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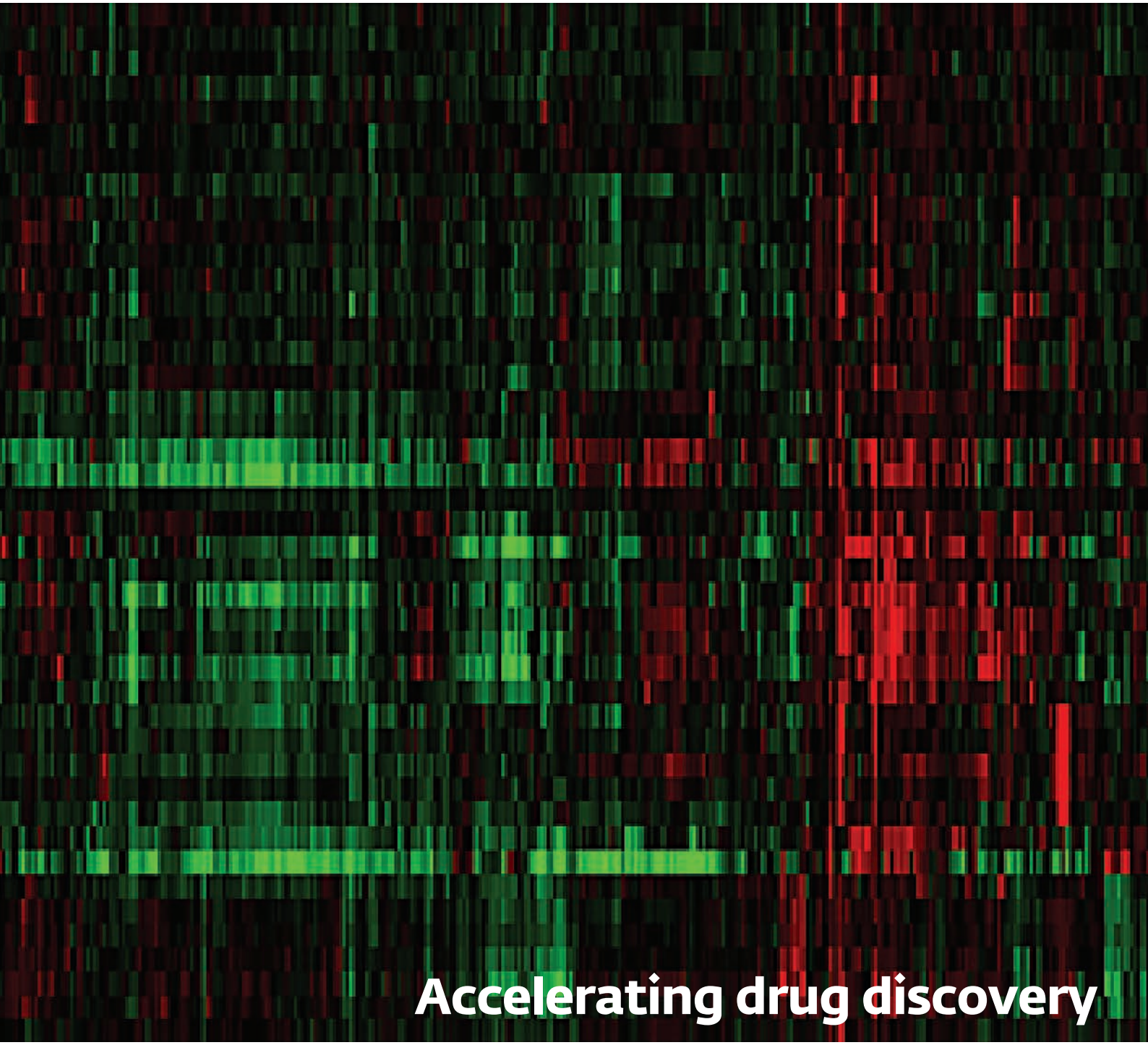

Accelerating drug discovery

RIKEN

Biology

Pausing to make memories

Adding breaks to a training regimen gives rodents an edge in learning new motor skills and provides an improved model for studying memory

Before the effects of training become hard-wired, the neural imprint of a newly learned motor skill is initially encoded in a temporary 'holding area' for memory, after which the memory 'trace' is transferred to a different region of the brain for long-term retention. The basis for this learning process has proven challenging to untangle, but new research from a group led by Soichi Nagao of the RIKEN Brain Science Institute in Wako has revealed some of the key steps involved[1].

Several years ago, Nagao and his colleagues studied the acquisition of the horizontal optokinetic response (HOKR), the mechanism by which the eye compensates for sideways movement of the visual field, such as scenery passing by the window of a moving car. HOKR offers a simple and broadly relevant model for understanding motor learning. "This behavior exists throughout most animal species ranging from fish to humans, and even works in invertebrates," says Nagao.

The researchers examined activity in the cerebellum (Fig. 1), the brain region responsible for motor function. They found that they could detect the shift in HOKR-related activity from a cerebellar region called the flocculus to another population of cells called the vestibular nuclei after three to four days of training sessions, in which the researchers tracked eye movement as the animals viewed an oscillating screen[2].

However, Nagao and colleagues wondered whether there might be a more efficient way to study this shift. "Three or four days is a very long time to maintain constant experimental conditions," says Nagao. "If the same phenomenon could be observed within three or four hours, we could use drugs or surgical treatments to study the underlying mechanisms."

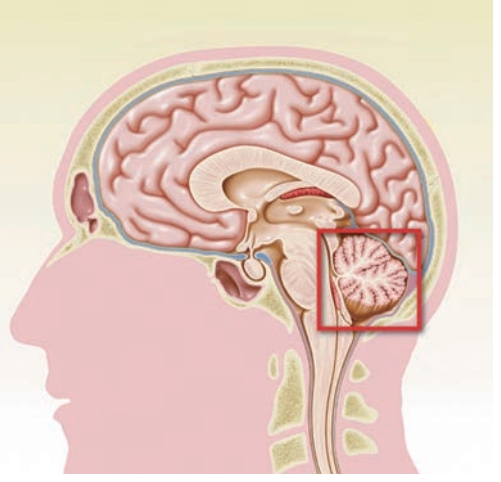

Figure 1: Neurons within the cerebellum are responsible for the construction of motor memory, which is associated with the learning of physical activities and behaviors.

Benefiting from breaks

The solution turned out to be an alternative approach to training based on what is known as the spacing effect. Neuroscientists have recognized this effect since the 19th century, but it remains poorly understood. "Very little has been revealed about its underlying neural mechanisms by biological experiments," explains Nagao, "and in particular, there have been very few studies in mammals."

Nevertheless, he and his colleagues observed clear benefits when they trained their mice with a series of spaced intervals rather than long individual 'massed training' sessions. Twenty-four hours after the completion of the training, all animals on spaced training protocols retained their gains in HOKR adaptation, while the mass trained animals lost approximately half of the gains they had obtained by the end of training.

Damage inflicted surgically to the flocculus (Fig. 2) prior to training impaired the acquisition of HOKR via either regimen, indicating that early learning is acquired via a common mechanism in both approaches. In subsequent experiments, the researchers used infusions of the anesthetic drug lidocaine to suppress neural activity within the flocculus an hour after the completion of training. Although this treatment suppressed the adaptation gains from massed training, the

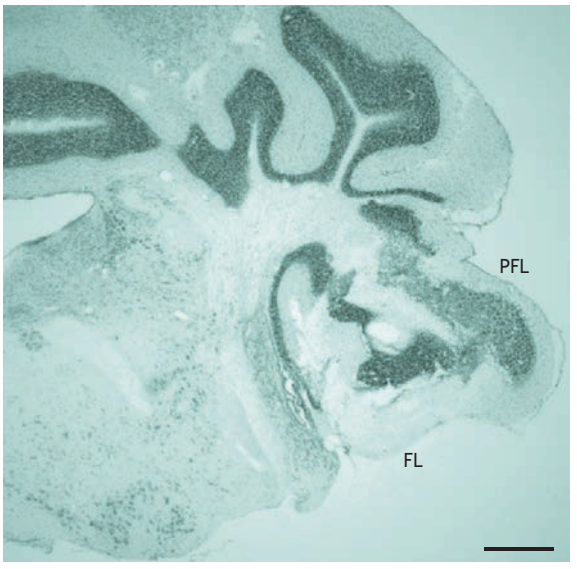

Figure 2: Physical damage inflicted on the neurons of the flocculus (FL) disrupts early stages of motor learning acquired via either massed or spaced training regimens (scale bar, 500 µm; PFL, paraflocculus).

researchers were surprised to find that it had virtually no effect on animals receiving spaced training.

This suggests that the span of the spaced training regimen was itself sufficient to see the memory trace transferred from the flocculus to the vestibular nuclei, indicating a considerably rate of long-term memory retention. "The transfer of the memory trace occurred within two and half hours after the start of training," Nagao notes.

Finally, the researchers tested whether active protein synthesis is required for HOKR adaptation by infusing into the flocculus drugs that inhibit the protein production machinery. This treatment had minimal impact on the gains from subsequent massed training, but mice that underwent spaced training after the infusion exhibited a marked reduction in HOKR adaptation. This suggests that protein synthesis is specifically required for motor learning via the spaced learning approach.

Similar circuits

Although this study focused on a single, relatively simple model of motor learning, Nagao points out that the principles demonstrated here are likely to hold true for most acquired physical behaviors. "The basic structure of this neural circuit is uniform throughout the entire cerebellar cortex," he says. "We believe that the control mechanism of HOKR suggested by our analysis of the flocculus–vestibular system applies to cerebellar control in general."

This study could also provide parallel insights into the rules governing the process by which we acquire declarative memory, which encompasses our capacity to recall learned information and prior experiences. This process takes place within entirely independent structures of the brain, namely the hippocampus and cerebral cortex, although the actual process by which declarative memory traces become consolidated from short-term to long-term retention may employ a more elaborate form of the mechanisms described here. "The information content is higher in declarative memory," says Nagao. "Memories get simplified in motor memory while many properties should be added during the transfer declarative memory."

To follow up this work, Nagao and his colleagues intend to uncover additional mechanistic details of the cerebellar memory transfer process. For example, it remains unclear exactly what proteins are being produced in the flocculus to facilitate memory encoding, or how they might be acting to rewire the neuronal circuitry. More fundamentally, neuroscientists are yet to determine how the connections between populations of cerebellar neurons change in direct response to the training process. "We are planning to examine how memory traces of motor learning are represented morphologically in the cerebellar nuclei," says Nagao.

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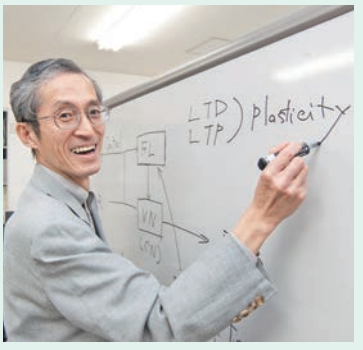
2. Shutoh, F., Ohki, M., Kitazawa, H., Itohara, S. & Nagao, S. Memory trace of motor learning shifts transsynaptically from cerebellar cortex to nuclei for consolidation. *Neuroscience* **139**, 767–777 (2006).

ABOUT THE RESEARCHER



Soichi Nagao was born in Osaka, Japan, in 1952. He graduated from the School of Medicine of The University of Tokyo in 1977. After two years' training as a clinical doctor at the university hospital, he entered the Postgraduate School of Medicine of The University of Tokyo, and obtained his PhD in the Department of Physiology. He studied the neurophysiology of motor control during his time as assistant professor at The University of Tokyo, and as associate professor at Jichi Medical University, in Tochigi, Japan. Since 2004, he has been Team Leader of the Laboratory for Motor Learning Control at the RIKEN Brain Science Institute. His research focuses on the neural mechanism underlying the acquisition and maintenance of motor memory through motor learning by the brain, combining electrophysiological, anatomical and molecular biological methods. He has developed a new eye movement measurement system and several behavioral paradigms.

Unaffected by imperfections

Current flowing along the edges of a promising quantum device is insensitive to its magnetic impurities

Conductors of electrical current, including copper, heat up and limit the ability to increase circuit densities. Unusual materials that exhibit the so-called 'quantum spin Hall effect', in which current can flow without dissipating heat, could provide an alternative to conventional metals. However, internal imperfections, such as magnetic impurities, were assumed to disrupt current flow. Now, using theoretical calculations, a research team from Japan and the US has shown that devices built from these alternative materials are surprisingly immune to the presence of magnetic impurities[1].

Soon after it was predicted in 2005, experimentalists discovered the quantum spin Hall effect in thin layers of the semiconductor mercury-telluride. The signature of the effect is two counter electric currents—with oppositely 'spin-polarized' charges—that circulate along the edge of the film (Fig. 1). Each current has the same universal quantum of conductance as a quantum wire. Because the currents are resistant to scattering, these 'edge states' flow without dissipating heat.

As the edge states appear only within a few degrees above absolute zero, however, devices made from these materials require further development to be of practical use. Magnetic fields are also known to disrupt the edge states, so physicists assumed that a magnetic impurity, such as a lone iron atom near the edge of the film, would do the same.

"We wanted to better understand how the conductance of the edge states might be affected by magnetic impurities," says Akira Furusaki, a scientist at the RIKEN Advanced Science Institute, Wako, who co-authored the work. Other groups have calculated how edge states scatter when encountering an impurity, and concluded that it would considerably lower the conductance of a spin-Hall device.

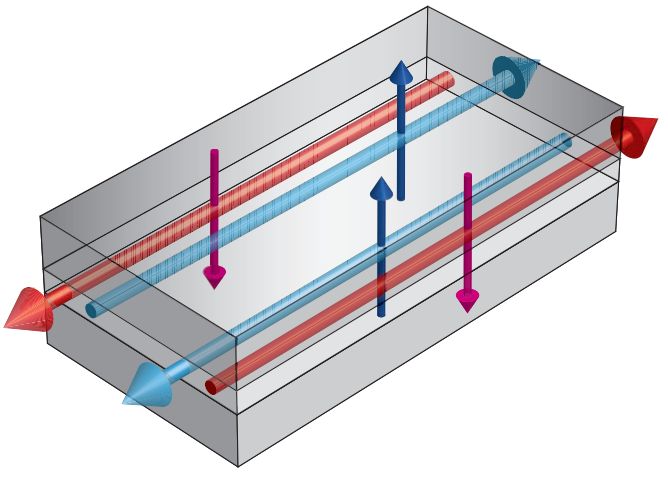


Figure 1: Electrons at the edge of the material mercury-telluride exhibit the quantum spin Hall effect, in which two oppositely spin-polarized charge currents (indicated in red and blue) circulate along the edge without generating heat.

Furusaki and his colleagues redid this calculation using the same theoretical model as the other groups, but included the frequency dependence of the current. They used a so-called 'rate equation approach', where the current is obtained by solving a master equation that describes the time evolution of the magnetic impurity that scatters the edge states.

Since the researchers found that magnetic impurities do not actually change the conductance of edge states, at least for direct currents (DC), they concluded that quantum spin Hall devices could be more robust to magnetic impurities than previously thought.

Furusaki plans to further extend the theoretical model to "study the stability of edge states in the presence of strong electron interactions, where the fractionalized quantum spin Hall effect is predicted." ■

1. Tanaka, Y., Furusaki, A. & Matveev, K.A. Conductance of a helical edge liquid coupled to a magnetic impurity. *Physical Review Letters* **106**, 236402 (2011).

Antimatter sticks around

The entrapment of antimatter for 16 minutes allows for tests of the foundations of physics

By successfully confining atoms of antihydrogen for an unprecedented 1,000 seconds[1], an international team of researchers called the ALPHA Collaboration has taken a step towards resolving one of the grand challenges of modern physics: explaining why the Universe is made almost entirely of matter, when matter and antimatter are symmetric, with identical mass, spin and other properties. The achievement is remarkable because antimatter instantly disappears on contact with regular matter such that confining antimatter requires the use of exotic technology.

The collaboration of 39 researchers, including Daniel Miranda Silveira and Yasunori Yamazaki from the RIKEN Advanced Science Institute, Wako, trapped antihydrogen inside a 'bottle' defined by a set of magnetic fields created by an octupole magnetic coil and a pair of mirror coils (Fig. 1). The bottle could not confine antihydrogen atoms unless they had extremely low energy, which represents a particular problem because antimatter is made through an extremely energetic process; and any cooling procedures must prevent antimatter and matter from meeting. In a previous ALPHA Collaboration experiment, the researchers succeeded in confining 38 antihydrogen atoms for at least one-fifth of a second.

Buoyed by their success, the collaboration focused on further cooling the antihydrogen atoms. Advances they made to two techniques proved especially fruitful. The first, evaporative cooling, relies on the fact that any collection of antiparticles will include some that are more energetic than others. By confining this collection inside an energy potential that lets only the most energetic particles escape, or evaporate, the entire collection can be effectively cooled, and can reach hundreds of degrees Celsius below freezing, Yamazaki explains. The second technique, autoresonant mixing, uses a technique called phase locking to mix the two constituents of antihydrogen—antiprotons and positrons—without warming the antiprotons.

Once cooled in this way, the ALPHA Collaboration was able to trap more antimatter atoms, some for times exceeding 1,000 seconds. Critically, this is much longer than the time it takes for antimatter to relax to its lowest-energy, or ground, quantum mechanical state, which is a prerequisite for studying its properties with laser and microwave spectroscopic techniques.

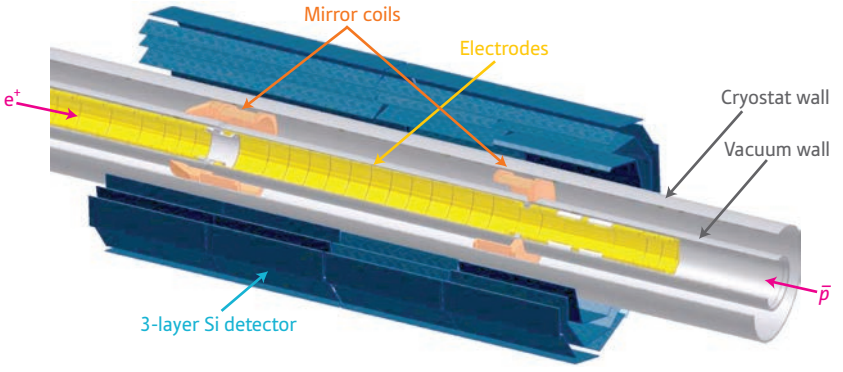


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Figure 1: The ALPHA Collaboration's antihydrogen trap and detector. Antihydrogen is made when antiprotons ($\bar{p}$) and anti-electrons (or positrons, e^+) meet. The octupole (not shown) and mirror magnetic coils confine the antihydrogen, and a silicon (Si) detector records matter-antimatter annihilation events.

Trapping antimatter atoms in this way will allow physicists to address questions regarding the symmetry between matter and antimatter, which is currently understood to be a foundational property of physics, says Yamazaki. "If we see even a slight difference between hydrogen and antihydrogen properties, then the standard model of physics will need to be rewritten, and our understanding of the Universe will change." ■

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Moving forward, spin goes sideways

Improvements to specialized valves that separate spin and electron currents may lead to higher-density magnetic media

Building electronic devices that work without needing to actually transport electrons is a goal of spintronics researchers, since this could lead to: reduced power consumption, lower levels of signal noise, faster operation, and denser information storage. However, the generation of pure spin currents remains a challenge. Now, YoshiChika Otani and colleagues at the RIKEN Advanced Science Institute, Wako, and five other research institutes in Japan and China, have produced a large spin current in an important spintronic device called a lateral spin valve[1].

Spintronic devices store information in the spin of electrons, rather than in their density or energy level. Information flows through the propagating waves of spin orientation, while electrical charges remain stationary. Inside a lateral spin valve, a current of electron spins—but not of electron charges—is injected into a nonmagnetic wire through a ferromagnetic contact (Fig. 1). The current travels down the wire, and creates an output voltage across a second ferromagnetic contact, which serves as the output of the device. This lateral arrangement is important because it allows charge and spin currents to flow independently and permits the use of multiple terminals. However, while a practical lateral spin valve would require a large output voltage, previous devices had produced only 1 microvolt or less.

To increase the output voltage of their device, Otani and colleagues concentrated on the quality of the junction between the two ferromagnetic contacts and the non-magnetic, silver wire. Between the wire and the ferromagnets made of nickel and iron, the researchers placed a thin layer of magnesium oxide, which served to increase the efficiency of spin injection. They found that the straightforward annealing of their device at 400 °C in a mostly nitrogen environment reduced the quantity of oxygen in this interfacial layer.

This lowered junction resistance by a factor of up to 1,000, and increased the efficiency of spin injection into the silver wire. As a result, the output voltage reached 220 microvolts, which is more than 100 times greater than that of existing devices. In addition, the research team was able to observe the injected spins rotating, of what is technically known as precessing, in response to a magnetic field along the entire length of their 6-micrometer silver wire, confirming high spin injection efficiency.

The spin valve could be further improved, says Otani, by using cobalt–iron ferromagnets, which are known to have greater spin injection efficiency than nickel–iron, with potential near-term application as sensors in high-density magnetic media. ■

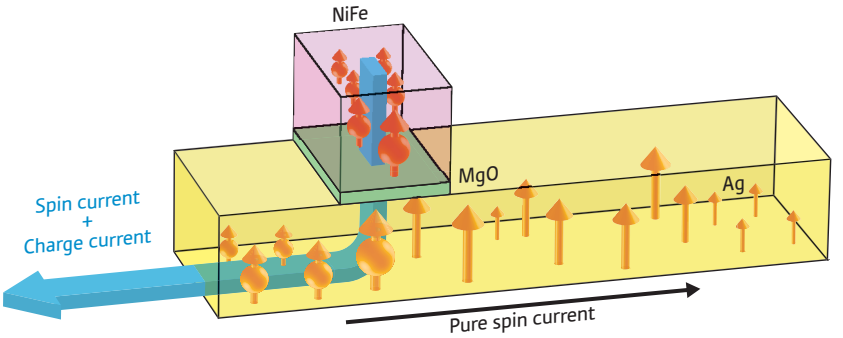

Figure 1: In this lateral spin valve, a current is applied to a ferromagnetic nickel–iron contact (pink), in which spins are aligned in a particular direction. A thin layer of magnesium oxide (green) separates the contact from a non-magnetic silver wire (yellow). While both spin and charge current flow to the left (blue arrow), only spin current flows to the right (black arrow).

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Splitting spin to get ahead

A bismuth-based semiconducting material could enable control of electron spin, a crucial requirement for advancing novel devices

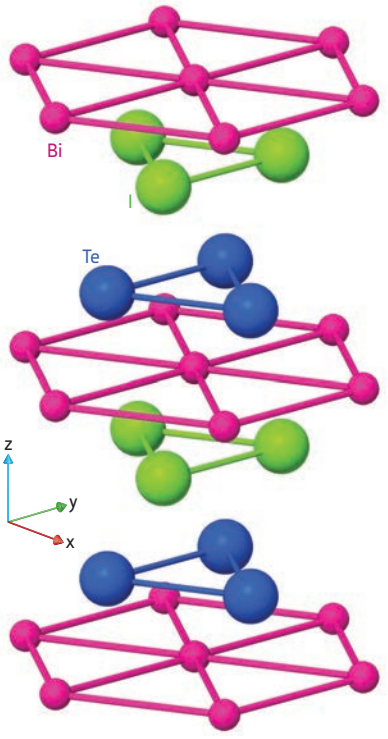

Figure 1: The layered atomic structure of BiTeI creates a three-dimensional version of the Rashba effect, normally seen at only two-dimensional surfaces and interfaces (pink, bismuth; blue, tellurium; iodine, green).

In the developing field of spintronics, physicists are designing devices to transmit data using the inherent axial rotation, or spin, of electrons rather than their charge as is used in electronics. Weak coupling of electron spin to electrical currents, however, makes gaining this level of control difficult. Yoshinori Tokura from the RIKEN Advanced Science Institute, Wako, working with colleagues from across Japan, has now shown that the semiconducting material BiTeI could provide the control needed because of its unusual atomic arrangement[1].

Spin can take one of two values, conventionally labeled 'up' and 'down'. Usually, an electron in a state with an up-spin has the same energy as an electron in the equivalent down-spin state. This so-called 'energy degeneracy' makes it difficult to control up and down spins independently. "A principle technique in spintronics is to manipulate spin by means of an electric current or voltage," says University of Tokyo scientist and co-author of the paper Kyoko Ishizaka. "Lifting this degeneracy will enable a number of novel spin-to-current conversion techniques."

One way to split the energy of the two spin states is to destroy the symmetry of the atomic lattice; at a surface or at the interface between two materials for example. This is known as the Rashba effect. Physicists have observed this effect; however, splitting energy in these two-dimensional (2D) systems was, in general, too small for real applications. Tokura, Ishizaka and their team demonstrated experimentally a Rashba-type effect in three-dimensional, or 'bulk', BiTeI. "In 2D Rashba systems, spintronic function is hindered by the electrons away from the surface, which remain degenerate," explains Ishizaka. "In BiTeI, on the other hand, all the carrier electrons are spin-split."

The researchers studied BiTeI using a technique called angle-resolved photoemission spectroscopy, whereby electrons excited from the surface of a sample by incoming light provided details about the material's energy structure. The measurements showed that the spin splitting was large enough to make BiTeI a potential material for various spin-dependent electronic functions. The researchers took a first-principles approach to modeling their material system to obtain a better understanding of the origin of this effect. They showed that the large amount of spin-splitting was a result of the layered atomic structure of BiTeI (Fig. 1) in which the bismuth, tellurium and iodine atoms arranged into separate tiers, each with a triangular lattice.

"Next we will study the spin-dependent transport and optical properties of BiTeI, with the aim of making a functional device," says Ishizaka. ■

1. Ishizaka, K., Bahramy, M.S., Murakawa, H., Sakano, M., Shimojima, T., Sonobe, T., Koizumi, K., Shin, S., Miyahara, H., Kimura, A. *et al*. Giant Rashba-type spin splitting in bulk BiTeI. *Nature Materials* **10**, 521–526 (2011).

A rare partnership pays off

The first chemical complex consisting of rare earth metals and boron atoms produces unexpected results heralding new synthetic chemistry techniques

Figure 1: Rare earth metals are critical components of hybrid vehicle engines, but a new partnership between these elements and boron atoms is set to have a transformative impact on synthetic chemistry.

Boron is an intriguing member of the periodic table because it readily forms stable compounds using only six electrons—two fewer than most other main-group elements. This means that chemists can easily add boron to unsaturated hydrocarbons, and then use electron-rich atoms, such as oxygen, to change organoborons into versatile units such as alcohols and esters. Recently, researchers found that combining transition metals with boron ligands produces catalysts powerful enough to transform even fully saturated hydrocarbons into new organic functionalities with high selectivity.

Now, Zhaomin Hou and colleagues from the RIKEN Advanced Science Institute in Wako have made another breakthrough in this field: they have created the first-ever complexes between boron ligands and rare earth metals[1]. Because these novel chemical combinations display a surprising ability to incorporate molecules such as carbon monoxide into their frameworks, they have potential applications that range from synthesizing organic substrates to controlling noxious emissions.

Rare earth metals are hot commodities because they are vital for products in high demand such as smartphones and electric cars (Fig. 1). However, full chemical studies of these elements are only in their infancy since they are difficult to handle under normal conditions.

According to Hou, typical methods to prepare transition metal–boron complexes—halogen or metal exchange reactions, for example—seemed unsuitable for rare earth metals. Instead, the team used a vigorous lithium–boron compound to handle the reactive rare earth precursors, producing previously unseen scandium-boron (Sc–B) and gadolinium–boron (Gd–B) complexes in good yields, but not without difficulty. "Rare earth–boron compounds are air- and moisture-sensitive and sometimes thermally unstable," says Hou. "They therefore require great care in isolation and handling."

To determine whether or not the Sc–B complex could act as a nucleophile—an important electron-donating reagent in organic chemistry—the team reacted it with *N*,*N*′-disopropylcarbodiimide, a molecule that easily accepts electrons to change into an amidinate salt. X-ray analysis revealed that initially, the carbodiimide became incorporated between Sc and carbon ligands on the rare earth metal, but extra quantities of the reagent became incorporated between the Sc–B bond. Furthermore, adding carbon monoxide to this mixture also caused a rare earth–boron insertion, accompanied by an unexpected rearrangement into a cyclic structure.

Because chemists rely on insertion reactions to efficiently transform ligands into a diverse range of products, these findings should enable development of brand new synthetic techniques—opportunities that Hou and his team are actively pursuing. ■

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Rapid profiling of drug candidates

A method that rapidly unveils the mode of action of anticancer compounds could soon streamline therapeutic drug discovery

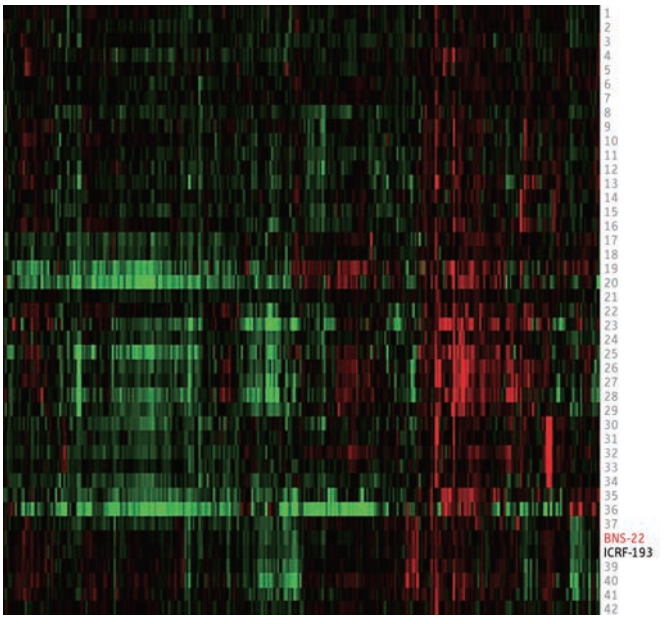

Figure 1: A heat map of protein production (columns) by cancer cells treated with BNS-22 and 42 different anticancer drugs (rows). BNF-22 and ICRF-193 have matching profiles. Proteins with increased levels of expression are colored red, and those with reduced levels are green.

In the hunt for new medicines, any technique that expedites drug candidates into the clinic is a welcome advance. A team led by Hiroyuki Osada at the RIKEN Advanced Science Institute, Wako, recently developed a faster way to unravel the mode of action of experimental anticancer drugs, an essential step in the drug development pathway[1]. The team—including RIKEN researchers Makoto Kawatani and Makoto Muroi—is now using this so-called 'proteomic profiling' technique to assess new drug leads, including a promising compound dubbed BNS-22[2].

Like many drug candidates, BNS-22 was developed from a natural compound. In this case, Osada and his colleagues derived BNS-22 from a compound named GUT-70, which other researchers had isolated from the Brazilian plant *Calophyllum brasiliense*. Since tests with GUT-70 on a culture of cancer cells revealed some activity in killing these cells, Osada and team decided to synthesize a range of closely related compounds that might exert stronger anticancer activity.

Traditionally, assessing the usefulness of novel anticancer compounds and how they work was a time-consuming process, often giving ambiguous results. Osada and his colleagues improved this process using their proteomic profiling technique, which maps protein production in cancerous cells. As cellular conditions change, including administration of an anticancer drug, so does the range of proteins that the cells produce.

To assess BNS-22, the researchers first mapped the proteomic profiles of 42 anticancer compounds with well-established modes of action. They then compared the proteomic profile of BNS-22 to this library of profiles, using a 'heat map' to identify any matches (Fig. 1). Matching profiles indicate that two compounds have the same mode of action.

Osada and colleagues found that BNS-22 matches the profile of ICRF-193, a compound known to inhibit an enzyme called TOP2. This enzyme is essential for numerous cellular processes, and is a good target for anticancer drugs. Surprisingly, the findings also show that BNS-22 works in a different way from GUT-70, despite its very similar structure. "In the process of [creating derivatives of] compounds, single structural differences frequently cause a loss of activity," Kawatani and Muroi explain. However, the team was fortunate enough to find a promising drug candidate.

To further improve the accuracy of their proteomic profiling approach, the researchers plan to further analyze their protein maps and identify significant changes in the expression of specific proteins in response to a drug. They also plan to use this technique to re-assess RIKEN's library of natural products for new drug leads. ■

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Keeping the immune system on track

Specialized motor proteins help control immune activation by physically hauling clusters of signaling receptors to a central site for eventual disposal

Specialized immune cells called T cells can recognize threats and induce immune responses through T cell receptors (TCRs), but these receptors do not act alone. Multiple receptors gather together at the cell surface to cooperatively switch on T cells. "The minimum unit for triggering T lymphocyte activation is known as the TCR microcluster [TCR-MC]," explains Takashi Saito of the RIKEN Research Center for Allergy and Immunology in Yokohama. "These are the key structure for T cells to recognize antigens and become activated."

At the interface between T cells and the antigen-presenting immune cells that switch them on, TCR-MCs accumulate at a structure called the central supramolecular activation cluster (cSMAC). Now, research from Saito and colleagues has revealed unexpected insights into how this accumulation occurs[1].

Saito and his team were the first to characterize TCR-MC function[2], but they were uncertain how these clusters make their way from the periphery to the core of the cSMAC. To understand this phenomenon, they performed a series of experiments in which T cells were placed on an artificial lipid layer that mimics the membrane of an antigen-presenting cell, allowing them to microscopically visualize activation-related events at the T cell surface.

Cellular structures are reinforced by protein fibers that form a network called the cytoskeleton, and Saito and colleagues revealed that TCR-MC movement is mediated by dynein, a 'motor protein' that shuttles cargos along these fibers. "We knew lymphocyte activation was regulated through the cytoskeleton," he says. "But it was most surprising that TCR complexes are physically associated with dynein and that their movement is mediated by assembling with this complex."

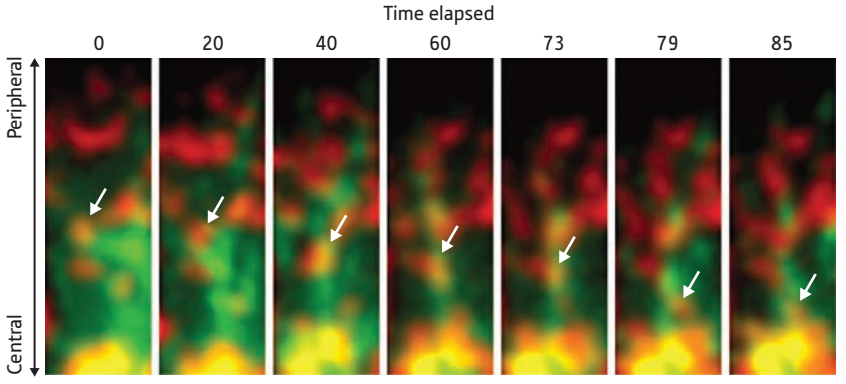

Figure 1: Following activation, a TCR-MC (white arrow) travels along microtubules of the cytoskeleton (green), making its way from the periphery to the cSMAC (time scale, seconds).

Upon TCR activation, the dynein-facilitated movement drags TCR-MCs laterally along the surface of the membrane towards the cSMAC (Fig. 1), a function previously unseen for this motor protein. Pharmacological inhibition of dynein strongly impaired migration of TCR-MCs and undermined their assembly within the cSMAC, as did the selective reduction of a key subunit of the dynein complex.

Intriguingly, the same treatments that impaired TCR-MC migration also enhanced T cell activation. Saito and colleagues therefore concluded that once these clusters reach the center of the cSMAC, they become internalized within the cell and thereby taken out of action. Saito hopes to exploit this effect by learning how the TCR-MC-dynein complex is assembled. "It would be ideal if we had a specific inhibitor of this assembly," he says, "which could lead to stronger immune status with enhanced activation of T cells." ■

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Sorting out gut health

Gastrointestinal inflammation is prevented by a protein sorting factor found in cells lining the gut

The gastrointestinal tract is lined with intestinal epithelial cells (IECs) that maintain gut health by keeping bacteria and pro-inflammatory immune cells from infiltrating gut tissues. Now, a team of researchers in Japan has shown that a protein in these cells, which is responsible for sorting many proteins to particular portions of the IEC surface, plays a key role in IEC modulation of gut inflammation[1].

IECs are polarized cells, with a bottom surface that attaches to deeper gut tissues, and a top surface that faces the inside of the gut, where it is exposed to ingested food and gut-resident bacteria. Proteins that are created in the cell are sorted preferentially to either the top or the bottom portion of the IEC. For example, cytokine receptors are shuttled mainly to the bottom of IECs so they can respond to cytokines released by immune cells within deeper gut tissues. Led by Koji Hase at the RIKEN Research Center for Allergy and Immunology in Yokohama, the researchers thought that disruption of proper protein sorting could affect the ability of IECs to properly respond to their environment.

To test their theory, the researchers generated mice lacking the μ1B subunit for a sorting protein called adaptor protein-1B (AP-1B). These mice developed an inflammatory gut disease called colitis, in which large number of immune cells infiltrated the gut. Mice lacking AP-1B expressed fewer antibacterial proteins, allowing bacteria to attack gut tissue (Fig. 1). Hase and colleagues showed that this bacterial entry enhanced immune cell recruitment into the gut, because antibiotics could reduce the inflammation in these mice.

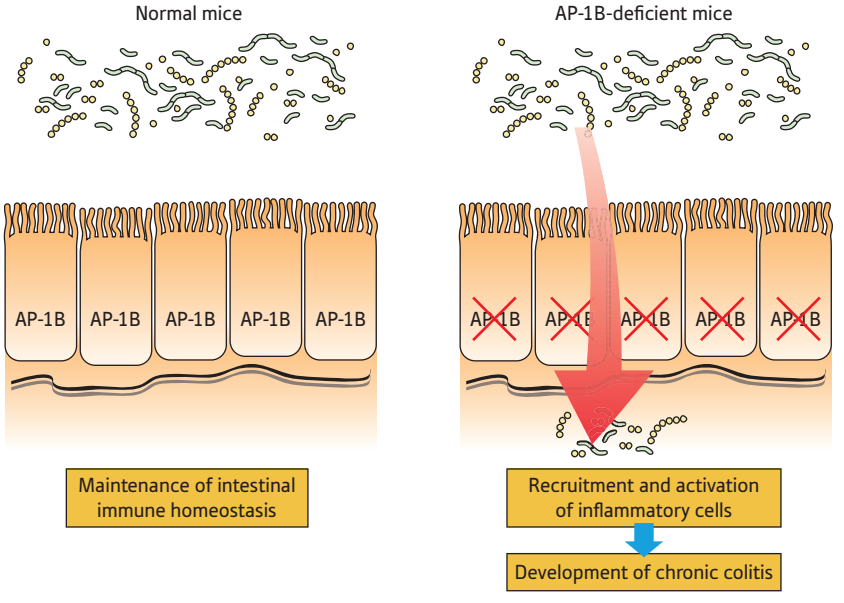

Figure 1: AP-1B expression in gut epithelial cells prevents bacteria from entering the gut and causing inflammatory bowel diseases.

Cytokines such as interleukin-17 (IL-17) are responsible for inducing antibacterial protein expression in IECs. However, the researchers found that cells lacking AP-1B were unable to properly sort cytokine receptors, including the IL-17 receptor, to the appropriate portion of the IEC membrane. This suggested that IECs may have failed to properly respond to IL-17 because its receptors were in the wrong part of the cell.

When Hase and colleagues examined IECs in humans with an inflammatory bowel condition called Crohn's disease, they found that expression of the μ1B subunit was reduced, and that one cytokine receptor seemed to sort to the wrong portion of the IEC surface. "AP-1B-dependent protein sorting therefore seems to control epithelial immune functions that keep the human gut healthy," explains Hase. Enhancing the expression of μ1B could be a potential therapy for Crohn's disease, the team concludes. ■

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Integrated bioinformatics gateways open data to the world

Access to multiple life science databases made easier by a web-based portal and interface developed at RIKEN

Figure 1: Accessing and analyzing raw biological data from millions of individual data records is now easier using RIKEN's bioinformatics portal BioLOD.org and interface, Semantic-JSON.

An easy-to-use bioinformatics interface has been developed by a research group led by Tetsuro Toyoda called the RIKEN Bioinformatics And Systems Engineering division (BASE), Yokohama[1]. The web-service-based tool, called Semantic-JSON (http://semanticjson.org) and the portal, BioLOD, integrate access to information contained within genomics, proteomics, and other 'omics'-based data repositories.

"Advances in life sciences increasingly depend upon cross-analysis and integration of diverse information from multiple large databases maintained on remote computer servers," explains Toyoda. "The challenge is to facilitate data retrieval, integration and collaboration while maintaining database security."

As a first step, various research organizations worldwide, including RIKEN, recently published 192 public and 190 private mammalian, plant and protein databases. The data are integrated by SciNetS.org, the Scientists' Networking System. These databases contain more than 8.2 million individual data records.

Pioneering a new global trend, BASE provides 'structured linked open data' and private data via the newly developed BioLOD.org portal connecting with the World Wide Web Consortium (W3C) Linking Open Data initiative. These self-described data are interlinked using standard web technologies allowing automatic reading by computers, thereby making them more useful to researchers. The system facilitates information sharing and collaboration between researchers, but brings new challenges.

"The sheer amount of data contained in our biological data cloud outstripped the capacity of existing bioinformatics interfaces to cope with the complexity of researcher queries, motivating us to develop Semantic-JSON," explains Toyoda.

Semantic-JSON has two major components. The secured, unified data repository integrates data meaningfully—or 'semantically' in computer parlance— from numerous sources. The web-based interface allows researchers to retrieve linked data seamlessly and securely using established bioinformatics programming languages and processing. Bioinformatics researchers can then use their specialized computational tools to analyze raw biological data (Fig. 1).

Databases already available through Semantic-JSON and BioLOD. org include the RIKEN Integrated Database of Mammals with 79 human and mouse omics databases, the RIKEN Integrated Database of Plants incorporating 30 similar databases for the plant species *Arabidopsis thaliana*, and the RIKEN Integrated Protein Database containing 18 databases.

Since December 2009, international researchers have successfully used the system to identify 28 million data relationships, generating some 4.5 terabytes of associated files. Around 134,000 programs from non-RIKEN researchers have accessed the server as of March 2011. Biological applications include genome design, DNA sequence processing, and the inference of phenotype biological characteristics from genomic information.

"Our next goal is to develop and improve the system to increase its functionality and the usefulness of its linked open data to the worldwide biological community," says Toyoda. ■

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Imaging inflammation in the living brain

A molecular probe that targets a pro-inflammatory enzyme allows visualization of inflammation during brain injury in rats

Inflammation occurs in the human brain during illnesses such as Alzheimer's disease, Parkinson's disease, stroke and traumatic brain injury. Now, a research team in Japan has developed a probe that can bind to the pro-inflammatory enzyme cyclooxygenase (COX). The probe, ^{11}C-ketoprofen methyl ester, enables researchers to observe when and where the enzyme is acting in the brains of living animals using positron emission tomography (PET) imaging[1].

In PET imaging, a radioactive tracer that binds specifically to a specific molecule in the body is injected into a living organism. Images are then taken with a PET scanner, indicating where in the body that tracer is found.

Led by Hirotaka Onoe at the RIKEN Center for Molecular Imaging Science in Kobe, the researchers had previously discovered that ^{11}C-ketoprofen methyl ester could recognize COX, but not which of its two forms[2]. To determine which isoform is responsible for binding their molecular probe, Miho Shukuri, a young member of Onoe's team, utilized a series of mice lacking the genes for either COX-1 or COX-2. She found that the PET probe could bind to the brains of COX-2-deficient mice, but not to those lacking COX-1. According to the researchers, ^{11}C-ketoprofen methyl ester is therefore the first PET probe that is specific to COX-1 in living animals.

When Shukuri injected bacterial antigens into the brain of rats to induce inflammation, she saw the PET probe build up in the brain within six hours to one day after antigen injection. The levels dropped a week later. Because COX-1 is rapidly activated by brain injury, this may mean that administration of drugs that block COX-1 soon after injury could prevent the progression of brain damage. "COX-1 could therefore be a promising target for the neurodegenerative diseases that exhibit neuro-inflammation," explains Onoe.

Microglia are immune cells in the brain that proliferate in response to injury, while macrophages are immune cells normally found within the blood that invade the brain after injury. The researchers observed that the injury-induced increase in brain COX-1 seemed to occur within microglia and macrophages (Fig. 1), which also became more numerous in the brain after exposure to bacterial antigens. Other research groups have found COX-1-expressing microglia in diseases such as Alzheimer's disease, Parkinson's disease and multiple sclerosis. This suggests to Onoe and colleagues that ^{11}C-ketoprofen methyl ester could be used to track the time course and localization of increased COX-1 expression in living organisms, including humans, suffering from diseases linked to neuro-inflammation. ■

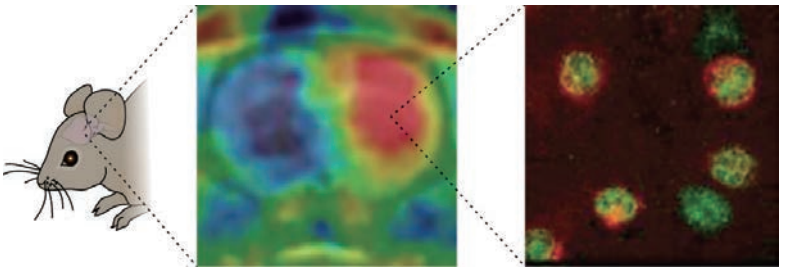

Figure 1: A PET imaging probe can be used to visualize COX-1 expression in living animals (red, middle image). Activated microglia and macrophages (red, right) in the mouse brain express the protein COX-1 (green, right) after injury.

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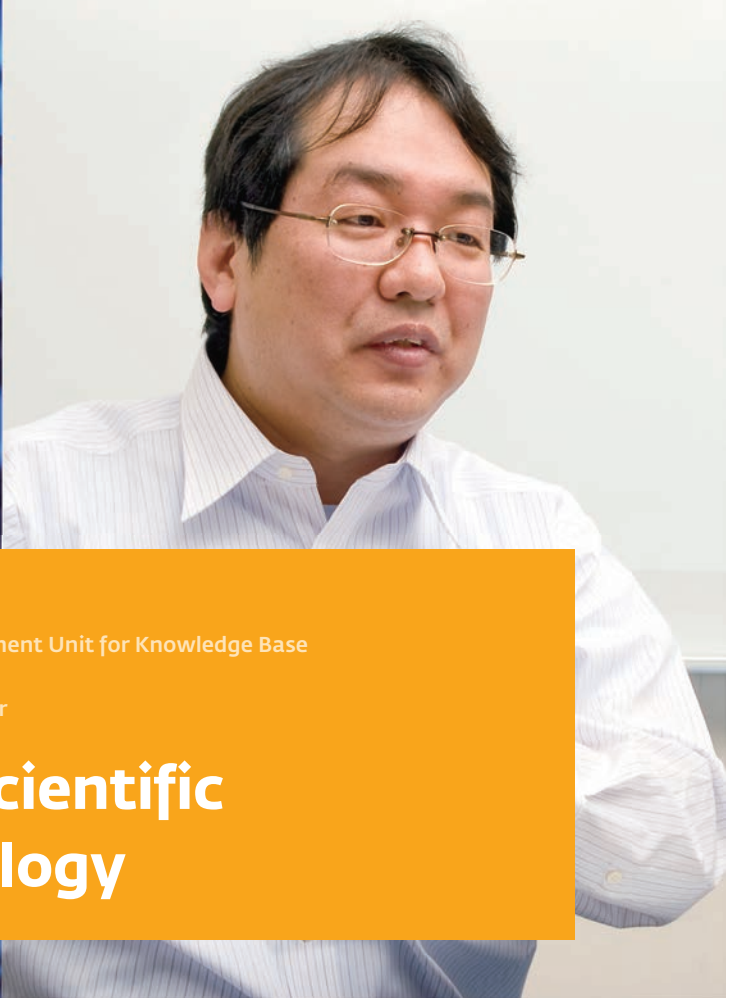


HIROSHI MASUYA

Unit Leader
Technology and Development Unit for Knowledge Base of Mouse Phenotype
RIKEN BioResource Center

Integrating the word's scientific databases through ontology

Researchers at the RIKEN BioResource Center led by Hiroshi Masuya of the Technology and Development Unit for Knowledge Base of Mouse Phenotype are developing a system that will be able to bring together all of the information saved in databases around the world to be accessible from a single terminal. This system will allow scientists to select the information necessary for their research instantaneously from any database in the world, analyze it, and display the results in a readily usable format. The key to the system is ontology, a philosophy dating back to the time of Aristotle but with technological relevance today. Ontological systems promise to revolutionize the way we share data, and the technology is attracting attention across the globe.

Barriers to research

There are many steps researchers must take in making their own experimental plans, including checking databases to find and analyze research trends in relevant fields and choosing the appropriate experimental materials. It is also necessary to compile papers and other reference materials, and review and interpret their contents. However, regarding the issue of the wordings used to describe pathologic conditions and other characteristics of laboratory animals, for instance, different researchers use somewhat different definitions. This linguistic vagueness makes it necessary to analyze the experimental methodology and context and reinterpret the terms in all cases. A great deal of time is taken with these painstaking preparatory arrangements before determining the optimum experimental methodology.

"In biology, there are numerous databases for genes, proteins, diseases and the like around the world, and they all operate separately. A researcher who wants to investigate a particular subject must search all the databases that seem to be appropriate one by one. In addition, each individual database has its own attributes. Because the databases are designed to be used in distinct ways that are suited to different research areas, it takes a great deal of time for researchers in other areas to become familiar with databases in areas other than their own," points out Masuya.

Ontology—correlating the essential nature of things

"Ontological technology allows computers to automatically arrange and extract the desired data so that the preparatory work for any investigation comes very easy," Masuya explains, "The term ontology has its origin in a Greek philosophical term meaning existence. In bioinformatics, ontology refers to the classification of concepts and terms and how to describe their relationships and systems."

In 2010, Masuya and his colleagues created the RIKEN Integrated Database of Mammals. The database incorporates YAMATO-GXO ('Yet Another More Advanced Top-level Ontology-Genetics Ontology'), an ontology tool they developed jointly with Riichiro Mizoguchi at the Institute of Scientific and Industrial Research (ISIR) of Osaka University. "We integrated the 18 major databases of the world using YAMATO-GXO. Our mammalian database is based on RIKEN's Scientists' Networking System (SciNetS)." Developed by a team led by Tetsuro

Toyoda, director of the RIKEN Bioinformatics And Systems Engineering Division (BASE), SciNetS can accommodate a wide variety of data, including ontological data, facilitating the integration of developed databases. To date, RIKEN's nine databases in biology have been integrated. They succeeded in integrating as many as 900,000 data items from 18 databases by incorporating YAMATO-GXO into SciNetS and other databases. "It is quite painstaking for a single researcher to find the data they want from among 900,000 entries. However, the RIKEN Integrated Database of Mammals makes it easy to obtain the data they want in a somewhat automatically analyzed form." This database is currently under development and expansion (see Fig. 1).

As an example, animal skin comprises a diverse range of tissues, and the presence or absence of hair is a good indicator for detecting tissue anomalies. 'Nude', 'hairless', 'hair loss' and 'loss of hair' are all terms used to describe the absence of hair on the skin. The most appropriate term to use depends on the audience and the journal's editorial policy. Using a conventional database, for example, the term 'nude' may get 18 hits concerning related genes, whereas 'loss of hair' might get only two hits. "All these terms share the essential meaning of 'no hair on the skin' and ontology helps to determine the essential meaning of words and sentences and to correlate a broad range of things and words. It arranges and systematizes biological concepts and the connections with their essential meanings. When we search in the Integrated Database of Mammals with a retrieval term such as 'nude' or 'loss of hair', all the relevant genes are retrieved and displayed instantaneously." Because the logical structures, including concepts, information and data intrinsic to those individually existing databases, have been integrated into YAMATO-GXO, a unified knowledge structure for biology, with accurate search and extraction functions has become possible.

Rapid integration of databases

Technology for knowing the meanings of words and sentences and forming correlations among them may sound relatively simple, but ontology is in reality a very profound activity. "Ontology is philosophy. It is underlain by a philosophical system that has been unbroken since the time of the ancient Greek philosopher Aristotle (BC 384–322). It took five years for us to be able to understand information

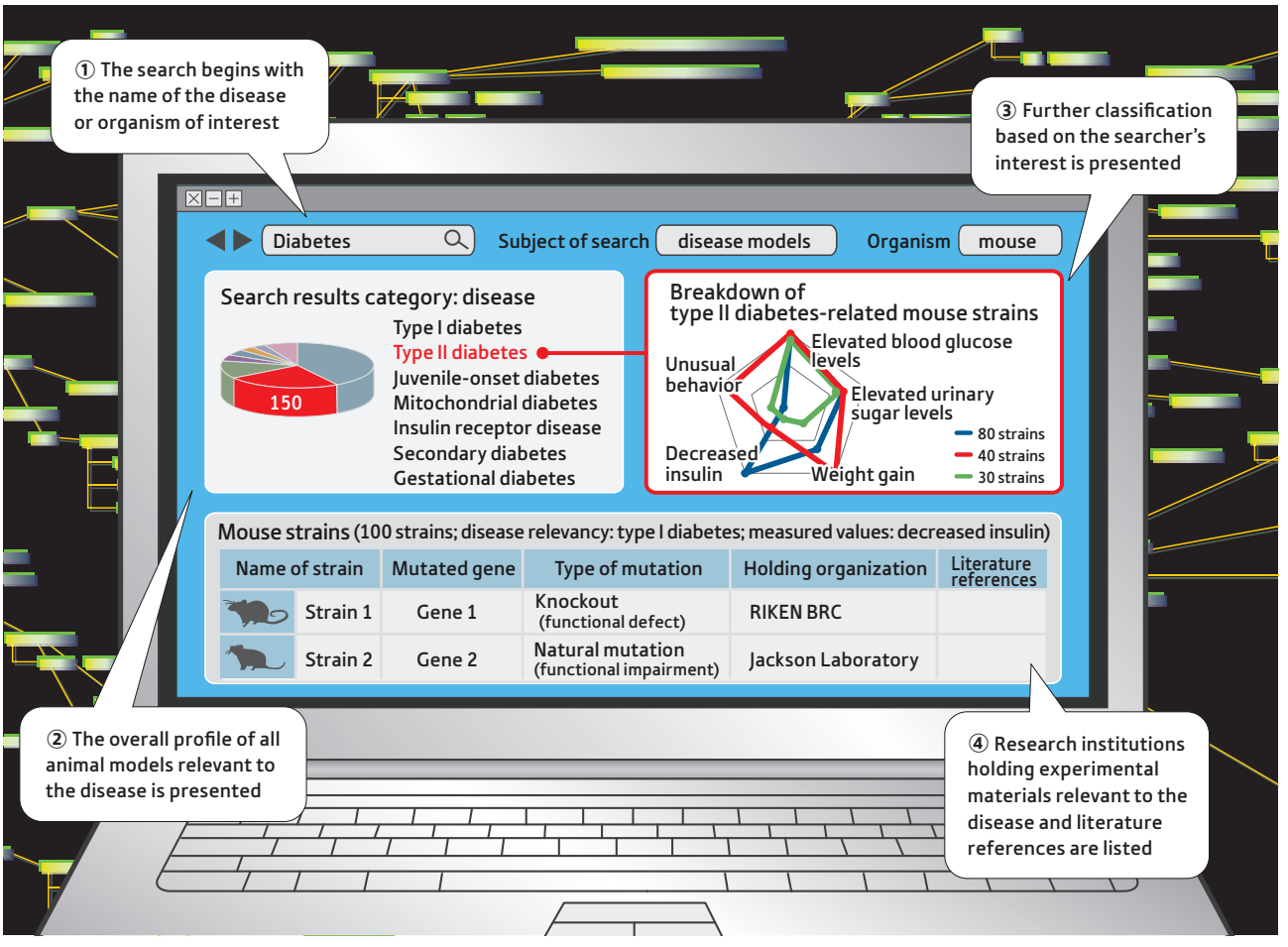


Figure 1: An integrated information view (in development) of RIKEN Integrated Database of Mammals

A user types in the name of a disease or organism of interest, and the relevant information is retrieved from the major databases of the world. Data on non-mammalian organisms such as plants and microorganisms will also be integrated.

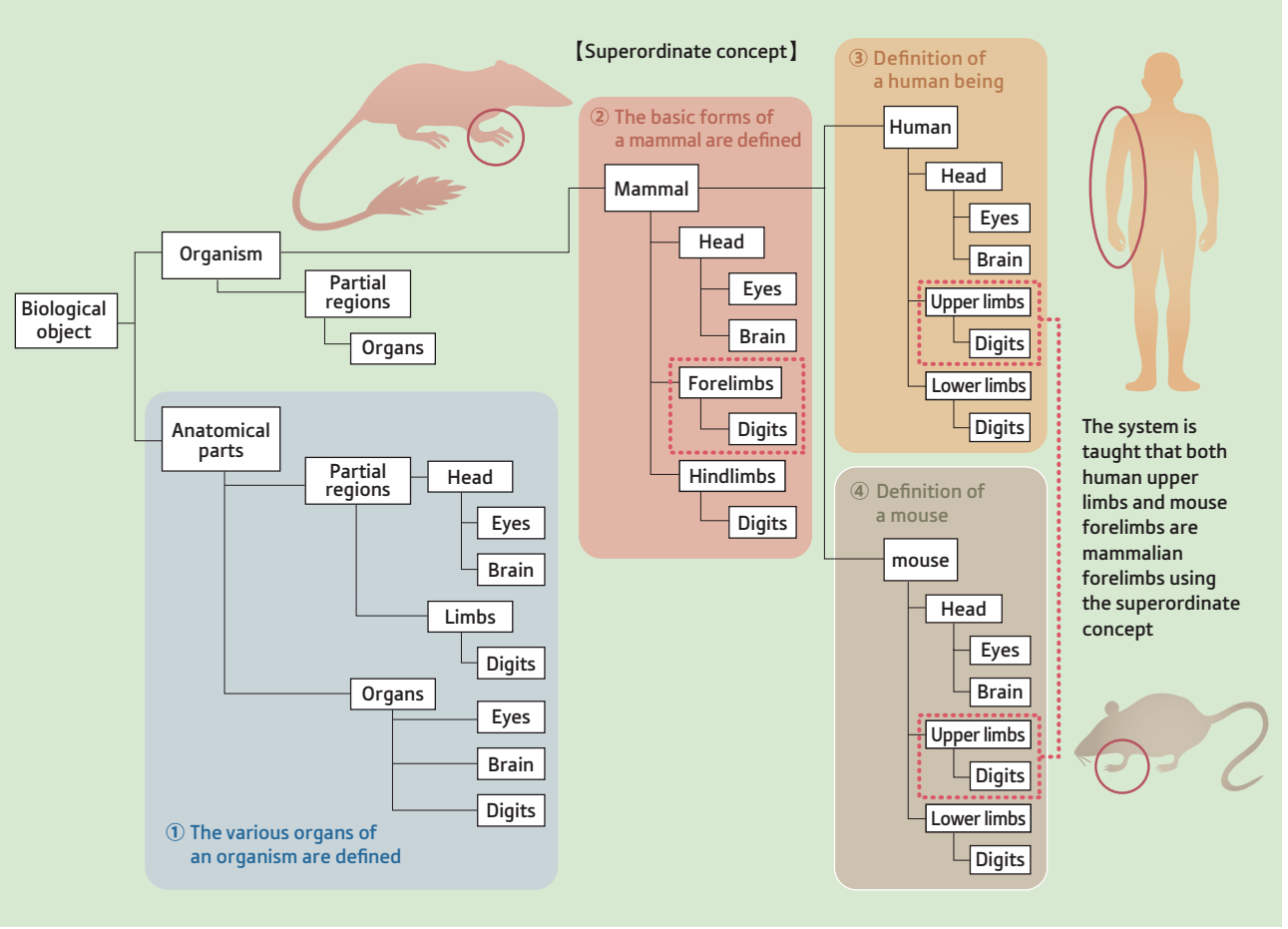


Figure 2: Example of data connection using a superordinate concept

An example of the application of ontology for simply characterizing humans as a mammal. After defining the various organs of the organism, a mammal is defined as an organism having a head and four limbs. This superordinate concept allows humans (five digits on each of the upper and lower limbs) and mice (four digits on each forelimb) to be defined alike as a mammal. Shown here is the fact that both human upper limbs and mouse forelimbs represent mammalian forelimbs.

technology based on a philosophy that has been nurtured over such a long historical period."

According to Masuya, "Ontology is used to teach the computer about this world." For example, the human being is a primate, a mammal, an organism and an animal. It is characterized by bipedal locomotion, a brain weighing 1,250 grams on average, five fingers on each limb, two eyes and so on. By fractionalizing things like this and systematizing the essential meanings, a more fundamental 'superordinate concept' is created (Fig. 2). If systematized, even databases with different logical structures can be combined relatively easily with ontology serving as a 'translator'.

Before ontology was integrated into practical applications, databases could not be linked together unless their logical structures, or intrinsic habits, were coordinated in all cases. The need to build other databases to separately connect different meanings was unavoidable. That work is painstaking and time-consuming. "Thanks to YAMATO-GXO, we were able to develop the RIKEN Integrated Database of Mammals, which integrates 18 databases, in just half a year."

Building on this achievement, in fiscal 2011 RIKEN launched the 'Biological and Environmental Phenomes Integration Database', a database integration promotion program sponsored by the Japan Science and Technology Agency in a joint initiative with Toyoda of the BASE. "This program will integrate nationally available data on 'phenotypes', which represent the characters manifested by the action of genes, and information on measurement techniques. We are working on developing a database that allows even a measurement technique with use limited to a particular area to be used in other areas, allowing it to contribute to advances in biology at large."

The attraction of ontology

Ontology research is currently attracting worldwide attention. The concept of gene ontology was first proposed in 1995 by Michael Ashburner of the University of Cambridge in the UK, and gene ontology even now represents a major technical breakthrough for the standardization and massive compilation of biological information. The introduction of this approach resulted in an explosion in research using DNA microarrays—chips that allows investigators to determine how a large number of genes are expressed, and the intensity of expression,

at one time. Using gene ontology, for example, it is possible to collate the availability of all reports on the functions of the gene expressed. With the spread of DNA microarray technology, a new discipline called transcriptomics emerged to analyze when, where and at what levels the more than 20,000 human genes are expressed, and to determine what is meant by the expression. "The microarray could not have become such a powerful research tool without gene ontology," says Masuya. Linkage of the two distinct technologies, microarrays and ontology, has been promoting advances in the new research domain of transcriptomics.

The trend of the times is also boosting ontology. It has been shown that in research into genes and proteins, causality does not always stand in a one-to-one relationship between cause and result. This is because many genes and biomolecules are involved in the processes for the generation of each protein. Additionally, techniques for visualizing the behaviors of many genes and biomolecules are already available. "By using an ontology-based integrated database, we can get a listing of the results from the concurrent functioning of multiple genes out of the vast amount of data obtained, rather than the one-to-one matched data on gene functions in conventional databases. Ontology is expected to really lead future research." Because it is capable of easily identifying disease-causing genes and proteins from among the vast number of biomolecules, ontology is expected to lead to major breakthroughs in the acceleration of new drug development and phase I clinical trials. While information is increasing explosively in the research domain, ontology that links a wide variety of databases can be described as a hidden but powerful tool that leads research activities that are prone to become chaotic.

Identifying knockout mouse phenotypes within an international framework

"We will proceed to develop ontology to standardize international mouse information," says Masuya. His laboratory has been requested to join the International Mouse Phenotyping Consortium (IMPC) to clarify the relationships between genes and phenotypes by examining all the phenotypes in knockout mice that have been manipulated to systematically delete each gene in the mouse genome. Mice represent a number of similarities (homologies) with humans in terms of the number and kinds of genes, as well as biological events and disease processes. The large project aims to link human diseases and phenotypes of knockout mice. "Currently, laboratories all over the world are working to design knockout mice and utilize them as investigational materials independently. However, a major loss of information resides here."

In conducting experiments, researchers create knockout mice that fit their research themes. For example, researchers studying limb development may generate a knockout mouse by inactivating a relevant gene. If researchers cannot find any morphological abnormality in the limb, they often give up on investigating that mouse further. However, a lot of genes have multiple functions. For instance, many signaling molecules involved in limb development are also involved in other biological processes in another organ—a fact that could be easily overlooked and a discovery that might never get published, even though the finding may have made all the difference to a physician struggling to elucidate metabolic disorders in a patient.

"Such occurrences have been prevalent since the birth of the first knockout mouse. The IMPC offers a decisive solution to this situation." In the large-scale project with its huge budget of nine million dollars, more than 20,000 mouse genes are being knocked out one-by-one to comprehensively analyze basic phenotypes and determine their influences on the mammalian body. The project also includes the development of an ontology-incorporating database and provides free access to information on the associations of the genes with biological phenomena and diseases. RIKEN's BRC is going to join the IMPC in a collaboration between the Technology and Development Team for Mouse Phenotype Analysis led by Shigeharu Wakana, the Experimental Animal Division headed by Atsushi Yoshiki, and Masuya's Technology and Development Unit for Knowledge Base of Mouse Phenotype. Once this information network is built, it will be possible to list all knockout mice that help research into a particular human disease from the database. "The network will enable us to select 'all' mice serving as disease models that exhibit similar symptoms, and even 'potential models' that exhibit near-morbid conditions. This encompassing 'all' is of paramount importance, and reducing the unidentified portions will dramatically move forward the whole field of research into disease."

A powerful tool that will lead research activities

Database integration using ontology has the potential to bring many breakthroughs. In a hospital, for example, physicians could download a listing of everything from the names of candidate diseases to the likely progression of the condition, candidate medications and therapeutic guides. Such an integrated database would make it possible to investigate therapeutic approaches to coping with complications from all angles using information from the component databases. "Our ultimate goal is to create a tool that will serve as the guide to researchers' activities by presenting information even at levels beyond human ponderings, and deducing and displaying potentially useful search results in an easily understandable way," says Masuya.

ABOUT THE RESEARCHER

Hiroshi Masuya was born in Osaka, Japan, in 1968. He graduated from the Biological Institute at Tohoku University and obtained his PhD in 1996 from the School of Life Science at the Graduate University for Advanced Studies. He joined the National Institute of Genetics in 1997 and became a research fellow of the Japan Society for the Promotion of Science in 1998. In 1999, he joined the RIKEN Genomic Sciences Center as a research scientist. Since 2008, he has been unit leader of the Technology and Development Unit for Knowledge Base of Mouse Phenotype at the RIKEN BioResource Center. His interests include bioinformatics and mammalian genomics.

Qibin Zhao

Research Scientist
Laboratory for Advanced Brain Signal Processing
RIKEN Brain Science Institute

Making great strides in brain research

What do you do at RIKEN?

My research focuses on the interface between computer science and neuroscience, particularly with regards to brain signal processing and brain–computer interfaces. My goals included developing advanced machine learning methods for multidimensional and multimodal brain data analysis, as well as extracting or predicting subjects' intentions based on their brain activities. I am trying to develop multiway analysis tools such as non-negative tensor decomposition and multilinear partial least squares to extract more effective features for the classification of brain signals. This will provide a better understanding of the working patterns or functional connectivity of the brain structure.

How and when did you join RIKEN?

As a PhD student in China, I became aware of the work of Dr Cichocki in the Laboratory for Advanced Brain Signal Processing at the RIKEN Brain Science Institute (BSI). Doctor Cichocki is world-renowned for developing software such as the Independent Component Analysis Laboratory toolbox. I applied for the RIKEN Brain Science Institute Summer Program in 2007 on the recommendation of my supervisor in China, who had spent five years at the RIKEN BSI, and I was fortunate to be accepted as an intern in Dr Cichocki's laboratory. I later joined RIKEN without hesitation after obtaining my PhD in 2009.

How was the transition to life at RIKEN?

When I first came to RIKEN in 2007, I was really worried about living in Japan because I couldn't speak Japanese at all. Fortunately, my Chinese language background allowed me to understand Chinese characters, which are also used in Japanese. My colleagues were friendly and helpful, and the laboratory secretary and staff at the Brain Science Promotion Division made my stay in Japan comfortable, productive and enjoyable.

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

My research focuses on non-invasive brain–computer interfaces and advanced brain signal processing, which are used to develop tools for analysis, extraction, enhancement, de-noising and the classification of brain signals, especially for measurements using high-density array electroencephalography systems. By determining intentions based on the electrical activity of a person's brain, modern machine learning and mathematical methods can be developed. I have recently been working on multiway data analysis techniques that allow the creation of new models by organizing data in a high-dimensional form.

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

Thanks to Dr Cichocki's excellent guidance, I have been able to achieve some favorable results for our brain–computer interface through the use of advanced brain signal processing methods and high-quality electroencephalography devices. My colleagues and I have also developed a fast brain–computer interface system to control cars, wheelchairs or robotic arms in three-dimensional virtual reality, and the results were picked up by the media. In 2010, one of our papers was awarded best paper by the Asia Pacific Neural Network Assembly. In 2011, we received a top-10 ranking in the nominations for The Annual Brain–Computer Interface Research Award. My wonderful experiences at RIKEN have been invaluable for my future career in research and science.

What is the best thing about working at RIKEN?

At RIKEN we not only enjoy top-level research but also many other activities. The staff at RIKEN are friendly and helpful because they offer a great variety of scientific and non-scientific activities.

What would you say to other people considering joining RIKEN?

The open, international research environment at RIKEN provides excellent opportunities for talented and ambitious researchers, especially for young scientists.

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

Third Noyori Summer School held in Kobe

On September 9–10, the third Noyori Summer School was held at Kobe Port Island, home to the RIKEN Kobe Institute and the RIKEN Advanced Institute for Computational Science (AICS). The summer school, launched in 2009, provides opportunities for young researchers from around the world to meet RIKEN leaders and interact with one another. The 69 participants included International Program Associates (IPA), Junior Research Associates (JRA) and Trainees. The two-day event featured various presentations and interactive sessions, including a discussion with RIKEN President Ryoji Noyori.

The first day began with a poster session, where participants had the opportunity to exchange ideas and explain their work to President Noyori and other RIKEN officers. A group discussion led by President Noyori allowed participants to put their questions directly to Dr Noyori about career paths, the response of scientists to natural disasters, and energy resources.

Participants enjoyed a tour of AICS, home to the 10-petaflop supercomputer called the K computer, which was recognized as the fastest computer in the world at the 26th International Supercomputing Conference in June 2011. The young researchers were divided into groups and had a chance to visit the RIKEN Center for Developmental Biology (CDB) and the RIKEN Center for Molecular Imaging Science (CMIS). A special tour of the International Medical Device Alliance (IMDA), an organization focusing on advanced medical devices R&D, was arranged courtesy of its president, Dr Koichi Tanaka.

The second day featured presentations by Executive Director Maki Kawai, who gave a talk entitled "On Being A Researcher", and AICS Director Kimihiko Hirao, who spoke about the K computer and other research being conducted at the center.

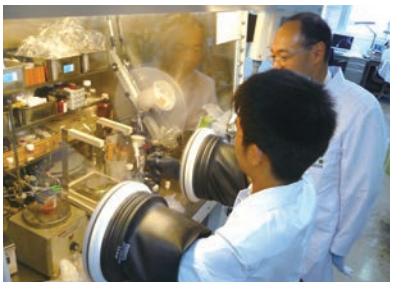
One of the highlights of the program was the presentation of the "Noyori Prize" for the best poster presentation. Virendra Kumar Rai of the Organometallic Chemistry Laboratory at the RIKEN Advanced Science Institute received the prize this year for his work on the development of novel electrophosphorescent materials for organic light-emitting diodes (OLEDs). A delighted Rai said, "The third Noyori Summer School in Kobe was a very good platform to meet young researchers, exchange knowledge, and work towards scientific collaborations in the future. I was really very happy to receive the Noyori Prize. It was a great honor, which I will never forget."

Executive Director Maki Kawai (left) and winners of the poster awards, including Virendra Kumar Rai, who received the Noyori Prize for best poster (third from right)

Budding scientists attend RIKEN's Summer Science Camp

On July 27–29, the RIKEN Wako campus hosted a series of events designed to inspire high school students attending RIKEN's Summer Science Camp 2011, organized jointly by RIKEN and the Japan Science and Technology Agency.

This year's program included lectures and presentations, as well as opportunities for students to gain hands-on experience performing experiments. At the RIKEN Advanced Science Institute (ASI), attendees were introduced to three key areas of research. One group of students learned how protein reaction networks determine the shape of living things at the Cellular Informatics Laboratory headed by chief scientist Yasushi Sako. A second group learned about the regulation of polymer properties using various catalysts at the Organometallic Chemistry Laboratory led by chief scientist Zhaomin Hou. A third group experimented with laser systems, guided by Satoshi Wada, unit leader of the Optical Green Technology Research Unit.



A high school student (left) conducts a chemical experiment at the Organometallic Chemistry Laboratory

The Summer Camp offers young scientists a unique glimpse into RIKEN's advanced science and technology programs and the opportunity to interact with researchers first-hand in various fields. RIKEN President Ryoji Noyori gave a talk to the students during the banquet held on the second day, and challenged students to ask themselves, "How can science contribute to solving global challenges?"

Students had the chance to give their own presentations on the final day of the program. One student commented, "I would love to work at RIKEN someday. It was very good to have the chance to talk with leading researchers and to be inspired by them. I hope to work in science in the future." RIKEN will host the next Summer Science Camp in July 2012.

ASI lecture series promotes greater collaborative research

The RIKEN Advanced Science Institute (ASI), with its large number of laboratories dedicated to fields ranging from physics to chemistry to the life sciences, is an ideal place for collaborative research. Strengthening the potential for such collaborative work by encouraging better communication among scientists from different fields is a key component of ASI's overall goals.

The "ASI Tutorial Science Dojo", playfully named to summon up a dojo—a training hall for Japanese martial arts—is one of the unique ways in which ASI offers a chance for researchers to broaden their perspective. Started in 2010, the program consists of a series of lectures delivered by ASI laboratory heads and chief scientists, with the aim of increasing mutual recognition and understanding between researchers active in today's highly specialized research environment.

From May to July in 2011, 8 lectures were held on topics in the life sciences, including a presentation by Hiroyuki Osada, director of the ASI's Chemical Biology Core Facility on integrative approaches at the interface of chemistry and biology, and a lecture on the structure of bio-membranes by Toshihide Kobayashi, Chief Scientist of the Lipid Biology Laboratory. Nine further lectures will be held later this year on topics in materials science, the first of which will be delivered by Kimitoshi Kono, Chief Scientist at the Low Temperature Physics Laboratory, on October 13th. The lectures will be held from October to December and are free and open to the public.

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RIKEN, Japan's flagship research institute, conducts basic and applied experimental research in a wide range of science and technology fields including physics, chemistry, medical science, biology and engineering. Initially established as a private research foundation in Tokyo in 1917, RIKEN became an independent administrative institution in 2003.

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