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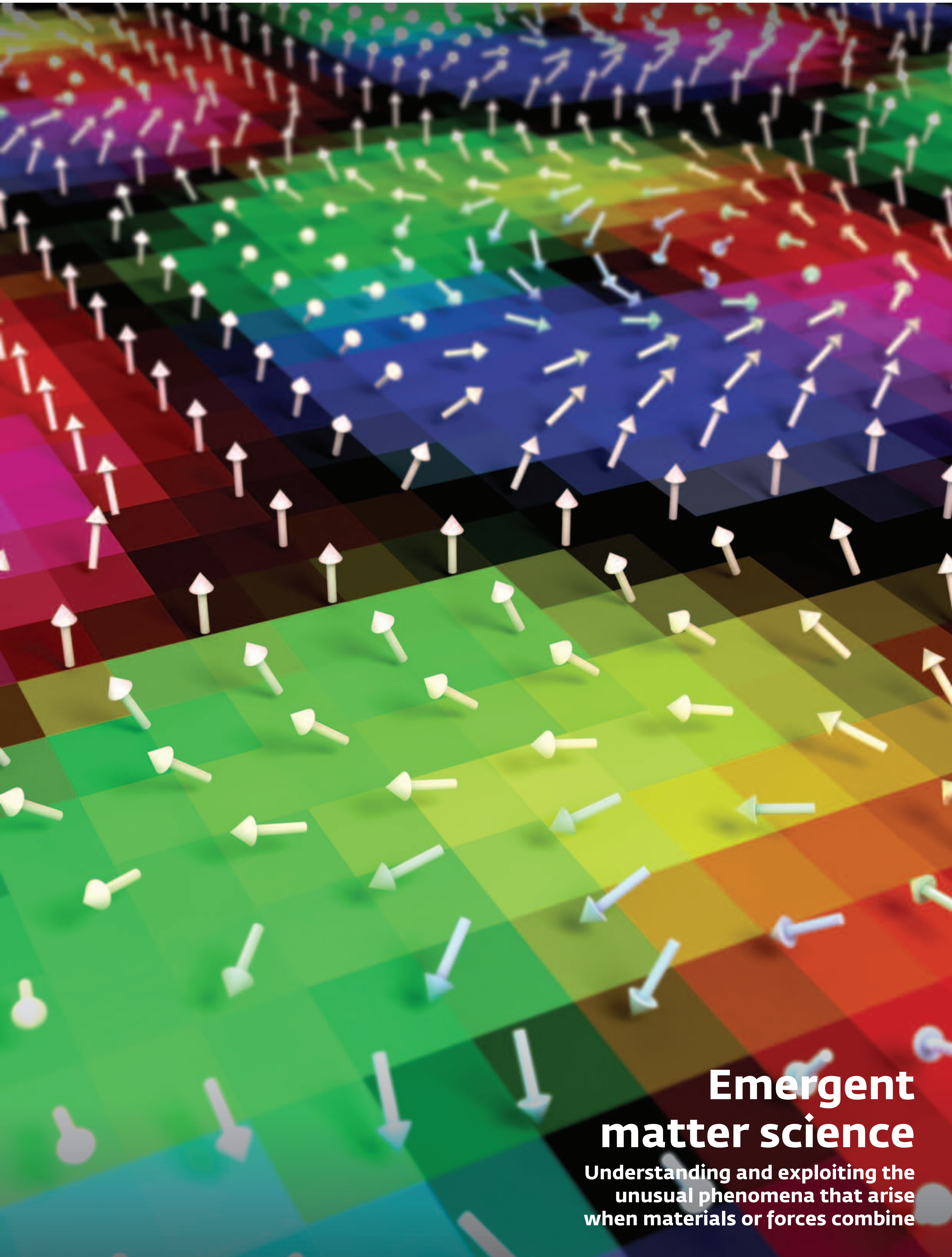

Emergent matter science

Understanding and exploiting the unusual phenomena that arise when materials or forces combine

RIKEN NMR Facility in Yokohama

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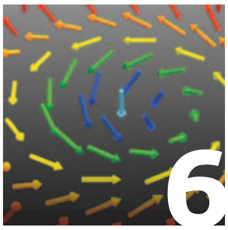

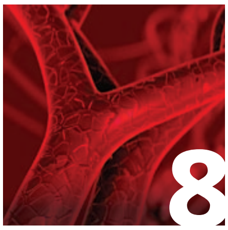

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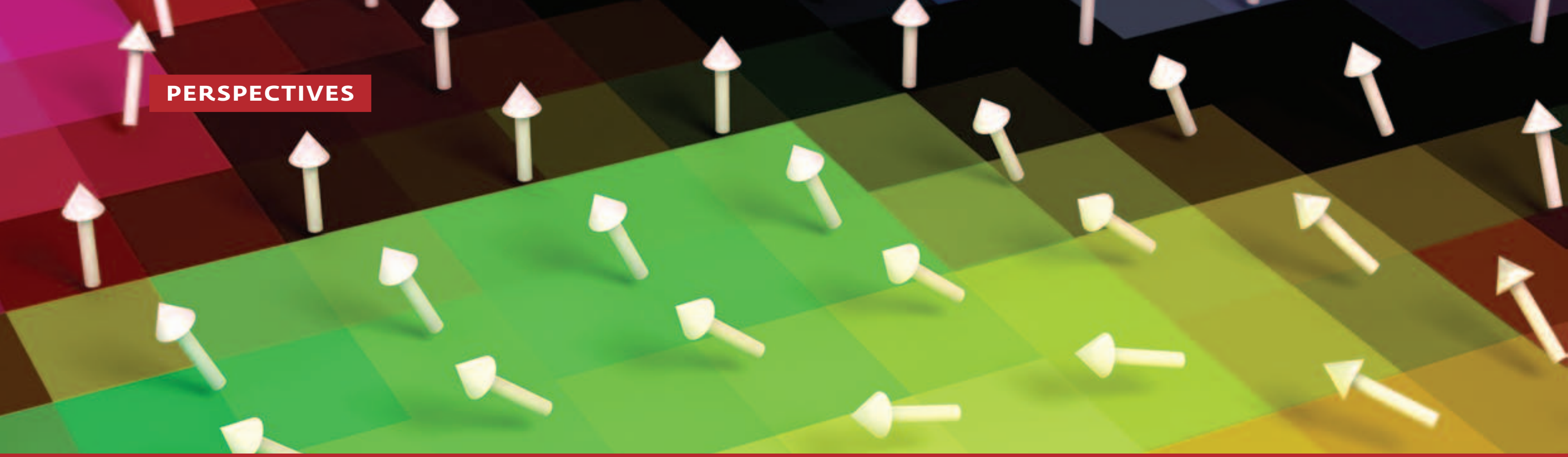


Emergent matter

Electronics, energy and emergence

YOSHINORI TOKURA
Director
RIKEN Center for Emergent Matter Science

Emergent matter science is a new and rapidly growing area of research that seeks to understand and exploit the unusual phenomena that arise when materials or forces are combined in novel ways. The field draws on a diverse range of disciplines, including condensed-matter physics, materials science and quantum physics, as well as the exciting discoveries that occur at the interface of these areas.

Modern computers, made possible by the semiconductor revolution of the 1950s and 1960s, are growing ever faster and more powerful. However, despite rapid changes in performance, the fundamental technology that underpins computers has changed surprisingly little since the invention of integrated circuitry over half a century ago.

More recently, the increasing demand for faster and more compact processors has pushed conventional systems to their physical limit. Additionally, the significant power requirements of advanced circuit boards have made improving their energy efficiency an enormous scientific and technical challenge for the microelectronics industry. In response, emergent matter scientists are re-examining the fundamental properties of materials and the ways in which they interact with heat, light, electricity and magnetism—paving the way for faster computers, superior methods for data storage and an improved flow of information around circuits.

Building better switches

A promising area of emergent matter science involves strongly correlated electron systems. Although metals generally behave as if their electrons diffuse freely through a continuous sea of electrical charges, in some materials these conducting electrons are 'locked' into specific positions around atoms. This phenomenon, known as 'strong correlation,' affects the properties of materials in unusual ways—for example, electrical insulators can become metallic conductors by applying just enough heat or pressure to slightly change their atomic structure. Since the two states are typically very close in energy, it only takes a small nudge to switch from one to the other, something that researchers could exploit to create microelectronic components that draw very little power.

In some cases, a magnetic field induces a similar transformation. Dubbed 'colossal magnetoresistance,' this effect can be used to store data by switching tiny regions of a material into either a metallic or insulating form. This type of non-volatile memory, which stores data even in the absence of a power supply, is read by measuring whether a current flows through the region. The exact mechanism governing this effect at the nanometer scale and its elucidation are of great importance to researchers, including those at RIKEN, who are engaged in developing microelectronic technologies.

Another class of important materials, known as Mott insulators, change from insulators to conductors when exposed to a small voltage. Equivalent to melting an 'electron ice'—where electrons are locked in place—into an 'electron liquid,' this property allows a current to flow, meaning that Mott insulators could be used as low-power transistors. Scientists at RIKEN have made significant contributions to this area through their discovery of how the change from insulator to conductor works at the atomic scale in vanadium oxide-based systems[1] (Fig. 1).

Resistance is useless

In conventional materials, an electric current typically encounters internal resistance, which leads to the generation of heat with a resulting loss of energy. Superconducting materials, conversely, conduct electricity without resistance. Yet superconductivity only arises in certain specialized materials, and then only at very low temperatures, making these systems impractical for most computers.

Materials in which electrons can flow down 'electron highways,' and consequently experience very little resistance,

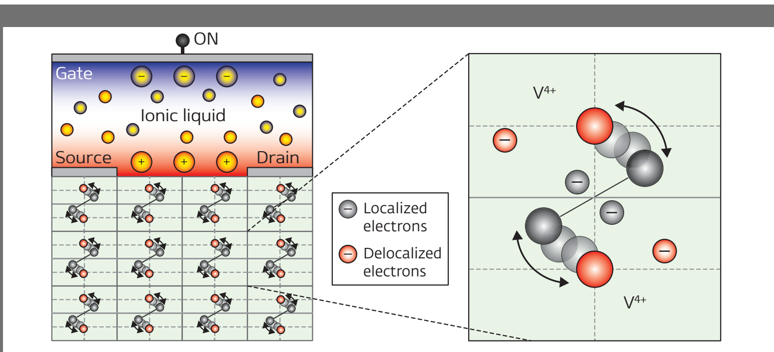


Figure 1: Vanadium oxide film

Vanadium oxide, a known Mott insulator, switches from an insulator to a conductor upon exposure to a small voltage. The organization of localized (black) and delocalized (red) electrons—which respectively correspond to the insulating and conducting states—and their movement within the material upon application of a voltage is shown.

offer an attractive alternative. The leading candidates are the so-called topological insulators—materials that mostly insulate but conduct very well at their surfaces. While the generation of topological currents usually requires a strong magnetic field, in theory topological insulators can conduct electricity with little resistance at room temperature and without the need for a large magnetic field. Conductivity at the surface could also be switched on or off with a very small stimulus.

A common method for establishing a topological current relies on the Hall effect, a phenomenon in which a magnetic field applied at right angles to a stream of moving electrons creates a voltage difference between opposite surfaces of the material. Systems developed at RIKEN, in which a spontaneous Hall effect helps current to flow along the edges of the material at low temperatures, have played a significant role in advancing the field. The protocol has been successfully demonstrated under low-temperature conditions, and the next step will be to develop systems in which this behavior is sustained at room temperature.

Magnetic tornadoes

Conventionally, data is carried using electric charges. However, an alternative method involves the use of swirling magnetic vortices, known as skyrmions, which result from the self-organization of magnetic moments in ferromagnetic materials. Skyrmions form when concentric rings of atomic magnets in the atoms of ferromagnetic systems become progressively more tilted, until the magnetic moments at the very center point in the opposite direction to those in the wider bulk of the material. These alignments—just tens of nanometers wide—behave like individual particles and can move through a material as a tornado twists its way across the land.

An understanding of how skyrmions behave, and how they might be manipulated, lies at the heart of progress in the field. RIKEN has made significant progress in predicting the mechanisms that govern skyrmion dynamics, such as by showing how their motion can be driven by tiny electrical currents[2]. This discovery may offer a low-energy way to transport information encoded in skyrmions. The next challenge will be to overcome a fundamental problem: as skyrmions move faster under higher current densities, a low-energy skyrmion-based computer would be accompanied by slower processing speeds.

Quantum bits

While many methods aimed at boosting the processing power of computers focus on the development of new and more efficient materials, another approach, termed 'quantum computing,' aims to tackle the fundamental way in which data is manipulated. In standard computers, data exists as a series of 'ones' and 'zeros' encoded by binary switches that are either on or off. However, in quantum computers data is stored in quantum bits or 'qubits' that exist as a combination of both states—known as a superposition. Multiple qubits can be linked by another quantum mechanical process called entanglement, and thus changing one qubit affects the whole group. Together, superposition and entanglement allow an array of qubits to access vastly more states than the same number of conventional bits, which increases the overall computing power of the system.

Researchers at RIKEN are at the forefront of efforts to create and control such qubits. One of the main challenges remains how to maintain the quantum coherence of qubits to avoid the loss of stored information due to interactions with their environment. Potential systems for exploiting qubits include the electron spins in semiconductor quantum dots and the charges and magnetic fluxes of superconducting circuits. Research is also focusing on correcting the errors that arise from quantum decoherence—a key issue for facilitating the scale-up of qubit systems to enable reliable and efficient quantum computing.

Research into quantum bits, skyrmions and topological currents has already provided a number of important advances in the quest for energy-saving applications. Before new forms of electronic devices can be developed, gaps that remain in our understanding of the fundamental issues in materials science, such as the behavior of electrons in solid matter, must be filled. These endeavors, and the research that will be carried out over the coming decade, will doubtless spark new concepts for electronic materials.

1. Nakano, M., Shibuya, K., Okuyama, D., Hatano, T., Ono, S., Kawasaki, M., Iwasa, Y. & Tokura, Y. Collective bulk carrier delocalization driven by electrostatic surface charge carrier accumulation. *Nature* **487,** 459–462 (2012).
2. Seki, S., Yu, X. Z., Ishiwata, S. & Tokura, Y. Observation of skyrmions in a multiferroic material. *Science* **336,** 198–201 (2012).

Physics

Taking the measure of skyrmions

Twisting magnetic patterns known as skyrmions could become effective data carriers in a new generation of computers if researchers can understand how to create and control them

Conventional computers process information by shuttling electric charges around circuits. Electrons also possess magnetic properties, which could be exploited to allow information systems to carry more data at higher speeds while using much less energy. Swirling magnetic vortices called skyrmions could become an essential vehicle for this form of computing because they are only nanometers in size and can be moved around using tiny electric currents.

A research team led by physicist Naoto Nagaosa at the RIKEN Center for Emergent Matter Science has now produced a detailed theoretical profile of these magnetic skyrmions. The researchers modeled how skyrmions behave as they move through a material, calculated the energy needed to create and destroy them and predicted how skyrmions could ultimately be controlled[1].

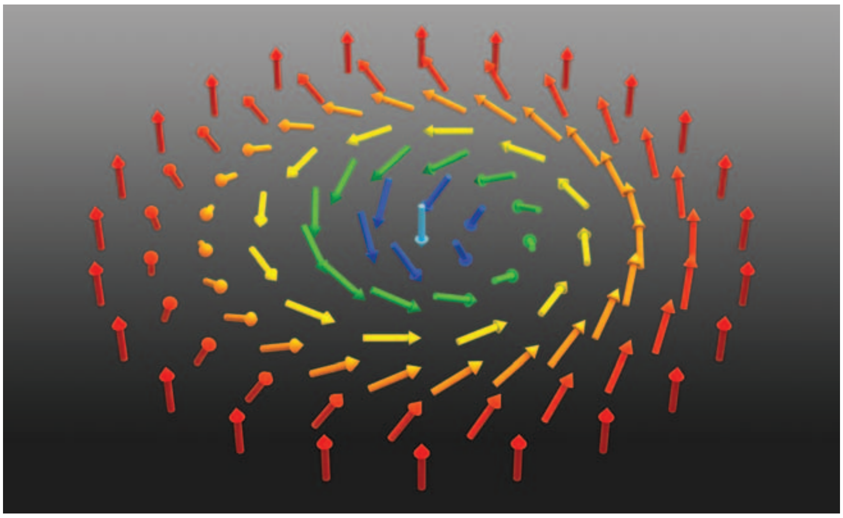


Figure 1: A skyrmion is a swirling pattern in the magnetic moments of atoms in a ferromagnetic material.

In a spin

All electrons generate a tiny magnetic moment as they spin, like a bar magnet that can point either up or down. In atoms, most electrons are arranged in pairs such that the 'down' magnetic moment of one electron is cancelled out by the 'up' of another. In certain materials, however, teaming up in this way generates a strong repulsion between the electrons' negative charges, causing the electrons to adopt the same magnetic orientation. This parallel alignment pushes the electrons further apart, which reduces their electrostatic repulsion. Such a situation leaves a lot of unpaired electrons throughout the host material, with the result that the sum of all the magnetic moments may be non-zero, leading to spontaneous magnetism. This is the permanent magnetism we commonly see in ferromagnets.

Skyrmions are swirling patterns in the magnetic orientation of atoms in ferromagnetic materials. Around the outside of a circular skyrmion, the atoms' magnetic moments point in the same direction as the rest of the material. Closer to the center, these magnetizations become increasingly tilted until, at the center of the circle, they point in the opposite direction (Fig. 1). Postulated in the early 1960s by Tony Skyrme, a British physicist, skyrmions were first observed roughly three decades later.

The magnetic moments can tilt because electrons produce an additional magnetic effect as they orbit their atoms. This orbital contribution is usually much smaller than the spin magnetism, so there is very little tilting. In a few ferromagnetic materials, however, interactions between the spins and orbits of neighboring electrons are strong enough to produce a more significant tilt. From one atom to the next, these interactions progressively push the magnetic moments further away from upright. "This twist is the origin of the helical structure embedded in the skyrmion," says Nagaosa.

Although skyrmions are formed over many atoms, each behaves like a distinct particle, presenting the possibility that the presence or absence of a skyrmion could be used to represent a single bit of binary data in a computer.

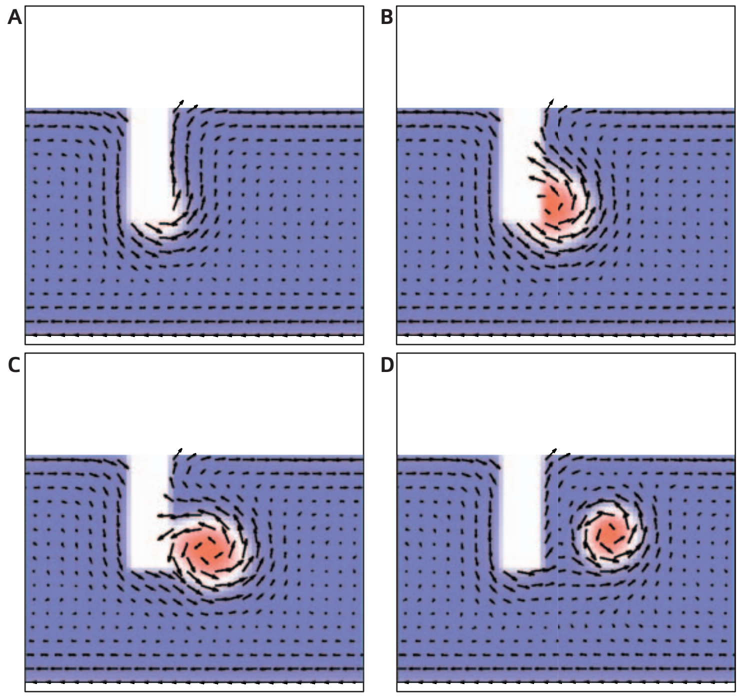


Figure 2: A skyrmion begins to form when an electric current forces atoms to twist away from a notch, until the swirling pattern takes on a life of its own.

Putting skyrmions through their paces

In 2010, Nagaosa was part of a RIKEN team that directly imaged magnetic skyrmions for the first time. Then, in 2012 other researchers showed that they could drive the motion of skyrmions with an electric current or create them using a short laser pulse.

Nagaosa's team built on these results to model skyrmion motion through a narrow channel. Skyrmions travel in the same direction as the flow of electrons, but the material's magnetic field forces them slightly off course, just like a spinning ball veering from its trajectory as it flies through the air. Known as the Hall effect, the researchers found that this process did not significantly impede the skyrmions. A skyrmion some 18 nanometers across, travelling through a channel 75 nanometers wide, covered more than 600 nanometers in a few tenths of a microsecond. They also found that fully formed skyrmions tend to be repelled from the channel edges.

Again using simulations, the research team modeled the formation of a skyrmion by applying an electric current to the corner of a square notch in a ferromagnetic material. The electrons transfer some of their spin to atoms in the material, forcing their magnetic moments to twist away from the notch and forming the seed of a skyrmion (Fig. 2).

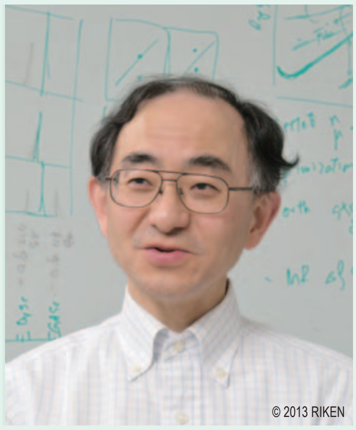
As the magnetic moments twist, they drag the moments of neighboring atoms with them, causing the spins to precess around like a gyroscope, creating a swirling effect. Eventually the skyrmion settles down to its most stable size and drifts through the material. Skyrmions require current densities of 10^{10} to 10^{12} amperes per square meter to form, but once created can be pushed around with current densities that are hundreds of thousands of times lower.

The simulations showed that the notch required to seed the skyrmion must be just the right size. If the base of the notch is too close to one side of the material, the skyrmion hits the edge and disappears before becoming fully formed. A 90° angle at the bottom of the notch produced the best results in the simulations, and both rounded corners and sharp edges generated skyrmions.

In a further study, the researchers simulated what happens when a skyrmion encounters a boundary between magnetic and non-magnetic materials. With a low current density, the skyrmion was found to bounce away from the boundary, but at higher current densities the skyrmion could be forced right to the edge, where it was annihilated. Nagaosa is now pursuing several different angles of skyrmion research. He and his colleagues are trying to develop materials that can support stable skyrmions at room temperature. They also hope to detect the motion of nanometer-sized skyrmions experimentally and to develop theories to describe how those skyrmions change over time.

1. Iwasaki, J., Mochizuki, M. & Nagaosa, N. Current-induced skyrmion dynamics in constricted geometries. *Nature Nanotechnology* **8,** 742–747 (2013).

ABOUT THE RESEARCHER



Naoto Nagaosa was born in Hyogo, Japan, in 1958. He graduated from the University of Tokyo in 1980 and obtained his PhD in 1986 from the same institution. Nagaosa then held a postdoctoral position at the Massachusetts Institute of Technology in the United States, before returning to Japan where he was appointed lecturer at the University of Tokyo and later promoted to professor in 1998. In 2007, he became a team leader at the RIKEN Advanced Science Institute and is now deputy director of the RIKEN Center for Emergent Matter Science. His main research interests are the theories of strongly correlated electronic systems, spintronics and the gauge theories of topological aspects of electrons in solids.

Putting a halt to blood vessel branching

A key regulator of blood vessel formation could be a potential new target for cancer drugs

During formation of the vascular system, successively smaller blood vessels sprout from existing ones to form networks of capillaries in patterns uniquely adapted to the function of the organ they enter. This process, called angiogenesis, involves complex interactions between several molecular signaling pathways, which are integrated within individual cells by various types of protein modification. Yoichi Gondo from the RIKEN BioResource Center in Tsukuba, in collaboration with a team of researchers from Canada, has now identified the molecule that regulates angiogenesis and determined its regulatory mechanism[1].

A research team led by Sabine Cordes of Mount Sinai Hospital in Canada discovered mutant mice exhibiting abnormal sprouting of the facial nerve and angiogenesis. Genetic analysis of the animals revealed a mutation in the 'gumby' gene (*Fam105b*) on chromosome 15. Gondo's team screened RIKEN's mutant mouse library for the gene and found nine different mutations. Cordes's group then examined two of the mouse strains in greater detail.

These gumby mice die around two thirds of the way through their three-week gestation period. The main structures of their vascular system appear normal, but the branches of blood vessels in the head and trunk are less complete than those in healthy mice.

The gumby gene encodes an enzyme that catalyzes a chemical reaction called deubiquitination. This reaction involves the removal of a small protein called ubiquitin from other protein molecules, and is one of many modifications known to alter protein function.

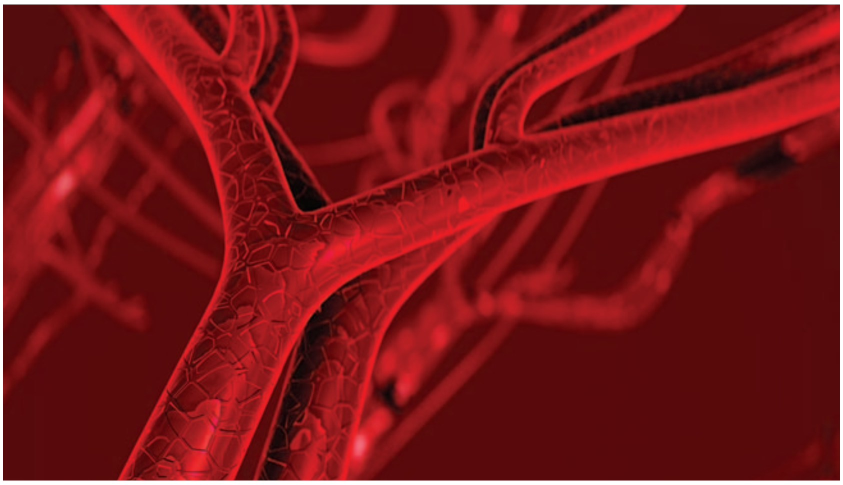


Figure 1: The role of the gumby gene in angiogenesis hints at possible targets for new cancer therapies.

Further experiments revealed that the gumby protein interacts with a molecule called DVL2 to modulate the canonical Wnt signaling pathway, and with another called HOIP to remove ubiquitin molecules from the transcription factor NF-κB, thus preventing it from activating the set of genes required for angiogenesis. Using x-ray crystallography, the researchers determined the atomic structure of gumby bound to a pair of ubiquitin molecules and found that both mutations alter its three-dimensional structure, preventing it from binding to NF-κB, or from removing ubiquitin from it.

The identification of gumby as a regulator of angiogenesis could eventually lead to new cancer drugs that prevent tumors from growing and spreading by inhibiting blood vessel formation.

Critical to the success of the study was the availability of specific mutant mouse strains at the RIKEN mutant mouse library. "Our mission is to provide mutant mouse strains for any particular target gene," says Gondo, "and we encourage researchers around the world to use our established mutant strains for screening."

1. Rivkin, E., Almeida, S. M., Ceccarelli, D. F., Juang, Y.-C., MacLean, T. A., Srikumar, T., Huang, H., Dunham, W. H., Fukumura, R., Xie, G. *et al*. The linear ubiquitin-specific deubiquitinase gumby regulates angiogenesis. *Nature* **498,** 318–324 (2013).

Exotic isotopes step on the scale

Measuring the masses of exotic isotopes will enable a better understanding of how heavy elements formed in stars

Elements heavier than iron are believed to have formed in supernovae or merging neutron stars through a series of complex nuclear reactions. Nuclear physicists are working to recreate these reactions by performing simulations, but such studies rely on highly precise masses for the relevant isotopes—many of which can only be created using high-energy accelerators. Michiharu Wada and colleagues from the RIKEN Nishina Center for Accelerator-Based Science in Wako have now demonstrated the utility of a new mass spectrograph at the Radioactive Isotope Beam Factory (RIBF) for measuring the masses of short-lived exotic isotopes[1].

Wada and colleagues built what is called a multi-reflection time-of-flight mass spectrograph (Fig. 1), which captures isotopes produced by the RIBF and slows them to a well-defined kinetic energy before measuring the ratio of their mass to charge based on the time it takes to travel a known distance.

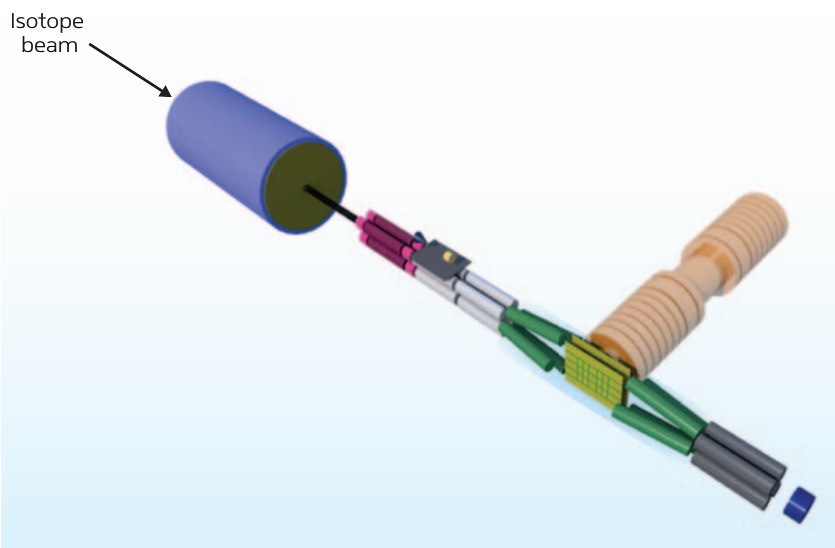


Figure 1: The multi-reflection time-of-flight mass spectrograph is designed to measure the masses of short-lived, heavy isotopes. The heart of the spectrometer is a long trap with electrostatic 'mirrors' on either end.

As the precision of the measurement improves the longer the distance travelled by the isotope, the researchers created a long, yet compact, trap by introducing electric-field 'mirrors' on either end to force the isotopes to bounce back and forth. Isotopes make several hundred roundtrips before they are released to a detector that registers the time elapsed in the trap.

In their first test, Wada and his team successfully measured the mass of singly ionized lithium-8 with an uncertainty of only 0.66 parts per million over a time-of-flight time of just 8 milliseconds. This isotope serves as a worst-case scenario for the spectrograph, which is optimized to study heavier isotopes with half-lives of 10–100 milliseconds.

In addition to studying short-lived isotopes relevant to astrophysical processes, the team plans to use the spectrograph to study isotopes heavier than uranium at the RIBF's gas-filled recoil ion separator (GARIS) facility. "Precise and systematic mass measurements of these isotopes are an important prerequisite for exploring the 'island of stability,' which is predicted to lie beyond the known super-heavy elements," says Wada.

One of the key advantages of installing the new mass spectrograph at the RIBF is the fact that it can be used to measure nuclei that cannot be created anywhere else in the world. "RIKEN's forthcoming slow radioactive nuclear ion beam facility, SLOWRI, will provide low-energy beams of all elements," says Wada. "The expected number of nuclides that will be available is the largest among existing radioactive isotope beam facilities in the world."

1. Ito, Y., Schury, P., Wada, M., Naimi, S., Sonoda, T., Mita, H., Arai, F., Takamine, A., Okada, K., Ozawa, A. & Wollnik, H. Single-reference high-precision mass measurement with a multireflection time-of-flight mass spectrograph. *Physical Review C* **88,** 011306(R) (2013).

Taking spin further

A theoretical device could bring practical spintronics closer to reality

One of the major hurdles in the development of faster electronic devices is the amount of heat produced by silicon microchips. This heat is created by the transport of electrical charges through transistors. Seiji Yunoki and colleague Shin-ichi Hikino from the RIKEN Center for Emergent Matter Science in Wako have now proposed a device that instead of moving electrons is able to transport information using electron spins over long distances[1].

Moving electrons through a material creates intense heat as the electrons bounce off the atoms in the device. Moving information by passing it from one electron to another without any electron movement would therefore eliminate this source of heat. The magnetic property of electrons—their spin—has been studied as a possible means of achieving such a scheme. However, conventional magnetic materials fail to provide the long-distance transport of information required for such a strategy. "It is well known that conventional spin current can propagate only short distances," says Yunoki. "This is one of the most critical problems in the research of spintronics."

The spintronics scheme proposed by Yunoki and Hikino is based on sandwiching two adjacent thin magnetic films between superconducting layers. In conventional superconductors, the electrons are bound together in pairs formed by antiparallel electron spins, called a spin-singlet Cooper pair. However, with a ferromagnetic layer nearby, the spin of the two electrons in such a Cooper pair will align itself in the same direction as the magnetic field. These spin-triplet Cooper pairs (STCs) can move from the superconductor into the ferromagnetic layer, where they are very stable and long-lived (Fig. 1).

The researchers have mathematically shown that within the ferromagnetic layer, the STC is able to carry spin currents over extended distances of several tens to hundreds of nanometers, and possibly even more if the magnetic material can be made with high purity. The spin transport happens without any charge current, and there is no voltage drop across the devices, meaning that no heat would be generated.

So far, devices showing spin currents have been very difficult to realize, and such currents in the STC have never been observed. However, the simplicity of the proposed scheme promises its realization and could open a new era, says Yunoki. "We expect that the proposed superconductor–ferromagnet multilayer device can provide a new platform to study the spin transport of Cooper pairs in this developing research field."

1. Hikino, S. & Yunoki, S. Long-range spin current driven by superconducting phase difference in a Josephson junction with double layer ferromagnets. *Physical Review Letters* **110,** 237003 (2013).

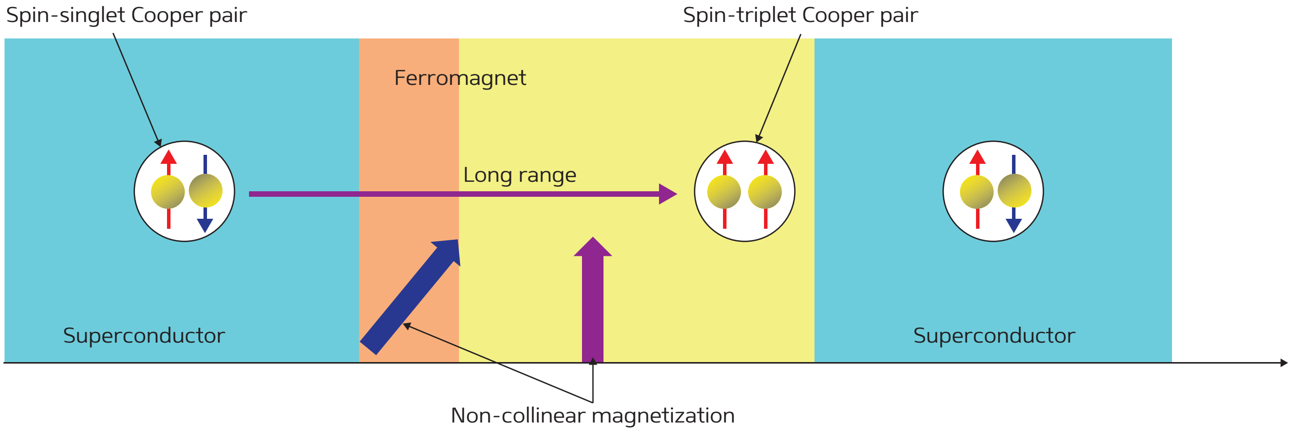


Figure 1: Spin currents in superconductor–ferromagnet multilayers. Sandwiched between two superconductors, spin-triplet Cooper pairs formed by two electrons can be sustained in the ferromagnet and carry spin currents over relatively long distances.

Tracking growth, row by row

Proper developmental patterning in worms is determined in part by the effective range at which a signaling molecule can act

Figure 1: Electron microscopy image of the posterior end of *Perinereis nuntia*, where new segment addition takes place as the worm grows.

During development, vertebrate embryos rely on a process called segmentation to establish fundamental body patterning. This entails the formation of orderly bands of cells, which can subsequently contribute to the formation of skeletal elements and associated tissues in response to developmental instructions. Insect and worm embryos undergo similar segmentation processes during development but with notable mechanistic differences that remain to be fully clarified. Now, a research team led by Shigeo Hayashi from the Laboratory for Morphogenetic Signaling at the RIKEN Center for Developmental Biology in Kobe has gained new insight into the process of annelid segmentation through a series of experiments using the marine worm *Perinereis nuntia*[1].

The *P. nuntia* worm (Fig. 1) is known to show vigorous regenerative activity. The researchers exploited this capacity for regeneration to monitor the timing of segment formation under controlled experimental conditions.

Segment formation typically occurs in an anterior to posterior (front to back) sequence and is governed in part by signaling proteins called Wingless and Hedgehog. Hayashi and his colleagues determined that regeneration of an amputated posterior segment begins with the production of Wingless in the cells immediately anterior to the site of regeneration. This leads to the production of Hedgehog in the next row of cells, which form the front of the new segment, followed by multiple rounds of cell division that lead to complete segment formation within approximately 24 hours. "We were surprised by the highly regular and periodic pattern of new segment addition that we observed at cellular resolution," says Hayashi.

Each of the segments that formed during the process of regeneration consists of five rows of cells. "This implies that segment addition is precisely controlled by a system that counts the number of cellular rows added per segmentation cycle," says Hayashi. He and his colleagues hypothesize that this count is established by the range of Wingless signaling, as their results showed that cells in the final row of the segment underwent cell division at a considerably lower rate than observed in the first row of cells. Conversely, worms treated with a chemical that stimulates excessive Wingless signaling formed more rows of cells per segment, suggesting that segment-forming activity was increased.

These results indicate a potentially critical role for Wingless in establishing both the timing and scale of segment formation, which may generally explain the essentially unlimited activity of segmentation in worms. "Exploring how this signaling system controls segment length measurement will be an interesting future challenge," says Hayashi.

1. Niwa, N., Akimoto-Kato, A., Sakuma, M., Kuraku, S. & Hayashi, S. Homeogenetic inductive mechanism of segmentation in polychaete tail regeneration. *Developmental Biology* **381,** 460–470 (2013).

Unblocking nerve fiber repair

Inhibiting the formation of a branched sugar molecule could lead to new treatments for multiple sclerosis

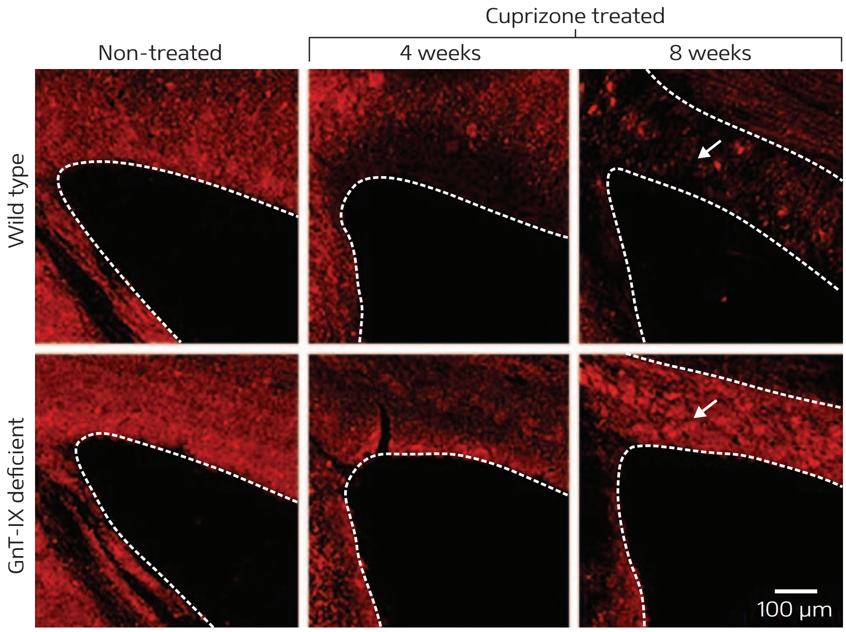


Figure 1: Brain slice images from healthy (top) and GnT-IX-deficient (bottom) mice, which show the corpus callosum (inner dashed lines) stained with an antibody to visualize myelin (red).

Multiple sclerosis is a debilitating condition that involves the degeneration of myelin—the fatty tissue that insulates nerve fibers and helps them to conduct impulses. This process, called demyelination, can lead to deficits in sensation, movement and thought processes, depending on exactly which nerve fibers are affected. Replacing lost myelin is a promising approach for treating multiple sclerosis and related diseases, but the mechanisms underlying demyelination and remyelination remain poorly understood.

In research that opens up an encouraging avenue for the development of new treatments, Naoyuki Taniguchi and colleagues from the RIKEN–Max Planck Joint Research Center for Systems Chemical Biology have shown that remyelination is inhibited by sugar molecules called branched *O*-mannosyl glycans[1].

Taniguchi and his colleagues genetically engineered a strain of mice carrying mutations in the gene encoding an enzyme called *N*-acetylglucosaminyltransferase-IX (GnT-IX), which catalyzes the branching of *O*-mannosyl glycan sugars on proteins in the brain. Using these mice, the researchers found that GnT-IX acts on a specific brain protein called receptor protein tyrosine phosphatase β (RPTPβ), which has previously been shown to play a critical role in demyelination.

Next, the research team fed normal and mutant mice a diet containing the neurotoxin cuprizone, which normally induces demyelination. Over the course of eight weeks, the normal mice were found to have experienced gradual demyelination of the corpus callosum—a major tract of white matter connecting the two hemispheres of the brain (Fig. 1). By contrast, although myelin in the corpus callosum had degraded by the fourth week in the mutants, myelination had markedly increased by the eight-week mark, suggesting that the defect in the *GnT-IX* gene enhanced remyelination.

Further experiments revealed that cuprizone treatment can activate non-neuronal cells called astrocytes into a disease state, which leads them to express RPTPβ containing branched *O*-mannosyl glycans. In wild-type mice, activated astrocytes express these branched *O*-mannosyl glycan molecules, which inhibit remyelination. In mice with a defective *GnT-IX* gene, however, astrocytes are rarely activated, and the absence of the branched *O*-mannosyl glycans allows the differentiation of myelin cells and the remyelination of nerve fibers in the corpus callosum.

"We would like to unveil the molecular mechanism by which branched *O*-mannosyl glycan activates astrocytes," says Taniguchi. "Understanding the underlying mechanism is important for developing a drug to treat multiple sclerosis."

The team next plans to screen for a GnT-IX inhibitor that attenuates astrocyte activation. "The difficult thing is that the drug has to pass through the blood–brain barrier, so collaboration with clinicians will be important," Taniguchi notes.

1. Kanekiyo, K., Inamori, K., Kitazume, S., Sato, K., Maeda, J., Higuchi, M., Kizuka, Y., Korekane, H., Matsuo, I., Honke, K. & Taniguchi, N. Loss of branched *O*-mannosyl glycans in astrocytes accelerates remyelination. *The Journal of Neuroscience* **33,** 10037–10047 (2013).

A nanoscale glimpse of batteries in action

Real-time observations of lithium–oxygen electrochemical reactions could aid development of lightweight rechargeable batteries for electric vehicles

Lithium-oxygen (Li–O_2) batteries are a new type of experimental battery that electric car manufacturers are hoping will address the issue of limited driving range. Unlike the lithium-ion batteries used today, lithium-oxygen batteries do not require metal oxide cathodes to produce electrochemical power, instead generating power from reactions with oxygen in the atmosphere. The significant weight savings realized through this design could potentially boost energy densities of batteries by up to four times. However, lithium-oxygen batteries have yet to leave the laboratory due to short battery lifespans caused by parasitic side reactions and accumulated charge polarization at battery cathodes.

Hye Ryung Byon with colleagues Rui Wen and Misun Hong from the RIKEN Byon Initiative Research Unit have now captured never-before-seen details of lithium-oxygen reactions using *in situ* atomic force microscopy (AFM) as a step toward resolving these drawbacks[1].

Byon and her colleagues set out to gather unambiguous evidence of nucleation, growth and decomposition of lithium-oxygen electrochemical products using AFM to trace out surface topographies down to nanometer scales. In their study, they crafted a model cell comprised of a highly oriented pyrolytic graphite (HOPG) working electrode, metallic lithium counter and reference electrodes, and an ether-based solvent packed with oxygen gas and lithium salts as an electrolyte.

As lithium-oxygen batteries discharge power, lithium ions react with oxygen to produce solid lithium peroxide (Li_2O_2) deposits on atomically flat HOPG substrates. When the team monitored this reaction by AFM, they saw tiny particulates less than 10 nanometers high begin to nucleate along the 'step edges' inherent to HOPG (Fig. 1). These nanoparticles swiftly grew into elongated 'nanoplate' structures of micrometers in length, and further reaction caused the nanoplates themselves to fuse into a new lithium peroxide film.

The researchers then observed the battery recharge process, where oxygen gas is released and lithium ions migrate to the metallic lithium electrodes. Their AFM images revealed that during the initial recharge cycle, the lithium peroxide film decomposes completely, leaving no residue on the HOPG. By the fifth cycle, however, many by-products emerged as a result of the oxidation of the HOPG electrode and degradation of the ether-based electrolyte and lithium salt.

Byon notes that these findings will help researchers to accurately correlate parameters such as electrode composition and size with changes in battery performance. "This could provide insight into the design of catalysts and electrodes for lithium-oxygen batteries," she says.

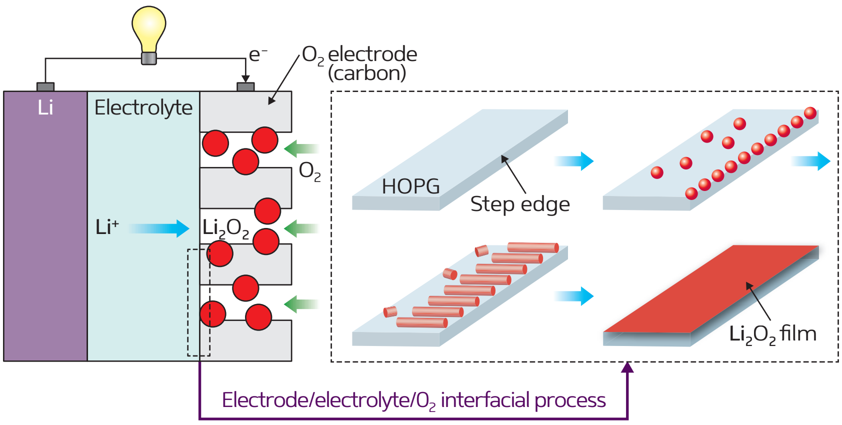


Figure 1: High-resolution microscopy reveals that lithium–oxygen (Li–O_2) batteries discharge power through a series of nanoscale product growth processes on atomically flat HOPG surfaces.

1. Wen, R., Hong, M. & Byon, H. R. In situ AFM imaging of Li–O_2 electrochemical reaction on highly oriented pyrolytic graphite with ether-based electrolyte. *Journal of the American Chemical Society* **135,** 10870–10876 (2013).

Breaking nature's superfluid symmetry

Observing the breaking of an intrinsic symmetry in superfluid helium-3 offers new insight into fundamental natural phenomena

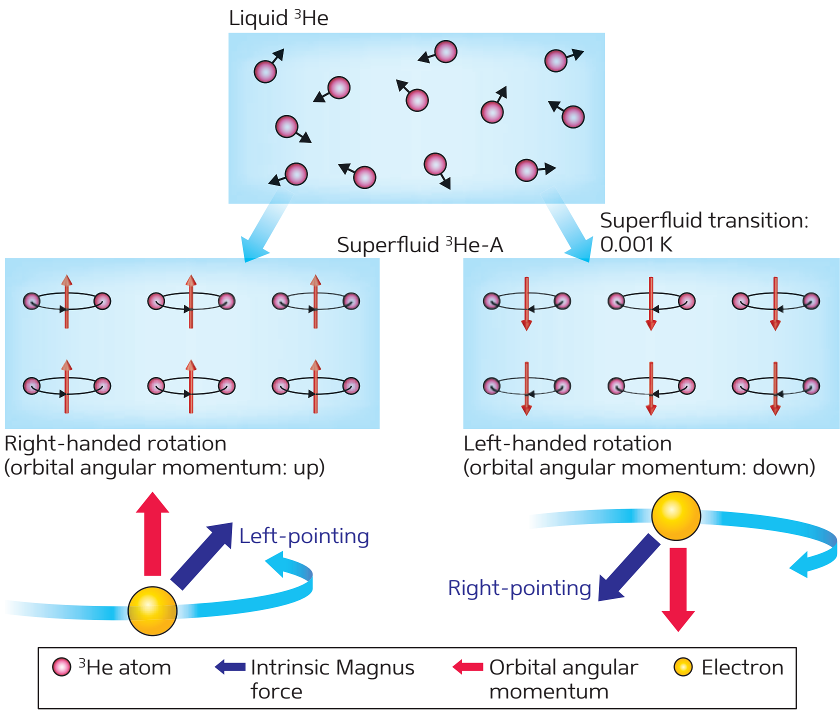


Figure 1: As superfluid helium-3 (^{3}He) reaches a temperature of just above absolute zero (0.001 kelvin), its constituent Cooper pairs spontaneously adopt either an upward or downward angular momentum, indicating a breaking of the superfluid's intrinsic chiral symmetry. This effect was measured directly by observing the intrinsic Magnus force of electrons, which reveals the Cooper pair's chiral 'handedness'.

Superfluids are an exotic state of matter in which particles flow without experiencing viscosity. Hiroki Ikegami and colleagues from the RIKEN Low Temperature Physics Laboratory in Wako have now observed another remarkable property of superfluids—the breaking of a fundamental natural symmetry in superfluid helium-3 (^{3}He)[1]. The finding is important for many areas of physics, says Ikegami. "Spontaneous symmetry breaking is a universal and fundamental concept found in various branches of physics. It describes that nature prefers taking a less symmetric state even if underlying laws are symmetric."

Superfluidity in helium-3 occurs at a temperature of just a few thousandths of a degree above absolute zero and involves two helium-3 atoms bonding together to form Cooper pairs that are able to move without hindrance. One of the properties of a Cooper pair is its angular momentum, which describes the rotation of the pair. In the superfluid helium-3, the angular momenta of the Cooper pairs all align in the same direction: either upwards or downwards. This spontaneous choice of one direction over the other breaks one of the fundamental symmetries of superfluid helium-3 that is related to chirality—left- and right-handed mirror-image symmetry.

To detect the broken symmetry, the researchers developed a system that allowed them to observe the intrinsic Magnus force, which causes any tiny object traveling orthogonal to an orbital angular momentum to deviate sideways (Fig. 1), thus revealing the chiral 'handedness' of the fluid. The researchers injected electrons beneath a liquid helium surface to form a thin electron layer, then set the electrons in motion using electrodes placed just above the helium. The deflection of the electrons was then measured using the same electrodes.

In most measurements, the helium-3 atoms had the same orbital angular momentum alignment across the entire sample. In some cooling runs, the angular momentum of the Cooper pairs pointed upwards, in others downwards. This means that the direction is selected spontaneously despite there being no intrinsically preferred direction for the angular momentum, providing direct evidence of chiral symmetry breaking.

Sometimes the samples showed multiple domains with different orientations of orbital angular momentum, which were attributed to topological defects in the fluid. Such observations are important for further study, explains Ikegami. "One of the important consequences of symmetry breaking is the formation of topological defects such as magnetic domain walls in ferromagnets and cosmic strings in the Universe. Studying these in detail may shed light on the role of defects in the breaking of symmetries in various branches of physics."

1. Ikegami, H., Tsutsumi, Y. & Kono, K. Chiral symmetry breaking in superfluid ^{3}He-A. *Science* **341,** 59–62 (2013).

Making memories

Modifying the activity of neuronal networks that encode spatial memories leads to the formation of an incorrect fear memory in mice

The formation and retrieval of memories allows all kinds of organisms, including humans, to learn and thrive in their environment. Yet our memories are not always accurate, and mistaken remembrances can have important consequences, such as in the justice system and in our navigation of the world. Susumu Tonegawa, Steve Ramirez, Xu Liu and colleagues at the RIKEN–MIT Center for Neural Circuit Genetics, have gained insight into the creation of mistaken memories by using light activation of neurons to generate an incorrect fear memory in mice[1].

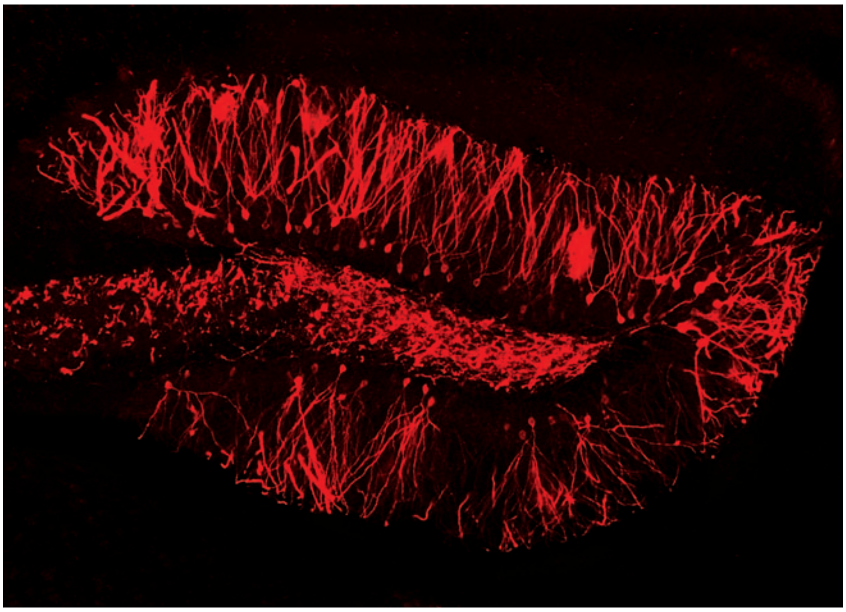


Figure 1: Channelrhodopsin-2 expression (red) in the dentate gyrus of the hippocampus.

The researchers allowed mice to explore a novel location and used genetic techniques to label neurons in the hippocampus—a part of the brain linked to spatial memory—that were activated in the process with a special channel called channelrhodopsin-2 (Fig. 1). The cells that expressed this channel could then be artificially activated by light. In this way, the researchers were able to reactivate neurons that fired in that particular location, even if the mice were no longer there.

They then moved the mice to another location where they were exposed to foot shocks, causing the mice to exhibit immobility, a fear behavior. At the same time, the researchers used light to activate the channelrhodopsin-2-expressing neurons that had fired in the first location.

When Tonegawa and his colleagues moved the animals to a third location, they did not show fear behavior. Yet when the mice went back to the first location, where they had never experienced a foot shock, the mice now exhibited prominent freezing behavior. The researchers had generated a 'false memory' in the mice of foot shocks in a location in which they had never been exposed to them.

The researchers showed that light reactivation of neuronal networks in the central area of the hippocampus, called the dentate gyrus, could create false memories, while reactivation of the outer 'CA1' area of the hippocampus could not. Tonegawa and his colleagues suggest that this is because mouse exploration of different locations leads to activation of more overlapping neuronal networks in the CA1 than in the dentate gyrus. "This may reflect the fundamental differences of how memories are encoded in these two regions," explains Liu.

The findings provide insight into how the brain encodes and processes memories and could one day lead to treatments for post-traumatic stress disorder. "Our work may also have implications for situations where patients mix reality with their own imaginations, such as in schizophrenia," says Liu.

1. Ramirez, S., Liu, X., Lin, P.-A., Suh, J., Pignatelli, M., Redondo, R. L., Ryan, T. J. & Tonegawa, S. Creating a false memory in the hippocampus. *Science* **341,** 387–391 (2013).

More to perception than meets the eye

Neuronal activity in the visual cortex of the human brain is controlled by both where the eyes are looking and what they see

Even though our eyes are constantly moving, the brain perceives the external world as stationary—a feat achieved by integrating images acquired by the retina with information about the direction of the gaze. An international team of investigators including Justin Gardner from the RIKEN Brain Science Institute in Wako has now found that neuronal activity in the visual cortex of humans depends on both the nature of the visual stimulus and the position of the eyes' gaze[1].

The researchers conducted a series of experiments in which five subjects were shown a screen displaying eight evenly spaced crosses. For each trial run, the subjects fixed their gaze on one of the crosses while a wedge of dots moved around that cross. This test was repeated for each of the crosses, and the activity within the visual cortex in response to the visual stimulus was continuously monitored using non-invasive functional magnetic resonance imaging.

The team found that the response of neurons in the visual cortex to visual stimulation was modulated by both the position of the wedge of dots and the direction of the subjects' gaze. For example, one area of the visual cortex would become active when the wedge of dots was in a particular location within its rotation, having a stronger response when that wedge was on the cross in the upper right of the screen and a weaker response when it was on the cross in the lower left of the screen. In this way, the neurons in the visual cortex simultaneously encoded not only the nature of the visual stimulus but also its location in space.

Figure 1: Humans use both the retinal location response and eye position to maintain a stable representation of the world.

Gardner and his colleagues interpret their findings to mean that neurons in the visual cortex respond selectively to visual stimuli that impinge on a given section of the retina in the eye but don't directly encode the locations of the stimuli in the world. Instead, the neurons in the visual cortex alter the amplitude of their responses based on eye position.

"Our research shows that every time we move our eyes, the population of neurons representing the stable outside world changes dramatically—a whole new set of neurons will become active to represent an object that has not moved," explains Gardner. "We've found that humans maintain both a retinal location response and an amplitude modulation with eye position to create a stable representation of the world and to locate objects in the environment."

1. Merriam, E. P., Gardner, J. L., Movshon, J. A. & Heeger, D. J. Modulation of visual responses by gaze direction in human visual cortex. *The Journal of Neuroscience* **33,** 9879–9889 (2013).

One pot, many possibilities

A simple, one-pot method for the synthesis of a range of biologically useful fluorine-bearing amine molecules could aid drug development

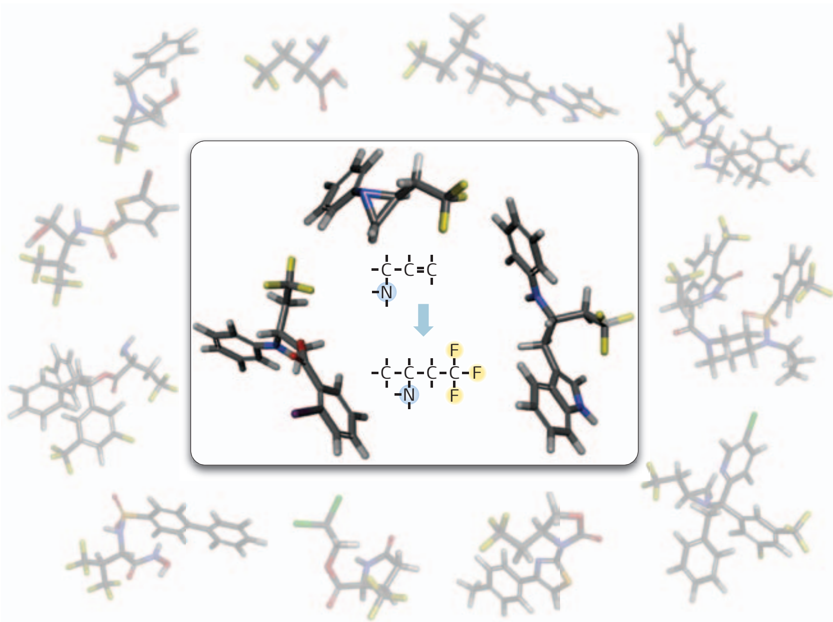


Figure 1: Three typical reaction products bearing the β-trifluoromethyl amine structure (center). The background shows a variety of bioactive compounds with the β-trifluoromethyl amine structure.

The trifluoromethyl group is present in many pharmaceutical and agrochemical products owing to its useful biological properties. A number of trifluoromethylated amine compounds display high bioactivity and are therefore of particular interest to medicinal chemists, but few synthetic methods for producing these compounds are known. Mikiko Sodeoka and colleagues from the RIKEN Synthetic Organic Chemistry Laboratory and RIKEN Center for Sustainable Resource Science have now developed a simple one-pot synthesis for a range of these important molecules[1].

The synthetic method developed by Sodeoka's team involves three different reactions, each starting with molecules containing both an amine group and an alkene. All are reacted with what is known as Togni's reagent, which contains the trifluoromethyl group, CF_3, in the presence of a catalytic amount of copper iodide. "The reaction uses the iodide salt of the inexpensive and highly abundant metal, copper, as a catalyst," says Sodeoka.

In the first reaction, called 'N-migratory oxytrifluoromethylation,' the trifluoromethyl group is added to one end of the starting molecule's double-bonded carbon–carbon moiety (Fig. 1), and the molecule's nitrogen atom migrates to the other end, to be replaced by carboxylic acid. This reaction establishes β-trifluoromethyl amine as a potentially useful intermediate molecule for the synthesis of various bioactive compounds.

When this reaction was stopped prematurely, the team discovered the presence of a small amount of a compound containing an aziridine group—a useful functional group due to its high reactivity. For their second reaction, the team therefore tweaked the reaction conditions to allow this compound to be produced at higher yields. In the third reaction, the aziridine compounds were functionalized by their reaction with a variety of nucleophiles in the reaction mixture. The whole process represents a one-pot, three-component coupling reaction.

"Our method provides highly functionalized amine derivatives from simple allylamine derivatives, which are commercially available or easy to prepare and handle," says Sodeoka. "We believe that our new synthetic method provides medicinal chemists with the opportunity to examine more trifluoromethylated amine derivatives in their lead-optimization processes." As Sodeoka explains, fluorine substitution near an amine center, such as by trifluoromethylation, is an important tool in the complex 'lead optimization' stage of drug development, where a potential drug compound is refined to produce a preclinical drug candidate. "Fluorine substitution not only lowers the amine's basicity but also enhances its metabolic stability," she notes.

"We are now planning to apply these reactions to the synthesis of bioactive molecules and will also try to develop new methods for the construction of other versatile structures containing a trifluoromethyl group," adds Sodeoka.

1. Egami, H., Kawamura, S., Miyazaki, A. & Sodeoka, M. Trifluoromethylation reactions for the synthesis of β-trifluoromethylamines. *Angewandte Chemie International Edition* **52**, 7841–7844 (2013).

FRONTLINE

Constructing the world's top-performing x-ray laser beam

HITOSHI TANAKA

Division Director
XFEL Research and Development Division
RIKEN SPring-8 Center

The year 2011 marked the first successful amplification of an x-ray free electron laser beam at the RIKEN SPring-8 Angstrom Compact Free Electron Laser (SACLA) facility. Later that year, Hitoshi Tanaka led the facility to its peak operation, producing a stable x-ray laser beam with a wavelength of 0.63 ångströms—the world's shortest. X-ray lasers such as SACLA permit researchers to directly observe microscopic structures, as well as molecules or atoms that move at extremely high speeds.

A 'dream light'

Researchers at SPring-8 (Super Photon Ring-8 GeV), a large-scale synchrotron radiation facility based at the RIKEN Harima Institute, analyze the structure of atomic-scale objects, such as proteins, using x-ray radiation. This requires the crystallization of samples, a process that is difficult to apply to the membrane proteins that are often important targets for drug discovery.

Alternatively, the structure of atomic-scale objects can be observed with coherent light—in which the peaks and dips are in phase—without requiring samples to be crystallized. Laser beams emit coherent light but until recently were believed to produce oscillations only in the infrared, visible or ultraviolet light ranges. A laser that could emit light in the x-ray spectrum—with the extremely short wavelength of approximately 1 ångström (Å)—was considered to be a 'dream light.'

The first conceptual designs for an x-ray free electron laser (XFEL), or an x-ray laser beam, were proposed in the 1980s. Within decades, projects to build XFEL facilities were planned in the United States, Europe and at RIKEN in Japan.

Eventually in 2009, researchers in the United States constructed the world's first x-ray laser in an XFEL facility—an improvement of an existing accelerator. Then, in June 2011, SACLA (SPring-8 Angstrom Compact Free Electron Laser)—RIKEN's own XFEL—successfully amplified an x-ray laser beam.

In an XFEL, a high-quality electron beam produced by an electron gun is accelerated using a linear accelerator and compressed with a bunch compressor. The high-density, high-energy electron beam is then made to snake through undulators to generate an intense light beam, which later interacts with another electron beam to produce an x-ray laser (Fig.1).

With a total length of 700 meters, the RIKEN SACLA facility is much smaller than the XFEL facilities in the United States or Europe, which are about 2 and 3.4 kilometers long, respectively. In spite of its compact dimensions, SACLA produces a stable x-ray laser beam with the world's shortest wavelength. SACLA's success did not come easily, however; the researchers who worked on its development faced a series of technical challenges.

Compressing the electron beam

RIKEN was able to create the highly compact SACLA facility by standardizing

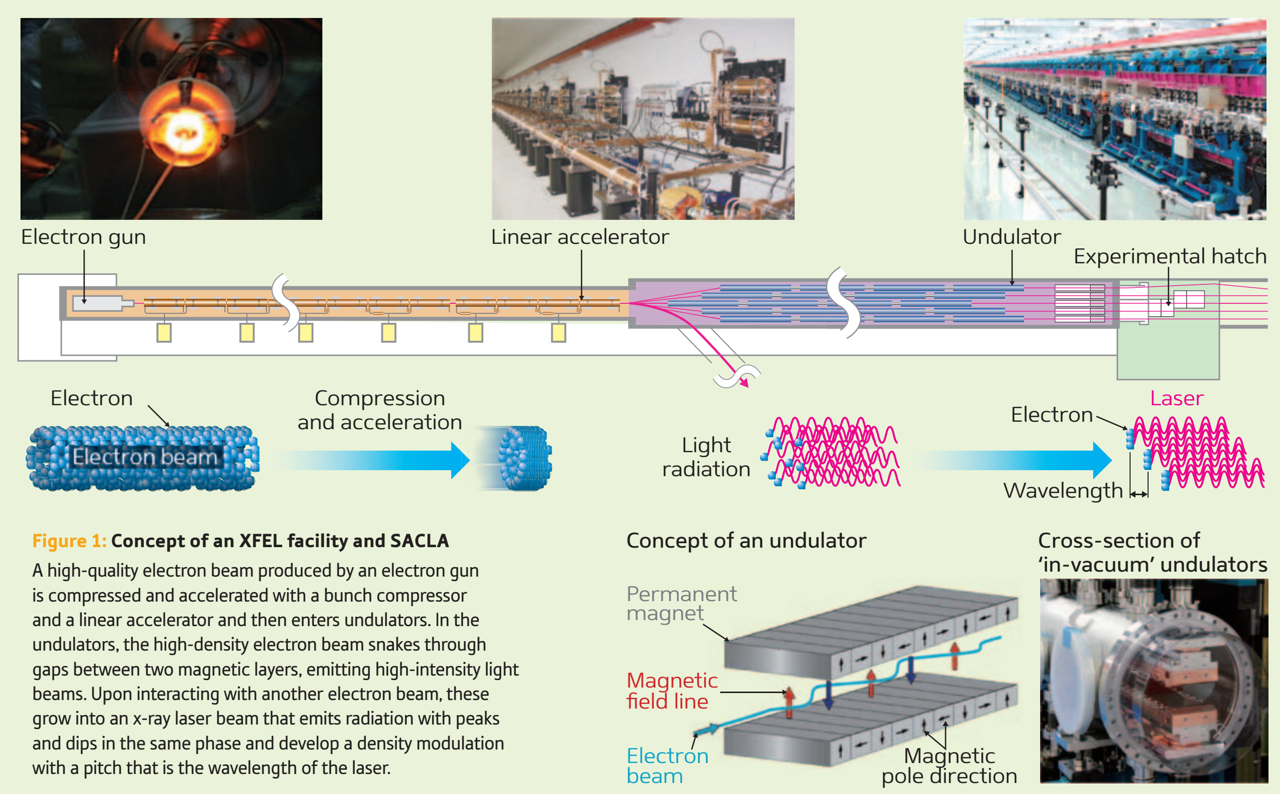


Figure 1: Concept of an XFEL facility and SACLA

A high-quality electron beam produced by an electron gun is compressed and accelerated with a bunch compressor and a linear accelerator and then enters undulators. In the undulators, the high-density electron beam snakes through gaps between two magnetic layers, emitting high-intensity light beams. Upon interacting with another electron beam, these grow into an x-ray laser beam that emits radiation with peaks and dips in the same phase and develop a density modulation with a pitch that is the wavelength of the laser.

and improving the performance of SPring-8's in-vacuum type undulators. Within an undulator, an electron beam is made to snake through a gap between two layers of alternately arranged north and south magnetic poles. Conventionally, two layers of magnetic poles are placed outside the vacuum vessel through which the electron beam is designed to pass.

However, when two layers of magnets, each consisting of north and south poles separated by a shorter fixed pitch, are placed close to the electron beam, these in-vacuum type undulators allow the electron beam to snake through them over a shorter distance, producing an x-ray laser beam with a shorter wavelength—even when the electron beam's energy is low. Using this approach, RIKEN was able to shorten the undulators, and correspondingly, the linear accelerator. The overall XFEL facility was further downsized by using a C-band accelerator, which accelerates the electron beam more efficiently.

RIKEN then developed an electron gun to improve the quality of the electron beam and offset lower levels of energy and acceleration. Composed of a heated single-crystal cerium hexaboride cathode, the electron gun produced a high-quality electron beam in which the electrons were uniformly distributed within the cylindrical shape.

The beam met the quality standards demanded of SACLA, but in order to verify whether it could actually produce an x-ray laser, in 2005 RIKEN began construction of the SPring-8 Compact SASE Source (SCSS), a prototype accelerator of 60 meters in length, and a precursor to SACLA.

Tanaka, director of the XFEL Research and Development Division, was chosen to lead the project because of his experience conducting research into the stabilization and densification of electron beams at SPring-8. A major challenge in developing the SCSS was how to compress the electrons to 300 times their original density, without compromising the electron beam's initial quality.

"Some people advised me not to accept the offer because the SCSS was technically too difficult to complete. But the task did not seem impossible to me," Tanaka recalls.

Assessing feasibility

Construction of SACLA began in April 2006. Compared to the SCSS x-ray laser's oscillator wavelength of 490 Å, the target wavelength for SACLA was set at around 1 Å. In order to achieve this, the electron beam would have to be compressed up to 3,000 fold—ten times more than what was required for the SCSS.

At the time, researchers thought that in order to produce such a high-density electron beam, equipment of a correspondingly high accuracy and stability would need to be procured. "There is a limit to the accuracy of equipment. A simple evaluation predicted that it would not be feasible to construct a facility that could produce a stable electron beam compressed 3,000 fold using current technology," says Tanaka. "In spite of the successful construction of the laser oscillator in the SCSS, laser oscillation in the x-ray band was considered to be difficult by all researchers. Therefore, we decided to run a simulation to find out what level of accuracy or stability would be required of the associated equipment."

The simulation revealed that the accuracy or stability required for the

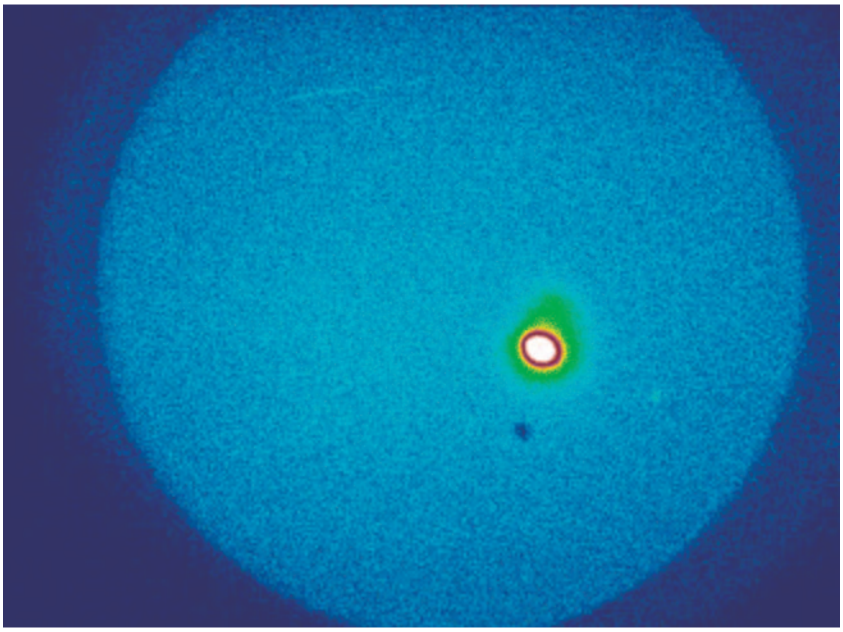


Figure 2: X-ray laser beam produced by SACLA
An x-ray laser beam is positioned at the white portion indicated by the small red circle near the center.

equipment in SACLA to function was almost the same as that required for the equipment in the US XFEL facility, where the compression ratio was about one-tenth of that in SACLA.

An electron beam is compressed in four stages, as Tanaka describes. "In the first stage, the speed of the electrons is adjusted along the direction of their forward movement. As with traffic during periods of congestion, we can compress an electron beam by creating a situation in which faster electrons at the back can catch up with slower electrons at the front. The simulation showed that an error in the compression process in the first stage would not contribute to an increase in the error after the compressed electrons passed through the subsequent compression stages. In this way, we began to see the light at the end of the tunnel in our quest to produce a stable x-ray laser."

A series of problems

By January 2011, SACLA was almost complete, and it was decided that beam tuning would begin in February. The first major problem faced by the researchers was the occurrence of anomalous light emissions that made observing the electron beam's condition impossible. "To diagnose the condition of a compressed electron beam, we observe its spatial distribution by forcing it to strike a thin metal film. However, it is not possible to diagnose its condition if the signal from the electron beam is hidden by anomalous light emissions," explains Tanaka.

"Anomalous light emissions were also a major issue for the US XFEL facility," he continues. "However, since the electron gun used in SACLA differed to the one used in the United States, we had underestimated the probability of there being any such emissions. Furthermore, experiments conducted with the SCSS to confirm the occurrence of anomalous light emissions under various operating conditions did not observe any such emissions."

Unfortunately, Tanaka and his team's conclusions did not hold up: anomalous light emissions were indeed present. "We held urgent meetings to discuss ideas for countermeasures and quickly created an observation system that could spatially separate any anomalous light emissions from the signal."

The team eventually solved the problem and continued with beam tuning, but the quality of the electron beam displayed on the monitor did not improve. "As we searched for the cause, I recalled an error that we had experienced with the monitor in an earlier experiment. We calibrated the monitor and finally succeeded in evaluating the quality of the electron beam correctly."

The final challenge faced by Tanaka and his team was to arrange the undulators in rows with an accuracy of 0.004 millimeters per 100 meters. "The technique used at the US XFEL facility—according to their report—was to analyze the observed data on the trajectory of the electron beam as it passed through the undulators and then to adjust the position of the undulators and ancillary devices. We were not satisfied with their method of analysis and came up with another idea," admits Tanaka. "We knew that electron beams follow the same trajectory when the undulators and their ancillary devices are arranged in rows, even if the beams are of different energies. Therefore, we decided to observe the trajectory of electron beams with different energies and adjust the position of the undulators and ancillary devices so that the beams would follow the same trajectory. Using this approach, we succeeded in arranging the undulators in straight rows."

As a precautionary measure, the team also observed the light radiation emitted from the electron beams, and found them not to be in perfectly straight rows. "In our first approach, we used data on the center of gravity of an electron beam. But later we noticed that an actual electron beam does not have a completely axisymmetric distribution and that the distribution can change slightly whenever the energy of the electron beam varies," points out Tanaka. "Therefore, we decided to change our approach by using light radiation instead of an electron beam to rearrange the undulators in straight rows. As we were the first to attempt this approach, we were able to set the undulators in perfectly straight rows to within the required accuracy, a fact that was verified by our subsequent success with laser amplification." Correspondingly, on 7 June 2011, the team finally managed to produce an x-ray laser with a wavelength of 1.2 Å (Fig. 2).

Producing the world's shortest wavelength

The researchers continued to tune the beam in SACLA to intensify the x-ray laser and stabilize its wavelength and intensity. "We adjusted the position of the electron beam to pass precisely through the center of the linear accelerator's acceleration tube and prevent the quality of the electron beam from deteriorating but regularly came across new locations where the beam would go off-center," continues Tanaka.

"Feeling that something was wrong, we examined these locations and discovered that eight of the acceleration tubes had significant curves in them, despite their having been straight when measured at the factory before shipment."

Tanaka later learned that curvature had been caused by packaging problems at the factory: the tubes were squeezed into boxes without sufficient space and eventually molded into their newly bent shapes.

The SACLA x-ray laser eventually succeeded in producing the world's shortest wavelength of 0.63 Å—almost half of the 1.2 Å achieved by the US XFEL facility. The SACLA facility opened to external users in March 2012, and the facility has been inundated with requests for experiments ever since. In addition, researchers in the United States are considering adopting the stabilization technique used by SACLA in the construction of their second XFEL facility.

Tanaka is aware of SACLA's low stability in comparison to SPring-8. For instance, the intensity of SACLA's x-ray laser tends to shift slightly when the facility is operated continuously, he explains. "Although we can use an advanced control program to automatically restore the intensity, we are actually correcting the deviation manually because we want our operating staff to understand the characteristics of the instability and to use their accumulated knowledge to investigate its cause. In this way, we hope to eliminate the factors of instability one by one in pursuit of ultimate stability."

Toward the observation of physical and chemical phenomena at the atomic scale

A main feature of the x-ray laser developed at SACLA is that the laser is emitted in a series of extremely short pulses, each with an emitting time of 10 femtoseconds. The light pulses should enable the observation of atoms or molecules that move at extremely high speeds when undergoing a dynamic process such as a chemical reaction, phase transition or structural deformation. "Unfortunately, the light in its current form does not allow us to continuously observe these phenomena because it is extremely strong and instantaneously destroys the samples," notes Tanaka. For now, samples must instead be measured at different stages of a reaction and the data then organized into chronological order.

"If we could directly observe and accurately reproduce the process of a phenomenon when matter fulfills a function, the results would produce enormous benefits for the whole of science. Drastically increasing the coherence of the x-ray radiation produced by the SPring-8 synchrotron radiation facility would allow us to continuously observe samples at the atomic scale without destroying the samples," says Tanaka. "I would really like to be able to measure the same samples with SPring-8 and with SACLA, but even in SPring-8, a top-performing facility with the world's highest level of brightness, coherent light accounts for only 0.1% of the x-ray light radiated."

A breakthrough in 2012 changed the situation. "European researchers published the design for equipment capable of increasing the proportion of coherent light in light radiation by combining multiple approaches that had not previously been used."

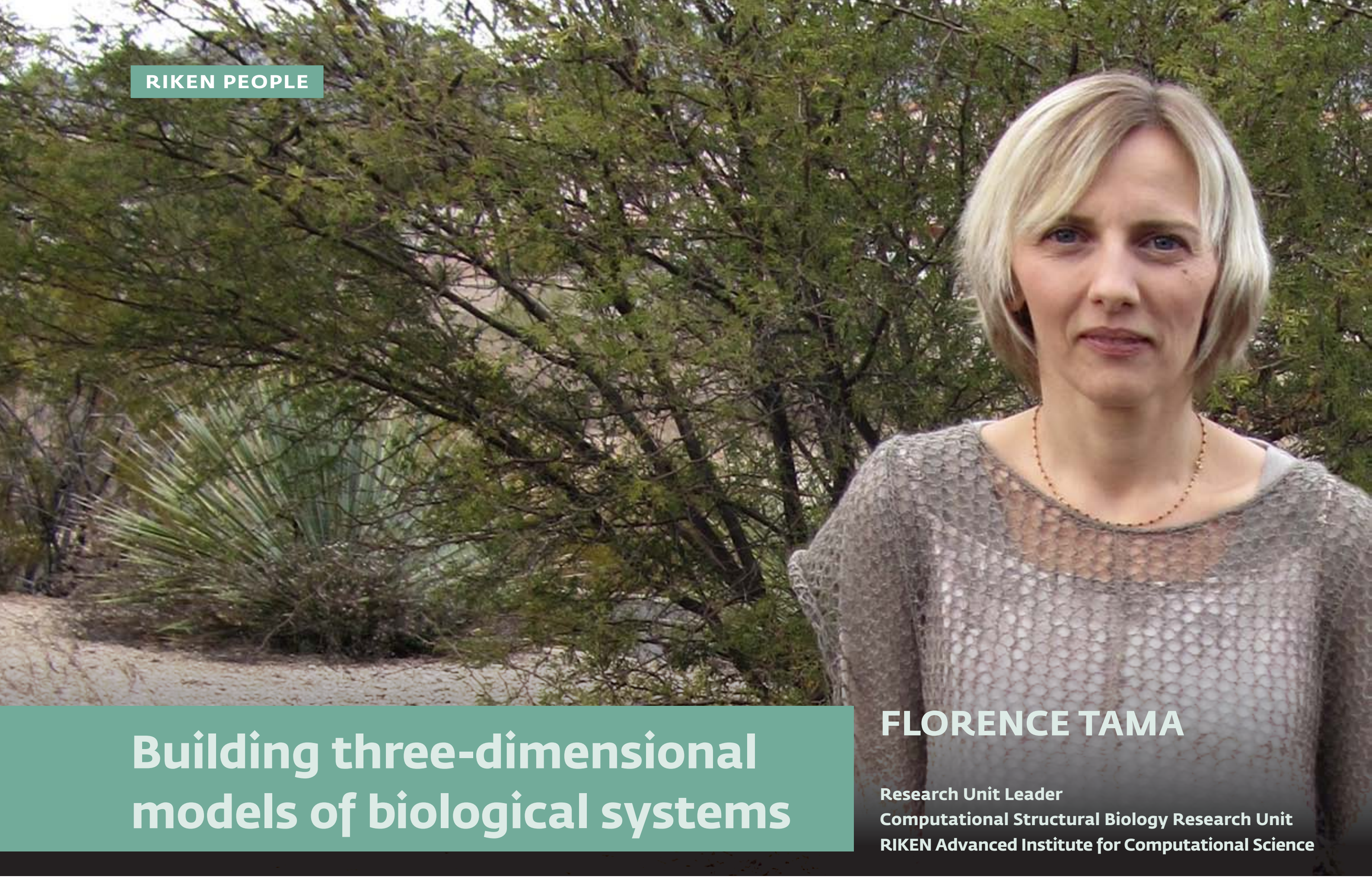
In May 2013, the RIKEN SPring-8 Center set up the Diffraction Limited Synchrotron Radiation Design Group, and Tanaka assumed the position of group director. "We aim to drastically increase the coherence of light radiation from SPring-8 by integrating our own ideas into the design published by the European researchers." Researchers at the SACLA facility also have plans to add more x-ray laser beam lines to the one currently available for measurements, as well as to further decrease the size of the facility.

"We will be able to add up to five x-ray beam lines," claims Tanaka. "Whereas in SPring-8, the light radiation from an electron beam that moves along the ring and the resultant 62 beam lines can all be used for simultaneous measurements, in the XFEL facility the number of beam lines is limited by its structure. This is why we focused on making the facility more compact," he explains.

"And if the overall length of the facility were to be further reduced to less than 100 meters by extending the technology developed at SACLA, we could even construct an XFEL facility at a campus or company's premises. This would offer many more researchers the opportunity to use an x-ray laser beam for their experiments."

ABOUT THE RESEARCHER

Hitoshi Tanaka was born in Tokyo in 1957 and was awarded his master's degree from the Interdisciplinary Graduate School of Science and Engineering of the Tokyo Institute of Technology. After working at the Atomic Energy Division of JGC Corporation, the RIKEN Cyclotron Laboratory, the Accelerator Division of the Japan Synchrotron Radiation Research Institute and the RIKEN XFEL Project Head Office, Tanaka joined the RIKEN XFEL Research and Development Division as divisional director in April 2011. Since May 2013, he has concurrently led the Diffraction Limited Synchrotron Radiation Design Group as group director.



Building three-dimensional models of biological systems

FLORENCE TAMA

Research Unit Leader
Computational Structural Biology Research Unit
RIKEN Advanced Institute for Computational Science

How did you join RIKEN, and what kind of support did RIKEN provide?

I first traveled to Japan in 1998 to conduct research at Kyoto University for my PhD. I later moved to the United States to take up a postdoctoral position and eventually joined the University of Arizona as a faculty member. In 2013—fifteen years after my first visit to the country—I decided to join RIKEN and moved to Japan with my family.

When I arrived at the RIKEN Advanced Institute for Computational Science, I was provided with a lot of assistance in setting up my research group. For example, dealing with Japanese documents can be challenging at times, and there was also much to learn about the functioning of the institute. Fortunately, the administrative staff at RIKEN were always happy to help me navigate the system.

Why were you drawn to RIKEN?

RIKEN is a globally renowned institution that offers excellent opportunities for research. In my field—computational biophysics—where we use computers to study biological molecules, RIKEN and its K computer are able to compete with the top computational centers around the world. RIKEN is also at the forefront of experimentation thanks to the SACLA X-ray Free Electron Laser (XFEL), which presents researchers interested in the structure of biological molecules with new opportunities to obtain potentially exciting results.

Please describe your current research at RIKEN.

At the Computational Structural Biology Research Unit, we develop computational tools to study biological systems. More specifically, we use a variety of experimental techniques to help determine the three-dimensional structure of biological molecular complexes and analyze their potential interactions with smaller molecules for the purpose of designing new drugs.

As macromolecular complexes undergo large conformational changes to achieve their core biological functions, characterizing their structure is crucial for understanding underlying mechanisms and for developing new drugs to treat diseases. Our ultimate goal is to integrate x-ray and XFEL experimental data with computational tools processed by the K computer to acquire knowledge about the structure of physiologically important protein complexes that cannot be obtained using existing experimental techniques.

What is the best thing about working at RIKEN?

RIKEN has many outstanding research groups with whom we can exchange ideas, making the institution a stimulating environment to work in. Furthermore, RIKEN offers excellent research facilities and a great support system. The work environment is conducive to purely focusing on research, on account of the experienced administrative staff who support other aspects of running a research group.

What would you say to other people considering joining RIKEN?

RIKEN is a great place to work, and as a non-Japanese scientist I should add that a lot of effort has been put into welcoming researchers like me. Some informational meetings about applying for grants in Japan are conducted in English. In addition, RIKEN organizes several events to bring doctoral students and postdoctoral researchers together, which helps to create a close-knit community at RIKEN.

CONTACT INFORMATION

For details about working at RIKEN, please contact the RIKEN Global Relations and Research Coordination Office:
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RIKEN attends tenth anniversary celebration of Biopolis

The year 2013 marks the tenth anniversary of Biopolis, an international research and development hub for the biomedical sciences based in Singapore. RIKEN—as a member of the Biopolis community, and in conjunction with the Japan Science and Technology Agency (JST)—was invited to host a booth at the Biopolis Carnevale, an event held to celebrate a decade of successful collaboration between public and private stakeholders in the field of biotechnology.

Kenichiro Kakihara, director of the RIKEN Singapore Representative Office, welcomed visitors to the joint RIKEN–JST booth at the tenth anniversary celebration of Biopolis in Singapore.

The event, which took place on 18 October, featured booths hosted by more than 30 research institutes. In addition, visitors were offered tours of key Biopolis facilities and open houses at several research institutes of the Singapore Agency for Science, Technology and Research (A*STAR). The event drew a crowd of more than 3,000 individuals.

RIKEN's booth gave the organization an opportunity to share its mission, programs and research activities with the public as well as to promote them among young researchers. Visitors to the booth included researchers, job seekers and high school students from local schools who were accompanied by teachers and parents.

RIKEN's relationship with Biopolis dates back to 2005, when it set up an office on the Biopolis campus as part of a Memorandum of Understanding (MoU) signed between RIKEN and A*STAR. The MoU served to seal the two institution's commitment to conduct joint research in the life sciences and biotechnology fields. ■

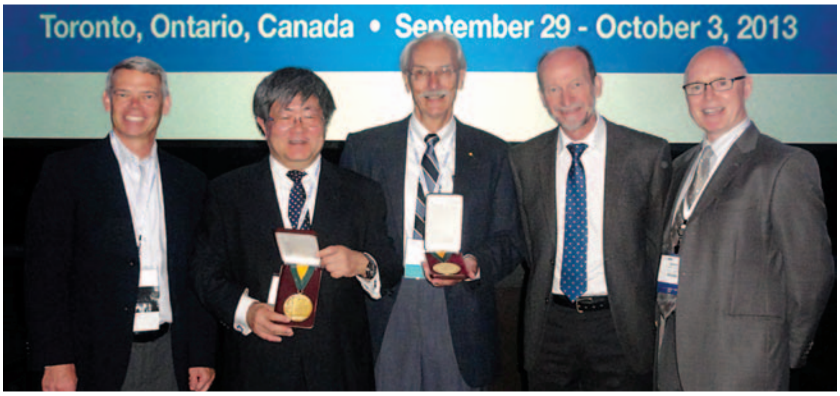
Yuichi Sugiyama honored with the R. T. Williams Distinguished Scientific Achievement Award

On 30 September 2013, Yuichi Sugiyama, head of the Sugiyama Laboratory at the RIKEN Innovation Center in Yokohama, received the 2013 R. T. Williams Distinguished Scientific Achievement Award for his four decades of work on drug transporters and pharmacokinetics. The award is conferred once every three years by the International Society for the Study of Xenobiotics (ISSX) and recognizes a scientist who has made substantial and seminal scientific contributions to the field over a sustained period.

The award ceremony was held at the 10th International ISSX Meeting in Toronto, Canada, and attended by professionals in the field of xenobiotics from around the world. To accompany the announcement of the prize, the ISSX described its reasons for awarding the prize to Sugiyama, noting that: "Sugiyama's work has highlighted the importance of considering pharmacokinetic properties in drug development, using good screening methods to test large numbers of drug candidates. Overall, he has produced a remarkable body of scientific work, with a profound impact on how we understand the pharmacokinetics, pharmacodynamics and use of drugs."

Sugiyama joined RIKEN in 2012 after retiring from a decade-long professorship at the University of Tokyo's Department of Molecular Pharmacokinetics. Previously, he served as president of the ISSX and the Japanese Society for the Study of Xenobiotics.

Over the years, Sugiyama has cultivated an expertise in molecular pharmacokinetics, a new area of research at the intersection of physiology, molecular biology, genetics and pharmacokinetics. Central to his work is the reliable and applicable prediction of *in vivo* drug activity, with the goal of advancing drug therapy. His groundbreaking studies have helped to explain the behavior of drugs in the body and how they exert their pharmacological and toxic effects, with a specific focus on their interaction with lipid membranes, receptors, enzymes, transporters and other components of cells. ■



Yuichi Sugiyama (second from left) with Bill Smith (far left), president of the ISSX, Robert Hanzlik (center), winner of the ISSX Frederick J. Di Carlo Distinguished Service Award, John Miners (second from right), chairman of the ISSX Awards Committee, and Denis Grant (far right), meeting chair.

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