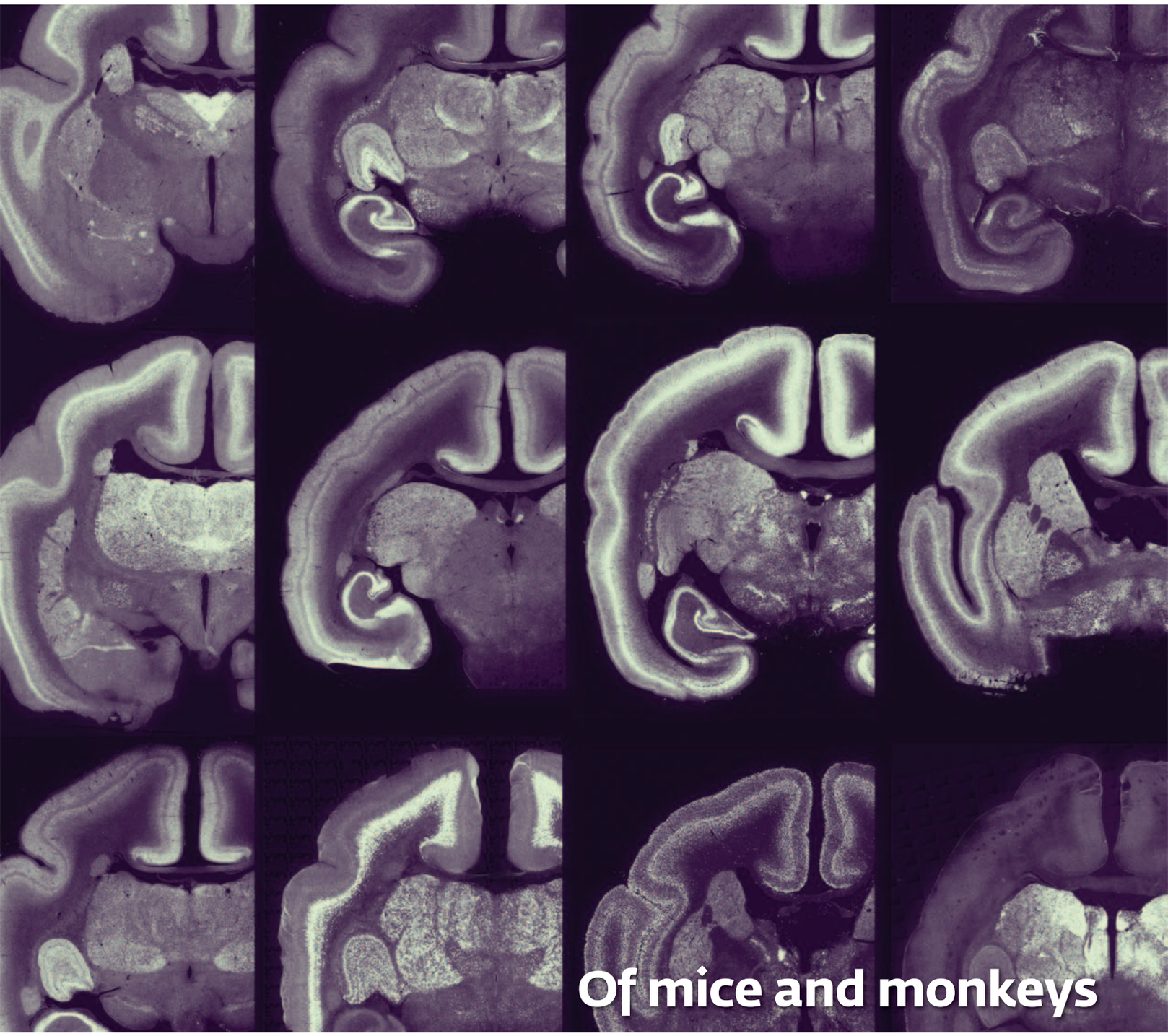
RIKEN RESEARCH

OCTOBER 2012
VOLUME 7 NUMBER 10



Of mice and monkeys

RIKEN

Physics

Catching a quantum effect in action

The first observation of a quantum effect that creates electrical resistance in nanoscale superconducting wires bodes well for new electronics and measurement applications

Superconducting wires, in contrast to conventional wires, can carry an electrical current without any resistance. This property is useful for transferring electricity with low energy loss and for creating powerful magnets. However, in very narrow wires—just a few billionths of a meter across—physicists have long predicted that quantum effects could increase the resistance to electrical flow. The first observation of this unusual phenomenon was reported recently by Jaw-Shen Tsai from the RIKEN Advanced Science Institute, Wako, and his colleagues from Japan, the USA, the UK, Finland and Israel[1]. Despite the deleterious effect of increased resistance, it could prove useful for high-precision measurements and new types of electronic devices.

Using a superconducting nanowire loop, Tsai and his colleagues clearly identified a quantum effect called coherent quantum phase slip. In general, a 'phase slip' occurs when a small region of a superconducting material momentarily changes into a normal, non-superconducting state. Electrical charge carriers can easily travel around these phase-slip regions when they are free to move in two or three dimensions; consequently, there is very little effect on the total electrical properties of the material. In superconducting nanowires, however, current is restricted to one dimension, so phase slips resist the flow of charge.

Tsai and colleagues, however, were faced with the challenge of identifying between two types of phase slip. 'Incoherent phase slips' result from thermal fluctuations in superconducting nanowires.

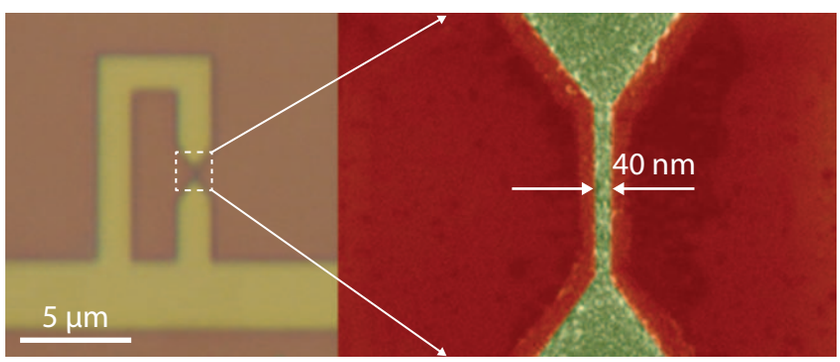


Figure 1: An indium oxide loop, incorporating a 40-nanometer-wide nanowire, has allowed physicists to make the first observation of coherent quantum phase slips.

Coherent quantum phase slips, on the other hand, occur due to fluctuations at a quantum level. Because the two phases manifest in a similar way, experimentally distinguishing coherent quantum phase slips from their thermal counterpart was considered very difficult.

Putting phase slips in the loop

Tsai and his team devised a clever method for identifying coherent quantum phase slips in a simple circuit, consisting of an indium oxide wire 35 nanometers thick, 40 nanometers wide and 400 nanometers long. They connected the ends of the nanowire using a wider wire to form a rectangular loop (Fig. 1). This circuit can store magnetic energy when a magnetic field passes through the loop. Under the laws of quantum mechanics, however, magnetic energy can be added or removed only in discrete finite chunks, known as flux quanta. Theoretical studies on superconducting nanowires had previously indicated that coherent quantum phase slips should lead to a shift in these discrete levels, such that two consecutive energy states could interact with one another. By experimentally observing these energy changes, Tsai and his team were able to provide clear evidence of coherent quantum phases slips.

The researchers investigated the properties of their superconducting loop by passing a microwave signal along a wire connected to the circuit, and then measuring how much power it transmitted. They built a full picture of the energy states supported by the device by changing the frequency of the microwave signal and varying the strength of the external magnetic field. In this way, they could clearly identify the distortions due to quantum phase slips.

The choice of material was vital for observing these phase slips. Indium oxide is a superconductor at temperatures below 2.7 kelvin, but it does not have the regular atomic structure common in

most superconductors. "We used indium oxide because it is highly disordered and therefore was expected to give a higher phase slip rate," says Tsai.

A better standard of current

The implications of this work are both practical and fundamental. From a philosophical perspective, the experiment is a demonstration of quantum effects in a relatively large system. A coherent quantum phase slip can be interpreted as a quantum flux travelling across the nanowire. This is impossible in classical physics because the nanowire acts as an energy barrier. In quantum mechanics, however, energy barriers can be tunneled through.

"In a superconductor, the conduction electrons are condensed into a macroscopic quantum state," explains Tsai. This means that quantum effects, such as tunneling, can be seen in the circuit even though it contains many millions of electrons.

The demonstration of coherent quantum phase slips could also contribute to the development of quantum computing. Scientists have previously demonstrated that a looped superconducting circuit could form the basic building block needed for a quantum computer, a so-called qubit. Just as a conventional computer operates on bits of information labeled '0' and '1', quantum information can be stored in a superconducting qubit, according to which energy state it is in. One energy state, for example, can represent the current flowing around the circuit in a clockwise direction, while the other represents counter-clockwise current flow. Unlike classical computing, however, quantum information requires a mechanism by which these two states can interact—exactly as Tsai and colleagues showed in their indium oxide circuit.

Although building a working quantum computer may be a long way off, the ideas considered by Tsai and his team might have technological applications that are nearer at hand: superconducting qubits could be a useful tool in metrology, the science of high-precision techniques for defining units of measurement. Specifically, quantum phase slips junctions could help to standardize the definition of electrical current, the ampere (Fig. 2).

"Coherent quantum phase slips convert a microwave photon [a single packet of microwave energy] into a current that is proportional to the photon's frequency," says Tsai. Thus, an accurate knowledge of the frequency translates to a precisely known current. "We are next going to perform direct-current measurements that should enable us to observe this quantization of current, which is vital for quantum metrology." ■

1. Astafiev, O.V., Ioffe, L.B., Kafanov, S., Pashkin, Yu, A., Arutyunov, K., Yu., Shahar, D., Cohen, O. & Tsai, J.S. Coherent quantum phase slip. *Nature* **484**, 355–358 (2012).

Figure 2: A more precise definition of the unit for measuring current flow, the ampere, could result from the demonstration of coherent quantum phase slips.

ABOUT THE RESEARCHER

Jaw-Shen Tsai was born in Taiwan in 1952. He graduated from the Department of Physics, University of California Berkeley, in 1975, and obtained his PhD in 1983 from the State University of New York at Stony Brook. Soon after graduation, he came to Japan as a research scientist at NEC Microelectronics Research Laboratories, where he started his career in superconductivity-related research. He was promoted to research manager in 1990, principal researcher in 1993, senior principal researcher in 1996, and fellow in 2001. He has concurrently worked as team leader of the RIKEN Macroscopic Quantum Coherence Lab since 2001. His research interests include quantum coherence in superconducting circuits, quantum bit and quantum information processing.

One material, two types of magnetism

By controlling electron numbers in a semiconductor material, researchers in Japan can dictate whether it is repelled or attracted to a magnetic field

When placed next to a bar magnet, an aluminum ball draws gently towards the magnet. In contrast, a ball made of silver moves out of the magnetic field. The mechanisms underlying these different behaviors are known as paramagnetism and diamagnetism, respectively. Surprisingly, the material called BiTeI—composed of layers of bismuth, tellurium and iodine atoms—can be either diamagnetic or paramagnetic, depending on how it is prepared[1].

The finding, by an international research team led by Naoto Nagaosa and Yoshinori Tokura from the RIKEN Advanced Science Institute in Wako, was unexpected because it requires an unusual mechanism to initially make the material magnetic. In BiTeI and related materials, the motion of electrons makes the most important contribution to their magnetism. Electrons move, roughly speaking, on orbital paths around atomic cores. "Orbital motion is usually associated with diamagnetism only," explains Nagaosa. "We were therefore surprised when our calculations [predicted] that there is [also] orbital paramagnetism in BiTeI." The experimental group headed by Tokura confirmed the prediction, as reported in the same paper.

Orbital diamagnetism is observed in a very wide variety of materials, including substances as common as water. Previously, the possibility of orbital paramagnetism, had been considered in only a few theoretical studies. One mechanism that can generate a paramagnetic response of electrons to a magnetic field is known as spin–orbit coupling (Fig. 1).

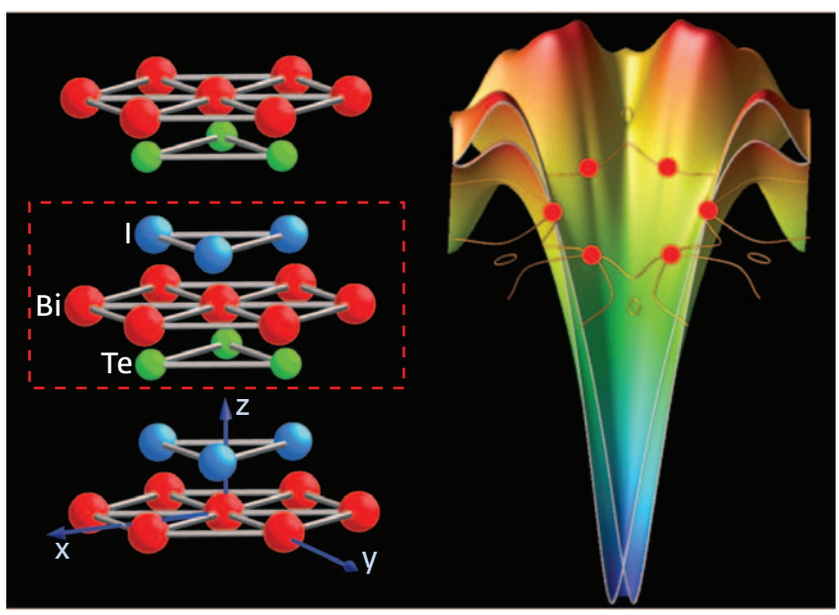


Figure 1: BiTeI is formed from layers of bismuth, tellurium and iodine (left). The energy surface of this material is composed of two sheets (right), which is a manifestation of spin–orbit coupling in this material.

This coupling connects the charge of the electron with its spin—the intrinsic angular momentum of the electrons, which is also responsible for their magnetic behavior. In BiTeI, spin–orbit coupling is particularly strong, making it an ideal material for exploring unusual effects of orbital magnetism.

To generate orbital paramagnetism in BiTeI, the trick is to control the number of electrons moving through the crystal. Nagaosa and his colleagues found a specific range where the material is paramagnetic. They showed, however, that there is also a regime when orbital diamagnetism is strongly enhanced, making it possible to fundamentally change the way the material reacts to a magnetic field.

Finding technological applications remains a task for the future, but Nagaosa expects that these unusual behaviors appear in a broad class of materials. "Other bismuth compounds related to BiTeI should exhibit similar effects, but there might be entirely different solids with orbital paramagnetism," he explains. "Indeed, we have theoretical evidence that the effects we describe will also occur, for example, in various situations in graphene-like materials." ■

1. Schober, G.A.H., Murakawa, H., Bahramy, M.S., Arita, R., Kaneko, Y., Tokura, Y. & Nagaosa, N. Mechanisms of enhanced orbital dia- and paramagnetism: application to the Rashba semiconductor BiTeI. *Physical Review Letters* **108**, 247208 (2012).

Optical microscopes delve deeper

Advances in nonlinear microscopy allow researchers to take detailed images deep below the surface of samples

Optical microscopes, also known as light microscopes, provide detailed images of sample surfaces, but their use in looking below the surface is limited. A workaround is to look for signals given off by a sample of interest when it interacts simultaneously with two particles of light (or photons), using a technique called nonlinear spectroscopy. Now, Keisuke Isobe and colleagues at the RIKEN Advanced Science Institute, Wako, have shown how nonlinear techniques can be used to peer even more deeply into a sample[1].

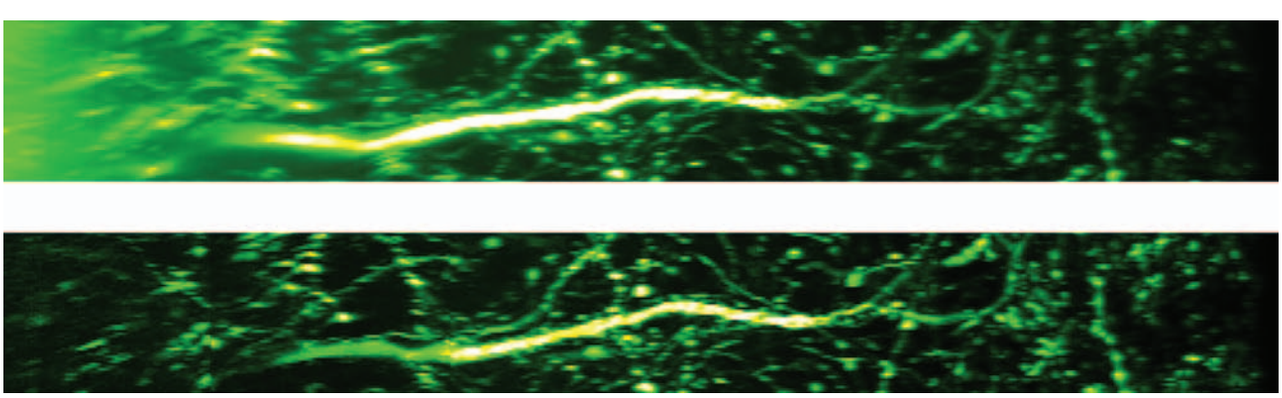
The most common type of optical microscope is a linear instrument. This means that the atoms of a sample of interest interact with only one photon at a time. As common and productive as it is, however, this linear approach has limitations that are surpassed by nonlinear microscopy. For example, a small volume of the sample can be isolated under a nonlinear microscope by illuminating it with two intersecting, nonparallel light rays. Background noise can be easily filtered out. The resulting high signal-to-noise ratio allows the operator to take detailed images, including from below the sample surface. However, when depths become particularly large, noise increases to the point that even nonlinear images begin to lack clarity.

Isobe and colleagues demonstrated a technique that can decrease background noise by a factor of 100 and can increase imaging depths by a factor of two over traditional nonlinear approaches. These traditional approaches maximize the volume of overlap of two different pulses of light at some point of interest inside the sample. Instead, the Japan-based team used beam-pointing optics to periodically modulate this spatial overlap. The signal produced in the center of the volume of interest was modulated at twice the overlap modulation frequency. Isobe says that the signals produced away from the center were modulated at lower frequencies.

By filtering out these lower-frequency signals, the researchers succeeded in greatly reducing background noise. When Isobe and colleagues applied this technique to the imaging of mouse brains, spatial overlap modulation allowed them to resolve structures at depths of 240 micrometers, where traditional nonlinear microscopy began to fail (Fig. 1). The overlap modulation also significantly increased resolution.

Isobe says this kind of visualization can be used to track signal transmission down axons in the brain, and can be readily implemented into existing nonlinear microscopes. "We also plan to investigate its use for medical interventions," he says, "like laser surgery." ■

1. Isobe, K., Kawano, H., Takeda, T., Suda, A., Kumagai, A., Mizuno, H., Miyawaki, A. & Midorikawa, K. Background-free deep imaging by spatial overlap modulation nonlinear optical microscopy. *Biomedical Optics Express* **3**, 1594–1608 (2012).



From Ref. 1 © 2012 The Optical Society

Figure 1: Nonlinear optical microscopy images of mouse brain tissues. The top image is the result of a traditional imaging approach, while the bottom image uses spatial overlap modulation. The images measure 300 micrometers across and 32 micrometers deep.

Reactivity on a string

Computer simulations show that impurity atoms impart remarkable control over water splitting reactions on insulator surfaces

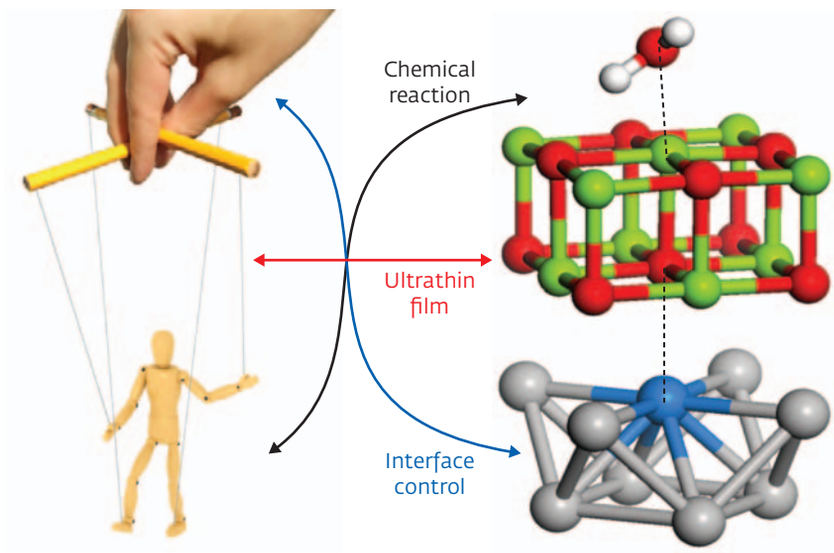


Figure 1: New computer simulations show that substituting a transition metal dopant atom (blue sphere, bottom right) into a silver crystal (grey spheres, bottom right) of an oxide-metal interface provides unprecedented control over water splitting reactions on a magnesium oxide surface (Mg (green) and O (red) top right).

Ultra-thin inorganic oxide films are set to play vital roles in future catalytic systems, according to findings from Jaehoon Jung and Yousoo Kim at RIKEN's Advanced Science Institute in Wako and two colleagues in Japan and Korea. Through high-level computer simulations, the team discovered that small amounts of impurity atoms, or dopants, in ultra-thin oxides can systematically lower chemical reaction barriers[1]—giving chemists a new tool for optimizing catalytic processes such as hydrogen-fuel generation.

Materials scientists are intrigued by ultra-thin oxides because they allow 'fine-tuning' of surface chemical reactions. For example, Jung, Kim and colleagues recently used silver crystals coated with magnesium oxide (MgO) to break individual water molecules into proton and hydroxyl ions through multiple vibrational excitations[2]. The insulating MgO layer decouples interactions between absorbed water molecules and the underlying silver substrate just enough to activate specific water-splitting pathways. Varying the oxide thickness provides an additional dimension of control over this catalysis[3].

Most recently, the team focused on a relatively unexplored technique to tailor the reactivity of MgO/silver surfaces even further: inserting transition metal dopant atoms into the interfacial surface structure. Jung explains that the '*d*-type' electrons of transition metals such as titanium, iron, and copper provide predictable charge effects that can influence the catalytic and magnetic properties of oxide materials.

To explore this concept, the researchers used quantum chemistry computations to model two-atomic-layer-thick MgO on top of a periodic silver crystal. When they replaced a silver atom with a dopant, they saw that oxygen atoms attracted transition metals to the MgO/silver interface through a 'drawing effect'. By systematically switching between transition metals containing ever-increasing *d*-electrons, the researchers found they could use this effect to precisely control interfacial dopant concentrations (Fig. 1)—a boon for practical applications of this technology.

The team's calculations revealed that hybridization between transition metal *d*-electrons and the ultra-thin oxide creates an effect that increases adhesion between the MgO and silver layers. In turn, surfaces with higher MgO/silver adhesion have sharply enhanced water-splitting capabilities. A linear correlation between dopant *d*-electron count and chemical reactivity leaves the researches hopeful this approach can lead to accurate interface engineering of other catalytic processes.

"To control surface reactions, we need to look beyond just surface modification, which usually has unwanted side effects," says Jung. "We revealed that chemical reactivity on MgO/silver surfaces is correlated with adhesion properties well-described by textbook theory. These are guidelines—sticks and wires that can be used to manipulate the 'marionette' of chemical activity." ■

1. Jung, J., Shin, H.-J., Kim, Y. & Kawai, M. Ligand field effect at oxide-metal interface on the chemical reactivity of ultrathin oxide film surface. *Journal of the American Chemical Society* **134**, 10554–10561 (2012).
2. Shin, H.-J., Jung, J., Motobayashi, K., Yanagisawa, S., Morikawa, Y., Kim, Y. & Kawai, M. State-selective dissociation of a single water molecule on an ultrathin MgO film. *Nature Materials* **9**, 442–447 (2010).
3. Jung, J., Shin, H.-J., Kim, Y. & Kawai, M. Controlling water dissociation on an ultrathin MgO film by tuning film thickness. *Physical Review B* **82**, 085413 (2010).

Expanding DNA's utility

A technique that dissolves DNA in organic solvents, without affecting its function, will advance the use of DNA in nanotechnology

Carrying the genetic code is already a vital job, but DNA is also proving to be a useful tool in nanotechnology applications. Since the DNA molecule is a versatile building block, it can be used to construct molecular devices. DNA structures known as 'DNAzymes' can also act as catalysts for certain chemical reactions. However, the inability to dissolve DNA in anything but water has hindered progress. Now, DNA can be dissolved in a range of organic solvents, without destroying its folded structure, thanks to a discovery by Hiroshi Abe, Yoshihiro Ito and their colleagues at the RIKEN Advanced Science Institute, Wako[1].

The researchers showed that DNA will dissolve in most organic solvents after attaching a long side chain called a polyethylene glycol (PEG) unit (Fig. 1). Organic solvents are typically much less polar than water, which prevents polar DNA molecules from dissolving in them. By attaching a non-polar PEG group to one end of a DNA strand, they were able to dissolve it in organic solvents ranging from methanol to 1,2-dichloroethane—solvents that scientists usually use for chemical reactions because many molecules are water-sensitive.

The team used an analytical technique called circular dichroism to show that a series of PEG-modified DNA structures called G-quadruplexes retain their shape in the organic solvents. Other teams had successfully dissolved DNA in an organic solvent by simply premixing it with another non-polar substance, but the process caused the DNA to lose its folded shape, Abe notes. "[The] PEG-modification allows us to keep the structure of DNA intact in organic solvents," he says.

Figure 1: DNA will usually only dissolve in water. However, by modifying it with a polyethylene glycol (PEG) side chain (left) and adding a typical laboratory organic solvent called 1,2-dichloroethane, the DNA will dissolve (right).

Surprisingly, one of the PEG-modified G-quadruplex structures tested by the researchers proved to be more stable in organic solvents than it is in water. While some of the forces that hold the DNA structure in its folded shape are weaker in the non-polar organic solvent, others, such as hydrogen bonding interactions, are strengthened, Abe explains.

Crucially, the retention of DNA's structure in organic solvents means that it can also retain its ability to function as a catalyst, for example. In water, the PEG-modified version of a G-quadruplex DNAzyme named HT6 oxidizes a molecule called luminol into a light-emitting form. When the researchers switched to an organic solvent, a telltale luminescent glow confirmed that the DNAzyme was still functioning.

Abe, Ito and colleagues are now focused on generating organic-solvent-soluble DNAzymes with more useful catalytic functions. They are using a technique called SELEX to generate libraries of DNAzymes tailor-made to work in organic solvents. ■

1. Abe, H., Abe, N., Shibata, A., Ito, K., Tanaka, Y., Ito, M., Saneyoshi, H., Shuto, S. & Ito, Y. Structure formation and catalytic activity of DNA dissolved in organic solvents. *Angewandte Chemie International Edition* **51**, 6475–6479 (2012).

Putting fluorine first

Introducing fluorine atoms into organic molecules using a highly selective technique could prove useful in the synthesis of pharmaceutical drugs

Despite its small size, the fluorine atom has had a vast impact on the pharmaceutical industry. More often than not, introducing fluorine to a drug molecule improves the drug's biological activity, earning it a reputation as a 'magic element'.

Amino acids—comprising an amino group and a carboxylic acid group—are also important to the medicinal chemist. Amino acids are not only the building blocks of proteins, they are commonly found in pharmaceutical drugs. Now, Mikiko Sodeoka and colleagues at the RIKEN Advanced Science Institute, Wako, have developed a synthesis technique that can selectively and efficiently combine fluorine and amino acids into the same organic molecule[1].

The starting materials are alpha-keto esters that contain a carbonyl group and an ester group. The first reaction of the team's technique is the substitution of a hydrogen atom, on the carbon atom adjacent to the carbonyl group, for a fluorine atom. As there are two hydrogen atoms that could be replaced, two mirror images, or enantiomers could result. Sodeoka and colleagues use a palladium catalyst that preferentially forms one of these enantiomers. This renders the reaction enantioselective; that is, one enantiomer is selectively formed over the other. The carbon atom to which the fluorine attaches becomes a stereogenic center as it has four different substituents. The interchange of any two substituents gives a pair of enantiomers. In the wider picture, these enantiomers are stereoisomers—molecules that differ only by their 3D orientation of the atoms.

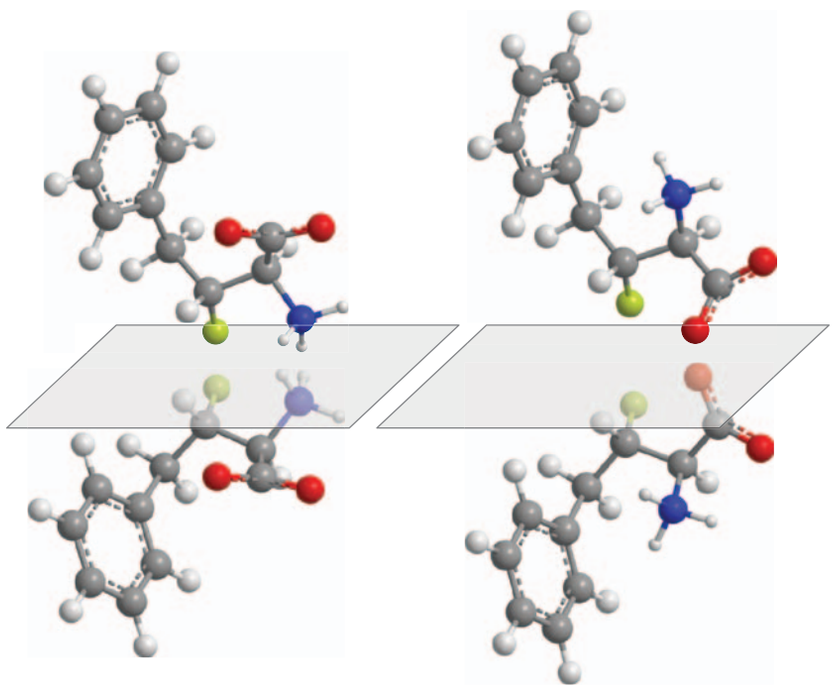


Figure 1: A schematic representation of the four different stereoisomers of the fluorinated amino acid derivatives that can be synthesized using the fluorination and hydroxy/amino derivative technique.

Next, the carbonyl group of the fluorinated alpha-keto ester transforms to a hydroxyl group. Again, two possible stereoisomers of the molecule could form. By exploiting the existing stereogenic center and using different reagents, the researchers could synthesize one stereoisomer in preference to the other. Hence, the technique not only introduces fluorine, but two stereogenic centers to the molecule. The formation of two stereogenic centers creates the possibility of four different stereoisomers (Fig. 1). By tuning the reagents, the team isolated all four stereoisomers in separate reaction sequences.

Overcoming the chemical instability of the intermediate, however, is challenging. "The fluorinated alpha-keto esters easily convert to their hydrated form, so care is required to exclude water from the reaction mixture," Sodeoka explains. "However, the hydroxy and amino acid derivatives are stable and easy to handle."

In the future, Sodeoka and colleagues hope to widen the scope of the fluorination reaction to other starting materials. This would create the possibility of making numerous biologically active compounds. ■

1. Suzuki, S., Kitamura, Y., Lectard, S., Hamashima, Y. & Sodeoka, M. Catalytic asymmetric mono-fluorination of α-keto esters: Synthesis of optically active β-fluoro-α-hydroxy and β-fluoro-α-amino acid derivatives. *Angewandte Chemie International Edition* **51,** 4581–4585 (2012).

Two heads are better than one

Comparisons of gene expression in the brains of marmoset monkeys and mice reveal molecular mechanisms underlying evolution of the cerebral cortex

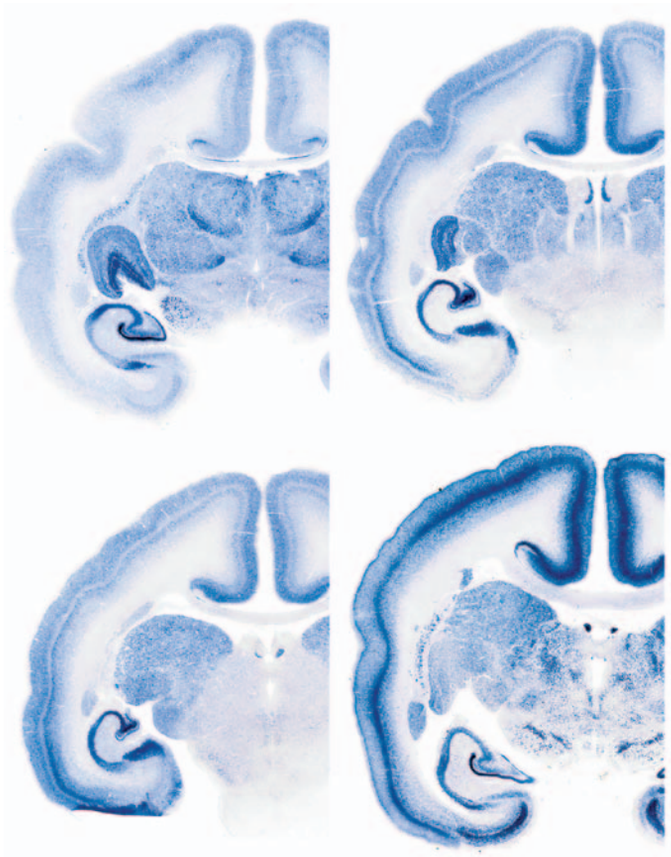


Figure 1: Gene expression patterns in the brain of the newborn common marmoset revealed by *in situ* hybridization.

Dramatic expansion of the human cerebral cortex, over the course of evolution, accommodated new areas for specialized cognitive function, including language. Understanding the genetic mechanisms underlying these changes, however, remains a challenge to neuroscientists.

A team of researchers in Japan, led by Hideyuki Okano of Keio University School of Medicine and Tomomi Shimogori of the RIKEN Brain Science Institute, has now elucidated the mechanisms of cortical evolution[1]. They used molecular techniques to compare the gene expression patterns in mouse and monkey brains.

Using the technique called *in situ* hybridization to visualize the distribution of mRNA transcripts, Okano, Shimogori and their colleagues examined the expression patterns of genes that are known to regulate development of the mouse brain. They compared these patterns to those of the same genes in the brain of the common marmoset (Fig. 1). They found that most of the genes had similar expression patterns in mice and marmosets, but that some had strikingly different patterns between the two species. Notably, some areas of the visual and prefrontal cortices showed expression patterns that were unique to marmosets.

The researchers observed that the *Btbd3* gene, for example, which encodes a transcription factor that regulates the expression of other genes, was expressed throughout the visual cortex of the mouse but restricted to layer 4 of the primary visual cortex, or the V1 area, of the marmoset. Similarly, the gene encoding connective tissue growth factor (CTGF) was expressed throughout the mouse cortex in layer 5, but was restricted to layer 4 of area V1 in the marmoset.

Some of the genes that are expressed widely throughout the mouse prefrontal cortex were likewise restricted to specific layers and sub-regions in the marmoset. Okano, Shimogori and colleagues also noted differences in expression patterns in the subplate region of the developing cortex, which contains the first neurons to receive inputs from the thalamus, a deep brain structure that relays sensory information to the cortex.

The researchers also found differences in gene expression within regions that connect the prefrontal cortex and hippocampus, a structure that is critical for learning and memory.

"The distinct gene expression patterns and anatomical differences between marmosets and mice provide enormous insights into the evolution of the brain," says Okano. "We are interested in characterizing the functions of genes that could act as driving forces of brain evolution and have started to investigate several candidate genes. Such approaches will eventually lead to a better understanding of brain function and mental disorders." ■

1. Mashiko, H., Yoshida, A.C., Kikuchi, S.S., Niimi, K., Takahashi, E., Aruga, J., Okano, H. & Shimogori, T. Comparative anatomy of marmoset and mouse cortex from genomic expression. *Journal of Neuroscience* **32**, 5039–5053 (2012).

Facing unease in early development

Infants show pronounced unease towards computer-morphed faces when the images are partly generated from photographs of a familiar person

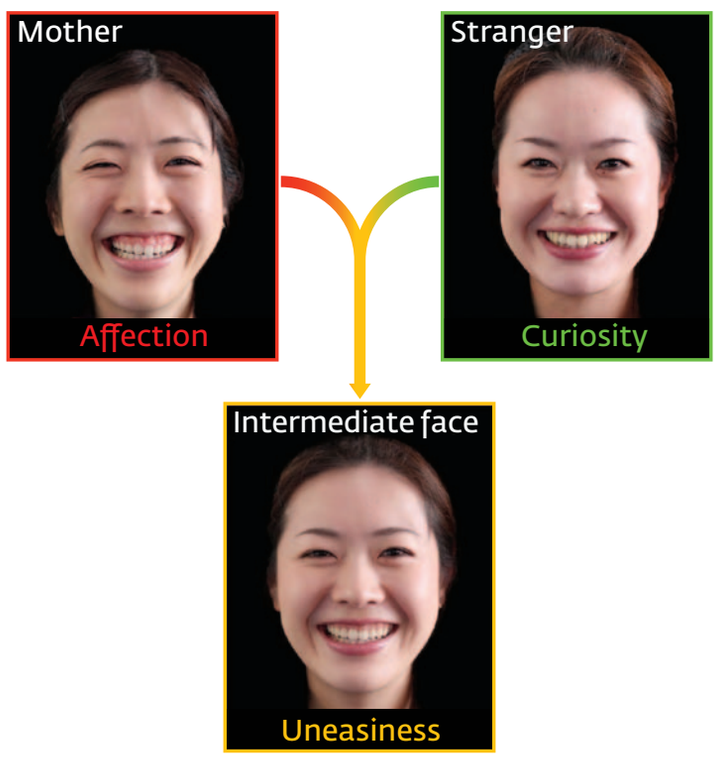


Figure 1: Infants spend less time looking at a morphed image of the face of their mother than at one morphed with that of a stranger's face, possibly due to the 'uncanny valley' effect.

When interacting with robots or animations with unnatural-looking faces, many people report a sense of unease. The face seems familiar yet alien, leaving the brain uncertain whether it is definitely human. To make robots more acceptable, it is necessary to understand the roots of these emotional reactions. Research from Japan has now shown that these reactions may begin in early infancy.

Yoshi-Taka Matsuda and colleagues at the Japan Science and Technology Agency, Saitama, and the RIKEN Brain Science Institute, Wako, together with scientists from the University of Tokyo and Kyoto University, studied the reactions of infants to computer-morphed photographs of faces. They showed that this unease, known as the uncanny valley effect, may begin as young as nine months, but only when the morphed image is partly developed from photographs of a familiar person—in this case, their mother[1].

"Infants like both familiarity and novelty in objects," explains Matsuda. "We wondered how their preference might change when they encountered objects that are intermediate between familiarity and novelty."

Matsuda and his team worked with 57 infants and their mothers. Each child was presented with both morphed and real photographs. The real image was either the child's mother, or a complete stranger. Each morphed photo was created using 50% of the mother's face and 50% of a stranger's face (Fig. 1), or a mix of two strangers' faces.

"Infants are as acute observers of human faces as adults are," Matsuda notes. "We created the intermediate faces as naturally as possible using morphing software. It took about six hours to create one morphed face."

The researchers used an eye-tracking system to record where and for how long the infants viewed the images. They found that the infants preferred looking at the photos of their mothers than the 'half-mother' morphed faces, but there was no significant difference between the times they spent looking at real and morphed photos of strangers.

"The 'half-mother' morphed faces could be perceived as lacking in novelty (like the strangers') or any positive connection (like the mothers'), [so] could cause infants to feel disinterest," Matsuda explains. "However, most adults also reported uneasiness related to morphed faces of their mothers, so we interpreted that infants might be having the same reaction."

The team intends to repeat the experiments with fathers' faces; and will test whether infants respond differently to the morphed faces if their relationship with their father is less pronounced than with their mother. ■

1. Matsuda, Y.-T., Okamoto, Y., Ida, M., Okanoya, K. & Myowa-Yamakoshi, M. Infants prefer the faces of strangers or mothers to morphed faces: an uncanny valley between social novelty and familiarity. *Biology Letters* published online before print, 13 June, 2012 (doi: 10.1098/rsbl.2012.0346).

Pinpointing a driver of liver cancer

Identification of mutations common to half of all liver cancers provides leads for new therapeutics

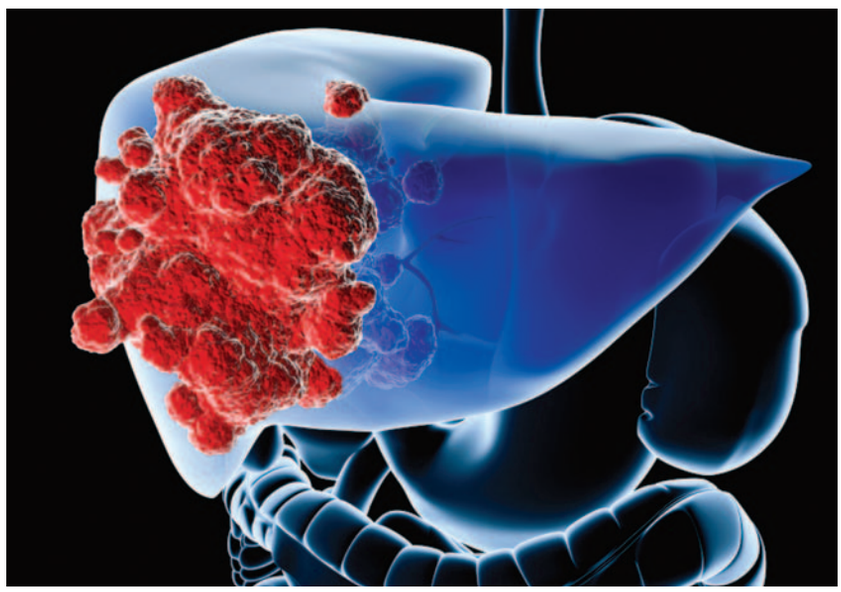


Figure 1: Some 50% of liver cancer tumors carry mutations in a gene that encodes chromatin regulators.

Liver cancer is the sixth most common cancer worldwide and the third leading cause of cancer-associated deaths. Yet even for such a frequent and deadly disease, the pathogenesis of this cancer remains obscure. Now, a team of scientists in Japan has shown that genes involved in regulating how tightly DNA is wound into chromosomes are commonly mutated in liver tumors[1] (Fig. 1). The finding points to potential new and much-needed therapeutic strategies.

"Several types of drugs under development target chromatin regulators, and these drugs may be effective in liver cancer," says Hidewaki Nakagawa, a cancer geneticist at the RIKEN Center for Genomic Medicine in Yokohama, who led the work.

Nakagawa and his colleagues decoded the entire genomes of liver tumors from 27 different patients—25 of whom carried hepatitis viruses, the most common cause of liver cancer, and two without associated infections. They also sequenced the DNA of matched healthy white blood cells for comparison.

No two cancers were alike, even when the researchers analyzed the whole genomes of pairs of liver cancers that arose independently in the same individual—not from metastasis. "Their whole genomic alterations were completely different and independent, indicating heterogeneity of liver cancers in the same patient," Nakagawa says.

Some striking patterns emerged. Across all 27 cancer genomes, the researchers discovered more than 2,000 protein-altering mutations, with frequent alterations occurring in 15 different genes—many of which affect chromatin, the mass of DNA and proteins that condense to form chromosomes and affect gene expression. Notably, 14 of the 27 tumors had mutations in at least one chromatin regulatory gene. In cell culture, liver tumors lacking these genes displayed a marked increase in cell proliferative capacity. "Genetic alterations in chromatin regulators can regulate and produce epigenetic alterations in cancer," Nakagawa explains.

The findings are consistent with those reported last year by an independent group that showed that *ARID2*, a chromatin remodeling gene also implicated by Nakagawa and his team, was mutated in six of the 33 liver cancers considered[2].

In addition to chronicling the mutational profile, Nakagawa and his colleagues determined where hepatitis B-associated tumors had the viruses inserted into their genomes. Consistent with independent findings reported in the same issue of *Nature Genetics*[3], in four of the 11 relevant cancers they found viral integration within or near the *TERT* gene, which is involved in maintaining the caps on the end of chromosomes. Targeting the *TERT* locus, therefore, offers another therapeutic drug lead for this nasty cancer. ■

1. Fujimoto, A., Totoki, Y., Abe, T., Boroevich, K.A., Hosoda, F., Nguyen, H.H., Aoki, M., Hosono, N., Kubo, M., Miya, F. et al. Whole-genome sequencing of liver cancers identifies etiological influences on mutation patterns and recurrent mutations in chromatin regulators. *Nature Genetics* **44**, 760–764 (2012).
2. Li, M., Zhao, H., Zhang, X., Wood, L.D., Anders, R.A., Choti, M.A., Pawlik, T.M., Daniel, H.D., Kannangai, R., Offerhaus, G.J. *et al*. Inactivating mutations of the chromatin remodeling gene *ARID2* in hepatocellular carcinoma. *Nature Genetics* **43,** 828–829 (2011).
3. Sung, W.K., Zheng, H., Li, S., Chen, R., Liu, X., Li, Y., Lee, N.P., Lee, W.H., Ariyaratne, P.N., Tennakoon, C. *et al*. Genome-wide survey of recurrent HBV integration in hepatocellular carcinoma. *Nature Genetics* **44**, 765–769 (2012).

New twists in the road to differentiation

A more complicated network than generally accepted may control maturation of B cells in the immune system

The process of blood cell development, known as hematopoiesis, gives rise to numerous different immune cell subtypes. Each of these in turn matures through a stepwise process governed by the action of transcription factors—specialized proteins that coordinate activation and deactivation of specific target genes.

Antibody-secreting B lymphocytes (Fig. 1) develop via a well-studied mechanism, but research from Ichiro Taniuchi's team at the RIKEN Center for Allergy and Immunology in Yokohama injects new complexity into this model[1]. The current mechanism involves three transcription factors—E2A, Ebf1 and Pax5—that progressively set the stage for maturation of functional B lymphocytes. "Not only does this trio of transcription factors function sequentially, but each one is also responsible for the expression of the next," explains Wooseok Seo, a researcher in Taniuchi's laboratory and lead author of the study. "E2A is required for the expression of Ebf1, and so on."

Seo and Taniuchi were studying another transcription factor, Runx1, which is a critical component of blood cell development. Without Runx1, hematopoiesis cannot take place. The researchers therefore decided to study its role in B cell development by engineering a genetically modified mouse that expresses Runx1 in every cell except early stage B cell precursors.

Without Runx1, these cells stalled early in development, at essentially the same stage where Ebf1 exerts its effects. Seo and colleagues determined that Runx1, in partnership with the Cbfβ protein, normally binds to the promoter sequence that regulates Ebf1 production. Interestingly, Ebf1 has two distinct promoters; and, Runx1-Cbfβ and E2A each bind a different promoter of Ebf1. "Our hypothesis is that E2A and Runx1 might be distinctive, but not necessarily exclusive, in their mode of function," says Seo.

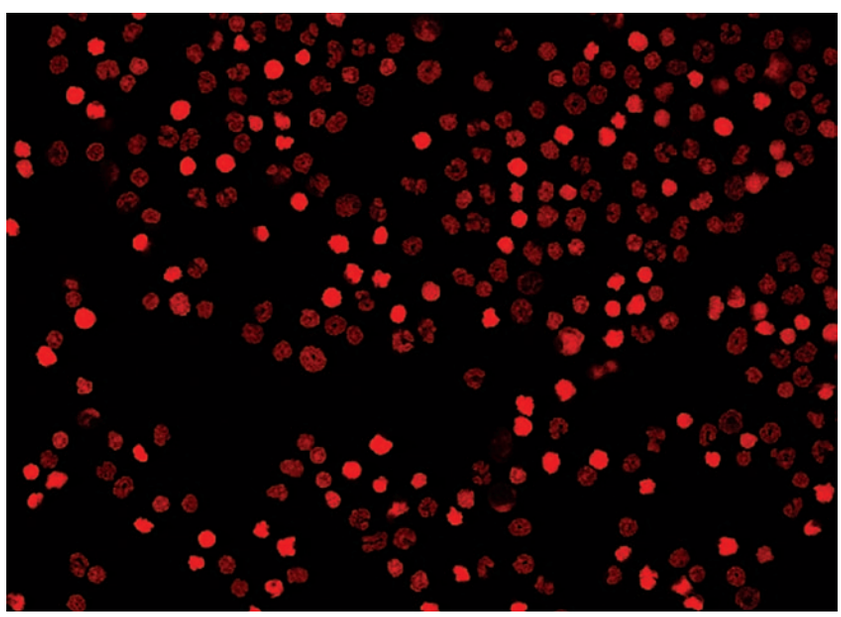


Figure 1: Fluorescently labeled early B cell progenitors.

In the absence of Runx1, *Ebf1* gene activity is drastically reduced, preventing downstream induction of the 'final step' in B cell differentiation. However, Runx1 also appears to activate a 'positive feedback' loop by switching on the gene encoding its upstream activator, E2A, thereby accelerating the process of B cell differentiation. Without Runx1, therefore, none of the three differentiation factors are properly expressed.

These findings suggest that earlier models of this process may be greatly oversimplified. "We propose that the simple hierarchy model of this trio of transcriptional factors for B cell development might not be true, and suggest a more complicated network," says Seo. He and his colleagues are now exploring the mechanisms Runx1 employs to control gene activity, and how these enable it to exert such a potent influence on hematopoietic development. ■

1. Seo, W., Ikawa, T., Kawamoto, H. & Taniuchi, I. Runx1–Cbfβ facilitates early B lymphocyte development by regulating expression of Ebf1. *The Journal of Experimental Medicine* **209**, 1255–1262 (2012).

Helping the nervous system pull itself together

A cascade of signaling proteins triggers a cellular 'tug of war' that creates the foundation for the embryonic central nervous system

In developing vertebrates, the brain and spinal cord originate from an embryonic structure known as the neural tube. This initially forms as a flat 'neural plate', which subsequently folds around and closes up to form a tubular structure. By performing an extensive series of experiments in developing chick embryos, Masatoshi Takeichi and his team at the RIKEN Center for Developmental Biology, Kobe, has now revealed valuable insights into the mechanism underlying the closure process[1].

The neural plate is formed from epithelial cells, which feature clearly defined 'top' (apical) and 'bottom' (basal) surfaces. At the apical surface, the cells are connected by structures called adherens junctions, which are in turn connected to a network of actomyosin protein fibers. "It is known that the contraction of these actomyosin fibers causes bending of these epithelial sheets in the apical direction through the constriction of their apical surfaces," says Takeichi. "We became interested in learning how this mechanism contributes to the formation of the neural tube."

The initial bending of the neural plate is most prominent near the midpoint of what will ultimately become the brain and spinal cord. Within this embryonic region, Takeichi and colleagues observed that neural plate cells tended to form polarized 'chains' of actomyosin fibers that extend across multiple cells, perpendicular to the head–tail axis of the embryo. As closure begins, the cells undergo extensive rearrangement in a process called 'convergent extension'.

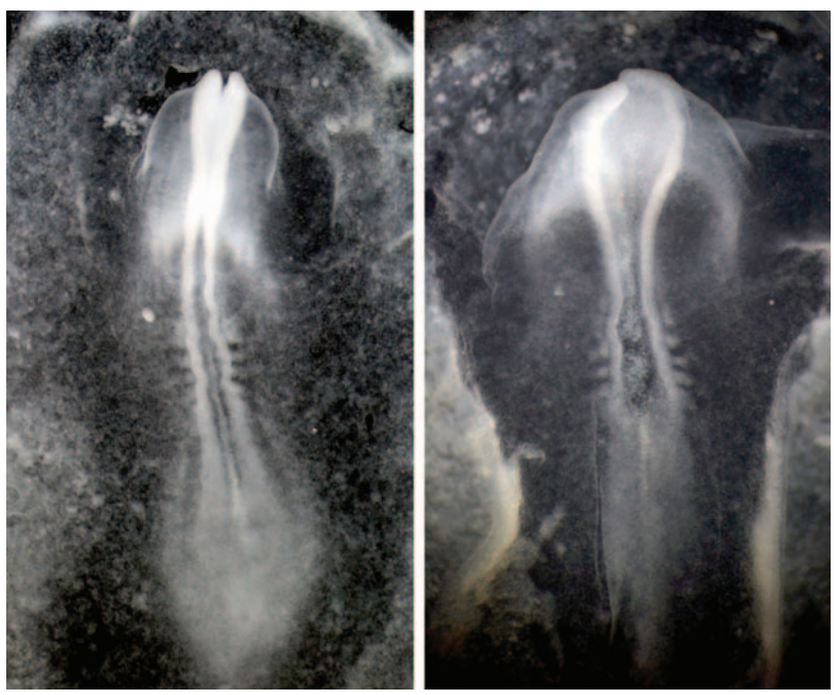


Figure 1: In a normal chick embryo (left), the protein Celsr1 helps to induce proper formation of the neural tube. In chick embryos lacking this protein (right), the neural plate fails to curve so cannot close properly.

Cells of the neural plate squeeze inward, pushing adjacent cells forward and backward and resulting in lengthwise extension of the developing neural tube.

The researchers determined that a protein called Celsr1 helps direct this convergent extension (Fig. 1). They subsequently identified a network of proteins that act downstream of Celsr1. Together, these proteins form a signaling cascade that induces the contraction of the long actomyosin fibers that tether the neural plate epithelial cells together. As the fibers contract, these cells' apical surfaces become pinched toward the midline of the neural plate, and this steady narrowing of the apical surface ultimately results in the curvature of plate.

These findings explain a critical step in the development of the nervous system, and could help illuminate the roots of conditions arising from faulty neural tube development, like spina bifida. "Mice in which these genes are mutated show neural tube closure defects," says Takeichi, "and irregularities in any of the genes or molecules identified here could cause birth defects [in humans]." ■

1. Nishimura, T., Honda, H. & Takeichi, M. Planar cell polarity links axes of spatial dynamics in neural-tube closure. *Cell* **149**, 1084–1097 (2012).

CHITOSHI ITAKURA

Director
Research Resources Center
RIKEN Brain Science Institute

Broadening the frontiers of brain research: The Research Resources Center

The Brain Science Institute (BSI) within the RIKEN Wako Institute continues to garner research accolades for its groundbreaking research in mind and intelligence, neural circuit function, disease mechanisms, as well as its advanced technology development. A unique feature of the BSI is its Research Resources Center (RRC), which has been attached to the BSI since its founding in 1997. Chitoshi Itakura, RRC director, says,"The RRC can be described as a technical support organization where all techniques and research materials needed for brain research are available at levels of unified activities that lead the world." In February 2011, the Neural Circuit Genetics Research Building, equipped with new animal facilities, went into operation. With the availability of these new facilities, and the center's other key resources, the RRC serves as a foundation which further advances the BSI's research strength.

Turning the wheels of technology and research at the BSI

The BSI was founded in October 1997. The first director of the institute was Masao Ito, an authority of worldwide fame in the field of cerebellum research, who is now serving as a special advisor to the BSI. "Since 1921, RIKEN has always had a department to provide technical support for researchers by fabricating laboratory equipment and instruments," explains Itakura. "Dr. Ito used to say that in neuroscience research as well, good achievements cannot be gained without technical aids to support research activities and that greater priority must be given to technology, rather than to research."

After studying veterinary medicine at Hokkaido University, Itakura joined RIKEN in 1961. He says, "When RIKEN was planning to conduct animal experiments in a cancer research project for the first time in its history, a research veterinarian was needed and I was invited." Itakura held positions at Gifu and Tottori universities, later returning to Hokkaido University where he conducted research into animal pathology at the School of Veterinary Medicine and mentored young veterinary researchers. He also served as the dean of the school and the vice-president of the university. "When I was about to leave Hokkaido University and retire from research, I was again invited to RIKEN to launch an internal organization for operating large-scale animal facilities and to provide technical support, which coincided with the time of the BSI's founding."

In May 1997, prior to the establishment of the BSI, Itakura started preparatory activities at RIKEN. He says, "Dr. Ito said to me, 'In Japanese universities and research organizations, they tend to regard technicians to be lower status than researchers, but this is not a good attitude. At the BSI, let's promote brain research on an equal footing among researchers and technicians.' I visited technical support organizations at top universities and research institutions in Europe and the USA, adopted their strong points, and launched the Advanced Technology Development Center, which was the predecessor to the RRC."

Unified activities leading the world

The RRC now consists of four units (see Fig. 1): the Support Unit for Animal Resources Development; the Support Unit for Bio-Material Analysis; the Support Unit for Functional Magnetic Resonance Imaging; and the Support Unit for Neuromorphological Analysis.

First, the Support Unit for Animal Resources Development operates animal facilities involving the use of mice, rats, cats, macaques, marmosets and other mammals as well as zebrafish, and provides a broad range of technical support for animal experiments, including the generation of genetically modified mice.

"When the institute was founded, it held about 26,000 cages, each able to hold up to five mice. Currently at the BSI, about 3,000 cages are used by the Laboratory for Behavioral Genetics alone," says Itakura.

In order to better examine the roles of genes and to illuminate brain function mechanisms, the BSI uses transgenic mice generated by introducing a particular gene from outside the body, as well as knockout mice that have a particular gene which is made to be no longer functional. Behaviors of such genetically modified mice are analyzed and if, for example, any changes are found in their learning and memory capabilities, the gene can be hypothesized to play a key role in the process of learning and memory.

"Brain research cannot progress so rapidly without genetic modification technology. Creating only one type of genetically modified mouse would require 50 to 100 cages. Because there are so many genes to be examined, the demand is not satisfied however many cages are available."

The second unit, the Support Unit for Bio-Material Analysis, provides assistance to researchers who analyze biological substances such as nucleic acids (DNA and RNA), amino acids and proteins.

"For example, in genetically modified mice with altered brain function, the amounts and modes of actions of a broad range of biological substances in the brain may have changed. By extensively analyzing them, we can work on elucidating the mechanisms behind brain function," explains Itakura. This unit also provides services for maintaining and managing common-use experimentation facilities for researchers who analyze biological substances.

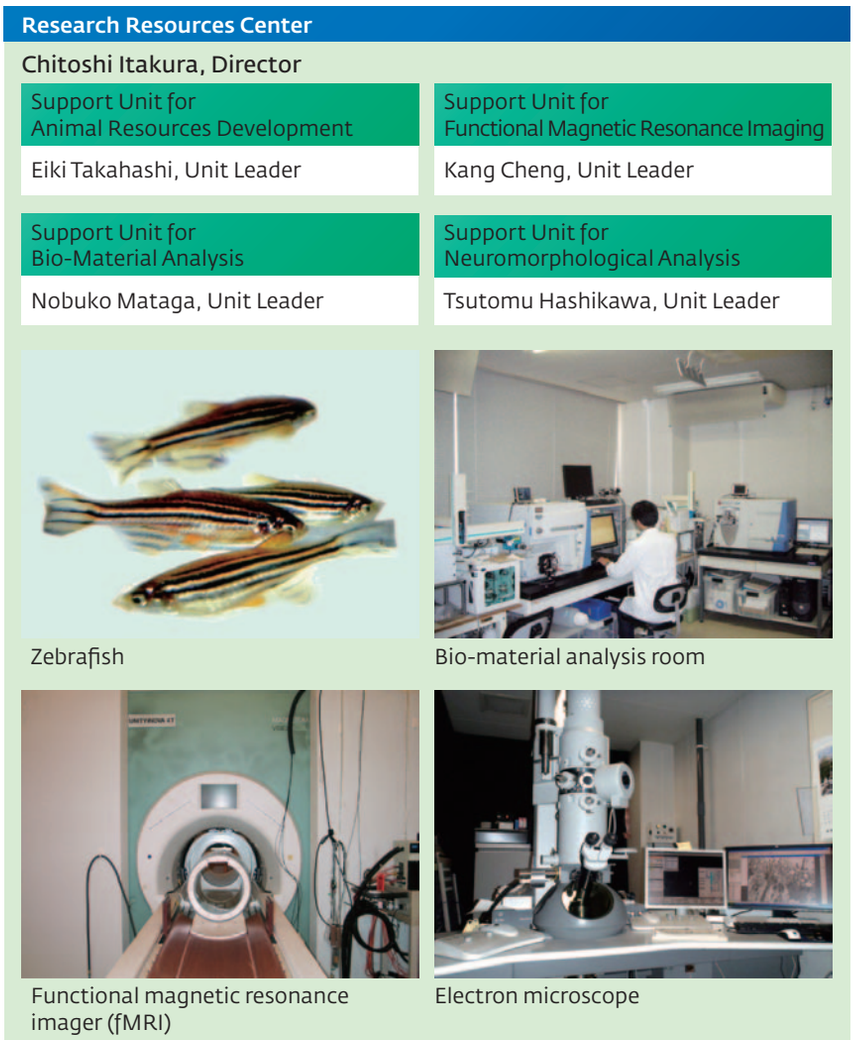


Figure 1: Organizational chart of the BSI's Research Resources Center

The third unit—the Support Unit for Functional Magnetic Resonance Imaging—gives technical knowledge and advice relating to imaging techniques for brain research. "Functional magnetic resonance imaging (fMRI) is a system that is essential for brain research because it is capable of measuring localized cerebral activities without physically invading the brain. However, such measurement requires sophisticated technical expertise, so highly skilled technicians at this unit provide necessary support."

At the BSI, researchers are working on measuring human and monkey brain activities with the use of fMRI. For example, an ongoing research project aims to unveil the mechanism behind expert intuition by locating the specific parts of the brain which are being activated during problem-solving activities, such as when a professional player of the Japanese board game *shogi* is solving a problem during the game.

Lastly, the Support Unit for Neuromorphological Analysis assists scientists with the morphological analyses of the brain through electron microscopy and other techniques that require specialized skills.

"In genetically modified mice with altered brain function, for example, morphological changes may have occurred in a particular neural circuit or neurons. By means of electron microscopy and other techniques, we can explore such changes." This unit also builds databases, such as brain atlas databases, to help expand our understanding of the brain's basic structure.

"In addition to the research support services provided by these key four units, the RRC is also engaged in providing

procedural support for clerical work that requires expert knowledge, which includes the preparation of written agreements on the transfer of research materials such as laboratory animals."

Itakura emphasizes that the RRC's wider mission is to accelerate research activities; make the best use of multi-angle research tools; provide constant, high-level technical support for all laboratories; and gather research materials and raw data, enabling the construction of databases and freeing up researchers from burdensome clerical work.

"Many joint researchers at the BSI are astonished by how smoothly and speedily experiments take place with the aid of the RRC. In addition, the RRC is a magnet that attracts prominent researchers to the BSI. Whenever the BSI advertises the recruitment of a new laboratory leader, candidates are taken on a tour of the RRC. Many of them see where we work and are drawn to the attractive and supportive research environment of the center, and decide to apply for the post."

The RRC is evaluated on its provision of world-class technical support services by the BSI Advisory Council, an international external evaluation committee comprising of top scientists in Japan and abroad. "In terms of individual facilities and systems, other research organizations and universities may surpass us in some aspects. However, the biggest advantage of the RRC resides in the fact that all the techniques and research materials that are essential to brain research are at hand. We are highly appraised for our unified activities. Furthermore, the RRC greatly contributes to the efficient use of RIKEN budgets, including the sharing of analytical systems and other equipment to reduce physical space requirements for investigative and experimental work, and the reuse of devices and instruments."

Most laboratories at the BSI enjoy the benefits of having the RRC on hand, and the RRC also provides technical support to other RIKEN laboratories outside of the BSI, as well as laboratories outside of RIKEN. For example, half the laboratories that utilize the services of the Support Unit for Bio-Material Analysis are laboratories at other RIKEN institutes, mainly the Advanced Science Institute (ASI). The zebrafish facility operated by the Support Unit for Animal Resources Development, as the core organization of the National Bioresource Project, collects and maintains useful zebrafish lines bred in Japan, and supplies them to researchers worldwide.

Behavioral analysis research at the Neural Circuit Genetics Research Building

In February 2011, the Neural Circuit Genetics Research Building and its animal facilities were opened at the RIKEN Wako Institute (Fig.2, A). "The construction plan for this new research building started in 2003, when the mouse facility, which had been established at the time the BSI was founded, became filled to capacity with 26,000 cages and the availability of laboratories for behavioral analysis was lacking. In the USA, animal facilities with a focus on behavioral analysis began to emerge some ten years before."

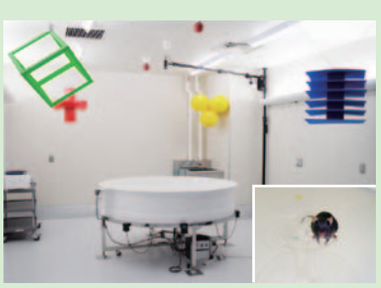
Although remarkable advances in genetic modification technology have been seen in recent years, without delving into behavioral analysis new tools cannot be as useful in elucidating brain function mechanisms.

"Laboratory animals, such as mice, must be microbiologically controlled, and, to prevent infections, they have to be grown in specific pathogen-free (SPF) facilities," explains Itakura. "Once brought outside the facility, laboratory animals can become infected, so they cannot be returned to housing rooms." For this reason, behavioral analysis cannot be performed unless a testing room for behavioral analysis is established within the facility where the housing rooms are located.

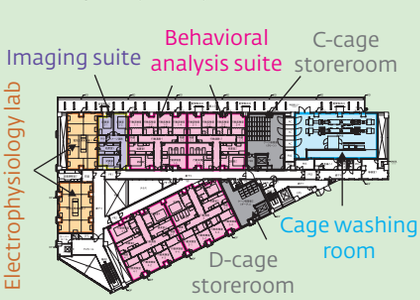
"In the US, it is generally recommended that the area ratio of housing rooms to behavior testing rooms should be between 3:1 and 4:1. At the RRC's previous facility, however, the ratio was 13:1. Susumu Tonegawa, director of the BSI and group director of the RIKEN-MIT Neuroscience Research Center at the BSI, is a leader in behavioral analysis. With his involvement, the Neural Circuit Genetics Research Building, which focuses on behavioral analysis, was brought to completion."

The area ratio of housing rooms to behavior testing rooms at the Neural Circuit Genetics Research Building was set at 1:1. It can house 20,000 cages of mice and 3,000 cages of rats (up to three animals in each cage). The building also has four behavioral analysis suites (about 250 m^2 each) to which six

A: View of the Neural Circuit Genetics Research Building and floor plan of the second floor (below)



B: Morris water maze



C: Elevated plus maze

Figure 2: Neural Circuit Genetics Research Building

This four-storey building has six laboratories (120 total seats for staff members) on the first floor, four rat and mouse behavioral analysis suites on the second floor, and six rat and mouse breeding suites on the third floor. The fourth floor is assigned to equipment rooms.

behavior labs and one housing room (420 cages) each are annexed.

Suites are arranged on a floor, in such a manner as to prevent infectious disease occurring in one suite from spreading to other suites. "I think the Neural Circuit Genetics Research Building is the world's first animal facility that has a 1:1 area ratio of housing rooms to behavior testing rooms," says Itakura. "In addition, the total floor area of behavior testing rooms makes the building number one among facilities of its kind. For the sake of behavioral analysis, experiments are sometimes performed on the same mice or rats that have been repeatedly trained over six months to a year. In the Neural Circuit Genetics Research Building, laboratory animals can be transferred between housing rooms and behavior testing rooms within the behavioral analysis suite, where they undergo behavioral analysis for an extended period. Infections are prevented because the animals do not have to be taken out of the facility for behavior analysis."

Several systems are used by researchers to analyze behavior in animals. The Morris water maze (Fig. 2, B) is used for experiments on learning and memory. The water pool contains only one platform for an animal resting at a depth of about 1 cm under the water's surface, so that the platform is not visible to the mouse swimming inside the maze. The tested mouse can memorize and locate the position of the platform by referring to the markers hanging down from the ceiling. The capabilities of learning and memory can be assessed by examining how the mouse learns this association, and in turn the platform's position under the markers.

Another system for behavioral analysis is the elevated plus maze (Fig. 2, C), which is used for experiments examining emotions such as anxiety and fear. Only one direction is closed and lined with walls of 50 cm in height. By determining the ratio of time the mouse stays in the open-arms with no walls and in the closed-arm, the anxiety and fear levels can be quantified.

"The Neural Circuit Genetics Research Building is equipped with almost all testing apparatuses for behavioral analysis. While a wide variety of apparatuses are currently in use in experiments on learning and memory, the development of apparatuses for emotion experiments is still in progress. Additionally, one of the major goals of current brain research is to overcome neuropsychiatric diseases such as depression and Alzheimer's disease. At the BSI, disease model mice that manifest symptoms similar to those in human neuropsychiatric diseases are generated as a tool that is expected to help elucidate the onset mechanism and develop new treatments. To this end, development of new testing apparatuses for behavioral analysis of mouse symptoms is ongoing."

Technical innovations and nurturing technicians

"Technical innovations are essential to maintaining high levels of technical support by the RRC. We are constantly reviewing the introduction of new technologies and research materials requested by researchers," explains Itakura. "We hone in on those technologies and research materials that are likely to be important for future brain research, and we plan for their introduction at the RRC. A good example of this is the introduction of marmosets."

The marmoset has several advantages as a laboratory animal compared to other monkeys (Fig. 3). In 1980, the Central Institute for Experimental Animals—based in Kawasaki City, Kanagawa, Japan—succeeded in establishing a line of marmosets as a laboratory animal. "We predicted that brain research using laboratory animals that are primates would be important to understanding the human brain and overcoming neuropsychiatric diseases. Although some people were doubtful about the utility of this laboratory animal, we began breeding and raising marmosets in 2007."

The prediction of Itakura and colleagues proved right. In 2009, Hideyuki Okano at the School of Medicine, Keio University succeeded in genetically modifying marmosets in collaboration with the Central Institute for Experimental Animals. RIKEN was selected by the Japan government's Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST Program) to be the organization responsible for a key research project using this new genetic engineering technology. This project—supported by the RRC with participation from BSI researchers—aims to explore the evolution of the brain and ways to overcome neuropsychiatric diseases such as autism, schizophrenia and Alzheimer's disease by utilizing this new technology.

Figure 3: Marmosets
The marmoset is a laboratory animal preferred for its small size and remarkable reproductive performance, reaching sexual maturity at 1.5 years of age and bearing two or three babies at each delivery.

"The RRC continues to nurture its technicians and provides a thorough system of evaluation and reward for employees. This approach sets a high standard which will hopefully act as an exemplary model to other research organizations in Japan."

Looking to the future, the RRC will continue in its mission to support the BSI as a world-leading research center for neuroscience by delivering the latest in cutting-edge technical innovations and human resource development. ■

ABOUT THE RESEARCHER

Chitoshi Itakura was born in Korea in 1934. He graduated with a Master's degree from the Graduate School of Veterinary Medicine, Hokkaido University, Japan, in 1960 and obtained his PhD in 1967 from the same university. Itakura then took up the positions of research assistant at RIKEN and Gifu University. He later held professorial positions at Tottori University, and was a visiting professor at the University of Guelph in Canada. At Hokkaido University, Itakura was appointed as professor, dean of the Graduate School of Veterinary Medicine, and vice-president. Since his retirement in 1997, he has served as group director and director to RIKEN's Research Resources Center at the Brain Science Institute. His research focuses on the pathology of domestic and laboratory animal diseases.

OCCUPATIONAL HEALTH CENTER TEAM

All RIKEN campuses

Working for a healthier RIKEN

Please tell us about your work at RIKEN.

The most important role of the Occupational Health Center is to prevent work-related diseases and accidents at RIKEN. To achieve this, we inspect laboratories for industrial hygiene, develop protocols for accident prevention and provide specific health examinations for the early detection of occupational diseases. Importantly, we also support employees on or returning from sick leave. As medical professionals, we provide various health services including regular medical examinations, follow-up advice and health consultations.

What is the most difficult aspect of your job?

It can be difficult to arrange health consultations because everybody at RIKEN is busy and often on the move, be it for a business trip or moving between their office and a laboratory. Language and cultural differences are also a part of life at RIKEN, and sometimes it is a challenge to effectively communicate technical medical concepts.

What kind of support does RIKEN offer to its non-Japanese staff?

We provide maps in Japanese and English to nearby medical facilities, maintain a list of doctors in the area who can speak foreign languages, and use medical history forms in several languages for our consultations. For patients who visit our office, we do our best to communicate in English. With prior permission from a patient, we can arrange for an interpreter to be present at consultations. Furthermore, as legislation for occupational health can vary between countries, we try to familiarize staff from abroad with related Japanese legislation and the rules at RIKEN.

Many RIKEN staff work in research laboratories. Does this present any particular healthcare issues?

RIKEN scientists conduct research requiring a variety of organic solvents and chemical substances, often in combination, that are potentially harmful. Our center takes appropriate precautions to keep RIKEN employees safe around these substances and to help prevent accidents. We also focus on education and accident prevention for research involving human serum or experimental animals.

How to do you work with the Occupational Health Centers at other RIKEN institutes?

In addition to our center at Wako, we also have centers at five other RIKEN locations. Each has occupational physicians specializing in internal medicine and psychiatry, nurses, psychologists and administrative personnel. Our staff stays up-to-date with the activities of our other offices and holds regular meetings with them to share information and decide on policy.

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

A very rewarding aspect of our job is when we see people restored to health and resuming their normal lives after going through a tough period of illness. It is also gratifying when people who are leaving RIKEN visit to thank us and say goodbye.

What would you say to people considering joining RIKEN?

While RIKEN is a leading research institution, not everybody at RIKEN works on the front line. We depend on a variety of behind-the-scenes support to function smoothly. RIKEN is a place where everyone can use their gifts and develop their skills.

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

RIKEN BSI Summer Program 2012

The 2012 RIKEN BSI Summer Program, held annually by the RIKEN Brain Science Institute (BSI) to nurture young neuroscientists from Japan and around world, consisted of a lecture course (3–10 July) taught at Ohkouchi Hall, RIKEN Wako campus and an internship course (13 June–8 Aug).

Young researchers gather at RIKEN's Wako campus for the 2012 BSI Summer Program

Although 2011's program was canceled in the aftermath of the Great East Japan Earthquake, the event was enthusiastically resumed in 2012. There was such strong interest in the 2011 topic–"The collective brain: how does the collective interaction of neurons make our mind?"–that it was used for the 2012 course. The title and the list of guest speakers attracted an unprecedented 200 applicants for the 30 slots.

In the 8-week lab training internship course, each participant gained hands-on experience in a BSI laboratory. There were about 90 applications for the internship course, of which only 15 students were accepted.

Three poster sessions were held during the program: the first for BSI labs to introduce their research and attract prospective "co-workers" to their labs; the second for the internship and lecture course students to present research from their own institutions to facilitate scientific discussion; and the third for the internship students to present their research activities and results at the end of their time at BSI.

Once again, the BSI Summer Program provided a valuable opportunity for promising young neuroscientists to hone skills and meet future collaborators. ■

RISP 2012

The seventh annual RCAI International Summer Program (RISP) was held on 22–29 June and co-sponsored by the Global Center of Excellence at Chiba University. The RIKEN Research Center for Allergy and Immunology (RCAI) was pleased to resume the program, cancelled in 2011 following the Great East Japan Earthquake and subsequent events, as it is one of the center's major annual events.

RISP 2012, held in Yokohama at the RCAI, drew 41 graduate students and postdoctoral fellows from 19 countries. The program included oral and poster presentations by the participants, as well as lectures by prominent scientists invited from the RCAI, Japanese universities, and abroad. The RISP students also attended the annual RCAI-JSI International Symposium on Immunology, themed "New Horizon in Immune Regulation–Bridging Innate and Acquired Immunity", at the Pacifico Yokohama Conference Center. Most participants returned home after the close of the meeting, but six students remained at the RCAI for a month-long research internship.

The RISP lectures at the RCAI were quite diverse and provided an expansive overview of the immune system and the numerous experimental approaches currently employed in immunological studies. The research interests of the participants were similarly varied, creating a unique opportunity for cross-fertilization among immunology subdisciplines. Collaborations established as a result of the RISP have the potential to be long-lasting.

The 2012 RCAI International Summer Program attracted 41 participants from around the world

RISP was unanimously well received by surveyed participants, who appreciated both the scientific and cultural experience. Planning is already underway for RISP 2013. ■

High school students study blood development at CDB summer school

Every summer the RIKEN Center for Developmental Biology (CDB) holds courses for local high school students to learn about the research activities of the center, and in 2012 there were two one-day courses, on 7 and 9 August. The theme–blood and blood proteins–was developed in cooperation with the Laboratory for Early Embryogenesis (Guojun Sheng, Team Leader) and included lectures by scientists and a tour of the lab. The talks focused on blood biology and the development of the blood system in chicks, and also introduced the lab's work on globin switching and how defects in this routine are linked to disease.

In the afternoon, students participated in experiments using SDS-PAGE, which is an electrophoresis method for separating specific proteins in mixed samples. In the experiments, students harvested blood samples from early chick embryos and separated out various protein components, estimating their molecular weights from their mobility through a gel. ■

www.riken.jp

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.

RIKEN RESEARCH is a website (www.rikenresearch.riken.jp) and print publication intended to highlight the best research being published by RIKEN (www.riken.jp). It is written for a broad scientific audience and policy makers interested in science and aims to raise global awareness of RIKEN and its research.

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