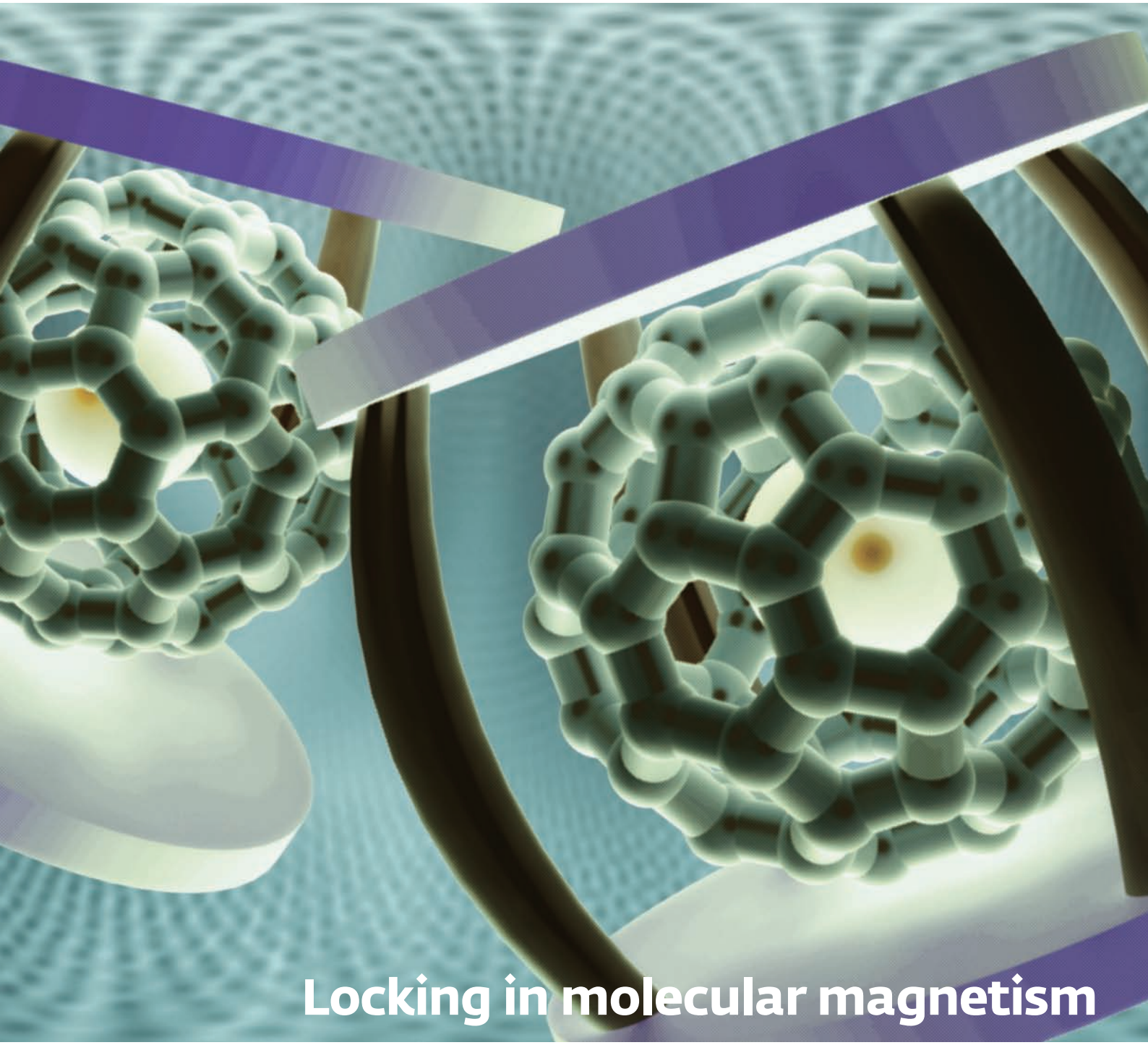
RIKEN RESEARCH

SEPTEMBER 2011
VOLUME 6 NUMBER 9



Locking in molecular magnetism

RIKEN

Biology

A journey of many steps

Identification of enzymes critical to natural bacterial drug production points to shortcuts for building better therapeutic agents

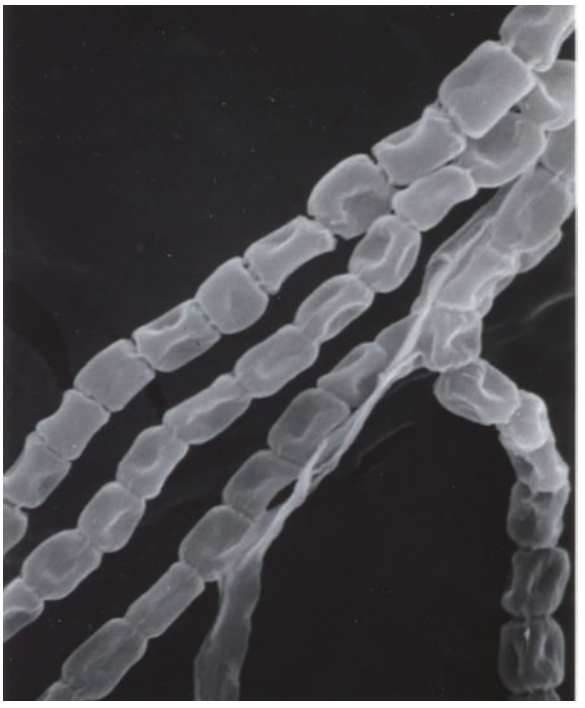


Figure 1: An electron micrograph of the bacterium *Streptomyces* sp. SN-593.

Some of the most promising drugs in the clinical pipeline are derived from compounds that microbes already produce naturally. With a time-scale of millions of years, their evolution-powered drug development process may not be the most efficient in terms of speed, but the resulting molecules can achieve remarkably specific and potent interactions with important biological targets.

The bacterium *Streptomyces* sp. SN-593 (Fig. 1), for example, produces the antibiotic reveromycin A (RM-A), explains Shunji Takahashi, a senior research scientist with Hiroyuki Osada's team at the RIKEN Advanced Science Institute in Wako. "RM-A was originally isolated as an inhibitor of cancer cell proliferation," says Osada. RM-A is also a potent inhibitor of metastatic tumor growth in bone—it induces cell death specifically in cells called osteoclasts, which makes it a promising anticancer drug candidate.

RM-A is one of a larger family of compounds known as spiroacetal polyketides, which are typically manufactured via a complex, multi-enzyme process. Synthesis of these compounds proceeds in the fashion of an assembly line, with each enzyme introducing a particular chemical modification to a precursor molecule before passing it along to the next enzyme.

By understanding the nuts and bolts of this process, scientists can potentially 'hack' production to manufacture more effective drugs. Osada, Takahashi and colleagues recently made important strides in this regard by identifying the enzymes that generate RM-A's distinctive core 'spiroacetal' structure[1].

Touring the factory floor

Previous attempts to dissect RM-A biosynthesis based on the analysis of individual candidate genes have run into signficant obstacles. "In most cases, we determine the physiological substrates of one enzyme in an unknown biosynthetic pathway by disrupting its gene and analyzing the accumulated biosynthetic intermediate," says Takahashi. Unfortunately, *Streptomyces* sp. SN-593 can be a difficult organism to manipulate genetically, and the production intermediates are too chemically unstable to isolate and characterize.

Fortunately, the researchers were able to devise a set of techniques that enabled them to comprehensively analyze the genetics and biochemistry of RM-A production in this organism. They began by cultivating *Streptomyces* under conditions that maximized the activity of the RM-A production machinery. This enabled them to zoom in on a cluster of genes that all participate in this drug assembly line, which they subsequently sequenced. The 'backbone' of RM-A is assembled over the course of a 62-step process by multiple gene products containing specialized functional domains that collectively form a complex known as the polyketide synthase (PKS) system, after which another set of enzymes introduces various post-PKS modifications that ultimately yield the final drug product.

Based on their analysis of the various enzymes in the PKS pathway as well as a series of experiments with isotope-labeled RM-A precursors, Osada, Takahashi and colleagues were able to identify a key intermediate in the synthetic pathway,

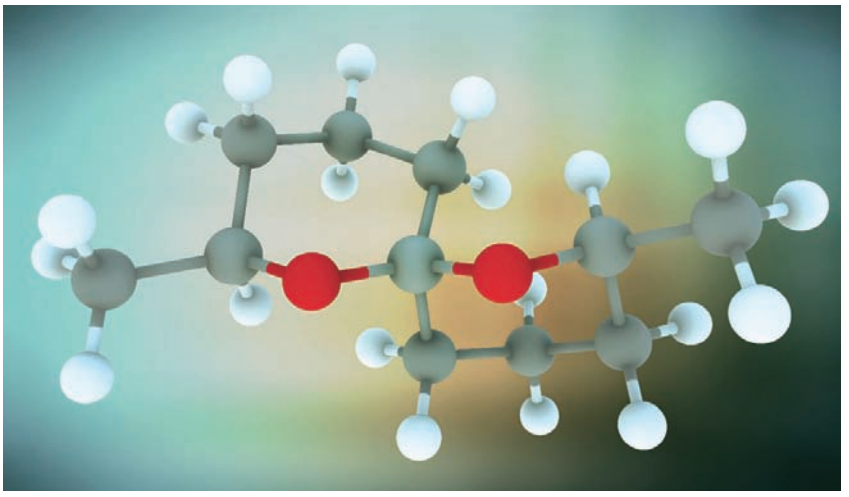


Figure 2: The stereochemically appropriate spiroacetal structure, as incorporated into the final reveromycin A molecule.

which they termed RM-A1a. Oddly, this intermediate contains a propionyl group, a small three-carbon 'tail' that is added during synthesis but is notably absent from the final target molecule. "We have not yet solved the physiological significance of this additional propionyl unit which must later be truncated," says Takahashi.

RM-A1a is a linear molecule that must subsequently be rendered circular, a process known as 'cyclization' that the researchers hypothesized would be enacted by an enzyme known as a dehydrogenase. They identified such an enzyme in their gene cluster, and demonstrated that disruption of the *revG* gene, which encodes this protein, leads to the accumulation of RM-A1a. Experiments combining RM-A1a with purified RevG confirmed that this enzyme facilitates the transition of this RM-A precursor into a cyclization-ready intermediate.

Getting oriented

Just like humans, molecules can be right- or left-handed. This property of 'handedness', also known as chirality or stereochemistry, depends on the relative positioning of their various chemical groups, and can radically affect a molecule's biological properties. Osada, Takahashi and colleagues were surprised to note that the intermediate generated by RevG ultimately gives rise to a mix of products of varying stereochemistry, even though the naturally occurring RM-A product only exhibits '15S' stereochemistry. "We had thought that the formation of the final spiroacetal stereochemistry would be non-enzymatically selected, but rather based on [differences in] thermodynamic stability," says Takahashi.

This hinted at the action of a yet-unidentified enzyme, and gene-disruption experiments revealed the protein RevJ as the missing link. Without RevJ, *Streptomyces* cells produced 75% less '15S' RM-A than their wild-type counterparts. Accordingly, the researchers were able to show that the sequential action of both RevG and RevJ is required to drive formation of the appropriate spiroacetal structure during RM-A synthesis (Fig. 2).

According to the researchers, by unearthing the secrets of production in this way, it should become possible to develop drug derivatives in a more rational fashion, rather than simply stumbling through a process of trial and error. "Most chemical modifications of RM-A result in the loss of its bioactivity," says Takahashi. Finding ways to bolster the stability of RM-A without undermining its overall capacity for preventing bone destruction will be a primary objective. He and Osada intend to 'fill in the gaps' in the production process as a means to expand their chemical modification palette.

In parallel, the researchers also hope to determine the coordinating mechanisms that enable all of these various biosynthetic enzymes to work together in harmony. "We will solve the regulatory mode of gene expression in the RM-A cluster," says Takahashi.

1. Takahashi, S., Toyoda, A., Sekiyama, Y., Takagi, H., Nogawa, T., Uramoto, M., Suzuki, R., Koshino, H., Kumano, T., Panthee, S. *et al*. Reveromycin A biosynthesis uses RevG and RevJ for stereospecific spiroacetal formation. *Nature Chemical Biology* **7**, 461–468 (2011).

ABOUT THE RESEARCHERS

Hiroyuki Osada was born in Shirakawa, Japan, in 1954. He graduated from the Department of Agricultural Chemistry of The University of Tokyo in 1978, and obtained a PhD in 1983 from the same university. Since 2008, he has held the position of director of the Chemical Biology Department at the RIKEN Advanced Science Institute. His research focuses on the elucidation of biological questions using chemistry techniques.

Shunji Takahashi was born in Yokohama, Japan, in 1967. He graduated from the Faculty of Horticulture of Chiba University in 1992, and obtained his PhD in 1997. Since 2007, he has worked as a senior research scientist in the Chemical Biology Department of the RIKEN Advanced Science Institute. His research focuses on the biosynthetic mechanisms of polyketide compounds.

Synchronized dynamic duos

The ability to control how magnetic vortices gyrate together has potential application in magnetic devices

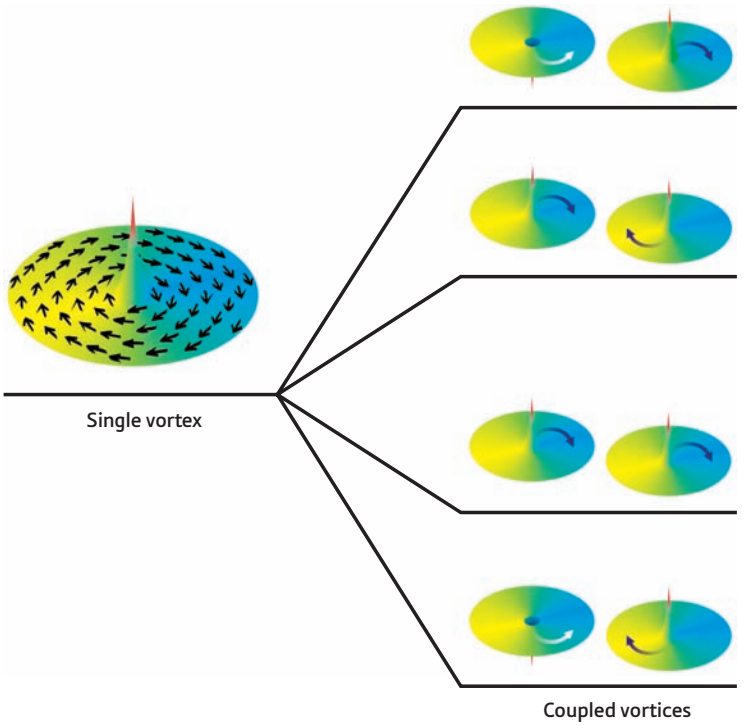


Figure 1: The magnetic domains in a single ferromagnetic disk arrange into a vortex (left). When two disks are brought close together (right), the magnetic vortices begin to move together. Their motion can be in-phase (bottom two levels), or out of phase (top two). The vortex cores can also point in the same direction, or in opposite directions, leading to four possible types of coupled motion.

Crystals can guide and control light and electricity by creating spatially periodic energy barriers. An electron (or photon) can pass through these barriers only when it has a particular energy, allowing engineers to create switches and other electronic devices. Now, a team of researchers from Japan and India has taken a key step towards using crystals to control waves of magnetic orientation (magnons)[1], with the potential to create magnetic analogues to electronic and optical devices, including memory devices and transistors.

Led by YoshiChika Otani at the RIKEN Advanced Science Institute, Wako, the researchers began by manufacturing tiny disks of ferromagnetic material. The magnetic domains of such disks arrange into vortices (Fig. 1, left), which consist of in-plane circular patterns surrounding a core with out-of-plane magnetization. By applying an alternating current with a particular frequency to such disks, physicists can excite the vortices into a gyrating motion, which they can detect by measuring the voltage across a disk.

Otani and his colleagues found that a current oscillating at 352 megahertz could set the vortex of a single disk into motion. When they brought a second disk near the first one, however, this single resonant frequency split into two: one was lower than the original frequency, and the other was higher. This kind of resonance splitting is characteristic of any pair of interacting oscillators with similar energies, whether it be two molecules that are covalently bonded to each other, or two swinging pendula.

The frequency splitting observed in the researchers' pair of disks indicated that the magnetic vortices in each were coupled together, even though the current was driving one disk only. The researchers showed through numerical simulation that the lower-frequency resonance corresponded to the two vortices rotating in phase with each other; the higher-frequency resonance corresponded to an out-of-phase rotation. Depending on whether the core polarizations of the two disks were pointing in the same or opposite directions, Otani and colleagues also observed different frequency pairs. This led to four distinct resonant frequencies in all (Fig. 1, right).

The researchers could control the differences among the four resonant frequencies by changing the distance between disks, as well as the disk sizes. By demonstrating controllable pairing between adjacent magnetic vortices, the results point the way to more complex chains, lattices and crystals in which magnons can be finely controlled, says Otani. "Our next target is to engineer a structure in which macroscopic spin waves propagate only along particular crystallographic directions." ■

1. Sugimoto, S., Fukuma, Y., Kasai, S., Kimura, T., Barman, A. & Otani, Y. Dynamics of coupled vortices in a pair of ferromagnetic disks. *Physical Review Letters* **106**, 197203 (2011).

Pushing the frontier of state control

The ability to use magnetic fields to control a newly identified state of matter could enable more efficient memory devices

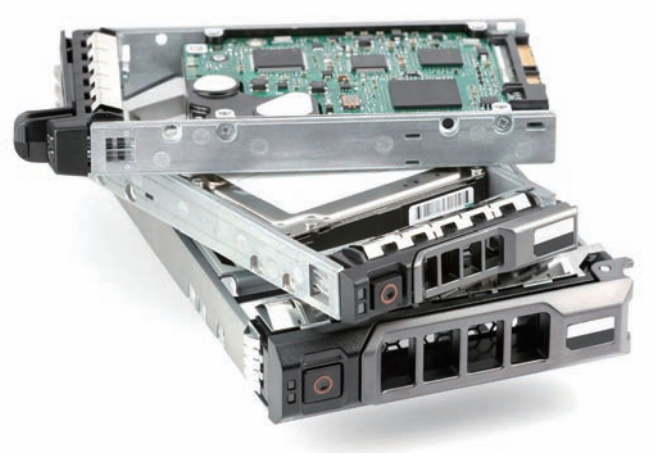


Figure 1: The ferromagnets in hard drives could one day be replaced by chiral spin liquids, achieving a lower-energy-consumption device.

Scientists in Japan have shown that the properties of a recently discovered state of matter—a chiral spin liquid—can be controlled by applying a magnetic field[1], a concept that could be harnessed for low-energy-consumption memory devices (Fig. 1).

Many ferromagnetic materials exhibit the so-called 'anomalous Hall effect' (AHE), whereby the electrons flowing through the materials experience a lateral force pushing them to one side as a result of the materials' intrinsic magnetization. In materials exhibiting the 'conventional' Hall effect, the lateral force is caused by an external magnetic field. The magnetic material $Pr_2Ir_2O_7$ is a special case because it displays AHE without possessing a uniform magnetization. This unusual behavior was recently recognized and analyzed for the first time by Shigeki Onoda from the RIKEN Advanced Science Institute, Wako, and his colleagues[2]. They interpreted this behavior as a good indication that $Pr_2Ir_2O_7$ exists as a chiral spin liquid in which effects such as AHE depend on which direction an electron is travelling.

The collaboration team of the theoretical physicist, Onoda, and colleagues at The University of Tokyo and the Tokyo Institute of Technology, Japan, and Florida State University, USA, discovered they could control this enigmatic material by experimentally investigating how the AHE in $Pr_2Ir_2O_7$ depends on applied-magnetic-field strength at temperatures below 2 kelvin. They found that the sign of the voltage drop associated with the anomalous Hall effect can be reversed by a sweep cycle of a magnetic field without causing an effect called hysteresis—where the magnetization depends on the direction in which the magnetic field is swept. "Magnetization hysteresis is a main cause of heat or energy loss," explains Onoda. "Thus, our results prove that this material could function as a nonvolatile memory device."

These properties arise because every physical system organizes in a way that minimizes its energy. In some materials, two competing influences—the arrangement of the crystal lattice and the ordering of local magnetic moments or 'spins' of electrons—cannot balance because they cannot simultaneously attain their minimum energy state. Known as geometric frustration, this situation prevents the system from settling in a particular state, and means that the spins fail to become ordered even at absolute zero. For this reason, physicists called these materials spin liquids.

"To practically harness the effects of AHE in a chiral spin liquid, the chirality must remain finite at room temperature," says Onoda. Although a difficult challenge, the current work is a positive start. ■

1. Balicas, L., Nakatsuji, S., Machida, Y. & Onoda, S. Anisotropic hysteretic Hall effect and magnetic control of chiral domains in the chiral spin states of $Pr_2Ir_2O_7$. *Physical Review Letters* **106**, 217204 (2011).
2. Machida, Y., Nakatsuji, S., Onoda, S., Tayama, T. & Sakakibara, T. Time-reversal symmetry breaking and spontaneous Hall effect without magnetic dipole order. *Nature* **463**, 210–213 (2010).

Out-of-shape nuclei

Adding neutrons to synthetic atoms can drastically alter the shape of their nuclei and affect their stability

To probe the evolution of atomic nuclei with different shape —a factor which affects atomic stability—a large team of international researchers has added neutrons to zirconium atoms and revealed the possibility of very unusual shapes[1]. "The shape of a nucleus reflects the symmetry of its quantum state," explains team member Hiroyoshi Sakurai from the RIKEN Nishina Center for Accelerator-Based Science in Wako. This result helps us to understand how many neutrons are needed for the most stable nuclei.

Most atoms can exist in one of several alternative forms called isotopes, depending on the number of neutrons in their core. Naturally occurring, stable, atoms tend to have between 1 and 1.5 neutrons per proton. However, synthetically generated atoms with higher neutron–proton ratios can reveal much about changes within an atomic nucleus.

The protons and neutrons in a nucleus usually form arrangements of concentric spherical shells. In some cases, however, the outermost particles exist further from the center than normal. This can lead to nuclei that are wider than they are long. Just as atoms with a specific number of protons can exist as different isotopes, atoms with a specific number of protons and neutrons can exist as different nuclear isomers—nuclei with different shapes. "By measuring the shape of nuclei, we are probing the internal symmetry in the nucleus—the so-called shell structure," explains Sakurai.

At the Radioactive Isotope Beam Factory in Japan, operated jointly by RIKEN and The University of Tokyo, the researchers experimented with zirconium atoms that have 40 protons and, in their stable form, between 50 and 52 neutrons. They created zirconium atoms with as many as 68 neutrons through collisions between uranium and beryllium atoms. After filtering isotopes from the remnants of the collision, they measured the rate of decay of beta and gamma radiation emitted by the quickly decaying, unstable synthetic atoms. The measurements showed that these nuclei changed shape from spherical to oblate (Fig. 1).

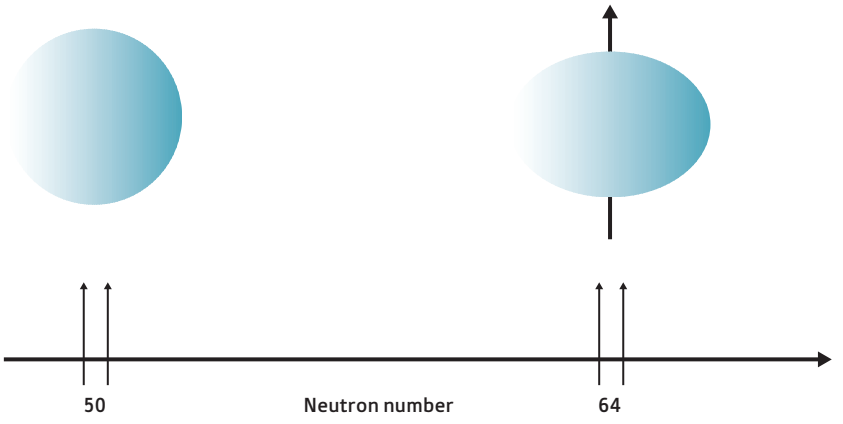


Figure 1: Adding neutrons to the nucleus of a zirconium atom changes its shape from spherical to oblate.

The degree of deformation of the zirconium nuclei increased as Sakurai and colleagues added more neutrons, but this trend stopped when they reached 64 neutrons. This result raises the intriguing prospect of a tetrahedral-shaped isomer of zirconium-108—an isotope with 68 neutrons—which has been predicted previously by other researchers. However, further work is needed to verify this.

"We next hope to gain further insight into the evolution of nuclear isomers by extending our study to strontium atoms," Sakurai says. ■

1. Sumikama, T., Yoshinaga, K., Watanabe, H., Nishimura, S., Miyashita, Y., Yamaguchi, K., Sugimoto, K., Chiba, J., Li, Z., Baba, H. *et al*. Structural evolution in the neutron-rich nuclei ^{106}Zr and ^{108}Zr. *Physical Review Letters* **106**, 202501 (2011).

Building towards better memories

Molecule-based memory devices edge closer with the development of supramolecular structures that act as tiny magnets

In a step towards realizing ultrahigh-density storage devices based on individual molecules behaving as magnets, researchers in Japan have developed a candidate building block[1]—a supramolecular ferromagnet, which is a caged molecule with magnetic properties. The research team was led by Takuzo Aida at the RIKEN Advanced Science Institute, Wako, and Kentaro Tashiro at the National Institute for Materials Science, Tsukuba.

The researchers' supramolecular magnet is based on a metallofullerene dubbed La@C_{82}—a lanthanum ion trapped within an 82-carbon spherical cage. La@C_{82} has well-known paramagnetic properties: it becomes magnetized in the presence of an external magnetic field. However, like all paramagnets, La@C_{82} loses its magnetization once the external field is removed, rendering it useless for data storage.

Endeavoring to overcome this loss of magnetization, Aida and his colleagues designed a molecular component that combines with La@C_{82} to form the supramolecular ferromagnet. They built a copper-containing structure, itself paramagnetic, to house La@C_{82} within an internal cavity. When mixed together, the two components self-assembled into a host–guest complex. To lock the La@C_{82} in place, the researchers clipped together extra arms on the host structure, converting it into a cage.

Assessing the magnetic properties of the locked and unlocked complexes, however, revealed a surprise, says Aida. Thanks to the interaction of the paramagnetic character of the two components, the unlocked caged complex did behave as a ferromagnet. However, when the researchers locked the supramolecular cage, that ferromagnetism was lost.

"It is difficult to predict the magnetic behavior of host–guest complexes," says Aida. "We envisaged that the caged structure would give rise to a ferromagnetic property, but this was not the case."

According to calculations run by the team, the switch in ferromagnetic behavior is all down to geometry. The La@C_{82} guest is a tight fit within the cavity of its host, and the unlocked cage forms an asymmetric, twisted structure. When the arms of the cage are closed, the structure is forced into a symmetrical shape for which the ferromagnetic state is no longer energetically favorable (Fig. 1).

The researchers are continuing to work with the unlocked supramolecular ferromagnet, building up arrays of the structure on a solid support—an essential step towards developing a practical memory device, says Aida. The most important point is that the cage must be properly oriented such that the resultant material retains its ferromagnetism, he says. ■

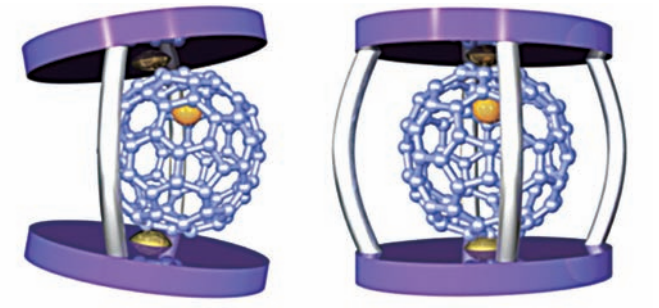


Figure 1: The spherical metallofullerene forms a ferromagnetic host-guest complex (left), but when the host structure is converted to a locked cage, the ferromagnetism is lost (right).

1. Hajjaj, F., Tashiro, K., Nikawa, H., Mizorogi, N., Akasaka, T., Nagase, S., Furukawa, K., Kato, T. & Aida, T. Ferromagnetic spin coupling between endohedral metallofullerene La@C_{82} and a cyclodimeric copper porphyrin upon inclusion. *Journal of the American Chemical Society* **133**, 9290–9292 (2011).

Flexibility: the key to carbon capture

Materials made from porous coordination polymers with flexing structures make better traps for harmful gases

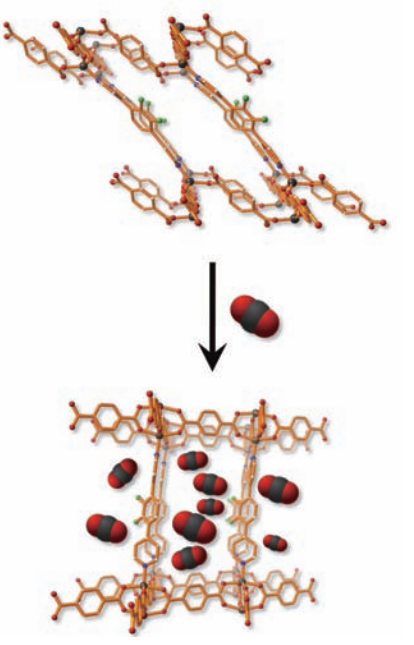


Figure 1: In the presence of carbon dioxide molecules (red and black), the molecular PCP cage expands to adsorb the gas.

From power plants that capture their own carbon dioxide emissions to vehicles powered by hydrogen, clean energy applications often demand materials that can selectively adsorb large volumes of harmful gases. Materials known as porous coordination polymers (PCPs) have great gas-trapping potential, and now their adsorptive properties can be boosted using a new technique developed by a research team in Japan[1].

The key to the development is making PCPs that can flex, since it allows the team to tune the gas-adsorbing properties of these materials—whether it is to improve the ability to selectively adsorb one gas from a mixture or to fine-tune the pressure at which the gas is captured and released.

While structural flexibility in PCPs is not new, team member Ryotaro Matsuda from the RIKEN SPring-8 Center, Harima, explains that he and his colleagues successfully incorporated this flexibility into a PCP built from molecular components known as secondary building units (SBUs). At the molecular scale, PCPs consist of vast networks of tiny interlinked cages, inside which gas molecules can sit. SBUs are made from clusters of metal atoms that can be used to form the corner of each cage. Their use gives materials scientists great control over the structure of a cage, but they can also lock the structure.

Matsuda and colleagues overcame the rigidity problem by connecting the cage corners into cubes using long, slim carbon-based linkers. In the absence of carbon dioxide, these slender linkers allow the cage framework to collapse into a non-porous solid; but in the presence of a gas, the material expands—a behavior known as gate-opening adsorption (Fig. 1).

It is a behavior that could prove useful, Matsuda explains. "Gate-opening-type adsorption, which is induced by the structural transformations from a non-porous structure to a porous structure at a certain pressure of gas, would provide a way to enhance the efficiency of pressure swing adsorption," he says. Pressure-swing adsorption is being investigated as a way to capture carbon dioxide emissions from power plants. The concept relies on finding materials that will release the gas in response to a drop in pressure, so that it can be piped away for long-term, underground storage.

The researchers are now looking to improve the performance of their material. "We are currently trying to tune the soft porosity of the prototype PCP to separate mixtures of gases," says Matsuda. "We have also been working to reveal the relationship between the structure, adsorption property and separation ability of [other] PCPs." ■

1. Seo, J., Bonneau, C., Matsuda, R., Takata, M. & Kitagawa, S. Soft secondary building unit: dynamic bond rearrangement on multinuclear core of porous coordination polymers in gas media. *Journal of the American Chemical Society* **133**, 9005–9013 (2011).

Screens set to go green

Electronic screens based on new energy-efficient technology could become more affordable thanks to the substitution of expensive metal components with copper ones

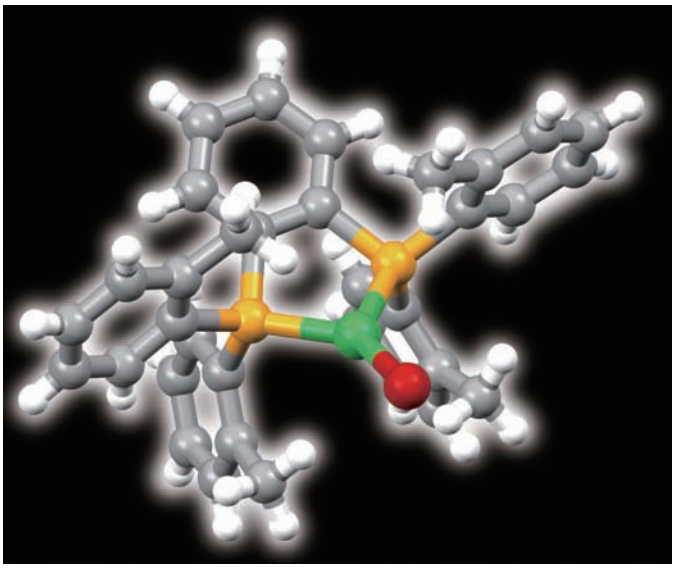


Figure 1: The molecular structure of the bulky organic ligand that turns copper (green) into an efficient light emitter (yellow, phosphorus; red, bromine).

Fitting the screens of electronic devices, such as televisions and smartphones, with a new display technology called 'organic light-emitting diodes' (OLEDs) will reduce their energy consumption, but such screens currently require rare and expensive metal components. Now, Masahisa Osawa and his colleagues at the RIKEN Innovation Center in Wako, along with researchers from electronics company Canon, have found a way to replace these costly metals with copper [1].

In addition to offering significant energy savings over conventional LCD-based displays, OLED screens improve picture quality by producing richer blacks; they also offer a wider viewing angle. In an LCD screen, each pixel is effectively a little filter, selectively blocking light produced by a large backlight. In an OLED screen, however, each pixel is a tiny light emitter such that no backlight is needed. This means that pixels in dark areas of the image consume no power, reducing energy use.

To maximize the energy-saving benefit, screen makers select OLED materials that most efficiently convert electrical current into light, a property known as high external quantum efficiency (EQE). Some of the best materials are phosphorescent metal complexes, but these are typically composed of rare and expensive metals such as iridium.

Copper complexes have long been known as potential alternatives, and would cost 1/2,000th that of iridium phosphors, according to Osawa. Until the work of Osawa and his colleagues, however, these copper complexes had a low EQE. Such complexes can be readily excited into a high-energy state, but they tend to physically distort, which dissipates their extra energy rather than emitting it as light.

The researchers resolved this problem by altering the molecular environment in which the copper sits. They wrapped each copper ion inside a newly designed bulky organic ligand. They then conducted X-ray diffraction studies, which revealed that the ligand had forced the copper to become three-coordinate—it had formed three bonds to the ligand, rather than the usual four (Fig. 1).

Osawa and colleagues also demonstrated that the EQE of their green-light-emitting copper complex increased dramatically and matched that of iridium complexes. "The three-coordinate structure is a crucial factor for high EQE, because it hardly distorts in the excited state," Osawa explains.

The team's next step will be to deploy the complex in a working device. Copper might not be limited to producing green light, Osawa adds. "Our goal is to make red-, green-, and blue-colored phosphorescent three-coordinate copper materials." ■

1. Hashimoto, M., Igawa, S., Yashima, M., Kawata, I., Hoshino, M. & Osawa, M. Highly efficient green organic light-emitting diodes containing luminescent three-coordinate copper(I) complexes. *Journal of the American Chemical Society* **133**, 10348–10351 (2011).

Helping neurons stay on track

Guidance signals prevent neurons from making bad connections by triggering a mechanism that causes growing axons to shrivel and retract

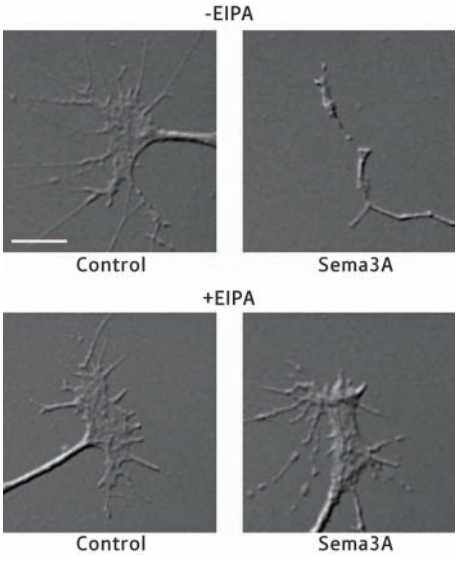


Figure 1: Compared to highly branched controls (left), axons of neurons treated with Sema3A tend to collapse (top right). However, this effect can be blocked by treatment with macropinocytosis inhibitor EIPA (bottom right), revealing the central importance of this mechanism in responses to repulsive signals (scale bar, 10 µm).

The complex inner wiring of the brain is coordinated in part by chemical guidance factors that help direct the interactions between individual neurons. As growing cells extend their axons outward, these tendrils are simultaneously drawn in the correct direction by attractive signals and steered away from 'wrong turns' by repulsive signals.

New work from a team led by Hiroyuki Kabayama and Katsuhiko Mikoshiba of the RIKEN Brain Science Institute in Wako has revealed insights into how one of these repulsive guidance cues, semaphorin 3A (Sema3A), gives axons their marching orders[1]. In an earlier study, the researchers found evidence that Sema3A causes large-scale internalization of the cellular membrane at the growth cone, the tip of the growing axon, and determined that this internalization occurs via a process known as macropinocytosis[2]. "These findings suggested an important role for massive, macropinocytosis-mediated membrane retrieval during Sema3A-induced growth cone collapse," says Kabayama.

The neurotoxin C1, a protease enzyme, induces similar effects on growth cones, and Kabayama and Mikoshiba and their colleagues were able to uncover Sema3A's mode of action via experiments using this enzyme. Based on a series of experiments with cultured neurons isolated from chick embryos, the researchers determined that the enzyme works by breaking down syntaxin 1B (Syx1B), a protein with a prominent role in membrane trafficking, thereby releasing an inhibitory mechanism that otherwise keeps macropinocytosis in check.

Accordingly, direct inhibition of Syx1B expression in neurons led to reduced axonal growth and increased growth cone collapse. On the other hand, treatment with the macropinocytosis-inhibiting compound EIPA countered the growth cone-collapsing effects of either neurotoxin C1 or inhibition of Syx1B. The researchers also found that this drug alone was sufficient to undermine Sema3A's axon-repulsive effects (Fig. 1).

Kabayama, Mikoshiba and colleagues obtained additional confirmation of the central role of Syx1B in experiments that revealed that the treatment of neurons with Sema3A triggers rapid degradation of this protein as a prelude to the initiation of macropinocytosis. This effect could be countered by forcing these cells to overexpress Syx1B. Kabayama also notes that another repulsive signal, ephrin A2, appears to act via the same cellular mechanism. "It is likely that repulsive axon guidance is generally mediated by syntaxin 1B-regulated macropinocytosis," he says.

In future studies, Kabayama and Mikoshiba intend to test this hypothesis by manipulating this pathway in transgenic animals. "We are going to generate Syx1B-overexpressing mice and investigate whether inhibition of macropinocytosis by Syx1B can prevent ephrin A2- or Sema3A-dependent growth cone collapse," says Mikoshiba. ■

1. Kabayama, H., Takeuchi, M., Taniguchi, M., Tokushige, N., Kozaki, S., Mizutani, A., Nakamura, T. & Mikoshiba, K. Syntaxin 1B suppresses macropinocytosis and semaphorin 3A-induced growth cone collapse. *The Journal of Neuroscience* **31**, 7357–7364 (2011).

2. Kabayama, H., Nakamura, T., Takeuchi, M., Iwasaki, H., Taniguchi, M., Tokushige, N. & Mikoshiba, K. Ca^{2+} induces macropinocytosis via F-actin depolymerization during growth cone collapse. *Molecular and Cellular Neuroscience* **40**, 27–38 (2009).

Ensuring the persistence of immune memory

A gene regulatory factor promotes long-term protection against infectious threats by effecting the maturation of a variety of immune cells

Structures within the lymph nodes known as germinal centers (GCs) help the body to maintain long-term immune defense against foreign threats. The GCs essentially act as sites where antibody-producing B cells undergo a process of 'evolution' to generate higher-quality antibodies. This evolutionary mechanism is in turn supported by a class of T cells known as follicular helper T (Tfh) cells.

Takaharu Okada and colleagues at the RIKEN Research Center for Allergy and Immunology in Yokohama recently tracked the process of B cell development in mouse GCs by monitoring expression of Bcl6[1]. This protein facilitates B cell evolution by regulating expression of key developmental genes.

The researchers were surprised to note a broader scope of Bcl6 activity than expected. "It became apparent that Bcl6 is important for Tfh cells as well," says Okada, "and I felt that we should track [the levels of] Bcl6 expression in both B and T cells at the same time."

They quantified Bcl6 levels by generating transgenic mice in which a DNA fragment encoding a fluorescent protein had been inserted into one copy of the *Bcl6* gene. Since this insertion partially disrupted Bcl6 function, this reporter system enabled the researchers to examine the effects of inhibiting this protein.

Following the induction of an immune response in the animals, Okada and colleagues observed an increase of Bcl6 expression in antigen-specific B cells within peripheral regions of the lymph node; these subsequently migrated to the GC, where they continued to strongly express Bcl6 (Fig. 1).

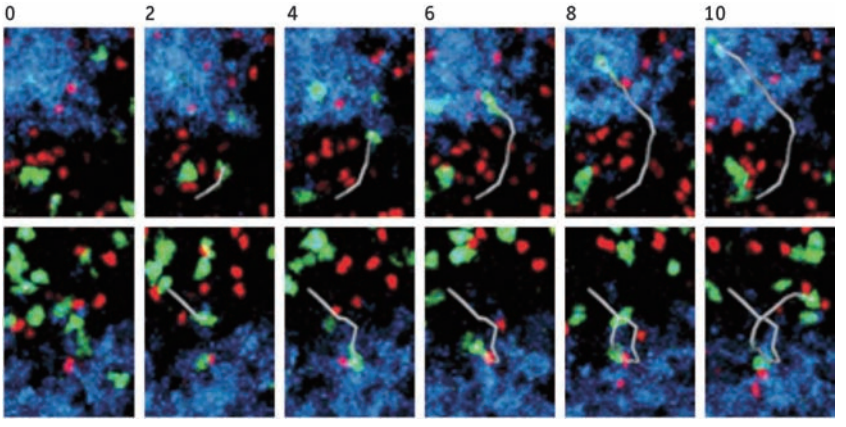


Figure 1: Time-lapse photography at two-minute intervals shows the migration (white trail) of a Bcl6-expressing B cell (green) into the GC (blue) following induction of an immune response (top). By comparison, B cells with inhibited Bcl6 function fail to migrate to the GC (bottom).

This migration and maturation process is dependent upon interaction with Bcl6-expressing helper T cells. All T cells expressing high levels of Bcl6 became Tfh cells, but many Tfh cells subsequently reduced Bcl6 production to varying degrees. Okada was surprised that the dynamics of Bcl6 expression differed between B and T cells. "This suggests that they employ different mechanisms for regulating expression of this important transcription factor," he says.

Okada and his team also recorded observations suggesting that Tfh cells expressing low levels of Bcl6 may give rise to 'memory cells', which enable the immune system to react quickly to recurring threats. However, this will require further investigation.

Understanding how these various cells employ this shared regulatory factor will also be a top priority moving forward. "We would like to learn the molecular mechanisms of Bcl6 expression in B and T cells by setting up collaborations with experts in the field of gene and protein expression control," says Okada. ■

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Overcoming amplification biases

A sequencing platform capable of analyzing single DNA molecules provides a powerful tool for identifying subtle changes in gene expression

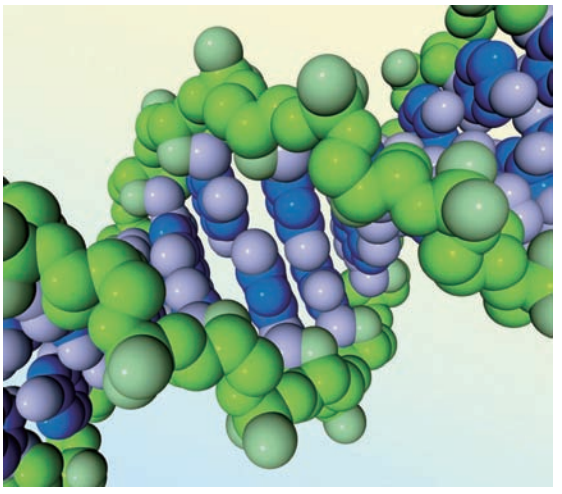

Figure 1: Sophisticated instruments capable of accurately sequencing single nucleic acid molecules make it possible to analyze gene expression without amplification-associated biases.

In a truly challenging task, the FANTOM5 Consortium, an international collaboration headed by scientists at the RIKEN Omics Science Center in Yokohama, is striving to profile the regulation of gene expression in every known human cell type. "We expect to generate on the order of 3,000 or more [datasets] for this project," says Masayoshi Itoh, a RIKEN scientist involved in the effort. "This will capture the majority of human cell types, tissues and cancer subtypes."

The work will benefit greatly from HeliScopeCAGE, a sensitive expression analysis technique developed recently by FANTOM5 researchers[1]. Previous FANTOM studies used techniques based on 'cap analysis of gene expression' (CAGE), which enables quantification of messenger RNAs transcribed from active genes by generating short DNA 'tags' that can be analyzed by sequencing. Conventional CAGE relies on the polymerase chain reaction (PCR), a method for amplifying target nucleic acid molecules. However, PCR can also introduce biases into libraries by preferentially amplifying some molecules—a serious impediment to the accurate measurement of gene expression.

A solution arrived in the form of the HeliScope, an instrument developed by Helicos Biosciences for the analysis of individual molecules of DNA (Fig. 1). "We realized that we could use this system to apply a much-simplified protocol that completely avoids PCR," says Itoh. To test their streamlined HeliScopeCAGE technique, he and his colleagues generated tag libraries from different cell types, which they analyzed with no intervening amplification step.

Remarkably, the researchers could obtain accurate results from as little as 100 nanograms of material (the mRNA content of approximately 20–100,000 cells), and chart differences in gene expression levels ranging across five orders of magnitude. The researchers noted that the observed differences between different cell types correlated with previous findings. HeliScopeCAGE even revealed changes in thousands of genes that had been overlooked by older platforms.

Itoh points out that their technique proved highly quantitative, based on trial experiments with different concentrations of control templates, and yielded consistent data in run after run. "The results were highly correlated," he says. "They almost looked identical, to the extent that I could not find any differences by eye."

FANTOM5 is already a third of the way to its 3,000-library goal, and an automated HeliScopeCAGE platform should accelerate their progress. However, this method is also being made available to the greater community through the RIKEN Yokohama Institute. "We believe HeliScopeCAGE could be useful not only to us, but to every scientist in Japan," says Itoh. ■

1. Kanamori-Katayama, M., Itoh, M., Kawaji, H., Lassmann, T., Katayama, S., Kojima, M., Bertin, N., Kaiho, A., Ninomiya, N., Daub, C.O. *et al* . Unamplified cap analysis of gene expression on a single-molecule sequencer. *Genome Research* **21**, 1150–1159 (2011).

Protecting young minds

A popular flu medication's neurologic side effects in children may be the result of inefficient drug clearance in the immature brain

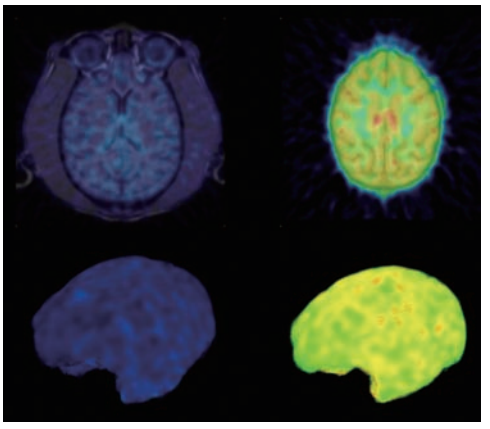

Figure 1: Positron emission tomography (PET) reveals markedly greater uptake of radioactively labeled verapamil in infant rhesus macaque brains (left) relative to adults (right). The top images represent individual scans, and the bottom images represent 3D reconstructions from those scans.

Oseltamivir is the weapon of choice for preventing influenza infection from taking hold, but like any other drug, it also has the potential for adverse effects. Children in particular are susceptible to neurological symptoms, including delirium and an increased tendency for self-injury.

In partnership with University of Tokyo researcher Yuichi Sugiyama, a team led by Hirotaka Onoe at the RIKEN Center for Molecular Imaging Science, Kobe, recently discovered how age might influence the effects of oseltamivir[1]. "We speculated that changes in drug transporter function may influence the penetration of oseltamivir and its effects in the brain," says Onoe.

The capillaries that oxygenate the brain are tightly sealed to prevent potentially toxic compounds or pathogens in the blood from penetrating the central nervous system. Specialized transporter proteins that pump toxic compounds out of the brain bolster the effectiveness of this 'blood–brain barrier'.

Oseltamivir and verapamil, a drug for cardiac arrhythmia, are believed to be exported by the P-glycoprotein (P-gp) transporter protein. Onoe and colleagues therefore tracked the circulation of radioactively labeled drugs in infant, adolescent and adult rhesus macaques to monitor whether or not P-gp function changes as monkeys age.

Strikingly, both drugs achieved considerably greater penetration into the brain in younger animals. For example, the maximum concentration of oseltamivir within the brain was 3.7-fold higher in infants than adults, and 2.7-fold higher in adolescents relative to their elder counterparts.

Similar results were observed with verapamil (Fig. 1). Some of this disparity could be accounted for by increased overall drug levels in the bodies of younger animals, possibly due to less efficient metabolic processing. However, even when this effect was accounted for, the researchers found clear evidence that older animals purge verapamil from the brain faster than infants and adolescents.

These results are in keeping with previous studies in rodents, which have indicated that P-gp levels increase as animals get older. "The most interesting finding from this study is the significant difference in P-glycoprotein function observed among nonhuman primates of different ages," says Onoe.

The extent to which the physiology of drug clearance in nonhuman primates mirrors that of humans remains the subject of debate. Nevertheless, these findings suggest a mechanism by which oseltamivir and other drugs could provoke adverse neurological effects in younger patients. Onoe and colleagues hope to further pursue their hypothesis. "We'd like to try clinical studies to assess the evidence found in this study, and understand the ontogeny of drug transporter function in humans," he says. ■

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JUN KIKUCHI

Team Leader
Advanced NMR Metabomics Research Team
Metabolomics Research Division
RIKEN Plant Science Center

Understanding the recycling of matter through research on biological metabolism

Heading the Advanced NMR Metabomics Research Team in the Metabolomics Research Division at the RIKEN Plant Science Center, Jun Kikuchi is engaged in analyzing metabolism within living organisms, mainly using nuclear magnetic resonance (NMR) spectroscopy. He uses a wide range of samples in his research, including not only higher plants, but also algae, complex microbial systems, insects, mice, fish, foods and beverages. "The goal of my research is to gain a comprehensive understanding of metabolic dynamics in a wide variety of organisms, with a view to elucidating the universal laws of nature," says Kikuchi. "This will lead to green innovations that may increase the potential of organisms to metabolize valuable substances, and to innovations that will contribute to better health. I want to be an innovator in these areas." Kikuchi is engaged in the technical development of NMR analysis, specifically for metabolic dynamics.

Genomics, proteomics and now metabolomics

Twenty-seven instruments are available at the nuclear magnetic resonance facility of the RIKEN Yokohama Institute, making it the foremost facility of its kind in the world. "Many of the NMR systems here are used to analyze protein structure," says Kikuchi. "As a researcher at the former RIKEN Genomic Sciences Center, I began analyzing proteins using NMR spectroscopy in 1998. I am currently working on analyzing metabolites using NMR spectroscopy to explore metabolic activities."

The term metabolism refers to cycles of chemical reactions carried out by cells in the body, and the resulting products are called metabolites. Metabolic activities in living organisms are constantly fluctuating, with the variations depending on the biological species. "In 2002, Dr Kurt Wüthrich of Switzerland received the Nobel Prize in Chemistry for his contributions to the development of NMR-based technology for protein structure analysis. At that time, I realized that the technology for protein structure analysis using NMR had reached its limit, so I needed to start something new. First, the genome, the 'blueprint of life', was decoded, and since then there have been constant advances in analyzing the structure of proteins produced on the basis of the genomic information. I thought of what could come next, and finally arrived at metabolic dynamics. I began analyzing metabolic dynamics using NMR spectroscopy around 2003. In those days, research of this kind was a great novelty around the world."

In later years, research into metabolites rapidly attracted attention. In 2005, the Metabolomics Research Group (headed by director Kazuki Saito) was organized in the RIKEN Plant Science Center. Kikuchi joined the group as leader of the Advanced NMR Metabomics Unit, which was reorganized into his current team in 2010.

The products of metabolic processes are called metabolites, and the entire set of metabolites contained in a cell or individual organism is collectively referred to as its 'metabolome'. The discipline of research into the metabolome is known as metabolomics.

However, Kikuchi's team uses the term 'metabomics'. "Doctor Jeremy Nicholson of the UK was the first researcher to undertake the analysis of metabolic dynamics using NMR spectroscopy. He called his study area 'metabonomics' to distinguish it from 'metabolomics'. According to him, metabolomics refers to the 'systematic study of metabolites', with the emphasis placed on metabolites as they are, whereas metabonomics refers to the 'systematic study of metabolism', where urine and other biological products involving all metabolic activities in individual organisms are statistically analyzed to provide comprehensive insights into metabolic dynamics. What I want to do is to achieve a broad overview of metabolic fluctuations, which are complex, and this corresponds exactly to Nicholson's concept of metabonomics. Since general awareness of both terms was low when I organized my team, I excluded both '-no-' and '-lo-' from the name of the team, but I did include this philosophical reasoning in the naming.

NMR enables comprehensive analysis of a wide variety of metabolites

There are many types of metabolites, including primary metabolites such as amino acids, sugars, lipids and nucleic acids, that are essential for the homeostasis, growth and reproduction of individual organisms, as well as secondary metabolites such as catechins and isoflavones, which are produced from primary metabolites. The properties of metabolites are similarly diverse. For example, some dissolve in water and others are insoluble, some are volatile, and some carry electric charges. "NMR spectroscopy allows us to analyze all metabolites, irrespective of whether they are soluble or insoluble, electrically charged or charge-free, or small molecules or macromolecules."

An outline of the procedural flow for analyzing metabolites by NMR is shown in Figure 1. First, a 'biofluid' comprising a mixture of more than one metabolite of the organism to be examined, as it is or in the form of 'squeezates', is placed in a test tube, and the tube is set in an NMR instrument with an intense magnetic field. When the sample is irradiated with electromagnetic radiation, the atomic nuclei that make up the molecules of the metabolites absorb the radiation, exhibiting nuclear magnetic resonance. Electromagnetic radiation is emitted at a resonant frequency specific to each isotope. The resulting radiation is amplified and detected to determine the spectrum. A database of NMR spectra obtained by analyzing discrete metabolites allows identification of the metabolite corresponding to each spectrum. Peak intensity data show the quantity and motility of the metabolite. Metabolic dynamics can then be clarified by analyzing organisms for a variety of species and physiological states.

"The gold standard for successful analysis of metabolites is mass spectroscopy, but it requires purification and extraction of the single desired metabolite. My long-held desire was to observe something chaotic and complex in its original form, and I believed NMR could make this possible. In addition, not only the quantity of each metabolite, but also the composition ratio is important in evaluating metabolic dynamics. NMR enables us to determine the composition ratio of metabolites from the intensity ratio of the peaks that have been identified in the analysis of the metabolite mixture."

Avoiding loss of samples and data

Nuclear magnetic resonance may be a revolutionary tool, but not all researchers are able to make the best use of its most important feature, which is enabling the analysis of metabolite mixtures. "When a sample containing insoluble metabolites is analyzed using conventional NMR, no useful data are obtained because of the low resolution. For this reason, people often dispose of the insoluble metabolites without performing analysis. However, metabolites disposed of in this way often carry useful information. I thought this was a waste. So in 2010, we developed a profiling method for the process of extracting metabolites from a mixture." This method enables easy identification of which solvents to use in which order to achieve the most efficient extraction of metabolites. "It has become possible to obtain information on those metabolites that were previously disposed of as they are insoluble. Even for the insoluble metabolites that cannot be analyzed, high-resolution data can be obtained by employing high-resolution magic angle spinning, a sophisticated technique for taking measurements while rapidly spinning the sample at a specific angle."

Kikuchi also developed the 'comprehensive metabolic annotation' method, which ensures that the data obtained can be used without any loss. The term 'annotation' refers to naming the spectrum obtained in relation to the assigned substance from a database. "Traditionally, spectral data has been disposed of if corresponding metabolites could not be found in any database. This is also a waste of useful information. With this new technique, we are able to statistically process the peak pattern data we

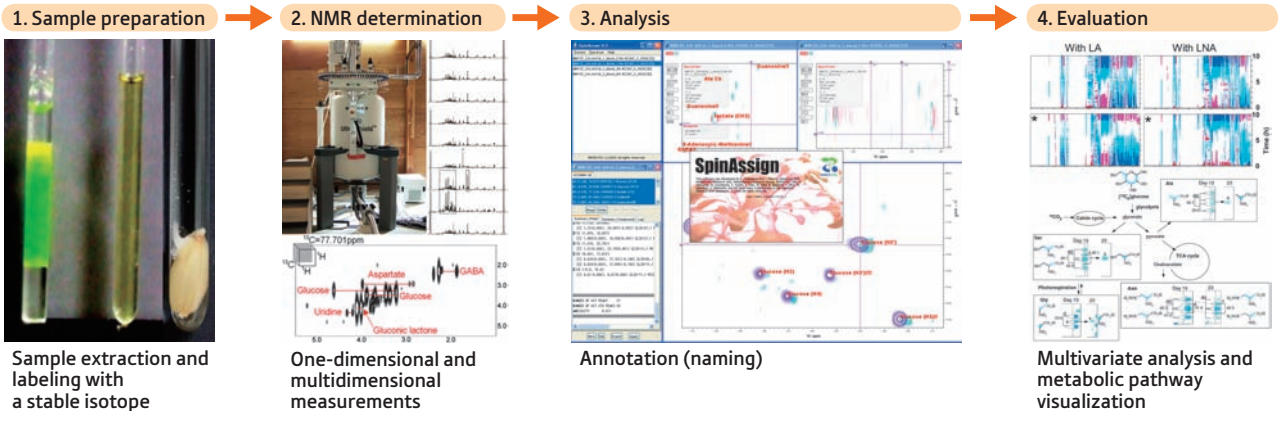

Figure 1: Flow diagram of NMR analysis of metabolite mixtures.

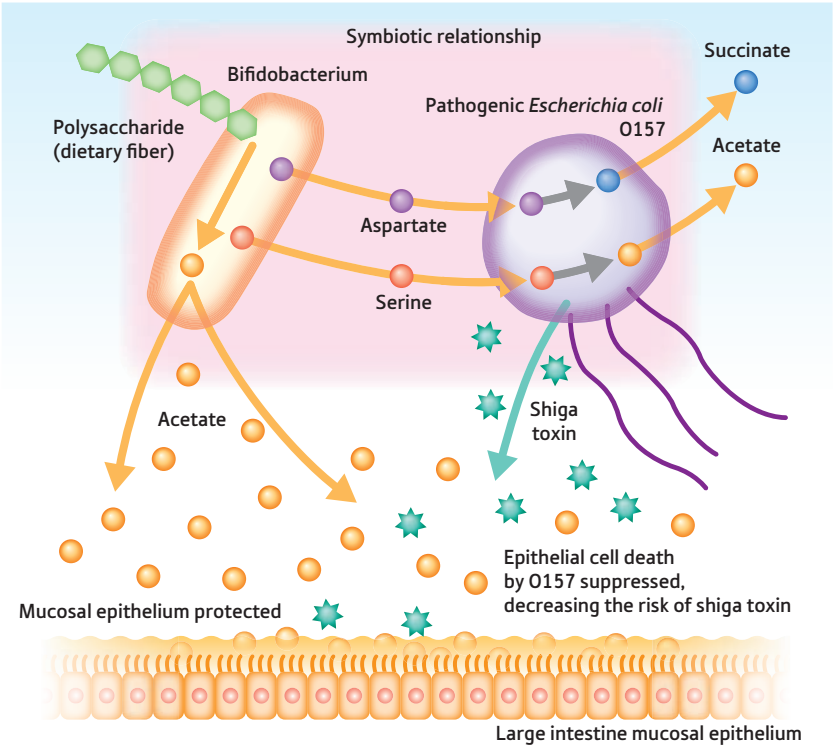

Figure 2: Bifidobacteria and pathogenic *Escherichia coli* O157.

Bifidobacteria consume polysaccharides (dietary fibers) and produce acetate. The resulting acetate protects the mucosal epithelium of the large intestine to enhance its defense against infection. As a result, epithelial cell death caused by O157 is prevented, decreasing the risk of O157-produced shiga toxin entering the body by bypassing the bowel mucosal epithelium. Meanwhile, O157 consumes the aspartic acid and serine produced by bifidobacteria to produce succinate and acetate. Bifidobacteria and O157 have a weakly symbiotic relationship.

have obtained, and select candidate metabolites with similar peak patterns from a database. Similarities in peak pattern are believed to suggest structural or functional similarities. Even though the substance may not be identical, the candidate may provide useful information if only its name includes an affix indicating that it is related to something."

Previously, about 50 metabolites had been annotated on the basis of data obtained by analyzing metabolite mixtures using NMR spectroscopy. With the use of this new technique, the number has been increased to 211. "This is definitely a record-setting achievement," says Kikuchi with pride.

Beyond metabolites toward macromolecular biomass

Kikuchi is now targeting macromolecular biomass. "In the case of plants, even when we apply the profiling method to the process of extracting metabolites, the residual biomass, which comprises a mixture of macromolecules such as cellulose and lignin, remains uncharacterized. Macromolecular biomass with molecular weights exceeding 1,000 is not usually referred to as metabolites. Biomass is always a mixture of macromolecules and insoluble components, so analysis is more difficult than with a metabolite mixture." The term biomass refers to organic matter produced from carbon dioxide and water through photosynthesis in plants using solar energy, and thus it is a renewable resource. Kikuchi continues, "Today, in the twenty-first century, we are being called upon to reevaluate society's dependence on finite resources such as petroleum and minerals, and to make a transition to a society oriented more toward the recycled use of biomass and other resources that can be renewed and that have a low cost per weight. Petroleum-derived products are not considered 'organic' in the consumer sense, whereas plant materials such as wood, bamboo and cotton have a natural beauty due to their nature as mixed substances. This creates a feeling of attachment. I want to establish a completely new analytical method for macromolecular biomass in order to make more efficient use of plant-derived biomasses."

Kikuchi has recently been enthusiastically using the keyword 'ecomics'. "It is a manifestation of my ambition to undertake research that will contribute to the resolution of environmental problems. In addition, removing the 'no' from 'economics' leaves 'ecomics'. I am planning to initiate comprehensive research aimed at creating a society committed to recycling biological resources without overemphasizing economic activities."

Mysterious relationships between probiotic and pathogenic bacteria

In January 2011, a study concerning the suppressive actions of the acetate produced by bifidobacteria on infection with the virulent O157 strain of *Escherichia coli* was widely covered in the media. The discovery was made by a joint research group mainly based around The University of Tokyo and the Laboratory for Epithelial Immunobiology (headed by Hiroshi Ohno) at the RIKEN Research Center for Allergy and Immunology, to which Kikuchi belongs. *E. coli* O157 is a pathogenic bacterium that causes food poisoning. Bifidobacteria, on the other hand, are probiotic bacteria that naturally inhabit the intestines, and are reportedly effective in maintaining good health. Although bifidobacteria were known to provide some defense against O157 infection, the underlying mechanisms were unknown.

"Bifidobacteria consume polysaccharides and produce acetic acid. In an experimental study using mice, we demonstrated that acetate protects the mucosal epithelium of the large intestine, enhancing the organ's resistance to pathogens and hence suppressing O157 infection," says Kikuchi (Fig. 2). Given this, taking vinegar would seem like an effective measure. However, vinegar is absorbed by the small intestine and does not reach the large intestine, and so is actually ineffective. Also, bifidobacteria can be obtained from yogurt and similar products, but their effect is low if taken as is. "A more effective approach is to ingest polysaccharides, or what are called dietary fibers, and bifidobacteria together. Our study clarified the relationship between probiotics and the polysaccharides that enhance their effects, and this represents a major achievement that is expected to find applications in maintaining health and preventing disease in humans."

This study was followed by further investigations. "I wondered about the relationship between probiotic and pathogenic gut flora. You may believe that beneficial bacteria extirpate pathogens. However, we discovered an unexpected relationship." Kikuchi analyzed metabolic dynamics while culturing O157 alone, bifidobacteria alone, and both O157 and the bifidobacteria together, in three test tubes set in an NMR instrument. One of the key features of NMR is the ability to analyze metabolic dynamics without killing the sample microbes, provided that they can be placed in test tubes.

The experiments revealed that the aspartic acid and serine produced by bifidobacteria were absorbed by O157, which in turn utilized these amino acids to produce succinate and acetate. The bifidobacteria and O157 were thus found to maintain a weak symbiotic relationship via the metabolites. "Since primary metabolites such as amino acids are produced in common by organisms, investigating how they function among different organisms has been difficult. In that study, making the best use of our own techniques for labeling metabolites with a stable carbon isotope, we found for the first time that amino acids play a key role in microbial symbiosis."

Amino acids occur universally among organisms and they can be produced at low cost. "If unknown functions of primary metabolism can be clarified by making the best use of our new analytical method, we will be able to open new prospects in food science. Introducing changes in our sense of value and lifestyle in a way that will allow society to become more sustainable by distributing substances at lower manufacturing cost is similar in some way to efforts to build a sustainable society in which inexpensive biomass is recycled."

Kikuchi is looking at diverse targets, including not only higher plants such as rice and poplar, but also algae, complex microbial systems, insects, mice, fish, foods and even beverages (Fig. 3). "My approach may seem inconsistent, because I dabble in everything," laughs Kikuchi, "but I want to achieve a broad view of metabolic dynamics in the biological world as a whole, as well as in individual organisms. Plants use photosynthesis to produce biomass from inorganic matter, animals ingest that biomass, and microorganisms decompose animal excreta and detritus into inorganic matter, which is returned to the soil. This process represents a profound world involving two aspects: 'dynamism', in which numerous substances are produced one after another by chemical reactions of small molecules; and 'stillness', in which macromolecular biomass remains accumulated as it is. In pursuing the laws of nature, I want to contemplate life through investigating the recycling of matter. For this, it is essential to analyze macromolecular biomass. I will give shape to this goal through my own efforts."

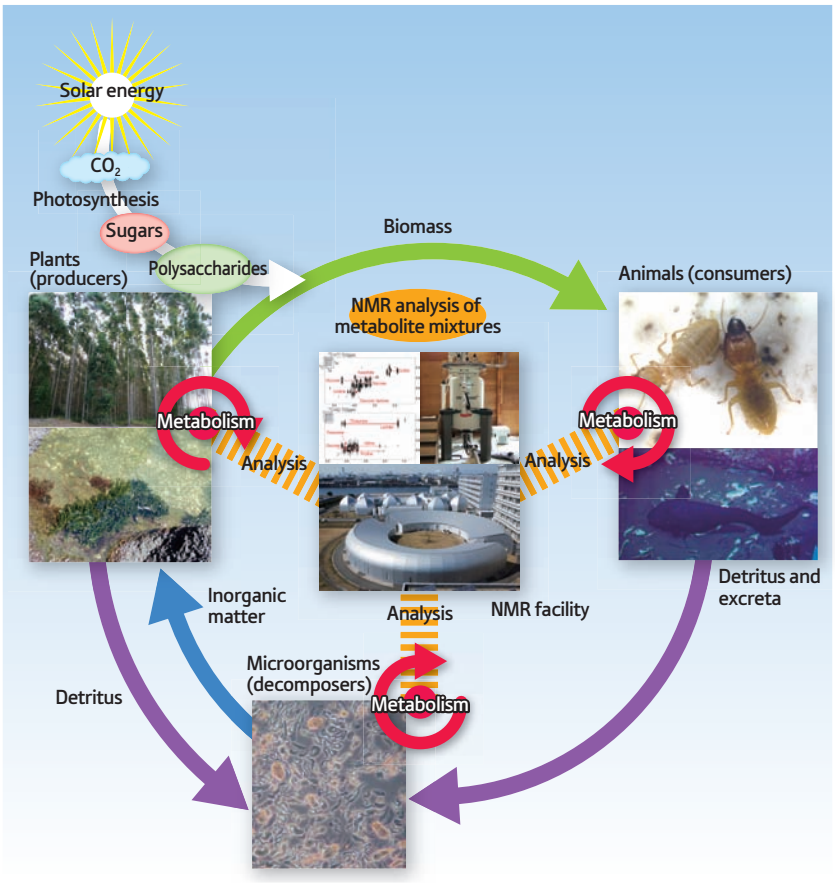

Figure 3: Viewing cyclical changes in materials from the perspective of metabolic fluctuations.
Individual organisms produce a wide variety of substances through the metabolic processes in their bodies. Plants use photosynthesis to produce organic matter from the inorganic, animals ingest that organic matter which they then move or disperse, and microorganisms decompose animal excreta and detritus back into the soil. In this way, materials move in a cycle. Kikuchi wants to reach a comprehensive view of biological life, not only from the viewpoint of metabolic dynamics in individual organisms, but also in terms of the recycling of materials among different organisms.

ABOUT THE RESEARCHER

Jun Kikuchi graduated from the Department of Biotechnology of the Tokyo University of Agriculture and Technology in 1993, and obtained his PhD at the Department of Engineering from the Graduate School there in March 1998. During this period, he studied at the University of Sheffield in the UK in 1994 and at Northwestern University in the US in 1996. In addition, he taught physical chemistry as a lecturer at the Tokyo National College of Technology from 1996 to 1997, and was awarded a pre-postdoctoral fellowship of the Japan Society for the Promotion of Science from 1996 to 1998. From April to October 1998, he was a research scientist for the ERATO program of the Japan Science and Technology Agency, and from 1998 to 2005 worked with the Protein Research Group of the RIKEN Genomics Science Center. In 2005, he became a unit leader in the RIKEN Plant Science Center (PSC). In April 2007, he was appointed visiting professor of the Graduate School of Agriculture, Nagoya University. In April 2010, he was promoted to team leader in the PSC, and became a visiting professor at the Graduate School of Bionanoscience of Yokohama City University.

Liang Zhang

Foreign Postdoctoral Researcher
Organometallic Chemistry Laboratory
RIKEN Advanced Science Institute

Finding a catalyst for breakthrough research

What do you do at RIKEN?

I work as a foreign postdoctoral researcher in the Organometallic Chemistry Laboratory at the RIKEN Advanced Science Institute. Our group focuses on the development of new organometallic catalysts for efficient organic synthesis. I am interested in the activation and utilization of carbon dioxide, which is causing great concern worldwide for its increased emission levels. I am trying to find suitable catalysts based on copper to facilitate the insertion of CO_2 into the framework of organic molecules. Such reactions generate carboxylic acids and derivatives, which are widely used in pharmaceuticals, agrichemicals and dyes.

How and when did you join RIKEN?

After my PhD thesis defense, I applied for a Japan Society for the Promotion of Science Postdoctoral Fellowship. In September 2009, I joined the research group of Dr Zhaomin Hou, who had previously given an interesting chemistry lecture at my university. I became a foreign postdoctoral researcher in the same laboratory in March 2011.

What attracted you to RIKEN?

I was attracted by the amazing research at RIKEN that spans the whole spectrum of natural sciences. RIKEN also provides researchers with a range of sophisticated facilities and good financial support. The Japanese culture is also quite appealing, which makes Japan a wonderful place for young researchers.

How was the transition to life at RIKEN?

From the start of my time at RIKEN, I have lived in the cozy and convenient environment of the RIKEN International House. Preparations made for my arrival beforehand, such as providing an ID card and computer, made my start at RIKEN go smoothly. Everyone in this group is kind and helpful.

Please tell us about your research or other work at RIKEN.

Our work focuses on developing efficient methods for converting a mixture of CO_2 and several different organic molecules at atmospheric pressure into carboxylic acids and esters to produce high yields of the desired compounds. Our methods have the unique advantages of employing CO_2 as an abundant, inexpensive, nontoxic carbon source. The process also uses unactivated organic molecules as substrates, and relatively cheap copper complexes as catalysts. This approach provides an economical and environmentally friendly process for synthesizing valuable compounds from CO_2. Moreover, careful capture and characterization have allowed us to achieve important insights into the mechanistic details of these transformations.

What have been the highlights of your time at RIKEN so far?

The most exciting thing for me is that we have already partially achieved our research goals. The catalysts we designed work well for CO_2 activation and the reaction process we anticipated was confirmed by our experiments. I have even managed to capture several reaction intermediates, which are very important for understanding reaction mechanisms. Two of our research papers, published in *Angewandte Chemie International Edition*, drew immediate attention from the academic community and the media.

What has been the best thing about working at RIKEN?

Besides the advanced facilities and generous financial support, RIKEN provides a very good platform for academic exchange. Since it is an international institute, researchers come from a diverse range of countries and research fields. Numerous high-level workshops and symposia are conducted on campus, so we get many opportunities to learn things beyond our main field.

What would you say to other people considering joining RIKEN?

RIKEN is not only a world-famous institute where you can do good research, it is also a nice place to make friends and learn about different cultures. RIKEN researchers endeavor to contribute to a better society while enjoying the natural beauty of a peaceful campus.

CONTACT INFORMATION

For details about working at RIKEN, please contact the RIKEN Global Relations Office:
Tel: +81-(0)48-462-1225 E-mail: gro-pr@riken.jp

New RIBA-II care robot unveiled

Researchers at the RIKEN–TRI Collaboration Center for Human-Interactive Robot Research (RTC), a joint project undertaken in partnership with Tokai Rubber Industries, have unveiled the second version of their care robot called RIBA-II. The new robot expands the abilities of the original Robot for Interactive Body Assistance (RIBA) developed in 2009 to lift heavier loads and crouch to lift from floor level, as well as being fitted with new tactile sensors and travel guidance controls.

With a record-low birthrate and a rapidly aging population, Japan faces a severe demographic challenge that is compounded by a chronic lack of nursing care staff. The elderly population in need of such nursing care in Japan is estimated to reach 5.69 million by 2015, 4.42 million of whom suffer from dementia. To avoid injury from falling, many such dementia patients sleep on futons at floor level rather than on beds, a situation that places a heavy burden on care-givers who need to lift patients from the floor.

The original version of RIBA released in 2009 was the first robot that could lift and transfer a person from a bed to a wheelchair and back. Lifting a person from the floor, however, was beyond its capabilities. To overcome this limitation, a new joint was installed in the lower back of RIBA-II to enable it to crouch down and lift a person of up to 80 kilograms from floor level and into a wheelchair, alleviating the most physically strenuous task for care personnel.

RIBA-II also has newly developed smart rubber sensors—the first capacitance-type tactile sensors made entirely of rubber—that allow RIBA-II to detect a person's weight and guide its actions safely. In addition, the new robot is equipped with a touch-screen panel and travel guidance controls that allow it to follow a line of magnetic tape on the floor to its destination.

RTC researchers will test RIBA-II with nursing care facilities and tailor it to the needs of care-givers and their patients, with plans to commercialize the robot in the near future. ■

RIBA-II can now lift a person from floor level

Celebrating ten years of the RIKEN BioResource Center

A ceremony was held on July 1 to mark the tenth anniversary of the establishment of the RIKEN BioResource Center (BRC). The event included a public symposium at the Tsukuba International Congress Center and a tour of the BRC's newest facility, the BioResource Building for Cell Research.

Yuichi Obata, director of the BRC, began by giving an overview of the activities of the center over the past decade and laying out his vision for the next ten years. Following his presentation, a series of special lectures and a panel discussion were held featuring Toshihiko Shiroishi, director of the Genetic Strains Research Center at the National Institute of Genetics, Shinya Yamanaka, director of the Center for iPS Cell Research and Application at Kyoto University, Hiroo Fukuda, professor of the Department of Biological Sciences at The University of Tokyo, Sumio Sugano, professor of the Graduate School of Frontier Sciences at The University of Tokyo, and Moriya Ohkuma, head of the Microbe Division of the BRC.

Since its establishment in 2001, the BRC has functioned as a core bioresource facility for researchers in Japan and around the world by collecting, preserving and distributing bioresources including model mice, experimental plants such as *Arabidopsis thaliana*, human and animal cell lines, genetic materials and microorganisms. Today, it is one of the world's top bioresource centers. ■

Celebrating the tenth anniversary of the RIKEN BRC. Present are RIKEN president Ryoji Noyori and BRC director Yuichi Obata (front row, fifth and sixth from right, respectively).

Genomic cancer research races ahead of schedule

The International Cancer Genome Consortium (ICGC), comprised of research organizations from around the world including RIKEN, the National Cancer Center and the National Institute of Biomedical Innovation in Japan, held its fifth workshop in Kyoto on 10–12 July 2011—the first ICGC workshop to be held in Asia. Harold Varmus, director of the US National Cancer Institute and 1989 Nobel Laureate in Physiology or Medicine, gave a lecture at the workshop.

In addition to the workshop, Hidewaki Nakagawa, head of the Laboratory for Biomarker Development at the RIKEN Center for Genomic Medicine, Tatsuhiro Shibata, chief of the Division of Cancer Genomics at the National Cancer Center, and Tom Hudson, president and scientific director of the Ontario Institute for Cancer Research in Canada and one of the founders of the ICGC, announced ICGC's sixth major data release. They also announced that the consortium was running ahead of schedule in its decade-long quest to generate high-quality genomic data on more than 25,000 tumors for up to 50 types of cancer that are of clinical and societal importance across the globe.

The data include new submissions to the ICGC from the US Cancer Genome Atlas and data from a study of 500 ovarian cancer patients published in the journal *Nature* on June 30 this year. The RIKEN Center for Genomic Medicine and the National Cancer Center have updated their whole genome data on 16 and 11 liver cancers, respectively. Researchers from Spain have provided complete genome sequences for patients with chronic lymphocytic leukemia, and described recurrent mutations associated with the disease in a publication in *Nature* on June 5. The Ontario Institute for Cancer Research in Canada has also updated its data on pancreatic cancer. The ICGC data portal (www.icgc.org) provides data on more than 2,800 tumors, including recently added information on breast, lung and skin cancer provided by researchers from the Wellcome Trust Sanger Institute in the UK. ■

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For further information on the research presented in this publication or to arrange an interview with a researcher, please contact
RIKEN Global Relations Office
2-1, Hirosawa, Wako, Saitama, 351-0198, Japan
TEL: +81 48 462 1225
FAX: +81 48 463 3687
E-Mail: rikenresearch@riken.jp

www.rikenresearch.riken.jp