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SPRING 2018

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INFECTIOUS MISERY

Evidence that the immune system can trigger anxiety

CELL ATLAS

A global effort to map every organelle of the human body

COLD CHIPS

Rippling films for cooler computers

PASSING THE SNIFF TEST

Triggers for smelling versus breathing

The RIKEN Advanced Institute for Computational Science (AICS)
The AICS in Kobe is home to the K computer, one of the world's top supercomputers.

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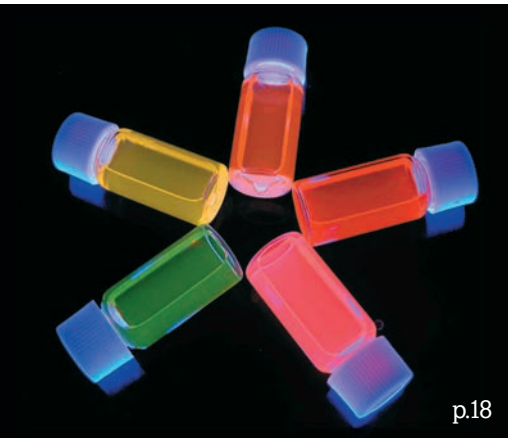
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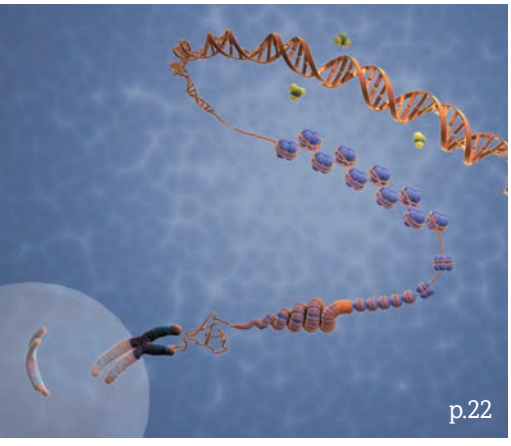
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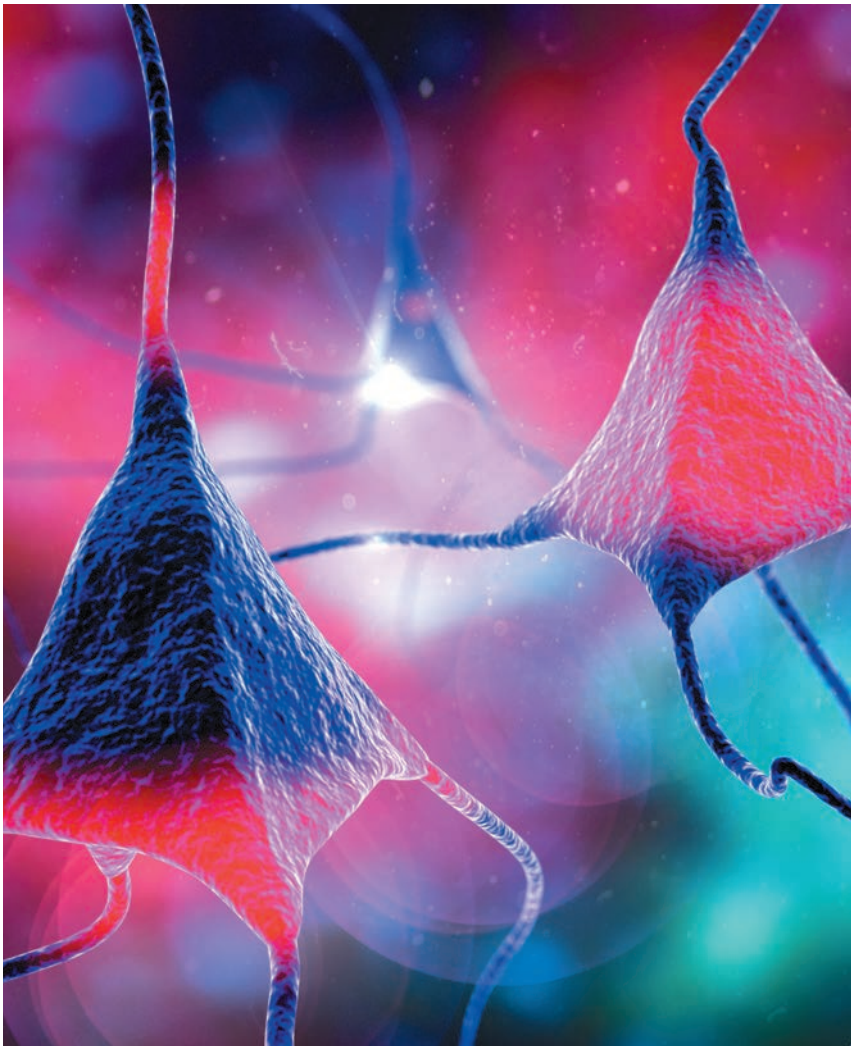

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Embarking on a new chapter

Shigeo Koyasu
Executive Director, RIKEN

As this issue of *RIKEN Research* goes to press, we are preparing to embark on our fourth mid- to long-term plan, encompassing the period between April 2018 to March 2025. As part of our continual efforts to strengthen interdisciplinary work—already a hallmark of RIKEN's structure—we are planning to establish a new collaboration hub called the Cluster for Pioneering Research (CPR). While our national guidelines articulate our main mission—to conduct research and development—the organization's charter described in the 'RIKEN Act' also calls for us to "raise the standards of science and technology" in Japan. Hence, we see pioneering new areas of science as an important component of our mission. The CPR will help us realize this objective. The CPR's principal investigators will be guaranteed employment until retirement age and will run Chief Scientist Laboratories within the cluster. These principal investigators will engage in independent research, while developing new areas of science through collaboration with colleagues in different disciplines. In addition, we will work on improving the progress management of interdisciplinary RIKEN projects. We also hope to maximize Japan's research output by encouraging the shared use of RIKEN's cutting-edge equipment and facilities.

As one example of the interdisciplinary work conducted at RIKEN, the Single Cell Project is highlighted in this issue (page 28). This project was set up in collaboration with several life-science centers with the aim of better understanding cell behavior at a single-cell level—a major advance from the genomics division at RIKEN, which until now has primarily focused on the genomes of entire organisms.

Future issues will bring further updates on the new mid- to long-term plan.

Cover story: Being sick is already a pain, but it turns out our immune reponse also affects our brain chemistry, and this could be creating extra anxiety and agitation. **Page 25**

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Drug production inside our bodies

Katsunori Tanaka

Chief Scientist, Biofunctional Synthetic Chemistry Laboratory
Chief Scientist Laboratories

What made you decide to become a scientist?
I wanted to become a guitarist in my youth. However, I quickly discarded this plan when I realized that there are much more meaningful career choices that provide more stable lifestyles. Since chemistry was my second love, my path in life was an easy choice to make.

How did you become interested in your current field of research?
I like to continually strive for new ideas and unexplored concepts. And since the fields of bio-orthogonal chemistry and biocompatible metal complex catalysts are booming, it will only be a matter of time before the next great discovery revolutionizes the field.

What excites you the most about your current research?
I'm most excited when we're able to apply our research clinically (in addition to writing good papers, of course). For instance, one of our chemical reactions has shown great promise in rapidly diagnosing and treating cancerous cells in human patients. Being able to explain the end result of our research in an understandable context to family and friends fills me with great pride. As scientists, I think it's critical that we always endeavor to conduct research that could potentially contribute to better care.

Please briefly describe your current research. Why is it important?
My lab is exploring a range of research projects, from developing glycan-directed molecular targeting strategies to searching for novel biocompatible chemical reactions. Our ultimate goal is to amalgamate these studies to develop 'therapeutic *in vivo* synthetic chemistry', which involves causing chemical reactions inside our bodies to create drug molecules only at specific locations (for example, near tumors). Currently, drug therapies are largely limited to administering already formed molecules, and there is very little control over how their effects are distributed throughout the body. Therapeutic *in vivo* synthetic chemistry promises to be a new way to deliver and control medicine that potentially could revolutionize the way illnesses are treated and help to limit the side-effects of drugs.

> *Therapeutic* in vivo *synthetic chemistry, involves causing chemical reactions inside our bodies to create drug molecules only at specific locations, for example, near tumors.*

How has being at RIKEN helped your research?
Aside from access to world-class facilities, RIKEN provides the chance to collaborate with a wide array of talented researchers. With the tremendous support and help of my peers, I am emboldened to pursue ideas from every corner of my mind, even if they require multidisciplinary techniques and approaches. I've also received valuable help and guidance in ensuring the clinical applicability and commercialization of my work. All of these elements inspire me to work for the future of my children.

How do you balance family life with your work at RIKEN?
Rather than be a 'jack of all trades, master of none', I think it's critical for young people to understand that sometimes success can only be obtained through pure devotion and dedication; just like focusing on one discipline during university. Eventually, all the other pieces fall into place as you learn to grow into your role as a researcher, spouse and parent. ●

The pillars of campus life

Takako Sawamura

Deputy Manager, Wako Human Resources Section
Wako Administrative Division

What first brought you to RIKEN?
Actually, my first connection to RIKEN was somewhat accidental; I was hired to be an editorial assistant for a scholarly journal edited by Masao Ito, the founder of the RIKEN Brain Science Institute (BSI). The editorial work was done at his office at BSI, and so I happened to be located at the Wako campus. I subsequently started to work on the Help Desk for foreign researchers at the Brain Science Promotion Office, the administrative division for BSI.

What are you doing now?
I now work at Wako International Support Services, a team inside the Wako Administrative Office that provides administrative support for non-Japanese researchers working on campus. For example, before researchers arrive, we give information on issues such as visas, social security and housing. We also run welcome sessions for arriving researchers and leaving sessions for those who are departing. We support families by providing advice on issues such as medical care, childbirth and education.

Has the situation changed in the time since you arrived here?
Support was almost non-existent when BSI was established roughly two decades ago. At that time, there were very few non-Japanese people working at RIKEN, but BSI was aiming to get that number up to 20 per cent. Across RIKEN, we have surpassed that number now. Back then, the individual laboratories were also essentially left to deal with their own support issues, and so the assistance researchers received varied a lot. Today, RIKEN has support teams on all our major campuses. Japan has also changed a lot, and it's easier these days for non-Japanese people to integrate into society. We focus on trying to provide accurate information consistently to allow personnel to be independent. For example, language is obviously often a barrier, and so we have a translation team that provides English versions of administrative documents.

We focus on trying to provide accurate information consistently to allow personnel to be independent.

Do you have any particularly vivid memories of your time at RIKEN?
One in particular stands out—not entirely for happy reasons! Because RIKEN is considered quite advanced, people from other research institutes and universities often come to visit us to learn from our experiences. I once advised a delegation of about ten people from another government research institute on dealing with diverse nationalities languages, cultures, ethnicities and religions, among other things. I later found out that they had compiled the information I had given them and published it as a book. I'd always wanted to publish that information myself and was a bit disappointed that somebody else beat me to it.

What are your plans for the future?
I'd like to really integrate our different campus support services. We do a lot of coordination—for example, our welcome sessions are also held at Yokohama and Kobe—but I would like to see support become more RIKEN-wide. I should emphasize, however, that we've made a lot of progress in the past few years and we actively share knowledge between our campuses. ●

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Celebrations took place at Himeji Castle and featured an incredible light show.

The SPring-8 synchrotron celebrates its 20th anniversary

On 13 October 2017, the SPring-8 synchrotron facility celebrated the 20th anniversary of its opening for public use. Since 1997, the facility, arguably the world's largest and most powerful synchrotron light source (see page 32), has been used to examine the structural characteristics of molecules, enabling discoveries in a variety of fields such as protein structure analysis and nanotechnology. The SPring-8 synchrotron facility operates with a high beam energy of 8 gigaelectron volts and has 57 beamlines. RIKEN and the Japan Atomic Energy Research Institute started construction of SPring-8 in 1991 with support from Hyogo prefecture. Roughly 15,000 users visit SPring-8 every year. At the anniversary event, several speakers, including Francesco Sette, the director general of the European Synchrotron Radiation Facility, gave addresses about the facility. The ceremony was followed by a symposium on 'Synchrotron Radiation for the Future of Humanity'.

K computer remains at the top of the HPCG list

K computer continues to perform on the world stage.

In November 2017, RIKEN's K computer took first place for the third consecutive time in the High Performance Conjugate Gradient (HPCG) benchmark. This relatively new index was developed to better reflect a supercomputer's ability to solve equations typically encountered in actual engineering and industrial applications. This, HPCG's creators say, requires a balance between calculation performance, memory performance and communication performance. In contrast, the LINPACK benchmark, which is used to produce the well-known TOP500 supercomputer list, looks at calculation speed alone. The computer scientists who have worked on the new benchmark have said that they aim to incentivize computer system designers to invest in capabilities that will have an impact on the collective performance of relevant applications. "The K computer remains number one on the HPCG list," says Mike Heroux of Sandia National Laboratories, who developed the HPCG benchmark. "This is a strong statement of the balanced design that continues to make it an attractive system for a broad spectrum of high-performance computing applications."

www.riken.jp/en/pr/topics/2017/20171116_3

Symposium

Fourth RIKEN/Karolinska Institutet/ SciLifeLab Joint Symposium

RIKEN Center for Life Science Technologies (CLST) hosted the fourth RIKEN/Karolinska Institutet/SciLifeLab Joint Symposium on Health, Disease and Aging in November 2017 at the Integrated Research Center of Kobe University, on the city's Port Island. The symposium was hosted in conjunction with Sweden's national center for molecular biosciences, which encompasses the Karolinska Institutet, The Royal Institute of Technology, Stockholm University and Uppsala University. The theme of this year's symposium was 'Life Science Frontiers in Health, Disease and Aging'. Honorary professor and 2016 Nobel laureate Yoshinori Ohsumi (below) gave the keynote lecture on autophagy, the process that cells use to dismantle and recycle cellular components. The annual event, which is open to the public and alternates between Sweden and Japan, featured 24 oral presentations and 42 poster presentations on a broad range of research.

www.riken.jp/en/pr/topics/2017/20171211_1

Nobel laureate Yoshinori Ohsumi.

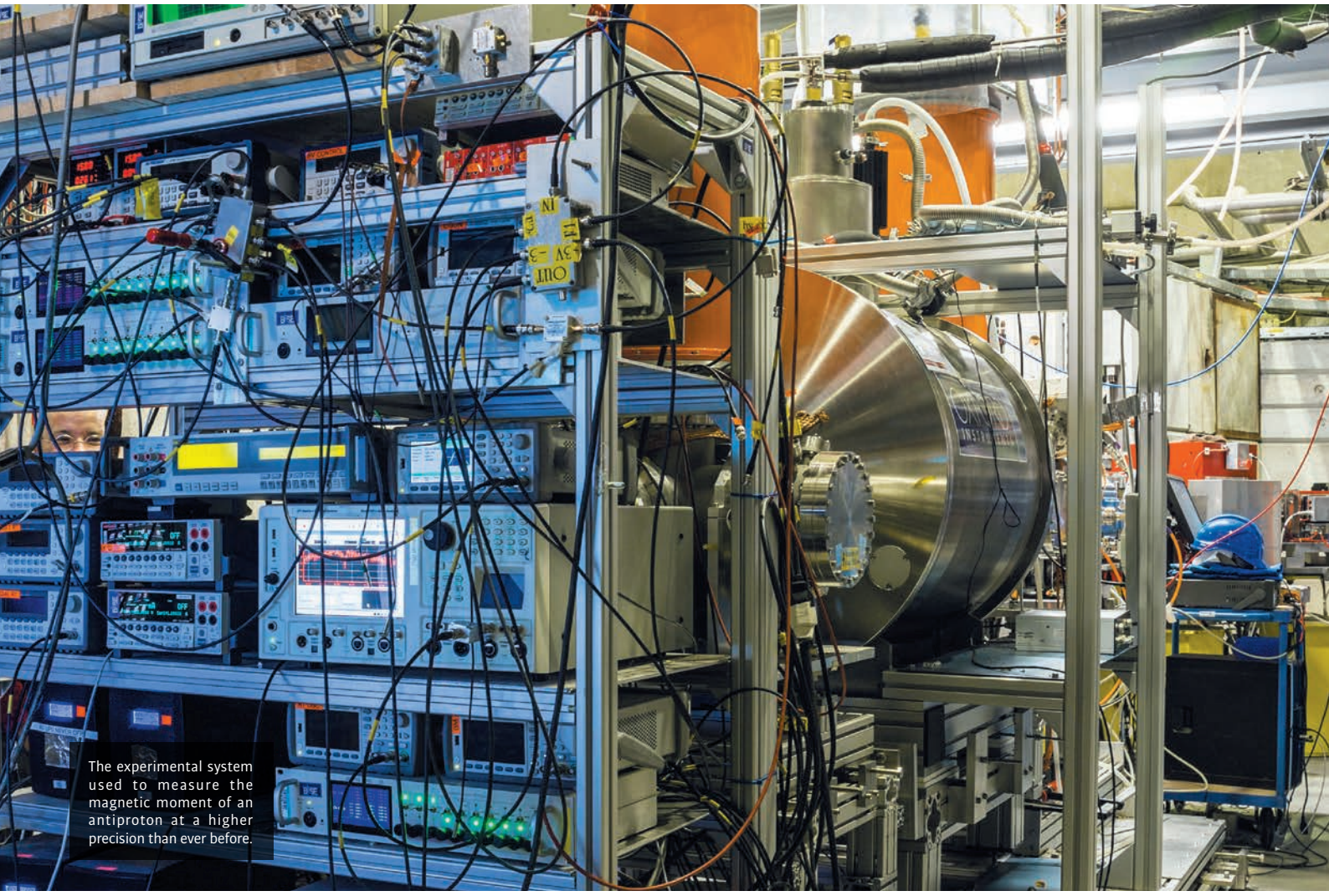
The centennial year ends with two bangs

The year 2017, which marked RIKEN's centennial, began with a big bash held in downtown Tokyo to thank people outside RIKEN who had contributed to the institution, to commemorate the past one hundred years and to map out a vision for the next. And the year closed with two other celebrations, meant to thank the people within the organization itself and help strengthen the RIKEN community. The first of these two centennial meetings, held in Kobe in November—bringing together personnel from Harima, Osaka, and Kobe—featured a panel discussion on 'Designing RIKEN for the Next 100 Years', followed by a reception. The second, held on the Wako campus, brought people from the Sendai, Tsukuba, Wako, Tokyo, and Yokohama campuses. It featured a lecture by President Hiroshi Matsumoto about RIKEN's future directions and the issues of nurturing outstanding personnel and linking research to social innovation. There were also several lectures on topics including neutron star mergers, artificial intelligence and advanced photonics devices. In the evening, personnel were able to attend a traditional ceremony featuring the opening of Japanese sake casks or a rice-pounding ceremony. These events gave researchers and staff from different parts of RIKEN the chance to interact and look ahead to the next 100 years.

Two researchers honored with government medals

Late last year, two RIKEN researchers, RIKEN Science Advisor Maki Kawai (left) and Brain Science Institute Deputy Director Atsushi Miyawaki (right), were awarded the Japanese Government's Medal with Purple Ribbon for their academic achievements. Kawai received the award for her work on chemical reactions at interfaces, while Miyawaki was awarded his for his pioneering discoveries in bioimaging technology. In 2002, Miyawaki helped improve real-time molecular imaging by developing the Kaede and Venus fluorescent proteins.

www.riken.jp/en/pr/topics/2017/20171122_1



The experimental system used to measure the magnetic moment of an antiproton at a higher precision than ever before.

PHYSICS/ASTRONOMY

Measuring the antiproton's moment as never before

Ultra-accurate measurements of the magnetic moment of antiprotons show no deviation from protons, meaning scientists still don't know why we are made of matter and not antimatter

A super-precise measurement by the RIKEN-led BASE collaboration at CERN has placed new constraints on the difference between matter and antimatter, as part of the quest to discover why the Universe consists almost entirely of matter[1]. Using a novel two-particle measurement method, the group measured the magnetic moment of the antiproton at a precision 350 times higher than previously. They found that the magnetic moments of the proton and antiproton are tremendously close, meaning that 'CPT asymmetry'—a key factor in understanding the imbalance between matter and antimatter—must be very small, if it exists at all. CPT symmetry refers to the idea that if two of three particle properties—charge, parity and time—change, the third must also change.

To perform the measurement, the group used an elegant, two-particle measurement method developed in Stefan Ulmer's RIKEN laboratory. The system involves the simultaneous trapping and measurement within an even magnetic field of two antiprotons:

one measured at a relatively high temperature of about 350 kelvin, a temperature equivalent to hot water, and the other at just 0.15 kelvin, close to absolute zero. The first antiproton is used to calibrate the magnetic field, by measuring a property called the cyclotron frequency, while the other is used to measure a quality known as the Larmor frequency, which is associated with the precession of the particle's spin, allowing precise measurements of the magnetic moment.

> **"The magnetic moment of the proton and the antiproton still look identical"**

Using this new method, the researchers found that the magnetic moment of the antiproton is extremely close to that of the proton, which was measured by several of the same collaborators in 2014. The results put strict limits on the possibility that a difference in the magnetic moments could be based on factors that, at the high energies that existed in the early Universe, could have caused a process of 'spontaneous symmetry breaking' leading to differences in matter and antimatter.

"We have shown, as has been demonstrated with other properties of a variety of particles, that CPT invariance seems to hold at very high precision, as the magnetic moment of the proton and the antiproton still look identical, apart from their signs," says Ulmer.

Christian Smorra, first author of the study, adds: "By upgrading the experiment with several new technical innovations, we feel that some further improvement can still be made, and in the future, following the CERN upgrade expected to finish in 2021, we will be able to achieve at least a ten-fold improvement." ●

Reference:
1. Smorra, C., Sellner, S., Borchert, M. J., Harrington, J. A., Higuchi, T., Nagahama, H., Tanaka, T., Mooser, A., Schneider, G., Bohman, M. *et al.* A parts-per-billion measurement of the antiproton magnetic moment. *Nature* **550,** 371–374 (2017).

BIOLOGY

Brains are like parallel computers

Researchers have found repeating units in the neocortex, the part of the brain responsible for motor actions, language and sensing

A hexagonal lattice organizes major cell types in the cerebral cortex, RIKEN researchers have discovered[1]. The pattern repeats across the brain, with similar cells synchronizing their activity in microcolumns, which could represent an essential computational unit in the brain.

The neocortex—a convoluted structure that covers much of the mammalian brain like a blanket and controls motor actions, language and sensing—is more than just a tangle of gray and white matter. Precision wiring connects cortical areas, but regular, repeating modules that could underlie neural information processing brain-wide have not been observed until now.

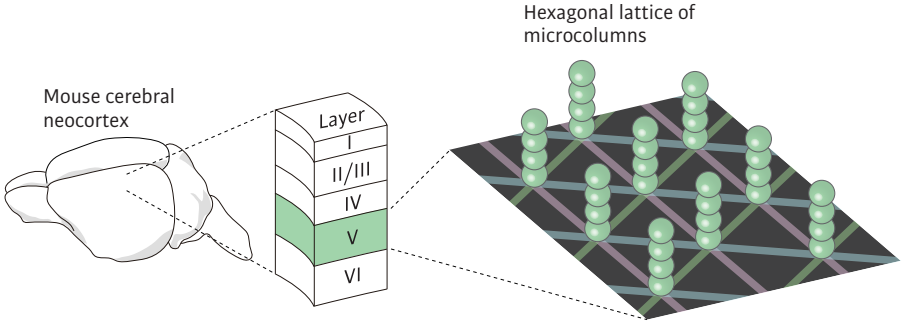
"We think we have found a functional unit of the cortex, a repeating 'processor' across which the brain's computation is distributed, like in parallel computers," says Toshihiko Hosoya of the RIKEN Brain Science Institute.

"The concept of columns in the brain is not entirely new," observes Hosoya. "What is new is finding neurons organized in columns across multiple brain areas. Our results suggest that the same functional units could underlie very different types of brain functions, from sensory perception to motor control."

Using three-dimensional anatomical methods, including two-photon imaging and cell-type-specific labeling, the researchers found that columns are arranged hexagonally in layer V of the cortex. This is a major output layer with two distinct pyramidal cell types that are comparatively large, sparse and easily labeled. Microcolumns contained only one or the other cell type, and neural activity within each column was also synchronized.

The cortical circuit—a metaphor borrowed from computers to explain how the wiring of neurons realizes information processing—has long been a holy grail in neuroscience. "In computers, a modular architecture can determine how the computation is executed, and many parallel computation models have a hexagonal structure," Hosoya notes. "Now we have some evidence that small identical computational units—microcolumn modules—underlie the architecture of the cortical circuit, at least in layer V."

One suggestion is that fundamentally understanding one elementary unit can reveal the whole brain's activity, says Hosoya. "Since



Researchers have found that there is a hexagonal arrangement of microcolumns in layer V of the cerebral neocortex.

we identified microcolumns across different brain regions, the same underlying computation may serve completely different functions. It's exciting to think that by understanding 10 or so neurons in 1 microcolumn, we could actually explain the activity of the 15 billion neurons of the neocortex."

Hosoya's group thinks it will be interesting to investigate whether other cortical layers also contain microcolumns, as well as whether this architecture is separate from or subsumes known visual cortical columns in other species—given that microcolumns show similar response properties. ●

Reference:
1. Maruoka, H., Nakagawa, N., Tsuruno, S., Sakai, S., Yoneda, T. & Hosoya, T. Lattice system of functionally distinct cell types in the neocortex. *Science* **358,** 610–615 (2017).

PHYSICS/ASTRONOMY

New-wave spintronics comes to light

Successful injection of tiny ripples into ultrathin magnetic films holds promise for computer chips that never overheat

Faint signals detected by a RIKEN team with a sensitive optical microscope have revealed a new way to realize low-energy spintronic devices[1].

Iron bar magnets possess a permanent magnetization because their atoms tend to align their electron spin with those of their neighbors. Materials with this property are known as ferromagnets.

Perturbing one spin in a ferromagnetic crystal can set off a wave of collective spin motion throughout the crystal. Such spin waves behave similarly to radio waves, making it easy to use them to carry encoded amplitude and phase information in a circuit. Unlike the conveyance of data by electric currents in conventional devices, this data flow does not involve the movement of electrons—eliminating unwanted heating, which plagues the design of modern devices.

When certain ferromagnetic materials are deposited on nonmagnetic insulators, the magnetic spins project perpendicularly from the interface, particularly if the ferromagnetic material is deposited as an ultrathin film. This orientation makes it simple to excite and manipulate spin waves using a static or oscillating electric field.

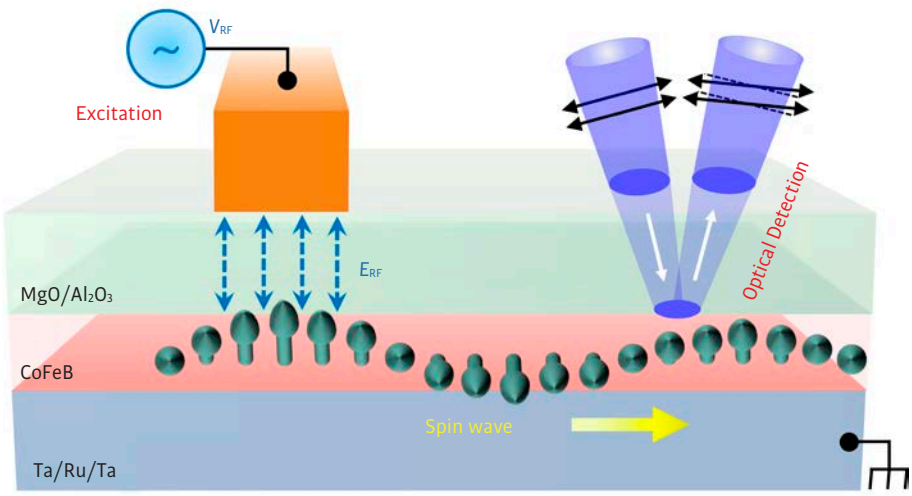
However, devices with sheet-like structures suffer from a different problem. "Since spin wave signals become weaker in thinner crystals, they are very small in ultrathin films,"

> **"It will help to develop spintronics devices with ultralow power consumptions"**

says Bivas Rana from the RIKEN Center for Emergent Matter Science. "It's difficult to detect them by conventional electrical means due to the huge background noise."

Rana and colleagues tried an alternative approach to eliminate stray electrical signals from spin-wave measurements. Through a special optical–magnetic microscope known as a Kerr microscope, they used changes in the intensity and polarization of light beams reflected off magnetic surfaces to detect time-dependent spin-wave motion with an accuracy of picoseconds (10^{-12} second) and a spatial resolution of a few hundred nanometers.

When the researchers tested a 2-nanometer-thick ferromagnetic film with their Kerr microscope, they spotted something unexpected—an electric field produced by a simple electrode excited linear propagating spin waves (see image). This is the first time this has been achieved. Since the excitation of these spin waves does not involve charge flow, it will help to develop spintronics devices with ultralow power consumptions.



A schematic diagram showing a special optical magnetic microscope, which used a reflected light beam (right) to detect previously unseen spin waves in the nanoscale regions under an electrode (left).

Unlike the conventional way of exciting spin waves that uses a magnetic field induced by an antenna, spin waves were initially excited in a localized area under the electrode. "Restricting the excitation area under the electrodes could prove crucial for submicrometer-scale spintronic devices since we can place several devices for voltage excitation very close to each other without cross-talk," Rana explains. "We're proposing voltage-controlled nanochannels to propagate spin waves, and the nanochannels can be integrated into any shape on a much wider waveguide."

Reference
1. Rana, B., Fukuma, Y., Miura, K., Takahashi, H. & Otani, Y. Excitation of coherent propagating spin waves in ultrathin CoFeB film by voltage-controlled magnetic anisotropy. *Applied Physics Letters* **111,** 052404 (2017).

BIOLOGY

Halting liver cancer with a sugar look-a-like

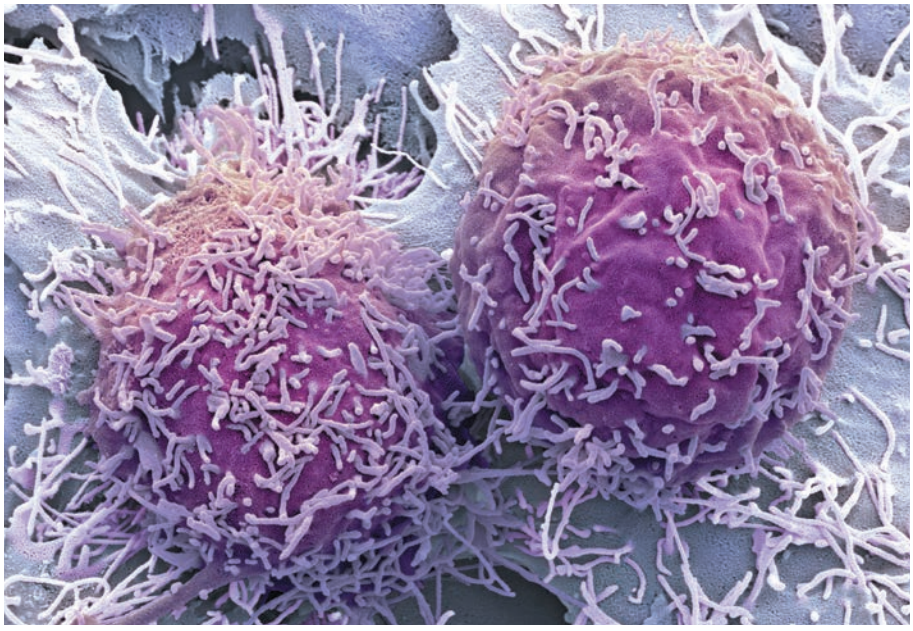
A molecule that resembles the sugar fucose could be used to suppress the spread of cancer in the liver

Using a modified fucose sugar to disrupt a biological pathway can prevent cancer from spreading in the liver, RIKEN researchers have discovered[1].

Many important biological functions depend on a process called fucosylation, in which the sugar fucose attaches to other molecules. In particular, fucosylated glycans form when fucose attaches to a chain of sugars called a glycan.

"Fucosylated glycans are critical in several cellular processes that affect development and immunity," says Yasuhiko Kizuka at the RIKEN Global Research Cluster. "At the same time, defective fucosylation can lead to life-threatening diseases."

One such disease is liver cancer, in which hepatoma—cancer cells in the liver—have excessive levels of fucosylated glycans. The RIKEN team reasoned that treatment targeting fucosylation in these cells might be effective in treating the cancer.



A fucose analog could be used to stop the spread of hepatoma, also known as liver cancer (shown above).

Biological pathways are chains of events in which certain molecules react with each other in defined steps, usually with the help of enzymes. In the case of fucosylated glycan formation, several events transform glucose into a compound called GDP-fucose. An enzyme then detaches fucose from GDP and joins it to a glycan.

One way to inhibit this type of biological signaling process is to introduce molecular analogs—molecules similar to those needed in a biological pathway.

Using this strategy, the team compared the effects of two fucose analogs on fucosylation. They found that one type of cell, 6-Alk-Fuc, virtually abolished all cellular fucosylation.

The researchers then determined how fucosylation was blocked. Experiments showed that the analog did not prevent the transfer of fucose from GDP-fucose to glycans, indicating that fucosylation itself was not affected and that the effect must occur earlier in the pathway.

Further experiments showed that 6-Alk-Fuc blocked GDP-mannose from becoming GDP-fucose. "The analog competed with GDP-mannose for attention from the enzyme FX, which prevented fucose from being made from GDP-fucose, making it impossible for downstream fucosylation to occur," explains Kizuka.

Armed with this knowledge, the team tested whether 6-Alk-Fuc has the potential to treat liver cancer. They used several cell lines of hematoma that had excessive levels of fucosylated glycans and found that the analog could prevent a healthy extracellular matrix from being invaded by the hepatoma, and was able to suppress migration of some hepatoma cell lines.

While the fucose analog suppressed cancer invasion, it did not stop hepatoma from proliferating. Thus, the number of cancer cells continued to increase, but they could not harm healthy cells.

Kizuka says that this fucose analog is promising for suppressing cancer metastasis in Fuc-high cancers, such as those found in the liver. ●

Reference:
1. Kizuka, Y., Nakano, M., Yamaguchi, Y., Nakajima, K., Oka, R., Sato, K., Ren, C.-T., Hsu, T.-L., Wong, C.-H. & Taniguchi, N. An alkynyl-fucose halts hepatoma cell migration and invasion by inhibiting GDP-fucose-synthesizing enzyme FX, TSTA3. *Cell Chemical Biology* **24,** 1467–1478 (2017).

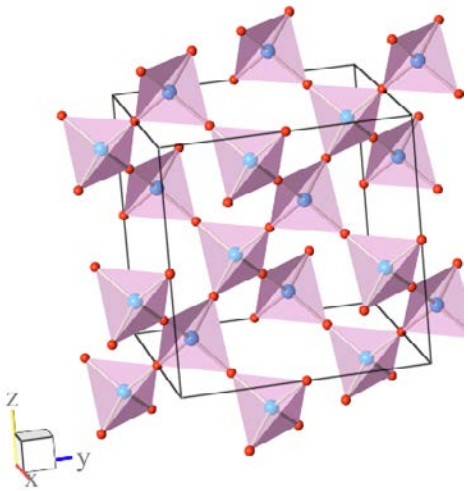
PHYSICS/ASTRONOMY

Monopole current offers means to control magnets

A technique to control magnetic monopoles in quantum spin ice may lead to more efficient magnetic devices

Two RIKEN scientists have discovered interesting new magnetic properties of an intriguing class of quantum materials, which could lead to a new way of controlling magnetism in memory devices[1].

Magnets invariably have two poles: a north and south one. Despite searching for over 70 years, physicists have yet to find a magnet with a single pole. But some special quantum materials known as quantum spin ice can exhibit the next best thing: virtual monopoles. That is because these materials behave as 'frustrated magnets'. When cooled to absolute zero (−273.15 degrees Celsius), most systems 'freeze' into a single configuration—their lowest energy state. But the special geometry of frustrated magnets permits them to settle into various magnetic states, making them interesting systems for physicists to study.



The lattice structure of the mineral pyrochlore. Electron spins are localized at lattice sites (red points).

Previously, the group led by Shigeki Onoda of the RIKEN Center for Emergent Matter Science proposed a model for a quantum spin ice to describe the low-energy magnetic properties of materials known as rare-earth pyrochlores.

This system includes a quantum spin liquid state where the electron spins—the property of electrons that gives rise to magnetic properties—are prevented from ordering and freezing by the zero-point motion of their monopoles, a motion that can occur even at absolute zero.

Since monopole charges cannot be created or destroyed, their motion affects the directions of magnetic moments in the system. Furthermore, as these monopoles do not carry electric charges, the monopole current is not accompanied by an electric current, which would cause energy losses through heating. "Monopole currents thus offer a potentially efficient way of controlling magnets without loss," notes Onoda.

In the present study, computer simulations revealed that successive transitions occur from the quantum spin liquid state when a magnetic field is applied along a certain direction. The system's magnetization rises smoothly to two-thirds of the maximum value in the quantum spin liquid state and remains there over a range of magnetic field strengths.

A coherent monopole current cannot flow in this plateau state because the zero-point motion of monopoles is localized. But increasing the magnetic field strength causes the material's magnetization to rise again, and the monopole charges show superfluidity. This monopole supersolid phase survives until the magnetization peaks.

"Our work indicates that the conductivity associated with the monopole current can be substantially controlled by applying a magnetic field to quantum spin ice, and that the monopole supersolid phase can host a dissipationless monopole current," says Onoda. "Our findings may also open a novel route to the efficient control of magnetism for a range of potential applications, such as memory devices." ●

Reference:
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The study of mouse behavior and physiology will be accelerated by a high-throughput system developed by RIKEN researchers.

BIOLOGY

Moving neuroscience into the fast lane

A new high-throughput system for studying mice can standardize experiments to facilitate reproducibility and data sharing

RIKEN researchers have constructed and deployed a high-throughput system for studying mouse behavior and physiology[1]. The system is designed to save time, reduce the number of experimental animals needed and deliver larger, standardized data sets.

Behavioral neuroscience research starts with training animals to do experimental tasks, such as pushing a button or associating certain stimuli with rewards. Training can take months and is a full-time job for one or more researchers. Furthermore, mice can get stressed from being handled by experimenters, and training varies between labs.

"It is hard to compare data across labs and even within the same lab, and we waste a lot of person-hours getting comparatively little data," says Andrea Benucci of the RIKEN Brain Science Institute.

Collaborating with Japanese laboratory equipment manufacturer O'hara & Co. Ltd., Benucci designed and built an automated experimental platform.

Without any human intervention, mice can engage in behavioral training tasks at will, and a single system can operate around the clock, training four or more mice per day. With multiple setups and mouse cages stacked in what resembles a row of server racks, the system has already been used to safely train 100 mice.

"Previously, training just one mouse took about 15 hours of a researcher's time," Benucci estimates. "Now, with 12 setups we are down to less than 1.5 hours."

Mice enter the apparatus to receive liquid rewards for doing visual or auditory discrimination tasks. They rotate a small toy wheel with their front paws to indicate whether they can hear a tone or not, for example. Crucially, mice learn to keep the position of their heads stable, which gives the system a lot of experimental versatility and represents a significant advance from existing attempts at automating rodent training.

Because mice learn to self-direct and become familiar with the system, the experimental possibilities extend beyond studying mouse behavior to real-time brain imaging and physiology. "Normally, we see a decline in mouse performance or other incompatibilities when moving from highly trained behaviors to different types of experiments for brain recordings, but that doesn't happen with our system," says Benucci.

RIKEN has patented the high-throughput neuroscience platform, and Benucci hopes it will be widely adopted in Japan and overseas. "Standard hardware and training protocols across labs that do not require the experimenter's intervention can go a long way to addressing data reproducibility in science," says Benucci. "In neuroscience in particular, there is a pressing need for large, shareable datasets to validate findings and push the field forward." ●

Reference:
1. Aoki, R., Tsubota, T., Goya, Y. & Benucci, A. An automated platform for high-throughput mouse behavior and physiology with voluntary head-fixation. *Nature Communications* **8,** 1196 (2017).

MEDICINE

Stem cell mutations don't translate

Mutations produced during the generation of induced pluripotent stem cells are found to be mainly in non-transcribed regions of the genome

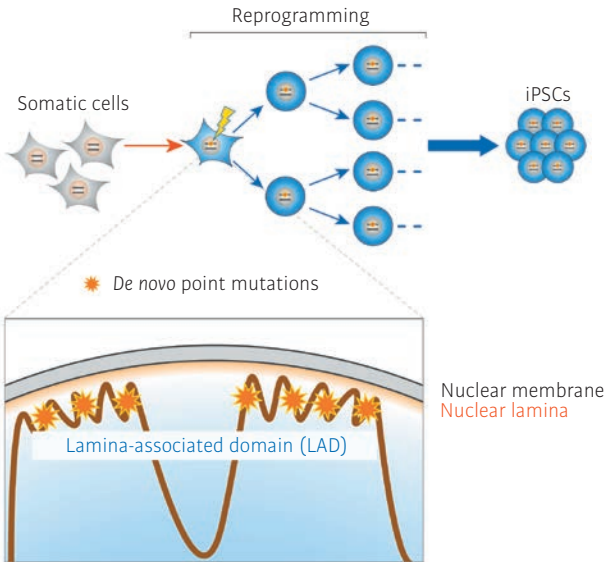
While many mutations arise during the production of induced pluripotent stem (iPS) cells, they are unlikely to lead to cancer in patients, a study by RIKEN researchers suggests[1].

Promising regenerative medicine therapies based on iPS cells, which are cells derived from normal body cells and reprogrammed into pluripotent stem cells, are currently being tested in clinical studies. But there are concerns that mutations occurring in these cells during their generation could cause problems such as cancer in transplant patients. Researchers are thus keen to understand the nature of these mutations.

Now, a team from RIKEN, Osaka University and the National Institute of Radiological Sciences has some potentially comforting news. They performed a genomic analysis on both mouse and human iPS cells and found that mutations in iPS cells tended to be concentrated in non-transcribed areas of the genome between genes. This is in contrast to single-nucleotide polymorphisms, which only involve a change to a single DNA building block and often cause genetic disorders and cancer. The researchers also showed that the mutations found in iPS cells are likely caused by oxidative stress, which seems to explain why they are concentrated in certain regions.

Mutations tend to occur differently in different parts of the genome, depending on factors such as the source of the damage, the accessibility of DNA-repair mechanisms and how tightly the DNA is wrapped. The new mutations in iPS cells tend to be found on the outer edge of the cell's nucleus, in the membrane that separates the nucleus from the cytoplasm (see image). This area is characterized by condensed chromatin and is sensitive to oxidative damage caused by mitochondria.

"We found that though mutations arise during reprogramming, many of them are



Most of the new mutations that arise during the generation of induced pluripotent stem cells from somatic cells are concentrated in transcriptionally repressed regions of the genome.

in transcriptionally repressed domains," says group leader Yasuhiro Murakawa from the RIKEN Preventive Medicine and Diagnosis Innovation Program and the RIKEN Center for Life Science Technologies. "It is tempting to speculate that this means they will not lead to adverse effects."

Most of the mutations found by the team that do not alter a protein were not listed in a catalog of cancer-related mutations, and so are essentially new mutations that need to be investigated.

"This study has given us insights into the broad mutational landscape of iPS cells, and it will give us a framework for looking at variations in iPS genomes," Murakawa says. "This will help us in the quest to develop new therapies."

Reference:
1. Yoshihara, M., Araki, R., Kasama, Y., Sunayama, M., Abe, M., Nishida, K., Kawaji, H., Hayashizaki, Y. & Murakawa, Y. Hotspots of de novo point mutations in induced pluripotent stem cells. *Cell Reports* **21,** 308–315 (2017).

BIOLOGY

The advantage of sniffing

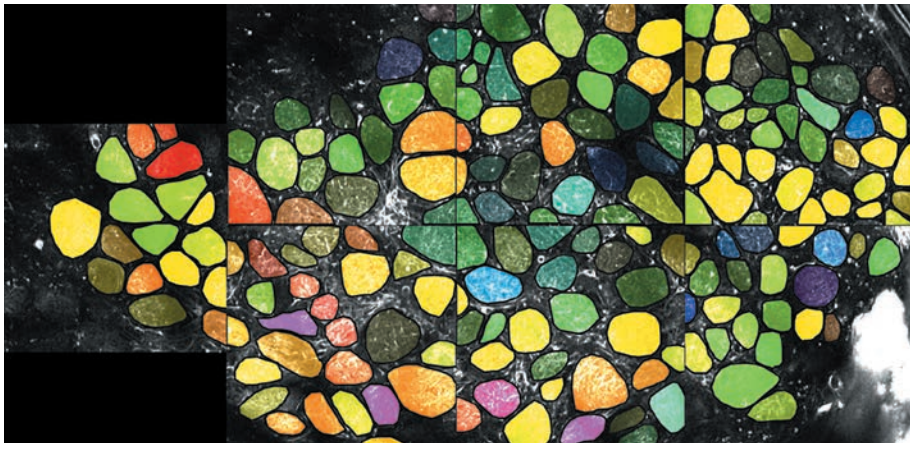
The brain uses the phase of incoming signals to distinguish between smelling and the sensation of airflow in the nostrils

RIKEN researchers have discovered how the sensations of smell and airflow in the nostrils are distinguished and how sniffing helps identify odors, two problems that have long puzzled scientists[1].

When you smell chocolate, each compound in the aroma activates specific neurons in your nose, which converge at the olfactory bulb of the brain on structures called glomeruli. Chocolate thus activates 'chocolate' glomeruli. The neurons in your nose also respond when pushed by air, but the activation is less specific. So sniffing activates 'chocolate' and 'non-chocolate' glomeruli. How does the brain distinguish between the two signals?

"Surprisingly, we found that temporal firing patterns of neurons can distinguish between airflow-driven mechanical signals and those generated by odors," explains Takeshi Imai at the RIKEN Center for Developmental Biology. "We also discovered that the mechanosensation improves olfaction by acting as a pacemaker for temporal patterning."

Imai's team devised a system to artificially control rhythmic sniffing in mice and used it to present deodorized air to the mice while they recorded activity from neurons in the glomeruli. They found that many glomeruli were activated by airflow, and that the activity went up and down in cycles that matched the artificial sniffing rate. However, the glomeruli were out of phase with each other.



A micrograph of glomeruli in the olfactory bulb of a mouse. The different colors represent different oscillation phases. These phases allow the brain to distinguish between smells and the sensation of airflow.

The team next examined how increasing airflow and odor stimulation affected the phase of activity in the glomeruli. They found that increasing the airflow speed increased the amount of glomeruli activity, but did not change their phases very much. In contrast, when they presented odors to the mice, they found that the timing of glomeruli activity shifted significantly within the sniff cycle. The phases shifted the same amount irrespective of the odor concentration. This shows that odor and airflow stimulation can be distinguished by the phase of activity in the glomeruli, and that the phase indicates the odor identity regardless of the concentration.

But why are neurons in the nose sensitive to air pressure? The team examined responses to odors when airflow was artificially constant, without any rhythm. They found that continuous airflow reduced the precision of the phase code, especially at low odor concentrations, which would make it harder to distinguish one odor from another.

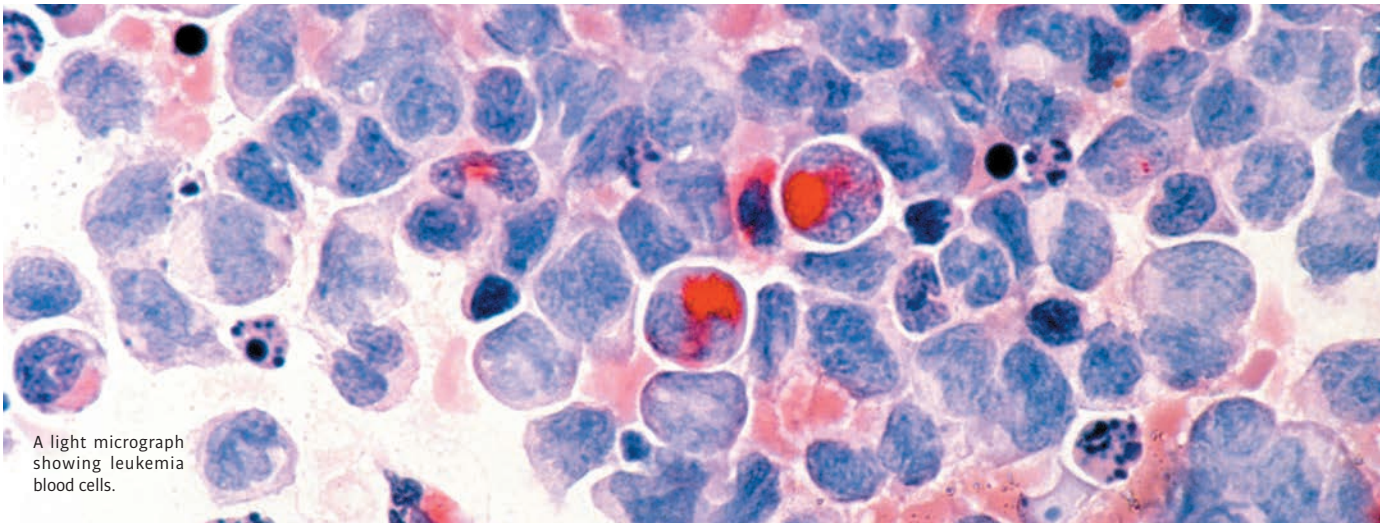
"Phase coding is not unique to the olfactory system," notes Imai. "Although it has also been found in the hippocampus in relation to memory formation, we still do not know much about it. Hopefully, our finding will facilitate a better understanding of how neurons communicate with each other and how meaning can be derived from their signals."

Reference:
1. Iwata, R., Kiyonari, H. & Imai, T. Mechanosensory-based phase coding of odor identity in the olfactory bulb. *Neuron* **96,** 1139–1152 (2017).

MEDICINE

Two-pronged approach defeats leukemia cells

A combination of drugs that target two important pathways is effective in destroying leukemia cells in mice



A light micrograph showing leukemia blood cells.

RIKEN scientists have found that, in mice carrying functioning human genes, a cocktail of drugs that blocks certain key pathways is effective in eliminating acute myeloid leukemia (AML), a disease estimated to kill more than 250,000 people a year around the world[1].

Most AML patients treated with chemotherapy relapse because cells called leukemia stem cells survive the onslaught of chemotherapy drugs and proliferate.

The group had previously discovered a compound known as RK-20449 that targets these stem cells. This compound targets a certain class of tyrosine kinases—receptors that play an important role in cell signaling in the bone marrow and blood, including signaling implicated in leukemia.

The team has now shown that targeting two important pathways simultaneously is a promising route for eliminating cancer.

One difficulty of developing targeted therapies against AML and other tumors is that cancers can be very genetically diverse—cells in different patients and even cells in a single patient may harbor different mutations, making it hard to determine which are important for tumor growth or survival. Many of the mutations found in cancerous AML cells, for example, are also found in the cells of people without leukemia, especially elderly people.

To elucidate which mutations are important, the group took cells from AML patients at various stages of the disease and transplanted them into immune-deficient mice engineered to accept human cells. They then examined how the cells behaved—in either a normal or leukemic way—in organs such as bone marrow and spleen. "We connected the genomic information and biological functions of the cells," explains Fumihiko Ishikawa of the RIKEN Center for Integrative Medical Sciences.

Using this method, the researchers discovered that a mutation in the gene coding FLT3, an important tyrosine kinase, is critical for transforming normal bone marrow cells into AML cells and that another gene, *BCL-2*, functions to promote therapeutic resistance in FLT3-mutated AML. This mutation, called FLT3-ITD, is one of the most common mutations found in AML patients. The group showed that by using RK-20449 to block abnormal signaling caused by FLT3-ITD, AML cells with multiple mutations could be effectively eliminated. In addition, by simultaneously targeting BCL-2 with a second drug called venetoclax, they could completely eliminate AML in the transplanted mice in most of the AML cases tested.

"This shows that determining which of the mutations in a diverse landscape are critical in leukemia onset and which of the pathways are critical for therapeutic resistance in leukemia, and simultaneously targeting those pathways is an encouraging way to treat difficult cancers such as AML," says Ishikawa. ●

Reference:

1. Saito, Y., Mochizuki, Y., Ogahara, I., Watanabe, T., Hogdal, L., Takagi, S., Sato, K., Kaneko, A., Kajita, H., Uchida, N. *et al.* Overcoming mutational complexity in acute myeloid leukemia by inhibition of critical pathways. *Science Translational Medicine* **9,** eaao1214 (2017).

Solutions containing quantum dots of different sizes emit light of different colors. The powerful light emission of quantum dots makes them excellent fluorescent probes.

CHEMISTRY

Quantum dots mark the spot

Small connecting proteins are the key to easy-to-make probes for biomedical imaging

A simple way to realize highly sensitive molecular imaging of cancer cells and other biomedical targets has been developed by researchers at RIKEN. They have done this by harnessing the incredible brightness of quantum dots—tiny fluorescent semiconductor crystals[1].

Previous research has shown that pairing quantum dots with antibodies can turn them into molecular imaging probes. In the body's immune system, antibodies recognize and stick to specific molecules on the surfaces of invading cells. In the lab, antibodies can be created to bind to almost any molecule of interest.

"For molecular imaging inside the body, highly fluorescent probes that can target specific molecules are desirable for obtaining high-quality images," says Takashi Jin from the RIKEN Quantitative Biology Center, who led the current study.

While quantum dots are at least ten times brighter than conventional fluorescent probes based on organic dyes and fluorescent proteins, it is challenging to attach antibodies to their surfaces, Jin notes. Attempting to directly connect the tail of an antibody to the quantum dot surface tends to cause the antibodies and the quantum dots to clump together. A more

successful approach has been to fix an adaptor protein to the quantum dot and then to attach an antibody to the protein. But the adaptor proteins used to date are so bulky that they impair the performance of the probe.

Jin and his team have now overcome this problem by developing an adaptor protein, called HisGB1, that is two to three times smaller than previously reported adaptor proteins. A further advantage that HisGB1 proteins have over adaptor proteins reported to date is that they more readily bind to the surfaces of quantum dots.

“The ability to light up specific molecules inside living creatures has many potential applications.”

“HisGB1 quantum dots can be used to simply prepare compact antibody–quantum dots conjugates that can enable highly sensitive molecular imaging,” says Jin.

The researchers tested their probe using antibodies that recognize Her2 receptors, which are found in large numbers on the surfaces of certain breast cancer cells. The antibody–HisGB1 quantum dot conjugates lit up the breast tumors of mice when the animals were examined under near-infrared illumination. Without the antibody, the quantum dots did not accumulate in the tumor tissue, confirming that the antibody was playing the targeting role.

The ability to light up specific molecules inside living creatures has many potential applications, Jin says. “We would like to use HisGB1 quantum dots to non-invasively visualize the cellular dynamics in immune reactions and cancer metastasis.” ●

Reference

1. Tsuboi, S., Sasaki, A., Sakata, T., Yasuda, H. & Jin, T. Immunoglobulin binding (B1) domain mediated antibody conjugation to quantum dots for *in vitro* and *in vivo* molecular imaging. *Chemical Communications* **53,** 9450–9453 (2017).

PHYSICS/ASTRONOMY

Spins line up for data duty

Electric fields produced by structural mismatches between two materials could be harnessed to manage data in spintronic devices

The electric field generated at the interface of two materials can marshal electrons so that their spins point in the same direction, researchers at RIKEN have shown experimentally for the first time[1]. This finding could help to develop new devices in the burgeoning field of spintronics, which uses electron spin rather than electron charge to encode and manipulate data.

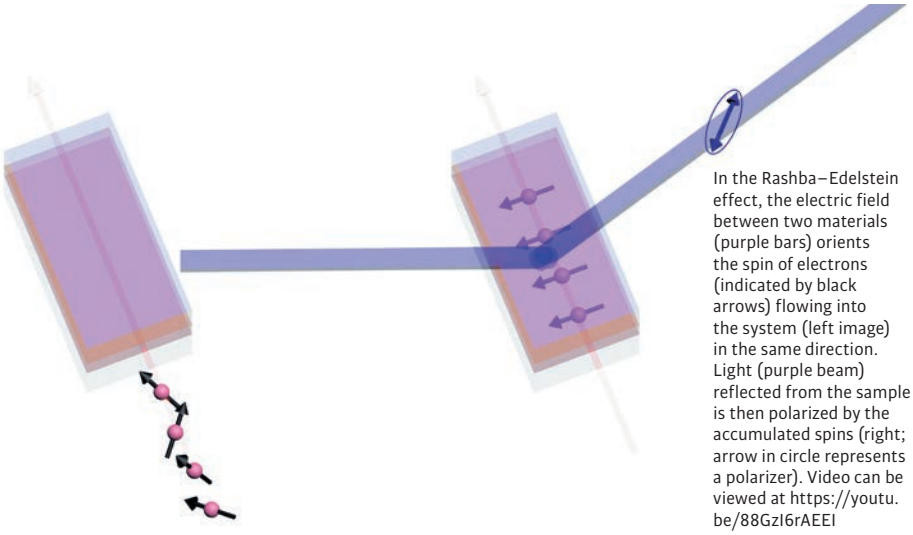
Spin imparts electrons with an intrinsic magnetism so that they act like tiny bar magnets. The direction of their spins can be altered at the interface between an oxide with a low hole conductivity and a non-magnetic metal, where the mismatch between the atomic structures of the two materials generates an electric field. Electrons moving through this field experience a magnetic field at right angles to the electric field, which aligns the electrons’ spins so that they point in the same direction, creating what is known as spin accumulation.

Jorge Puebla of the RIKEN Center for Emergent Matter Science and his colleagues have now measured this phenomenon, known as the Rashba–Edelstein effect, at the interface between the insulator bismuth oxide and the non-magnetic metals copper and silver.

While passing an electric current along the interface, the researchers looked for spin accumulation by taking spectroscopy measurements using laser light. Since blue laser light reflected off the sample was polarized by an excess of one type of spin at the interface, measuring the polarization of the reflected laser beam revealed the amount and direction of spin accumulation.

By performing these measurements at five positions on the interface, the researchers confirmed theoretical predictions that the spin accumulation was evenly distributed across the interface. “Our experiments directly confirm this hypothesis for the first time at nonmagnetic interfaces,” says Puebla.

They also found that the copper and silver samples accumulated spins that pointed in opposite directions. “The orientation of the spins directly relates to the direction of



In the Rashba–Edelstein effect, the electric field between two materials (purple bars) orients the spin of electrons (indicated by black arrows) flowing into the system (left image) in the same direction. Light (purple beam) reflected from the sample is then polarized by the accumulated spins (right; arrow in circle represents a polarizer). Video can be viewed at https://youtu.be/88GzI6rAEEI

the electric field produced at the interface," explains Puebla. The team is now working to understand why this difference arises.

One potential application of the direct Rashba–Edelstein effect is in spin-filter devices. These allow certain spin orientations to pass through while blocking others, which could be used to read digital spintronic signals. The effect could also be used to switch a material's magnetization on the nanometer scale, forming the basis of a data storage device.

The team is now studying spin accumulation in other materials at a range of temperatures and is also exploring whether the inverse Rashba–Edelstein effect can be used to enhance the performance of solar cells.

Reference

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BIOLOGY

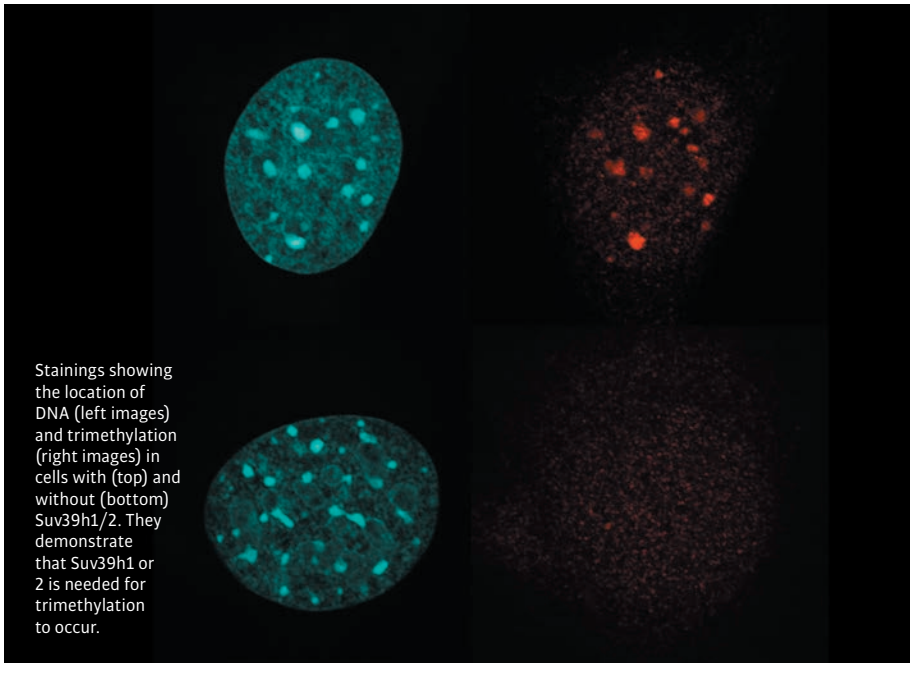
The workings of a gene silencer

A protein that silences genes by packing DNA into an inactive form is guided into place by RNA

RIKEN researchers have a better understanding of how damage to an embryo's genetic material can cause birth defects. They have uncovered the molecular mechanisms guiding a key protein that regulates gene activity by modifying DNA[1]. They also discovered that RNA plays a crucial role in the process. These findings may enable researchers to artificially induce the process, allowing them to further dissect the mechanism and arrive at a full picture of its workings.

The proteins encoded by the two Suv39H genes are key players in modifying the protein–DNA complex to control gene activity. They chemically modify DNA-associated proteins called histones through a process known as methylation (see image). DNA domains tagged with these epigenetic marks are packaged into heterochromatin, a tightly bound form of DNA that silences genes by making them inaccessible.

The Suv39H proteins are known to bind to histones. Experiments on yeast in 2012 revealed they also bind to RNA to properly target histones for trimethylation. Many of the researchers involved in that study have now extended our understanding of these genes by showing that the same mechanism occurs in mammals.



Stainings showing the location of DNA (left images) and trimethylation (right images) in cells with (top) and without (bottom) Suv39h1/2. They demonstrate that Suv39h1 or 2 is needed for trimethylation to occur.

> **"Our study has clearly shown that RNA binding helps guide Suv39h1 to the correct location"**

Atsuko Shirai and Yoichi Shinkai (see also page 22) of the RIKEN Cellular Memory Laboratory and co-workers used various protein analyses to demonstrate that Suv39h1 from mice binds to nucleic acids, particularly RNA, and that this binding helps to correctly target the protein. They also identified the RNA-binding domain of Suv39h1 and showed that it is distinct from the histone-binding domain; in other words, Suv39h1 binds to RNA and histones independently. Finally, by studying various Suv39h1 mutants, the researchers showed that binding to both RNA and histones is necessary for correct Suv39h1 targeting and heterochromatin assembly.

"Suv39h1 is one of the most well characterized heterochromatin-regulating molecules," says Shinkai. "If we can understand how Suv39h1 is targeted to accumulate at specific target loci, we may find

that this mechanism generalizes to other epigenetic regulators."

"Our study has clearly shown that RNA binding helps guide Suv39h1 to the correct location," notes Shirai. "But it remains unclear whether RNA plays a role in the methylation reactions—we are now working on clarifying this."

The team is also developing a system that uses Suv39h1 to induce heterochromatin formation at new regions in the genome. Shinkai hopes to artificially target Suv39h1 by introducing RNA guide molecules at novel locations, establishing a tool that will enable his team to dissect the mechanisms involved in trimethylation and heterochromatin formation and to distinguish the involvement of Suv39h1 in establishing and maintaining heterochromatin. ●

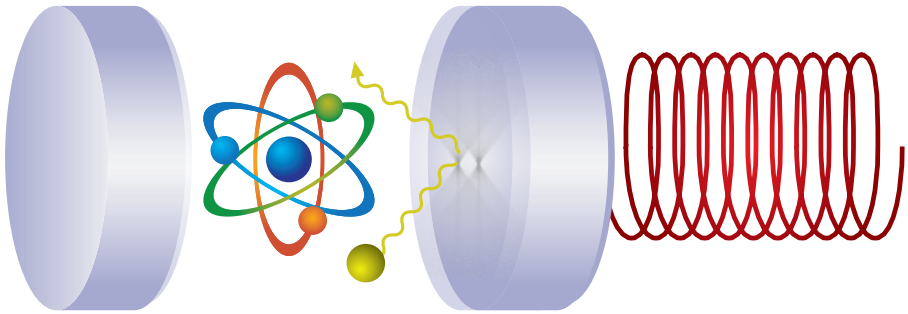
Reference

1. Shirai, A., Kawaguchi, T., Shimojo, H., Muramatsu, D., Ishida-Yonetani, M., Nishimura, Y., Kimura, H., Nakayama, J. & Shinkai, Y. Impact of nucleic acid and methylated H3K9 binding activities of Suv39h1 on its heterochromatin assembly. *eLife* **6,** e25317 (2017).

PHYSICS/ASTRONOMY

Measuring the unmeasurable

Virtual excitations, which are typically hidden, can be revealed by the pressure they exert on a movable mirror



Combining an optical cavity (two mirrors) and an optomechanical system (spring on the right) could enable virtual photons (yellow particle) to be detected.

A new scheme for observing the influence of light particles that fleetingly form out of nothing before vanishing has been proposed by an all-RIKEN team[1].

Quantum theory predicts that particles can briefly spring into existence from an otherwise empty space before disappearing again. In the case of light, these quantum fluctuations are dubbed virtual photons.

Now, calculations performed by Mauro Cirio and three co-workers from the RIKEN Center for Emergent Matter Science predict that an optical cavity could be used to amplify the physical force exerted by such virtual photons to detectable levels.

Optical cavities trap light between mirrors. They can host a wide range of fascinating physics because of their ability to enhance the strength with which light interacts with any matter placed within them. If this interaction can be engineered to be sufficiently strong, quantum fluctuations will become relevant.

"In the ultrastrong-coupling regime, light and matter are intertwined and become mixed concepts," explains Cirio. In this strong-interaction case, the lowest energy state of a system consisting of a single atom in a cavity contains excitations in the atom 'intertwined' with virtual photons, which can exist only within the cavity. And just like conventional photons, these virtual photons will exert a force on the cavity mirrors as they bounce off them.

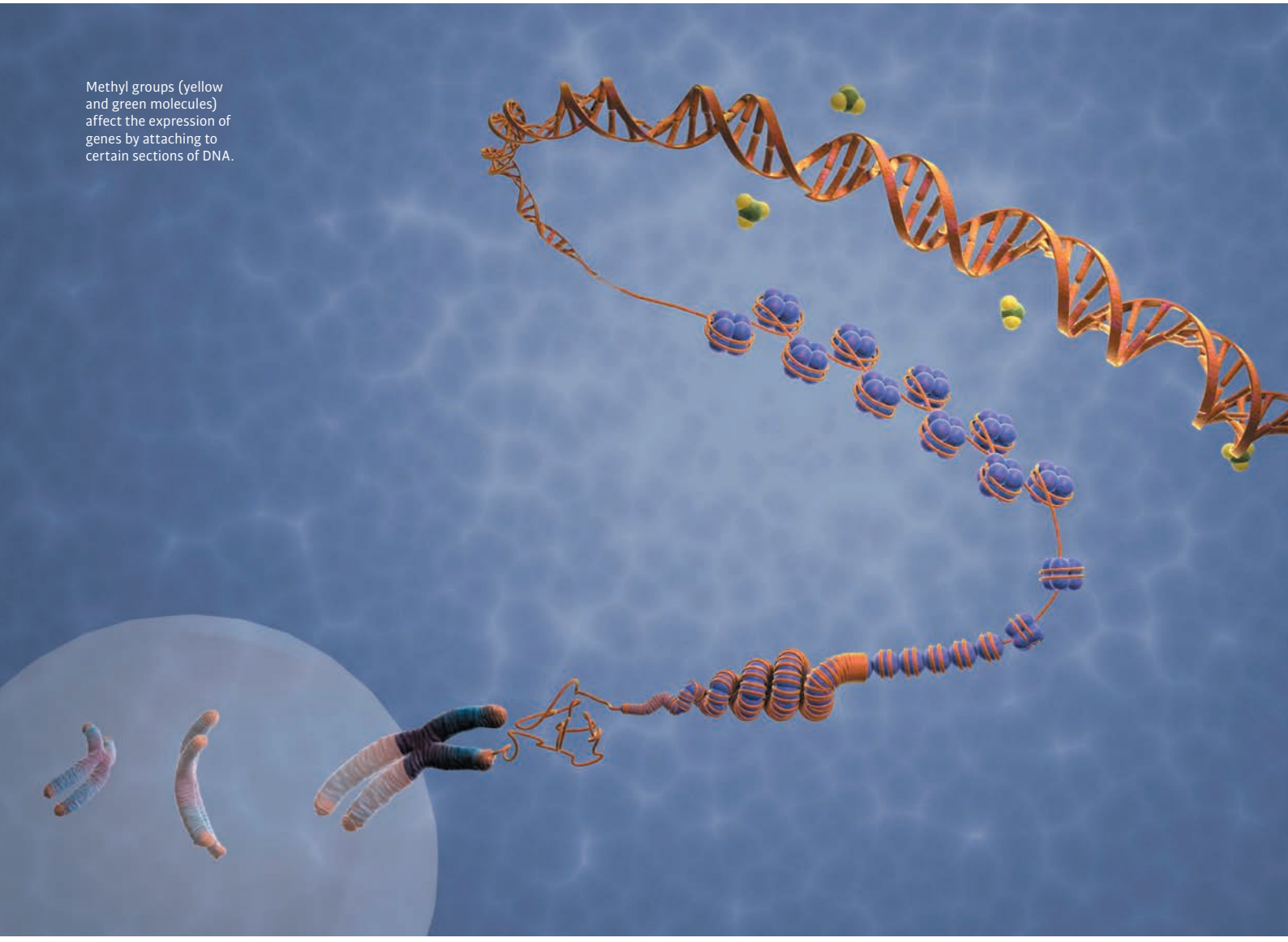
"We were interested in finding a way to measure the presence of the virtual photons trapped in the system, without destroying them," says Cirio. "This led us to the new idea of quantifying how much force the virtual photons exert on a mirror as virtual radiation pressure."

But the size of this force is miniscule. To measure it, Cirio and the team proposed using a set-up that combines an atom in an optical cavity and an optomechanical system (see image). Such a system effectively couples light and mechanical vibrations. The researchers numerically analyzed this hybrid set-up and showed that their powerful protocol can amplify the tiny force acting on the mirror by several orders of magnitude. This amplification is large enough to make the force, in principle, detectable with current state-of-the-art technology. For example, the scientists believe that the idea could be achieved using a microwave cavity that is capacitively coupled to a micromechanical membrane whose motion varies the frequency of the cavity.

The proposed measurement system could have wider application. "We are very much interested in extending the amplification process to other contexts that require the detection of tiny forces," says Cirio. ●

Reference

1. Cirio, M., Debnath, K., Lambert, N. & Nori, F. Amplified optomechanical transduction of virtual radiation pressure. *Physical Review Letters* **119,** 053601 (2017).
2. Measuring the very real pressure of virtual photons, *Physics Central Physics Buzz Blog*



Methyl groups (yellow and green molecules) affect the expression of genes by attaching to certain sections of DNA.

BIOLOGY

Copy that

A DNA replication protein helps copy chemical tags to newly synthesized genetic material

The way in which a cell's machinery goes straight from replicating DNA to adorning the newly synthesized DNA with chemical tags has been discovered by a team co-led by RIKEN researchers[1]. Unexpectedly, they have implicated a protein previously thought to be involved only in DNA replication in the process. This discovery could help scientists find new drugs for cancer.

Cells use small chemical tags—methyl groups—in the genome to lock genes in the 'off' position (see image). During replication of DNA, these tags must be copied from the original strands of the double helix to their new copies. Aberrations in the patterning of these tags have been implicated in many forms of cancer.

Thus, the newly revealed molecular mechanism linking DNA replication and methylation could point researchers to new drug targets for cancer, says Yoichi Shinkai (see also page 20), chief scientist of the RIKEN Cellular Memory Laboratory, who led the study.

The researchers focused on a protein called UHRF1. Scientists knew that it binds to half-methylated DNA and recruits another protein to copy the methylation information to the other genetic strand. But it was unclear how UHRF1 recognized the partially methylated

DNA to begin with. Was it an intrinsic property of the protein, Shinkai wondered, or were other actors involved in recruiting UHRF1 to these sites of the genome?

To find out, Shinkai's group teamed up with Pierre-Antoine Defossez's group at Paris Diderot University, as well as scientists from the RIKEN Center for Sustainable Resource Science and around the world. Together, they isolated UHRF1 from human cells and found that it formed a complex with several other proteins, including DNA ligase 1 (LIG1)—an enzyme that is important for DNA replication and repair. Further experiments identified the region within the LIG1 protein that, when methylated itself by two other enzymes, binds UHRF1. This interaction, the researchers showed, explains why UHRF1 is drawn to DNA replication sites.

> **"We might be able to prevent tumors from growing by manipulating the LIG1 methylation state"**

Takeshi Tsusaka, a PhD student in Shinkai's lab, says the results came as a shock to the team. "Everyone, including us, believed that LIG1 functioned just as a DNA ligase and that it had no other functions," he says. "This is the most surprising and important finding of our work."

The finding that LIG1 plays a role in DNA methylation suggests it could be important in cancer development as well. While it has yet to be proven, Tsusaka says: "If anybody reveals the relevance of LIG1 to cancer, we might be able to prevent tumors from growing by manipulating the LIG1 methylation state to alter UHRF1 binding."

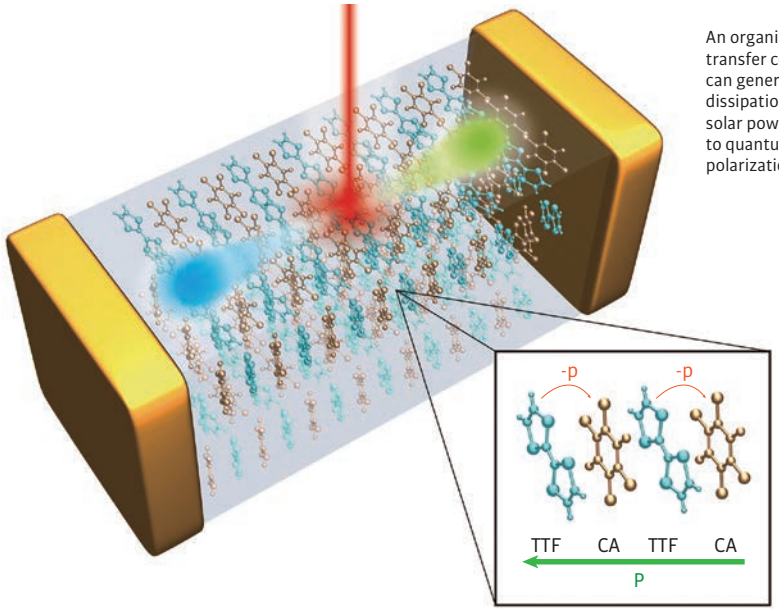
Reference

1. Ferry, L., Fournier, A., Tsusaka, T., Adelmant, G., Shimazu, T., Matano, S., Kirsh, O., Amouroux, R., Dohmae, N., Suzuki, T. *et al.* Methylation of DNA ligase 1 by G9a/GLP recruits UHRF1 to replicating DNA and regulates DNA methylation. *Molecular Cell* **67,** 550–565 (2017).

PHYSICS/ASTRONOMY

Solar cells with a quantum shift

A quantum-mechanical way of generating photocurrents may help solar devices overcome existing inefficiencies



An organic charge-transfer complex can generate dissipation-free solar power thanks to quantum-based polarization effects.

A much quicker, less wasteful way to extract current from solar cells that uses a quantum-mechanical process has been demonstrated by RIKEN researchers[1].

When sunlight strikes a typical solar panel, it creates pairs of electrons and positively charged holes. Normally, an electric field is used to separate these charges and produce electrical power, but this approach requires charges that have high mobilities and lifetimes, which makes it hard to develop new photovoltaic materials.

An alternative approach for extracting current from solar cells involves exploiting the symmetry of the repeating structural units that make up crystals. Certain semiconductors lack 'inversion' symmetry—meaning that if their atoms are flipped about the center of the repeating unit, a different atomic arrangement will be produced.

For such semiconductors, light-induced transitions of charges to excited states become unbalanced, creating a 'shift current' along a specific crystal direction. This shift current propagates rapidly and with less energy loss than a current generated by applying an electric field. But shift currents usually generate insufficient photovoltaic power for practical uses.

Now, Masao Nakamura from the RIKEN Center for Emergent Matter Science and colleagues have overcome this shortcoming by using ferroelectric organic molecules that spontaneously separate their positive and negative charges. Because ferroelectric materials naturally disrupt inversion symmetry, they have potentially large shift currents—particularly when charge separation occurs due to quantum-mechanical differences in the covalent bonds holding a crystal together.

The team investigated an organic ferroelectric with strong quantum polarization to explore its shift-current

capabilities. Composed of alternately stacked tetrathiafulvalene (TTF) and *p*-chloranil (CA) aromatic rings (see image), this complex undergoes instantaneous charge separation when cooled to around −200 degrees Celsius and is particularly sensitive to sunlight.

"Most ferroelectric materials need light with energy in the ultraviolet region to excite carriers over a large band gap," says Nakamura. "With TTF–CA, the band gap is narrow and responds to visible and infrared light, which is really important for applications like solar cells."

When the researchers measured the photovoltaic properties of the organic complex, they were taken aback by the amount of shift current generated—nearly ten times higher than comparable oxide ferroelectrics. The quantum-based charge transfer dramatically improved solar output power and allowed the current to travel as far as 200 micrometers before dissipating.

Because the shift-current effects in TTF–CA are so sizeable, Nakamura expects that it could be used as a platform to implement this photoelectric conversion in next-generation devices. "We'll be looking at other ferroelectrics to try for room-temperature operation," he says. "And we think we can improve extraction efficiency by employing thin-film device structures." ●

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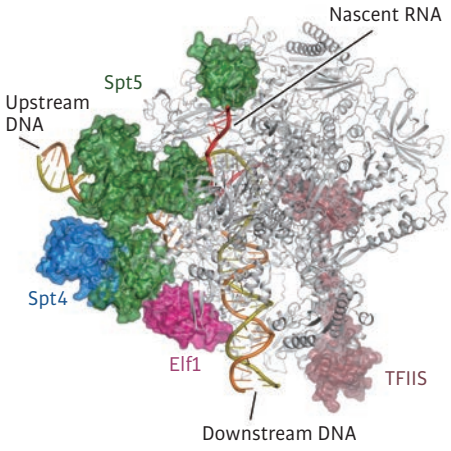
BIOLOGY

The shape of transcription

The newly revealed structure of a key complex involved in copying DNA will lead to a better understanding of the process

By using x-ray crystallography and cyro-electron microscopy data, an all-RIKEN team has elucidated the structure of a trasnscriptional 'factory', or complex, that plays a critical role in the copying of DNA into RNA[1]. This structural information provides vital clues as to how the complex functions.



The elongation complex of polymerase II establishes well-defined paths for DNA and RNA.

Before genes encoded in DNA can be expressed, the relevant section of DNA has to be transcribed into RNA. It is simple to transcribe DNA in a test tube—all you need are DNA, RNA polymerase and nucleotides—but the situation is more complex in a cell's nucleus. "Many components, including transcription factors, associate with RNA polymerase II and form huge transcription complexes, many of which have not been structurally explored yet," notes Shun-ichi Sekine from the RIKEN Center for Life Science Technologies.

His team is working on determining the structure of these large transcriptional complexes. In the current study, they focused on the elongation complex that forms in the early steps of transcription. It both ensures that transcription proceeds and regulates other essential processes linked to transcription, such as DNA repair. Sekine believes it is crucial to gain a full understanding of the complex's mechanism in order to ascertain how this regulation can fail in diseases such as cancer.

His team focused on three proteins known to be essential for the elongation complex: the multidomain protein Spt5, its binding partner Spt4 and the elongation factor Elf1. They determined the domains that are important for the interaction between Spt5 and the RNA polymerase. The researchers then solved the crystal structure of one Spt5 domain, called KOW5, combined with the polymerase and Elf1. They also obtained a model of the entire complex by merging this crystal structure with cryo-electron microscopy data of a complex that included Spt4, Spt5 and a transcription factor.

These results provide information on how the complex operates. "We found that the elongation factors Spt4/5 and Elf1 bind to functionally important parts of polymerase II," says Sekine, adding that they act like subunits of the polymerase.

Sekine likens the polymerase's structure to a needle, where DNA is a thread that can pass through the needle's eye. Elf1 forms an entry tunnel that helps thread the DNA into the polymerase and keep it in place. Spt4 and 5 make up an exit tunnel that separates DNA from RNA and ensures efficient exit of DNA and nascent RNA from the complex (see image). This aspect is critical for avoiding DNA–RNA hybridization, which can prematurely terminate transcription.

"Our structure provides a firm foundation for further structural, molecular and cellular biology studies and research on disease mechanisms," says Sekine. ●

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Immunology

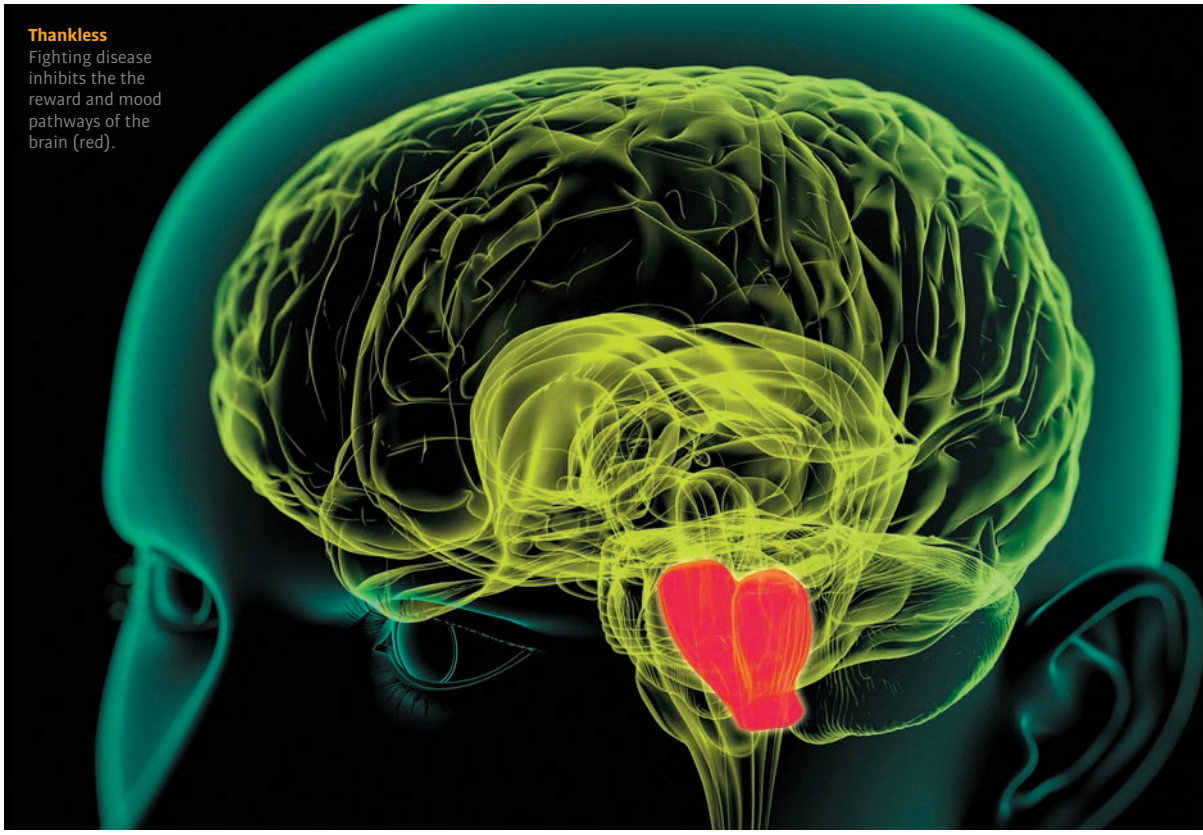
Anxiety is infectious

Being sick could be making you more worried say researchers, who have linked changes in mice immune cell metabolism to altered brain chemistry and behavior

By attacking diseases, T cells (darker green) could impede your brain's mood boosting chemicals.

This feature looks at the work of Sidonia Fagarasan

Sidonia Fagarasan is the team leader of Laboratory for Mucosal Immunity at RIKEN's Center for Integrative Medical Sciences. Her research activity includes work on the impact of immune systems on the diversity, structure and resilience of gut microbiota. In 2013, she received the National Institute of Science and Technology Policy (NISTEP) Award from the Ministry of Education, Culture, Sport, Science and Technology (MEXT) for work explaining the relationship between digestive tract microbes and immune function. She has been published in many highly-regarded journals, such as *Science, Immunity, Nature, Cell and Proceedings of the National Academy of Sciences.*



Thankless
Fighting disease inhibits the the reward and mood pathways of the brain (red).

Often when you come down with a heavy cold or the flu, you don't just feel sick, you feel downright miserable. RIKEN researchers have found a possible physical explanation for the feeling of wretchedness that can accompany infections. In a study straddling several fields, the team have broken new ground by tracing behavior in mice that links anxiety to a switch in the metabolism of their immune cells[1].

It turns out that when an infection activates the immune system, infection-fighting T cells switch to a mode that consumes more amino acids. This switch, the team found, leads to fewer amino acids in the bloodstream and the brain. The shortage of amino acids in the brain reduces the amount of serotonin and dopamine that the brain can produce, leading to anxious mice.

This is the first time activation of immune responses has been linked to behavioral changes, which could have very real implications for treating disease-linked anxiety and depression.

A history of grumpy mice

A casual remark from a colleague first made immunologist Sidonia Fagarasan consider there might be a connection between the activation of the immune system and mouse behavior. "[This colleague] came to me one day and said, 'Sidonia, I hate infecting the mice because they become so aggressive'." Then the question just hit her she recalls: Why exactly are sick mice particularly difficult?

Fagarasan, a team leader at the RIKEN Center for Integrative Medical Sciences, suspected the answer lay in white blood cells known as T cells. In their normal, non-activated state, these blood cells produce energy using a process called oxidative phosphorylation. But when they become activated to fight a pathogen in the body, they switch to another metabolic process called aerobic glycolysis. While this process consumes more amino acids and is not as efficient at generating energy as oxidative phosphorylation, it has the advantage of producing more molecular building blocks the cell needs to proliferate and mount a protective immune response.

A crucial clue came from mice that lacked the ability to make a protein known as PD-1. This protein acts as a brake on the immune system and returns T cells to metabolism by oxidative phosphorylation. Fagarasan and her co-workers measured the amino acid levels in the bloodstream of mice that lacked PD-1 and were permanently in infection-fighting mode, with the mice's T cells using aerobic glycolysis metabolism. To their surprise, the team

found that these mice had lower levels of amino acids in their blood than control mice.

"We were surprised to see the depletion of almost all amino acids in the serum," recalls Fagarasan. "We'd thought that blood chemistry is dictated by the liver... But we were stunned when we realized that activation of the immune system actually alters blood chemistry. That was our first 'wow' moment."

Is an amino-acid deficiency the reason mice become more anxious?

In the second stage of the investigation Fagarasan explored the effect on brain chemistry of reduced amino acid levels in the bloodstream. The researchers measured the levels of two amino acids, tyrosine and tryptophan, in the brain and found that they were present in lower levels in mice lacking PD-1 compared to normal mice.

They then looked to see whether this had an effect on the levels of serotonin and dopamine in the brain, since these neurotransmitters contribute to a feeling of well-being in humans and are both made from tyrosine and tryptophan. This part of the experiment was no trivial undertaking, says Fagarasan. "The biggest challenge was measuring dopamine levels in the brain. Two Nobel prizes have been awarded for discoveries involving dopamine and yet measuring dopamine in the brain is still a huge challenge."

Again, Fagarasan and her team found that mice without PD-1 had lower levels of serotonin and dopamine than control mice.

The last link in the chain was to see whether this noticeably affected mouse behavior. The team discovered that the mice lacking PD-1 were indeed more anxious than normal mice. "It took us two years to set up all the behavioral studies," says Fagarasan. "We saw that these mice act strangely: they don't move; they're lazy; they're scared; they behave differently. That was our second 'wow' moment."

Mood trade-off for immune system boost

With the final piece of the jigsaw in place, the picture became clear. Essentially, it suggests that the body is channelling resources from the brain to the immune system. "It's a trade-off," explains Fagarasan. "When fighting an infection or cancer, your body uses resources earmarked for the brain to boost your immune system."

The team is now working to see whether the same mechanism operates in humans. If it does, it could have implications for treatments when a person's immune response has been activated, such as in those receiving cancer therapy.

Indeed, importantly, when the researchers fed the PD-1-deficient mice with a high-amino acid diet of tryptophan for example, the mice recovered and behaved normally.

"These findings may have implications in any clinical condition that results in a systemic immune response including infections, autoimmunity and cancer immunotherapy," comments Vassiliki Boussiotis of Harvard Medical School, who wrote a News & Views article on the study for *Nature Immunology*.

And it's even quite likely, says Fagarasan, that a diet high in certain amino acids could help make you feel better next time you're battling a common cold. ●

"Two Nobel prizes have been awarded for discoveries involving dopamine and yet measuring dopamine in the brain is still a huge challenge."

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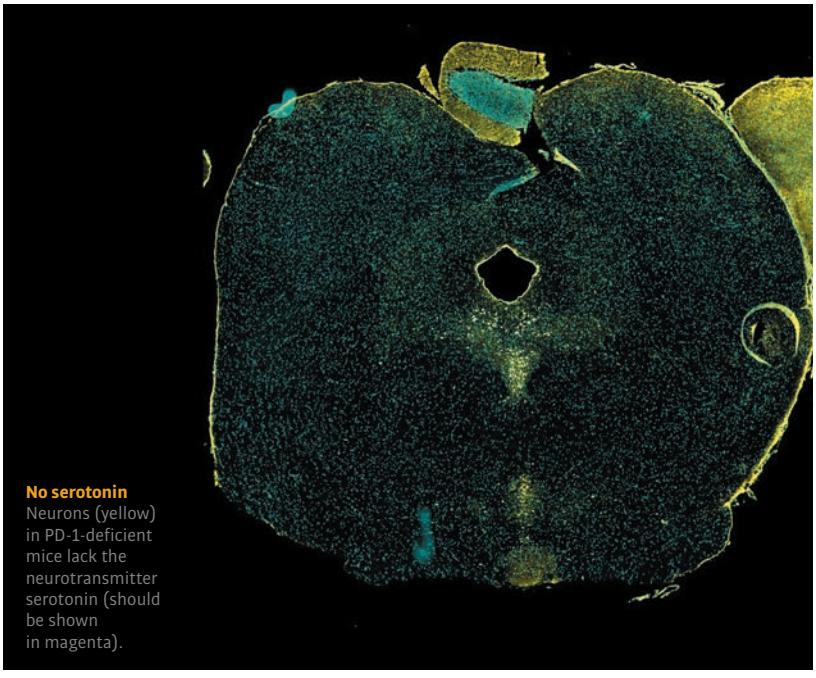

No serotonin
Neurons (yellow) in PD-1-deficient mice lack the neurotransmitter serotonin (should be shown in magenta).

Single-cell biology

Looking at every cell

Ever-advancing technologies are helping researchers better probe individual cells. As single-cell research takes off, two leaders at ***RIKEN's Single Cell Project*** *explain why they are carefully synchronizing their technological specialities. This, they say, is helping lay the foundations for a cellular-level 'Google Earth of the body' for people of Asian descent through a project called the Human Cell Atlas.*

Genomics technologies accelerating research

Piero Carninci,
Project Leader,
Single Cell Project
RIKEN Center
for Life Science
Technologies (CLST)

We don't yet know how many cell types there are in the body—but advances in precise RNA and DNA sequencing technologies mean it's time to find out. Understanding individual cells better will make it possible to drill deeper into human biology than ever before to identify different subpopulations of cells. Already this work has revealed the cells responsible for a growing number of biological functions. Some of this work is gaining insights into the dysfunctional cells that cause cancers and the immune cells that fight infections or cause inflammation, important insights that are potentially treatment altering.

The technology for single-cell genomic analysis is the most advanced in the field, and it will generate huge amounts of information. Fortunately, RIKEN has been a leader in large-scale genomic projects for some time.

Almost two decades ago the former RIKEN Genome Science Laboratory at the RIKEN Tsukuba Life Science Center started to put together a method to develop libraries of complementary DNAs (cDNAs)—this became the FANTOM project in 2000[1]. In 2013, RIKEN's Center for Life Science Technologies absorbed the project. Since it was initiated, the FANTOM database has grown to become one of the most comprehensive catalogues of mammalian genes in the world.

In 2003, my group also published a method called Cap Analysis of Gene Expression (CAGE). This would aid FANTOM in detecting the exact location of transcription start sites and promoter activity on the genome at a single base-pair resolution[2]. In fact, the most recent iteration of FANTOM used CAGE to profile the gene expression of homogeneous primary cell populations, and it was able to identify promoters, enhancers, regulatory elements and the expression of non-protein coding RNAs[3,4]. Using this data, we've tried to infer what regulates the production of cell types and to identify other regulatory elements and long non-coding RNAs.

Adding to these types of data advances, for the last five years we have been using next-generation sequencers to analyze RNAs from individual cells and advanced pipelines to help us understand subpopulations of cells. But while rapidly developing tools for single-cell RNA sequencing are providing detailed single-cell data, scientists working in other biological fields have often been left with quite different techniques—such as advanced microscopy or spectrometry—for crucial spatial or development information. Currently, these produce statistics that are frequently based on many different cells measured together. We hope to soon help these fields to work more closely with transcriptomes, allowing them to adjust any biases that might crop up in this type of data.

> "Many people thought that delving deeply into this ... field was too complex and ambitious, but now researchers globally are working to catch up with its vision."

RIKEN's Single Cell Project

At RIKEN, the single-cell movement began roughly five years ago when I hatched the idea of widely seeding broad cross-disciplinary collaborations in the field with the late Tsutomu Masujima, a team leader at RIKEN's Quantitative Biology Center (QBiC) and a pioneer in studying the metabolism of single cells.

In 2007, Masujima had developed an instrument to extract a small part of a live cell and analyze its metabolism using a metal-coated glass capillary (called a nanospray tip), mass spectrometry and video imaging[5]. He later suggested that we use the same cell and look at both its metabolites and RNA to develop a sort of 'multi-single-cell-omics' to really get ahead of the field—and so RIKEN's Single Cell Project was born.

At the time, many people thought that delving deeply into this cross-disciplinary and evolving field was too complicated and ambitious, but globally researchers are now working to catch up with its vision.

The Human Cell Atlas

The Human Cell Atlas began work in 2016. This huge international endeavor is being spearheaded by institutions such as the Broad Institute at MIT and Harvard in the USA, the Wellcome Trust in the UK, Karolinska Institutet in Sweden and our group at RIKEN, among others.

Researchers working on the Atlas are seeking to establish baseline data by mapping RNAs and imaging cells, ultimately in three dimensions. Later, perhaps, we will also map epigenomes.

All this information will be very useful for comparison with induced pluripotent stem cells intended for use in regenerative medicine. It could also help us to understand why we sometimes can't get tissues to work with organoids (organs developed in a lab from stem cells) and could provide insights on how to make organoids more like real human organs. Furthermore, findings might be able to make pathology, which currently uses stained images, much more sophisticated.

The project has already started to connect data on individual human cell expression and spatial organization, largely on transcriptomes. Our team's job will be also coordinating the project across Asia, as well as having significant input into the coordination of the international movement. Sometime in 2018, we will start the pilot ↗

project, which will begin to collect cells and start a low-resolution atlas of some human organs. This phase could take up to five years to collect the full catalogue of standard cells. Of these, we will begin with cells, such as blood cells, that are easier to collect. Others like liver, kidney and brain cells are considered a priority for study. We will start by using a standardized, conservative transcriptome method called 10x Genomics, which is commercially available and can be easily distributed to many labs. Initial efforts will go into sample collection, allocation, understanding the sample transcriptomes, as well as developing all the protocols around quality control, permissions and ethics.

I think the project will likely be a bit like Google Earth—I imagine that in phase one, we'll be able to look at some of the body's 'regions' and outlines, but in phase two we'll be able to zoom in on the detail of DNA, RNA, epigenomes, structure, shape and weight. Ultimately, this should help create an incredible set of baseline references for normal cells and tissues. ●

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Future diagnoses by imaging cells?

Professor Yasushi Okada, Deputy Project Leader, Single Cell Project
RIKEN Quantitative Biology Center (QBiC)

One of the challenges of single-cell analysis is that three of its key modalities—imaging, metabolomics and transcriptome analysis—have evolved independently. As a result it's difficult to compare results as they often differ in appearance and come from different cell sets.

Each modality of single-cell analysis technology has its own strengths and weaknesses. For example, single-cell transcriptome analysis lets us examine gene expression profiles in a comprehensive and unbiased manner. However, we need to isolate and kill the cell before analysis, which means we lose the spatial information and we can't do time-course analyses. Imaging, on the other hand, gives us spatial information and is less invasive, enabling live-cell analysis.

To join the analyses types up, the Single Cell Project has started to integrate technologies at RIKEN, and we have been working to establish a platform that enables multimodality single-cell analyses. By including all these elements, biologists hope to better understand the mechanisms of cellular function and dysfunction that show up in disease, among other things.

Including spatial information

Currently, the strongest technologies in the Human Atlas Project are for single-cell RNA sequencing and genomics, but, as I've mentioned, these don't capture spatial information in the same way as imaging.

One of the most powerful scientific imaging technologies today is single-molecule florescence imaging, which has been emerging since the 1990s. The RIKEN Quantitative Biology Center (QBiC) has a strong background in this area; in fact, Toshio Yanagida, the director of QBiC, was the first to image a single-molecule in real-time under a microscope using florescence. This important milestone in the development of super-resolution imaging allowed scientists to finally peer into the nano-world, and, indeed, develop next-generation DNA sequencing.

Today, international projects such as the 4D Nucleome Program, based in the USA, are advancing technology that will help bridge the gap between genomics and imaging technologies. The program hopes to understand: the principles behind the three-dimensional organization of the cell nucleus in space and time (the fourth dimension); the role nuclear organization plays in gene expression and cellular function; and, how changes in the nuclear organization affect normal development, as well as various diseases.

Single Cell Project

RIKEN's Single Cell Project was born about five years ago during discussions between Piero Carninci, director of RIKEN's Division of Genomic Technologies, and the late Tsutomu Masujima of RIKEN's Quantitative Biology Center (QBiC). Yasushi Okada from QBiC's Cell Dynamics Research Core Laboratory for Cell Polarity Regulation came on board with cell imaging expertise and succeeded Tsutomu as the deputy leader of the project. The project's aim is to look at the characteristics of individual cells and develop advanced technologies in transcriptomics, genomics, proteomics, metabolomics, and cell visualization and its control. It currently has at least one or two pilot projects within each biology-related center at RIKEN.

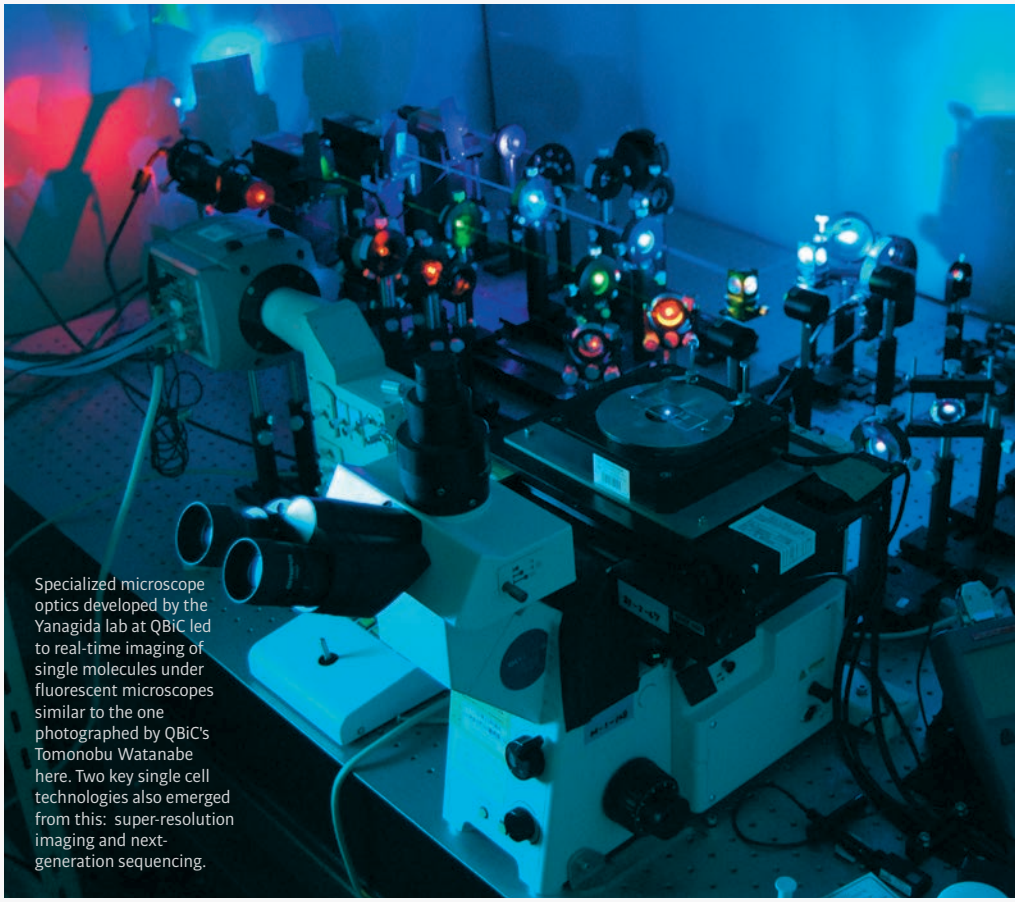
One of the 4D program's core members, biophysicist Xiaowei Zhuang from Harvard University in Massachusetts in the USA, also works on the Human Cell Atlas. In 2016, she helped advance the field hugely when she pioneered MERFISH[1], an imaging method capable of simultaneously measuring the number and spatial distribution of hundreds to thousands of RNAs in individual cells. This method is based on single-molecule fluorescence imaging, which lets scientists look at single RNA molecules in cells. Zhuang's lab is now working on the super-resolution imaging of chromatin—a DNA, protein and RNA structure that is fundamental to many of the workings of a cell—with regards to nuclear genomes and single-molecule detection of RNA transcripts.

Part of my personal contribution to the field has also touched on chromatin through working on the difficult job of imaging the transport within cells, especially within neurons. To examine the fine details of this process, the temporal resolution (the measurement precision with respect to time) of the imaging system needs to be high and proportional to the spatial resolution; otherwise the image will be blurred due to the rapid movement of the transport process. This has meant that I've had to develop my own super-resolution microscopes for live-cell imaging at high temporal resolutions[2]. Interestingly, the high temporal resolution of our microscope has also produced a high imaging throughput.

Many researchers at RIKEN now see potential applications for this technology in genomics and epigenomics, because the size of the single-gene locus of a nucleus matches the resolution of our super-resolution microscope. This has prompted us to start to visualize the dynamics of the genome in living cells with collaborators in this field, and we've recently published a paper on super-resolution imaging of chromatin structure and dynamics in the nucleus of living cells[3,4].

What should healthy cells look like?

The next step will be to work with informatics and artificial intelligence people to analyze the vast amounts of data that are being generated worldwide.



Specialized microscope optics developed by the Yanagida lab at QBiC led to real-time imaging of single molecules under fluorescent microscopes similar to the one photographed by QBiC's Tomonobu Watanabe here. Two key single cell technologies also emerged from this: super-resolution imaging and next-generation sequencing.

At RIKEN, we're currently proposing a project to match image and genomics data in the next stage of the Single Cell Project, which will involve collaborating with researchers working on high-powered computing at the RIKEN Center for Advanced Intelligence Project. The hope is that with their help the shape and behavior of the cell can be analyzed and shown to reflect the health of the transcriptome or metabolism. We could then assess a cell image in a similar manner to the way we assess the state of the human body or mind by looking at a face.

This type of analysis has already been shown to be somewhat effective in breast cancer studies, in which pathological classifications using classical haematoxylin and eosin stains have been shown to be consistent with the molecular classification of transcriptome analysis. The dream is to one day estimate cellular states, metabolic states or transcriptome states just by observing cell shapes or behaviors.

To this end, I'm leading a cooperative project involving several laboratories at QBiC to develop a platform that will help us do this—I hope to extend this network throughout the Single Cell Project. ●

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RIKEN WORLD RECORDS
FINDS & FACILITIES

With access to some of the world's best facilities, RIKEN researchers are making discoveries at Earth's known extremes.

FINDS

The world's smallest **genome sequenced** in 2006. The sequence came from a bacterium that lives inside the bacteriocyte cells of a sap-feeding insect. This has helped inform our understanding of the minimum set of genes necessary for life.

The world's smallest **nanocrystal** was made with just 19 atoms by RIKEN's Center for Life Science Technologies in 2015. This could help scientists build nanodevices in areas such as biopharmaceuticals and biosensors.

SMALLEST

The world's thinnest **100% glass-based flexible microfluidic chip** was made in 2016. Weighing in at 3.6 milligrams (or 0.0036 grams), these chips could contribute to medical nanodevices that may one day be inserted into the body to deliver very precise hormone therapies.

THINNEST

In 2015, RIKEN made the world's most precisely **synchronized atomic clocks**. These clocks have helped unravel how time slows near strong gravitational centers, an effect long predicted by Einstein's theory of relativity.

The world's most extensive **ensemble simulation** of global weather. In 2014, the Advanced Institute of Computational Science (AICS) ran 10,240 parallel simulations of global weather—a feat that could help improve forecasts.

MOST PRECISE

The world's most precise **measurement of antimatter magnetism** was made by the BASE project in 2017. The project aims to help us understand why the universe is made of matter and not antimatter.

The SPring-8 facility is arguably the world's largest and most powerful **third-generation synchrotron radiation facility**. The radiation emitted by bending an electron traveling at almost the speed of light helps scientists reveal different atomic structures and the dynamics of ultrafast chemical reactions.

LARGEST

The world's largest collection of **mammalian full-length complementary DNAs** has been cataloged by the FANTOM Consortium. They have also mapped the all 27,919 human long non-coding RNAs (see page 28).

MOST ENERGY EFFICIENT

In 2017, the world's most energy efficient supercomputer is **the Shoubu system B**. According to the Green 500 list it is 6 times more efficient than the average supercomputer.

MOST COMPREHENSIVE

RIKEN's BioResource Center is the world's most comprehensive **mouse repository** and distribution center.

The Superconducting Ring Cyclotron at RIKEN's Radioactive Isotope Beam Factory is the largest **accelerator** of its kind in the world and it has the highest intensity beam. It creates unstable nuclei for nuclear physicists.

FACILITIES

RIKEN'S CENTERS AND FACILITIES

across Japan and around the world

Established in 1967
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(RIKEN Headquarters)
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Center for Advanced Photonics
Center for Sustainable Resource Science
Brain Science Institute
Nishina Center for Accelerator-Based Science
Advanced Center for Computing and Communication
Cluster for Industry Partnerships
Cluster for Science and Technology Hub
Chief Scientist Laboratories*
Research Groups
Global Research Cluster
Interdisciplinary Theoretical and Mathematical Sciences Program
*Chief Scientist Laboratories are located throughout Japan

Established in 1984
TSUKUBA
BioResource Center

SENDAI
Center for Advanced Photonics

Established in 2000
YOKOHAMA
Center for Sustainable Resource Science
Center for Integrative Medical Sciences
Center for Life Science Technologies
Distinguished Senior Scientist Laboratory

TOKYO
Tokyo Liaison Office
Center for Advanced Intelligence Project

NAGOYA

Established in 2002
KOBE
Center for Developmental Biology
Center for Life Science Technologies
Advanced Institute for Computational Science
Quantitative Biology Center

OSAKA
Quantitative Biology Center

Established in 1997
HARIMA
SPring-8 Center

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

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