence to show the importance of IL-4," says Kubo. "That was one of the surprises of this study for me."

"We believe both processes are needed for generating broadly active antibodies: viral duplication in the lungs and expansion of the minor population of B cells," says Kubo. "These two processes mostly likely occur when a person is infected by the influenza virus itself."

The team now plans to investigate if a similar mechanism operates for other viral infections, including COVID-19.

Reference

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2. Kubo, M. & Miyauchi, K. Breadth of antibody responses during influenza virus infection and vaccination. *Trends in Immunology* **41,** 394–405 (2020).

IMMUNOLOGY

GABA blunts immune response to tumors

New strategies for empowering the immune system to fight tumors could come from the discovery of the role that GABA plays in regulating the immune response

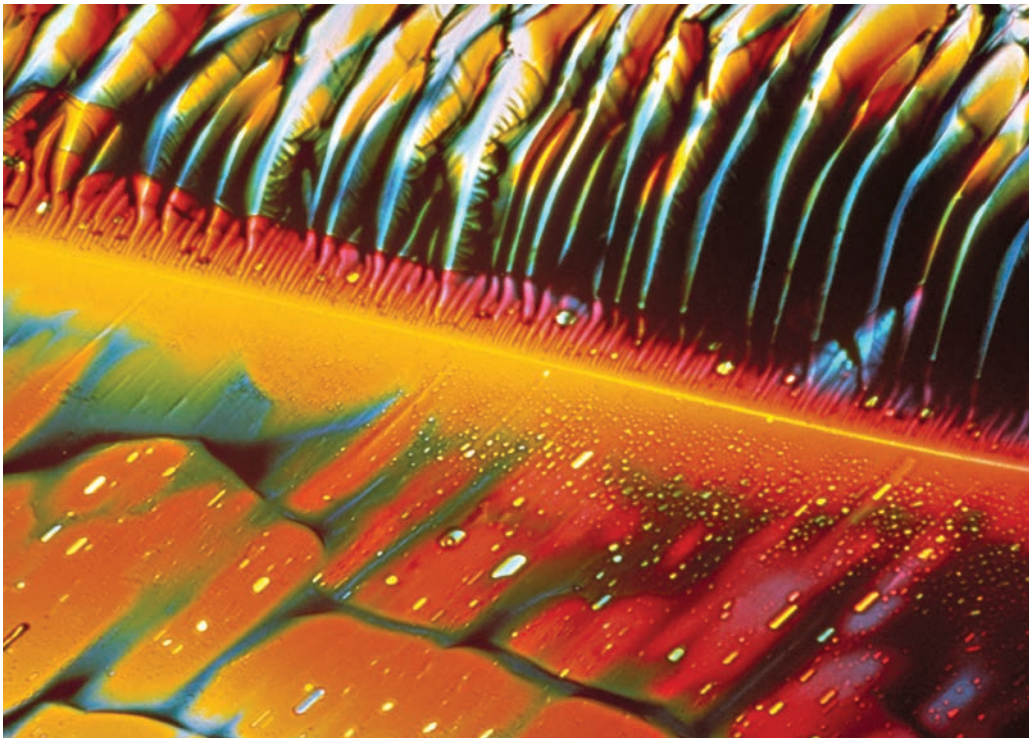
Immune cells known as B cells secrete the neurotransmitter gamma-aminobutyric acid (GABA), which promotes the emergence of anti-inflammatory macrophages that blunt the body's cytotoxic T-cell-based response to tumors, a mouse study by RIKEN scientists has shown[1]. This finding could lead to the development of therapies that fine-tune the immune response.

GABA is produced in plants in response to environmental stress and by bacteria in the gut. It is also a neurotransmitter that can help calm feelings such as anxiety, stress and fear.

To investigate the effect of infection on metabolite molecules at mouse lymph nodes, the researchers stimulated an immune response in mice by injecting them with ovalbumin and then compared activated lymph nodes on the same side of the body as the injection with inactivated ones on the other side. Surprisingly, the activated nodes had a higher amount of GABA than the non-activated ones.

Comparing mice that were deficient in T cells or B cells or neither revealed that the GABA was being released by immune B cells—an unexpected finding.

"We're very happy to have demonstrated that immune cells, particularly B cells, secrete the neurotransmitter GABA, highlighting this metabolite's position at the intersection between neurology, immunology, symbiology and physiology," says Sidonia Fagarasan of the RIKEN Center for Integrative Medical Sciences (IMS).



A light micrograph of the neurotransmitter gamma-aminobutyric acid (GABA) crystals. RIKEN researchers have shown that GABA from B cells plays a role in regulating the immune response.

The team found implanting a GABA-releasing pellet in B-cell deficient mice that had tumors led to faster tumor growth, indicating that GABA had a negative effect on tumor control. Indeed, the researchers found that GABA led to a decrease in cytotoxic T-cells, which are important players in fighting tumors. Drugs that block GABA prevented this.

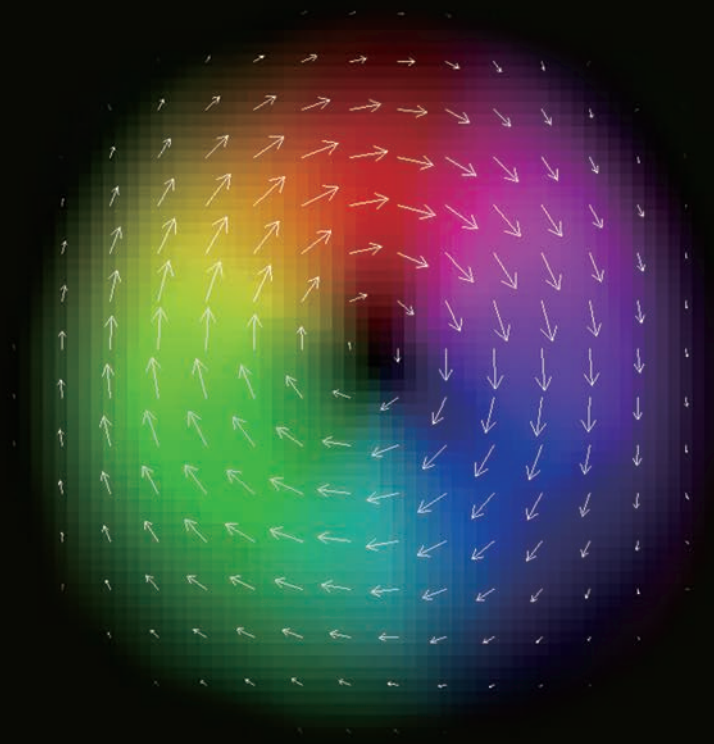
The team also found that GABA stimulated the differentiation of monocytes into anti-inflammatory macrophages, which are known to blunt T-cell reaction to tumors. "The implication is that the GABA caused the increase in anti-inflammatory macrophages, leading to a reduction in the activity of the cytotoxic T cells," explains Baihao Zhang of IMS. "It was very surprising to find that immune cells regulate each other through such small soluble metabolites produced by themselves."

"We found that B-cell-derived GABA has an immunoregulatory function," says Fagarasan. "In some cases, this inhibition can be harmful. In particular, we showed that GABA made by B cells limited immune responses to cancer. In other cases, such as autoimmune inflammatory responses or virus-triggered inflammation, GABA's inhibitory effect could be beneficial."

"There's still much to learn and biology continues to astonish us," Fagarasan adds. Drugs that are currently being used to modulate the neurological system might be repurposed to enhance the immune system's ability to fight certain types of cancer, she notes.

Reference

1. Zhang, B., Vogelzang, A., Miyajima, M., Sugiura, Y., Wu, Y., Chamoto, K., Nakano, R., Hatae, R., Menzies, R. J., Sonomura, K. *et al.* B cell-derived GABA elicits IL-10^{+} macrophages to limit anti-tumour immunity. *Nature* **599,** 471–476 (2021).



Skyrmions are tiny magnetic whirlpools that are promising for low-power data-storage devices. A team at RIKEN has, for the first time, used electrical currents to manipulate single skyrmions at room temperature in chiral-lattice magnets.

SKYRMIONS

Manipulating a single skyrmion at room temperature

A single nanoscale magnetic whirlpool has been controlled at room temperature for the first time

Single skyrmions—tiny magnetic vortices that are promising for use as computing bits in future ultra-dense, low-power data-storage devices—can be manipulated at room temperature by applying ultrashort pulses of electric current, an all-RIKEN team of physicists has shown for the first time[1]. This is a critical step toward developing skyrmion technology that can be used in practical applications.

Skyrmions are tiny whirlpools of magnetic flux that can be shunted around using electric currents that are several orders of magnitude lower than those needed to drive magnetic domain walls. This makes them promising for application in next-generation data-storage devices that have low-energy consumption. Furthermore, their small size should allow very high data-storage densities to be realized.

One key to creating practical spintronics devices is the ability to manipulate and measure a single skyrmion at room temperature. Many previous studies had focused on the dynamics of skyrmions that are about a micrometer or more in size or of clusters of skyrmions that are stable only at temperatures well below room temperature. Neither case is particularly amenable to practical applications.

Now, a team of six researchers led by Xiuzhen Yu of the RIKEN Center for Emergent Matter Science (CEMS) has directly observed the dynamics of a single skyrmion, with a size of about 100 nanometers, in a thin plate made of a special magnetic material known as a chiral-lattice magnet. They performed this observation at room temperature using an advanced microscopy technique called Lorentz transmission electron microscopy, which can image the local magnetic properties in a sample.

The researchers were able to track the motion of the skyrmion and control its Hall motion directions by flipping the magnetic field when they subjected it to ultrashort pulses (on the scale of nanoseconds) of electric current. "This is very exciting because, for the first time, we have been able to use electrical currents to manipulate single skyrmions at room temperature in a helimagnet-based device," explains Licong Peng of CEMS.

The researchers found that the skyrmion's motion underwent a dynamic transition from a pinned static state to a flow motion by way of creep motion under the stimulus of an electric current. They also measured the velocity of the skyrmion, which was relatively fast, being more than 3 meters per second.

The team is excited about the potential of their demonstration. "This research will lead to further studies of dynamics of various topological spin textures, leading to the development of skyrmion-based devices," says Yu.

Reference

1. Peng, L. C., Karube, K., Taguchi, Y., Nagaosa, N., Tokura, Y. & Yu, X. Z. Dynamic transition of current-driven single-skyrmion motion in a room-temperature chiral-lattice magnet. *Nature Communications* **12,** 6797 (2021).

ORGANIC SEMICONDUCTORS

Molecular tweak boosts performance of organic semiconductors

Sulfur-based chemical groups coax pyrene molecules into a brickwork crystal structure that offers enhanced electrical properties in a transistor device

Adding a simple, sulfur-containing chemical group to a semiconducting molecule can dramatically boost the molecule's performance in a transistor, RIKEN chemists have found[1]. This suggests that the properties of carbon-based semiconductors could be tuned by incorporating these groups.

Most electronic devices are currently based on silicon. However, organic semiconductor molecules offer a way to make cheaper, flexible devices such as display screens, wearable sensors and disposable radio-frequency identification tags. But most organic semiconductors cannot yet match the performance of their silicon rivals.

Two benchmark organic semiconductors are pentacene and its derivative TIPS-pentacene. They contain electrons that smear out across the molecules, forming the so-called π-conjugated system, which aids the transport of electrical charge.

In pentacene crystals, the molecules are arranged in a herringbone pattern, a common structure for organic semiconductors. When these herringbone patterns form a sandwich-like structure, the charge transport is very poor. In contrast, TIPS-pentacene molecules have a more unusual pattern—stacking like bricks in a wall. This shapes the molecules' π-conjugation in a way that improves charge transport and reduces the impact of imperfections in the crystal. However, it has been difficult to ensure that new organic semiconductors adopt the brickwork structure.

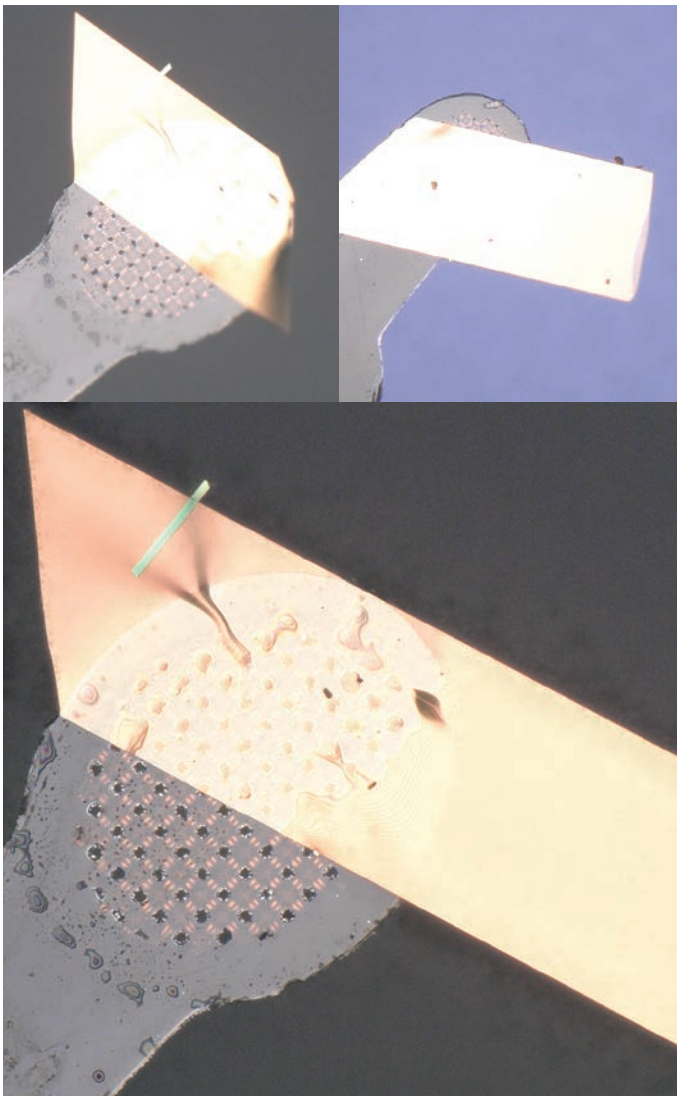
Now, Kazuo Takimiya of the RIKEN Center for Emergent Matter Science and his colleagues have found that adding methylthio groups (CH_3S–) to organic semiconductors can help molecules to form this beneficial pattern.

The researchers tested their approach on a molecule called pyrene, modifying each molecule with either two or four methylthio groups. Pyrene itself has a sandwich herringbone structure, but the compound carrying four methylthio groups, called MT-pyrene, had a brickwork structure.

The team then grew 50–150 nanometer-thick plates of crystalline MT-pyrene and used them to produce 26 field-effect transistors. The devices all performed well, exhibiting one of the highest recorded charge mobilities for any organic semiconductor with the brickwork structure.

The researchers found that when each molecule had four methylthio groups, they disrupted certain interactions between neighboring molecules. This prevented them from forming a sandwich herringbone structure, and ensured that they could only stack face-to-face, like bricks. This optimized the interactions between π-electrons and ultimately enhanced charge transport.

The team is confident that this strategy can be extended to other organic molecules. "We think that methylthiolation is a promising approach that can be applied to many other organic semiconductors," says Takimiya. The team plans to assess how other simple chemical groups affect the crystal structures of materials. They also hope to develop simpler methods to produce larger amounts of such crystals. ●



Optical microscopy images of a single crystal of MT-pyrene (gold trapezoid). It boosted the performance of a field-effect transistor.

Reference

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FLEXIBLE ELECTRONICS

Achieving flexibility without glue

Flexible electronics can now be made without using adhesives or high temperatures and pressures

A technique that is suitable for fabricating flexible, ultrathin electronics for bendable and wearable devices has been developed by RIKEN researchers[1].

Conventional methods for fabricating electronic devices are impractical for making bendable and wearable electronics. A big problem is connecting and integrating device components that reside on separate ultrathin polymer films. Conventional fabrication techniques that use adhesive layers to stick electrodes together reduce device flexibility and require high temperatures and pressures that can damage super-thin electronics. Ways to directly bond metal to metal are available, but they require extremely smooth and clean surfaces that are difficult to achieve.

"This is the first demonstration of ultrathin, flexible gold electronics fabricated without any adhesive"

Now, Kenjiro Fukuda of the RIKEN Center for Emergent Matter Science and co-workers have developed a method to secure connections that does not require adhesives, high temperatures and pressures, or extremely smooth and clean surfaces. It creates stable bonds between gold electrodes printed onto ultrathin polymer sheets using a water-vapor plasma. The process takes less than a minute at room temperature, followed by about a 12-hour wait.

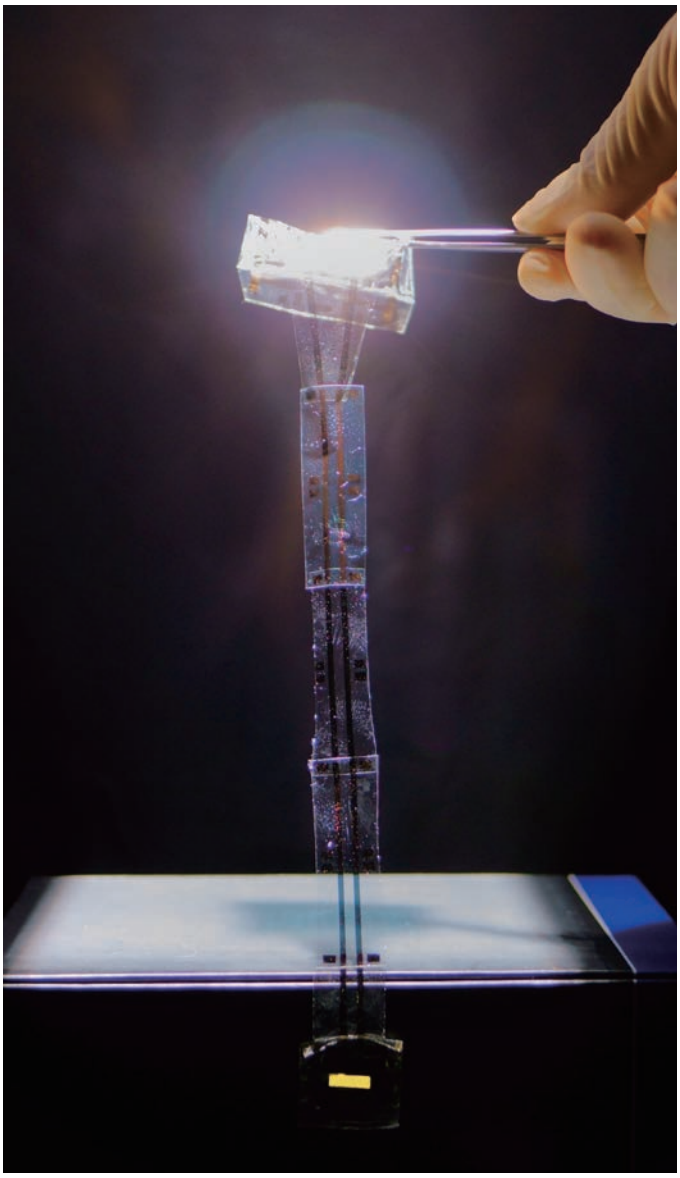
"This is the first demonstration of ultrathin, flexible gold electronics fabricated without any adhesive," says Fukuda. "Using this new direct bonding technology, we were able to fabricate an integrated system of flexible organic solar cells and organic LEDs."

The new technique performed better than conventional adhesive or direct-bonding techniques. In particular, the bonds were stronger and more consistent than those produced by standard surface-assisted direct bonding methods. The material also conformed better to curved surfaces and was more durable than those fabricated by using standard adhesive techniques.

The method is surprisingly simple. Gold electrodes are fixed onto polymer sheets and the electrode sides of the sheets are exposed to water-vapor plasma for 40 seconds. The polymer sheets are then pressed together so that the electrodes overlap in the correct locations. After being left at room temperature for 12 hours, the devices are ready to use.

The team demonstrated their method by using it to integrate ultrathin organic photovoltaic and LED-light modules that were printed on separate films and connected by five additional polymer films. The devices withstood extensive testing and the LEDs' power efficiency did not drop. The technique was also able to join pre-packaged LED chips to a flexible surface.

"We expect this new method to become a flexible wiring and mounting technology for next-generation wearable electronics that can be attached to clothes and skin," says Fukuda. "The next step is to develop this technology for use with cheaper metals, such as copper or aluminum."●



Photograph showing the operation of an ultraflexible integrated device consisting of an organic photovoltaic module (bottom) and an organic LED (top) connected by five wiring films.

Reference

1. Takakuwa, M., Fukuda, K., Yokota, T., Inoue, D., Hashizume, D., Umezu, S. & Someya, T. Direct gold bonding for flexible integrated electronics. *Science Advances* **7,** abl6228 (2021).

COMPUTATIONAL BIOPHYSICS

Discovering how potential drugs cope with crowds

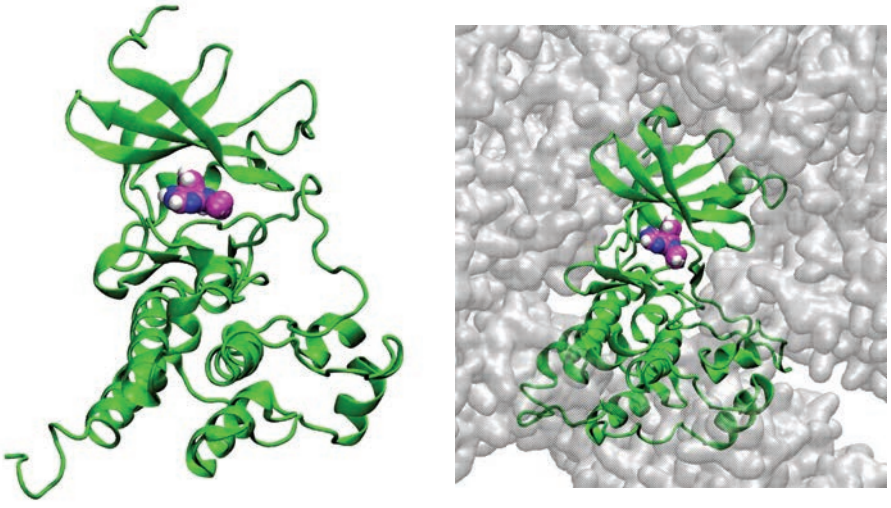
Microsecond-scale simulations are helping scientists understand how drugs 'navigate the crowd' inside cells

Supercomputer simulations by RIKEN researchers have revealed how drug binding to a protein target changes as the surrounding environment becomes more cluttered with other proteins[1]. These simulations could help improve drug development since they shed light on why some drugs work in theory but flop in practice.

The initial stages of drug development usually involve simulating the interactions between a molecule and its target protein. Although these simulations can suggest a drug is effective, the interaction can frequently fail to live up to its promise when tested on living cells. Computational biophysicist Yuji Sugita of the RIKEN Center for Biosystems Dynamics Research (BDR) and his colleagues wanted to make simulations more accurate by accounting for cells' normally crowded environments.

The team now wants to examine how crowding affects other target proteins and drugs.

"Many proteins and macromolecules are present inside cells, making it a crowded environment," explains Sugita. "In fact, large molecules account for anywhere between a fourth to a half of the volume of a cell's cytoplasm. We wanted to discover how these crowded environments affect drug binding to target proteins."



Simulations of the interaction of the enzyme c-Src kinase (green) with inhibitor PP1 (magenta, blue and white spheres) in the presence of low (left) and high (right) concentrations of bovine serum albumin (BSA; gray). The simulations reveal that crowding by BSA reduces the ability of PP1 to bind with c-Src kinase.

To do this, they developed a highly optimized software program called GENESIS for use with supercomputers in Japan. They then conducted microsecond-scale simulations of the interaction of an enzyme (c-Src kinase) with an inhibitor (PP1) in the presence of different concentrations of bovine serum albumin (BSA). Sugita's collaborator, Michael Feig, a professor at Michigan State University, also performed simulations of the same systems using a molecular-dynamics supercomputer in the United States. The team chose c-Src kinase because the enzyme regulates signal transduction pathways and its dysregulation is associated with many diseases, including cancers.

The researchers found that crowding by BSA reduced the amount of PP1 able to reach the enzyme by physically blocking its access and also by weakly and non-specifically interacting with it.

Still, small amounts of PP1 were able to slip through the crowds. But the simulations showed that BSA crowding also covered some binding sites on c-Src kinase and changed the enzyme's shape, altering the pathways available for it to reach its main binding site.

The team validated their results by performing laboratory tests using the actual proteins in similar conditions. These experiments conducted by Mikako Shirouzu and her colleagues in RIKEN BDR showed that PP1's efficacy in inhibiting c-Src kinase decreased with increasing BSA crowding.

The team now wants to examine how crowding affects other target proteins and drugs. They also intend to use their supercomputers to study protein function inside biological membranes and cell organelles. "These different environments could affect protein functions similarly or differently," says Sugita. "We just don't know." ●

Reference

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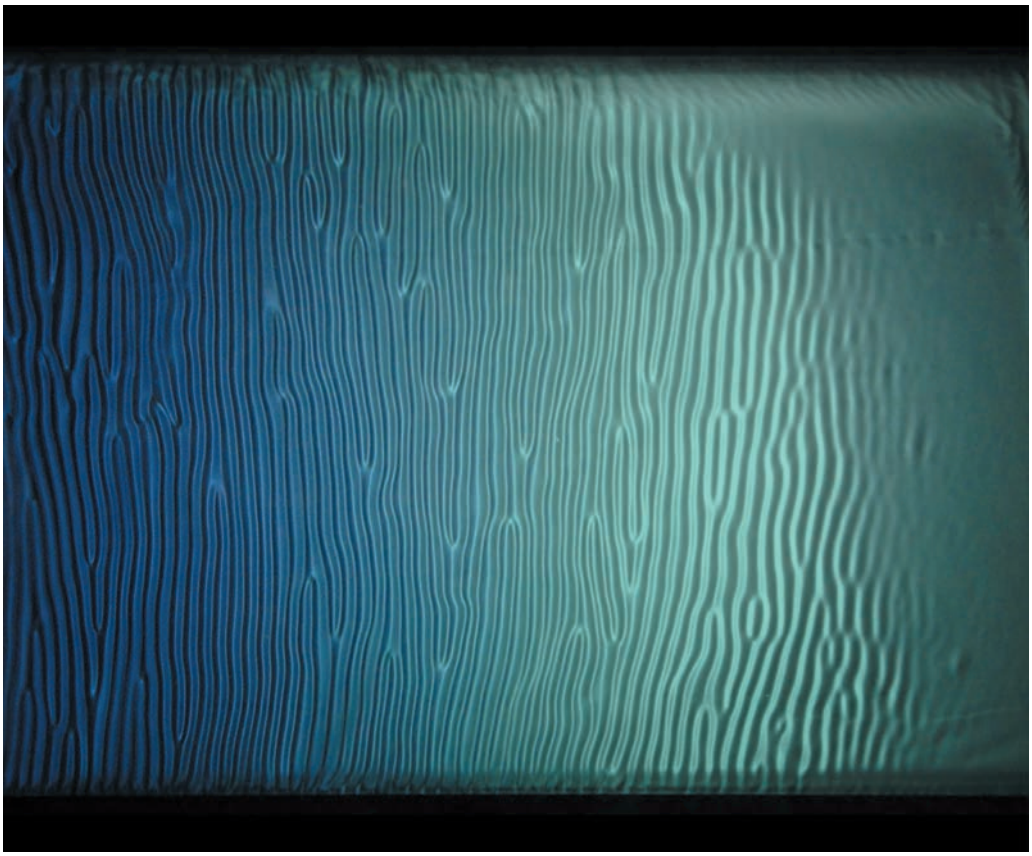
COLLOIDS

Mimicking the way nature moves

Resembling movement in natural systems, billions of aligned nanosheets have been made to move in concert



Time streaks showing the motion of microparticles being transported by titanium nanosheets.

Scientists are closer to fabricating devices that can use microscopic movements in a coordinated way to create coherent motion on a macroscopic scale, thanks to a system produced by RIKEN material scientists that mimics the way living organisms move[1].

The motion of human muscles occurs through a complex process in which individual 'molecular motors' move in a coordinated way. Similarly, the wave-like motion of hairy appendages known as cilia enables bacteria to propagate in fluids in a well-controlled manner. In contrast, just a small number of moving elements tend to drive artificial machines. Consequently, living organisms can generate fine and intricate motions on demand, whereas engines can only repeat simple linear or circular motions.

Scientists have tried to mimic living systems, but without much success, until now. "Researchers have previously tried to replicate nature by creating macroscopic motion using coordinated motion of tiny components, but it seemed difficult to achieve," says Yasuhiro Ishida of the RIKEN Center for Emergent Matter Science (CEMS).

"It was very exciting to see the microparticles actually moving through the material."

Ishida and his co-workers set out to create an artificial material that could recreate the movement of natural systems. They succeeded in coaxing ten billion colloidally dispersed titanium nanosheets in an aqueous solution to operate coherently and create a wave that propagated through the material even though the nanosheets were not attached to one another.

The nanosheets were initially induced to each line up with a large, uniform separation of about 420 nanometers. They were held in place by the competitive electrostatic repulsion and van der Waals attraction between the negatively charged nanosheets. "Our approach was different in that the individual units were not attached through bonds but rather held in place by the competition between attractive and repulsive forces," notes Ishida.

When the researchers weakened the repulsive force by adding ions to the solution, the nanosheets drew closer to each other, creating a wave that spread through the material.

The team used the wave to transport microparticles in one direction and at a constant speed. "It was very exciting to see the microparticles actually moving through the material," recalls Koki Sano, also of CEMS. "We know that this kind of movement is very common in nature, so it was definitely an achievement to see that we could actually replicate that in some way."

"We hope that this discovery will provide a general principle for designing macroscopic machines from huge numbers of tiny components," adds Ishida. ●

Reference

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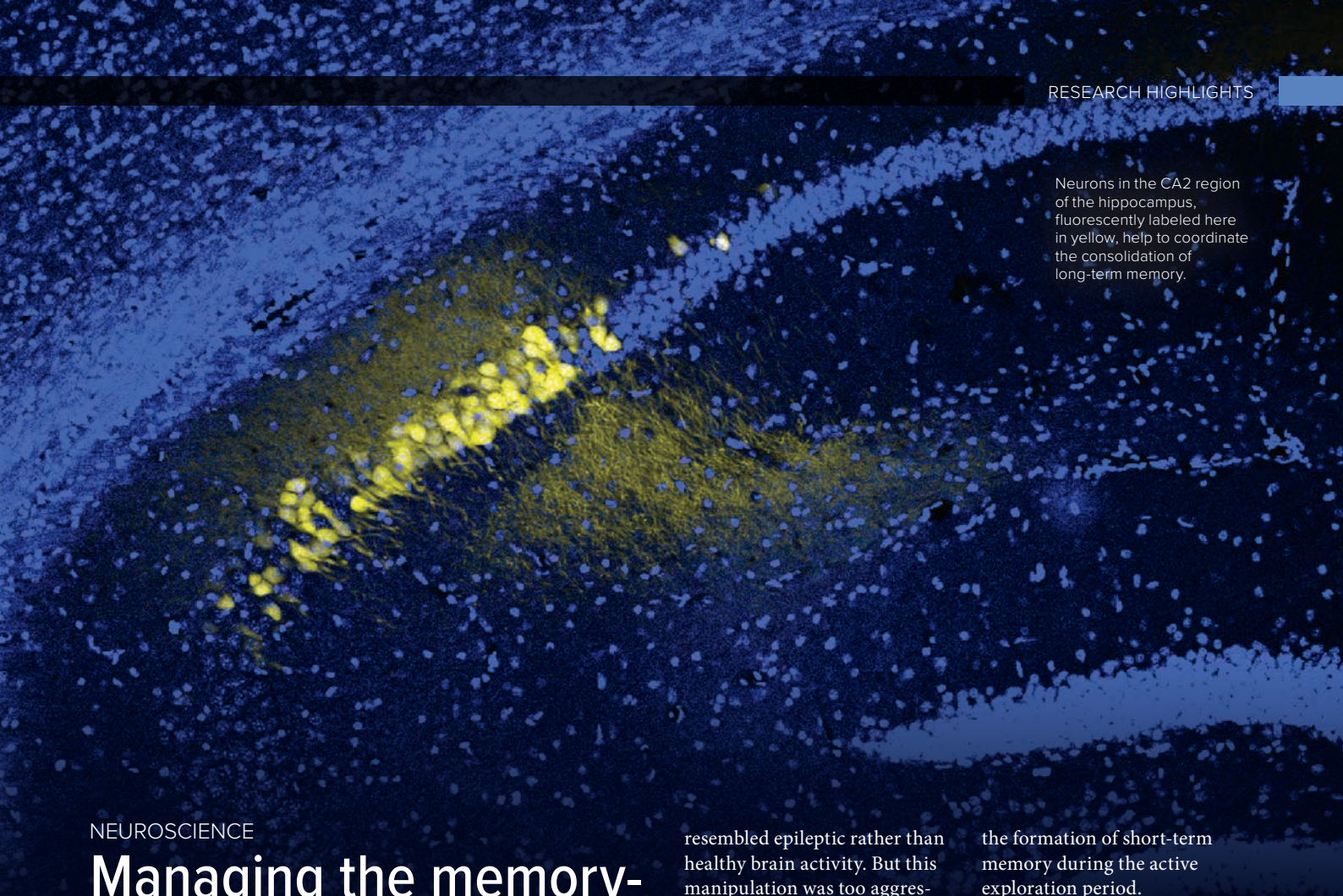

Neurons in the CA2 region of the hippocampus, fluorescently labeled here in yellow, help to coordinate the consolidation of long-term memory.

NEUROSCIENCE

Managing the memory-making process

A brain structure that coordinates the consolidation of short-term memories into long-term ones during sleep has been identified

A brain region in mice that plays a key role in coordinating the playback process that consolidates memories during sleep has been identified by RIKEN neuroscientists[1]. This finding could have implications for neurological disorders in people such as schizophrenia.

Activities we do while awake produce short-term memories that are subsequently consolidated into long-term storage within a brain structure called the hippocampus. This process has been linked to distinctive brain wave patterns known as sharp-wave ripple activity in the CA1 region of the hippocampus, which trigger selective reactivation of neural circuits associated with recent experiences.

A team led by Thomas McHugh of the RIKEN Center for Brain Science has been interested in how another hippocampal region, CA2, contributes to sharp-wave ripple activity in CA1. CA2 is thought to be mainly involved in forming memories related to social interactions. "However, some data—including from our lab—suggests that CA2's role extends to other domains of memory," says McHugh.

Previously, McHugh's team had found that inactivating CA2 in mice gave rise to highly irregular sharp-wave ripple patterns in CA1, which resembled epileptic rather than healthy brain activity. But this manipulation was too aggressive to meaningfully dissect the interplay between these regions.

In their latest work, the researchers employed a subtler approach in which mice were genetically manipulated so that their CA2 neurons could be briefly silenced rather than broadly inactivated. They then examined how this transient inactivation of CA2 affected memory formation during rest after the mice had explored an experimental environment.

This manipulation radically altered the replay process in the hippocampus. "Normal memory formation occurs through the discrete, sequential reactivation of subsets of neurons linked with particular experiences," explains McHugh. "But when we temporarily inhibited CA2, these different experiences were reactivated concurrently in time, which may lead to interference and problems in memory consolidation." Notably, CA2 inactivation didn't seem to greatly affect the formation of short-term memory during the active exploration period.

These findings strongly support the notion that CA2's role goes well beyond social interaction, and it may extend to the broader orchestration of memory making in general. Since this region is also wired into numerous other brain regions, McHugh is keen to further explore CA2's involvement in integrating neural information in both health and disease. "One intriguing link is to mental disorders such as schizophrenia where inappropriate links between memories can underlie symptoms such as disordered thinking or paranoia," he notes.

Reference

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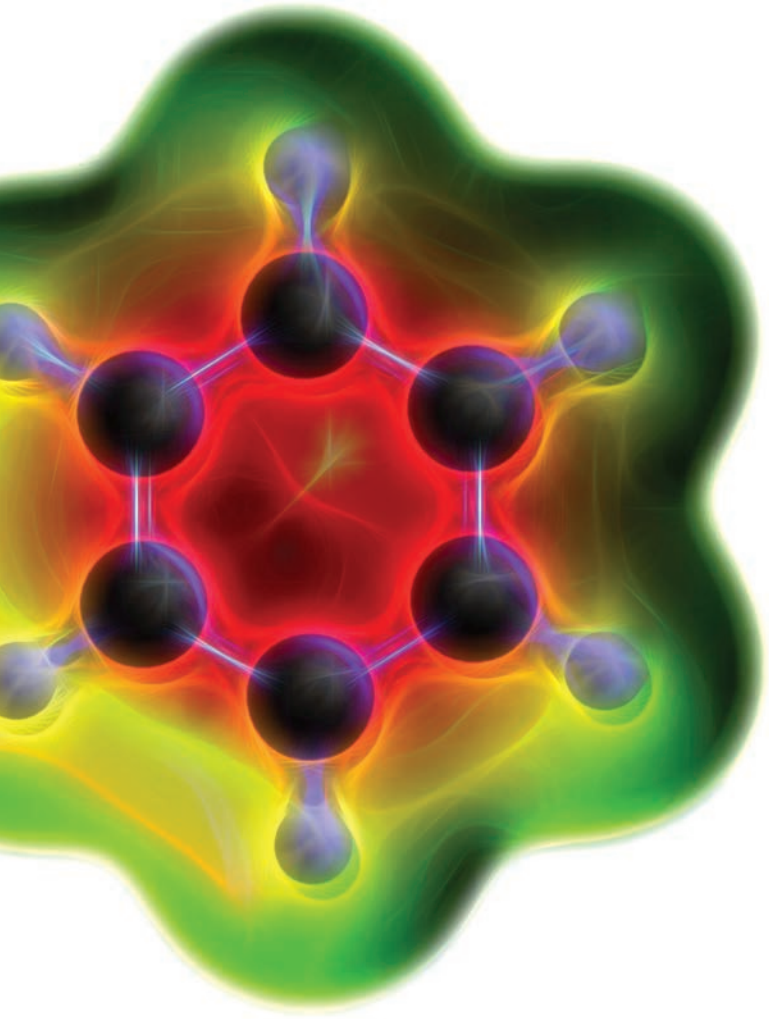
CHEMOTHERAPY

Manufacturing anticancer drugs inside the body

Synthesizing anticancer drugs near tumors promises to drastically reduce harmful side effects



RIKEN researchers have created benzene rings near cancer cells in the body by using a transition-metal-catalyzed complex designed for selective delivery to tumorous tissue.

RIKEN chemists have treated cancer in mice using metal catalysts that assemble anticancer drugs together inside the body[1]. Because this technique avoids indiscriminate tissue damage, it should significantly reduce undesirable side effects.

Chemotherapy often causes debilitating side effects because drugs that damage cancer cells can also harm healthy cells. Current methods for reducing side effects include selective delivery of anticancer drugs to cancerous tissue and the conversion of non-toxic compounds, known as prodrugs, into toxic compounds near cancerous tissue.

"We believe this is a paradigm shift for pharmaceuticals and drug discovery"

Now, Katsunori Tanaka at the RIKEN Biofunctional Synthetic Chemistry Laboratory and co-workers have developed a method for activating prodrugs that relies on transition-metal catalysis inside the body and have demonstrated it in mice.

The catalyst is usually destroyed by antioxidants when it is injected into the body, but Tanaka's team avoided this problem by placing it inside pockets within a protein.

To ensure that the drug targeted cancerous cells, the team attached chains of cancer-binding sugar molecules to the protein's surface. In addition to reducing side effects, this inhibited cancer growth and spread.

This is the first time that cancer in mice has been treated by assembling anticancer drugs inside the body near cancer cells. "In the past, we used similar methods to attach anticancer drugs to tumors," explains Tanaka. "But here, we were able to avoid putting any toxic drugs into the body at all."

Since the basic skeleton of most anticancer drugs contains a benzene ring, the researchers started by making benzene rings inside the body using transition-metal catalysts. "No one believed that artificially synthesizing benzene rings inside the body was possible, but I was confident that we could do it based on our previous achievements," says Tanaka. Using a transition-metal-catalyzed complex designed for selective delivery to cancerous tissues, they efficiently created the benzene rings needed by cancer drugs in the vicinity of cancer cells.

By using non-toxic substances, and only joining them together to form active anticancer drugs at the tumor site, the team saw a 1,000-times increase in the cancer-inhibiting activity of the drugs. Simply administering the ingredients needed for the drug, along with the transition-metal catalyst, through a vein, inhibited cancer growth in mice without side effects such as weight loss.

The method is expected to enable various other molecules to be synthesized inside the body. "Many cancer patients are dying because of the side effects of treatment. We believe our technology, which attacks cancer cells highly effectively without side effects, will be able to save lives," says Tanaka. "We believe this is a paradigm shift for pharmaceuticals and drug discovery."

Reference

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GUT MICROBIOME

Bacteria and bile acid may hold the secret to a long and healthy life

The unique gut microbiome of centenarians could be part of the secret of their long life

People over 100 years old may owe their longevity in part to having certain species of bacteria in their guts that, via bile acids, help to ward off infections and maintain a healthy gut, a RIKEN-led team has found[1]. This finding may help to develop diets that enable those bacteria to flourish.

People who live to 100 years old or older are surprisingly robust, often being less susceptible to infections and age-related diseases than many who are decades younger than them. Scientists are eager to discover the causes of this robustness as they could hold the keys to promoting healthy aging.

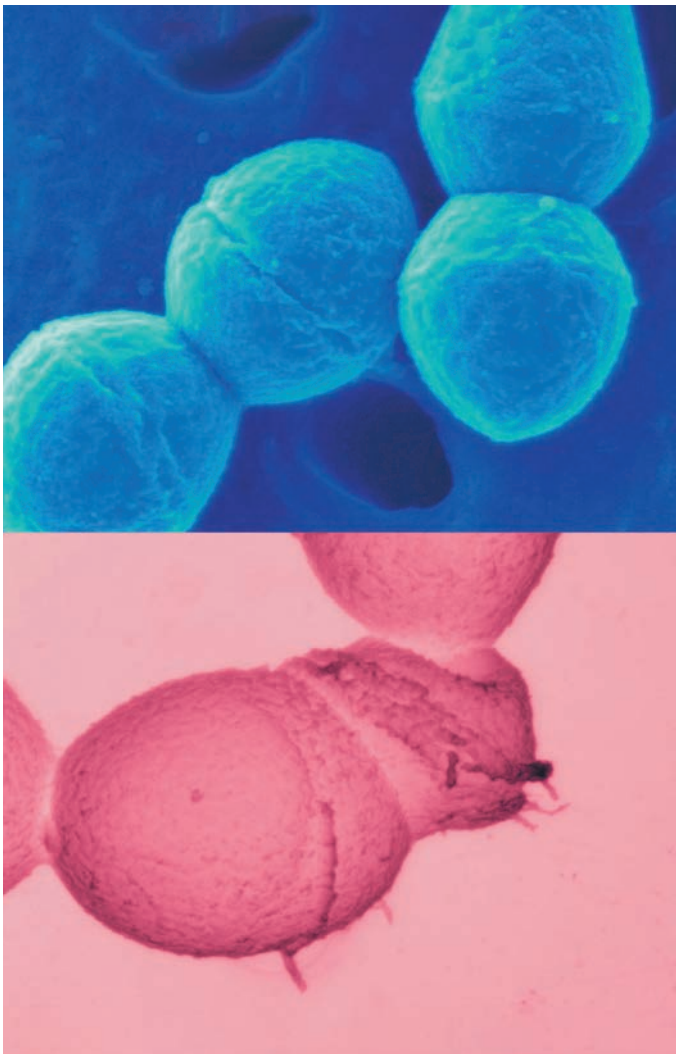
"We were surprised and excited to find active metabolism by gram-negative bacteria."

The community of microorganisms that inhabit our guts has increasingly been shown to play a key role in both preserving health and the development of certain diseases. This led Kenya Honda of the RIKEN Center for Integrative Medical Sciences to speculate whether some species of gut bacteria may be contributing to the longevity of centenarians.

To investigate this, Honda and co-workers analyzed stool samples from three groups of healthy Japanese individuals: young people (average age 31), older people (average age 86) and centenarians (average age 107). The microbiome profiles of the centenarians differed from those of the other two groups in that they contained genes that encoded for bile acids. Analysis of the bile acids of the three groups indicated the centenarians had higher levels of specific secondary bile acids—bile acids that have been modified by bacteria.

Interestingly, the increased levels of secondary bile acids were due to the action of a group of bacteria that hadn't been previously known to be related to secondary bile acids. "Most previous studies on the biosynthetic pathways of secondary bile acids described the role of gram-positive bacteria," says Honda. "So we were surprised and excited to find active metabolism by gram-negative bacteria."

The team found that one of these secondary bile acids exhibited potent antibacterial effects against harmful gut bacteria that are resistant to multiple drugs (see image). They suspect that this antibacterial effect imparts centenarians with better defense against infections and also helps keep harmful gut bacteria under control.



Scanning electron micrographs of drug-resistant bacteria grown in medium without (top) and with (bottom) the secondary bile acid isoalloLCA. The bacteria grown with isoalloLCA exhibit changes to their shapes.

The unique make-up of the centenarians' microbiomes is probably partially due to their diets. "Although we didn't investigate the influence of diet, it's highly likely that the centenarians have diets rich in fiber and fermented foods, which affected the microbiota configuration," says Honda. "We hope that advances in microbiome and diet research can address this question in the future."

The team plans to explore two directions. "We want to study the effects of secondary bile acids on the host physiology," says Honda. "We also intend to extend the research to other steroidal compounds." ●

Reference

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STARCH

Making tapioca even healthier

Genetically modified tapioca contains a higher proportion of starch that is healthier because it is harder to digest

RIKEN researchers have produced a healthier form of tapioca by genetically modifying it to have a higher proportion of starch that is harder to digest.

A form of starch that is more resistant to digestion and hence healthier has been created in the cassava plant by RIKEN researchers[1].

Most of the starch we eat comes from cereal or tuber crops. Starch consists of two molecules—amylose and amylopectin. Amylose is a straight chain of glucose molecules connected end to end, whereas the chains branch out like a tree in amylopectin.

Edible crops have different relative amounts of amylose and amylopectin. For example, rice starch contains about twice the amount of amylose as cassava starch, commonly called tapioca.

Starch consisting mainly of branching amylopectin is easily digested by enzymes in saliva. That sounds good, but amylose and less-branched amylopectin are healthier because their structures resist digestion—instead of giving unhealthy blood sugar spikes, resistant starch travels to the gut where it nourishes beneficial bacteria that help maintain health.

The team focused on the cassava plant because it is often overlooked, despite being one of most important crops in tropical and subtropical regions. "By suppressing multiple genes one by one, we were able to increase the amount of resistant tapioca by about 63%," says Yoshinori Utsumi of the RIKEN Center for Sustainable Resource Science. "Not only will this starch improve intestinal function, but it will also improve blood sugar and insulin responsiveness."

Resistant starch contains less amylopectin and more harder-to-digest amylopectin that has fewer branches and longer chains. To generate resistant starch, the researchers focused on starch branching enzymes (SBEs)—enzymes needed to create branches in amylopectin. They reasoned that reducing this enzyme's activity would produce resistant starch.

The team identified three SBE genes, with a few subtypes, in the cassava genome. *SBE1* and *SBE2a* appeared to be involved in making amylopectin in cassava leaves and roots, whereas *SBE2c* was only in the roots. The researchers next created several lines of transgenic cassava to compare with unmodified wild-type cassava. The most successful transgenic lines were those in which both *SBE1* and *SBE2* expression had been reduced to about 10% of wild-type expression.

Looking at factors that increased starch resistance, the researchers found that the roots of two transgenic lines in which both *SBE1* and *SBE2* were reduced contained about 40% amylose, whereas wild-type cassava contained about 17% amylose. These lines also produced root amylopectin with fewer branches and longer chains. Overall, the amount of resistant tapioca starch rose from 0.4% to about 25%, a whopping increase of about 63 times, although the total amount of starch decreased a little.

"In addition to advancing cassava molecular breeding, we hope our findings will lead to more functional foods that improve human health," says Utsumi. ●

Reference

1. Utsumi, Y., Utsumi, C., Tanaka, M., Takahashi, S., Okamoto, Y., Ono, M., Nakamura, Y. & Seki, M. Suppressed expression of starch branching enzyme 1 and 2 increases resistant starch and amylose content and modifies amylopectin structure in cassava. *Plant Molecular Biology* **108,** 413–427 (2021).

REPRODUCTIVE BIOLOGY

Chromosome coordination gives dad's DNA a helping hand

After fertilization, the mammalian egg organizes itself to safeguard paternal genomic material and ensure healthy offspring

RIKEN researchers have shown how the genomic sorting that occurs during fertilization—the incorporation of genomic material from both parents and the elimination of excess maternal DNA from the egg—takes place in mice[1]. If the same process occurs in humans, the finding could help to improve some assisted reproductive technologies.

The team now hopes to find clinical collaborators

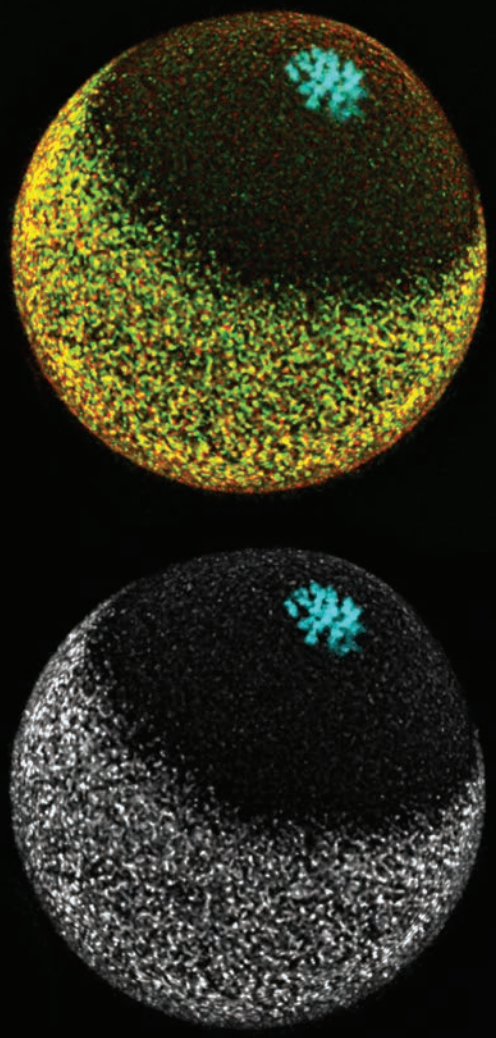
Sperm and ova are produced through a cell-division process known as meiosis, whose end product is cells containing one copy of each chromosome. But in many vertebrates, including humans, this process naturally pauses for unfertilized ova, leaving these cells with both copies of each maternal chromosome. Meiosis proceeds after fertilization, eliminating one of these extra maternal genome copies.

There are mechanisms to prevent accidental ejection of the paternal genome when meiosis resumes, as the presence of maternal DNA alone will cause development to stall. But this sorting process has been tough to untangle. "The lack of robust techniques for high-resolution imaging of live cells has hampered the study of fertilization as a continuous process," explains Masashi Mori of the RIKEN Center for Biosystems Dynamics Research.

Now, Mori and his colleagues have developed a microscopy strategy that allowed them to directly visualize chromosomal dynamics in a fertilized mouse egg.

Using this technique, they discovered that the unfertilized egg organizes its internal protein infrastructure in a way that biases sperm fusion at sites far from the maternal chromosomes (see image). This is achieved partially through the formation of structures on the surface of the egg that appear to physically transport the sperm to an appropriate fusion site.

When fertilization occurs, the same arrangement of proteins helps to sequester paternally and maternally contributed DNA. This keeps those chromosomes secure when meiosis resumes and divides up the maternal DNA—one set of maternal chromosomes will be shed entirely, while the other will remain behind to form a complete set with paternal DNA in the newly formed zygote.



Sperm receptors (red and green) cover the surface of an unfertilized egg except near the maternal chromosomes (blue).

The team now hopes to find clinical collaborators who can help confirm whether the same process plays out in humans. If it does, these findings could have important implications for assisted reproductive technologies. For example, intracytoplasmic sperm injection, in which sperm are directly fused with ova in the laboratory, could fail if clinicians aren't mindful of where they aim. "In some intracytoplasmic sperm injection zygotes, injected sperm may be too close to maternal chromosomes and the paternal chromosomes might be eliminated," says Mori. "Our study suggests that the visualization of maternal chromosomes by a non-invasive technique would help to prevent this."

Reference

1. Mori, M., Yao, T., Mishina, T., Endoh, H., Tanaka, M., Yonezawa, N., Shimamoto, Y., Yonemura, S., Yamagata, K., Kitajima, T. S. *et al.* RanGTP and the actin cytoskeleton keep paternal and maternal chromosomes apart during fertilization. *Journal of Cell Biology* **220,** e202012001 (2021).

NANOSPECTROSCOPY

Acquiring spectra from single molecules

The ability to take spectra from individual molecules promises to be a vital addition to the toolkit of researchers looking at excited molecules

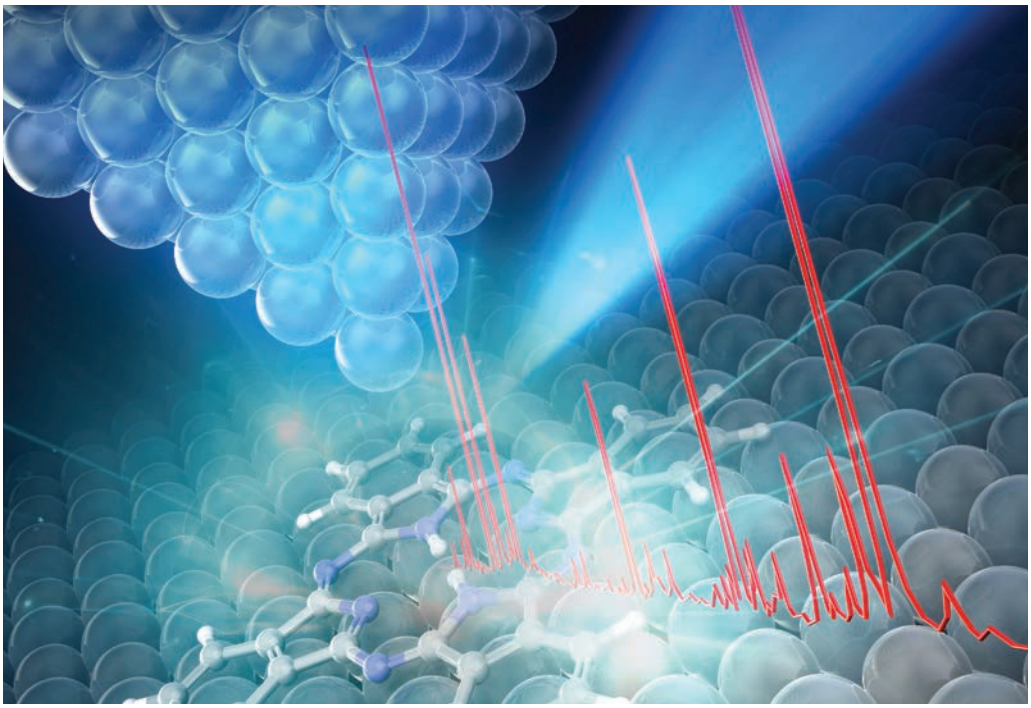
RIKEN physicists have taken a spectrum from a single molecule using a new nanospectroscopy technique they developed[1]. This ability to probe individual molecules will be invaluable for tailoring the properties of organic materials for use in devices such as light-emitting diodes (LEDs) and solar cells.

Exciting a molecule, either by shining light on it or applying an electric field, can cause it to behave in interesting ways. For example, excited molecules can emit light, participate in chemical reactions that non-excited molecules cannot participate in, or give off electrons when illuminated by light. Many natural systems and artificial devices exploit these abilities of excited molecules.

Light-based spectroscopy methods are useful for investigating excited molecules en masse, but the inability to focus light beams below a certain width makes it challenging to apply them to nanoscale samples. In contrast, electron and scanning probe microscopes can image objects on an atomic level, but they don't provide the wealth of spectroscopic information that optical methods give. Researchers dream of combining the advantages of both approaches.

Now, Hiroshi Imada of the RIKEN Surface and Interface Science Laboratory and his co-workers have realized this goal by developing a laser nanospectroscopy technique that can acquire a spectrum from a single molecule.

"We combined scanning tunneling microscopy with laser spectroscopy to simultaneously achieve high spatial and energy resolutions," explains Imada. "That allowed us to reveal the nature of molecules with unprecedented precision."



By using the tip of a scanning tunneling microscope (inverted pyramid) and the beam of a tunable laser (blue beam), RIKEN physicists have taken a spectrum (red line) from a single molecule lying on a surface.

The team demonstrated the sensitivity of this method by taking two molecules that differed only slightly: at the center of one molecule, two hydrogen atoms each had an additional neutron. The nanospectroscopy technique could detect this tiny mass difference between the molecules.

Their technique uses a laser beam to drive the electromagnetic field of a plasmon—electrons in a metal vibrating in concert—that forms between the tip of a scanning tunneling microscope and the metal substrate where the sample is located. Since the plasmon is a mere two nanometers in diameter—roughly 100 times smaller than the narrowest width of a focused laser beam—the technique's spatial resolution is very high.

Using the precise nanospectroscopy, the team also found a novel way to tune the energy levels of single molecules by applying a static electric field. "The resonance energy of a single molecule can be tuned by applying a voltage," says Imada. "This mechanism, which hadn't been visualized previously, emerged unexpectedly as a result of symmetry breaking at the molecular level."

The team now wants to develop a time-resolved version of nanospectroscopy. "We plan to develop ultrafast nanospectroscopy to shed light on energy conversion in molecular systems," says Imada. ●

Reference

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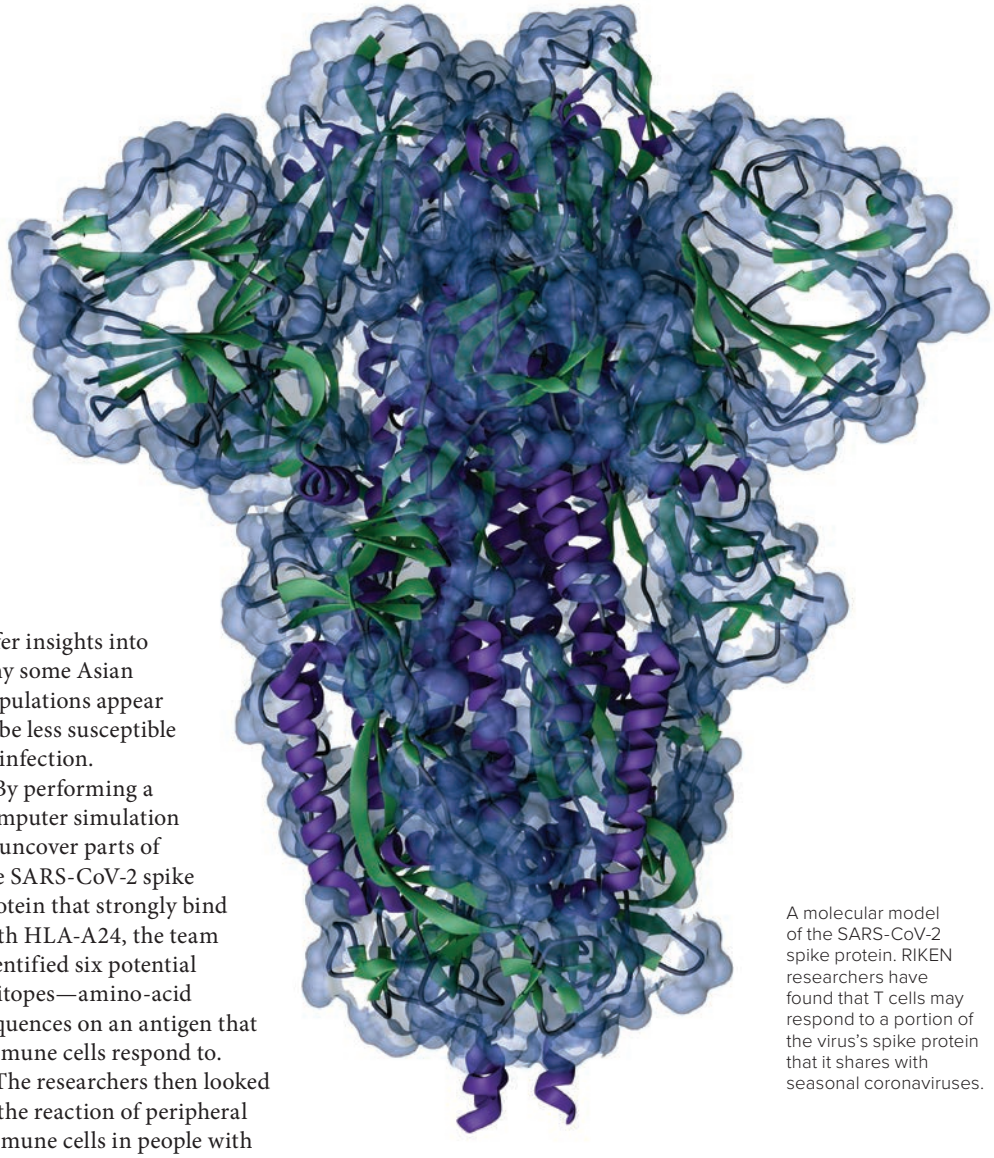
COVID-19

Finding COVID-19's hotspot

The identification of an amino-acid sequence on SARS-CoV-2's spike protein that T cells respond to raises hopes of developing a new kind of vaccine



A molecular model of the SARS-CoV-2 spike protein. RIKEN researchers have found that T cells may respond to a portion of the virus's spike protein that it shares with seasonal coronaviruses.

RIKEN researchers have found that people with a certain type of human leukocyte antigen (HLA) may be able to mount a killer T cell response to COVID-19 thanks to the T cells responding to a portion of the virus's spike protein that is also present in seasonal coronaviruses that cause the common cold[1]. This finding could potentially help to develop a new type of vaccine against COVID-19.

Most studies on the immune response to SARS-CoV-2, the virus that causes COVID-19, have focused on the antibody response to the virus, which prevents initial infection. However, once the virus infects cells, natural killer cells and memory T cells become critical to eliminate viruses quickly.

Since the natural killer cell response should be relatively similar across people, a team led by Shin-ichiro Fujii of the RIKEN Center for Integrative Medical Sciences focused on memory killer T cells, which lead an attack against viruses they 'remember'. They looked at individuals with HLA type A24, which is a relatively common HLA type in Japan and other Asian countries and hence may offer insights into why some Asian populations appear to be less susceptible to infection.

By performing a computer simulation to uncover parts of the SARS-CoV-2 spike protein that strongly bind with HLA-A24, the team identified six potential epitopes—amino-acid sequences on an antigen that immune cells respond to.

The researchers then looked at the reaction of peripheral immune cells in people with the HLA-A24 type who hadn't been infected with SARS-CoV-2, to see whether they had memory killer T cells that would respond to antigens from the virus. About 80% of uninfected healthy donors with the HLA-A24 type showed a reaction for a single peptide—a sequence the team called the QYI epitope.

Finally, the team found that QYI-specific memory killer T cells from donors with the A24 serotype showed cross-reactivity against the relevant epitopes, which are relatively conserved from human coronaviruses including seasonal coronaviruses.

When the researchers looked at the responses of blood-cancer patients, who are particularly susceptible to serious COVID-19, they found a much smaller response than from non-exposed healthy individuals. Importantly, however, even in blood-cancer patients, there is a hotspot in the spike protein of the virus—a sequence of 27 amino acids around the QYI epitope. T cells responding to this hotspot can still mount a vigorous immune response: 100% of healthy people and 65% of blood-cancer patients responded to this hotspot.

"This leads to the hope of developing vaccines that could boost the immune response even in immunocompromised patients," says Fujii. ●

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SKYRMIONS

Heat flow shifts skyrmions

Magnetic vortices could be manipulated by waste heat to realize low-power computing applications

Tiny amounts of heat can be used to control the movement of magnetic whirlpools called skyrmions, RIKEN physicists have shown[1]. This ability could help to develop energy-efficient forms of computing that harness waste heat.

Skyrmions are minuscule vortices that form when the magnetic flux of a group of atoms organizes into swirling patterns. Skyrmions can move around inside a material, and under certain conditions they cluster together to form a regular arrangement known as a skyrmion lattice (upper part of image).

The team is now studying the heat-induced dynamics of skyrmions

Skyrmions are promising information carriers in next-generation computer chips that have very low power requirements. Researchers can already control skyrmions by applying electrical currents and magnetic fields, but they are seeking to manipulate them using heat flow instead. "This is an exciting prospect since it would raise the possibility of using waste heat to move skyrmions around," says Xiuzhen Yu at the RIKEN Center for Emergent Matter Science.

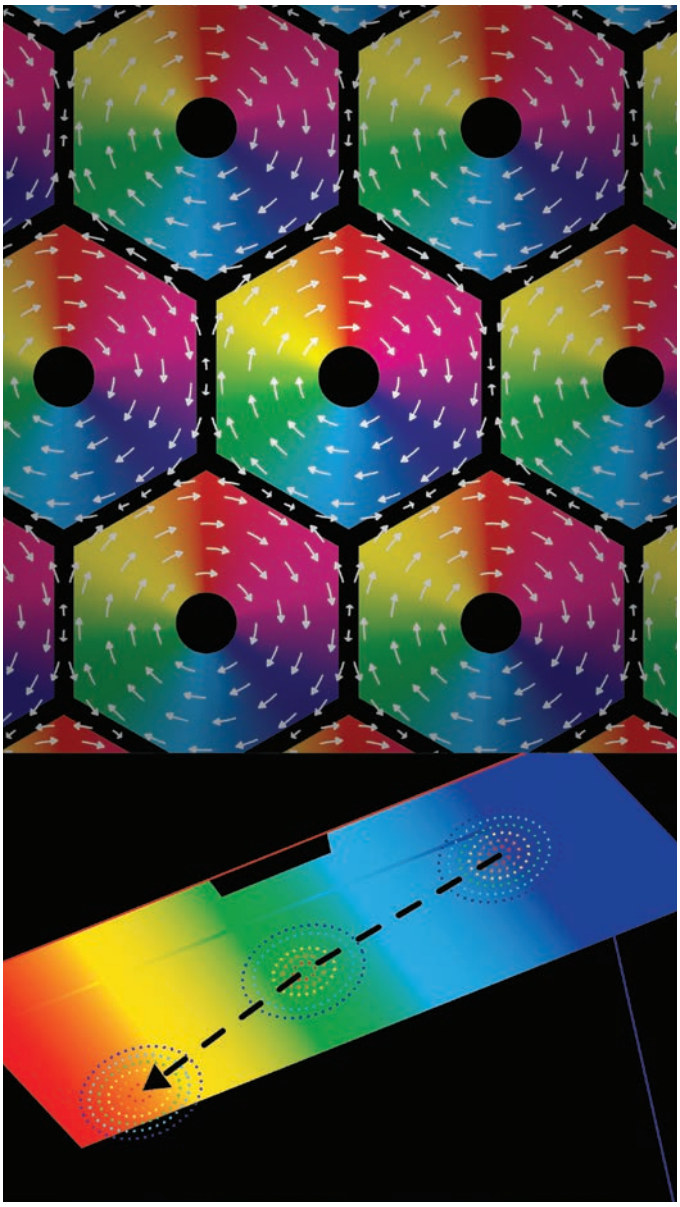
Now, Yu and her colleagues have shown how a temperature gradient can be used to propel skyrmions in an electrically insulating magnetic material.

The team built a device that consisted of a plate of this material, a miniature heating element and two electric thermometers. They then generated skyrmions that were roughly 60 nanometers wide in the plate by cooling it to about –253 degrees Celsius and applying a magnetic field. These skyrmions gathered into a stable honeycomb structure known as a hexagonal skyrmion lattice.

Yu's team then increased the temperature slightly at one end of the plate and used a transmission electron microscope to watch how this affected the skyrmions. A temperature gradient of 100th of a degree per millimeter of plate was enough to nudge the skyrmions into motion. Above this threshold, the edge of the honeycomb lattice drifted from the cooler to the warmer end of the plate, traveling in the opposite direction to the flow of heat (lower part of image). This required a very low heat power of just 10 microwatts, which is hundreds or thousands of times smaller than the power needed to move skyrmions using electrical currents or magnetic fields. Using a slightly higher power, individual skyrmions could be driven through the plate by the temperature gradient.

The researchers say that this is the first time that heat-driven skyrmion motion has been seen in an insulating magnet. "This finding should stimulate researchers to develop energy-efficient devices by using skyrmions," says Yu.

The team is now studying the heat-induced dynamics of skyrmions, including their transformation into their anti-particles—anti-skyrmions in metallic systems at room temperature.



Skyrmions often arrange themselves into hexagonal lattices (top). RIKEN researchers have shown that a temperature gradient in a thin plate of an insulating magnetic material (bottom) can be used to propel such skyrmion lattices from the cooler (blue) to the warmer side (red) of the device.

Reference

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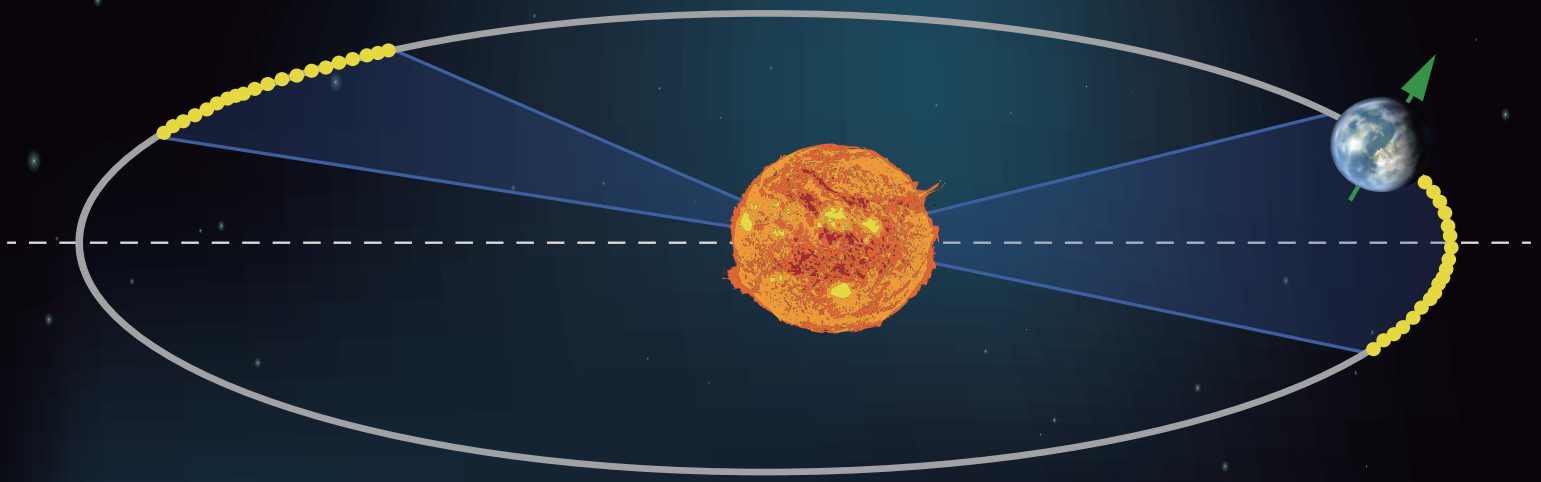
The BASE team performed measurements at two different periods during the Earth's orbit around the Sun to investigate whether there was any difference in how matter and antimatter responded to gravity.



ANTIMATTER

Matter and antimatter are all the same to gravity

Gravity seems to accelerate protons and antiprotons equally

To a high accuracy, matter and antimatter respond to gravity identically, an experiment by the RIKEN-led BASE collaboration at CERN has found[1]. While this measurement confirms existing theories, discrepancies with other experiments could reveal new physics.

It could lead to the dawn of a completely new physics

Besides having opposite charge, a particle and its antimatter counterpart are essentially equivalent. However, one of the great mysteries of physics today is why the Universe seems to be made almost entirely of matter.

To discover why matter preponderates, physicists are striving to find some difference between matter and antimatter. As part of this quest, they are exploring whether matter and antimatter interact similarly with gravity.

Now, the BASE collaboration has shown that, within strict boundaries, antimatter responds to gravity in the same way as matter.

This work involved 18 months of experiments at CERN's antimatter factory. The team confined antiprotons and negatively charged hydrogen ions, which they used as a proxy for protons, in a Penning trap. In this device, a particle follows a cyclical path with a frequency close to the cyclotron frequency, which scales with the trap's magnetic-field strength and the particle's charge-to-mass ratio. By feeding antiprotons and negatively charged hydrogen ions into the trap, one at a time, the researchers could measure, under identical conditions, the cyclotron frequencies of the two particle types.

"By doing this, we were able to obtain a result that they are essentially equivalent, to a degree four times more precise than previous measures," explains Stefan Ulmer, the leader of the project. "To this level of CPT invariance, causality and locality hold in the relativistic quantum field theories of the standard model."

The team used the measurements to test a fundamental physics law, namely that, in the absence of frictional forces, different bodies experience the same acceleration in the same gravitational field. Because the BASE experiment was conducted on the Earth's surface, the measurements of the proton and antiproton cyclotron frequencies were made in the gravitational field at the Earth's surface. Consequently, any difference in the gravitational interactions of protons and antiprotons would show up as a difference in their cyclotron frequencies.

By sampling the gravitational field of the Earth as it orbited the Sun, the scientists found that matter and antimatter responded to gravity in the same way up to a degree of three parts in 100. This means that the gravitational acceleration of matter and antimatter are identical to within 97% of the experienced acceleration.

These measurements could reveal uncharted territory. "If the results of our study differ from those of the other groups, it could lead to the dawn of a completely new physics," says Ulmer.

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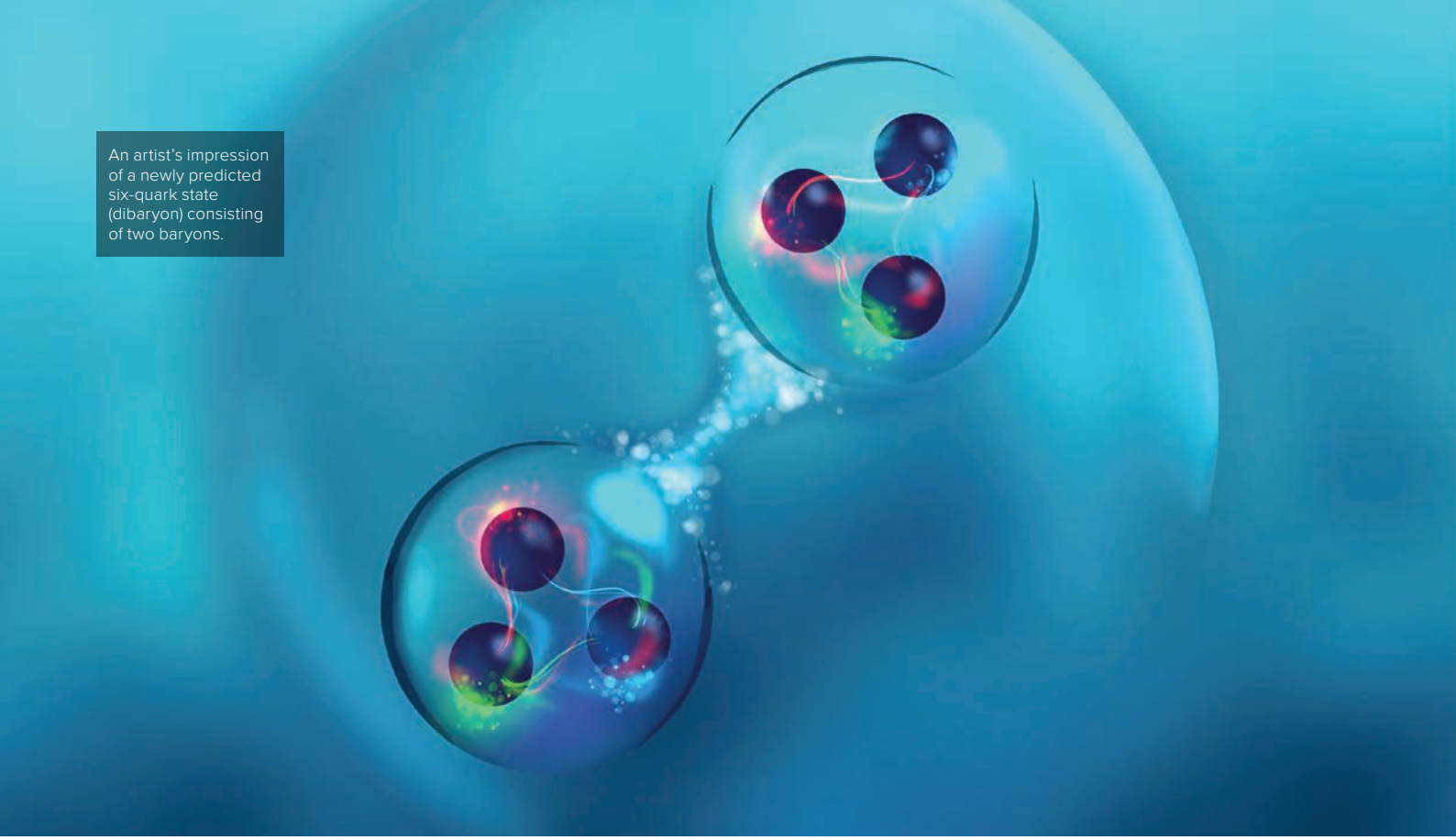

An artist's impression of a newly predicted six-quark state (dibaryon) consisting of two baryons.

DIBARYONS

Quantum calculations work like a charm

A new particle predicted by supercomputers could shed light on how matter is formed

The predicted existence of an exotic particle made up of six elementary particles known as quarks by RIKEN researchers could deepen our understanding of how quarks combine to form the nuclei of atoms[1].

Quarks are the fundamental building blocks of matter. The nuclei of atoms consist of protons and neutrons, which are in turn made up of three quarks each. Particles consisting of three quarks are collectively known as baryons.

Scientists have long pondered the existence of systems containing two baryons, which are known as dibaryons. Only one dibaryon exists in nature—deuteron, a hydrogen nucleus made up of a proton and a neutron that are very lightly bound to each other. Glimpses of other dibaryons have been caught in nuclear-physics experiments, but they had very fleeting existences.

"Although the deuteron is the only known stable dibaryon, many more dibaryons may exist," says Takuya Sugiura of the RIKEN Interdisciplinary Theoretical and Mathematical Sciences Program. "It's important to study which pairs of baryons form dibaryons and which do not because this provides valuable insights into how quarks form matter."

Quantum chromodynamics is a highly successful theory that describes how quarks interact with each other. But the strong coupling that occurs between quarks in baryons complicates quantum chromodynamics calculations. The computations become even more complex when considering bound states of baryons such as dibaryons.

Now, by calculating the force acting between two baryons each containing three charm quarks (one of the six types of quarks), Sugiura and his co-workers have predicted the existence of a dibaryon they called the charm di-Omega.

For this calculation, the team solved quantum chromodynamics with large-scale numerical calculations. Since the calculations involved a vast number of variables, they used two powerful supercomputers: the K computer and the HOKUSAI supercomputer. "We were extremely fortunate to have had access to the supercomputers, which dramatically reduced the cost and time to perform the calculations," says Sugiura. "But it still took us several years to predict the existence of the charm di-Omega."

Despite the complexity of the calculations, the charm di-Omega is the simplest system for studying interactions between baryons. Sugiura and his team are now studying other charmed hadrons using the supercomputer Fugaku, which is the K computer's more powerful successor. "We're especially interested in interactions between other particles containing charmed quarks," says Sugiura. "We hope to shed light on the mystery of how quarks combine to form particles and what kind of particles can exist." ●

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EMBRYOLOGY

Holding a mirror to left–right asymmetry

Degradation of mRNA induced by fluid flow causes the left side of an embryo to develop differently from the right side

A better knowledge of the causes of disease, birth defects and genetic syndromes could come from new insights gleaned by RIKEN biologists into how mice embryos develop asymmetry between their left and right sides[1].

Embryos start off as symmetric bundles of cells, but then eventually develop into animals whose left sides differ from their right sides. Developmental biologists want to discover the origins of this left–right asymmetry since such knowledge will shed light on the basic biology of development, as well as on the causes of birth defects and genetic syndromes.

"Our study has revealed how cells respond to fluid flow generated by cilia"

The first step in establishing left–right asymmetry in an embryo is the left–right breaking event. In fish, frog and mouse embryos, this begins with hair-like cilia generating fluid flow that runs leftwards. This fluid flow then down-regulates *Dand5* mRNA on the left-hand side of the embryo.

Now, Hiroshi Hamada of the RIKEN Center for Developmental Biology and his team, together with researchers in Switzerland and elsewhere in Japan, have investigated the factors that suppress *Dand5* mRNA.

They first tracked down the critical portion of the mRNA by comparing sequences between mammalian genes to uncover the conserved portion. This revealed a conserved 200-nucleotide region of the proximal 3'-UTR.

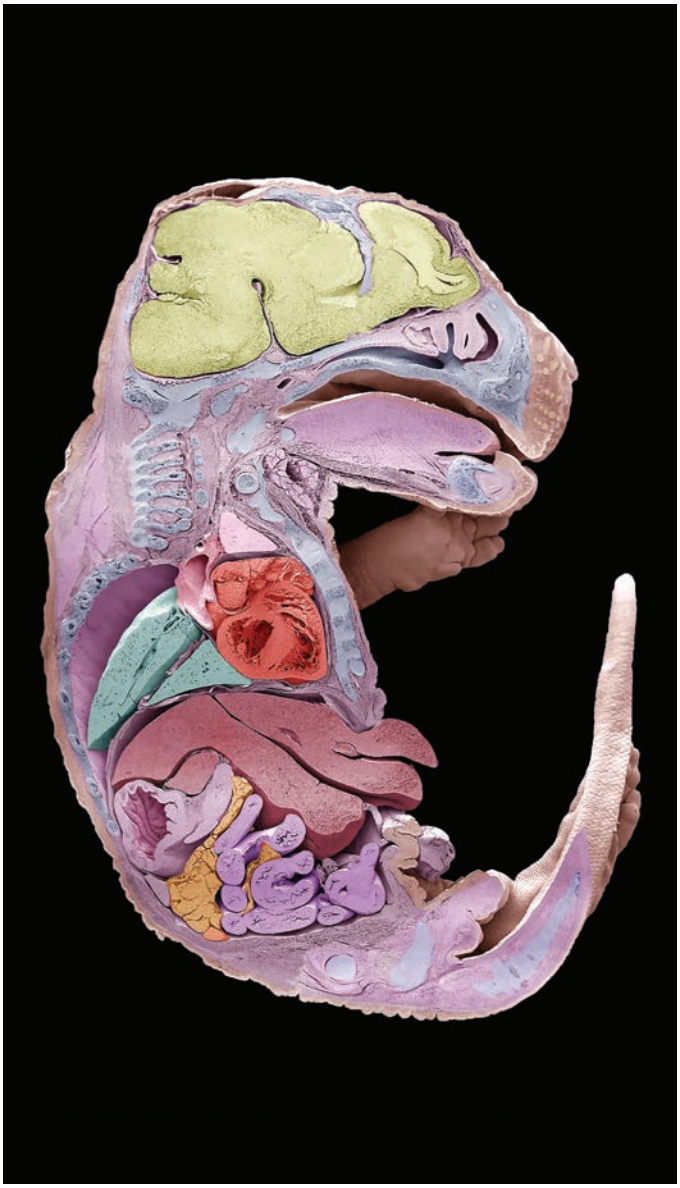
Embryos lacking a functional copy of the *Bicc1* gene exhibited defects in left–right patterning, linking the *Bicc1* protein with left–right asymmetry. When the researchers deleted the first exon of *Bicc1* using CRISPR–Cas9 gene editing, the resulting mouse embryos developed symmetrically.

The team discovered that the Bicc1 protein binds to the GACGUGAC sequence in the untranslated region of *Dand5* mRNA. Further work showed that Bicc1 also needed to interact with the Cnot3 component of the Ccr4–Not deadenylase complex.

These findings significantly advance knowledge of the development of left–right asymmetry. "Our study has revealed how cells respond to fluid flow generated by cilia," says Hamada. "We have confirmed that left–right symmetry is broken by degradation of a particular mRNA on the left side in response to the directional fluid flow. Discovering the involvement of the RNA degrading system in sensing the fluid flow is an exciting breakthrough."

Since *Bicc1* has been implicated in kidney disease, Hamada thinks a similar mechanism may operate when cells sense other types of fluid flows, such as kidney epithelial cells detecting urine flow.

The team next wants to see how calcium activates the Bicc1–Ccr4 complex, and, in particular, whether calcium affects complex formation or phosphorylation of Bicc1 and Ccr4 components. ●



A scanning electron micrograph of one half of a mouse embryo. The other half would be different in some respects. RIKEN biologists have discovered the role that genes play in the development of this left–right asymmetry.

Reference

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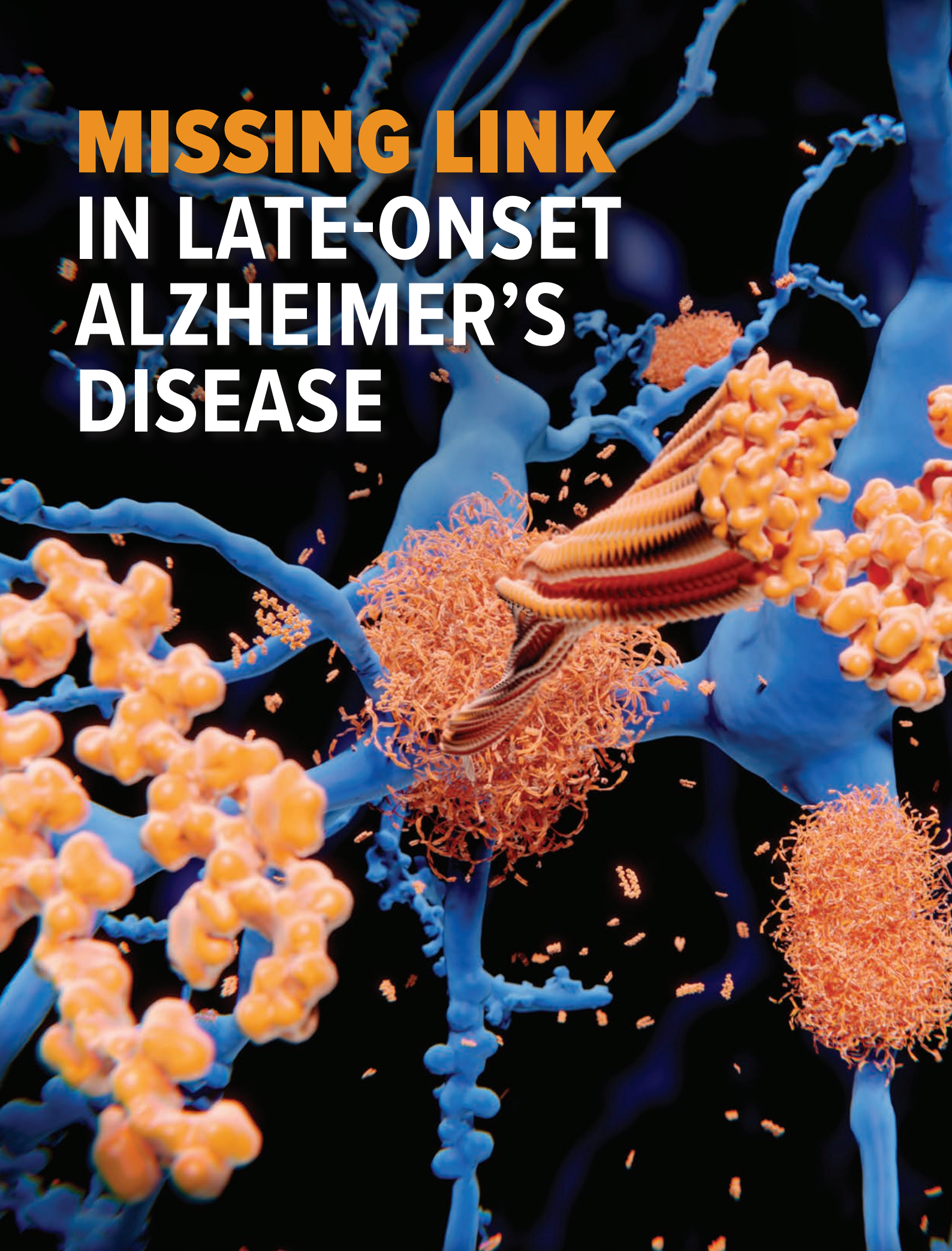
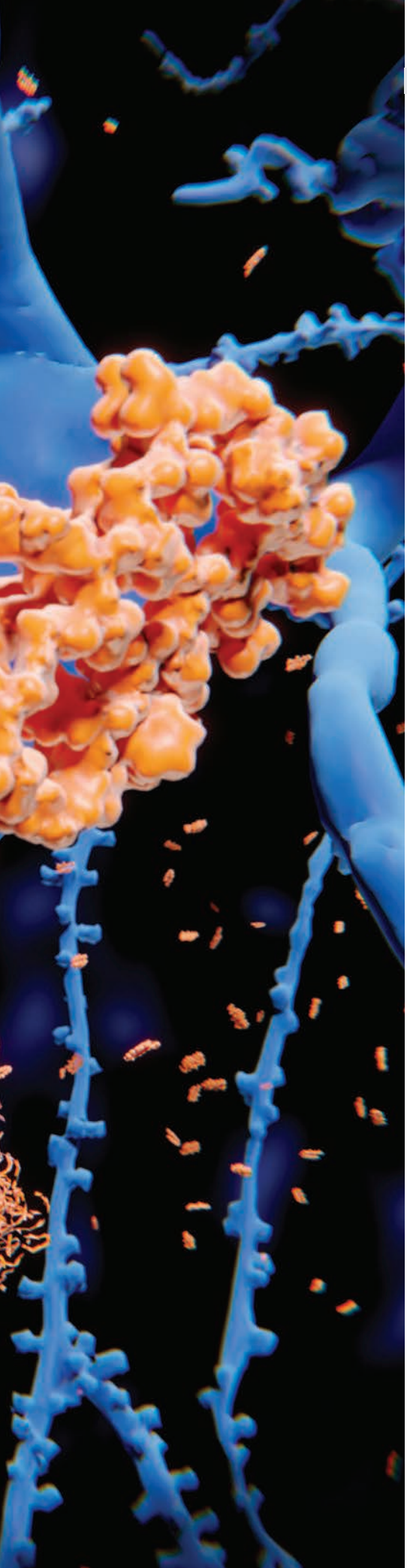


MISSING LINK IN LATE-ONSET ALZHEIMER'S DISEASE



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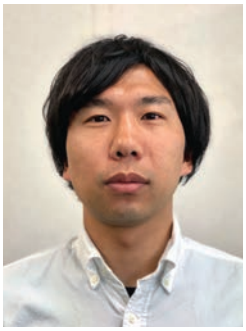
A hitherto unknown connection between a neuropeptide and an enzyme provides a more complete picture of why some people develop late-onset Alzheimer's disease



This feature looks at the work of
NAOTO WATAMURA

Naoto Watamura is a researcher in the Proteolytic Neuroscience Team at the RIKEN Center for Brain Science (CBS). He received his PhD in Advanced Science and Engineering from Waseda University in 2018. His thesis focused on the therapeutic effect of retinoic acid on Alzheimer's disease. While part of a Master's program, he moved to RIKEN and joined Takaomi Saido's lab at the RIKEN Center for Brain Science. In 2018, he received the Young Scientist Award and Young Science Encouraging Prize at the Annual Meeting of Japan Society for Dementia Research. In 2022, he also received a junior faculty award at the AD/PD™ International Conference on Alzheimer's and Parkinson's Diseases in Barcelona, Spain. He is working on the elucidation of amyloid beta catabolic pathways in the brain.

After 17 years, an all-RIKEN team has uncovered the connection between two links in the chain that leads to the proliferation of amyloid beta in the brain—a hallmark of Alzheimer's disease[1]. The team also demonstrated that a drug can reverse this link in a mouse model of the disease, raising hopes that the discovery could lead to an effective treatment.

Alzheimer's disease exacts a devastating toll on patients as it relentlessly erodes memory and cognitive ability. It's also a tremendous burden on families, caregivers and society as a whole. Naoto Watamura of the RIKEN Center for Brain Science knows well the sorrows surrounding the neurodegenerative disorder. "My grandmother suffered from Alzheimer's disease, and I saw the effect it had on my family," he says. "That experience motivated me to devote my career to studying the disease."

Despite decades of research conducted on Alzheimer's disease, it still lacks a cure. There was a ray of hope in 2021 when the Food and Drug Administration in the United States approved aducanumab, the first drug to address the underlying biology of the disorder. This approval is all the more remarkable against a backdrop of so many promising drugs that have stumbled in the late stages of development.

But aducanumab only slows the progress of Alzheimer's. Furthermore, it's expensive and there is controversy concerning conflicting results on its effectiveness in clinical trials.

AN AMYLOID BETA CHOMPER

Aducanumab is a human monoclonal antibody that helps clear clumps of the peptide amyloid beta that build up in the brains of people with Alzheimer's disease. These plaques accumulate because something goes wrong with the normal mechanism for disposing of amyloid beta (pictured left, orange).

Back in 2000, a RIKEN team led by Takomi Saido discovered that an enzyme called neprilysin breaks amyloid beta into smaller components and that people with Alzheimer's tend to have low levels of neprilysin in their brains.

This discovery was one of the main reasons why

Watamura chose to join Saido's team after completing his Masters degree. "I've always been intrigued by why some people develop Alzheimer's disease," he says. "Saido's lab found that neprilysin is the most important amyloid degrader. I joined the team because I'm very interested in neprilysin and the mechanism that regulates neprilysin action in the brain."

The findings on neprilysin led the researchers to the obvious question: what causes the low levels of neprilysin in the brains of people with Alzheimer's?

In 2005, Saido's team made a discovery that helped shed light on this query: a neuropeptide known as somatostatin promotes the production of neprilysin. Somatostatin levels tend to decrease with age and were found to be low in the post-mortem brains of people who had late-onset Alzheimer's disease.

But for the past 17 years, no-one has been able to explain why low levels of somatostatin lead to low levels of neprilysin.

Illustration depicting tangled amyloid plaques amongst neurons. Amyloid plaques are a characteristic feature of Alzheimer's disease, and they lead to degeneration of the affected neurons. A RIKEN study has found that high levels of the protein alpha-endosulfine give rise to these plaques in a mice model of the disease.

THE MISSING PIECE?

Now, Watamura and his co-workers have found the missing piece of the puzzle—a protein known as endosulfine. Specifically, they have shown that low levels of somatostatin lead to high levels of endosulfine, which in turn results in low levels of neprilysin.

The team first screened various compounds in a medium formed by neurons from the hippocampus—the brain region that plays a critical role in learning and memory, and where Alzheimer's first strikes before spreading to other parts of the brain. This test exposed endosulfine as the prime suspect.

The finding was borne out in experiments involving mice. The group generated the mice, which genetically lack endosulfine. When these mice were crossed with a mouse model for Alzheimer's disease, their offspring accumulated fewer amyloid beta plaques than the mouse model.

The researchers went a step further and showed how endosulfine causes low neprilysin levels by deleting each potassium channel in the mice. When they activated the specific channel by other means, they observed similar results as in the mice lacking endosulfine.

This demonstration also suggested a way to counteract the effects of high endosulfine levels—using a drug that activates the potassium channel. When the researchers gave this drug to the Alzheimer's model mice, the mice had much better memory than untreated mice and also lacked amyloid beta plaques. "I was surprised at how well the drug worked," says Watamura. He notes that there are already approved drugs for treating diabetes and insulinomas that target the same potassium channel, although ensuring that they are specific enough will be a challenge.

Watamura also notes that the study is unusual in that it is both a fundamental study that revealed the biology behind Alzheimer's disease and demonstrated a potential drug for its treatment. "Many studies propose drug treatments, and it's only later that the mechanism is determined," says Watamura. "But we discovered the mechanism first, and then found a drug to correct it."

The team is now exploring the mechanism more deeply. "We want to find the mechanism downstream of the potassium channel," says Watamura. "In other words, how the potassium channel regulates neprilysin in the brain."

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HOW THE NATURAL SCIENCES WILL BE ENRICHED BY THE HUMANITIES

In his final days at RIKEN, President Hiroshi Matsumoto calls on the research community to embrace those asking big ethical, social, philosophical and political questions

科学道

Kagakudo
RIKEN has adopted a concept that has been dubbed *kagakudo* that suggests that science is a path that should be linked to the greater good.

One of the things I like to do is to ask scientists a question that often takes them a surprisingly long time to answer. The query: what will your work contribute to the world in 50 or 100 years? Mostly, researchers reach for answers that highlight contributions to their field, but I'm really asking what they will contribute to humanity.

Scientists will need to ask themselves bigger, more searching questions in the coming decades. The challenges we face today, such as climate change, an increase in neurological diseases, and how to integrate AI ethically into daily life, are multifaceted and will involve deeper thought on how we want to live.

It's actually an old model of thought. The natural sciences were once called natural philosophies. But in the 17th century, in order to deeply understand how the Universe works mechanistically, philosophy was separated out. Since then, the natural sciences have become more and more specialized. And that move was necessary; it was a tool to help us understand the intricacies of each field, but now we must stretch our minds even further by both drilling down into detail and thinking in broader systemic and theoretical frameworks.

I believe there are many problems that can only be solved by the incorporation of three types of thinkers: researchers in the humanities and social sciences, who mostly deal with social phenomena; religious people and philosophers, who often deal with issues of the mind; and scientists in the natural sciences, who deal with the physical world mechanistically.

The study of the mind, for example, is greatly enriched by religious and philosophical insights. If we just mechanistically examine molecules, cells, neural networks and brains, it's still very difficult to understand the complexity of the mind. I believe that there are many areas in which theologians and philosophers have a more advanced understanding of how we construct the world around us: they have thoroughly debated what thoughts are, what their limits might be, and how they might be interacting with our sense of self and perception. Buddhism, too, has long examined how our mindset affects our experience of the world and the reactions of our bodies. These understandings can only be reached using a highly theoretical view, which is quite different to the approach of the natural sciences. Indeed, many RIKEN researchers are interested in how intentions and emotions are created in the brain and could benefit from such insights.

The COVID-19 pandemic has also underlined how important these types of thought are to understanding what is happening to us today. Many researchers in the natural sciences are working to characterize the virus and create vaccines and therapeutic agents. However, the impact on people's minds can't be addressed in this way, nor the impacts our mindsets have on our bodies. These forces must be better understood to prepare for what is to come.

JAPAN'S CHANGING PUBLIC POLICY

I'm not alone in calling for change; the Japanese government has recognized the need for more input from the humanities too.

In 1995, the *Basic Act on Science and Technology*, which described the Japanese government's science and technology priorities, largely excluded the social sciences. As a consequence, the Japan Science and Technology Agency didn't provide aid grants for study proposals focusing only on the humanities or social sciences. Companies collaborating with social science research organizations missed out on tax breaks and other incentives. Humanities and social sciences researchers on public payrolls tended to receive lower salaries compared to their natural science counterparts.

But this position has been revised in response to the growing importance of the social sciences amid advances in the life sciences and artificial intelligence (AI) research. In April 2021, the wording of the act was changed to include increased promotion of the

humanities, and it was renamed the *Science, Technology and Innovation Basic Law.*

As a result, the scope of RIKEN's research can now more easily expand. We can recruit key talent from the humanities. One of my final wishes as president of RIKEN is to incorporate rich discussions from the humanities into RIKEN's daily activities. To do this, it is necessary for natural science researchers and people with vivid imaginations, such as philosophers and literary scholars, to become part of each other's daily lives.

Our epidemiologists, neuroscientists, robotics and AI experts are primed to benefit from this move.

Even prior to the change in law, the RIKEN executive had been aware of the need for this change. To smooth the way, we adopted the concept of *kagakudo*, which can be loosely translated as 'the path of science', to emphasize that scientific research is a path that should be linked to society and to the humanities.

We also established the Innovation Design Office, which has taken a humanities-style approach and held forums that developed many written scenarios looking ahead several decades. The idea was to more holistically explore possibilities, challenges and bottlenecks. These scenarios included what it might look like if humans were living in space or if we all lived to 120 years of age. They are designed to trigger deeper thought, ideas and innovation in scientists.

RICH RESOURCES

There are reasons that different fields have increasingly come together. When I was a young researcher in the area of radio space science, I called for increased collaboration in theory, mathematics and experimental research. It was common back then to use approximate values in simulations, and I did not want to do that. I wanted mathematics and experimental research to help stimulate the theory and vice versa. But in those days computational power was still low. Now with increasing power, such as that of our Fugaku supercomputer, we have been able to achieve greater precision in simulations so that in theory, mathematics and experimental research should easily work in tandem.

Indeed, many fields ignore the huge holes that theoreticians try to unpick. Natural science researchers such as physicists and chemists, examine fundamental questions about how the world works. But why the Universe, life and human beings exist in the first place is still a mystery. Some physicists argue that the Universe exists because of human beings' existence, but this 'anthropic principle' is closer to an idea than a science. I don't know if we can fully examine this issue at the core of science using the natural sciences in isolation.

Although the SARS-CoV-2 pandemic has caused a tragic loss of life, it has also helped wider society ask more searching abstract questions. It has never been clearer to the global population that we must tackle this problem from a mechanistic, social and moral stance. In addition to this, we are reaching the limits of capitalism, as evidenced by a rising child poverty rate among other things, meaning that today's politicians must work with the sciences to marry evidence-based policy with new theoretical paradigms of how to create a healthy social order.

The ultimate goal for most researchers is to connect their research results to the happiness of people. However, I believe that this goal is sometimes difficult to see in the midst of daily research and increasing specialization. I would like to provide researchers with more opportunities to think about the mind and recognize social issues, in a sense, to help them go back to the basics.

It will be fascinating to watch research evolve in this unprecedented time and I look forward to observing new inspiration and richness in the sciences. ●

REFERENCE

For a full list of references, please see the online version of this article: https://www.riken.jp/en/news_pubs/research_news/

HIROSHI MATSUMOTO
President, RIKEN

Hiroshi Matsumoto is an atmospheric scientist. He was President of Kyoto University from 2008 to 2014, and became President of RIKEN in 2015. In 2015, he also became a Chevalier in the French Legion of Honor, in 2017 he became an Honorary Officer of the Most Excellent Order of the British Empire (OBE), and in 2021 he became a Grand Cordon of the Order of the Sacred Treasure, an award established in 1888 by Japan's Emperor Meiji.

> I'm not alone in calling for change; the Japanese government has recognized the need for more input from the humanities too.

PICKING MANY BRAINS

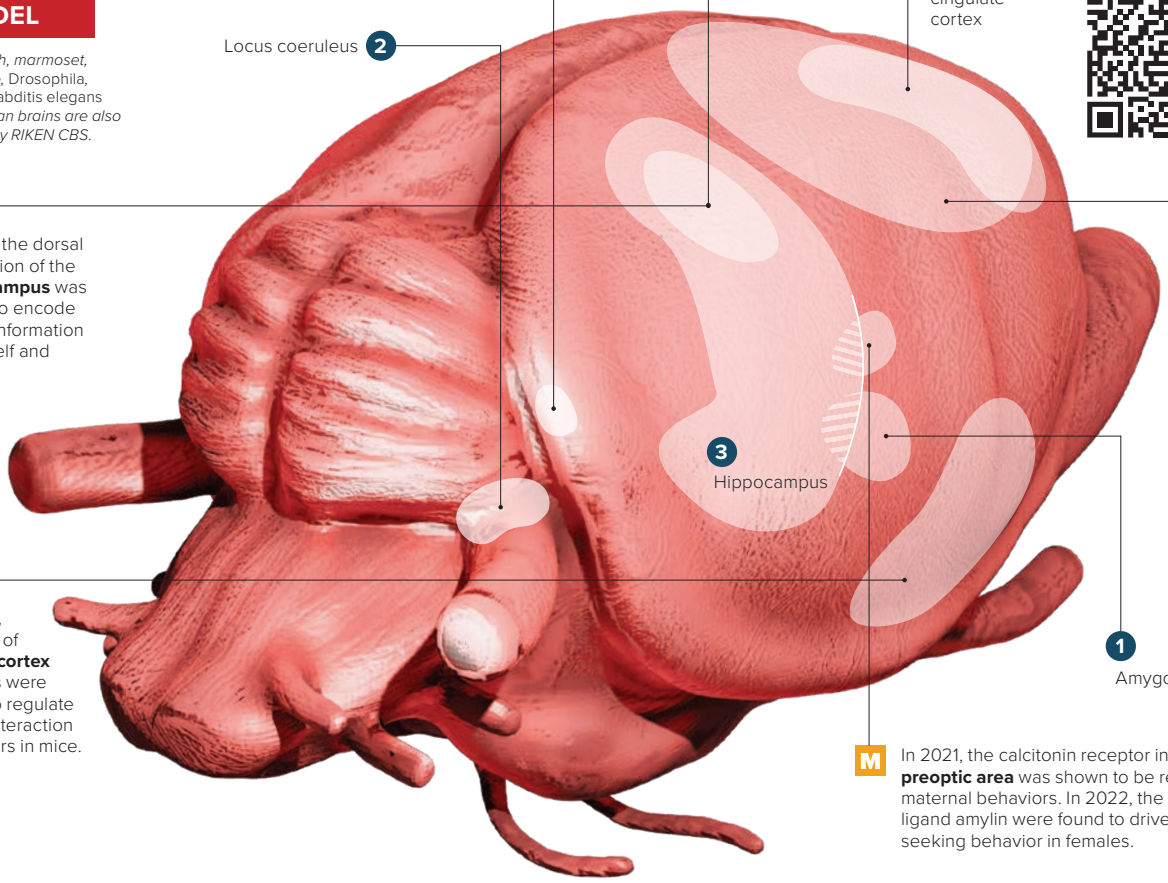
Researchers from the RIKEN Center for Brain Science (CBS) are constantly revealing where and how brains store memories and drive behaviors.

Legend

- R Rat brain research
- M Mouse brain research
- ⬇ Scan QR code for links to references

RAT BRAIN MODEL

**Zebrafish, marmoset, macaque,* Drosophila, Caenorhabditis elegans *and human brains are also studied by RIKEN CBS.*



R In 2018, the dorsal **CA1** region of the **hippocampus** was shown to encode spatial information of the self and others.

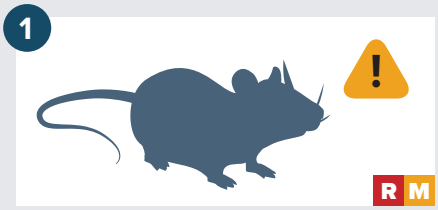
M In 2020, subsets of **insular cortex** neurons were found to regulate social interaction behaviors in mice.

M In 2020, the **claustrum** was shown to coordinate cortical slow-wave activity, which is associated with sleep and consciousness.

M In 2021, the calcitonin receptor in the **medial preoptic area** was shown to be required for maternal behaviors. In 2022, the receptor and its ligand amylin were found to drive social contact-seeking behavior in females.

FEAR FORMATION IN THE BRAIN

1

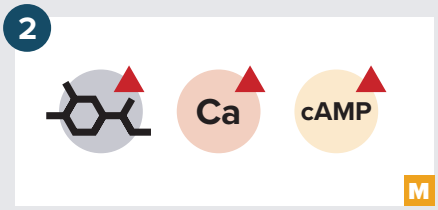


R M

STORED STORIES

In 2019, a RIKEN group suggested that older fear memories are stored in the **anterior cingulate cortex**, noting high synchronization with the hippocampus' CA1 area during mouse fear recall. In 2016, a group showed the **periaqueductal gray** (PAG) controls fear memory storage in the **amygdala** and, in 2021, linked this to a population of neurons in the dorsolateral region of the PAG.

2



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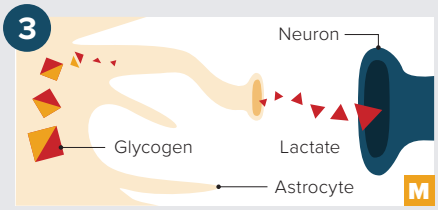
THE HOLD OF HORMONES

After an unpleasant experience, a noradrenalin neuromodulator is released from the brain stem's **locus coeruleus** nucleus. In 2020, RIKEN researchers showed the released noradrenalin activated astrocytes to elevate calcium. After a sustained stressor, the calcium peaked and tapered off, but a messenger chemical, cyclic adenosine monophosphate, remained elevated longer.

3



M

Because cyclic adenosine monophosphate helps break down glycogen into quick energy, the elevation mentioned at left might be readying neurons for a flight-or-fight response. Glycogenolysis in astrocytes is also necessary for the conversion of memory from a short-term form to a more stable long-term one due to an increase in extracellular lactate levels in the hippocampus.

scyrus / TurboSquid

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across Japan and around the world

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- ● Center for Emergent Matter Science (CEMS)
- ● RIKEN Center for Quantum Computing (RQC)
- ● Center for Sustainable Resource Science (CSRS)
- ● Center for Brain Science (CBS)
- ● Interdisciplinary Theoretical and Mathematical Sciences Program (iTHEMS)
- ● RIKEN Nishina Center for Accelerator-Based Science (RNC)
- ● RIKEN Center for Advanced Photonics (RAP)
- ▲ RIKEN Cluster for Science, Technology, and Innovation Hub (RCSTI)
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- ◆ Radio Isotope Beam Factory (RIBF)
- ▼ RIKEN Information R&D and Strategy Headquarters (R-IH)

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- ● Strategic Research Center
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HARIMA

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- ◆ SPring-8
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- ▼ Guardian Robot Project (R-IH)

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- ● Center for Biosystems Dynamics Research (BDR)
- ■ RIKEN Center for Computational Science (R-CCS)
- ◆ Molecular Imaging
- ◆ Supercomputer Fugaku

OSAKA

- ● Center for Biosystems Dynamics Research (BDR)

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

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