RIKEN RESEARCH

FALL 2021

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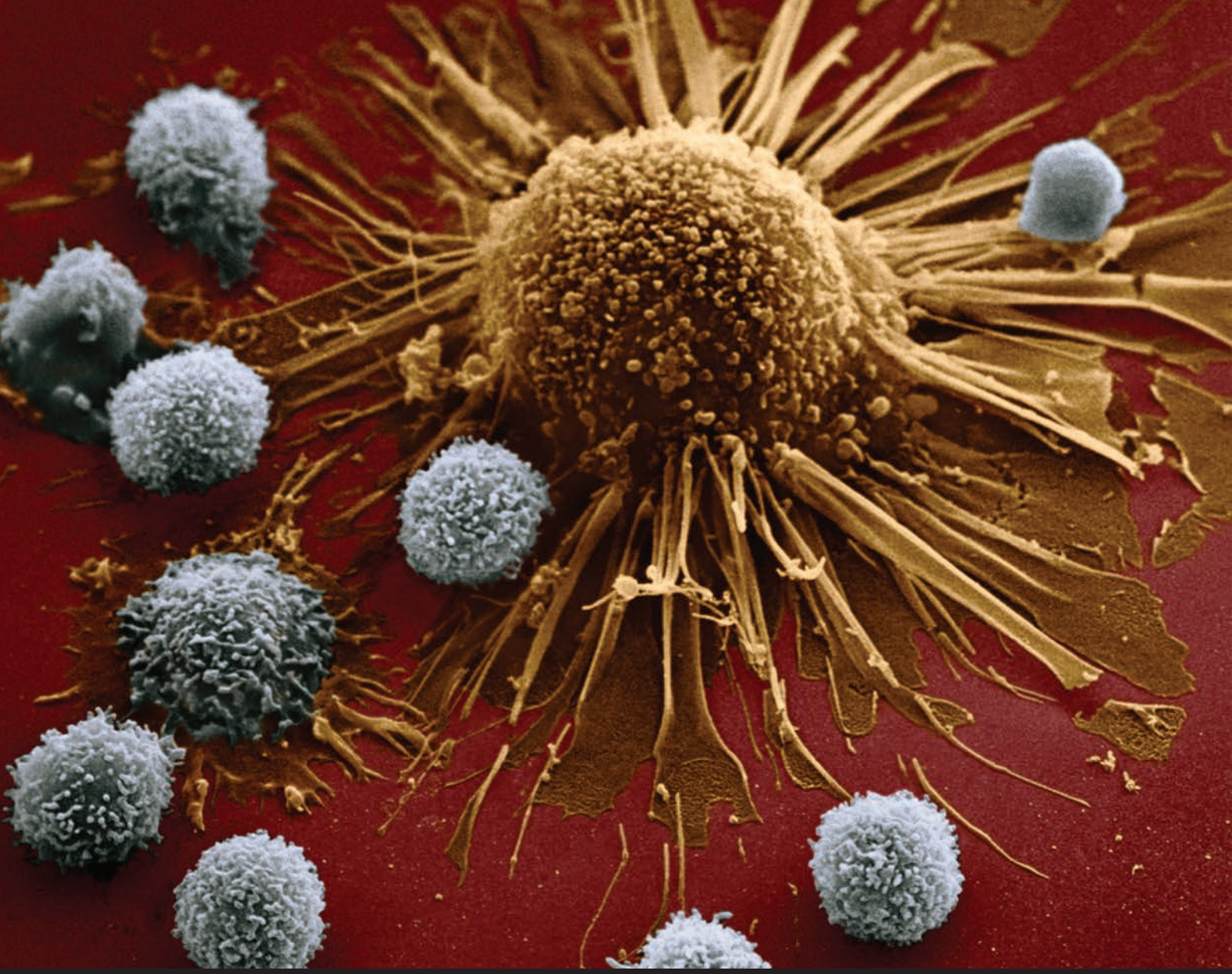
OVA EASY

Geneticists crack marsupial eggs

PLANETARY ORIGINS
Revising dust disk timelines

CULTIVATING KILLERS
Harnessing stem cells to tackle cancer

PROTECTIVE MOTHERS
Key to maternal instinct found in brain



▲ **Killer instincts**
Natural killer T (NKT) cells are a subset of T cells (blue) that can induce the death of cancer cells (brown), making NKT cells a fresh target for therapeutic development. A treatment based on induced pluripotent stem cell derived NKT cells is currently being trialed on head and neck cancer patients through the RIKEN Center for Integrative Medical Sciences, a world first (page 28).

RIKEN RESEARCH

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

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

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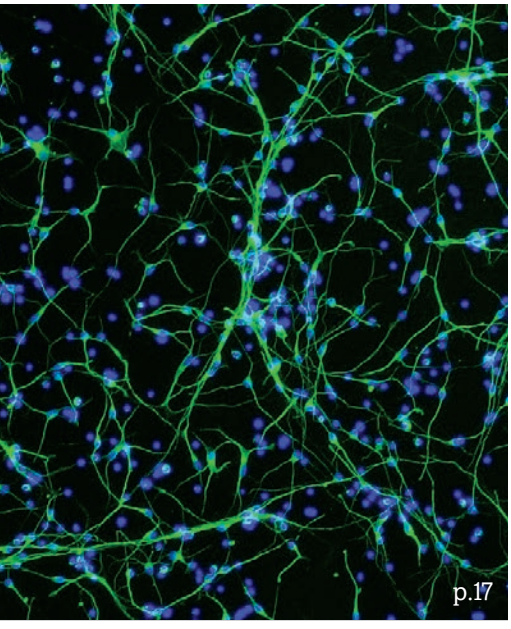
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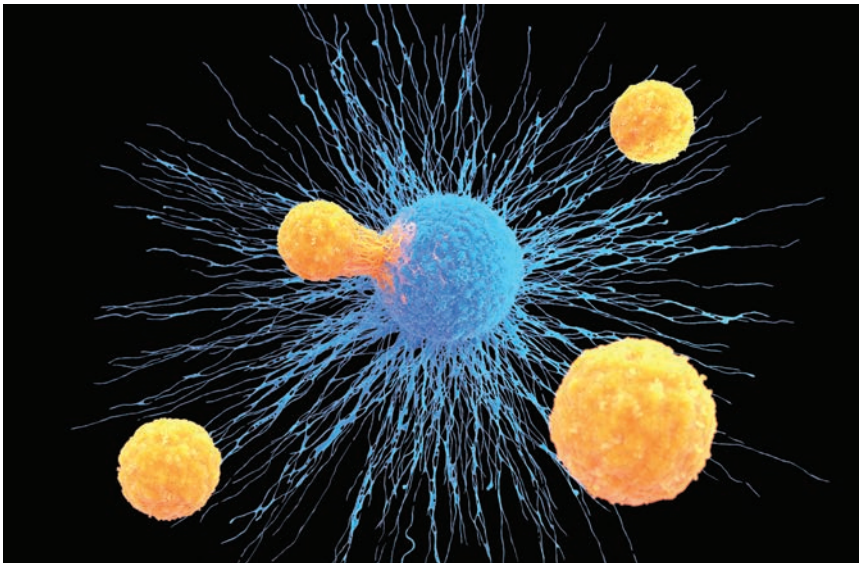

The future calls for a new style of research

Yuko Harayama
Executive director

In a previous issue, we discussed how work has changed under the pandemic, through the increased use of online meetings, for example. In this issue, I would like to talk a bit about how our research style is shifting, partly under the influence of COVID-19 and partly as a means to strengthen our research capacity.

Increasingly, we have come to the conclusion that interdisciplinarity is critical for our work. RIKEN has always encouraged collaboration between different disciplines in the natural sciences, but we are now beginning to emphasize the need for co-operation between natural scientists and researchers in other areas of social science and the humanities.

This is partly driven by the idea, suggested by RIKEN President Hiroshi Matsumoto early in his term and borne out by the pandemic, that research —even basic research—should be carried out based on a vision of what we hope the future will bring. As part of our effort to put this into practice, four years ago we established an Innovation Design Office, where a select group of 'innovation designers' look at the future of research and draft blueprints outlining how the basic research we are conducting today could be used to power innovation tomorrow. They also look at how these could address areas such as the United Nations Sustainable Development Goals, as well as benefiting society as a whole, and we plan to mobilize their schemes to experiment with our new research style.

I hope that these changes to the way we carry out research will be of interest to our collaborators, and I would be very happy to hear about things that our collaborators around the world are doing in their own way, perhaps based on the same understanding. We would be delighted to have the chance to share thoughts, so please do not hesitate to contact us if you would like to share ideas.

原山優子

COVER STORY:
The genes of opossums can now be edited thanks to a new method developed by RIKEN geneticists. While rodents such as mice and rats have been used extensively for gene editing, this is a first for a marsupial. *Page 21*

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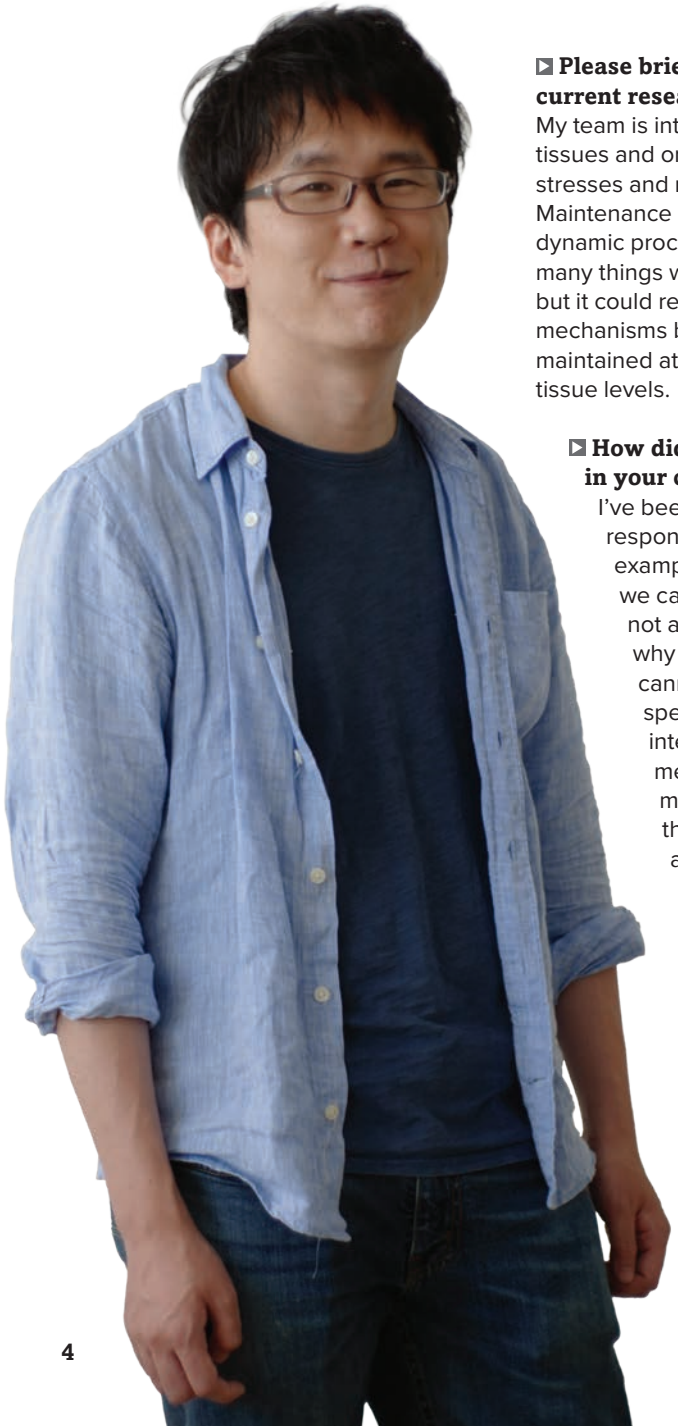
Stress and stability in cells and tissues

Sa Kan Yoo

Team Leader, Laboratory for Homeodynamics, RIKEN Center for Biosystems Dynamics Research/Chief Scientist, Physiological Genetics Laboratory, RIKEN Chief Scientist Laboratories



Please briefly describe your current research.
My team is interested in how cells, tissues and organisms respond to stresses and maintain their homeostasis. Maintenance of homeostasis is a very dynamic process, and there are still many things we don't understand, but it could reveal the fundamental mechanisms behind how our body is maintained at the molecular, cellular and tissue levels.

How did you become interested in your current field of research?
I've been interested in stress responses since I was a kid. For example, I was interested in why we can heal a small wound, but not a big one. I wanted to know why and how animals can and cannot repair tissues. More specifically, I've always been interested in regenerative medicine. But when I was a medical student, I noticed that many people were already working on human regenerative medicine so I felt there was not much for me to do. I decided to use more unusual animals such as zebrafish and fruit flies to study tissue repair mechanisms. While pursuing tissue repair mechanisms, I felt that we need to understand how tissues are maintained in normal conditions too. So that's how I got into the fields of homeostasis and stress responses.

What do you think has been the most interesting discovery in your field recently?
In 2006, two groups in the US demonstrated that tissue stem cells exist in the fruit fly gut. That was a huge finding because before that no one expected that tissue stem cells would exist in the fly gut. After the papers were published, research on the intestinal stem cells of the fruit fly exploded.

How and when did you join RIKEN?
I originally joined RIKEN as an associate chief scientist in the summer of 2015 and became a chief scientist in 2017. In 2018, I also started a team at the RIKEN Center for Biosystems Dynamics Research.

> *I decided to use unusual animals such as zebrafish and fruit flies to study tissue repair mechanisms.*

What are some of the technologies that you use to conduct your research?
We combine classic *Drosophila* genetics and modern techniques such as confocal imaging, RNA-seq, whole-genome sequencing, metabolomics and proteomics.

How do you balance family life with your work at RIKEN?
I'm not a big fan of 'work–life balance' stuff. I never felt doing research was work, and still don't. Maybe my current mentality is the same as when I was a student: doing research has always been like 'play'. So for me 'play–chore balance' sounds like a more reasonable phrase. Chores are the things I need to do, but don't feel like doing, such as administrative paper work... Personally, I easily intersperse my research activities and family life and I think of both as mainly 'play'. ■

Floating quantum ideas

Erika Kawakami

Team leader, Floating-Electron-Based Quantum Information RIKEN Hakubi Research Team, RIKEN Center for Quantum Computing

Please describe your role.
I lead a team that aims to realize quantum computer information processing bits (known as quantum bits, or qubits) using electrons floating on helium. My team is funded by the RIKEN Hakubi program and we are part of the RIKEN Center for Quantum Computing, which was newly founded in April 2021.

Please briefly describe your current research.
Quantum computers can solve certain problems that would take classical computers longer than the age of the Universe. We aim to physically realize qubits, but their quality and scalability are key issues.

I've always worked on developing hardware for quantum computing. However, we don't even know which material is the best to realize quantum computers. Here at RIKEN, I hope to realize qubits using electrons floating on the surface of liquid helium.

This is a relatively new field of research and there are many unknowns. But since electrons float in a vacuum, they have the advantage of being an extremely clean physical system and this may help to protect fragile quantum states and produce reliable qubits.

How did you become interested in your current research?
I love weird things. There are some laws of physics that appear to be inconsistent with how we make sense of the Universe in our daily life, but do, in fact, explain the world amazingly well. In quantum mechanics, an object can possess a superposition of two states, and measurements change these states. Quantum computers make use of the weirdness of the quantum world and it's exciting to imagine a world with quantum computers.

Since electrons float in a vacuum, they have the advantage of being an extremely clean physical system and this may help to protect fragile quantum states and produce reliable qubits.

What made you decide to become a scientist?
When I was a high school student, I was fascinated by Newton's laws. That a simple formula can describe how the world works is amazing! I also loved to read biographical novels of scientists and I thought that being a scientist would be the most exciting job.

How and when did you join RIKEN?
I found an advertisement about the RIKEN Hakubi research fellowship in 2019, was appointed in 2020 and given the funds to create my own team.

What do you wish you had known before you came to RIKEN?
I didn't know that the RIKEN Wako campus is famous for its cherry blossoms before this spring. It was wonderful! ■

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Ophthalmologist made French knight

Masayo Takahashi, a visiting scientist at the RIKEN Center for Biosystems Dynamics Research (BDR), was awarded the rank of Knight of the French National Order of Merit—one of the highest awards conferred by the French government—for her "dynamic contribution to scientific cooperation between Japan and France." While Takahashi, an ophthalmologist, was project leader at the Laboratory for Retinal Regeneration at RIKEN BDR (and previously at the RIKEN Center for Developmental Biology), she initiated the world's first clinical study using induced pluripotent stem cells.

The award was presented on 18 June 2021 by the French ambassador to Japan, Philippe Seton. "It was an unexpected honor to receive this award. The award was the result of our exchange with the Institut de la Vision in Paris, which served as a model for the Kobe Eye Center, which was established near BDR in Kobe," Takahashi said in her acceptance speech. "I would like to thank RIKEN and Kobe city for making our project a reality, as well as my team and the patients who brought us here."

www.riken.jp/en/news_pubs/news/2021/20210630_1

Masayo Takahashi.

Supercomputer Fugaku is still top of the TOP500, HPCG, HPL-AI and Graph500 rankings.

Fugaku tops the charts for third time in a row

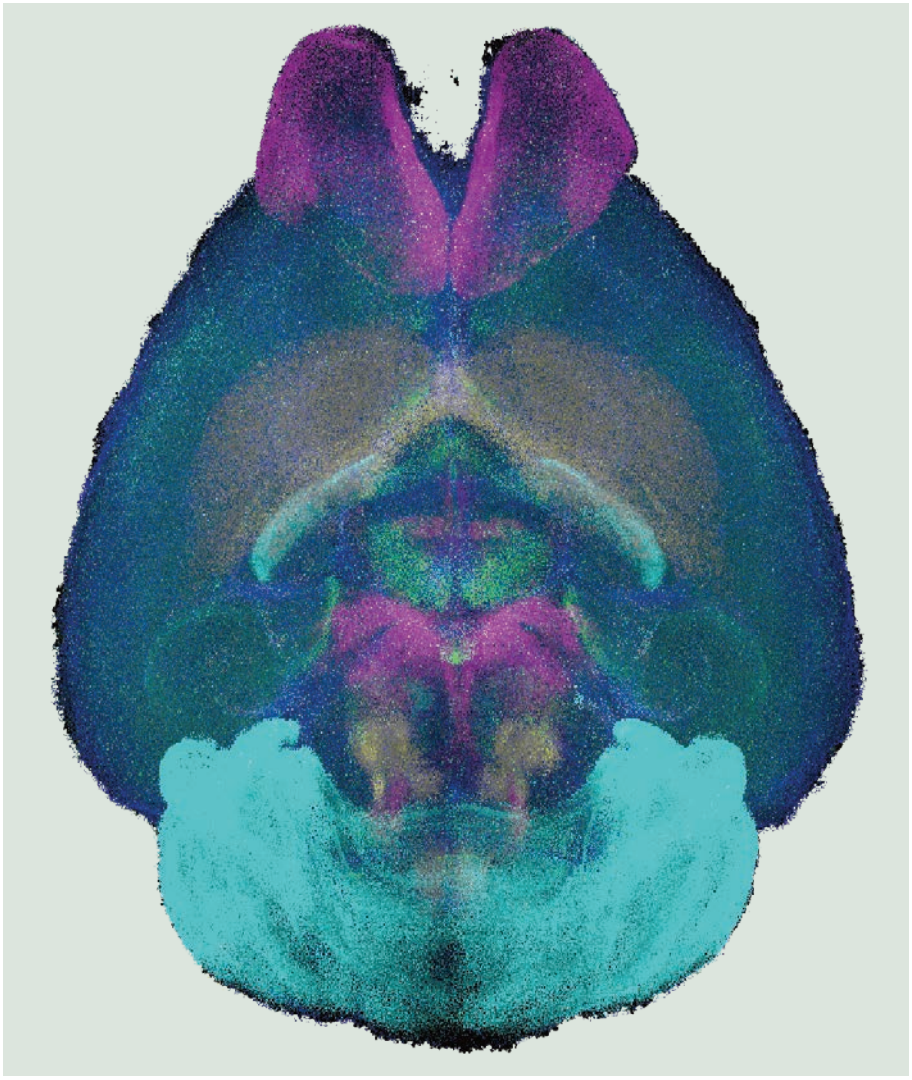
The supercomputer Fugaku has maintained its place at the top of the high-performance computing world for the third consecutive term. At ISC2021, an online high-performance computing conference, it was awarded first place on the TOP500 list—the best known supercomputing benchmark. It was also ranked first by the High-Performance Conjugate Gradient (HPCG) benchmark, a measure of supercomputer performance in real-world applications, and HPL-AI, which ranks computers on tasks related to artificial intelligence, and Graph500, which gauges a computer's ability to handle data-intensive loads. Jointly developed by RIKEN and Fujitsu Limited, Fugaku became available for shared use in March 2021.

"Fugaku is a crystallization of the world's most advanced IT technology, combining high performance, low power consumption and user friendliness," says Satoshi Matsuoka, director of the RIKEN Center for Computational Science. "In addition to topping the major benchmarks of simulations, big data, and AI for the third consecutive term, it has also made a major contribution to the establishment of COVID-19 safety guidelines for the government and private sector, and has helped lead a digital transformation in the area of infectious diseases."

"Key to winning these four awards for the third consecutive term is the fact that we worked together with RIKEN to further enhance application performance, and we were able to achieve very well balanced performance," said Naoki Shinjo, corporate executive officer of Fujitsu Limited. "With the start of shared use in March, we believe that many people are already taking advantage of Fugaku's high performance. We ourselves are planning to use it for joint research on drug discovery in partnership with the University of Tokyo's Research Center for Advanced Science and Technology. We hope that the results we obtain will lead to the discovery of new drugs, the advent of a safer and more secure society, and the achievement of Society 5.0."

www.riken.jp/en/news_pubs/news/2021/20210628_3

Handling big data from small brains



CUBIC-Cloud is a cloud-based, whole-brain analysis and visualization platform for mice that is openly available for use and mining without powerful local computer resources.

High-resolution imaging of the whole mouse brain has been attracting much attention in neuroscience research thanks to the development of tissue clearing and three-dimensional observation techniques. However, one bottleneck has been the difficulty in efficiently analyzing large amounts of image data and sharing it with other researchers. Now, researchers from the RIKEN Center for Biosystems Dynamics Research have developed CUBIC-Cloud, a public, cloud-based, whole-brain analysis platform for mice. It can register brains and perform quantitative analysis and visualization, all within a graphical user interface. Since all computations are performed in the cloud, users can process large-scale image data without a powerful local computing environment. Furthermore, the analysis results obtained by CUBIC-Cloud can be shared and published to researchers around the world through the cloud, offering the possibility of data mining using a large number of whole-brain data in the future. The team demonstrated CUBIC-Cloud's capability by analyzing the brains of more than 60 mice. They found several new insights, including the distributions of various neuronal cell types, identification of activated and inactivated brain regions by drugs, and depiction of neural circuits using the rabies virus. CUBIC-Cloud will provide the neuroscience community with a software platform to more easily perform whole-brain analysis. The team anticipates that many researchers will use this platform to further accelerate the collection and analysis of whole-brain data and contribute to a more unified understanding of the brain.

Access: http://cubic-atlas.riken.jp/

Predicting torrential rain with supercomputer precision

Between 20 July and 8 August and between 24 August and 5 September, a group led by scientists from the RIKEN Center for Computational Science used the supercomputer Fugaku to make precise rain predictions for the Tokyo metropolitan area. During this experiment, predictions of conditions up to 30 minutes into the future were updated every 30 seconds, with a resolution of 500 meters. These predictions were based on observational data gathered by the state-of-the-art Multi-Parameter Phased Array Weather Radar operated by the National Institute of Information and Communications Technology. Using advanced data assimilation, the observational data was incorporated in simulations run on Fugaku. The group ran an ensemble of 1,000 simultaneous simulations. "We believe this research will help contribute to the Japanese government's vision of an ultra-smart society, dubbed Society 5.0, by linking the virtual world on Fugaku to the real world in real time, to help predict sudden torrential rain, which has become an increasing risk due to climate change," said group leader Takemasa Miyoshi. The forecast data generated by the experiment were made publicly available on RIKEN's weather forecast research website and a smartphone app.

www.riken.jp/en/news_pubs/news/2021/20210713_1/index.html

OPTOELECTRONICS

Insulators as potential solar-cell materials

A class of insulating materials is predicted to hold promise for highly efficient solar cells

Materials in which electrons are strongly localized are promising for use in next-generation solar cells and optoelectronic devices, calculations by a RIKEN theoretical physicist and a collaborator have indicated[1].

Conventional photovoltaic devices such as solar cells and light detectors use a phenomenon known as the photovoltaic effect to convert light into electricity. An essential element of such devices is an interface between a material with an excess of electrons and one with a deficiency of electrons (a p–n junction). But devices based on a single p–n junction have several limitations: for example, their light conversion efficiency is capped at around 34%.

"The photovoltaic effect is the hottest topic in my view"

Another effect, known as the bulk photovoltaic effect—a phenomenon whereby light generates an electrical current in materials that meet certain conditions—is attracting increasing attention because it has the potential to overcome these limitations, making it attractive for use in next-generation solar cells and light detectors.

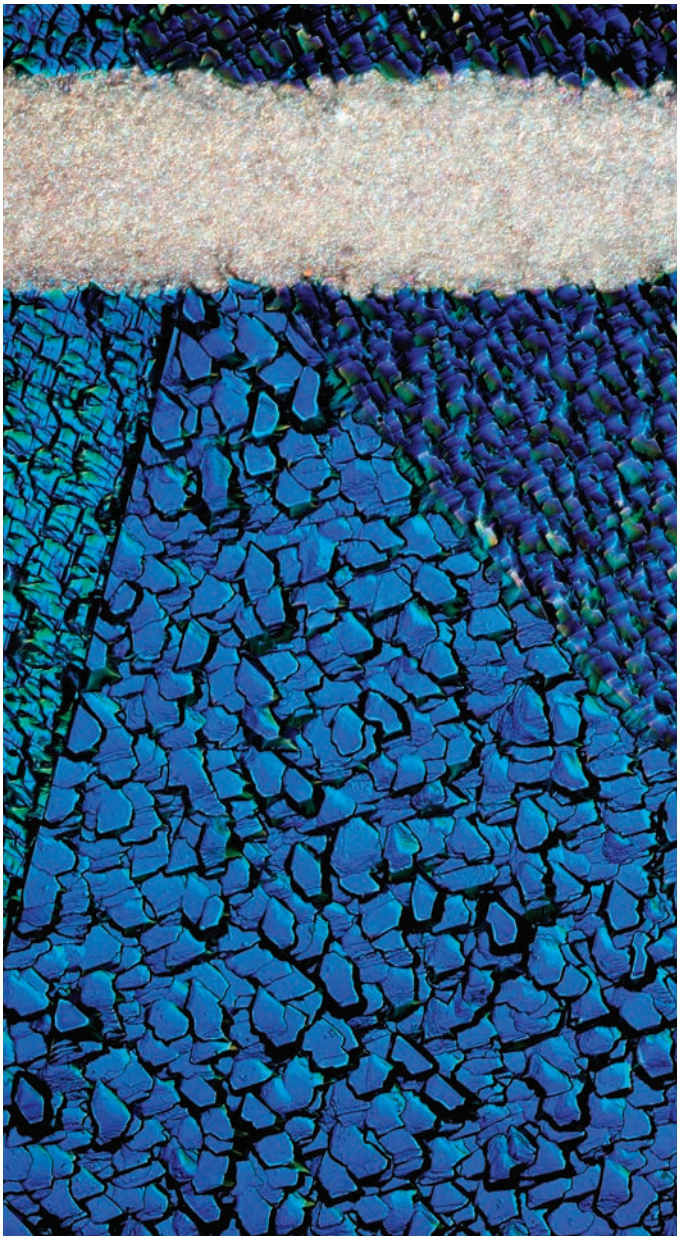
"I've been working on the geometric current in solids for nearly two decades, and the photovoltaic effect is the hottest topic in my view," says Naoto Nagaosa from the RIKEN Center for Emergent Matter Science.

Now, Nagaosa and a colleague have calculated that the bulk photovoltaic effect can occur in a one-dimensional (1D) disordered system known as a 1D Anderson insulator as long as there is sufficient coupling between electrons and particle-like vibrations known as phonons.

The researchers used a tight-binding model with a disorder potential to study the photocurrent in a 1D chain attached to metallic leads. They found that a photocurrent flows through the system even in the presence of substantial amounts of disorder, thanks to the weak dissipation arising from electron–phonon interactions.

In agreement with recent experiments on a ferroelectric semiconductor, the bulk photovoltaic current was found to be nearly independent of the amount of disorder, as long as the disorder potential is smaller than the band gap. However, there is a characteristic dependence on bulk dissipation, which manifests as a temperature dependence of the photocurrent. At room temperature, the photocurrent can reach the value it would have in a perfectly ordered system even when the chain is very long.

"Taken together, these results imply that Anderson insulators can be promising material candidates for efficient solar cells and photodetectors," says Nagaosa.



A light micrograph of a conventional photovoltaic cell based on polycrystalline silicon (blue crystals). Such solar cells use the photovoltaic effect to convert light into electricity. Photovoltaic devices based on the bulk photovoltaic effect could overcome some of the limitations of conventional devices.

In 3D Anderson insulators, the contribution of the localized states to the photocurrent should become dominant under illumination with light of a frequency resonant with the band gap. Thus, it will be possible to test the new theory not only in 1D chains, but also in 3D systems. ●

Reference

1. Ishizuka, H. & Nagaosa, N. Theory of bulk photovoltaic effect in Anderson insulator. *Proceedings of the National Academy of Sciences USA* **118,** e2023642118 (2021).

X-RAY FREE-ELECTRON LASERS

Making liquid diamond with x-rays

The mechanism by which ultra-intense x-ray pulses cause diamond to melt has been determined

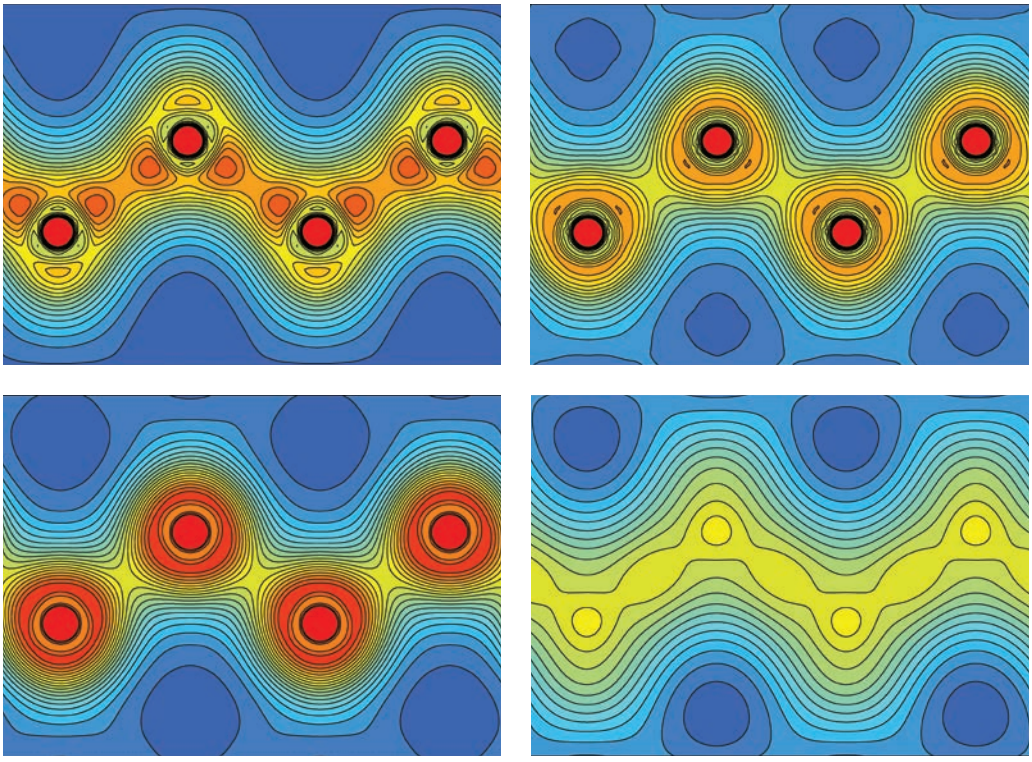
The ultrafast melting of diamond under intense x-ray irradiation has been visualized for the first time by RIKEN researchers[1]. This observation will help scientists improve experimental methods that use high-intensity x-ray pulses to determine the structures of materials.

Theoretically, to melt a diamond you would need to put it in an oven and set the temperature to over 3,500 degrees Celsius (in fact, it would turn into graphite well before melting). But RIKEN scientists have observed diamond melting at much lower temperatures by hitting it with ultrashort pulses from an x-ray free-electron laser (XFEL).

XFELs are powerful instruments that have been available for little more than a decade. They produce trains of intense x-ray pulses that can be used to study the structure and dynamics of many kinds of samples. Their ability to image individual atoms on a time scale of femtoseconds (quadrillionths of a second) makes them ideal for studying biological and chemical processes and material structures in great detail.

XFEL pulses are known to excite many electrons at once, causing irreversible disorder in the sample. But the exact mechanism by which this damage happens was unknown.

Now, Ichiro Inoue and Makina Yabashi, both of the RIKEN SPring-8 Center, along with their collaborators, have used a technique that employs a first x-ray pulse to excite a sample, and a second pulse with different energy and a small time delay to probe the effects of the first pulse. This method enabled them to follow closely what happened in the sample after it was hit by the x-rays.



Plots showing the distribution of electrons in diamond before (top left) and 5 (top right), 20 (bottom left) and 50 (bottom right) femtoseconds after being irradiated by a pulse of x-rays from an x-ray free-electron laser. They show that the carbon–carbon bonds break after about 5 femtoseconds.

The experiments were conducted at the SPring-8 Angstrom Compact free electron Laser (SACLA), which in 2011 became the second XFEL in the world to start operations. "Among XFEL facilities in the world, SACLA has a unique capability to produce ultra-intense, double x-ray pulses with different wavelengths," comments Yabashi. "This property is desirable for conducting the present type of new research."

The researchers visualized the distribution of charges around the carbon atoms in a diamond sample after XFEL irradiation. The carbon–carbon bonds broke after about 5 femtoseconds, and the atoms started behaving like isolated atoms, moving from their original positions and causing the material to melt.

This time scale is much faster than the bond breaking caused by heating, and supporting simulations showed that the melting is indeed non-thermal. Instead, it is induced by a modification of the potential energy felt by the atoms.

Such non-thermal melting can be expected to happen in many XFEL experiments, and is thus an important factor to consider in any study of structure determination with XFEL pulses. ●

Reference

1. Inoue, I., Deguchi, Y., Ziaja, B., Osaka, T., Abdullah, M. M., Jurek, Z., Medvedev, N., Tkachenko, V., Inubushi, Y. *et al.* Atomic-scale visualization of ultrafast bond breaking in X-ray-excited diamond. *Physical Review Letters* **126,** 117403 (2021).

CATALYSIS

Making useful products from carbon dioxide

Nickel plays a key role in the reduction of carbon dioxide into more complex carbon-based compounds

Scientists are closer to finding ways to convert carbon dioxide in the atmosphere into industrially useful chemicals thanks to a RIKEN study that looked at how nature converts carbon dioxide into more complex organic compounds—one of the processes underpinning the origin of life[1].

Finding an energetically efficient means to convert carbon dioxide gas into useful compounds is highly attractive for reducing the emission of the greenhouse gas in an economically viable way. In nature, carbon dioxide is converted into carbon monoxide and then into more complex organic compounds through reactions that are most likely linked to the origin of life on Earth.

These reactions can follow different pathways, but a particularly efficient one employs the enzyme carbon monoxide dehydrogenase (CODH), which helps reduce the energetic costs associated with the first step of the reaction: the reduction of carbon dioxide into carbon monoxide. Understanding the catalytic mechanism of the CODH enzyme could thus pave the way to environmentally friendly technological applications as well as offer important insights into the origin of life on our planet.

Every enzyme has a specific active site where the relevant reactions occur. Now, Ryuhei Nakamura of the RIKEN Center for Sustainable Resource Science (CSRS) and colleagues have proposed that a specific atom, nickel, is key to the reaction mechanism that take places at the active site of the CODH enzyme.

Knowing how a nickel iron sulfide catalyst helps reduce carbon dioxide to carbon monoxide and other carbon-based products could lead to technologies that can convert carbon dioxide in the atmosphere into industrially useful chemicals.

"CODH is a rare enzyme that uses a nickel-iron sulfide active site instead of the more common iron sulfide clusters," explains Hideshi Ooka, co-author of the paper. "While our group and others have already reported that adding nickel into iron sulfides improves the efficiency for carbon dioxide reduction, the reason why nickel is important wasn't known due to the lack of *in situ* spectroscopic studies," says Ji-Eun Lee, also of CSRS.

The team used three inorganic analogues of the CODH active site—one featuring iron and sulfur and two featuring nickel, iron and sulfur—and followed the carbon dioxide reduction on the three analogues using infrared spectroscopy while varying the applied electric potential.

Carbon dioxide reduction occurred only in the presence of nickel, which binds to carbon while iron binds to oxygen. As the potential was increased, the iron sulfur and nickel cluster catalyzed the further reduction of carbon monoxide into the formyl group, which was then converted into methane and ethane.

Through their work, Nakamura and co-workers have provided a molecular-level understanding behind nickel-enhanced reduction of carbon dioxide, offering important insights for the development of biomimetic catalysts.

"Our results also show that carbon dioxide reduction is possible on the surface of minerals, suggesting that nickel-iron sulfides may have contributed toward prebiotic fixation of carbon dioxide," says Nakamura. ●

Reference

1. Lee, J.-E., Yamaguchi, A., Ooka, H., Kazami, T., Miyauchi, M., Kitadai, N. & Nakamura, R. *In situ* FTIR study of CO_2 reduction on inorganic analogues of carbon monoxide dehydrogenase. *Chemical Communications* **57,** 3267–3270 (2021).

An optical micrograph showing a large anthracene crystal (the purple streak) with smaller anthracene crystals (silver flecks). RIKEN researchers have used large anthracene crystals to pick up and convey carbon nanotubes to where they want them.

CARBON NANOTUBES

Manipulating atomically defined nanotubes

A solvent-free method precisely positions carbon nanotubes without sacrificing their optical properties

A solvent-free technique developed by RIKEN physicists that realizes precise manipulation of carbon nanotubes with atomically defined structures promises to facilitate the fabrication of electronic and optical devices that have unprecedented properties[1].

Carbon nanotubes are sheets of carbon atoms wrapped into cylinders. They hold promise for use in a wide range of applications, including light-emitting diodes, single-electron transistors, and single-photon sources.

To create devices with desired properties, it is necessary to precisely manipulate the position and orientation of nanotubes. It is also crucial to control the twisting of the atomic arrangement, since nanotube properties depend critically on how they are twisted. However, precise manipulation of nanotubes is difficult since using solvents or high-temperature treatments inevitably contaminates them, degrading their optical characteristics.

To find a way around this problem, a team led by Yuichiro Kato of the RIKEN Cluster for Pioneering Research has been looking for a method to engineer carbon nanotubes without using solvents.

Now, the team has experimented by using large, thin crystals of anthracene, a chemical derived from oil, as a scaffold for picking up and transporting nanotubes to desired positions. After serving its purpose, the anthracene could be easily vaporized by heating, leaving the nanotubes in an optically pristine condition.

The researchers also developed a method for monitoring the photoluminescence of the nanotubes during this transfer, ensuring that a nanotube with the desired atomic arrangement was placed at the right location.

Following the dry transfer, the nanotubes had a bright photoluminescence—up to 5,000 times as bright as the original molecule—making them ideal for optical devices. In addition, the light-emission properties of the nanotubes could be enhanced by precisely positioning them on top of nanoscale optical resonators.

The team is excited about the potential of this technique to achieve new levels of fabrication precision. "We believe that this technology could contribute not only to the creation of nanodevices from carbon nanotubes with desired properties, but also to the construction of higher-order systems that are based on the free combination of atomic layer materials and other nanostructures," says Keigo Otsuka of the RIKEN Nanoscale Quantum Photonics Laboratory.

"Beyond that, this technology has the potential to contribute to the development of atomically defined technologies that go beyond nanotechnology, in which materials with precise structures at the atomic level are used as building blocks to design and build functions that are different from those of existing materials," says Kato.

Reference

1. Otsuka, K., Fang, N., Yamashita, D., Taniguchi, T., Watanabe, K. & Kato, Y. K. Deterministic transfer of optical-quality carbon nanotubes for atomically defined technology. *Nature Communications* **12,** 3138 (2021).

Chemotherapy causes many side effects including hair loss. RIKEN chemists have developed a glycosylated metalloenzyme that attaches itself to specific lectins on the outside of human cancer cells. The targeted nature of this mechanism should minimize side effects.

CANCER TREATMENT

New approach targets cancer cells, sparing the rest

A two-stage approach for selectively targeting cancer cells shows promise in mouse study

Cancer therapy with minimal side effects could result from an approach demonstrated by RIKEN chemists that reduced tumor growth in mice when cancer cells were tagged with various therapeutic molecules[1]. The technique was also effective in preventing cancer cells from clumping together to form tumors.

Many conventional cancer treatments such as chemotherapy affect healthy cells as well as cancerous ones, giving rise to side effects that vary in severity. For a long time, researchers have been striving to develop therapies that target only cancer cells, thereby minimizing any side effects.

Now, a team led by Katsunori Tanaka of the RIKEN Biofunctional Synthetic Chemistry Laboratory has demonstrated a promising new way to achieve this goal. "We've succeeded for the first time in treating cancer using metal-catalyzed chemistry in mice," says Tanaka.

Tanaka's team has been using artificial gold-based enzymes called metalloenzymes to tag proteins inside the body. The tagging agent and the metalloenzyme are separately injected into the body, and sugar chains called glycans attached to the surface of the metalloenzyme can bind to target cells. For instance, different cancer cells can be identified by the unique types of glycan-binding proteins known as lectins, which are embedded in the cells' outer membranes.

Now, Tanaka's team has developed a glycosylated metalloenzyme that attaches itself to specific lectins on the outside of human cancer cells. After reacting with the metalloenzyme, the tagging agent can tag the protein of interest on the cancer cell. In this way, only cancer cells targeted by the glycosylated metalloenzyme are tagged.

The team demonstrated the effectiveness of this approach in two targeted drug-delivery tests in mice. In the first one, they succeeded in disrupting tumor formation in mice by targeting cancer cells with a compound that makes it difficult for the cells to clump together and form tumors. Of the mice that received this treatment, 40% survived, whereas all the control mice died.

In the second test, the team targeted cancer cells with a compound that became toxic after reacting with the metalloenzyme. Mice that received this treatment showed reduced tumor growth and a higher survival rate compared to control mice.

Encouraged by these results, the team intends to investigate if the same strategy can be used in humans. "We were able to use our system to carry metalloenzymes to cancer cells in living mice, which reacted with tagging agents to deliver targeted drug therapies that reduced tumor onset and growth," says Tanaka. "The next step is clinical application in humans."

Reference

1. Vong, K., Tahara, T., Urano, S., Nasibullin, I., Tsubokura, K., Nakao, Y., Kurbangalieva, A., Onoe, H., Watanabe, Y. & Tanaka, K. Disrupting tumor onset and growth via selective cell tagging (SeCT) therapy. *Science Advances* **7,** eabg4038 (2021).

SPINTRONICS

A new spin on magnetic devices

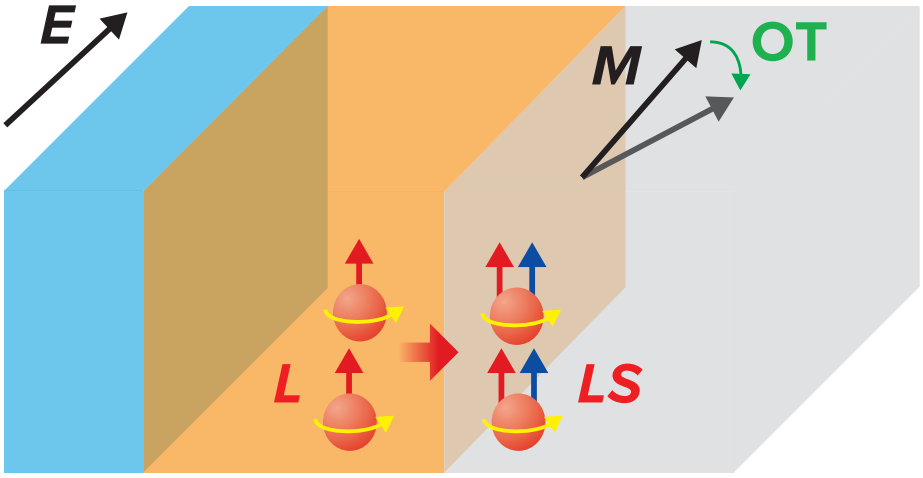
A new way to electrically generate rotation in materials made up of light elements could open the way for magnetic nanodevices

The development of innovative magnetic nanodevices is one step closer to reality thanks to the observation by RIKEN physicists of a type of rotation that can be realized in materials consisting of light elements[1].

The ability to use electric currents to turn revolving mechanical parts led to the development of electric motors and caused an explosion in electrical devices. Now, physicists are trying to do the same thing but on a nanoscale. However, the development of innovative magnetic nanodevices requires the efficient electrical generation of rotation, or torque.

Usually, torque is generated in magnetic systems by converting electric charge to spin by using the strong spin–orbit interaction of a heavy-metal layer. The resulting spin current is then injected into adjacent ferromagnetic layers. But heavy-element materials are often incompatible with scalable production processes, and their high resistance makes them unsuitable for some applications.

A recent theoretical proposal suggested that torque could be produced by injecting orbital angular momentum into ferromagnetic layers. The orbital angular momentum can be generated by passing an electric current through light-element materials. It can then be converted to spin by the spin–orbit interaction of a ferromagnetic layer. This type of torque is called orbital torque, and it can be similar in magnitude to the torque induced by spin injection.



RIKEN physicists have demonstrated a new method to electrically control (indicated by *E*) the magnetization (*M*) of a ferromagnetic layer (gray band). It involves injecting orbital angular momentum (*L*, red arrows) from a non-magnetic layer (orange band) into the ferromagnetic layer, which generates orbital torque (OT), which in turn rotates the magnetization.

These results widen the material choices for magnetic nanodevices

Now, Junyeon Kim, YoshiChika Otani and their co-workers at the RIKEN Center for Emergent Matter Science, together with international collaborators, have realized such an efficient torque generation in three-layer systems composed of a ferromagnetic layer, a copper layer and an alumina (Al_2O_3) layer.

In this system, the orbital angular momentum is generated at the copper–alumina interface and then transported by the copper layer to the ferromagnetic layer, where it is converted into spin.

While the torque-generation efficiency of this system rivaled that in materials containing heavy elements, the underlying physics is fundamentally different. The team found that the torque-generation efficiency varied by two orders of magnitude when different ferromagnetic layers were used. This is very different from the behavior of spin-injection systems, confirming that a new type of torque is at work.

A CoFe/Cu/Al_2O_3 trilayer system—the one that gave the best results—exhibited an effective spin Hall conductivity, which is proportional to the torque generation efficiency, ten times larger than that observed in heavy-element materials. This exceptional spin conductivity will translate to energy-efficient device operation and high cyclability thanks to lower production of waste heat. These results widen the material choices for magnetic nanodevices, promising remarkable efficiencies and the possibility of mass production. ●

Reference

1. Kim, J., Go, D., Tsai, H., Jo, D., Kondou, K., Lee, H.-W. & Otani, Y. Nontrivial torque generation by orbital angular momentum injection in ferromagnetic-metal/Cu/Al_2O_3 trilayers. *Physical Review B* **103,** L020407 (2021).

AUTISM SPECTRUM DISORDERS

A direct genetic link to autism spectrum disorders

A variant gene could play a key role in the disruption of key pathways in brain development

New therapies for mental disorders could flow from the discovery by RIKEN researchers of the first direct link between the *SUV39H2* gene and autism spectrum disorders in mice[1].

Genes are turned on and off throughout our development. But genetic variation means that what is turned off in some people remains turned on in others. One way that genes can be turned on and off is through a process called histone methylation in which special enzymes transfer methyl groups to histone proteins, which are wrapped around by DNA.

The team verified the importance of *SUV39H2* in human autism spectrum disorders

Variations in genes related to methylation during brain development can lead to serious problems. One such variation occurs in a rare disorder called Kleefstra syndrome, in which a mutation prevents methylation of H3K9—a specific location on histone H3.

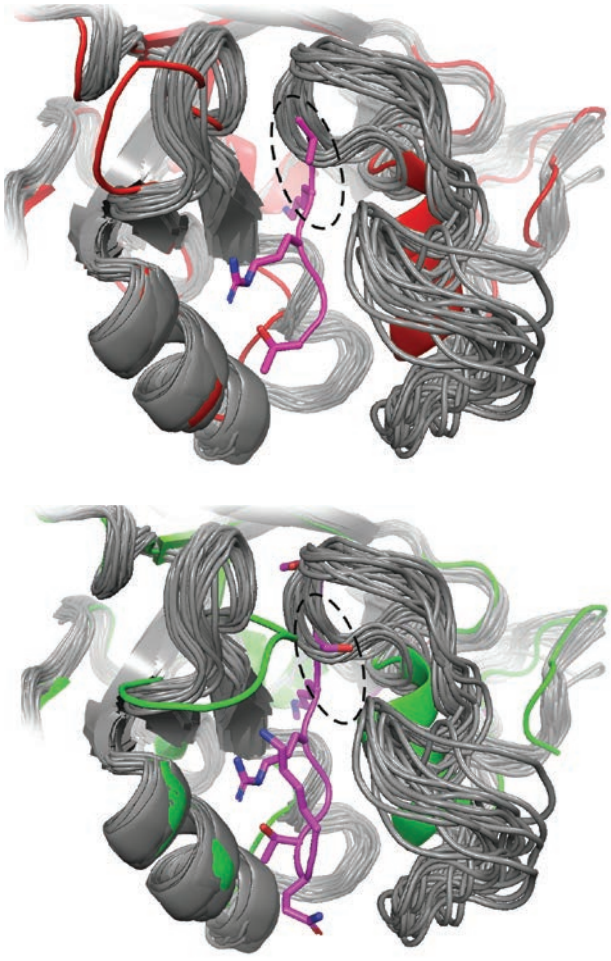
Because Kleefstra syndrome resembles autism in some ways, a team led by Takeo Yoshikawa of the RIKEN Center for Brain Science looked for autism-specific variations in genes that can modify H3K9. Among nine such genes, they found one variant in an H3K9 methyltransferase gene—*SUV39H2*—that was present in autism. When tested in the lab, this variant prevented methylation, and the mouse version of the variant exhibited similar loss-of-function results.

Mice lacking *Suv39h2* could learn a simple cognitive task, but had difficultly learning a task requiring cognitive flexibility. When the mice were challenged to alternate randomly between these two tasks, wild-type mice adapted quickly, but *Suv39h2*-deficient mice took much longer.

"This serial reversal-learning task was essential," says first author Shabeesh Balan. "Cognitive inflexibility is a core symptom of autism spectrum disorders."

The researchers examined what happened in the mouse brain when H3K9 methylation failed to occur, and found that important genes that are usually silenced in early development were turned on in the experimental mice.

"*Suv39h2* is known to be expressed in early neurodevelopment and to methylate H3K9," explains Yoshikawa. "This keeps a check on genes that should be switched off. But without it, genes in the protocadherin β cluster were abnormally expressed at high levels in embryonic mice."



Two possible structures of proteins derived from mutant *SUV39H2*. Changes in structure relative to the protein produced by the wild-type gene affect the interaction with H3K9 peptide (indicated by dashed ovals).

Because protocadherins are critical for the formation of neural circuits, the researchers believe they have found an important biological pathway that could be central to several neurodevelopmental disorders. The team verified the importance of *SUV39H2* in human autism spectrum disorders by finding that it had lower expression in the postmortem brains of people with autism spectrum disorders than of controls.

"What began with a loss-of-function mutation in only one person with autism spectrum disorders has led to a general causal landscape for autism spectrum disorders that culminates in brain circuit abnormality," says Yoshikawa. ●

Reference

1. Balan, S., Iwayama, Y., Ohnishi, T., Fukuda, M., Shirai, A., Yamada, A., Weirich, S., Schuhmacher, M. K., Dileep, K. V., Endo, T. *et al.* A loss-of-function variant in *SUV39H2* identified in autism-spectrum disorder causes altered H3K9 trimethylation and dysregulation of protocadherin β-cluster genes in the developing brain. *Molecular Psychiatry* advanced online publication, July 2021.

MELATONIN

Breeding melatonin back into lab mice

Special lab mice will help reveal the effects of the hormone melatonin on sleep and other activities

Researchers will be able to investigate how melatonin signaling affects the circadian clock and sleep in mice thanks to lab mice, specially bred by RIKEN biologists, that naturally produce the hormone melatonin[1].

Melatonin is released by the brain in response to darkness, so that the body can switch to 'night mode'. Other hormones can be easily studied in the laboratory, but it has been difficult to study how the body reacts to melatonin because lab mice don't actually have any.

To solve this problem, the researchers crossed lab mice with wild-derived mice—which do produce melatonin, but whose different genetic make up from lab mice makes it hard to compare experimental results — and bred new lab mice that can produce melatonin innately. This took more than ten generations of mice.

The researchers used the melatonin-producing lab mice to study how the hormone affects entrainment—the alignment of the body clock with the outside world. Mice like to run on wheels regularly, and researchers can use this to measure entrainment after suddenly changing the light/dark cycle, which mimics sudden changes in times zones. Compared with regular lab mice, the mice with innate melatonin adapted their wheel running times faster to darkness, starting six hours earlier, similar to east-bound jet lag.

The team also resolved a debate about whether life span is affected by melatonin, which has been hard to study because lab mice lack melatonin. "Now we finally have an answer—endogenous melatonin has no life-extending effects," says Takaoki Kasahara of the RIKEN Center for Brain Science.

Mice with innate melatonin differed from regular lab mice in several ways. The regular lab mice were heavier, had bigger reproductive organs, and produced more pups. On the other hand, melatonin-producing female mice were able to enter a state called daily torpor, a kind of low-power mode similar to hibernation that can last a few hours a day. Daily torpor is a way for mice to deal with food scarcity and cold temperatures by conserving energy.

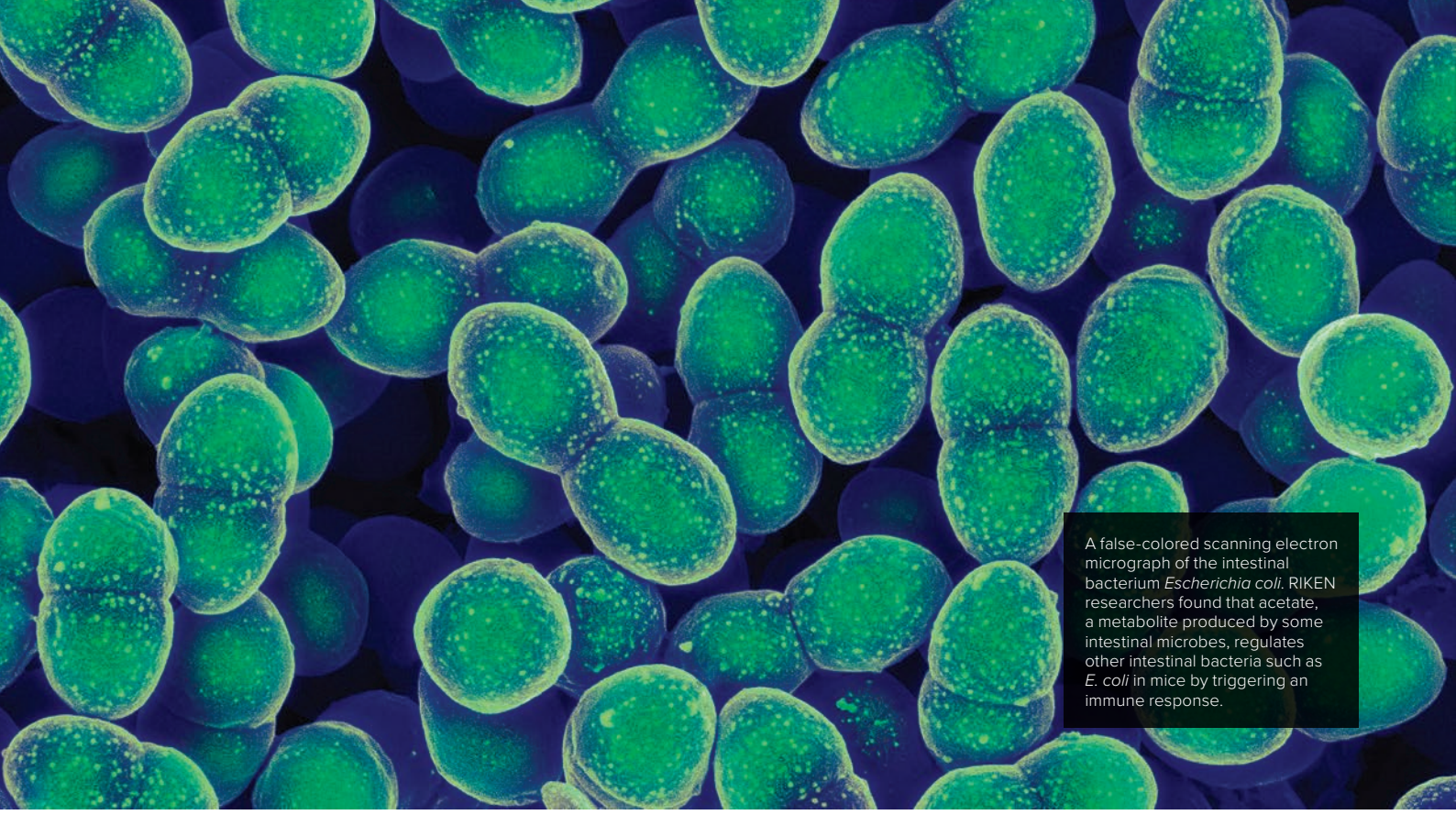
"There is an evolutionary advantage to producing melatonin, because it protects wild mice from losing weight when they can't find enough food. Lab mice, however, are typically given unlimited food and live in warm cages," Kasahara observes. "Our finding that mice lacking melatonin are more successful at reproducing can explain why lab mice lack melatonin. Over the years, by selecting for mice that produce the most pups, we might have also been inadvertently selecting for mice with lower and lower levels of melatonin."

The melatonin-proficient mice will be valuable for studying the detailed molecular and neural mechanisms of melatonin signaling on the circadian clock and sleep, as well as the effects of melatonin on immunity and bone formation. ●

Reference

1. Zhang, C., Clough, S. J., Adamah-Biassi, E. B., Sveinsson, M. H., Hutchinson, A. J., Miura, I., Furuse, T., Wakana, S., Matsumoto, Y. K., Okanoya, K. *et al.* Impact of endogenous melatonin on rhythmic behaviors, reproduction, and survival revealed in melatonin-proficient C57BL/6J congenic mice. *Journal of Pineal Research* e12748 (2021).

RIKEN researchers have produced a new lab mouse that naturally produces melatonin (inset) by breeding a normal lab mouse (left) with a wild-derived mouse (right). It took ten generations of breeding to produce the melatonin-producing lab mouse.



A false-colored scanning electron micrograph of the intestinal bacterium *Escherichia coli*. RIKEN researchers found that acetate, a metabolite produced by some intestinal microbes, regulates other intestinal bacteria such as *E. coli* in mice by triggering an immune response.

MICROBIOME

Gut microbe metabolite helps keep other microbes in line

A metabolite produced by microbes boosts the production of an antibody that preferentially attacks potentially harmful gut bacteria

New ways to regulate the balance of intestinal bacteria could result from the finding by RIKEN researchers that acetate—a key metabolite produced by some intestinal microbes—regulates other intestinal bacteria in mice by triggering an immune response against potentially harmful ones[1].

Our intestines are home to about 40 trillion bacteria, which promote health by producing essential nutrients and eliminating pathogens but can be detrimental if they become out of control. It is thus important to understand how the body regulates the balance of intestinal bacteria.

The most abundant antibody produced in the human body, immunoglobulin A (IgA), is mostly secreted from the mucosal surfaces of the intestinal tract. It is thought to regulate the growth, colonization and function of intestinal bacteria by binding to them.

Intestinal bacteria help us to break food down into smaller pieces called metabolites. Recent studies have suggested that metabolites significantly affect the immune function of the intestinal tract. In particular, short-chain fatty acids (SCFAs), a major metabolite of intestinal bacteria, are involved in creating and regulating immune-cell function. They are thought to increase IgA production, but it wasn't known what triggers this behavior.

Now, by feeding mice food that increases SCFAs in the large intestine, a team led by Hiroshi Ohno of the RIKEN Center for Integrative Medical Sciences has found that acetate, a type of SCFA, increases the number of IgA-producing cells and the amount of IgA. It also regulates how much IgA binds to each intestinal bacterium. In contrast, other SCFAs did not affect IgA.

The team found that the type of bacteria to which IgA binds depends on the presence of acetate. Normally, IgA binds mostly to common symbiotic bacteria, but in mice treated with acetate, it tended to bind to potentially harmful bacteria. Further analysis showed that when acetate leads to IgA production in the colon, IgA binds to those potentially harmful bacteria, preventing them from invading the mucus layer.

The finding that acetate produced by bacteria can alter the balance of IgA in the intestines was unexpected. "At first, we thought that acetate simply increases IgA equally against all commensal bacteria," explains Ohno. "It was rather surprising to see that it preferentially enhances production of IgA against certain microbes through collaboration with other immune cells."

"Accumulating evidence suggests the involvement of gut microbiota in many human diseases," says Ohno. "IgA is one of the most efficient ways to control the microbiota, and therefore we think our findings are a basis for this regulatory mechanism." ●

Reference

1. Takeuchi, T., Miyauchi, E., Kanaya, T., Kato, T., Nakanishi, Y., Watanabe, T., Kitami, T., Taida, T., Sasaki, T., Negishi, H. *et al.* Acetate differentially regulates IgA reactivity to commensal bacteria. *Nature* **595,** 560–564 (2021).

EPISODIC MEMORY

The rat brain records time flexibly

The temporal-recording system of the rat brain shows a similar flexibility as the spatial-recording system

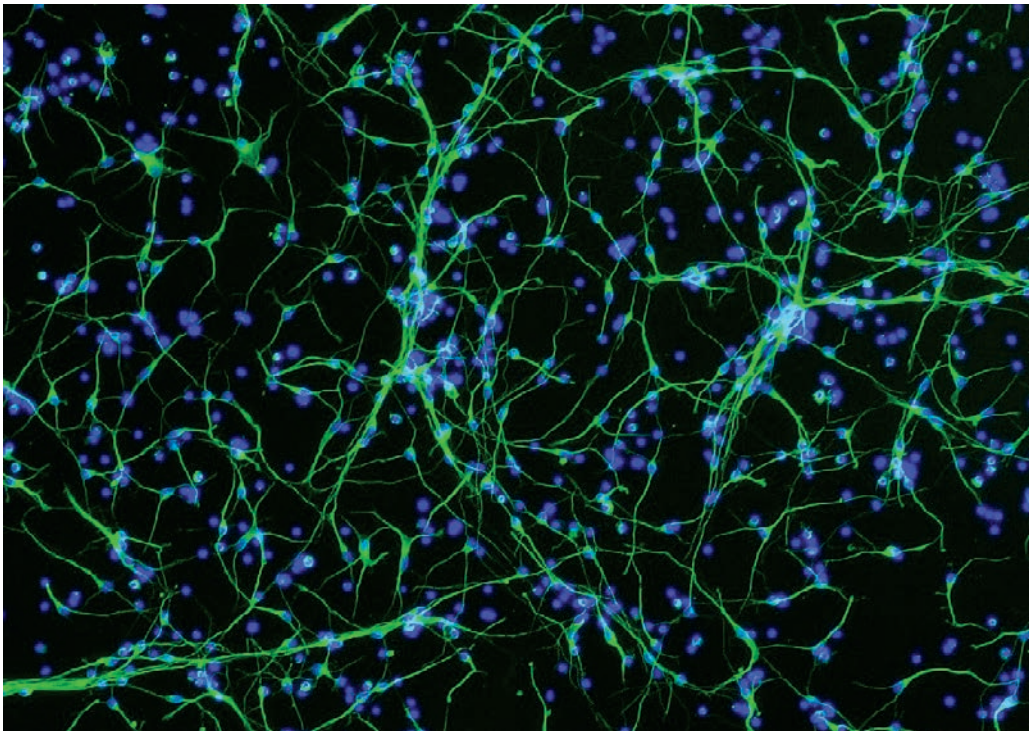
RIKEN neuroscientists have discovered how temporal information is managed and accessed in the rat brain[1]. As a similar mechanism likely operates in the human brain, these findings could inform research into disorders that affect temporal memory.

When you tell someone about an event that happened to you, you are relying on your brain's ability to recall events as time sequences. This form of memory is known as episodic memory. Previous studies have suggested that the hippocampus—a brain region long associated with memory—stores episodic memory.

Special neurons within the hippocampus called place cells fire when a rat is at a specific physical location. Each place cell fires at a different spot, and in this way place cells build up a memory map of physical locations. Research has shown that this map is flexible, being able to expand and adjust to accommodate new locations as they are visited.

"Our results indicate the similarity of neuronal processing for spatial and temporal information in the hippocampus"

Now, Shigeyoshi Fujisawa at the RIKEN Center for Brain Science and two co-workers have shown that time cells—the temporal equivalents of place cells, being the markers for episodic memory—exhibit a similar sort of adjustability.



A fluorescence light micrograph of human hippocampus neurons. RIKEN researchers have found that special neurons in the hippocampus known as time cells can form scalable temporal representations in a similar manner to place cells, which code for spatial information.

"We were surprised to find that the neuronal representation of time in the rat brain can expand and contract flexibly depending on the measured time length," says Fujisawa.

To make this finding, the team trained mice using a treadmill and a water reward in one arm of a two-arm maze. The rats were trained to distinguish between long and short spells on the treadmill: if the spell on the treadmill was long, the reward would be located in the left arm, whereas if it was short, the reward would be in the right arm. When the researchers doubled the durations of the long and short times on the treadmill, they found the rate of firing of time cells in the hippocampus scaled by a factor of two. They also found that a type of neuronal sequence activity associated with brain waves that represents recent events, known as theta sequences, scaled by the same amount.

These findings show that time cells can scale with the different timings, much like place cells can with different spacings, and may hint that there is a common mechanism underlying the two neural processes. "Our results indicate the similarity of neuronal processing for spatial and temporal information in the hippocampus," says Fujisawa. "They are important for understanding how the hippocampus recognizes and integrates temporal and spatial information to form episodic memory." ●

Reference

1. Shimbo, A., Izawa, E.-I. & Fujisawa, S. Scalable representation of time in the hippocampus. *Science Advances* **7,** eabd7013 (2021).

CANCER BIOLOGY

Dietary amino acid determines fate of cancer cells

A cancer-causing gene causes cells to simultaneously proliferate and perish in parallel pathways

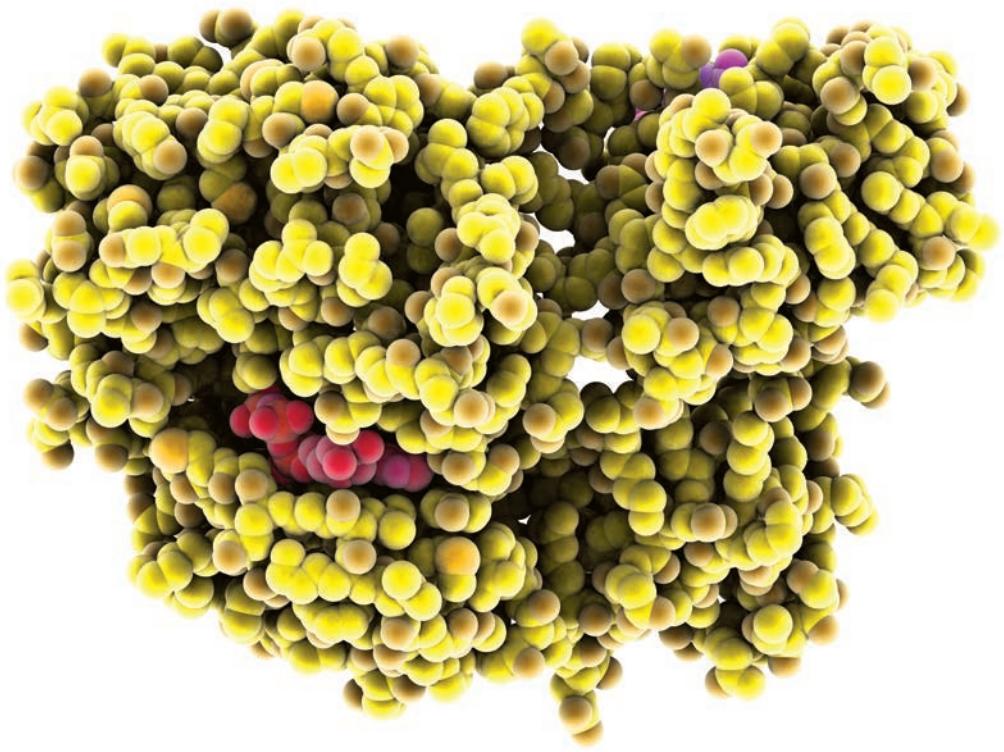
In a finding that raises the possibility of developing dietary therapies for cancer, RIKEN biologists have discovered that a dietary amino acid determines whether cancer cells in fruit flies flourish or perish[1].

A tumor is a clump of cancer cells that multiply uncontrollably. Tumors originate from single cells that become cancerous when oncogenes—genes that cause cells to proliferate—are over-activated. However, because oncogenes often also cause cell death, activation of a single oncogene in a cell is not enough for the cell to become cancerous. This phenomenon is thought to provide a 'fail-safe' mechanism that prevents cells from readily becoming cancerous, since several other oncogenes, along with cancer-suppressing genes, need to be activated in a multi-step process before a cell can become cancerous.

Now, a team led by Sa Kan Yoo at the RIKEN Center for Biosystems Dynamics Research has investigated the details of this process in fruit flies.

The team focused on the oncogene *Src* and investigated how cell proliferation—oncogenesis—and cell death are regulated in the fruit fly. They showed that *Src* does not induce cell death as a result of cell proliferation, but instead it drives both processes independently and simultaneously.

When they inhibited the function of specific genes through RNA interference, the team found that the gene *p38* was involved in cell proliferation and the gene *JNK* was involved in cell death. They also discovered a gene that simultaneously activates both genes.



A molecular model of the Src protein, which can turn on protein synthesis and cellular growth in cells. RIKEN researchers have found that the gene that encodes Src promotes cell death and cell proliferation by parallel pathways.

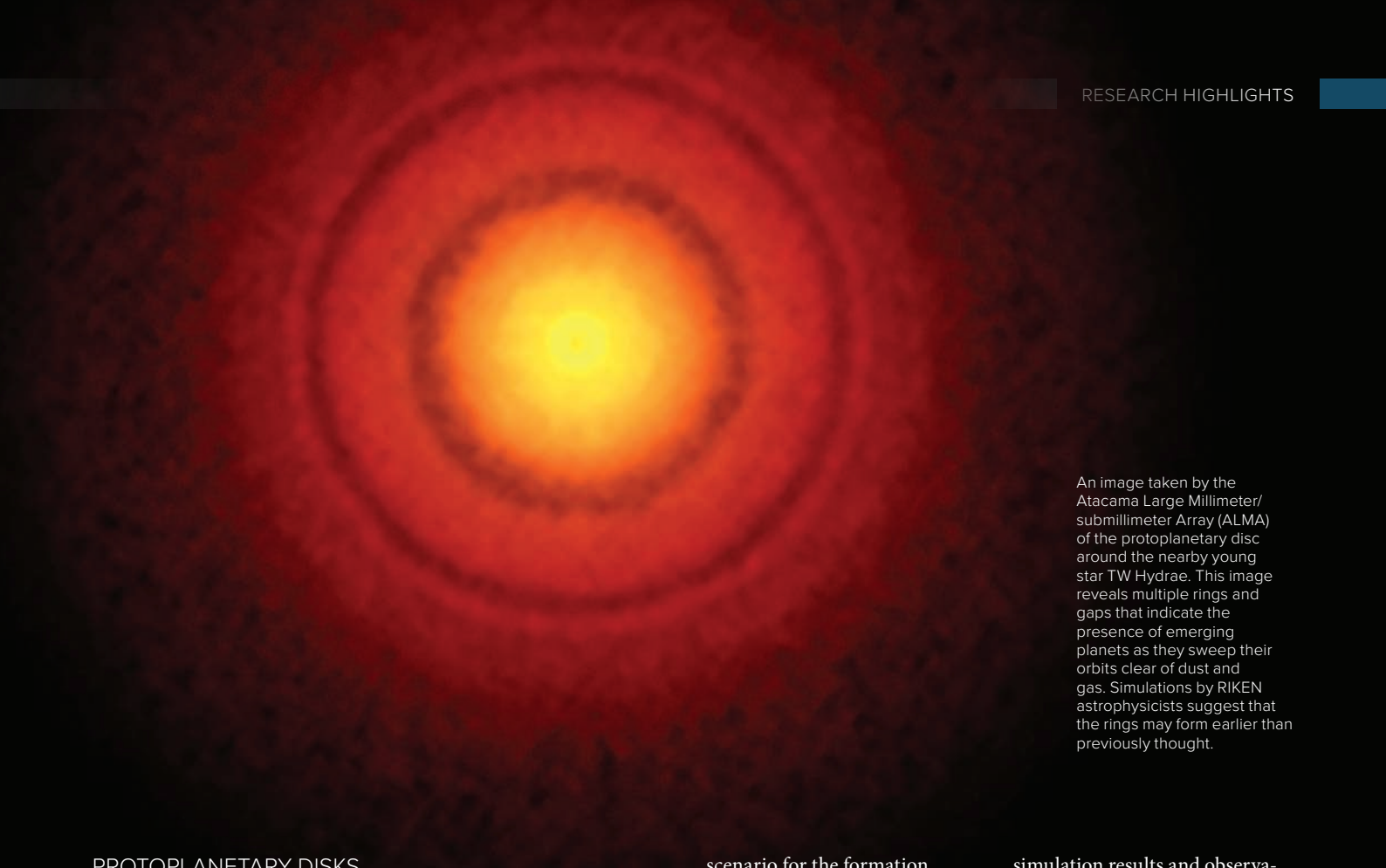
"How oncogenes simultaneously promote cell death and cell proliferation has been controversial," says Yoo. "Our major finding was that the oncogene *Src* promotes cell death and cell proliferation via parallel pathways."

The finding could lead to dietary treatments for cancer. One potential way to treat cancer involves exploiting the fail-safe mechanism by inhibiting cell proliferation but not cell death. The team realized they could make this concept a reality by using nutrients in the diet to control the activity of *p38*. When they tested this hypothesis by investigating the relationship between food fed to fly larvae and cell proliferation, the team found that reducing the amount of the amino acid methionine in the diet prevented *p38*-controlled oncogenesis.

"We were excited to find that manipulating the amount of dietary methionine can affect cell proliferation but not cell death," says Yoo. "We don't know whether our finding in flies will translate to cases of human cancer, but we speculate that it will in particular cases because some human cancers also activate the *Src* gene." ●

Reference

1. Nishida, H., Okada, M., Yang, L., Takano, T., Tabata, S., Soga, T., Ho, D. M., Chung, J., Minami, Y. & Yoo, S. K. Methionine restriction breaks obligatory coupling of cell proliferation and death by an oncogene Src in Drosophila. *eLife* **10,** e59809 (2021).



An image taken by the Atacama Large Millimeter/submillimeter Array (ALMA) of the protoplanetary disc around the nearby young star TW Hydrae. This image reveals multiple rings and gaps that indicate the presence of emerging planets as they sweep their orbits clear of dust and gas. Simulations by RIKEN astrophysicists suggest that the rings may form earlier than previously thought.

PROTOPLANETARY DISKS

From dust to planets

Rings in protoplanetary systems may develop much earlier than in conventional scenarios of planet formation

On their long journey to form planets, dust grains may coalesce with each other much earlier than previously thought, simulations by RIKEN astrophysicists suggest[1]. This may mean revisiting conventional theories of planet formation.

Massive planets start off life as specks of dust that are too miniscule to be observed by the human eye. "Planets like the Earth that are thousands of kilometers in diameter evolved from submicron particles of interstellar dust—that's quite a jump in scale," notes Satoshi Ohashi of the RIKEN Star and Planet Formation Laboratory. "We're interested in discovering how dust grains come together to form objects that are thousands of kilometers in size."

"This suggests that the dust grains may become bigger earlier than we had previously thought"

Planets are birthed from protoplanetary disks—swirling disks of gas and dust around new stars. Ring-like structures have been observed in these disks, and the rings are thought to merge into larger and larger structures over time, eventually leading to the formation of planets. But much remains unknown about the process.

Now, Ohashi and his co-workers have studied a possible scenario for the formation of these rings by performing computer simulations. The results they obtained indicate that dust may aggregate into larger particles during the protostellar stage, while the star itself is still forming and much earlier than predicted by current theories of planet formation. "We found that ring structures emerged even in the early stages of disk formation," says Ohashi. "This suggests that the dust grains may become bigger earlier than we had previously thought."

This is an unexpected finding because the dust disk is still in a state of considerable flux during the protostellar stage—hardly a promising place for dust to agglomerate. "It's really surprising because during planet formation the dust grains should stay in the disk, but material is still falling into the central star during the protostellar stage," says Ohashi. "So we are thinking that planet formation could be a highly dynamic process."

The team found good agreement between their simulation results and observations of 23 ring structures in disks by the Atacama Large Millimeter/submillimeter Array (ALMA) in Chile and other telescopes. Their results could also explain the recent observation of rings in protostellar disks. "Recent ALMA observations have found at least four ring structures in protostellar disks, which are consistent with our simulations," notes Ohashi.

In the future, the team hopes to obtain images of ring structures around protoplanetary disks in multiple wavelengths, since that would enable them to better compare their simulation with observations.

Reference

1. Ohashi, S., Kobayashi, H., Nakatani, R., Okuzumi, S., Tanaka, H., Murakawa, K., Zhang, Y., Liu, H. B. & Sakai, N. Ring formation by coagulation of dust aggregates in the early phase of disk evolution around a protostar. *The Astrophysical Journal* **907,** 80 (2021).

Mice employ a range of decision-making strategies in which the visual stimulus is processed separately from information related to the decision, making them suitable for exploring the strategies people employ when making decisions.

NEUROSCIENCE

Eeny, meeny, miny, mouse

Experiments on mice reveal the different strategies they use in decision making

Mice are suitable for shedding light on the strategies humans employ for making decisions, four RIKEN neuroscientists have shown[1]. That's because they employ a range of decision-making strategies in which the visual stimulus is processed separately from information pertaining to the decision.

Neuroscientists desire to discover what causes people to make different choices based on sensory information. Do they arise from differences in how we visually perceive the options or do our brains perform some fuzzy computations? Scientists can 'ask' mice these questions by analyzing their choices and behaviors in well-designed experiments.

A team led by Andrea Benucci of the RIKEN Center for Brain Science (CBS) has done this by using a computer-controlled system that shows mice two different images of slanting lines side by side on a computer screen. Mice could obtain a water reward by rotating a wheel with their paws to indicate which image had lines closest to being vertical (or at other times, horizontal).

On average, mice could tell two images apart if the angles of the lines differed by 9 degrees. The mice could train themselves on this task and didn't need to compare the lines to an 'absolute' vertical or horizontal example.

The team was mainly interested in the strategies mice used to make their choices. "Mice, just like humans, make judgments using more than just visual information," says Benucci.

To describe these judgments, the team built a model that incorporated what mice had previously viewed in the task and their reaction times.

When a mouse reacted too impulsively, spinning the wheel as soon as the stimuli appeared, an analysis of its decisions revealed that they were heavily influenced by what the mouse had seen in previous trials. Some animals relied more on only one of the two images on the screen to make their decisions. Overall, though, mice were strategic, performing just well enough to get the water that they wanted.

"What we're seeing are individual choices that go beyond just visual estimation," says Dmitry Lyamzin, also at RIKEN CBS. "These choices show non-perceptual biases, and are similar to what is found in human studies in which people's decisions are unconsciously affected by what they have already seen and by their previous choices."

"We show that variations in available cognitive resources, which can be gauged by how impulsive or engaged the animal is on any given trial, directly correlate with how prone the animals are to falling back on their habitual, history-dependent strategies," says Benucci.

Reference

1. Lyamzin, D. R., Aoki, R., Abdolrahmani, M. & Benucci, A. Probabilistic discrimination of relative stimulus features in mice. *Proceedings of the National Academy of Sciences USA* **118,** e2103952118 (2021).

MARSUPIAL GENETICS

Editing the genes of marsupials

The genetics of marsupials can now be explored by gene editing thanks to modifications to the gene-editing methods used for rodents

Watch video of opossum egg being injected.

The creation of the world's first genetically engineered marsupials by RIKEN biologists will help scientists to decipher the genetics of characteristics unique to marsupials[1].

Genetically modified animals, particularly mice and rats, are essential for researching biological processes. For example, researchers often silence genes to find out what their normal functions are. Since marsupials have unique characteristics, studying them necessitates developing a representative animal model. The researchers selected the opossum because its size and breeding characteristics are similar to those of mice and rats.

Like other marsupials, the opossum has characteristics not found in other mammals. For example, it develops without a functional placenta, its pups are born prematurely, and newborn opossum pups with spinal-cord injuries can heal themselves. These unique characteristics are generating interest in marsupial biology.

Now, a team led by Hiroshi Kiyonari of the RIKEN Center for Biosystems Dynamics Research has developed a new gene-editing technology for opossums.

Genome editing requires the systematic collection of fertilized eggs, but this is difficult since a pair of opossums living together require about a week to mate due to a long estrus cycle. The team significantly shortened the time required for mating by administering a hormone used in mice to stimulate estrus in females.

RIKEN researchers have demonstrated the ability of their method for editing genes in marsupials by using it to disrupt a gene responsible for making body pigments and thereby producing some albino offspring.

To generate a genome-edited fertilized egg, an embryo has to be transplanted into a surrogate mother. As is done in rodents, the researchers transferred the fertilized egg into the uterus of a fertile female opossum, and successfully obtained pups—the first time that embryo-transfer technology has been realized in marsupials.

A fine needle is usually used to inject the genome-editing solution into the fertilized egg, but it cannot penetrate the thick layer of proteins and hard shell-like structure that encase fertilized opossum eggs. "One of the tricks to our success was using a piezoelectric element along with the needle, which allowed the needle to penetrate the hard shell coat and thick layer surrounding the egg," Kiyonari explains.

The team demonstrated their method by targeting a gene responsible for making body pigments. When this gene is disrupted, skin lacks color. Some of the offspring obtained in this experiment were albino (see image), and their genes were inherited by the next generation. This represents the first successful gene editing in marsupials.

Researchers can now focus on answering their questions about marsupial biology. "Having established the technology in this proof-of-concept experiment, future studies can create genetically modified marsupials that will impact the fields of mammalian embryology, genomic imprinting, reproduction, neurobiology, immunogenetics, cancer biology, and even comparative evolution," says Kiyonari. ●

Reference

1. Kiyonari, H., Kaneko, M., Abe, T., Shiraishi, A., Yoshimi, R., Inoue, K. & Furuta, Y. Targeted gene disruption in a marsupial, Monodelphis domestica, by CRISPR/Cas9 genome editing. *Current Biology* **31,** 3956-3963 (2021).

SUPERNOVAE

Supernova simulations reconstruct stellar explosions

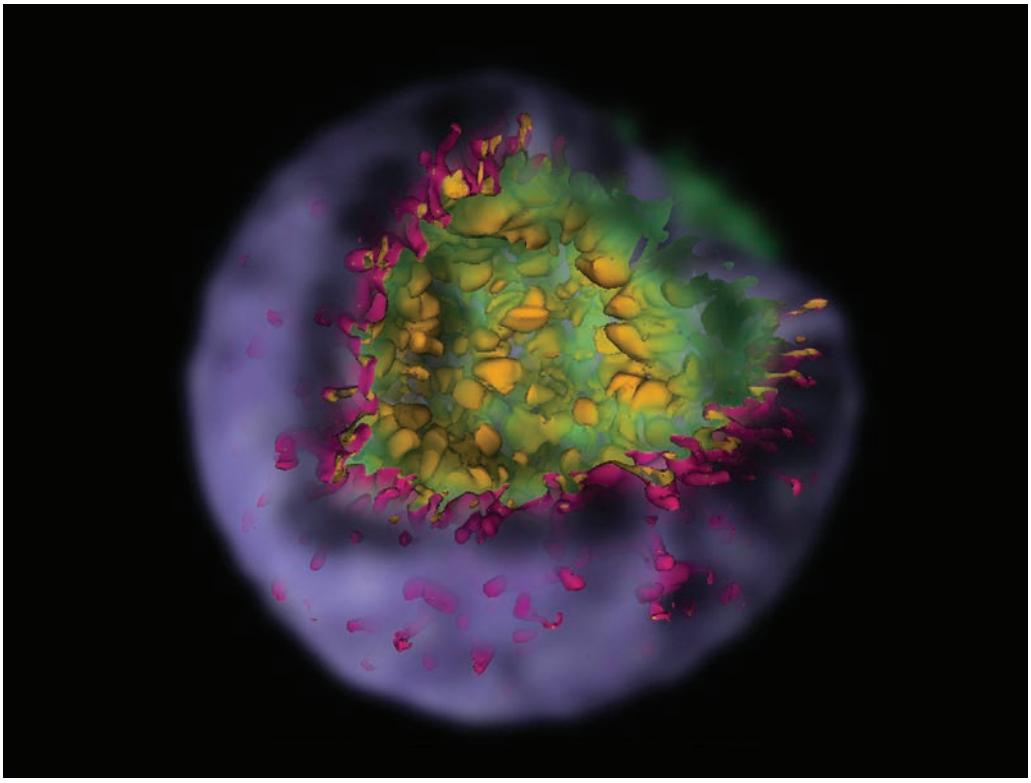
Ignition and combustion processes leave their imprint on supernova remnants

Astronomers are now in a better position to interpret observations of supernova remnants thanks to computer simulations of these cataclysmic events by RIKEN astrophysicists[1].

When certain types of stars die, they go out in a blaze of glory—an incredibly powerful explosion known as a supernova. One of the most common forms of supernova, type Ia, starts with a dense white dwarf star that has burned up its hydrogen fuel. Matter flowing from a companion star can jump-start a runaway nuclear fusion reaction in the dwarf, triggering a massive conflagration that creates many of the heavier elements in the Universe. These are hurled outward in a luminous cloud known as a remnant, which bears an imprint of the explosion.

Gilles Ferrand of the RIKEN Astrophysical Big Bang Laboratory and colleagues in Japan and Germany have been developing three-dimensional computer simulations that recreate supernovae. Their simulations involve two steps: the first one models the supernova explosion itself, while the second one uses that as the input for a model of the supernova remnant. "Our goal is to explore how different explosion conditions produce remnants with characteristic shapes and compositions, similar to those we observe in our Galaxy," explains Ferrand.

The team's latest simulations focus on two aspects of supernovae: how the explosion ignites inside a white dwarf, and how combustion rips through the star. Ignition can start at just a few places inside the white dwarf, or it can be triggered at many points simultaneously. Meanwhile, the combustion might be a deflagration—a turbulent fire that moves slower than the local speed of sound—or it may involve deflagration followed by supersonic detonation.



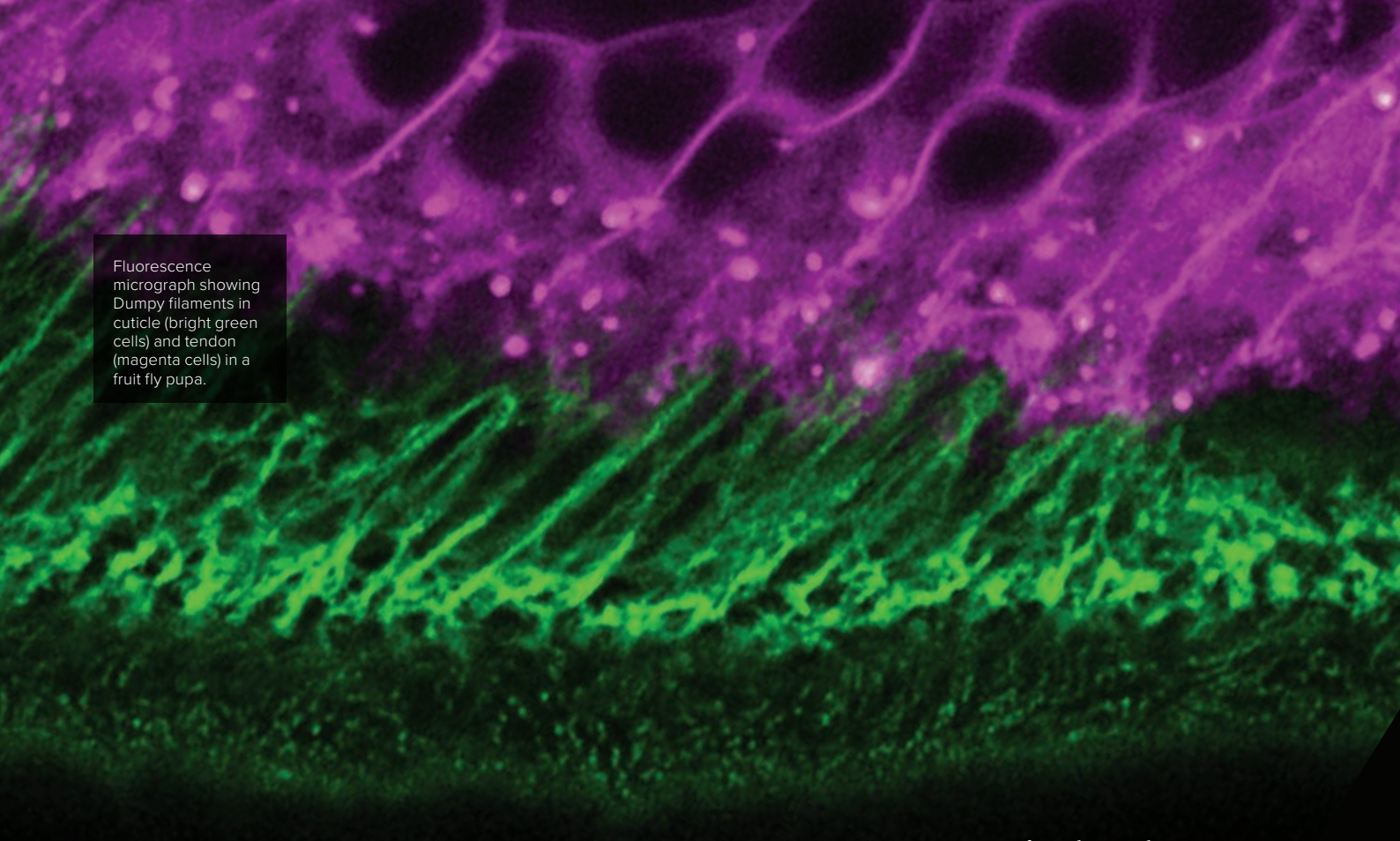
A supernova creates a cloud of debris that bears an imprint of the explosion. In this visualization of the simulation data, one quarter of the remnant's outer shell has been removed to reveal the clumps of matter within (colors denote different materials).

By putting these options together in different ways, the researchers produced four models of supernova remnant. "Each model has its distinctive properties," says Ferrand. For example, a supernova with few ignition points and a deflagration explosion produced a remnant with a symmetric shell that was offset from the center of the explosion. In contrast, a simulation involving few ignition points and a detonation produced a remnant in which half of the outer shell was twice as thick as the other half. Remnants from the deflagration simulations also featured unexpected 'seams' of denser material.

These results suggest that the best time to see a supernova's imprint on its remnant is within roughly 100–300 years after the explosion. This imprint is visible for longer in supernovae with fewer ignition points, and all the remnants in the simulations became spherical overall within 500 years. These results will guide astronomers as they interpret observations of supernova remnants.

Reference

1. Ferrand, G., Warren, D. C., Ono, M., Nagataki, S., Röpke, F. K., Seitenzahl, I. R., Lach, F., Iwasaki, H. & Sato, T. From supernova to supernova remnant: Comparison of thermonuclear explosion models. *The Astrophysical Journal* **906,** 93 (2021).



Fluorescence micrograph showing Dumpy filaments in cuticle (bright green cells) and tendon (magenta cells) in a fruit fly pupa.

DEVELOPMENTAL BIOLOGY

How tendons and muscles grow in step with each other

Two proteins strengthen the extracellular matrix between the tendon and exoskeleton of fruit flies—but in very different ways

Two proteins play a key role in the development of flight muscles and their tendons in fruit flies, two RIKEN developmental biologists have shown[1]. Their study reveals how the components of the muscle–tendon system develop in sync with each other, thereby avoiding catastrophic results.

During the development of an animal, its cells construct non-cellular structures outside of themselves called the extracellular matrix—a complex mesh of proteins and polysaccharides that provides physical scaffolding for cells and also helps regulate cell growth and differentiation.

While biologists know a lot about the internal mechanisms of cells and how cells are assembled into tissues, they know comparatively little about how cells secrete materials and assemble them into external structures such as the extracellular matrix, says Shigeo Hayashi of the RIKEN Center for Biosystems Dynamics Research (BDR). "The construction of extracellular structures is an engineering challenge, especially at the very small scale of molecular assembly," he explains. "This is why my group is studying the assembly mechanisms of the extracellular matrix."

Now, by looking at mutant fruit flies, Hayashi and Wei-Chen Chu (also of BDR) have uncovered the roles two proteins—Dumpy and Quasimodo—play in the development of the extracellular matrix that forms between the tendons attached to a fly's flight muscles and its exoskeleton during the pupal stage.

The flight muscle is the most powerful muscle in the insect body. It is critical that the tendon develops in step with the muscle because otherwise the muscle will pull the tendon away from the exoskeleton, resulting in a flightless fly.

Hayashi and Chu discovered that an extracellular matrix made of Dumpy filaments anchors the tendon cells to the hard exterior layer of the pupa. During development, tension generated by the flight muscles causes this extracellular matrix to remodel and form nanoscale filaments, which increases the strength of the matrix. "We found that stimulus from the muscle promotes tendon development and that, in this way, the tendon develops in tandem with the muscle."

But that mechanism alone is not enough to produce a sufficiently strong tendon and extracellular matrix—Quasimodo is also needed to enhance the strength of the extracellular matrix. Unlike Dumpy, Quasimodo is not a component of the extracellular matrix; rather it strengthens the matrix by some indirect mechanism that is currently not well understood. "This was the biggest surprise for us," says Hayashi. "Quasimodo is an unconventional extracellular matrix protein that diffuses through the whole body and modifies the activity of other extracellular matrix proteins."

Reference

1. Chu, W.-C. & Hayashi, S. Mechano-chemical enforcement of tendon apical ECM into nanofilaments during Drosophila flight muscle development. *Current Biology* **31,** 1366–1378 (2021).

LEUKEMIA

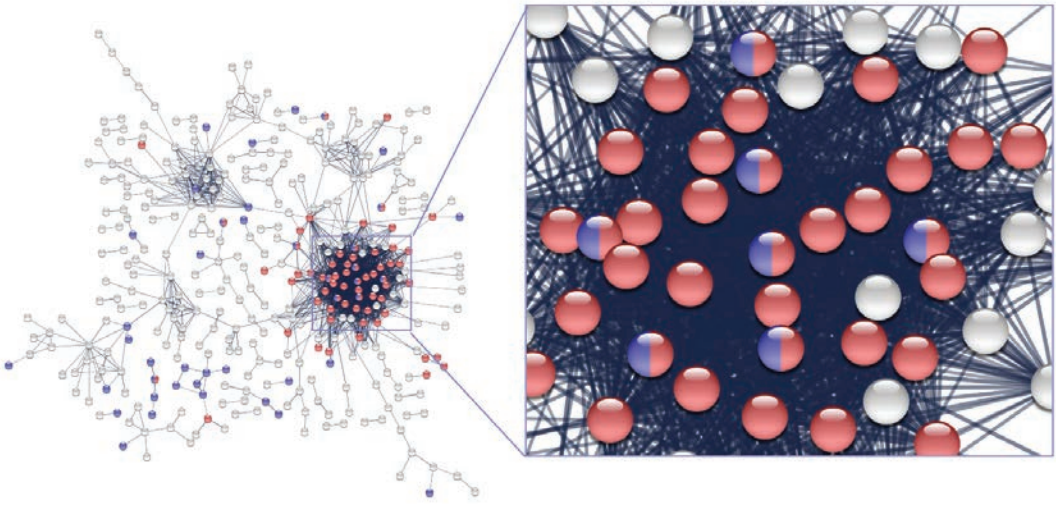
Precision medicine takes on aggressive leukemia

Shared vulnerabilities in genetically diverse cases point to a new way to treat acute myeloid leukemia

A new combination of drugs that may have the potential to treat a type of leukemia has been uncovered by a detailed molecular examination of leukemia cells by RIKEN researchers[1].

Acute myeloid leukemia (AML) is a cancer of the bone marrow and the blood. If left untreated, it develops rapidly and can cause death within weeks or months. While there are several treatments for the disease, current options for treating aggressive, therapy-resistant AML are limited and clinical outcomes remain poor.

In search of new ways to attack the disease, Fumihiko Ishikawa of the RIKEN Center for Integrative Medical Sciences and his colleagues compared the gene-expression profiles of normal blood stem cells with those of leukemia-initiating cells from AML patients. "By checking which mutations are present in individual patients, we may be able to provide clinicians with information on which molecules should be targeted to eliminate leukemic cells," explains Ishikawa.



An interaction map of proteins produced by genes differentially expressed in acute myeloid leukemia cells revealed vulnerabilities that could be targeted using drugs.

"We now hope to apply our interdisciplinary approach to other diseases that are difficult to treat"

The researchers analyzed 126 patient samples, all from poor-prognosis cases. They discovered several pathways involved in cell survival and proliferation that were consistently more active in the gene sets from AML cells than in those from non-cancerous controls. This suggests there are common signaling pathways and regulatory networks that can be therapeutically targeted in most cases of AML, even though the specific genetic underpinnings of the disease vary from one patient to the next.

Ishikawa's team tested small-molecule drugs known to block these pathways and then checked their efficacy in humanized mouse models of the disease. They discovered that, despite their genetic differences, AMLs from diverse backgrounds were all susceptible to inhibition of four key proteins: three involved in preventing cell death and one in facilitating cell division.

A combination of two drugs, each aimed at different proteins that normally ward off cell death, proved to be the most effective at eliminating AML in mice implanted with patient-derived leukemia cells. One of these drugs, called venetoclax, is already approved in many countries for treating AML, while another, termed AZD5582, has yet to be evaluated in patients but has shown anti-leukemia potential in other preclinical studies.

The findings, says Ishikawa, underscore the value of further developing AZD5582 (or drugs like it) as a treatment, in tandem with venetoclax, for highly aggressive AML.

The precision-medicine strategy developed by the RIKEN team also provides a blueprint for drug discovery more broadly, he adds. "We now hope to apply our interdisciplinary approach to other diseases that are difficult to treat," Ishikawa says. ●

Reference

1. Hashimoto, M., Saito, Y., Nakagawa, R., Ogahara, I., Takagi, S., Takata, S., Amitani, H., Endo, M., Yuki, H., Ramilowski, J. A. *et al.* Combined inhibition of XIAP and BCL2 drives maximal therapeutic efficacy in genetically diverse aggressive acute myeloid leukemia. *Nature Cancer* **2,** 340–356 (2021).

Moms risk life and limb for their young. WHY?

RIKEN researchers have identified the brain cells responsible for risk-taking parenting behavior in mice.

It is often said that a mother will do anything for her children, even if it means risking her own life. Remarkably, this protective instinct is observed in all mammalian mothers, regardless of species.

Hormones involved in female reproduction, such as estrogen, are known to facilitate maternal motivation to care for their young. But the specific population of neurons that receives this hormonal information and affects maternal behavior has remained murky—until now. RIKEN researchers have recently identified specific brain cells involved in maternal care. The neurons they identified in mice contain a special protein called the calcitonin receptor, which, when silenced, drastically affects a mother's nurturing abilities[1].

"All mammalian parents, especially mothers, are highly motivated to sustain the life of their offspring," says Kumi Kuroda at the RIKEN Center for Brain Science (CBS), who led the study. When cared for by their parents, baby animals have a higher chance at surviving in the wild, while human infants demonstrate better developmental outcomes.

"But in life there are so many difficulties and sometimes parents lose this motivation and abandon their infants," she says. "So we wanted to find out what is happening when parental motivation is sustained even under difficult conditions. And to do that, we needed to identify the neural mechanisms involved in care," says Kuroda, whose training as a psychiatrist inspired her to delve deeper into how the parental brain works.

A TELLING BIOMARKER

For the past decade, Kuroda's team has been studying the parent–infant bond in mammals. A few years ago, they discovered that the part of the brain responsible

for nurturing behavior is the central medial preoptic area (cMPOA), which is located next to the hypothalamus just above the brainstem.

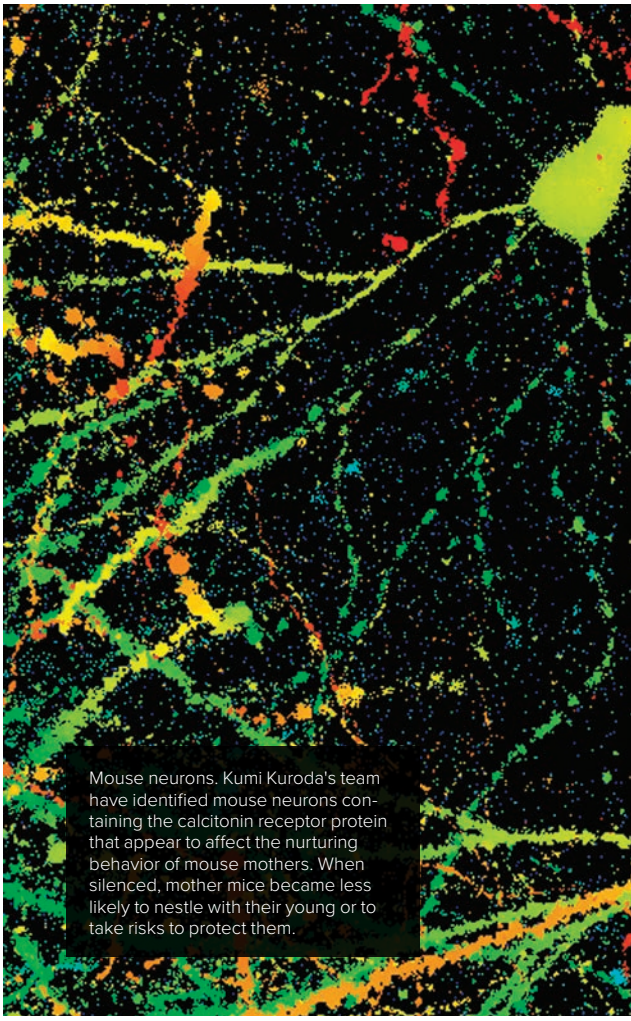
The team then explored further. The cMPOA is anatomically complex, containing more than seven different types of neurons. "We wanted to pin down which particular neuron is involved in the regulation of parental behavior," explains Kuroda.

To do this, her team's first task was to identify a biomarker that could reliably indicate which cMPOA neurons were active during nurturing behavior. From more than 20 candidate molecules, they identified one: a protein called the calcitonin receptor.

The receptor is found throughout the body and as its name suggests, usually binds to a hormone called calcitonin. "Its most famous function is calcium regulation in bone," says Kuroda. However, calcitonin isn't found in the brain and a different hormone—called amylin—binds to the receptor instead.

Upon further testing, Kuroda and her team discovered that postpartum mother mice had a higher number of cMPOA neurons expressing the calcitonin receptor compared with virgin females, males or fathers. These neurons also express estrogen receptor, and can mediate parturition-induced facilitation of maternal motivation.

"In mothers, the expression of the calcitonin receptor is eight times higher," says Kuroda. "It is upregulated in postpartum mice and heightens maternal motivation to care for their young, even under risky conditions."



Mouse neurons. Kumi Kuroda's team have identified mouse neurons containing the calcitonin receptor protein that appear to affect the nurturing behavior of mouse mothers. When silenced, mother mice became less likely to nestle with their young or to take risks to protect them.

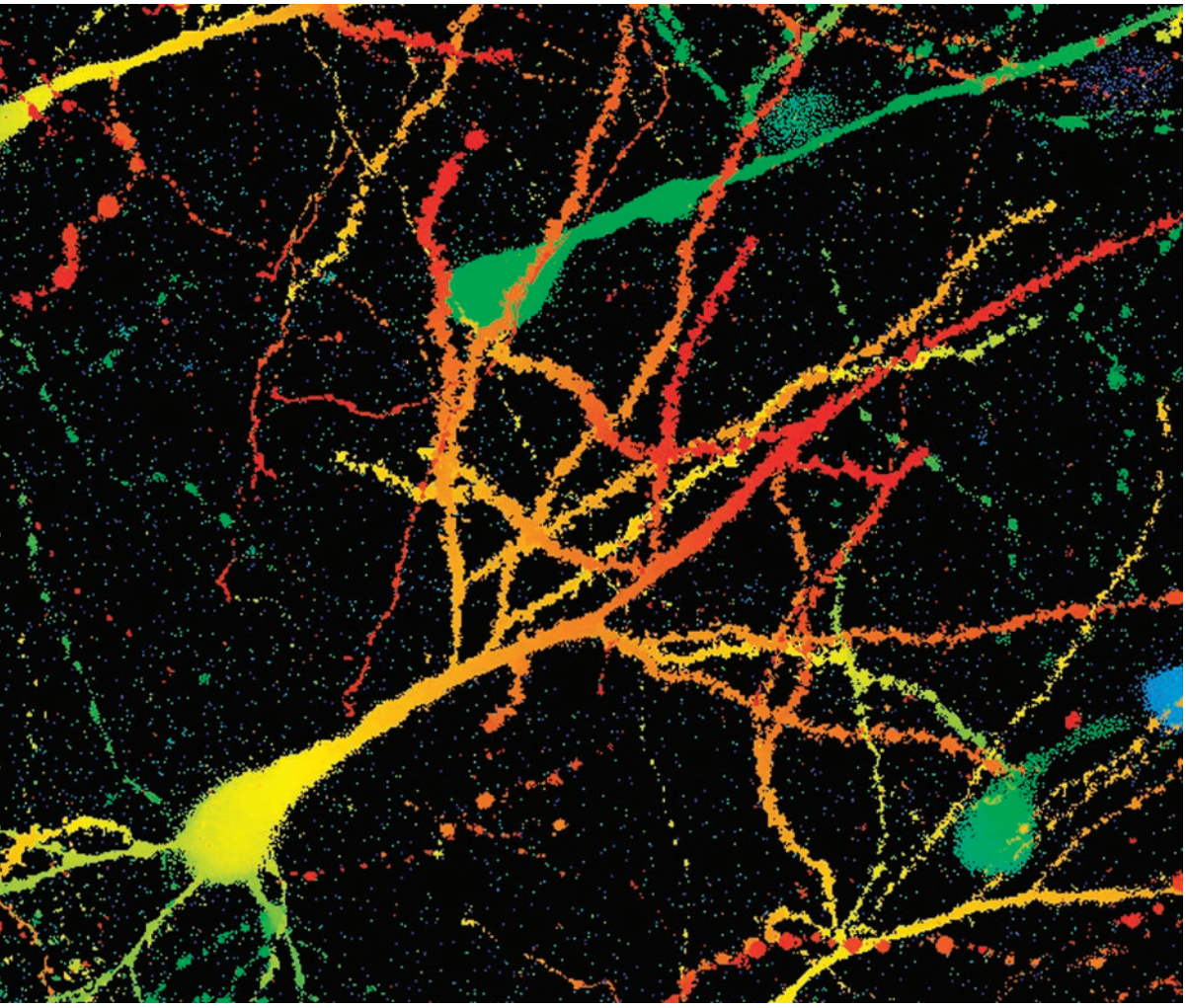
MORE THAN JUST A MARKER

After identifying the calcitonin receptor as a marker for active neurons, the researchers then wondered: does the receptor itself play a role in enhancing nurturing behavior? "We wanted to see if the receptor was necessary for parental behaviors, and not just activated during nurturing," explains Kuroda.

To explore this question, the team first genetically engineered mice (called Cre-transgenic), in order to specifically modify the calcitonin-receptor expressing neurons. The researchers then conducted two experiments.

In the first, they found that blocking the function of the calcitonin-receptor-expressing cMPOA neurons did not affect the ability of female mice to mate, become pregnant or deliver healthy pups. But what did change was the nurturing instincts of the mother mice: instead of gathering pups and grouping them together in a nest for warmth and feeding, they left them scattered throughout the cage. As a result, 83% of pups died the day after their birth, compared with 23.4% in the regular cMPOA group.

For the second experiment, Kuroda and her team devised an experiment involving a raised cross-shaped platform. The adult test mouse was placed on an enclosed (safe) arm of the cross, while mice pups were positioned on the three open arms, which were considered unsafe and scary for the mouse. The aim was to see if an adult mouse (either a postpartum mother or a virgin female) would venture out onto the open arms to rescue young.



"It seems a pretty scary task for mice," says Kuroda. The platform is narrow and the mice have to pivot when they reach the edge containing the pup. "Sometimes their hind legs also drop down—it's a 40 centimeter drop. In human terms, it's like a two- to three-storey building."

The bright lights of the lab made the whole scenario even more stressful, she says. "They're already quite frightened and don't want to go out."

"But because mothers are highly motivated to care for their young, they will take the risk and save the pups on the high platform," says Kuroda. However, mother mice with knocked-out calcitonin receptor genes exhibited measurable delays in rescuing the pups, and most virgin females in the experiment refused to do so.

"The conclusion is that the calcitonin receptor is not just a marker for nurturing-required neurons, but itself plays a role in the stimulation of postpartum maternal motivation, especially under risky conditions," she says.

Kuroda's team has now extended their studies to mammals other than mice—specifically, a species of long-tailed monkeys called marmosets.

"Examining the calcitonin-receptor-expressing cMPOA neuron's role in these non-human primates should be more similar to what happens in humans," says Kuroda. Her team has already begun work and are aiming to publish a paper in the near future.

Ultimately, Kuroda hopes her work will help children at risk of abuse and their parents. "The early experience children have with their parents directly affects their mental health and attitude towards others," she says. "To prevent child abuse, we have to supportively look at parents' behavior."

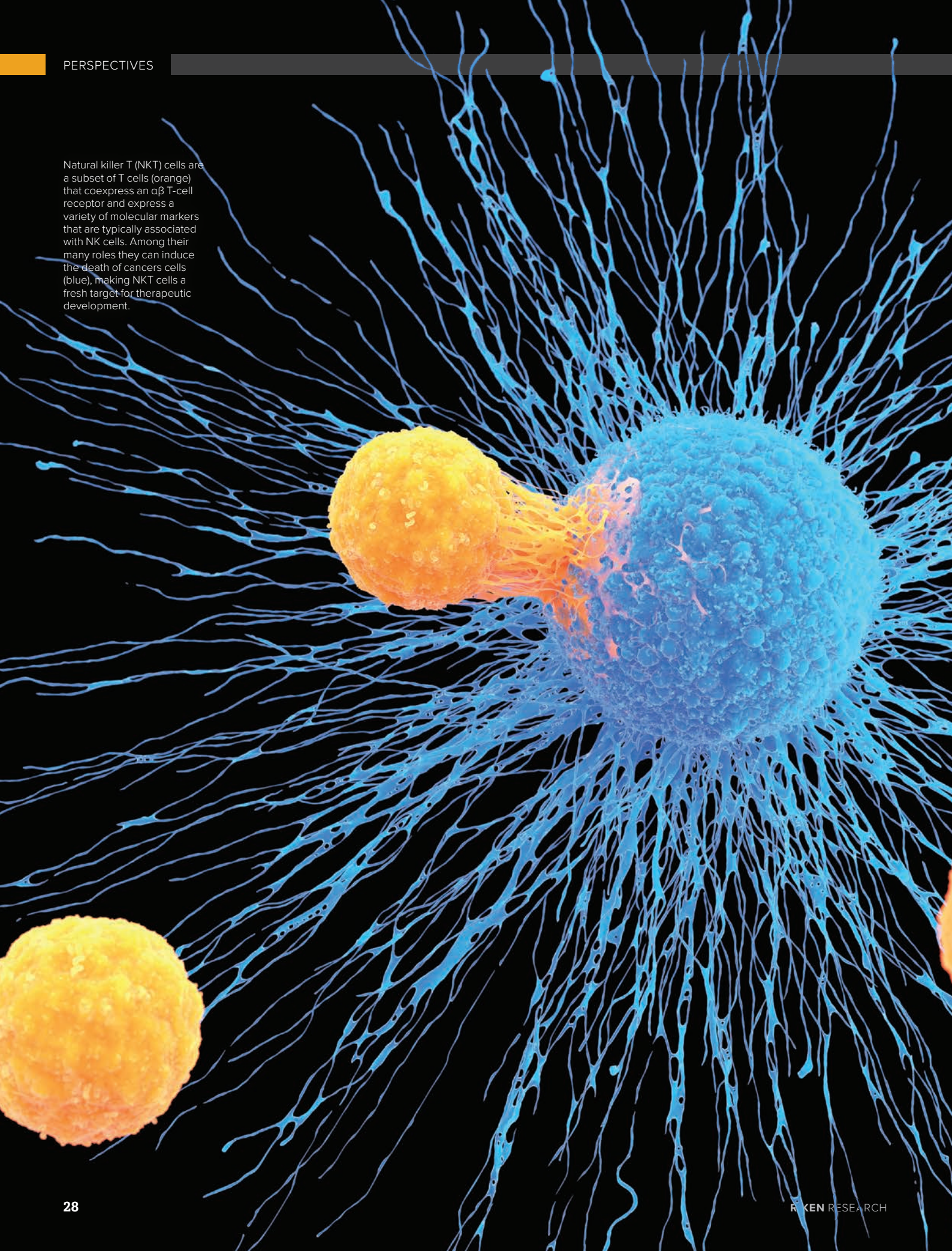
She adds: "That's why we really want to understand the brain mechanism for parental behavior."

REFERENCE

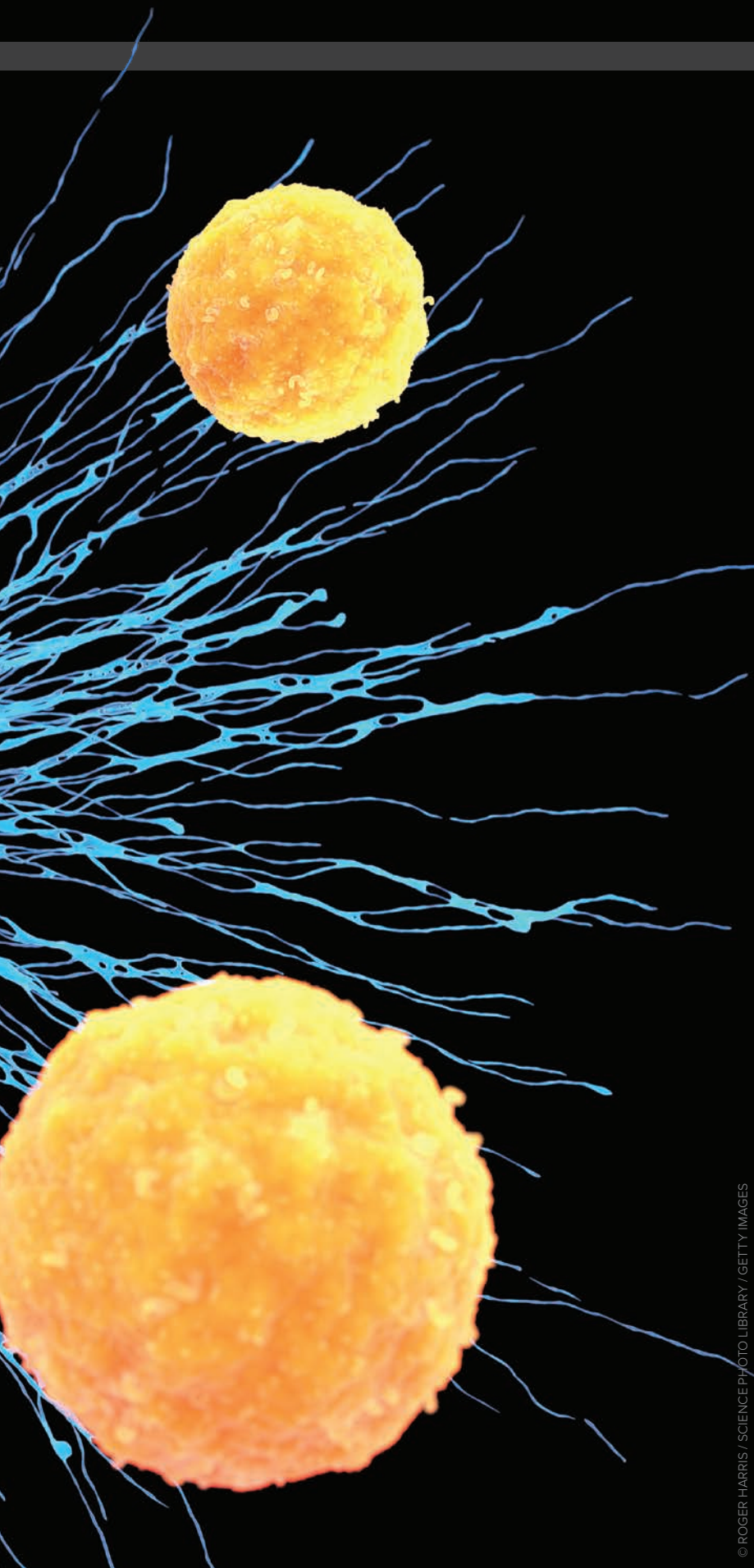
1. Yoshihara, C., Tokita, K., Maruyama, T., Kaneko, M., Tsuneoka, Y., Fukumitsu, K., Miyazawa, E., Shinozuka, K., Huang, A. J., Nishimori, K. *et al.* Calcitonin receptor signaling in the medial preoptic area enables risk-taking maternal care. *Cell Reports* **35**, 109204 (2021).

This feature looks **at the work of KUMI KURODA**

Kumi Kuroda leads the Laboratory for Affiliative Social Behavior at the RIKEN Center for Brain Science. She received her Ph.D. in molecular biology from Osaka University's School of Medicine in 2002. She was a Human Frontier Science Program long-term fellow at McGill University in Canada from 2002–4, a Special Postdoctoral Researcher at the RIKEN Brain Science Institute from 2004–7, and was appointed as a laboratory head at RIKEN in 2008. Her lab has been studying the brain mechanisms of parent-infant relations in mice, monkeys and humans. Her team discovered that the central medial preoptic area in the basal forebrain is responsible for parental care and identified the 'transport response', in which infants are calmed by being carried by their parents. Her goal is to contribute to evidence-based support for healthy families.



Natural killer T (NKT) cells are a subset of T cells (orange) that coexpress an αβ T-cell receptor and express a variety of molecular markers that are typically associated with NK cells. Among their many roles they can induce the death of cancers cells (blue), making NKT cells a fresh target for therapeutic development.

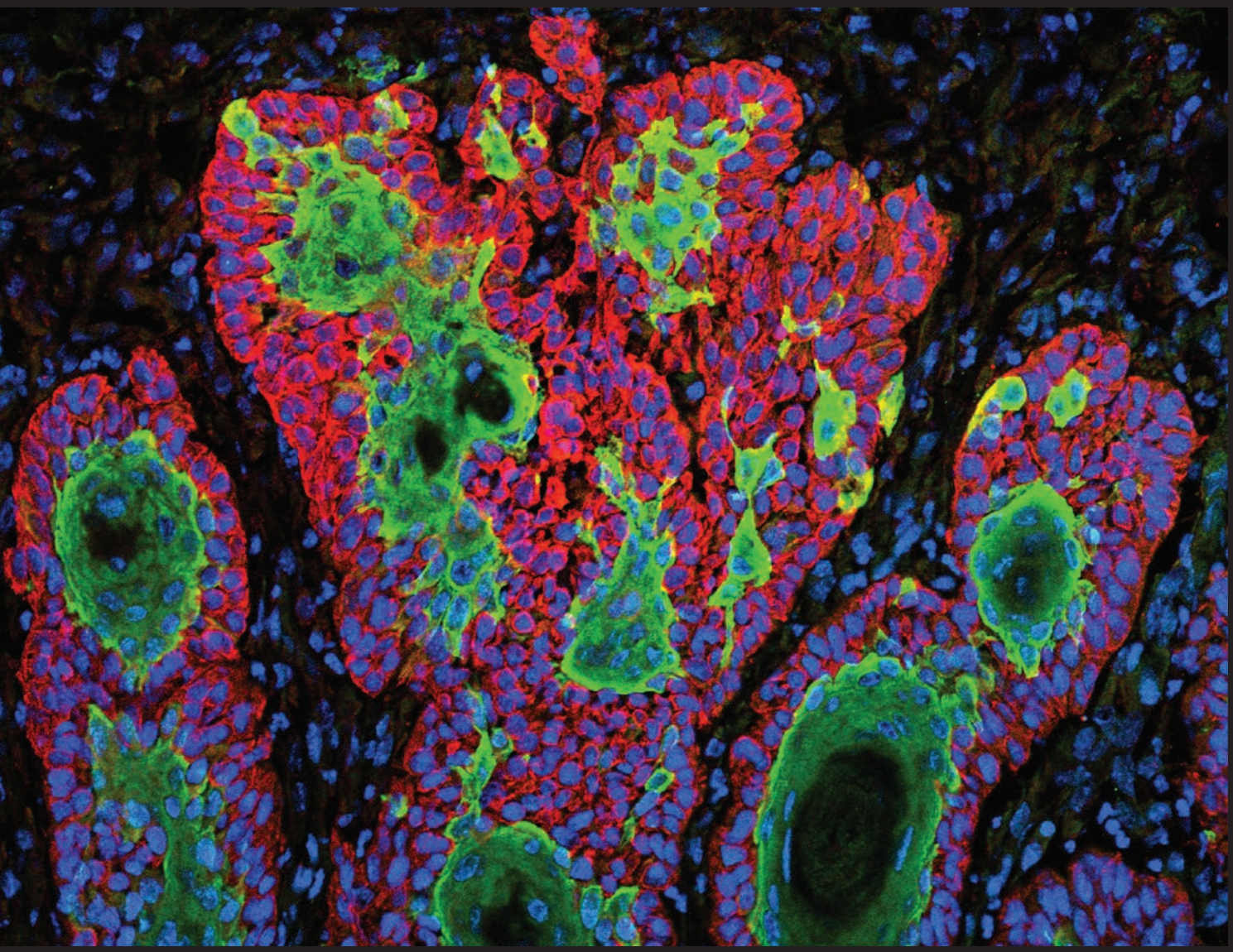


Harnessing natural killer T cells to stop cancer

Innovative use of stem cell technology to ramp up production of natural killer T cells could hold the key to improved cancer treatments.

Cancer accounted for nearly 10 million deaths worldwide in 2020 and is the leading cause of death in Japan. Immunotherapy primes the patient's immune system to fight cancer cells and offers a promising alternative to the usual treatments of chemotherapy, radiation therapy and surgery. Researchers at the RIKEN Center for Integrative Medical Sciences (IMS) are investigating a number of immunology and cancer therapies, and our team at the RIKEN IMS Laboratory for Developmental Genetics is spearheading efforts to develop new cancer immunotherapy strategies by harnessing the power of natural killer T (NKT) cells.

In September 2020, we started recruiting for the world's first clinical trial using NKT cells derived from induced pluripotent stem (iPS) cells to treat patients with head and neck cancer. This followed more than a decade of intensive basic research and validation studies with colleagues at Chiba University. Four to 18 patients will be enrolled in the trial and may undergo the novel treatment over the next two years. While it is too soon to evaluate efficacy, confirming the safety of iPS-derived NKT cell therapy will be a key step toward the development of this potentially groundbreaking treatment for many different types of cancer.



Since late 2020, a clinical trial designed to suppress tumors using iPS-derived NKT cells has been conducted on Japanese patients with squamous cell carcinoma (pictured), a condition accounting for 80–90% of all head and neck tumors.

ROOTS AT RIKEN

The unique invariant antigen receptor (Vα14Jα18 in mice) of NKT cells was discovered in 1986 by immunologist Masaru Taniguchi, then at Chiba University and now senior visiting scientist at RIKEN IMS. His work spurred research into the role of NKT cells in the regulation of immune responses, opening up the development of anticancer therapeutics. The discovery of NKT cells has been designated as a 'Pillar of Immunology' by the American Association of Immunologists.

Because of their unique receptors, NKT cells recognize lipid antigens presented by the cell surface molecule monomorphic CD1d. They rapidly produce large amounts of cytokines (such as interferon-gamma, IFN-γ) which are critical to activating antitumor functions. Studies of NKT cell-deficient mice have demonstrated that NKT cells play an essential role in triggering antitumor immune responses and establishing immunological memory against tumor cells.

With a view to unlocking the potential of these rare cells as a cancer therapy, the search was on for a suitable molecule to trigger NKT cells. Taniguchi and his team succeeded in singling out alpha-galactosylceramide (α-GalCer), a glycolipid derived from the sea sponge *Agelas mauritianus*, in 1997. They showed that α-GalCer binds to CD1d. The resulting complex leads to enhanced NKT cell activity and high levels of cytokine production, which mediates adjuvant activity and activates various other antitumor immune cells.

A preclinical breakthrough came in 1999 with intravenous administration of α-GalCer to mice with liver cancer. The treatment, involving the use of dendritic cells pulsed with α-GalCer, resulted in complete inhibition of melanoma metastasis within just one week.

Subsequent studies have shown that after stimulation with α-GalCer, NKT cells appear to activate both CD8+ cytotoxic T cells (to destroy major histocompatibility complex (MHC)-positive tumor cells) and natural killer cells (to eliminate MHC-negative tumor cells). As tumors frequently contain both MHC-positive and -negative cell types, this remarkable ability to attack cancer cells on two fronts has led researchers to hail NKT cells as "an ideal anti-tumor immunotherapeutic" that could potentially lead to "complete eradication of tumors without relapse".

In 2001, a series of studies to assess the effects and safety of α-GalCer-pulsed dendritic cell therapy began at Chiba University Hospital, led by Shinichiro Motohashi. A clinical trial of NKT cell-targeted immunotherapy using α-GalCer for patients with advanced non-small cell lung cancer began in March 2004. A cohort of 17 patients showed increased IFN-γ production and had a median survival time of 18.6 months, which is considerably longer than the typical survival time of less than 12 months. The results also suggested a mechanism by which NKT cells are able to induce long-term immune memory.

While α-GalCer treatment continues to be developed and explored, both in Japan and overseas, the stark fact remains that many cancer patients are ineligible for this treatment because their NKT cell count is too low. Even in the blood of healthy individuals, NKT cells comprise only 0.1% of total lymphocytes. This makes it extremely challenging to harvest NKT cells from the body and culture them to numbers sufficient for clinical use.

To overcome this problem, a multidisciplinary team at RIKEN developed a technique to generate large quantities of NKT cells using induced pluripotent stem (iPS) cells in mice in 2010. They succeeded in generating millions of functionally competent iPS-derived NKT cells, which secreted high levels of IFN-γ and suppressed tumor growth in live mice.

Following proof of concept for clinical application of human iPS-derived NKT cells in 2016, a clinical trial began at Chiba University Hospital in late 2020. iPS cells were made from NKT cells collected from the blood of healthy donors and cultured into large numbers. These iPS cells were then redifferentiated to NKT cells and injected into patients. Each patient received around 50 million iPS-derived NKT cells in one injection, followed by two further injections spaced two weeks apart.

The focus of the study is on patients with squamous cell carcinoma (a condition accounting for 80–90% of all head and neck tumors) who have previously not responded to surgery, radiation therapy, chemotherapy or a combination of these therapies. Those with cachexia (a wasting disease seen in many end-stage cancer patients) were excluded from the study, which limits participant recruitment.

The most important investigation is safety. The two biggest risk factors are iPS cells becoming cancerous themselves and patients exhibiting allogeneic responses (rejecting immunologically incompatible cells created from another person).

Provided that the preliminary results are satisfactory, a combination therapy of α-GalCer-pulsed dendritic cell treatment and iPS-derived NKT cells may be explored for tumor suppression. We will see results in 2022 at the earliest.

FUTURE PROSPECTS

Devising new ways to make iPS-derived NKT cells more active presents an ongoing challenge.

Human leukocyte antigen (HLA) molecules mediate allogeneic rejection, but HLA can be knocked out at the iPS phase by using technologies such as CRISPR-mediated editing.

This process could also extend the retention period of iPS-derived NKT cells in the body. Efforts are also underway to make iPS-derived NKT cells more immunogenic through the application of chimera antigen receptor (CAR) T-cell therapy. This involves genetically engineering iPS-derived NKT cells to express a synthetic receptor that can bind tumor-specific antigens. As CD19-specific CARs are already successfully used in the treatment of patients with B cell-derived leukemia, this is another promising avenue of research.

In order to scale up, there is a need for a simpler, more optimized protocol. It currently takes 40–50 days to generate sufficient numbers of NKT cells for treatment. However, based on evidence that NKT cells appear in mice on day 11 after fertilization, this could be shortened to as little as 2–3 weeks. A long-term goal will be to develop a cocktail of differentiation factors to facilitate the industrial generation of iPS-derived NKT cells, which would make the cells more cost effective.

Before such dreams can be realized, there is still a great deal of basic research to be done. There is much scope for informatics and data scientists to help us trace the developmental trajectory of iPS cells to NKT cells. Shin-ichiro Fujii, team leader at the RIKEN IMS Laboratory for Immunotherapy, is working on artificial adjuvant vector cell therapy, another variation of NKT cell-targeted therapy, for the treatment of relapse and refractory acute myeloid leukemia. In addition to the fruitful collaboration with Motohashi's group at Chiba University, there may be more collaborations with other university hospitals nationwide and around the globe.

REFERENCE

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

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Deputy director, RIKEN Center for Integrative Medical Sciences

Haruhiko Koseki received his Doctor of Medicine and Ph.D from Chiba University. He was a professor at the Graduate School of Medicine Department of Immunology at Chiba University between 1998 and 2004. He served as director of the Developmental Genetics Research Group at the RIKEN Research Center for Allergy and Immunology from 2001, where he studied the epigenetic regulation of Polycomb group genes in development. He serves as deputy director at the RIKEN Center for Integrative Medical Sciences and leads the Laboratory for Developmental Genetics.

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