SUMMER 2015

RIKEN RESEARCH

SHOWCASING THE BEST OF RESEARCH AT RIKEN

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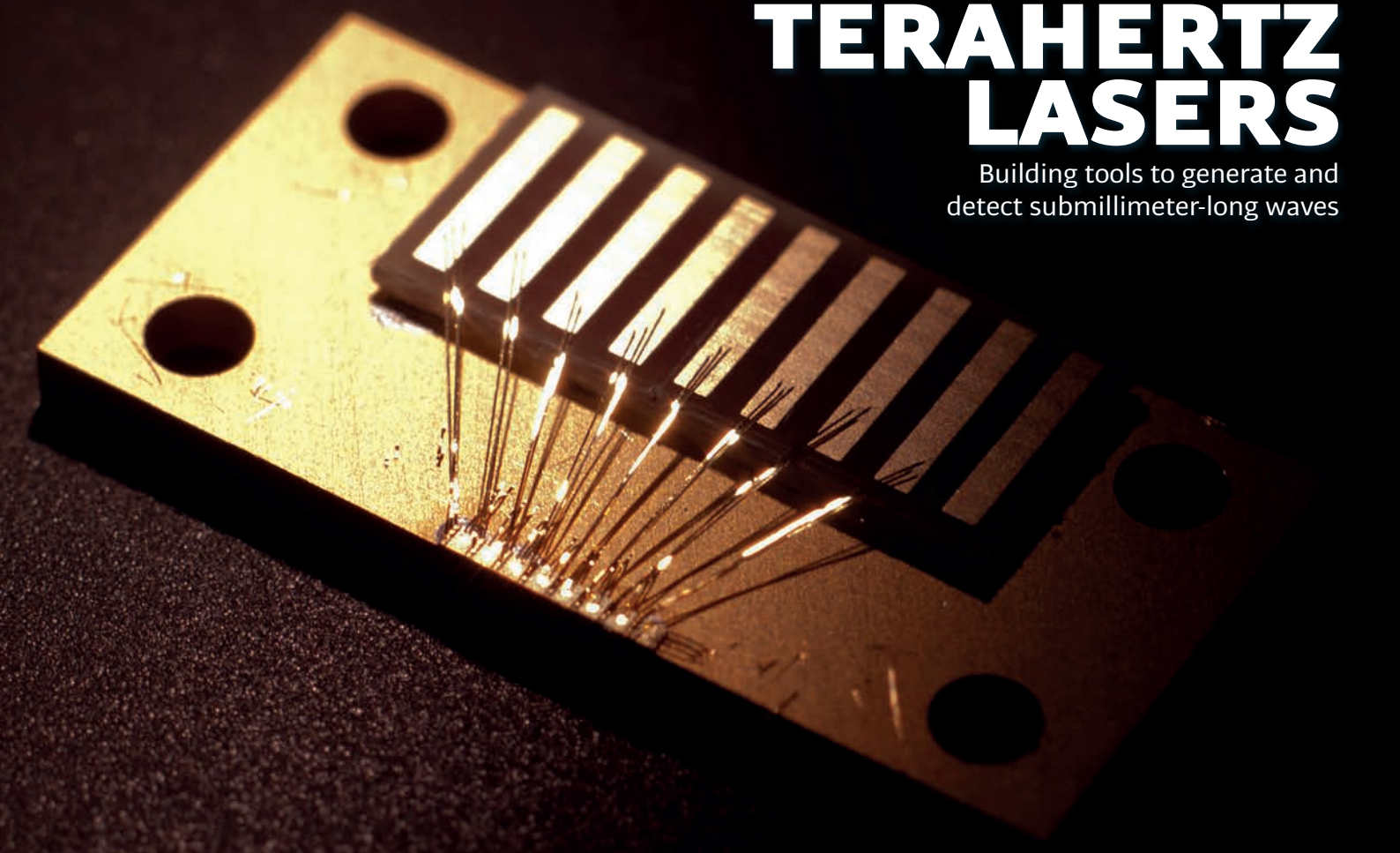

TERAHERTZ LASERS

Building tools to generate and detect submillimeter-long waves

FADING STAR

Snapshots of GK Persei 14 years apart

SUBVERSIVE GENES

Mapping patterns of expression in multidrug-resistant bacteria

ON TIME?

Synchronizing clocks to atomic precision

RIKEN Integrated Innovation Building
Constructed in April 2015 at the heart of the Kobe Biomedical Innovation Cluster, the RIKEN Integrated Innovation Building houses research teams involved in collaborative research with industry and academia.

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

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

RIKEN RESEARCH is an online and print publication that highlights the best research published by RIKEN. This publication is a selection of the articles published by RIKEN at: www.riken.jp/en/research/rikenresearch Please visit the website for recent updates and related articles. Articles showcase RIKEN's groundbreaking results and are written for a non-specialist audience.

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

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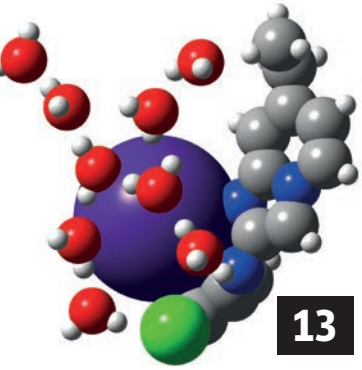

New leadership at RIKEN

Cover story: Researchers at the RIKEN Terahertz-wave Research Group are building tools to generate and detect terahertz waves. **Page 34**

Welcome to the summer 2015 issue of *RIKEN RESEARCH*. On 1 April 2015, RIKEN changed from being an independent administrative institution to a national research and development institute. That same day, former president of Kyoto University, Hiroshi Matsumoto, succeeded Ryoji Noyori as president of RIKEN, and four new executive directors were appointed.

Under Noyori's 12-year presidency, researchers at RIKEN have made many significant contributions to science and technology, including discovering element 113, establishing the SACLA X-ray Free Electron Laser facility and developing the K computer. Most recently, RIKEN launched the world's first clinical trial in regenerative medicine using induced pluripotent stem cells.

RIKEN's new mission is to maximize results in research and development, efficiently and effectively. Together with collaborators in Japan and abroad, we will continue to work on basic research, while also developing outstanding and innovative technologies. This issue features a "Special interview" with President Matsumoto, in which he unveils his exciting plans for the year ahead.

The "Feature highlight" presents new findings by distinguished senior scientist Shigeyuki Yokoyama on the crystal structure of obesity-related adiponectin receptors, with implications for treating diseases such as type 2 diabetes. And our "Research highlights" cover articles that have attracted significant global attention, including research on a supramolecular polymer that grows by the addition of one monomer at a time.

"Places" focuses on the Sendai campus—home to the Terahertz-wave Research Group of the RIKEN Center for Advanced Photonics. Finally, in "Perspectives", Yoshihide Hayashizaki, director of the RIKEN Preventive Medicine & Diagnosis Innovation Program, explains how RIKEN is leveraging its strengths in omics technologies to boost health, wealth and longevity. As Japan's sole comprehensive research institute, we will continue to make every effort to better society.

Visionary science

Interview with President Hiroshi Matsumoto

You were appointed president of RIKEN in April 2015. Do you have plans to change the way research is conducted at RIKEN and in Japan as a whole?

Over the years, I have come to believe that researchers should not simply publish journal articles based on their investigations. Rather, they should achieve results based on a vision of the world that societies want to create.

I find it strange that scientists often only consider applications of their work as an afterthought, once their research is complete—it should be the other way around. As has been said: "Necessity is the mother of invention." Japan offers many examples of this approach, and the problem seems to stem from the nature of Japanese academia. Most researchers spend their entire careers in a single laboratory, joining a university as a graduate student or postgraduate researcher, and rising up the ranks from assistant professor to full professor. They work with the simple goal of becoming the top researcher in their particular field, reading every paper published in their specific branch of science, but no papers published in other branches. As a result, although they gain a deep knowledge of a very narrow subject area, they sacrifice a broader understanding—especially of things outside of the natural or physical sciences.

My view is that while scientists should carry out science, they should first and foremost be members of their communities, contributing to the more universal goals of society. This is a conviction that I have maintained throughout my tenure as president of Kyoto University and will continue to uphold as president of RIKEN, where I hope to introduce changes that bring science closer to achieving our societal vision.

Why is it important for scientists to work based on a vision?

It is amazing to think that more than seven billion people live on this small planet of ours. Eventually, our civilization will colonize the solar system, taking advantage of the resources available in this immense Universe around us. As scientists, our primary duty is to ensure that the human race can survive until that time comes.

The irony is that science and technology underpin the affluence of modern society, but could also lead to its demise. As we advance, we are fooled by our affluence into consuming more and more of our limited resources. Eventually, we will run out of resources and will have to rely even more on science to make up for the deficit.

This is a vicious circle that we can only break through personal and cultural philosophy. Every individual must understand that science alone is not the solution. We need philosophy working hand-in-hand with science to ensure that we do not wipe ourselves out. This is partly why one of the recently appointed executive directors at RIKEN is a philosopher rather than a natural scientist. I believe that the two fields must never be separated.

How do you plan to encourage RIKEN to pioneer new fields of research under your presidency?

RIKEN today has many research centers, where outstanding scientists are engaged in research of the highest standard in their fields. While there are an infinite number of things that researchers at RIKEN can study, we need to be selective and concentrate on the most powerful subjects to retain our leading position.

RIKEN should model how science can be done. Under our new status as a national research and development institute, it is particularly vital that we maintain an environment that allows scientists to conduct their research freely and autonomously, even while remembering that their work must serve society in some way.

It is also crucial to keep in mind that interdisciplinary exchange is essential for pioneering new fields. Opportunities for exchange at RIKEN have been established through forums such as the RIKEN Science Council, the RIKEN Scientists' Assembly and the RIKEN Interdisciplinary Exchange Evenings, but I would like to encourage more exchange on a day-to-day basis. New ideas tend to emerge when people converse through informal avenues.

These exchanges must go beyond the boundaries of RIKEN as well. I plan to take a fresh look at how we recruit researchers. Typically, laboratory heads look for good researchers within their area of speciality. While these new hires can flourish and produce outstanding results, the field as a whole stagnates. As president, I will encourage our laboratory heads to recruit talented researchers from outside their own disciplines—even extending to people who work in the humanities and social sciences. Essentially, all science springs from a single tree trunk. By encouraging crosstalk between the many branches of science, we will contribute to a new and sustainable civilization.

Engineering plants

Jo-Ann Chuah

Postdoctoral Researcher

Enzyme Research Team
RIKEN Center for Sustainable Resource Science

Please describe your current research.
The Enzyme Research Team seeks to develop functional materials. I am contributing to this goal by studying the structural and biological properties of biopolymers to design peptide-based vectors that can deliver foreign genes to plant cell compartments through a process known as transgenesis. The resultant transgenic plants could be used in the large-scale production of valuable chemicals for the pharmaceutical industry. By developing a simple, reproducible and efficient method for generating transgenic plants, I hope to bring us closer to establishing such biofactories.

How did you become interested in this field?
Peptides are naturally occurring molecules that regulate a wide range of biological processes. Synthetic peptides have also been engineered for use in applications such as adhesives and cosmetics. I find it fascinating to work with these versatile building blocks and tailor their properties to perform different functions.

What excites you the most about your current research?
Recently, my colleagues and I devised a simple peptide-based vehicle that could effectively introduce plasmid DNA to the mitochondria of living plants. Other members of our team have used peptides to successfully transport genetic material across cellular and subcellular membranes. Simply by linking different amino acids together, we can create peptide chains with specialized characteristics. I am excited about exploring the endless combinations to create new tools that can perform many functions in living systems.

What made you decide to become a scientist?
I have always been interested in science. As a teenager, I was engrossed by television shows of sharp-eyed forensic scientists collecting evidence or analyzing samples using high-tech gadgets to put criminals behind bars. In the first year of my undergraduate degree, I took a course on recombinant DNA technology, which convinced me to take up a career in science.

What has been the most interesting discovery in your field recently?
Recently, a team of researchers announced that they had engineered rice plants to carry out photosynthesis more efficiently, which could substantially increase crop yields to feed a rapidly growing population. I am eager to see how the technology we have developed can be applied to plant genetic engineering, and where it will take us.

> *I hope to bring us closer to establishing large-scale biofactories.*

What is the best thing about working at RIKEN?
The RIKEN Yokohama Campus operates a shared facility that houses a 900-megahertz nuclear magnetic resonance spectrometer. I have used the remarkable instrument and associated expertise in my research to determine the atomic structure of peptides. I am greatly impressed by the access to such cutting-edge research facilities, sufficient funding and the freedom to choose our own research focus, even for junior researchers like myself.

What do you wish you had known before coming to RIKEN and Japan?
Coming from Malaysia, I wish I had known that I did not need to worry about the language barrier—it certainly has not affected my ability to make friends in Japan from day one.

Please tell us about your professional and personal goals.
My goal is to learn something new every day.

Finding treatments for leukemia

Fumihiko Ishikawa

Group Director and Chief Scientist

Laboratory for Human Disease Models
RIKEN Center for Integrative Medical Sciences

Please describe your current research and its importance.
My laboratory researches blood cell production, immunity and leukemia in humans, with the goal of establishing effective therapies. We have used hematopoietic stem cells derived from humans to develop mouse models of blood cell production and immunity, which have enabled us to analyze how these systems develop and function. We have also succeeded in introducing human leukemia to immunodeficient mouse models, systems that provide vital information for overcoming the intractable cancer.

> *I spent my days and nights caring for patients suffering from various blood diseases and cancers.*

How did you become interested in the field?
I started my career as a clinical hematologist–oncologist, spending my days and nights caring for patients suffering from various blood diseases and cancers. Sadly, even with the best treatments available at the time, many of my patients succumbed to leukemia or other malignancies. I was torn between wanting to continue to support patients directly through, perhaps incomplete, therapies, and desiring to contribute to the discovery of more effective treatments for cancer. It was a tough decision, but I eventually decided to transition from clinical practice to research.

What has been your most exciting discovery?
Through cross-disciplinary collaboration, we identified a small molecule that targets kinases expressed in human leukemia stem cells. By introducing the compound to our mouse models of leukemia, we were able to almost completely eliminate the cells of a subtype of leukemia. We were very excited by the striking therapeutic effect and are currently working to develop the compound into a drug that can be used to treat patients.

What has been the most interesting development in your field in recent years?
Genomic studies have demonstrated the presence of multiple mutations in leukemia patients. Some of these mutations seem to appear as people age, regardless of the type of disease they acquire. We are now trying to decipher the heterogeneity and complexity of leukemia by developing mouse models of patient-specific disease. We are also working with scientists who specialize in genomics, epigenetics and protein science to understand the link between molecular events and clinical outcomes.

What is the best thing about working at RIKEN?
The support we receive from those within and outside the institution. Our research would not have progressed without the cooperation of many scientists and laboratories, as well as administrative staff who help with hiring, contracts, patents and laboratory safety. We also benefit from direct interaction with specialists who develop advanced technologies such as flow cytometry, high-performance computing and next-generation sequencing to suit our research needs. Of course, we could not conduct our research without the help of clinical collaborators and patients who provide invaluable samples.

Please tell us about your professional goals.
My goal is to develop safe and effective therapeutics that help save the lives of leukemia patients. During my nine years at RIKEN, I have come closer to achieving this goal and will continue to strive to support patients who are awaiting effective treatments for complex diseases. ■

Careers at RIKEN

For further information, visit our Careers page:
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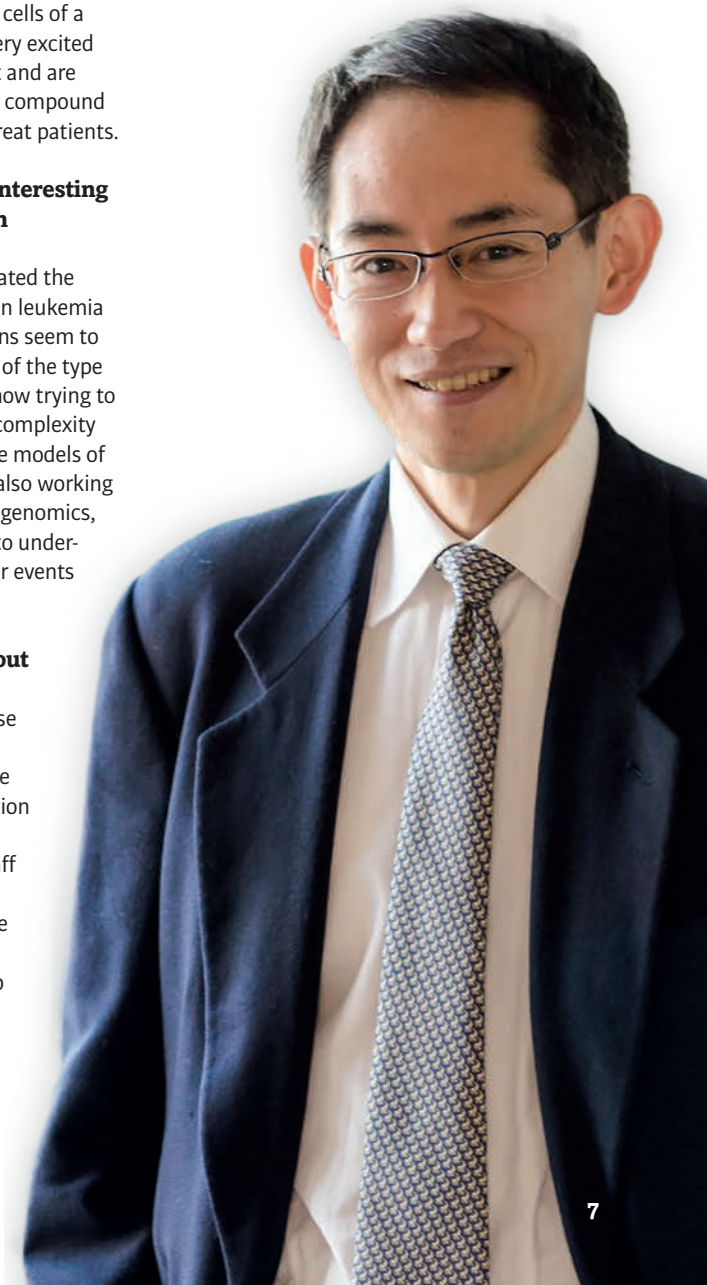


Supercomputer HOKUSAI's great wave

On 1 April 2015, RIKEN launched the supercomputing system HOKUSAI GreatWave, designed to support research at the institute in physics, chemistry, biology and medical science. The supercomputer is named after Japanese artist Katsushika Hokusai, who is best known for his woodblock prints made in the *ukiyo-e* style. Hokusai's most famous artwork depicts an enormous wave raging off the coast of Kanagawa—a piece that inspired many impressionist paintings and musical compositions, including *La Mer* by French composer Claude Debussy.

HOKUSAI GreatWave is based at RIKEN's Wako campus and is operated by the RIKEN Advanced Center for Computing and Communication. The main system Massively Parallel Cluster has a great computing environment with 1,080 nodes (34,560 cores) that can together achieve a peak performance of just over a quadrillion floating-point operations per second (one petaflop). Air- and water-cooling systems are used to reduce its operating temperature.

GreatWave is the first of two HOKUSAI systems, which will replace their predecessor, RIKEN Integrated Cluster of Clusters, launched in 2009. The second is HOKUSAI BigWaterfall; it is expected to be launched in 2016.

accc.riken.jp/en/

The genesis of GENESIS

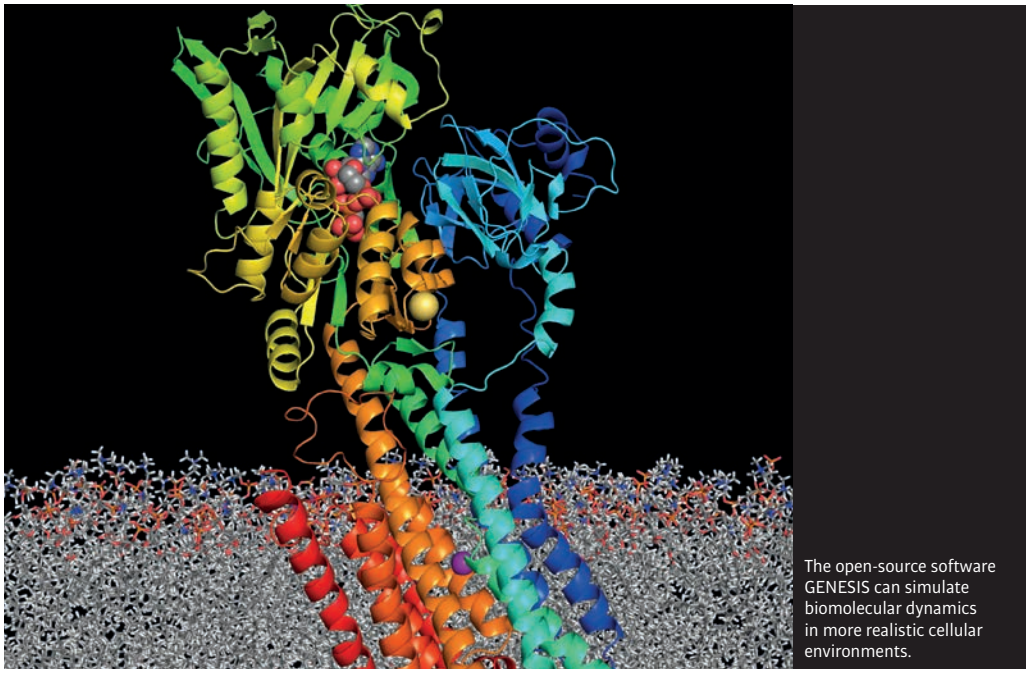
On 8 May 2015, the RIKEN Advanced Institute for Computational Science released GENESIS 1.0—software that harnesses the power of massively parallel supercomputers like the K computer to simulate complex biological processes.

Molecular dynamics simulations are vital for determining the fundamental properties of biological molecules like mRNA and proteins. But conventional computers and software cannot calculate the dynamics of these individual elements in large systems containing 10–100 million atoms such as whole-cell environments and over long time periods.

GENESIS (GENeralized-Ensemble SImulation System) is molecular dynamics modeling software that can perform simulations at different scales using coarse-grained and all-atom models. The system can be used to gain insights into the movement of proteins and RNA molecules in crowded cellular environments, protein stability and binding between proteins and ligands.

GENESIS has been released under the free and open-source license GNU General Public License version 2, and it can be accessed by registering online. A detailed user guide includes instructions on installing and using the software.

www.riken.jp/TMS2012/cbp/en/research/software/genesis/index.html



The open-source software GENESIS can simulate biomolecular dynamics in more realistic cellular environments.

25th anniversary of Special Postdoctoral Researcher Program at RIKEN

RIKEN celebrated 25 years of the Special Postdoctoral Researcher Program (SPDR) with a symposium in Tokyo on 22 April 2015. RIKEN President Hiroshi Matsumoto warmly welcomed researchers, alumni, program committee members and guests affiliated with the program. His address was followed by congratulatory messages from Yutaka Tokiwa, director general of the Research Promotion Bureau at the Ministry of Education, Culture, Sports, Science and Technology, and Masatoshi Koshiba, Nobel laureate and chairman of the Board of Directors of the Heisei Foundation for Basic Science, who served as the first chair of the SPDR screening committee.

Invited speakers gave presentations on the program's history, importance and future challenges. The speakers included three alumni, who shared their experiences of the program and its influence on their current work.

The plenary session followed with a reception featuring a *kagami-biraki* ceremony, in which a barrel of sake was broken open to share among the participants. The sake was made with a yeast strain that SPDR alumni Tomoko Abe bred using the heavy-ion accelerator at the RIKEN Nishina Center for Accelerator-Based Science.

www.riken.jp/en/pr/topics/2015/20150430_2/

Open Day at RIKEN

Close to 15,000 visitors attended RIKEN's annual Open Day, which was held in April 2015 at three campuses: Wako, Tsukuba and Harima. More than 7,000 participants in Wako, 1,500 in Tsukuba and 5,000 in Harima learned about the cutting-edge research and innovative technologies being developed at the institute.

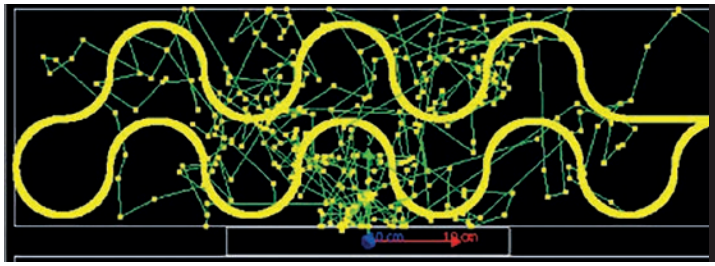
The newly installed supercomputing system HOKUSAI GreatWave made its first public appearance at Wako. Also, Hideki Hirayama of the Quantum Optodevice Laboratory gave a lecture on invisible, submillimeter electromagnetic waves known as terahertz radiation and high-efficiency deep-ultraviolet light-emitting diodes using aluminum-gallium-nitride-based semiconductor crystals, and their applications.

In Tsukuba, Yoichi Gondo of the Mutagenesis and Genomics Team at the RIKEN BioResource Center talked about genetics and biological resources. Children were shown the huge collection of bioresources stored at the center, including cells and plants. At display in Harima were the SPring-8 Synchrotron Radiation Facility and the SACLA X-ray Free Electron Laser Facility that in 2012 generated an x-ray laser beam with a wavelength of 0.06 nanometers—the shortest wavelength generated in the world.

openday.riken.jp

News

Space-tech-certified food



A Monte Carlo simulation used for differentiating isotopes.

Researchers at RIKEN and G-Tech Corporation have applied space technology to realize safe, cheap and rapid detection of radioactive cesium contamination in food. The Large Food Non-destructive Area Sampler, or LANFOS, released in March 2015, detects cesium levels independent of background radiation from naturally present radioactive potassium by using a lightweight plastic scintillator coupled to a silicon photomultiplier device first used in space-based observatories.

The low cost and power consumption of silicon photomultipliers make them a good choice for use in space and for producing the detector, says Marco Casolino from the RIKEN Global Research Cluster EUSO Team, who led the project.

The researchers tested a prototype on whole vegetables and fruit at a festival in Fukushima in November 2014. Farmers in the area have faced hardship due to consumer fears about contamination caused by the nuclear power plant accident in 2011. Measuring contamination in agricultural products was seen as the key to restoring public confidence, but earlier devices required food to be ground to pieces for accurate measurement. "[LANFOS] gave them hope that consumers might become more confident about buying their products," says Casolino.

www.riken.jp/en/pr/press/2015/20150309_1

Clearing the skies of space debris

Image courtesy of NASA

An international team of scientists has proposed a space-based system that can prevent valuable assets in space from being destroyed by centimeter-sized debris. "Our proposal is radically different from the more conventional approach that is ground based," says Toshikazu Ebisuzaki from the RIKEN Computational Astrophysics Laboratory who led the research published in *Acta Astronautica* in August 2015. He describes the system as an "accurate, fast and cheap" approach for clearing space of hazardous centimeter-sized garbage within five years of operation.

Space debris consists of spent satellites, rocket bodies and collision fragments produced by human space activities. Scientists track 500,000 pieces of junk orbiting the Earth, but millions more are too small to track, jeopardizing space development. The new system uses a telescope with a super-wide field of view to detect fast-moving objects near the International Space Station and hits them with an intense laser beam that slows them down and redirects them toward the Earth's atmosphere. The team plans to deploy a small proof-of-concept experiment on the International Space Station, eventually installing a full-scale version with a 100-kilometer range, or even a free-flyer mission orbiting at an altitude of nearly 800 kilometers, where the greatest concentration of debris is found.

www.riken.jp/en/pr/press/2015/20150421_2

Speaking less clearly to babies

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Contrary to popular belief, the cute, lulling singsong used to speak with infants sounds less clear than regular speech between adults, finds a team of researchers at the RIKEN Brain Science Institute and the Laboratoire de Sciences Cognitives et Psycholinguistique. "This finding is important because it challenges the widespread view that parents do and should hyperarticulate using very robust data," says Alejandrina Cristia, one of the French scientists.

As part of the study published in *Psychological Science* in March 2015, the researchers recorded speech samples of 22 Japanese mothers speaking both to their child and to an adult. They examined the 118 most frequent syllable contrasts in both the adult- and child-directed speech by measuring the acoustic similarity between any two syllables, like 'pa' and 'ba', or 'po' and 'bo'. The results were surprising: mothers spoke slightly less clearly when talking to their child than to the experimenter. "Our results suggest that, at least for learning sound contrasts, the secret to infants' language-learning genius may be in the infants themselves," said first-author Andrew Martin from RIKEN.

www.riken.jp/en/pr/press/2015/20150129_1

Robotic care bear

Scientists at RIKEN and the Sumitomo Riko Company have developed an experimental robot that can lift a patient out of bed and into a wheelchair—a strenuous task that nursing-care personnel perform 40 times a day on average.

Launched in February 2015, ROBEAR has the strength and appearance of a bear but the soft touch of a person. "We really hope that this robot will lead to advances in nursing care, relieving the burden on caregivers," says Toshiharu Mukai, who heads the RIKEN Robot Sensor Systems Research Team in Nagoya. As the elderly population in Japan continues to grow rapidly, researchers are developing robots to support healthcare professionals with difficult tasks. But no robots have been deployed in care facilities to date.

Weighing 140 kilograms, ROBEAR is half the weight of its predecessors RIBA and RIBA-II and exhibits superior control, dexterity and sensitivity. Its roller legs can extend to prevent falls and retract to fit through narrow doorways. And its joints move with exceptional speed and precision thanks to advanced actuators and sensors, including a tactile sensor made entirely of rubber to ensure that ROBEAR does not endanger patients with its strength. "We intend to continue with research toward more practical robots capable of providing powerful yet gentle care to elderly people," adds Mukai.

www.riken.jp/en/pr/press/2015/20150223_2

Research highlights

Administering interleukin-33 increased the number of T_{reg} cells in fat tissue in obese mice, improving glucose tolerance.

BIOLOGY

Controlling inflammation in fat cells

A signaling mechanism that controls inflammation in fat cells could offer a way to prevent obesity-induced diabetes

The excess fat tissue associated with obesity causes inflammation and reduces glucose tolerance, which increases the risk of diabetes. The mechanism responsible for these physiological effects, however, has been unclear. An international team including researchers from the RIKEN Center for Integrative Medical Sciences (IMS) has now identified a signaling pathway that is crucial for controlling obesity-associated inflammation[1], offering hope for a therapeutic target to prevent glucose intolerance.

The researchers focused on immune cells called regulatory T (T_{reg}) cells. These cells respond to inflammation and proliferate within inflamed tissue. "Whereas most T cells are activated by a specific antigen and induce inflammation, T_{reg} cells suppress inflammatory responses," explains Shigeo Koyasu from the Laboratory for Immune Cell Systems at the IMS.

Previous work by the Walter and Eliza Hall Institute (WEHI) of Medical Research in Australia showed that T_{reg} cells can be in either an activated state in which they suppress inflammation, or a resting state. In collaboration with the WEHI, Koyasu and his RIKEN colleagues searched for genetic differences between resting and activated T_{reg} cells. By analyzing gene expression in the two states, they discovered approximately 2,700 differences.

Interestingly, the researchers discovered that T_{reg} cells in fat tissue, known as visceral adipose tissue (VAT), expressed an exceptionally high level of a receptor called ST2 for the signaling molecule interleukin-33 (IL-33). By genetically manipulating the expression of ST2 in mice, the researchers showed that IL-33 signaling is crucial for the development of VAT-T_{reg} cells. When applied to cultured cells and injected into mice, IL-33 was found to induce the proliferation of VAT-T_{reg} cells, increasing their population by over ten fold.

"T_{reg} cells suppress inflammation, which improves glucose tolerance, so an increase in T_{reg} cells is beneficial," says Koyasu. "A lack of IL-33 greatly reduced VAT-T_{reg} numbers, resulting in impaired glucose tolerance. Administration of IL-33 restored glucose tolerance."

Finally, the team administered IL-33 to mice that were either genetically obese or obese owing to a high fat diet. In both cases, IL-33 increased the number of VAT-T_{reg} cells and improved glucose tolerance. The findings have therapeutic potential.

"Human T_{reg} cells in fat tissue also express IL-33 receptors, so it is possible that IL-33 could increase T_{reg} cells in humans," explains Koyasu. As a possible therapy, however, IL-33 comes with strings attached. "IL-33 also induces allergic inflammation, so it is critical to control the dose to avoid an allergic response while maintaining the ability to control VAT-T_{reg} cells." ■

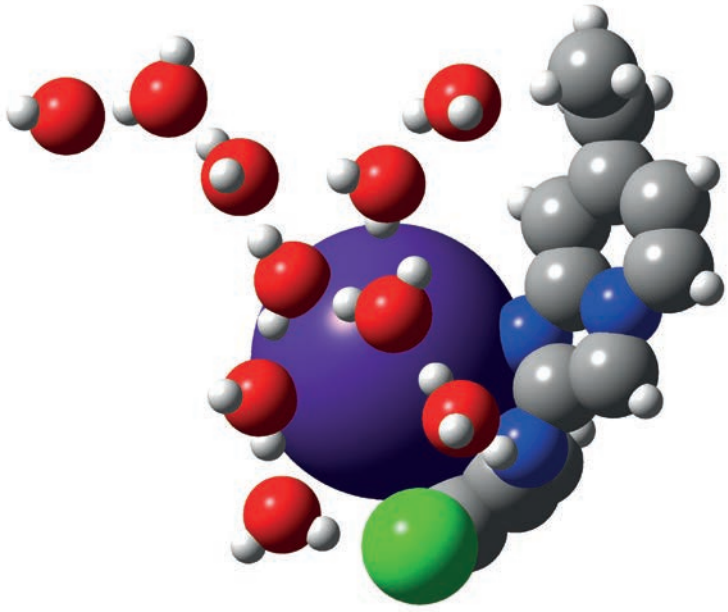
Reference

1. Vasanthakumar, A., Moro, K., Xin, A., Liao, Y., Gloury, R., Kawamoto, S., Fagarasan, S., Mielke, L. A., Afshar-Sterle, S., Masters, S. L. *et al*. The transcriptional regulators IRF4, BATF and IL-33 orchestrate development and maintenance of adipose tissue-resident regulatory T cells. *Nature Immunology* **16**, 276–285 (2015).

BIOLOGY | PRESS RELEASE

Protecting crops from radiation-contaminated soil

Compound found that blocks the uptake of radioactive cesium by plants



Quantum mechanical modeling indicates that CsTolen A (gray, white, blue and green spheres) will preferentially bind to cesium (purple sphere) in the presence of water molecules (red and white spheres) over other alkali metal ions, such as potassium and sodium.

Four years after the accident at the Fukushima Daiichi Nuclear Power Plant, contaminated farmland still has higher-than-natural levels of radioactive cesium in some regions of Japan. RIKEN researchers have now identified a chemical compound that hinders plants from taking up cesium, thus protecting plants—and people—from its harmful effects[1].

Cesium is readily absorbed by plants in contaminated soil because of its water solubility and chemical similarity to potassium, a critical plant nutrient. It competes with potassium in plant cells, disrupting physiological processes and retarding plant growth. Consequently, a group at the RIKEN Center for Sustainable Resource Science led by Ryoung Shin has been focusing on ways to prevent cesium uptake.

Using seedlings of the model plant *Arabidopsis thaliana*, the researchers tested 10,000 synthetic compounds to determine if any could reverse the harmful effects of cesium. They found five compounds that made plants highly tolerant to cesium.

The researchers then looked at how these five compounds—termed

CsTolen A–E—produced their effects. They found that when *Arabidopsis* was grown in cesium-containing liquid media with CsTolen A, more cesium remained in the liquid medium and much less was found in the plants. Importantly, the CsTolen A concentration needed for this effect did not prevent the plants from absorbing the potassium they need to grow. Further tests showed that CsTolen A prevented cesium from entering the roots.

Quantum mechanical modeling indicated that CsTolen A should preferentially bind to cesium in aqueous solutions (see image) over other alkali metal ions, such as potassium and sodium. This was confirmed by experimental results, which indicate that the effects of CsTolen A appear to be specific to cesium.

Most importantly, applying CsTolen A significantly reduced cesium absorption and resulted in greater growth for plants grown in cesium-contaminated soil.

"Our findings shed light on the possibility of using chemicals to prevent agricultural products from being contaminated," notes lead author Eri Adams. "Unlike other methods such as genetic modification, the use of chemicals is a powerful tool that can alter plant responses to the environment regardless of their species, which is especially true in the case of CsTolen A because it binds to cesium before it can enter the plants."

Not only will the current findings help plants, but by reducing the amount of radioactive cesium that enters them, they should also ensure the safety of agricultural products grown in contaminated soil. As decontaminating large areas of farmland is difficult, CsTolen A could prove a game saver for cesium-contaminated regions. ■

Reference

1. Adams, E., Chaban, V., Khandelia, H. & Shin, R. Selective chemical binding enhances cesium tolerance in plants through inhibition of cesium uptake. *Scientific Reports* **5**, 8842 (2015).

CHEMISTRY

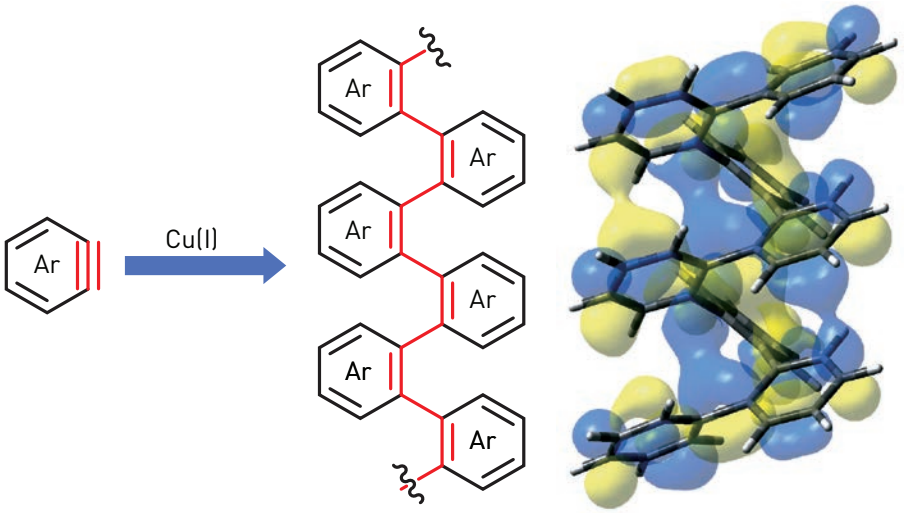
Finding the chemists' missing link

The construction of ordered nanostructures from benzene could pave the way for a revolution in nanotechnology

A way to link benzene rings together in a highly ordered three-dimensional helical structure using a straightforward polymerization procedure has been discovered by researchers from RIKEN Center for Sustainable Resource Science and the University of Tokyo[1]. "We expect our achievement to open up new areas of nanocarbon and materials science," says Koichiro Mikami from the research team.

Benzene (C_6H_6) is the simplest of the wide range of 'aromatic' compounds, which have rings of carbon atoms surrounded by 'delocalized' electrons that circulate around the molecules. A long-standing challenge for chemists has been the development of a straightforward way to link rings of benzene together in a regular manner such that the carbon atoms are bonded directly to their neighbors in adjacent rings to form a structured material.

Masanobu Uchiyama from RIKEN and the University of Tokyo and his colleagues Mikami and Yoshihide Mizukoshi developed their linking procedure starting with the molecule aryne, which is very similar to benzene but has a triple bond between two adjacent carbon atoms in the ring (see image). After investigating many different combinations of chemicals and solvents, the researchers found a procedure involving copper ions that reliably links the rings together at the *ortho* position by a self-propagating polymerization reaction.



Aryne (Ar) is reacted using a copper catalyst (Cu(I)) to assemble an ordered helical structure.

The product, called poly(*ortho*-phenylene), is the simplest member of a wide range of possible poly(*ortho*-arylene)s that could carry a selection of different atoms or chemical groups in place of one or more of the hydrogen atoms on the benzene-derived rings. The researchers found that their poly(*ortho*-phenylene) molecules have a regular and highly ordered three-dimensional structure consisting of stacked six-carbon rings. Such highly ordered materials are precisely the kinds of chemical building blocks that might be put to good use as components for nanotechnology.

Having made this crucial breakthrough, the researchers' next steps will be to explore the size and variety of structures that can be assembled by their technique. The team has so far managed to link approximately 100 rings together, but plans to extend this further and to control chain lengths and physical characteristics.

"We are exploring the electrical, photodynamic and thermal properties of these poly(*ortho*-phenylene)s toward creating novel electronic devices and liquid crystals," explains Mikami. In addition to providing scaffolding structures, nanocompounds become most interesting when they can respond to light, electric fields or the presence of other chemicals in precise and useful ways. Mikami says the team is also looking at forming chemical cross-links between individual helical chains, extending the fabrication possibilities to another dimension. ■

Reference

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PHYSICS | PRESS RELEASE

Time-lapse snapshots of a nova's fading light

X-ray images obtained 14 years apart provide a rare glimpse into nova and supernova explosions

For the first time, researchers have obtained detailed 'time-lapse' x-ray images of a classical nova, GK Persei—a binary star that exploded as a nova in 1901 (see image). The images promise to enhance our understanding of gas expansions in the Universe, including those in supernovae—tremendous stellar explosions believed to be responsible for creating heavy elements such as uranium.

Image of the nova GK Persei obtained by superimposing optical, radio and x-ray images.

X-ray: NASA/CXC/RIKEN/D. Takei *et al.*; Optical: NASA/STScI; Radio: NRAO/VLA

There is great interest in understanding the dynamics of stellar explosions, especially supernovae, which can outshine an entire galaxy. But since supernovae occur over enormous time spans, it is impossible to observe the whole process. Consequently, scientists have resorted to comparing snapshots of different supernovae believed to be in different evolutionary stages and to performing computer simulations.

"We wanted to understand how stellar explosions unfold, but there were many obstacles," says Dai Takei of the RIKEN SPring-8 Center, who led the research team. "Thus instead of looking at supernovae, we studied the expansion of a classical nova explosion, since this process is expected to develop within approximately a human lifetime." Although classical novae and supernovae are different processes, we see them through essentially the same fundamental mechanism—an explosion-induced shock wave.

"The GK Persei nova," Takei continues, "provided the perfect model for our study." It is believed to be a binary star consisting of a white dwarf—a dead star at the end of its thermonuclear phase—and a red-dwarf

companion that is still alive. Matter from the companion accretes onto the surface of the white dwarf, and occasionally, when it reaches a certain critical point, thermonuclear runaway starts, explosively ejecting the white dwarf layer outward.

The team examined x-ray snapshots of the nova taken in 2000 and 2013 by NASA's space-based Chandra X-ray Observatory and compared the x-ray emissions produced by the expanding gases heating the interstellar medium into a plasma.

The researchers found that although the nova remnant had expanded by approximately 90 billion kilometers during the 14 years, the plasma temperature remained at a nearly constant 1 million degrees Celsius. The light was fading, but the energy of the dominant photons had not changed, implying that the nova remnant is expanding into a lower density region. "For the first time, we have a detailed image of how the nova propagates through space," says Takei. "Through this kind of study, we hope to understand exactly how these powerful explosions expand into interstellar space, and it may ultimately give us new insights into the history of the cosmos." ■

Reference

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MATERIALS

Nanosheets line up to mimic nature

A composite material mimics the properties of natural cartilage by exploiting the repulsion of like charges

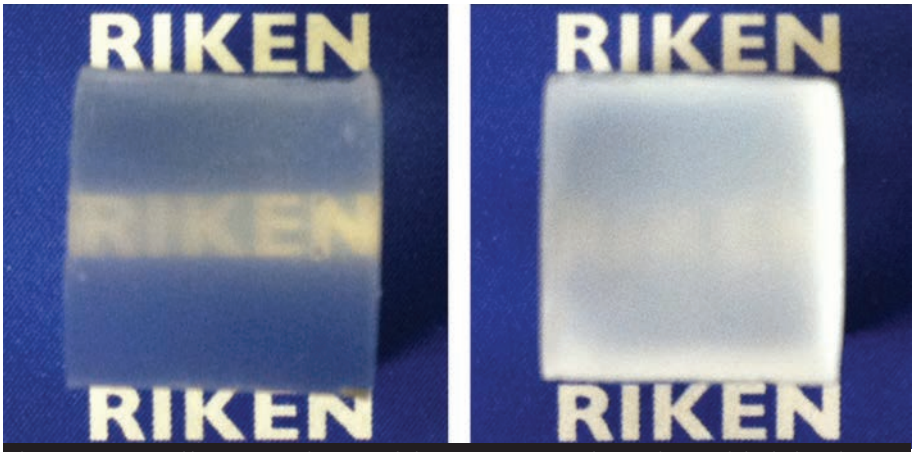
A soft material that mimics natural cartilage in that it is easily deformed by shear forces in one direction yet resists compressive forces applied in other directions has been developed by a team led by scientists from the RIKEN Center for Emergent Matter Science[1].

Cartilage is the solid but pliable tissue that allows joints to move with very low friction, but it has been difficult to replicate artificially. "The functions of biological materials have been acquired through evolution over the course of millions of years," explains Yasuhiro Ishida from the research team at RIKEN. "We hope to develop soft materials with functions similar or even superior to their natural counterparts."

Ishida and his co-workers developed a hydrogel—a crosslinked polymer that entraps a large amount of water yet retains a relatively firm structure—containing titanate nanosheets. These nanosheets have a very large aspect ratio, being less than a nanometer thick but about 10,000 times wider, and the nanosheet surfaces are highly negatively charged. This charge gives rise to electrostatic repulsion between the sheets, causing them to disperse readily in the hydrogel.

When placed in a magnetic field, the titanate nanosheets align face-to-face, parallel to the magnetic field—an alignment that differs from that of other metal oxides. The ordering can then be fixed in place by the formation of a crosslinked hydrogel around the nanosheets. Although the alignment direction of the nanosheets can be confirmed using techniques such as transmittance spectroscopy and x-ray diffraction, the alignment is actually apparent to the naked eye—viewed along the direction of the applied magnetic field, the material is opaque, but from other directions it is highly transparent (see image).

Materials design has often exploited attractive forces between oppositely charged components to improve material strength. The use of repulsive forces as in this titanate nanosheet hydrogel is rare but in this system affords some potentially useful applications, such as artificial cartilage.



The composite material has properties that vary with direction. Here, a RIKEN logo can be viewed clearly through the material from two directions, whereas the material is opaque when viewed orthogonally to the aligned titanate nanosheets.

"As people age," explains Ishida, "their cartilage becomes weak, and once someone begins to have difficulty walking, they quickly lose other abilities. The mechanical properties of this new material mimic those of natural cartilage, tolerating heavy loads vertically, but deforming easily horizontally. This anisotropic behavior is also maintained for a long time in physiological saline." To achieve the goal of developing a fully compatible artificial cartilage material, the research team is now working to improve the material's mechanical toughness, anisotropy and durability for long-term use. ■

Reference

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MEDICINE

Closing in on cancerous clusters

A switch that promotes the formation of signal-generating protein aggregates provides a promising therapeutic target for a subset of largely incurable blood cancers

Many blood cancers are associated with excessive activation of molecular pathways that fuel the proliferation of immune cells. Some particularly lethal lymphomas are driven by uncontrolled signaling via the transcription factor NF-κB in immune cells called B lymphocytes. Researchers led by Takashi Saito from the RIKEN Center for Integrative Medical Sciences and Hiromitsu Hara from Kagoshima University have now revealed a process that sets this activation in motion[1].

Previous work by the same research group had shown that NF-κB activation in immune cells might be driven by assembly of the protein CARMA1 into ring-shaped aggregates. These microclusters form near immunological synapses—structures at the cell membrane that enable communication between immune B- and T-cells and the antigen-presenting cells that direct the immune response. "We thought a structural analysis of CARMA1 might reveal how this protein is required for NF-κB activation and tumorigenesis," says Saito.

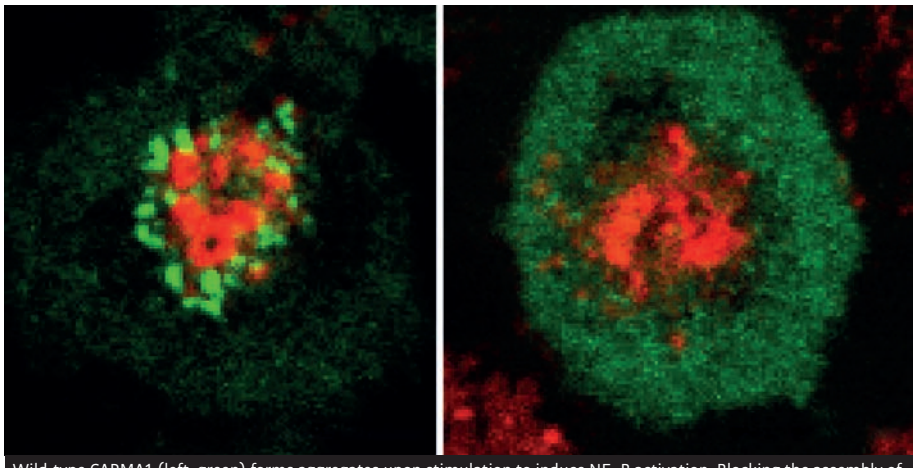
Hara and Saito focused on subdomains of CARMA1 that seemed likely to contribute to this aggregation process. As CARMA1 is part of a family of proteins that interact with other proteins via domains known as SH3 and GUK, the researchers performed an assay that allowed them to 'fish' for proteins that interact with either of these domains from CARMA1.

Remarkably, they found that these two domains bind directly to each other, implying that CARMA1 interacts with itself. Subsequent structural analysis suggested that although such self-interaction within a single protein molecule is CARMA1's preferred state, multiple CARMA1 molecules can also assemble with each other through SH3–GUK interactions.

Functional experiments showed that activation of immune cells via antigen receptors promotes CARMA1 microcluster assembly (see image) and NF-κB signaling. The interaction of SH3 and GUK was found to be essential for this activation, as was the 'hinge' domain that connects the two. The researchers hypothesize that this represents a switch that modulates whether CARMA1 molecules interact with themselves or with others.

"Our analysis indicated that CARMA1 has a closed structure in the resting stage and an open structure upon activation," notes Saito. "This open structure induces CARMA1 aggregation, which in turn induces NF-κB activation." Spontaneous CARMA1 aggregation with mutated CARMA1 can result in cancer through continuous NF-κB activation.

Drugs that lock this switch could therefore interfere with the hyperactivation observed in NF-κB-driven lymphomas. Accordingly, Saito and Hara are now examining the effects of impaired CARMA1 aggregation in animal models and exploring whether this interference might successfully halt tumor formation and growth. ■



Wild-type CARMA1 (left, green) forms aggregates upon stimulation to induce NF-κB activation. Blocking the assembly of SH3–GUK prevents the aggregation of CARMA1 (right) and hence stops NF-κB activation.

Reference

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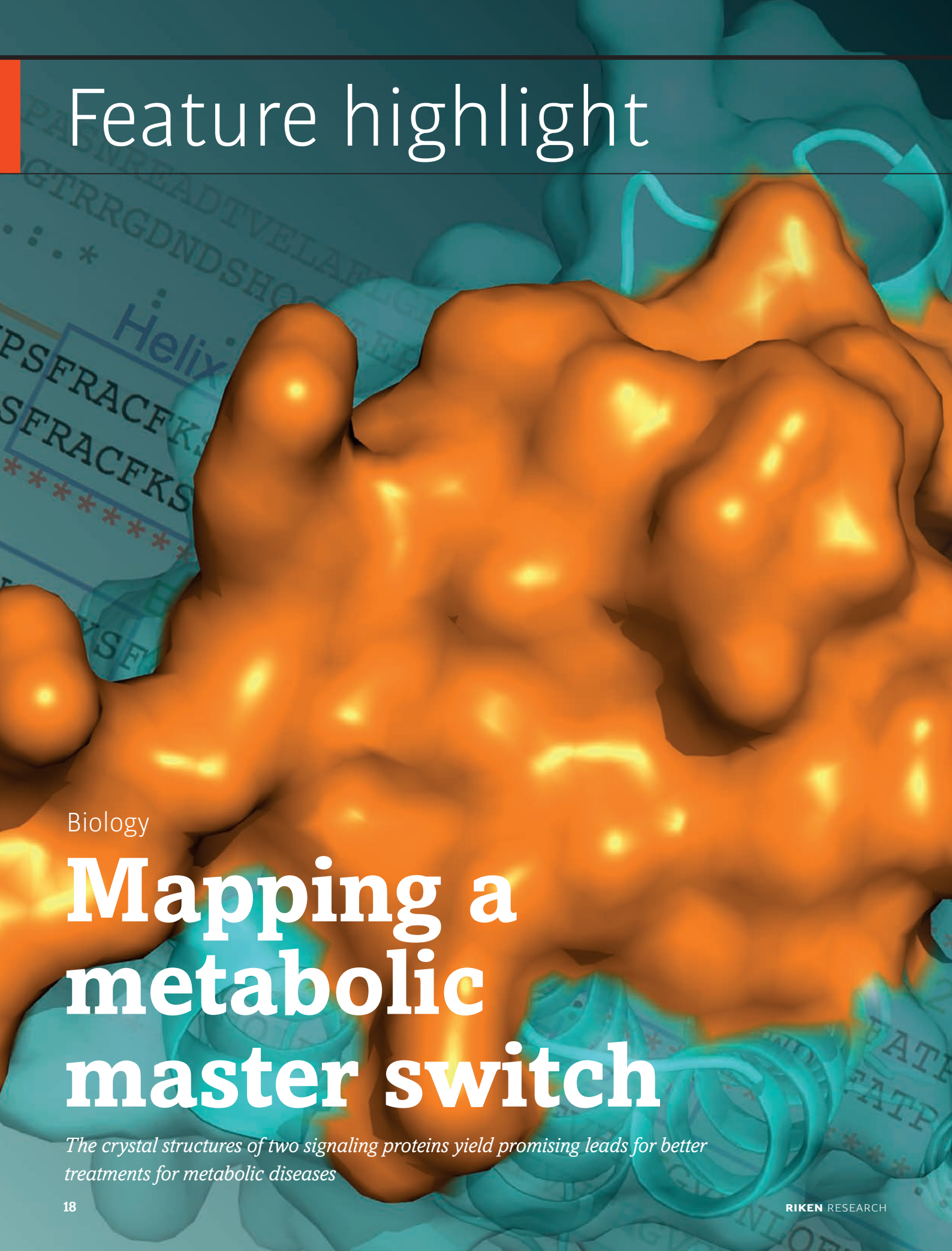
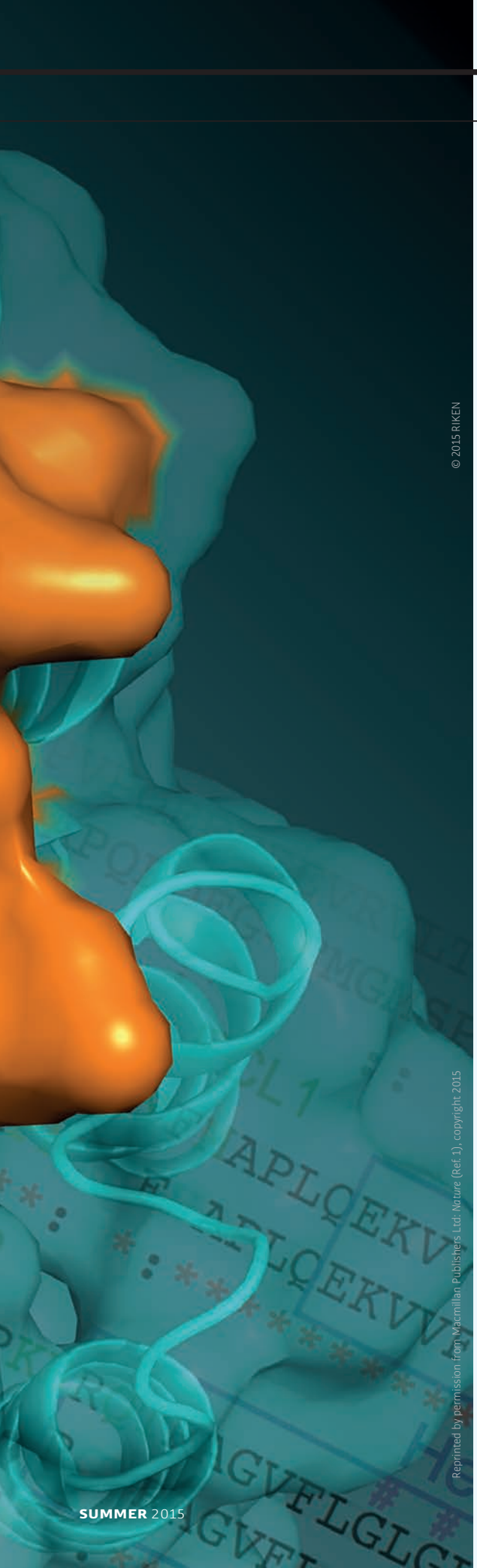


Biology

Mapping a metabolic master switch

The crystal structures of two signaling proteins yield promising leads for better treatments for metabolic diseases



A detailed structural analysis of a pair of unusual proteins involved in metabolism by a RIKEN-led research team gives valuable insight into a newly discovered class of receptors[1]. The results could help guide the development of drugs that more effectively target the physiological processes underlying diabetes and obesity.

The protein adiponectin is secreted into the bloodstream by fat cells and subsequently binds to receptors in the muscle, liver and other tissues to initiate physiological processes such as sugar and fat metabolism. Adiponectin triggers these responses through two different receptors, AdipoR1 and AdipoR2, which have recently emerged as appealing drug targets.

"AdipoR1 and AdipoR2 are key molecules associated with metabolic syndrome," explains Shigeyuki Yokoyama, director of the RIKEN Structural Biology Laboratory. Indeed, scientists have already uncovered at least one drug candidate that can act on these receptors and has been shown to improve health and lifespan in diabetic and obese rodents.

AdipoR1 and AdipoR2 both penetrate the cell membrane. The external portion binds to adiponectin, and the internal portion interacts with cellular machinery (Fig. 1). These receptors contain the same seven-trans-membrane-helical architecture as an important class of proteins called G-protein-coupled receptors (GPCRs), which transmit signals critical in a variety of disease states. However, the adiponectin receptors are essentially 'backward' compared to GPCRs—the domain that faces into the cell in one family faces outside the cell in the other. This suggests that these proteins may differ considerably in their mechanism.

To better understand these receptors, Yokoyama's group teamed up with the researchers from the University of Tokyo who originally cloned AdipoR1 and AdipoR2, Takashi Kadowaki and Toshimasa Yamauchi. The joint team was able to generate extremely detailed structural models for both receptors, and learn more about how they interact with adiponectin.

Differences large and small

It is very difficult to convert highly dynamic membrane-bound proteins into the orderly crystals required for x-ray analysis, but Yokoyama and his colleagues were able to successfully employ some tricks that had previously proved useful for analyzing the GPCR structure. They trimmed off short segments of AdipoR1 and AdipoR2 that are particularly poorly structured, and used an antibody fragment that binds tightly to the exterior of the receptor to lock the protein into a more stable state. The resulting crystals were of sufficient quality to yield x-ray structures with a resolution of higher than 0.3 nanometers.

The data showed that the two receptors are much more than just 'backward GPCRs'. "We expected that the structures of AdipoR1 and AdipoR2 would be very different from those of GPCRs," says Yokoyama.

Shigeyuki Yokoyama

Shigeyuki Yokoyama was born in Tokyo, Japan, in 1953. He received his Bachelor of Science and PhD degrees from the University of Tokyo in 1975 and 1981, respectively, followed by five years of postdoctoral work. Yokoyama became an associate professor at the University of Tokyo's Department of Biophysics and Biochemistry in 1986 and a professor in 1991. In 1993, he joined RIKEN as chief scientist of the RIKEN Cellular Signaling Laboratory, later becoming project director of the Protein Research Group at the RIKEN Genomic Sciences Center. Between 2008 and 2013, Yokoyama directed the RIKEN Systems and Structural Biology Center and since April 2013 has been heading the RIKEN Structural Biology Laboratory as distinguished senior scientist.

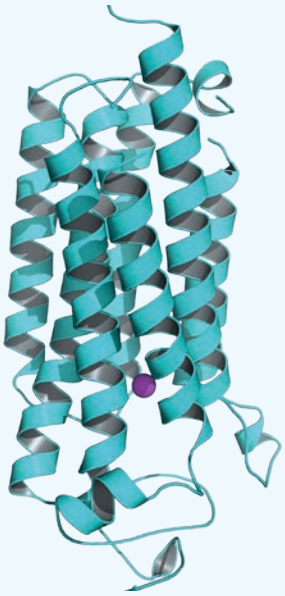


Figure 1: The structure of the AdipoR2 receptor, showing the intracellular (bottom) and extracellular (top) components, and the position of the zinc ion (purple).

"However, the structures we determined are completely new and surprising." Indeed, a search of other known protein structures revealed no obvious relatives to the two proteins, although the two receptors were highly similar to each other.

Among the most distinctive features of the adiponectin receptors is a cavity containing a zinc ion, situated deep within the inner membrane of the cell (Fig. 2). Yokoyama and his colleagues subsequently generated a series of mutants lacking the amino acids that hold this zinc ion in place. Although these mutations appeared to destabilize the AdipoR1 protein, they had a more notable effect on AdipoR2: altering just one of the four amino acids reduced adiponectin-mediated activation of gene expression, and multiple mutations essentially eliminated this activity. The researchers hypothesize that AdipoR2 may employ the zinc ion to directly catalyze the production of intermediary biomolecules that stimulate gene activation, and note that the large cavity surrounding this ion may facilitate the entry and exit of substrates.

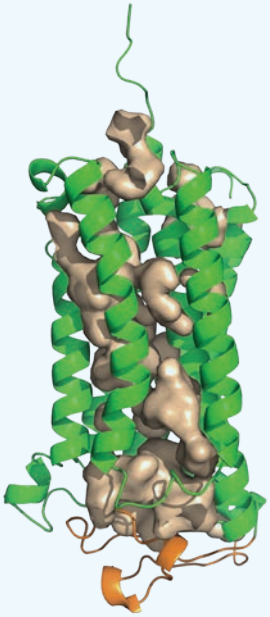


Figure 2: Both AdipoR1 (right) and AdipoR2 maintain immobilized zinc ions within cavities that lead deep into the protein (light brown).

Each of these receptors initiates a distinct series of downstream signaling events. Although the two proteins are largely similar in structure, the research team noted striking differences in the amino acid content of a particular intracellular segment. "This may be relevant to the difference in the downstream signaling pathways between these receptors," notes Yokoyama. The outward-facing adiponectin-binding sites, on the other hand, were highly similar, and the researchers identified multiple loops in the protein structure that may contribute to the recognition of this molecule.

From structure to function

Researchers have been able to develop a drug that can selectively bind and activate both AdipoR1 and AdipoR2, even in the absence of a detailed structural map. With the new structural details obtained by Yokoyama's team, however, it should be possible to generate even more effective therapeutic agents that are designed based on a more in-depth understanding of the atomic-scale interactions between adiponectin and its receptors. Yokoyama and his colleagues are now investigating how these structures can be translated into accurate functional models of adiponectin signaling. "One of our goals is to understand the activation mechanisms of AdipoR1 and AdipoR2," says Yokoyama. "Therefore, we would like to solve the structures of AdipoR1 and AdipoR2 in a complex with adiponectin."

These findings will be of significant interest to the research community as well as to scientists pursuing clinical applications. The mammalian adiponectin receptors have counterparts even in distantly related forms of life, including plants and yeast, suggesting that this newly characterized class of proteins has played a critical role throughout the course of evolutionary history. Although plants do not grapple with fat and blood sugar regulation, they appear to exploit a related signaling process for self-defense. "Plants secrete an antifungal protein, osmotin, which causes cell death in the yeast species *Saccharomyces cerevisiae* by acting on its version of AdipoR," says Yokoyama. Intriguingly, osmotin can also exert anti-obesity effects by acting on human AdipoR1 and AdipoR2, and his group will also be characterizing how these receptors interact with this protein in comparison to adiponectin. ■

Reference

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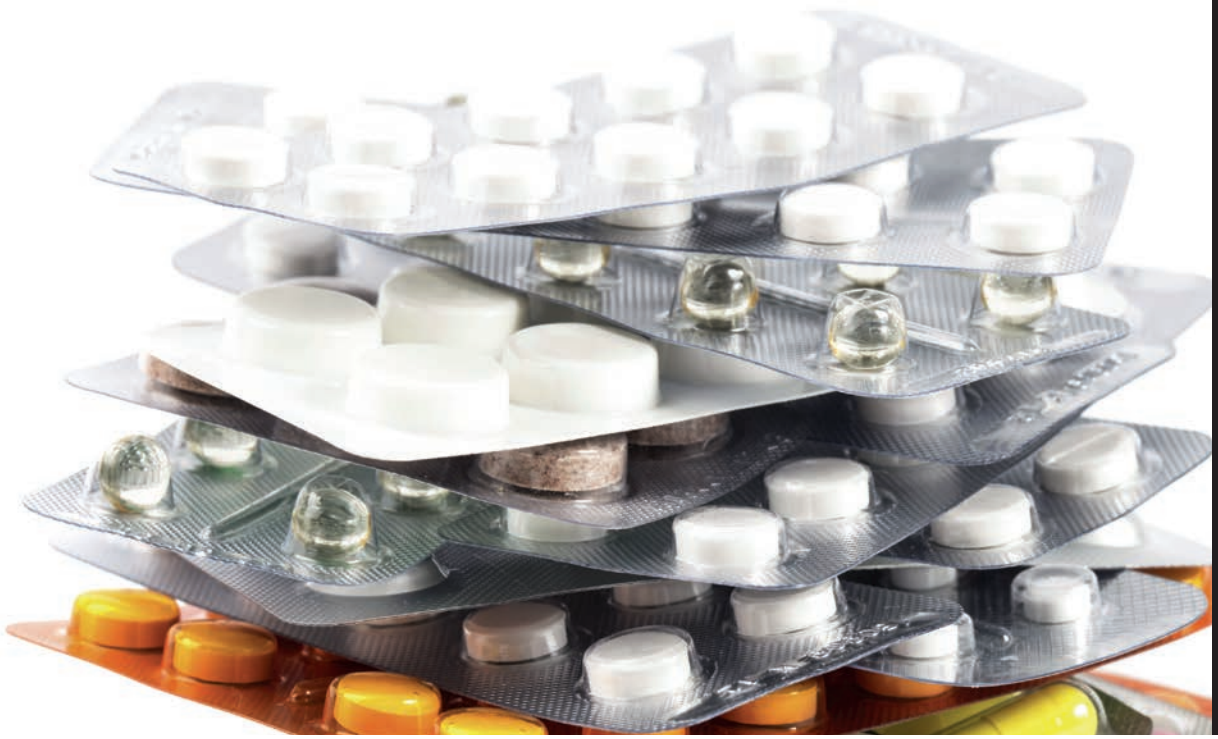

Surveys of gene expression changes could help scientists understand the processes by which bacteria evolve resistance to antibiotics.

BIOLOGY

Getting to the roots of resistance

In-depth genetic profiling reveals some of the processes by which bacteria acquire resistance to various antibiotics

A detailed examination of genetic changes in antibiotic-resistant *Escherichia coli* bacteria by researchers from the RIKEN Quantitative Biology Center has shed new light on inherited drug resistance in bacteria[1]. The findings could one day help scientists prevent resistance from emerging during infection.

Antibiotics can decimate bacterial populations, but some microbes acquire genetic differences that provide a slight survival edge. These lucky few can subsequently produce descendants with fully fledged resistance. This can be a relatively simple process in which bacteria acquire mutations that alter a particular protein targeted directly by a given drug. However, recent evidence suggests that bacteria may become resistant through a variety of mechanisms.

Chikara Furusawa and his RIKEN colleagues are deeply interested in understanding such evolutionary processes. "One reason for this study is the emergence of multidrug-resistant bacteria, which are a serious problem for global public health," he says. "Developing ways to control the evolutionary dynamics of bacterial cells is important for this problem."

The researchers treated *E. coli* cultures with 11 different drugs representing a variety of antibiotic mechanisms, and then isolated and cultivated multiple bacterial strains that manifested resistance to each drug. After three months, they re-tested the newly evolved resistant strains against the original drug and also examined how these cells responded to dozens of other antibiotics. In many cases, strains acquired cross-resistance to multiple drugs that work in a similar fashion, but some resistant strains also became increasingly vulnerable to other classes of drugs.

The team delved deeper, analyzing differences in gene expression patterns for all of these drug-resistant strains. The results confirmed that resistance is acquired through changes in the activity of multiple genes, although these adaptations proved less

extensive than expected. "The changes in the expression profile in the resistant strains were represented by only a small number out of thousands of genes," says Furusawa.

Importantly, these gene expression data also allowed the researchers to identify patterns that are predictive of cross-resistance or cross-susceptibility to other drugs. Their analysis revealed numerous 'repeat offenders'—genes and pathways routinely associated with resistance to a particular class of drug, or even multiple types of antibiotics. However, DNA sequencing also showed that bacteria may follow many different evolutionary roads to reach the same resistance endpoint.

"Our preliminary data suggest that the acquisition of antibiotic resistance cannot be completely explained by genetic alternations," notes Furusawa, whose group is now exploring some of the 'epigenetic' processes that help pathogens elude destruction. ■

Reference

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BIOLOGY | PRESS RELEASE

Cells target giant protein crystals for degradation

A crystal that grows rapidly in living cells permits in-cell analysis of proteins

A fluorescent protein that rapidly assembles into large crystals inside living cells has been engineered by researchers at the RIKEN Brain Science Institute. They also found that cells actively targeted the crystals for degradation.

The unprecedented size and purity of these crystals allowed the scientists to analyze the protein's structure directly within the intact cell. They could observe the crystallization process and the cell's responses in real-time, potentially transforming the production and study of protein crystals.

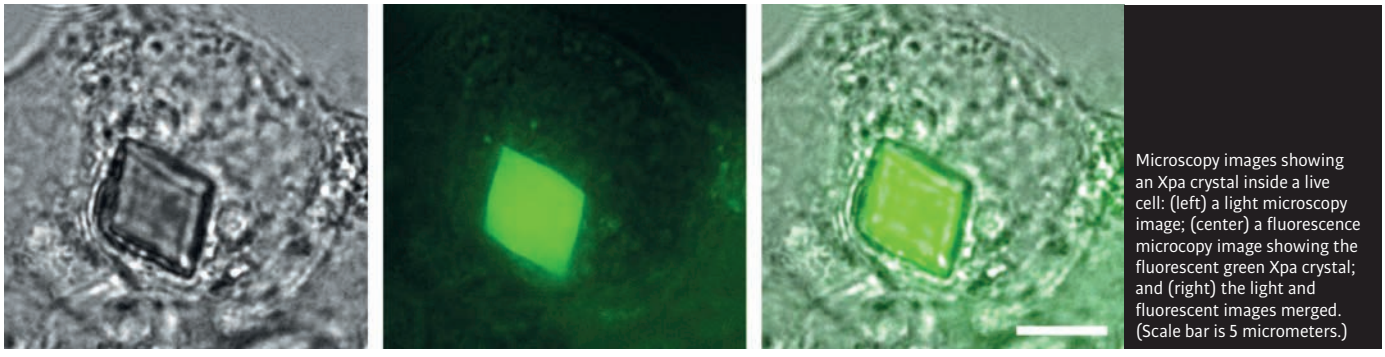
The team led by Atsushi Miyawaki genetically engineered a fluorescent protein that can rapidly self-assemble into well-formed single crystals in living mammalian cells, based on a sample of a fluorescent coral from Okinawa, Japan[1].

They isolated the gene encoding the green fluorescent protein, called KikG, and tweaked its structure so that it changed from green to red when illuminated by light of a particular wavelength. The resulting mutant protein is called KikGR. During further mutation of KikGR, the researchers surprisingly observed the emergence of large, micrometer-sized fluorescent crystals in the cells used to make the proteins, which they named Xpa (see image).

Before crystallization, the Xpa proteins are distributed evenly throughout the cell, but once crystallization commences Xpa proteins are rapidly recruited into the growing crystal.

According to Miyawaki, "This was quite a fortuitous discovery, because the ability to crystallize proteins makes it possible to determine their atomic structure." Normally, creating a crystal big enough for analysis requires weeks or months, and sometimes no crystal forms. In contrast, the crystals appeared within minutes and were so pure that they could be examined directly within the cell. This is the first time this has been accomplished in animal cells, opening the door to analysis of protein structures directly inside cells.

A second intriguing finding was that the cells attempted to rid themselves of the crystals. The group discovered that the crystals were rapidly covered by a membrane structure, which usually efficiently breaks down proteins. However, because Xpa came from coral, the crystals could not be digested and remained in the cell.



Microscopy images showing an Xpa crystal inside a live cell: (left) a light microscopy image; (center) a fluorescence microcopy image showing the fluorescent green Xpa crystal; and (right) the light and fluorescent images merged. (Scale bar is 5 micrometers.)

Miyawaki believes there may be undiscovered protein crystals inside cells that may be beneficial or harmful to cells, but have been overlooked because they are not fluorescent. "There may be similarities between Xpa protein crystallization and the formation of pathogenic protein aggregates in diseases like Alzheimer's," says Miyawaki. "We hope to develop fluorescence detection systems for crystal growth to screen for molecules that affect the cell's response to pathogenic protein aggregates, with the hope that this will lead to medical advances in the future." ■

Reference

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PHYSICS

Shrinking x-ray pulses to the limit

RIKEN's free-electron laser could soon generate bursts of x-rays just a single wavelength long

An x-ray laser source proposed by Takashi Tanaka from the RIKEN SPring-8 Center could be capable of generating the shortest x-ray pulses possible[1]. Such a light source would allow physicists to observe never before seen details of physical systems, such as the movements of individual electrons within atoms.

"To be honest, it is not clear what kind of phenomena will be observed by such an ultimately short pulse," says Tanaka, "but we know that new tools are always followed by unexpected findings."

Conventional lasers can produce bursts of light just a single wavelength long, which last for mere femtoseconds. However, generating such 'monocycles' of x-ray light, which are a thousand times shorter, is a much harder challenge.

The x-ray free-electron laser (XFEL), called SACLA (see image), at the SPring-8 synchrotron facility produces some of the most intense x-ray beams available, which are already used to probe the properties of materials in amazing detail. In this facility, electrons accelerated to close to the speed of light are funneled through a series of magnetic fields that make the electrons 'wiggle' from side to side. This wiggle causes the electrons to emit x-ray light at each change in trajectory to produce an intense x-ray pulse. At ultrashort pulse lengths, however, the x-rays tend to overtake the electrons inside the XFEL, which prevents the electrons from building up the power needed to produce a usable pulse of light.

Tanaka developed a solution that produces a train of electron 'microbunches'. A seed pulse of monocycle laser light wiggles one of the microbunches, which then passes through magnetic fields that gradually increase its wiggle rate. With every turn, these electrons generate x-rays with a rising frequency.

As these x-rays speed away from the microbunch, they catch up with the next microbunch in the train and make them move in synchrony. A second set of magnetic fields

An x-ray pulse generation scheme developed for the SACLA x-ray free-electron facility (pictured) could produce the shortest possible x-ray pulses, just one wavelength long.

then forces the electron microbunch to generate more x-rays that pile up together into a single, intense, monocycle pulse.

By adjusting the timing between the electron beam and the x-rays, the system could generate high-power x-ray pulses just 1.6 wavelengths in length, lasting for 46 attoseconds. Feeding those x-rays back into the process as seed pulses would ultimately generate even briefer x-ray bursts with shorter wavelengths.

Tanaka notes that the equipment needed to build the system already exists at the SACLA facility, but the existing system will need major modifications to test his theory. ■

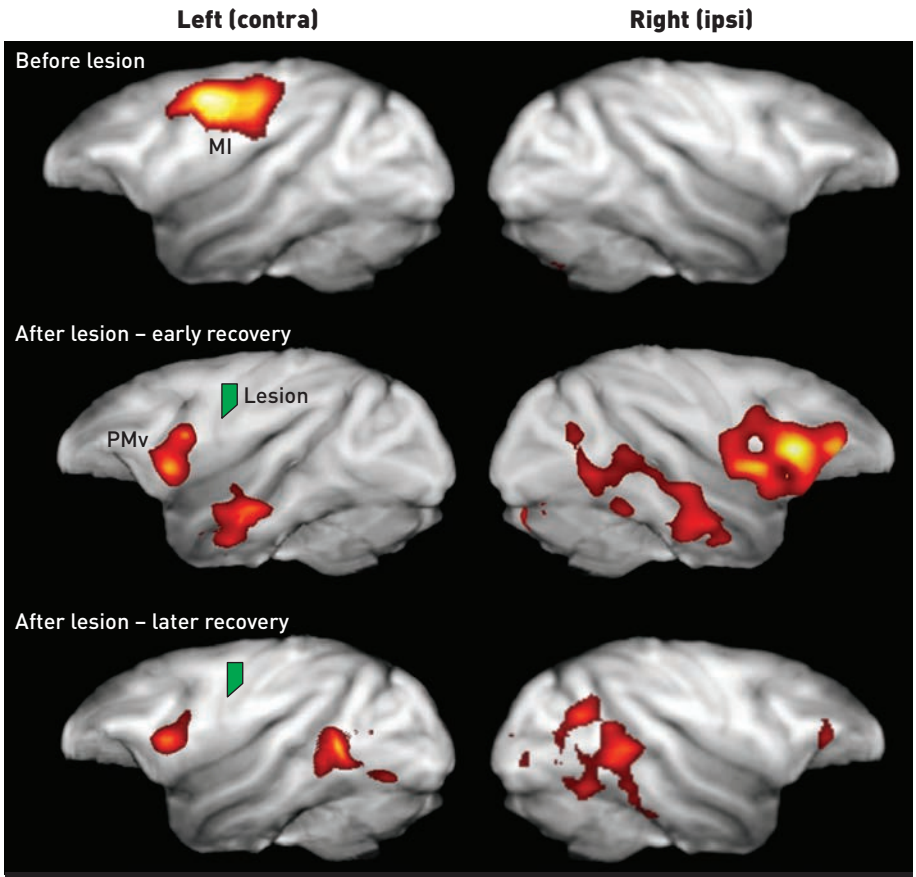
Reference

1. Tanaka, T. Proposal to generate an isolated monocycle X-ray pulse by counteracting the slippage effect in free electron lasers. *Physical Review Letters* **114,** 044801 (2015).

BIOLOGY

Watching rehabilitation rewire the damaged brain

Rehabilitation can recover precise movements lost through brain damage, but the brain has a roundabout way of doing it



Positron emission tomography imaging reveals that after damage to the primary motor cortex, motor control is recovered in the ventral premotor cortex.

A study in which movement of the fingers is lost, but then recovered through daily rehabilitation, reveals that different brain areas are important over time as motor function returns[1]. The finding by RIKEN researchers could help in the rehabilitation of stroke victims.

Hirotaka Onoe and his team from the RIKEN Center for Life Science Technologies, in collaboration with Yumi Murata and Noriyuko Higo from the National Institute of Advanced Industrial Science and Technology, examined macaque monkeys recovering from small lesions made to their primary motor cortex, called M1.

The researchers first trained four monkeys to grasp food through an aperture. A small region of the monkeys' M1 controlling the hand was then damaged, causing one hand to become flaccid. Immediately after this damage, the monkeys were unable to reach the food through the aperture, but after a month of daily training, the animals managed to get the food 80 per cent of the time. After two months, the monkeys were almost as dexterous as before the lesion (see image).

The experiment showed that despite permanent damage to that small region of M1, the monkeys recovered their motor function, presumably by using a different area of the brain.

To investigate how the brain was rewired to control the monkeys' grasp, the researchers

conducted positron emission tomography scans on two of the monkeys while performing the task. This revealed that the ventral premotor cortex (PMv) was very active, particularly one to two months after lesioning.

"The role of the PMv is not fully understood, but it has close connections with M1 and directly projects to the spinal cord. It is thought to plan, guide and control movement," says Onoe.

The team corroborated this result by temporarily knocking out the PMv in two other monkeys recovering from similar M1 lesions. While the PMv was incapacitated, the monkeys' recovery stalled, and they were once again unable to grasp the food.

"Because of its projection to the spinal cord," notes Onoe, "it seems relatively easy for the brain to adapt and use the PMv to control motor movement after an injury to the M1." Later in the recovery process, the researchers observed increased connectivity in the M1 area bordering the lesion. "This would require plastic changes of neurons neighboring the lesioned area, and that takes time," notes Onoe.

Although most strokes cause far more brain damage than the lesions in these experiments, Onoe observes that such models add incrementally to our understanding of stroke rehabilitation. ■

Reference

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MATERIALS

A light switch for superconductivity

A single layer of molecules allows an insulator to be turned into a superconductor using light

A device that can be switched between insulating and superconducting states by irradiation with light has been developed by researchers from RIKEN and the Institute for Molecular Science (IMS)[1]. The development could ultimately lead to more efficient superconducting microelectronics.

The properties of solid materials can be dramatically altered by applying an electric field. In a common electronic component called a field-effect transistor, the flow of electrons through a semiconducting channel is controlled according to the strength of an internal electric field, which is created by applying a voltage to an insulating material—a dielectric. Higher field strengths provide more efficient conduction, but at very high fields the dielectric material begins to break down and conduct itself.

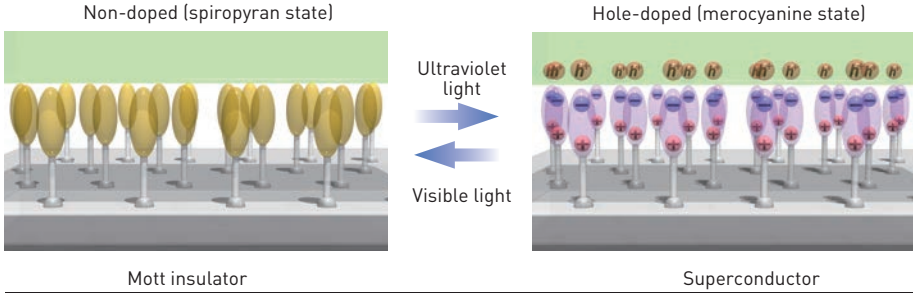
To overcome this limitation, scientists have turned to the use of ionic liquids. When a voltage is applied to an ionic liquid, the charged particles in the liquid move to the surface of the channel material, creating an 'electric double layer' (EDL) that is not susceptible to dielectric breakdown.

The high electric fields enabled by this technique have previously allowed researchers to convert the channel material from an insulator into a superconductor. So far, switching of the electric field has only been possible at relatively high temperatures because the ionic motion freezes at approximately 200 kelvin. Masayuki Suda and Hiroshi Yamamoto from the IMS and RIKEN, in collaboration with RIKEN's Reizo Kato, have now shown that a light-sensitive molecule can be used to switch on a superconducting state at temperatures as low as 5 kelvin.

The team replaced the ionic liquid with a single layer of spiropyran molecules, which are ionic under ultraviolet light and non-ionic under visible light. To test this strategy, they placed an organic crystal called κ-Br, which is known to have a superconducting state, on a single layer of self-assembled spiropyran molecules mounted on a thin oxide film. They confirmed that the resistance of the κ-Br switched from a high-resistance state under visible light to a low-resistance state when illuminated with ultraviolet light, due to the formation of an EDL (see image).

"Even at low temperatures, ultraviolet light induces a zwitterionic structure in spiropyran molecules and a situation very similar to an EDL without an applied voltage, leading to superconductivity," says Suda.

"In this system, light induces the superconducting state by photoisomerization of the spiropyran molecules," says Suda. "If we could get light to generate the superconducting carriers directly, other types of light-driven devices could also be possible." ■



Irradiating a thin crystal of κ-Br on a monolayer of spiropyran molecules with visible (left) and ultraviolet (right) light switches the κ-Br material between insulating and superconducting states due to the formation of an electric double layer.

Reference

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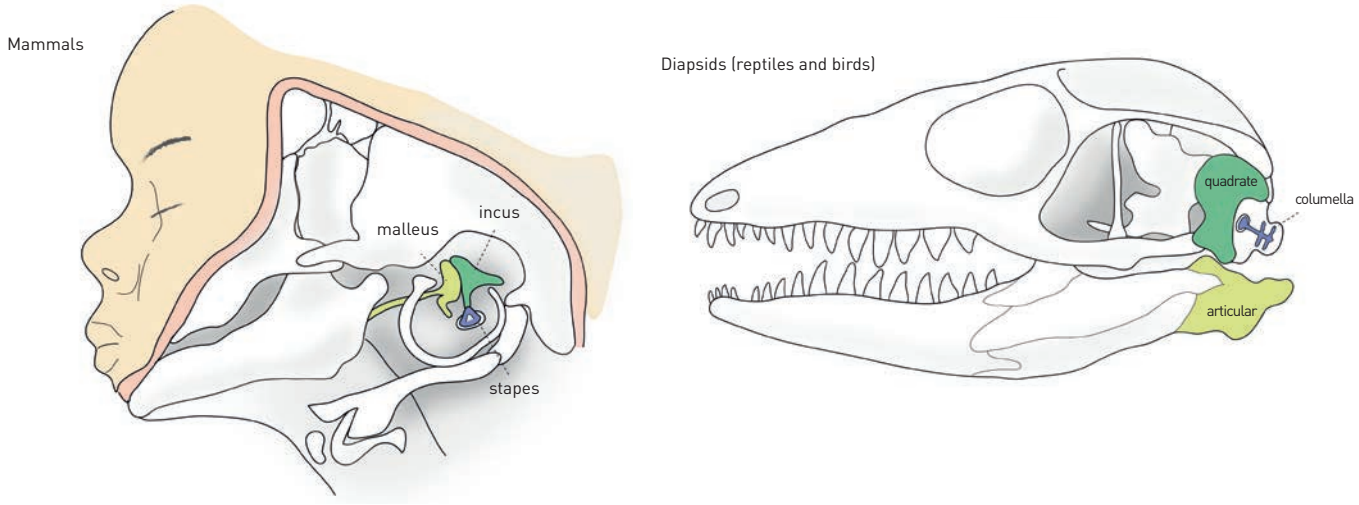
BIOLOGY | PRESS RELEASE

Look mom, no eardrums!

An evolutionary developmental biology study confirms suspicions that the eardrum evolved independently in mammals, and reptiles and birds



The fact that in mammals, the eardrum attaches to a bone derived from the lower jaw (left), whereas in diapsids it attaches to an upper jawbone (right), caused scientists to suspect that the eardrum evolved independently in these two groups.

The eardrum evolved independently in mammals and diapsids—the taxonomic group that includes reptiles and birds—find researchers at the RIKEN Evolutionary Morphology Laboratory and the University of Tokyo[1]. The scientists discovered that the mammalian eardrum depends on lower jaw formation, whereas that of diapsids develops from the upper jaw. Significantly, they borrowed techniques from evolutionary developmental biology—or 'evo-devo'—to answer a question that had long intrigued paleontologists.

The evolution of the eardrum and the middle ear enabled mammals, reptiles and birds to hear through air. While their eardrums are similar in appearance and function, the fossil record shows that the middle ears in the two lineages fundamentally differ.

Although scientists suspected that the eardrum developed independently in mammals and diapsids, they could not confirm this from the fossil record because the eardrum never fossilizes. So instead, the researchers turned to evo-devo. They noted that in mammals, the eardrum attaches to a bone derived from the lower jaw, whereas in diapsids it attaches to an upper jawbone (see image). Hypothesizing that eardrum evolution was related to these different jawbones, they manipulated lower jaw development in mice and chickens.

They examined eardrum development in mice having a condition that inhibits lower jaw development and found that the mice lacked eardrums and ear canals, showing that their development was contingent on lower jaw formation. They then blocked development of the lower jaw in chickens. This created duplicate eardrums and ear canals, with the additional set forming from upper jaw components that had developed within the malformed lower jaw.

To understand how the eardrum evolved twice and why it is associated with different jaw components, the researchers examined the expression and position of a marker for the primary jaw joint. They found that in mouse embryos, the marker is expressed in cells slightly below the first pharyngeal pouch, whereas it is expressed considerably lower in chickens. Consequently, the eardrum develops below the primary jaw joint in mammals and above the joint in diapsids.

While scientists are still unclear about how or why the primary jaw junction shifted upwards in mammals, the study shows that the middle ear developed after this shift and must therefore have occurred independently after mammal and diapsid lineages diverged. Emphasizing the importance of this evo-devo approach, Shigeru Kuratani, one of the researchers, notes that, "convergent evolution can often result in structures that resemble each other so much that they appear to be homologous. But, developmental analyses often reveal their different origins." ■

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Yoshihide Hayashizaki is director of the RIKEN Preventive Medicine & Diagnosis Innovation Program
Hayashizaki established the international research consortium FANTOM (Functional Annotation of the Mammalian Genome) in 2000, building on his work developing technologies to produce full-length cDNA libraries. He became program director in 2013.

Personalized medicine

Health, wealth and longevity

Faced with rapidly aging populations, societies need to adopt a more holistic approach to medicine that balances longevity with quality of life. Recent advances have provided researchers with tools to improve the diagnosis and treatment of diseases with unprecedented precision. RIKEN is bringing these technologies closer to hospitals, clinicians and ultimately patients.

The phrase 'the Japan syndrome' has often been used to describe socioeconomic upheavals unique to the island state, such as nuclear disasters, financial crises and reliance on grain imports. Recently, it has come to refer to the dramatic demographic changes Japan is facing and which also threaten nations globally.

Japan tops the list of the most aged countries in the world, with more than 30 per cent of its population over the age of 60 and an average life expectancy of almost 84. Combined with a low birth rate, this high life expectancy has seen the workforce shrink, slashing tax revenues needed to pay for ballooning social security expenses. In Japan, there are now only two working-age adults per elderly person, down from nearly six in 1990. And spending on medical care rose by almost USD 171 billion between 1995 and 2013, reaching 10.3 per cent of the gross domestic product.

Improved medical care offers many opportunities for alleviating the burden of this vicious demographic cycle by extending the number of active and healthy years available to an exploding elderly population. In this way, societies can benefit from increased productivity and economic growth. The RIKEN Preventive Medicine & Diagnosis Innovation Program (PMI) is driving advances in treatment and diagnosis by bringing the results of research at RIKEN in biology, physics, chemistry and engineering to the clinic.

Preemptive seven

Elias Zerhouni, former director of the US National Institutes of Health, first emphasized the necessity of shifting from curative to preventive medicine to maximize wellness at a national level. He argued for the need to manage the entire life cycle of a disease, from susceptibility and risk, to prevention, diagnosis, treatment and cure. Zerhouni identified four long-term goals, branded "the 4 'P's of medicine", of making medical care more 'predictive', 'personalized', 'preventive' and 'participatory'.

Recent large-scale studies of the genome and its many 'ome' derivatives, such as proteomics and metabolomics, together with other breakthrough technologies, have opened the possibility of adding three more 'P's—we can now strive to deliver 'precise' and 'preemptive' medicine at the 'point of care'. When executed together, these seven ambitious goals will lead to diagnoses and treatments that account for the unique biological characteristics of individual patients as well as those of different types of diseases. It will, for example, catch emerging malignancies earlier than before and consider inherited variations when prescribing drugs.

Precision medicine will intervene at the right time and place, taking snapshots of a patient's health that reflect their present state. Take influenza, for example, a common viral infection typically left to run its course of sniffles, fever and misery, which can rapidly deteriorate into more serious lung and brain infections. Dangerous complications can be prevented by precisely identifying the causative virus at the point of care.

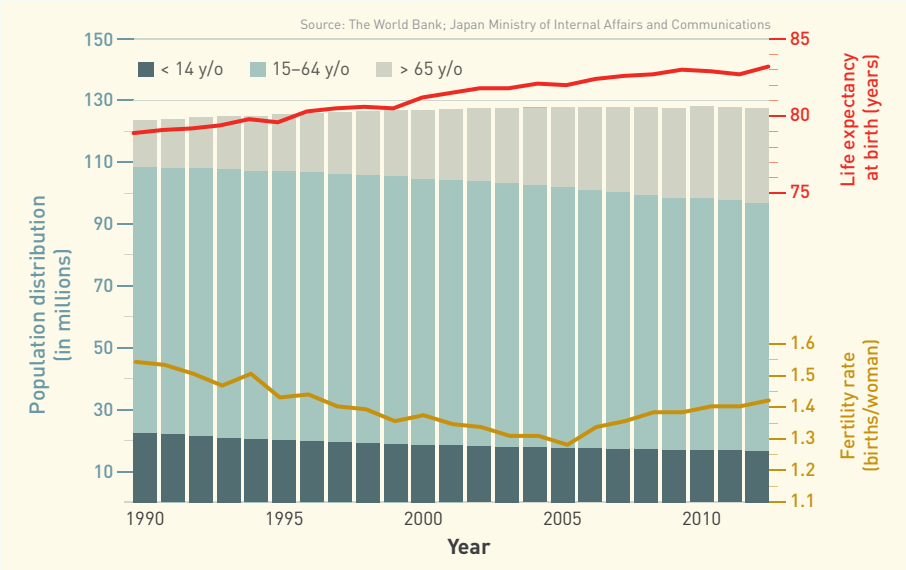
In 2009, a virulent strain of the influenza virus A (H1N1), or swine flu, spread across Japan and the world, causing about 18,000 deaths. While diagnostic tests were used to detect the virus, they proved unreliable during the early stages of infection. In 2012, researchers at the RIKEN Omics Science Center, the PMI's predecessor organization, developed the RT-SmartAmp assay, a simple, quick and sensitive method for clinically detecting swine flu within 24 hours of fever onset. The technique involves reverse transcribing a specific sequence of viral RNA into DNA and isothermally amplifying the complementary DNA strands—all in one reaction tube, in contrast to the two-step process of conventional polymerase chain reaction amplification. The technique could be applied to various other infectious diseases.

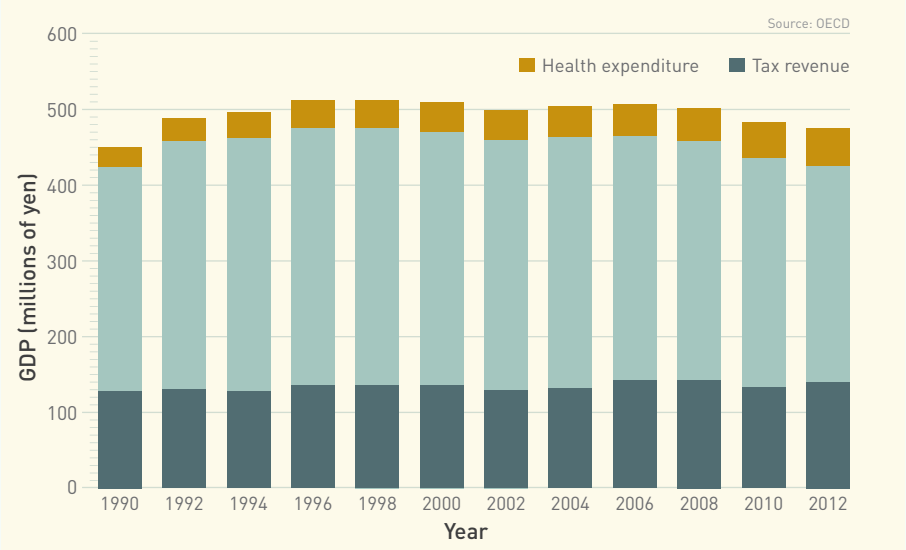
Omics prognostics

Immediate and accurate detection and diagnosis of many more diseases will soon be possible as omics research advances, allowing practitioners to spot unusual developments before they mature into debilitating diseases, and administer targeted treatments.

Sequencing the entire human genome has provided researchers with tremendous information about the genetic basis of disease. The field of genomics is saturated with scientists searching for correlations between specific diseases and germline mutations, which are passed down from generation to generation. Some genetic errors are associated with serious disorders, like the single-nucleotide swap in the β-globin gene that causes the production of sickle-shaped red blood cells. Other mutations increase the risk of acquiring a disease, such as the abnormal *BRAC1* gene that makes actress Angelina Jolie and thousands of others more susceptible to breast and ovarian cancers.

While genomics can provide important information about an individual's risk of succumbing to a disease, it offers only a static profile. Cells are teeming with activity. The expression of genes is closely regulated by short nucleic acid sequences





and proteins to ensure proper cell development, differentiation and homeostasis. These regulatory mechanisms can vary between the nearly 400 distinct cell types in the body.

Scientists are only just beginning to identify the many elements of this regulatory process, which include promoter and enhancer sequences of DNA, enhancer RNA, messenger RNA, microRNA sequences and long non-coding RNA that facilitate protein translation. These discoveries have opened up new areas of research.

FANTOM5's interdisciplinary approach

PMI researchers are leading these efforts through their contributions to the research consortium established in 2000, named FANTOM (Functional Annotation of the Mammalian Genome).

FANTOM takes a multi-omics approach, integrating large-scale analyses of the genome with maps of transcripts, transcription factor proteins, promoters[1] and enhancers[2] to develop new biomarkers of disease. The fifth edition, FANTOM5, now provides proteome, transcriptome, promotome and enhancerome analyses for 180 mammalian cell type.

In one of many potential applications of these cell-specific expression profiles, a team of researchers, including Masayoshi Itoh and Hideya Kawaji affiliated with the PMI, are developing biomarkers to specifically tag corneal endothelial cells derived from induced pluripotent stem cells. Corneal endothelium is crucial for maintaining transparency in the eye's outer layer. The technique could be used in the regeneration and surgical transplantation of corneal endothelium into patients with damaged corneal tissue due to injury or inherited degenerative diseases such as Fuchs' Dystrophy.

Recently, the FANTOM5 consortium and an international team of researchers, including Itoh, Kawaji and Jun Kawai at the PMI, identified associations between common diseases and single-nucleotide errors in non-protein-coding enhancer regions—mutations previously overlooked by researchers focusing primarily on the protein-coding segments of DNA. They also found a disproportionately high number of mutations in enhancers predominantly expressed in pathologically relevant cell types. The researchers were then able to link abnormal enhancer activity to disorders primarily found in that type of cell, such as Grave's disease and thyroid tissue, or chronic lymphocytic leukemia and lymphocytes.

In a separate study on transcribed enhancer sequences known as enhancer RNA, FANTOM5 researchers concluded that enhancer RNA molecules are the first to become active in a wave of transcriptional activity that occurs when cells differentiate into more specialized states.

A crucial factor of FANTOM's success has been its interdisciplinary approach. The consortium brings together more than 500 researchers from 20 countries with expertise in areas as far-reaching as molecular biology, bioinformatics and engineering. The PMI is replicating this strategy to introduce precision technologies enhanced by omics to research laboratories and hospitals.

From lab to patient

As Japan's largest research institute, RIKEN is uniquely positioned to address the multifaceted needs of researchers, clinicians and the medical industry.

To identify linkages across disciplines and encourage the sharing of ideas and learning across the institute, the PMI conducted an institution-wide survey of 400 research projects and 39 principal investigators. The initiative led to 90 new projects and two PMI research units embedded in the RIKEN Center for Life Science Technologies and the RIKEN Advanced Center for Computing and Communication.

After identifying the critical needs of research, the PMI has gone on to investigate the demands of practice by conducting hundreds of in-depth interviews with clinicians at Juntendo University Hospital and several other universities in Japan. Doctors were asked to reflect on the seven 'P's and to specify the kinds of information, tools and equipment that could improve diagnostics, therapeutics and data management in their fields. The PMI is now mining these statements to develop innovative research projects at RIKEN, which could lead to some of the safest hospitals in the world.

With sharper physiological profiling, earlier disease recognition, targeted treatment and faster recovery, people in rapidly aging societies will enjoy longer, healthier and more productive lives. ■

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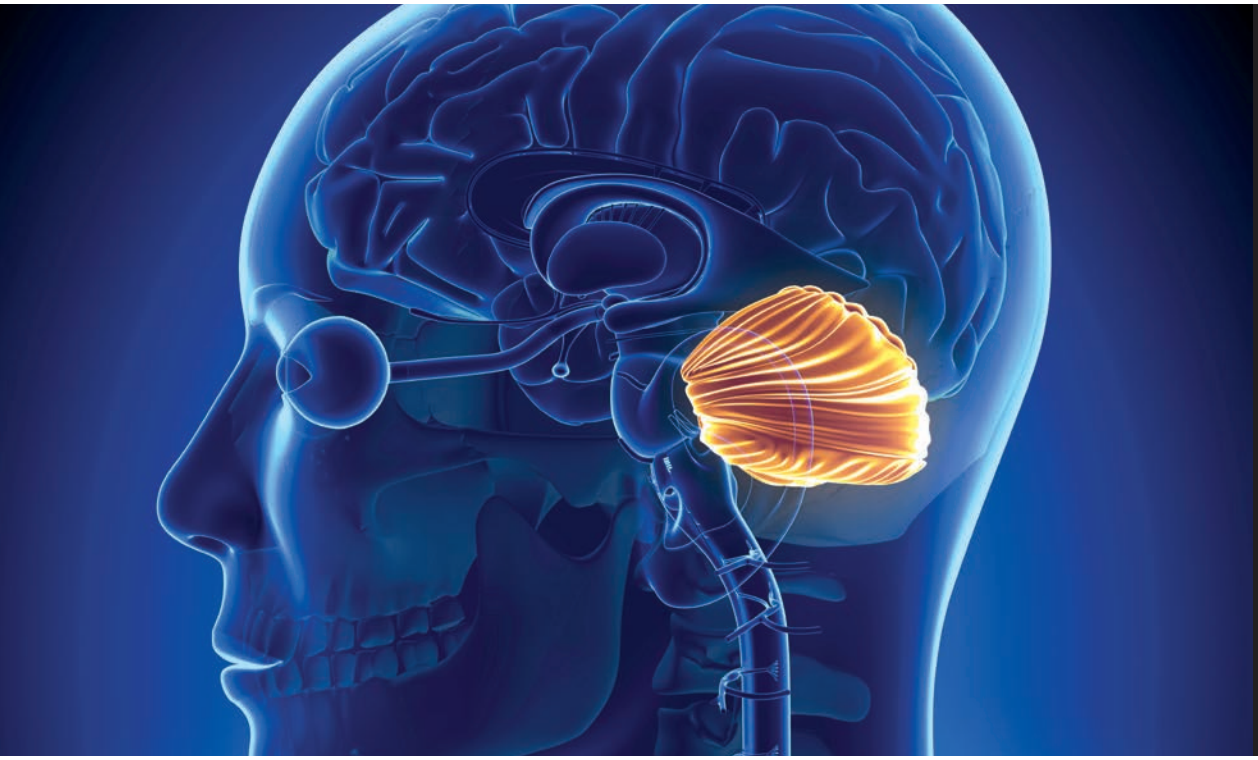
For additional references, visit the online version of this article at:

www.riken.jp/en/research/rikenresearch/perspectives/8062



Human embryonic stem cells have been induced to self-organize into a three-dimensional structure that resembles the cerebellum.

BIOLOGY | PRESS RELEASE

Growing functioning brain tissue in three dimensions

Researchers grow structures that resemble brain tissue from stem cells

RIKEN researchers have grown a three-dimensional structure that resembles the cerebellum from human embryonic stem cells[1]. This provides tantalizing clues in the quest to recreate neural structures in the laboratory.

A primary goal of stem-cell research is to replace damaged body parts with tissues grown from undifferentiated stem cells. This is particularly challenging for the nervous system because not only do specific neurons need to be generated, but they must also be coaxed into connecting to each other in very specific ways.

Researchers at the RIKEN Center for Developmental Biology have taken up this challenge. By sequentially applying several signaling molecules to three-dimensional cultures of human embryonic stem cells, they prompted the cells to differentiate into functioning cerebellar neurons that self-organize to form the dorsal–ventral patterning and multilayer structure found in the natural developing cerebellum.

The scientists found that, under specific conditions, culturing human embryonic stem cells with fibroblast growth factor 2 (FGF2) leads to neural differentiation particular to the midbrain–hindbrain region (the location of the cerebellum) within three weeks and the expression of markers for the cerebellar plate neuroepithelium (the part of the developing nervous system specific for the cerebellum) within five. These cells also showed early markers specific to developing Purkinje cells, granule cell or deep cerebellar projection neurons—types of neurons found only in the cerebellum.

The researchers then looked for mature cerebellar neurons and found that cells treated with FGF2 expressed late Purkinje-cell markers and developed structures characteristic of those cells. Electrophysiological recordings of these cells after about 15 weeks of culturing revealed that function had developed along with structure.

Where these neurons form and how they locate in relation to each other are critical in the developing brain. Early in cerebellar development, particular cell types become distributed unevenly from top to bottom, creating

a dorsal–ventral separation. Adding FGF19 around day 14 to FGF2-treated cells caused several flat-oval neuroepithelium to form by day 35, expressing dorsal-specific markers on the outside and ventral-specific markers on the inside. Adding stromal cell-derived factor 1 between days 28 and 35 generated a continuous neuroepithelial structure with dorsal–ventral polarity.

"The principles of self-organization that we have demonstrated here are important for the future of developmental biology," says lead author Keiko Muguruma. "Attempts to generate the cerebellum from human iPS cells have already met with some success, and these patient-derived cerebellar neurons and tissues will be useful for modeling cerebellar diseases such as spinocerebellar ataxia." ■

Reference

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MATERIALS | PRESS RELEASE

Toward dissipationless electronics

RIKEN researchers show for the first time that surface states on a topological insulator are quantized

The first evidence of an unusual quantum phenomenon—the integer quantum Hall effect—in a new type of film, called a three-dimensional topological insulator, has been uncovered by researchers from the RIKEN Center for Emergent Matter Science (see image)[1]. This discovery demonstrates that a particular form of massless electrons known as surface Dirac states are quantized in these materials; that is, they only take certain discrete values. These findings could help move science forward toward the goal of dissipationless electronics—electronic devices that can operate without producing the vast amounts of heat generated by current silicon-based semiconductors.

Topological insulators are unusual materials in that they conduct electricity on their surfaces but not in their interiors. Their surfaces are populated by massless electrons and electron holes—known as Dirac fermions—which can conduct electricity in a nearly dissipationless fashion, like a superconductor. Consequently, their properties are being intensively studied in the hope of creating electronic devices with low power consumptions. However, impurities in the crystal structures of these topological conductors have, up to now, made it difficult to realize this potential.

In the current study, the team was able to overcome these limitations through carefully engineering the material. The researchers fabricated a three-dimensional topological insulator made from bismuth, antimony and tellurium, and they succeeded in eliminating the impurities that have plagued previous efforts. By fixing the material on an indium phosphide semiconductor substrate and then placing an insulating oxide film and electrodes on top, they transformed the films into electronic gating devices known as field-effect transistors.

They then measured the Hall resistance—a type of electric resistance—while applying a constant magnetic field and tuning the strength of the electric field. By doing this, they were able to show that the resistance became constant at certain plateaus, demonstrating the presence of the quantum Hall effect in the material.

In addition, by tuning the external voltage applied to the films, they showed that the Dirac states could be switched between the integer quantum Hall state and the insulating state by changing the electrical current.

Schematic showing the integer quantum Hall effect on the surface of a topological insulator. The effect allows dissipationless current, without energy loss, along the surface of the material.

"It was very exciting to see this exotic effect in a three-dimensional topological insulator, and we plan to continue our work to show how materials can be finely tuned to have various electronic properties," says Ryutaro Yoshimi of the Strong Correlation Physics Research Group, who led the research. "In the future, these results could, I hope, be used for the creation of high-speed and low-power-consumption electronic elements." ■

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PHYSICS

Cryogenic clocks keep time

Atomic clocks with an unprecedented level of synchronization accuracy could allow more sensitive detection of gravity variations

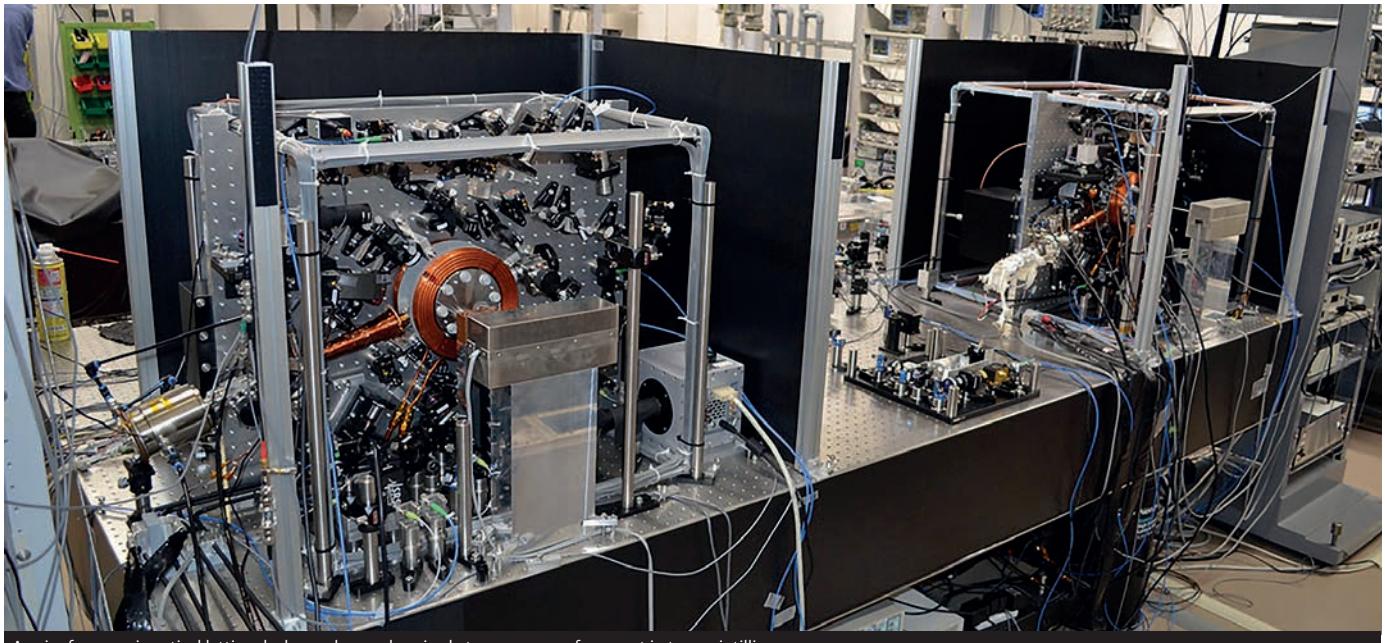
A pair of atomic clocks that can be synchronized at the highest accuracy ever achieved have been constructed and demonstrated by RIKEN researchers[1]. The clocks are so accurate that it would take 16 billion years for them to drift apart by a single second.

Atomic clocks are used as a highly precise basis for our time system, as well as for a range of scientific applications, from the global positioning system to detecting variations in the frequency of pulsars and in relativistic particle experiments. Although highly accurate, the ultimate accuracy of conventional atomic clocks, such as the cesium-beam atomic clock and the rubidium clock, is limited by electromagnetic perturbations from their environment.

Optical lattice clocks, which use atoms trapped by laser beams as the basis for timekeeping, are capable of even higher accuracy. Yet these systems are also susceptible to perturbations due to heat radiating from surrounding objects.

A team of researchers led by Hidetoshi Katori from the RIKEN Quantum Metrology Laboratory and RIKEN Center for Advanced Photonics has now overcome these interference problems by cooling a pair of optical lattice clocks based on strontium atoms to −178 degrees Celsius (see image). "Thermal radiation from surrounding walls has been the biggest source of uncertainty for optical lattice clocks with strontium atoms," explains Katori. "Cryogenic clocks cut this uncertainty by two orders of magnitude."

The researchers used a laser to generate a one-dimensional optical lattice with an 'egg-box'-like profile and trapped individual strontium atoms in the egg cups. The laser wavelength was then tuned to a 'magic' wavelength at which the laser field has no effect on the oscillation of the atoms, and the optical lattice was used as a conveyor belt to transport the atoms into a cryo-chamber, where the timing measurements were made.



A pair of cryogenic optical lattice clocks can be synchronized at an accuracy of one part in two quintillion.

Comparisons of time measurements taken over a month revealed that the clocks were in agreement to one part in two quintillion, or one in 0.5×10^{18}. This is the first time that clocks have been synchronized at this level of accuracy.

One promising application for this clock is in the measurement of tiny variations in the Earth's gravitational field—an application that exploits the slowing of time that occurs in a stronger gravitational field described by Einstein's general theory of relativity.

"At an accuracy of one in 10^{18}, a pair of clocks can detect a one centimeter height difference on Earth," says Katori. "To demonstrate this, we are now measuring the frequency difference between two clocks located 15 kilometers apart." ■

Reference

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CHEMISTRY

One at a time, please

Polymers held together by multiple weak intermolecular interactions but with tight control over the number of monomer units in each chain have been prepared for the first time

The first example of a supramolecular polymer that grows by the addition of one monomer at a time has been reported by researchers from the RIKEN Center for Emergent Matter Science[1]. This process, and the understanding of the particular properties of the monomer that drive it, could lead to the development of precision polymer transistors and other applications requiring tightly controlled polymer dispersity.

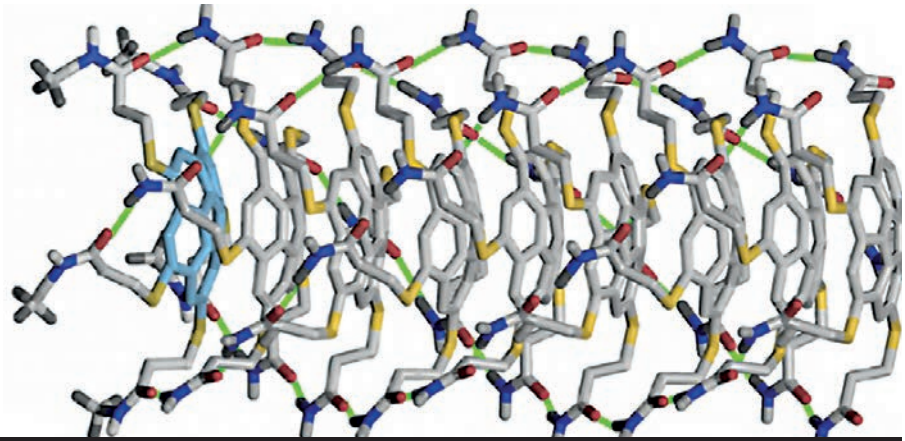
Supramolecular polymers consist of monomer units held together by relatively weak intermolecular forces. As their electronic and physical properties are usually highly dependent on the number of monomers in the chain, controlling the polymer growth process so that all the polymer chains are of similar length—producing polymers with low 'dispersity'—has been a long-term goal of both scientists and engineers. Yet the goal has often been thought to be impossible because short polymers would sometimes join together, resulting in step-growth polymerization rather than the desired monomer-by-monomer chain-growth polymerization.

The research team, led by RIKEN researchers Takuzo Aida and Daigo Miyajima, has been working for over a decade on monomers based on corannulene—a polycyclic aromatic hydrocarbon with a bowl-like structure that can flip inside-out to form a mirror image of itself. In the polymer, the corannulene monomer units stack together like soup plates and are held in place by hydrogen bonds formed between amides that decorate the edges of the bowl.

"In more than ten years of research, this is the first monomer that we have found that did not spontaneously polymerize at room temperature," explains Miyajima. "We attribute this to the formation of hydrogen bonds between amides in the monomer."

These intramolecular hydrogen bonds tie the monomers up in unreactive, ball-like structures. The addition of a small amount of a special monomer that cannot form these intramolecular hydrogen bonds can initiate polymerization, but because each ball-like monomer must open up before adding to the chain, monomers can only be added to the chain one at a time. The 'stack of soup plates' structure of the growing polymers, with one end blocked by the initiator (see image), inhibits step-growth polymerization and provides tight dispersity control.

The resultant polymers have a nanofibrous structure that can be seen using atomic force microscopy. "The corannulene structure is known to have semiconducting properties," says Miyajima, "so we hope to be able to fabricate very small transistors using these polymers. We are also working on developing the concept of metastable monomers for the production of other dispersity-controlled supramolecular polymerizations." ■



A molecular model of the supramolecular corannulene polymer showing the stacked-bowl structure of the polymer with the initiator highlighted at the left end.

Reference

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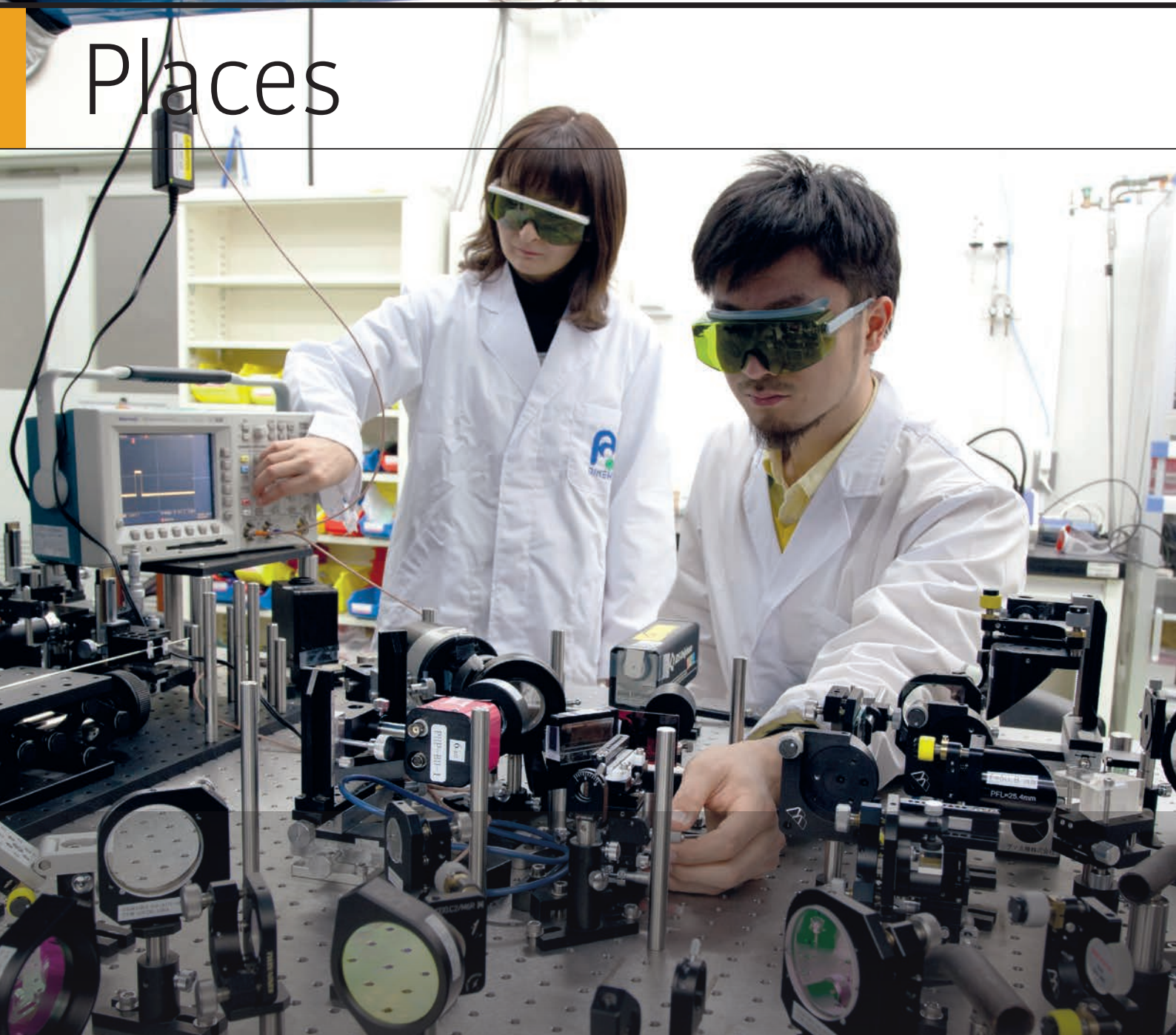


RIKEN Center for Advanced Photonics

Seeing technology through

Researchers at the RIKEN Terahertz-wave Research Group are developing technologies that can generate, detect and visualize invisible electromagnetic waves shorter than a millimeter

Contact information
Website: www.riken.jp/en/research/labs/rap/thz_wave/
E-mail: thz-info@riken.jp

Imagine having a toolbox full of small- and large-sized screwdrivers and attempting to tighten a medium-sized screw. This is the current state of research into terahertz radiation, which is squeezed between infrared light and microwaves in the electromagnetic spectrum.

Terahertz radiation consists of sub-millimeter-long waves with frequencies around one terahertz. These waves can travel through soft materials like wood and plastic, penetrate the body without damaging tissue or DNA, and sense bonds between molecules. Terahertz radiation has huge potential for a wide range of applications, including airport security, telecommunications, tumor detection and remote sensing from space. But there is a lack of efficient and practical technologies for generating, detecting and visualizing these invisible waves, since they are too long to produce using conventional, high-frequency optical devices and too short to generate using electronic transmitters. The RIKEN Terahertz-wave Research Group was established in 2008 with the goal of plugging this 'terahertz gap'.

Researchers at the RIKEN Terahertz-wave Research Group use nonlinear optical crystals to produce intense laser beams with terahertz frequencies (above and opposite page).

Beaming strong

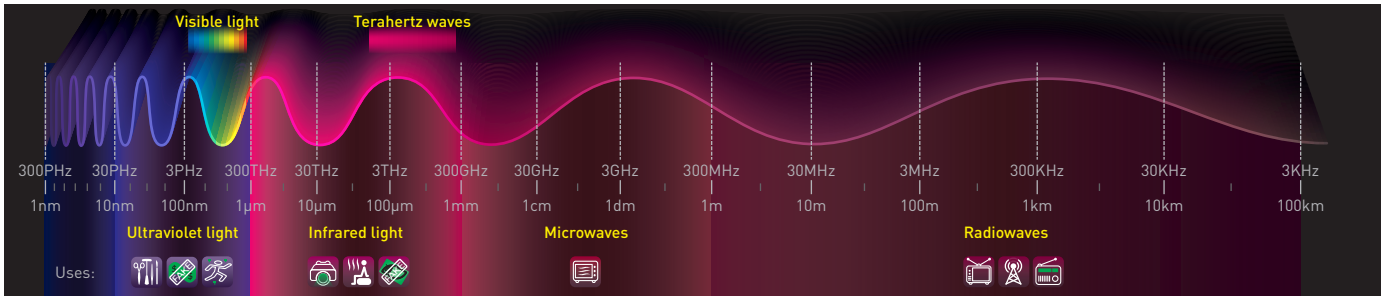
RIKEN has been researching the interaction between light, materials and living organisms for the last three decades. It dedicated an entire program to the study of terahertz waves in 2005 and set up the Terahertz-wave Research Group as part of the RIKEN Advanced Science Institute (later reorganized into the RIKEN Center for Advanced Photonics). Based in Sendai, the group has an average annual budget of 400 million yen and employs 42 personnel. Research is divided between three key laboratories, each employing novel techniques to generate, sense and image terahertz waves.

Terahertz sources must be practical as well as powerful. Consequently, Hiroaki Minamide, who leads the Tera-Photonics Research Team, has used nonlinear optical crystals to produce intense terahertz laser beams at room temperature. The system can generate narrow waves with frequencies between 0.7 and 3 terahertz that are as strong as those produced by larger, costlier and more complex free-electron lasers. Meanwhile, Hideki Hirayama's Terahertz Quantum Device Research Team is extending the reach of more ubiquitous quantum cascade lasers down to the terahertz region by fabricating them, for the first time in the world, using gallium nitride, instead of the traditional aluminum gallium arsenide. Hirayama's team is also reducing the operating temperature of these lasers for use in everyday working environments.

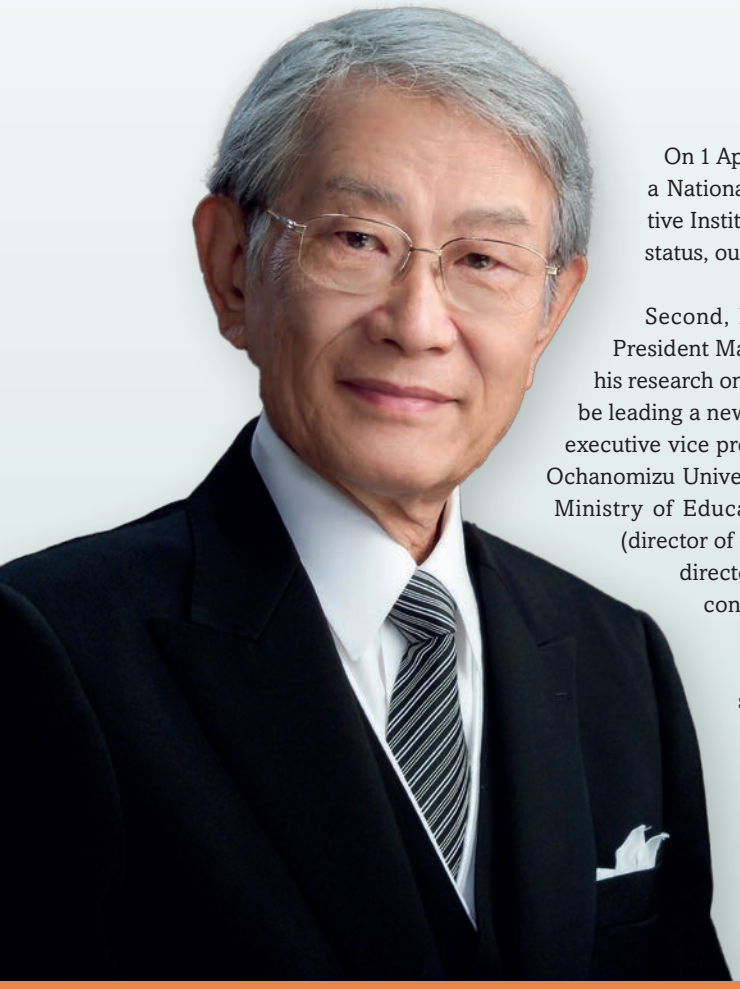
Detective work

The detection of terahertz waves is as crucial as their generation. Chiko Otani and the Terahertz Sensing and Imaging Research Team have developed a spectroscopic system that covers a broad frequency range of 0.5 to 30 terahertz to probe materials and measure the reflected wave characteristics. The team has also contributed to the development of highly sensitive superconducting detectors for millimeter and terahertz waves. Since 2008, Minamide's team has been amassing absorption and emission profiles of hundreds of medically and industrially relevant materials in a free online database, accessed by researchers from nearly 80 countries. A similar database of potentially dangerous drugs and explosives is being used by RIKEN to test the suitability of terahertz spectroscopy for screening the 100,000 international packages that pass through Japanese post offices every day.

Researchers could also use these submillimeter waves to control the activity of soft materials and biomolecules, but not until they fill their toolbox with the right tools.



RIKEN new designation & new management



On 1 April 2015, RIKEN underwent some fairly major changes. First, we became a National Research and Development Institute. As an Independent Administrative Institution, we were tasked with streamlining government work. With our new status, our mission is to maximize the results of our research and development.

Second, Hiroshi Matsumoto succeeded Ryoji Noyori as president of RIKEN. President Matsumoto is a former president of Kyoto University and is well known for his research on outer space, focusing on radiowaves, plasma physics and energy. He will be leading a new board of executive directors that includes Yoichiro Matsumoto (former executive vice president of the University of Tokyo), Sawako Hanyu (former president of Ochanomizu University), Shigeharu Kato (former director-general for international affairs, Ministry of Education, Culture, Sports, Science and Technology) and Shigeo Koyasu (director of the RIKEN Center for Integrative Medical Sciences). They join executive director Mutsuhiro Arinobu, and auditors Itaru Shimizu and Kenji Ito, who will continue to serve on the board.

President Matsumoto feels strongly that our research must be aimed at solving the many problems that will face humanity in the coming years. At the same time, we must balance this mission with our desire for free and autonomous scientists who can conduct their research with creativity. As a national institute with new management and a new guiding philosophy, RIKEN will focus more globally and take its place as one of the leading scientific research institutes in the world.

New board of executive directors

Mutsuhiro Arinobu | Yoichiro Matsumoto | Sawako Hanyu | Shigeharu Kato | Shigeo Koyasu

RIKEN

centers and facilities across Japan and around the world

Sendai

Center for Advanced Photonics

Tsukuba

BioResource Center

Wako

Center for Emergent Matter Science
Center for Advanced Photonics
Center for Sustainable Resource Science
Brain Science Institute
Nishina Center for Accelerator-Based Science
Radioactive Isotope Beam Factory
Advanced Center for Computing and Communication
Research Cluster for Innovation
Chief Scientist Laboratories
Associate Chief Scientist Laboratories
Distinguished Senior Scientist Laboratories
Initiative Research Units
Special Research Units
Research Groups
Global Research Cluster

Yokohama

Center for Sustainable Resource Science
Center for Integrative Medical Sciences
Center for Life Science Technologies

Nagoya

Osaka

Quantitative Biology Center

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Center for Developmental Biology
HPCI Program for Computational Life Sciences
Center for Life Science Technologies
Advanced Institute for Computational Science
K computer

Harima

SPring-8 Center
SPring-8 Synchrotron Radiation Facility
SACLA X-ray Free Electron Laser Facility

USA

RIKEN-MIT Center for Neural Circuit Genetics
RIKEN BNL Research Center

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RIKEN-Max Planck Joint Research Center (Germany)
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RIKEN-XJTU Joint Research Center (China)
RIKEN-SJTU Joint Research Center (China)
RIKEN-SIOM Joint Research Laboratory (China)
NCTU-RIKEN Joint Research Laboratory (Taiwan)
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