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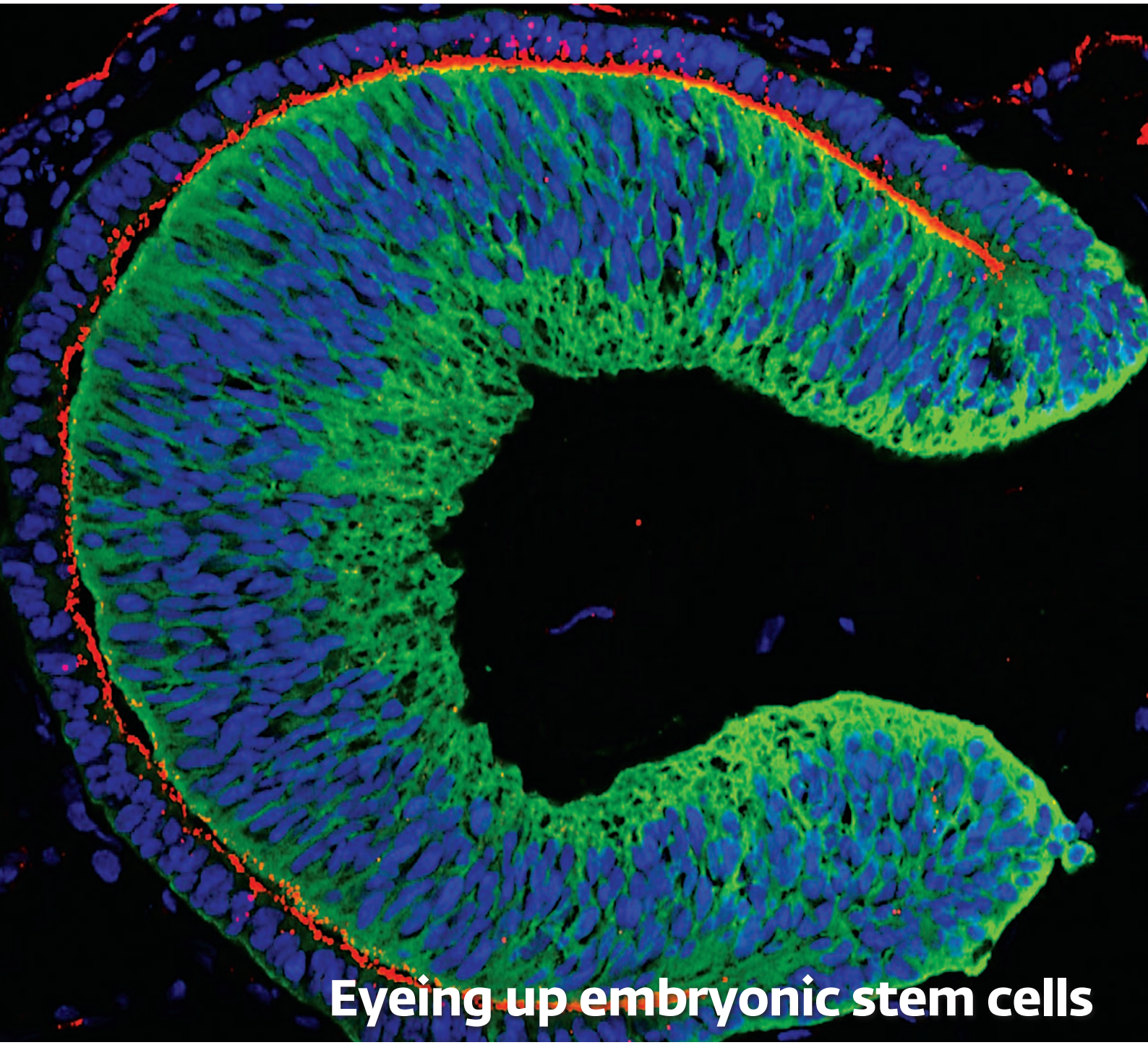

Eyeing up embryonic stem cells

HIGHLIGHT OF THE MONTH

Lucky number 113

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RIKEN

Chemistry

Lucky number 113

The creation of an atom with 113 protons adds a new element to the periodic table

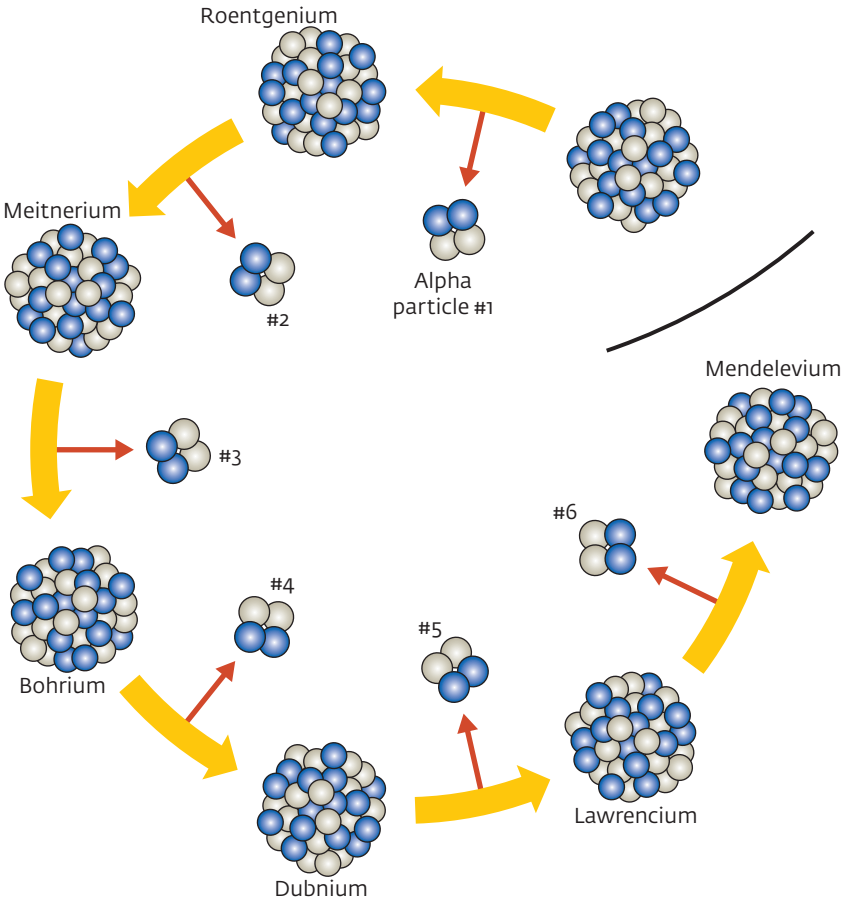


Figure 1: Element 113 was identified by the alpha particles that are created when a heavy nucleus decays to a lighter one. Six alpha particles were measured at times corresponding to the half-life of the six decays matching element 113 decaying sequentially to mendelevium.

The heaviest element that occurs naturally on earth is uranium. More massive atoms have, however, been created in the laboratory. These so-called superheavy elements have more than 103 protons in their nucleus, but the complicated nuclear interactions between these subatomic particles makes such nuclei highly unstable. Further, these particles live for only a fraction of a second. A team of scientists across Japan and China led by RIKEN researcher Kosuke Morita has now seen an indirect signature of element 113 by measuring the particles generated when superheavy elements disintegrate[1]. This new addition to the periodic table will improve our understanding of the building blocks of the Universe.

The scientists created element 113 by fusing together zinc and bismuth atoms. First, they generated a beam of zinc atoms travelling at 10% of the speed of light using the RIKEN Linear Accelerator. They then fired these high-energy particles at a thin bismuth film. To ensure that the beam did not damage the target, the scientists mounted 16 such foils on a 30-centimeter-diameter wheel and spun it at more than 3,000 revolutions per minute. At such high velocity, the zinc nucleus, made up of 30 protons and 40 neutrons, fused with the 83 protons and 126 neutrons in the nucleus of the bismuth atoms to form a nucleus with 113 protons and 165 neutrons, plus one free neutron. This seems simple enough, but this nuclear interaction is rare. The experiment, which began in September 2003, has been running for 553 days and yet only three atoms of element 113 have been identified in that time. "This has been a painstakingly long experiment," says Morita. "First, we had to create the 108th, 110th, 111th and 112th elements. This gave us confidence that we had the right experimental conditions to produce element 113."

Timing is crucial

The difficulty faced by the team was how to prove that a superheavy element had been created. Element 113 cannot be seen directly because it only exists for a short time before decaying through a process known as alpha decay. Instead, the team searched for the particles created when element 113 disintegrates. In alpha decay, a large nucleus breaks into a lighter one and a particle made of two protons and two neutrons, known as an alpha particle. Element 113, for example, should decay into an isotope of element 111 with 163 neutrons, which is known as roentgenium-274, plus an alpha particle. Roentgenium, in turn, also undergoes alpha decay to produce meitnerium-270 and another alpha

particle (Fig. 1). This process continues until an atom with a stable nucleus is created.

Once created, the nucleus of element 113 was separated from any unwanted ions in a piece of equipment known as GARIS—the gas-filled recoil ion separator (Fig. 2)—and directed into an arrangement of detectors that could measure the chain of alpha particles. Morita and his co-workers measured a sequence of six alpha particles in August 2012. The timing of these detection events was crucial in showing that they started with the creation of an atom of the element 113 nucleus. Each decay occurs on a characteristic time scale known as the half-life. The sixth decay from lawrencium-258 to mendelevium-254 has a half-life of 3.9 seconds. This corresponded to the observation of the sixth alpha particle 3.8 seconds after the fifth. Two further alpha particles were detected about 7 hours after the sixth decay that could have corresponded to a decay from fermium to californium (mendelevium decays to fermium via a process that does not create an alpha particle). However, the scientists could not discount the possibility that this was just a coincidental background alpha particle. The next decay, from californium to curium has a half-life of more than 13 years.

Studying the nuclei of superheavy elements gives important information on 'stability'. It is known from the elements lower down in the periodic table that nuclei with a certain number of neutrons or protons are particularly stable. The first six of these so-called magic numbers are known but the next has not yet been shown experimentally. "It is important that the created superheavy atom has 113 protons because it closely approaches one of the predicted proton magic numbers of 114," explains Morita.

What's in a name?

The next big question is what to call this new element. It is currently known by the provisional name ununtrium (one-one-three), and has also been referred to as eka-thallium. But the discoverer of an element is traditionally awarded the honor of giving it a permanent name. First, however, the International Union of Pure and Applied Chemistry (IUPAC) must confirm the 'sighting', and they have some very tough criteria. Morita and his colleagues also saw a signature of element 113 in 2004 and 2005. On these two previous occasions only four alpha decays were detected. This was not enough to convince IUPAC, nor were experiments conducted in a Russian laboratory. "I do not want to speak about the possible name until the naming-rights are confirmed," says Morita. "However, in general, I can say I would like element 113 to be named after a country or a famous scientist."

While evidence of the 118th element has already been demonstrated, Morita believes that with the high levels of motivation shown so far by his colleagues at RIKEN and the Nishina Center for Accelerator-Based Science, the team can go even further: "I would like to challenge the totally unreached parts of the periodic table and produce the 119th and 120th elements."

1. Morita, K., Morimoto, K., Kaji, D., Haba, H., Ozeki, K., Kudou, Y., Sumita, T., Wakabayashi, Y., Yoneda, A., Tanaka, K., *et al.* New result in the production and decay of an isotope, ^{278}113, of the 113th element. *Journal of the Physical Society of Japan* **81,** 103201 (2012).

Figure 2: The Gas-filled Recoil Ion Separator (GARIS) separates the nucleus of element 113 from any unwanted ions and directs the nucleus into a detector chamber.

ABOUT THE RESEARCHER

Kosuke Morita was born in Kitakyushu, Fukuoka, Japan, in 1957. He graduated from the Faculty of Science, Kyushu University in 1979 and obtained his PhD from the same university in 1993. He joined the Cyclotron Laboratory at the RIKEN Nishina Center for Accelerator-Based Science as a research scientist in 1984. In a world-first in September 2004, Morita succeeded in observing a signature of the 113th element. In 2006, he became associate chief scientist of the Superheavy Element Laboratory at the RIKEN Nishina Center.

Metal oxides get heavy

X-ray resonance scattering can reveal the magnetic properties of transition metal oxides made out of heavy elements

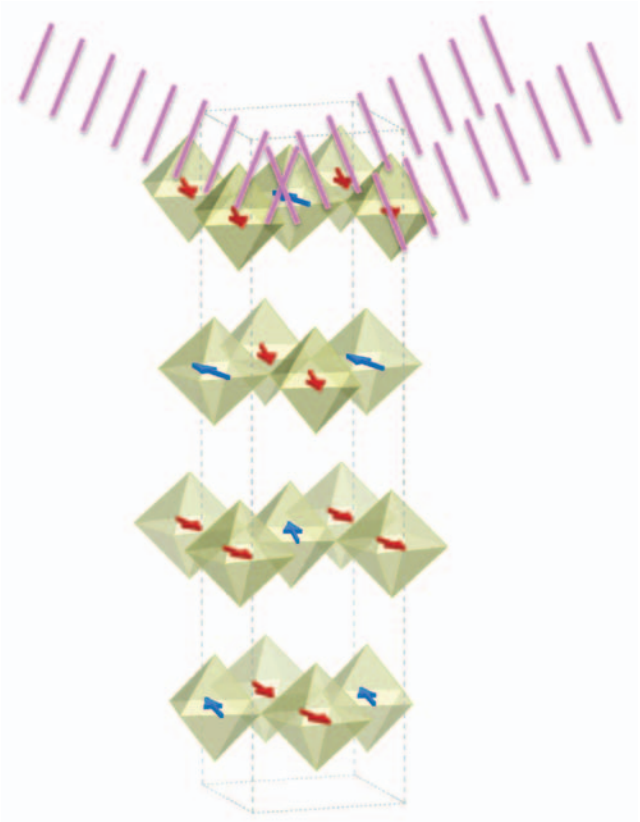


Figure 1: The scattering of x-rays with a wavelength 'in resonance' with an ion's absorption edge depends on the direction of the ion's magnetic moment (red and blue arrows). The researchers used x-rays (pink) with a wavelength of 0.11 nanometers—close to two absorption edges in iridium—to study the onset of magnetic order in Sr_2IrO_4. X-rays scattered at the blue arrows are out of phase with those scattered at the red arrows.

Transition metal oxides are known for their interesting properties, including high-temperature superconductivity and resistance that can be tuned with a magnetic field. Researchers have mainly focused on oxides made from '3*d*' transition metals—the elements from scandium to zinc—but they are starting to uncover new material properties in oxides containing the much heavier '5*d*' transition metal elements found between hafnium and mercury.

Unfortunately, scientists have not been able to rely on their usual tool, neutron scattering, to study magnetic structure in these materials because the samples are often too small and 5*d* elements strongly absorb neutrons. Now, Shigeki Fujiyama at the RIKEN Advanced Science Institute and his colleagues have shown they can use x-rays to study magnetism in the 5*d* transition metal oxide Sr_2IrO_4 over a wide temperature range[1]. "The sample size needed is three orders of magnitude smaller than what is needed for conventional neutron scattering experiments," explains Fujiyama, who says the technique will be important for studying other 5*d* transition metal oxides.

Atoms in a solid are magnetic if their valence electrons have a net (non-zero) angular momentum. The valence electrons' total angular momentum is a combination of their orbital motion about the nucleus and their 'spin'. In heavy elements, like iridium (Ir), a relativistic effect called the spin-orbit interaction causes the electrons' orbital momentum to drag their spin momentum with it. In materials where the spin-orbit effect is large, the electronic motion can be controlled to affect the magnetic properties (and vice versa).

In Sr_2IrO_4, a large spin-orbit interaction makes the material a 'Mott insulator', similar to La_2CuO_4, a 3*d* metal oxide that can be chemically modified to become a superconductor. In both materials, the magnetic ions (iridium and copper) also form the same magnetic structure—an antiferromagnet—at low temperature. It has not been clear if both magnetic structures can be described by the same models.

Fujiyama and his team therefore used resonance x-ray scattering, where the x-ray wavelength matches an absorption edge of the iridium ion so it is sensitive to the ion's magnetic state (Fig. 1), to study the onset of magnetic order in Sr_2IrO_4. Their measurements, performed at the RIKEN SPring-8 synchrotron, show that magnetic order in Sr_2IrO_4 develops in two-dimensional planes first and only becomes three-dimensional near the anti-ferromagnetic transition, similar to La_2CuO_4. Similar oxides containing iridium may exhibit superconductivity or a 'quantum spin liquid' and Fujiyama's group is examining these possibilities. ■

1. Fujiyama, S., Ohsumi, H. Komesu, T., Matsuno, J., Kim, B.J., Takata, M., Arima, T. & Takagi, H. Two-dimensional Heisenberg behavior of $J_{eff} = ½$ isospins in the paramagnetic state of the spin-orbital Mott insulator Sr_2IrO_4. *Physical Review Letters* **108**, 24721 (2012).

Powerful x-rays for less

Design improvements enable construction of compact x-ray lasers at ultra-short wavelengths, which can measure individual atoms

Studying small objects typically requires big machines. For example, the study of single atoms with a laser requires x-ray radiation of such high energy that it is only produced by accelerating electrons in large facilities. Researchers at the RIKEN SPring-8 Center in Harima have developed a more affordable electron laser design, the SPring-8 Angstrom Compact free-electron Laser (SACLA), which is not only compact and therefore economic to build but also delivers x-rays with unprecedented short wavelengths[1].

User operation of SACLA began in March 2012. Makina Yabashi from the research team describes typical research as non-linear interactions of light and matter, biological imaging and ultrafast phase-transition in materials.

Construction of a high-energy laser is based on the concept that electrons accelerated by going very fast around a curve also emit radiation. The energy of this radiation, and therefore its wavelength, depends on the acceleration. The tighter the curved path, the shorter the wavelength of the light emitted. This is the operating principle of free electron lasers (Fig. 1).

At SPring-8 the aim was to push free electron lasers to new limits by producing ever shorter wavelengths. This means sending electrons on a very tight twisting path in a section of the laser known as the undulator. Normally, the period of the curved electron beam is about several centimeters. The SACLA team have realized a period of only 1.8 centimeters by directly placing the magnets that deflect the electron beams into the vacuum chamber of the beam. This has enabled a reduction of laser wavelength down to 0.6 ångström, which is about the radius of a hydrogen atom.

The benefit of SACLA is that, in comparison to other free-electron lasers, the device is also smaller. "Our x-ray free electron laser facility has been designed to achieve a much more compact scale compared to those in the US and Europe," explains Yabashi. "The major reduction in construction and operating costs enables many research institutes or universities to build such a machine, and to utilize powerful laser light in a broad range of applications from biology, chemistry to physics," he says.

The team plans to increase the energy density of the laser beam, which would, for example, make biological imaging easier. Already there is strong interest from scientists to use the laser and other institutions are planning similar machines. In the meantime, SACLA is open for business. ■

1. Ishikawa, T., Aoyagi, H., Asaka, T., Asano, Y., Azumi, N., Bizen, T., Ego, H., Fukami, K., Fukui, T., Furukawa, Y., *et al*. A compact X-ray free-electron laser emitting in the sub-ångström region. *Nature Photonics* **6**, 540–544 (2012).

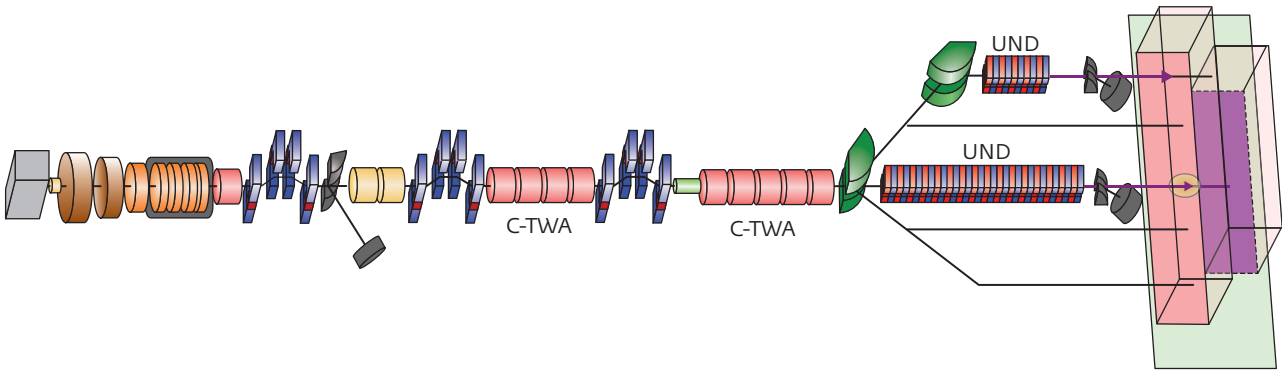


Figure 1: A conceptual diagram of SACLA. The laser consists of various electron acceleration stages (C-TWA) and focusing elements. Key to achieving short wavelength operation is, however, the design of the undulator (UND).

The sweet sights of glycoproteins

An imaging technique helps scientists profile the sugar structures on protein molecules

The body's cell machinery often attaches sugar chains onto proteins to create molecules that play a crucial role in everything from protective immunity to structural stability. However, distinguishing between the different sugar tags applied to these so-called 'glycoproteins' can be difficult. Now, investigators in Japan have developed a way to visualize the profile of sugar molecules (known as 'glycans') on specific protein targets[1].

The new method could help scientists investigate the expression and trafficking of glycoprotein targets with therapeutic potential. For example, recent studies have revealed that changes in glycan structures accompany the progress of disease. "Our technique may help us to understand why this is happening," says Tadashi Suzuki of the RIKEN Advanced Science Institute in Wako.

To determine the nature of attached sugars, Suzuki and his postdoctoral fellow Yoshimi Haga turned to an imaging technique known as 'fluorescence resonance energy transfer', or FRET. The researchers labeled sugar molecules with a fluorescent probe that is activated only when signals are emitted from a nearby protein tagged with green fluorescent protein (GFP). These signals are picked up by the FRET assay, which can reveal the complex spatial and geometrical characteristics of the glycoprotein structures, even those that span the thick cell membrane.

As a proof of principle, Suzuki and Haga first applied the method to two well-studied glycoproteins—the glucose transporter GLUT4 and the epidermal growth factor receptor—each tagged with a specific type of sugar tag, sialic acid (Fig. 1). The researchers then set up an experiment in human cell culture where they adjusted the levels of insulin. This hormone triggers the transport of GLUT4 to the cell surface, where the glycoprotein begins pumping glucose into the cell. The scientists found that lowering insulin levels led to GLUT4 proteins with sugars containing sialic acid re-entering the cell more slowly than GLUT4 proteins without this kind of sugar adornment. "We do not know why it happens," Suzuki says. "This finding may shed some light on the cell trafficking of closely related glycoproteins."

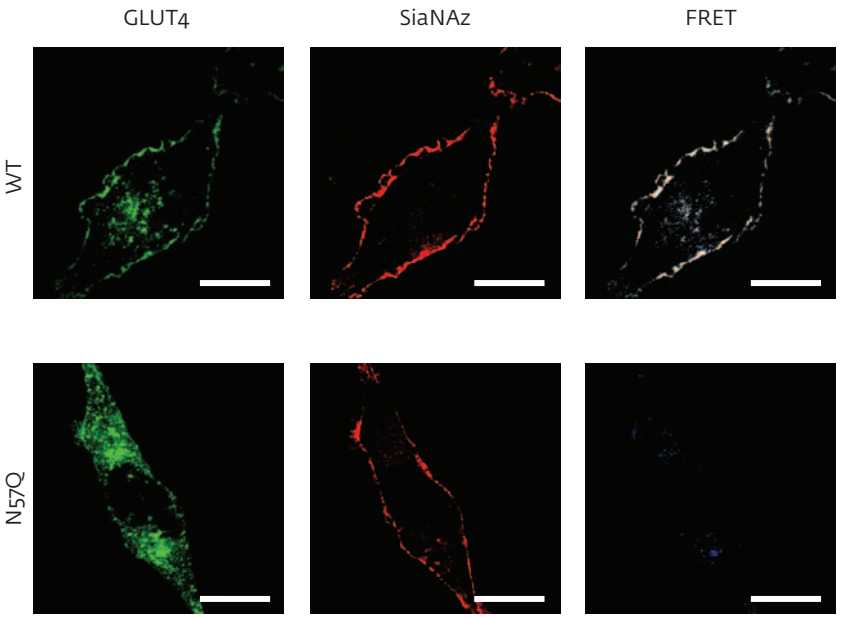


Figure 1: The azide-tagged sialic acid (SiaNAz) sugar molecules on GLUT4 can be seen through FRET imaging in the wild-type glycoprotein (top) but not in the N57Q mutant lacking this glycosylation site (bottom). Scale bar equals 20 micrometers.

The researchers now want to adapt the technique so they can visualize sugars on more complex glycoproteins. "GLUT4 happens to be fairly easy as it only contains a single glycan," Suzuki says, "but for proteins bearing multiple glycans, it is not going to be so easy, as the structural diversity is much greater." ■

1. Haga, Y., Ishii, K., Hibino, K., Sako, Y., Ito, Y., Taniguchi, N. & Suzuki, T. Visualizing specific protein glycoforms by transmembrane fluorescence resonance energy transfer. *Nature Communications* **3**, 907 (2012).

Head-mounted device manipulates reality

A virtual reality-like device mixes real life with make believe

A research team led by Naotaka Fujii of the RIKEN Brain Science Institute in Japan has developed a cheap virtual reality-like system that can be used to manipulate people's perceptions of reality[1]. The 'substitutional reality' system consists of a video camera, a computer for storing recorded footage and a head-mounted device that displays, and switches between, recorded footage and a live feed captured by an attached camera and microphone.

Fujii and his colleagues recorded participants while giving them instructions about the experiment. Each participant was then asked to wear the head-mounted device, which displayed a sequence of recorded and live scenes designed to surreptitiously substitute the live scenes with recorded ones.

The first scene was a recording of one of the researchers appearing at the door and asking if the participant felt comfortable wearing the device and to test it by looking around. This was followed by a 'doppelgänger' scene, in which participants saw the recording of themselves receiving instructions from the researcher and a fake live scene in which the experimenter re-entered the room and explained how the experiment was designed. Finally, the device played a live feed of the researcher returning to reveal that the previous scene was actually a recording (Fig. 1).

The participants realized that the doppelgänger scene could not be real but failed to distinguish between the live and recorded scenes during the rest of the experiment, showing that the device can successfully substitute reality with recorded scenes and that the participants subjectively experienced the recorded scenes as real. The researchers determined that head movements and motion parallax—how objects change shape and depth with changes in head position—did not influence the performance of the system and that participants were less likely to notice the switch between live and recorded scenes if it was done while they looked around the room. They also established that some of the participants had noticed a difference in the audio quality of the live and recorded scenes and used these differences to establish when the switch between the two was made.

"We can replicate the delusions of psychiatric patients but the system is not directly usable for diagnosis or treatments," says Fujii. "We are expanding the quality of the technology and trying to extend the system for people to use as an experience platform. It can be useful not only for scientific experiments but also for entertainment and art." ■

1. Suzuki, K., Wakisaka, S. & Fujii, N. Substitutional reality system: a novel experimental platform for experiencing alternative reality. *Scientific Reports* **2**, 459 (2012).

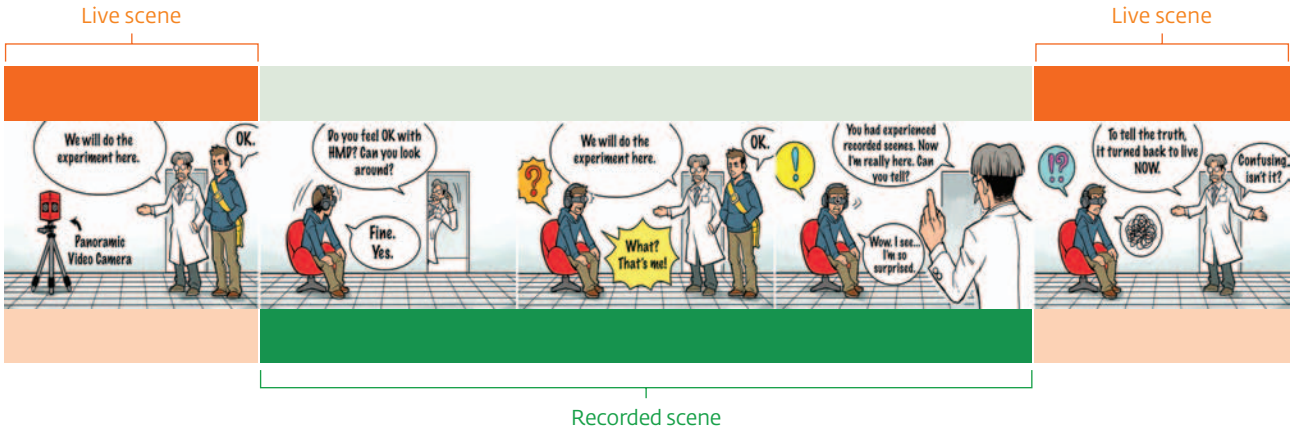


Figure 1: The experimental procedure for substituting a live feed with pre-recorded footage.

Learning to simulate other people's decisions

The brain recruits its own decision-making circuits to simulate how other people make decisions

A team of researchers led by Hiroyuki Nakahara and Shinsuke Suzuki of the RIKEN Brain Science Institute has identified a set of brain structures that are critical for predicting how other people make decisions[1].

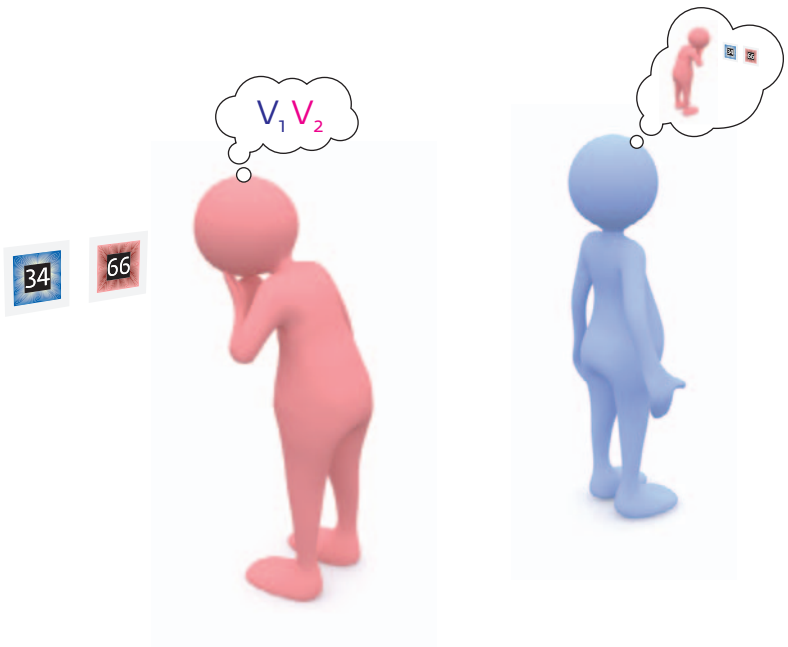
This phenomenon is thought to involve simulation learning, a process by which the brain generates a model of how another person will act by directly recruiting its own decision-making circuits. However, little else is known about the underlying brain mechanisms.

Nakahara and his colleagues used functional magnetic resonance imaging to scan participants' brains while they performed two simple decision-making tasks. In one, they were shown pairs of visual stimuli and had to choose the 'correct' one from each, based on randomly assigned reward values. In the second, they had to predict other people's decisions for the same task (Fig. 1).

The researchers confirmed that the participants' own decision-making circuits were recruited to predict others' decisions. The scans showed that their brains simultaneously tracked how other people behaved when presented with each pair of stimuli, and the rewards they received.

Effective simulated learning occurs when the brain minimizes two different prediction errors—the discrepancies between its prediction of others' actions and the rewards they received and how they actually acted and were rewarded. The researchers found that each of these variables was associated with activity in a distinct part of the prefrontal cortex (PFC).

The bigger the prediction error in simulating other people's rewards, the more activity was observed in the ventromedial prefrontal cortex (vmPFC) an area located at the base of the frontal lobe of the brain that is associated with decision making, while the larger the prediction error in simulating another's actions, the more active were the dorsomedial and dorsolateral prefrontal cortices.



Modified from: © 2012 Hiroyuki Nakahara, RIKEN Brain Science Institute

Figure 1: The researchers scanned participants' brains while they made a simple decision and while they predicted other people's decisions about the same task.

The ability to attribute mental states to others is referred to as theory of mind, or 'mentalizing', and is widely thought to involve the PFC. This, however, is the first study to show that activity in the PFC encodes prediction errors of one's own rewards as well as those of the simulated decisions of other people, and that both of these signals are required for simulated learning. "We showed that simple simulation is not enough [to predict other peoples' decisions], and that the prediction error of other people's simulated decisions is used to track variations in another person's behavior," says Nakahara. "In real life, some people are similar to us but others are not. Yet, we still interact with different types of people somehow, and next we hope to understand how this is possible." ■

1. Suzuki, S., Harasawa, N., Ueno, K., Gardner, J.L., Ichinohe, N., Haruno, M., Cheng, K. & Nakahara, H. Learning to simulate others' decisions. *Neuron* **74**, 1125–1137 (2012).

Re-tuning responses in the visual cortex

Mice wearing goggles show how early sensory experience alters the properties of visual cortical neurons

New research led by Shigeru Tanaka of the University of Electro-Communications and visiting scientist at the RIKEN Brain Science Institute shows that the responses of cells in the visual cortex can be 're-tuned' by experience[1].

Experiments on kittens in the 1960s showed that the primary visual cortex contains neurons that fire selectively to straight lines of specific orientations. These cells are organized into alternating columns that receive inputs from the left or right eye. The kitten experiments also showed that proper brain development is highly dependent on sensory information. Closing one eye altered the organization of the columns, so that those that should have received inputs from the closed eye were reduced in width, whereas those that received inputs from the open eye were much wider than normal.

The normal columnar organization can be restored if the closed eye is re-opened within a critical period of brain development. The effect of sensory experience on the orientation selectivity of neurons in the primary visual cortex is, however, unknown.

To investigate, Tanaka and his colleagues reared mice and fitted them with specially designed goggles (Fig. 1) through which they can only perceive vertically oriented visual stimuli, for a one-week period, between 3 and 15 weeks of age. Immediately after removing the goggles, they created a 'window' in the skull bone lying over the visual cortex to examine the cell response under the microscope.

Rearing the mice in this way had a significant effect on the properties of neurons in the primary visual cortex.

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Figure 1: Specially designed goggles modify visual input so that only vertically oriented stimuli are perceived.

The researchers found that the number of cells responding to vertical orientation increased, while the number responding to other orientation decreased. They also found that the extent of these changes depended on the age at which they fitted the animals with the goggles. Mice fitted with the goggles between 4 and 7 weeks of age had more cells that were sensitive to the experienced (vertical) orientation than those fitted later.

These findings show that there is a critical period of plasticity between 4 and 7 weeks, during which cells in the primary visual cortex are particularly sensitive to sensory experience and that plasticity persists in older animals, albeit to a lesser extent. They also suggest that plasticity in younger and older animals involves different mechanisms.

"When we put similar goggles on kittens, the age at which we started goggle rearing determined the reversibility of orientation selectivity," says Tanaka. "We would now like to clarify the differences and commonalities of the mechanisms in cats and mice." ■

1. Yoshida, T., Ozawa, K. & Tanaka, S. Sensitivity profile for orientation selectivity in the visual cortex of goggle-reared mice. *PLoS ONE* **7**, e40630.

Uncovering the gene for a rare skeletal disease

Short stature and skeletal abnormalities arise from mutations in the *PAPSS2* gene

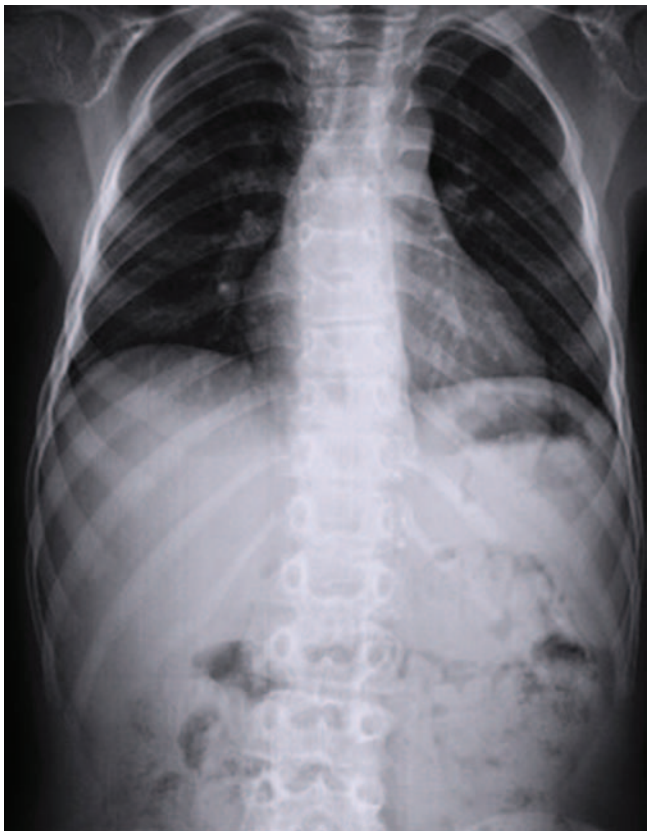

Figure 1: X-ray image of the spine of a young girl with brachyolmia.

The hereditary disease known as brachyolmia is characterized by a short stature and various bone abnormalities that start becoming apparent in late childhood. The vertebrae take on a flattened shape, with irregular spacing between the spinal discs (Fig. 1). This rare skeletal disease can be caused by dominantly inherited mutations in the gene *TRPV4*, but there are also more than a few recessive forms of brachyolmia for which the genetic cause has been a mystery—until now.

Reporting in the *Journal of Medical Genetics*, researchers in Japan have pinpointed the gene responsible for recessive brachyolmia[1]. By sequencing the entire protein-coding regions of the genome of a young Turkish girl with the disease and two of her affected family members, the scientists found that an insertion in the *PAPSS2* gene was the causative mutation.

The team, led by Shiro Ikegawa, an expert in the field of bone and joint diseases at the RIKEN Center for Genomic Medicine in Tokyo, also examined the DNA of three more children—two from Japan and one from Korea. All three had forms of brachyolmia that clinically mirrored those found in the Turkish family, and all three had loss-of-function mutations in both copies of their *PAPSS2* gene, which encodes an enzyme involved in the formation of cartilage proteoglycan. "This finding indicates that brachyolmia caused by the *PAPSS2* mutation is not unique to the Turkish family but a universal disease potentially common among different populations," Ikegawa says.

Mutations in the *PAPSS2* gene have been found occasionally in other bone growth disorders with autosomal recessive inheritance patterns. For example, researchers in the United States previously identified such mutations in a large, inbred Pakistani family with a form of spondyloepimetaphyseal dysplasia, another disease marked by short stature and other skeletal disorders. More recently, clinicians from Western Europe have described a girl of Turkish origin with *PAPSS2* sequence variants who suffered from precocious puberty and bone problems, although her skeletal defects were far milder than those found in other people with mutations in the same gene.

The finding that the six people with brachyolmia studied by Ikegawa's group had overlapping, but distinct, clinical features compared to the individuals with these other *PAPSS2*-associated diseases suggests that the loss of this key gene can lead to a gradient of disease states. "One gene mutation sometimes presents with a variety of phenotypes," says Ikegawa. "The task now is to explain on a molecular scale why this happens with this particular gene." ■

1. Miyake, N., Elcioglu, N.H., Iida, A., Isguven, P., Dai, J., Murakami, N., Takamura, K., Cho, T.-J., Kim, O.-H., Hasegawa, T. *et al.* *PAPSS2* mutations cause autosomal recessive brachyolmia. *Journal of Medical Genetics* **49**, 533–538 (2012).

Managing cellular security systems

Cells that act as critical regulators of general immune function also play a key part in enabling prompt elimination of bacterial and viral threats

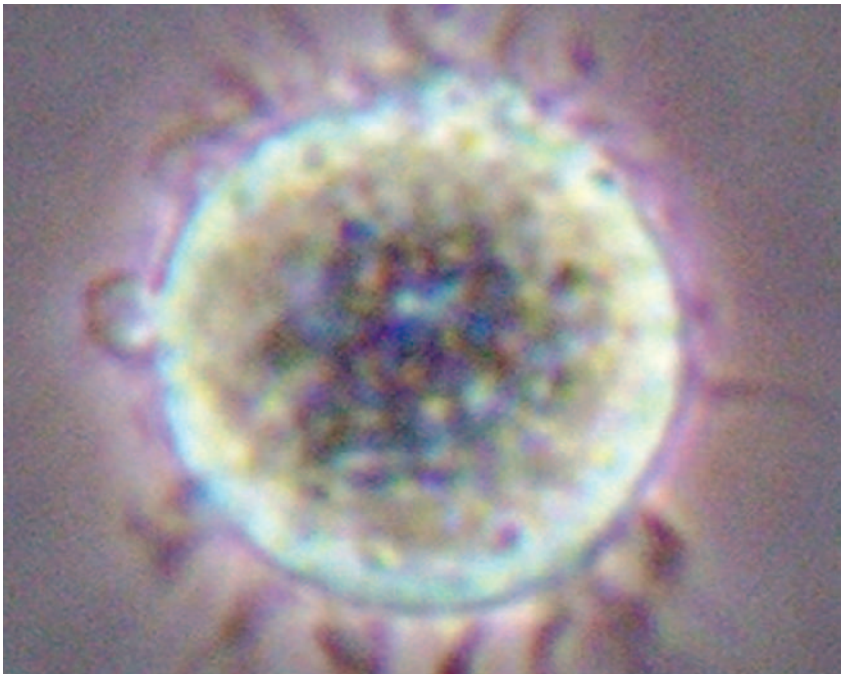

Figure 1: Microscopic image of a mouse cDC.

Conventional dendritic cells (cDCs) are the immune system's patrol (Fig. 1). They recognize foreign threats and trigger a defensive response, while restraining immune reactions against inappropriate targets like host proteins. They achieve the former via a mechanism called cross-presentation, which displays pieces of pathogens to cytotoxic T lymphocytes (CTLs)—the immune system's 'attack dogs'—while the latter function relies on cDC interactions with regulatory T (T_{reg}) cells.

Katsuaki Sato's group at the RIKEN Research Center for Allergy and Immunology in Yokohama recently identified a subset of cDCs with an especially important role in fighting infection[1]. These cells can be classified based on the proteins they show on their surface and Sato's team became especially interested in cDCs featuring a protein called CD205. "$CD205^+$ cDCs are more efficient in the cross-presentation of cell-bound or soluble antigens to CTLs than other dendritic cell subsets," explains Sato. "However, their role in the immune system under physiological conditions was unclear."

To clarify the function of these cDCs, Sato and colleagues genetically engineered mice in which $CD205^+$ cDCs could be quickly and selectively killed off via injection with diphtheria toxin. This depletion lasted for several days, giving the researchers a powerful way to study the specific contribution of these cells to immune function. Initial experiments with the mice provided compelling evidence that $CD205^+$ cDCs are required to marshal an effective CTL response. Loss of these cells also resulted in abnormal T_{reg} levels in various tissues, indicating that $CD205^+$ cDCs are required to maintain appropriate levels of other T cell populations throughout the body.

Animals infected with high doses of the pathogenic bacterium *Listerium monocytogenes* normally perish quickly due to septic shock resulting from immune overreaction, but $CD205^+$ cDC-deficient animals proved resistant to septic shock and tended to survive longer, revealing a crippled inflammatory response. In the end, however, these animals were more vulnerable to bacterial infection and proliferation, resulting from impaired cDC cross-presentation of bacterial antigens to CTLs. The researchers observed similar effects with viral infection.

These results position $CD205^+$ cDCs at a critical juncture for regulating overall immune system function as well as directed counterattacks against pathogens and the researchers see clear potential for exploiting these cells in clinical applications. "Further elucidation of $CD205^+$ cDC function might provide insights into immune regulation and pathology and aid therapeutic interventions for infectious diseases as well as autoimmune and inflammatory disorders," says Sato. "For example, we would like to develop vaccines that selectively target $CD205^+$ cDCs with bacterial and viral antigens." ■

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A blueprint for the gut's antimicrobial defenses

The identification of a developmental 'master switch' helps scientists explore the function of intestinal cells that help prevent infection

Every bite of food or drink of water is an invitation for potentially harmful bacteria and viruses to set up shop in the body. In order to protect against such invaders, the mucous membrane that lines the intestine contains clusters of specialized microfold cells (M cells), which can absorb foreign proteins and particles from the digestive tract and deliver them to the immune system.

New work from Hiroshi Ohno's group at the RIKEN Center for Allergy and Immunology in Yokohama, in collaboration with Ifor Williams and colleagues at Emory University in Atlanta, Georgia, has revealed valuable insights into how these M cells develop[1]. Previous research from Williams' group showed that a signaling protein called RANKL switches on M cell development[2] but virtually nothing was known about the subsequent steps in this process. To find out, Ohno and Williams looked for genes that get switched on when intestinal cells undergo differentiation in response to RANKL exposure.

They discovered that treatment with RANKL causes immature intestinal epithelial cells to sharply increase the production of Spi-B, a protein that regulates the expression of other developmental genes. To test the specific contribution of this protein to M cell maturation, the researchers collaborated with Tsuneyasu Kaisho's group at Osaka University, which had engineered a genetically modified mouse strain lacking the gene encoding Spi-B. The resulting animals were devoid of mature M cells (Fig. 1). On the other hand, intestinal development as a whole was unaffected by the absence of Spi-B, demonstrating that this protein's impact is limited to this specific class of cells within the gut.

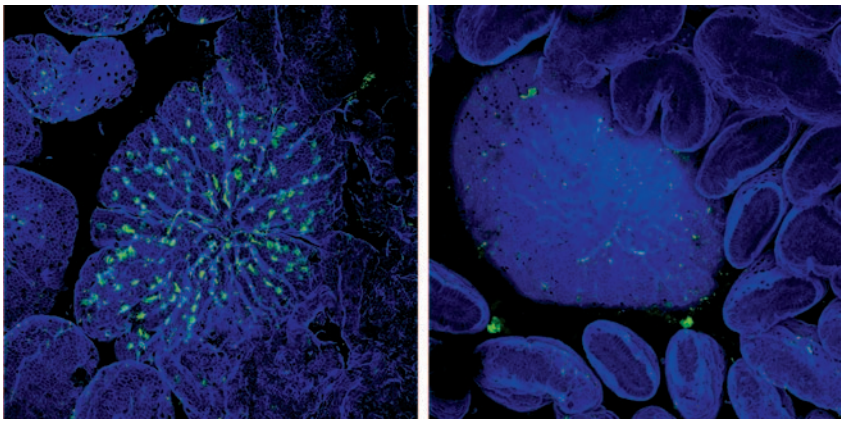

Figure 1: Fluorescent labeling of GP2, a protein expressed in M cells (left) reveals that this cell population is virtually absent in mice lacking the gene encoding Spi-B (right).

M cells normally localize to immune structures known as Peyer's patches (PPs). Bacteria such as *Salmonella enterica* Typhimurium (*S.* Typhimurium) will normally accumulate within these PPs shortly after inoculation. This uptake was considerably reduced in Spi-B-deficient mice, indicating the absence of a functional M cell population. The mice showed a considerably weakened immune response following oral administration of *S.* Typhimurium bacteria relative to wild-type animals, demonstrating the importance of M cell-mediated microbial uptake.

The identification of this critical 'master switch' for M cell development opens exciting new avenues of research into these mysterious cells. Ohno is eager to investigate the details of how the cells perform their critical immunity-training function. "These questions could not be answered previously because of the lack of M cell-deficient mice," he says. "But now, 'knockout' mice that specifically lack Spi-B in their mucosal epithelium will provide the ideal tool for such studies." ■

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First mouse, now human, lab-grown eye tissue

Human embryonic stem cells can self-organize into eye-like structures via a cell-culture technique developed at RIKEN

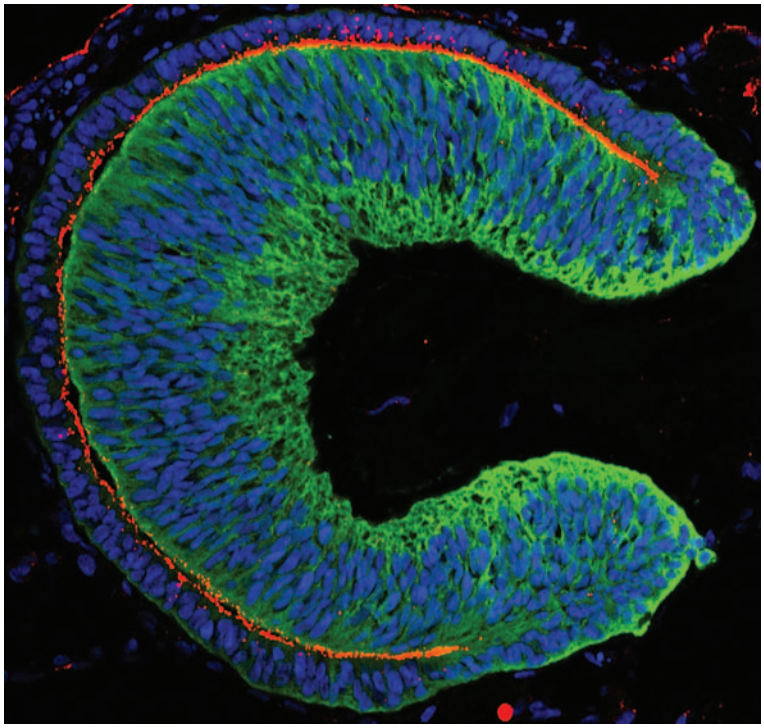

Figure 1: An embryonic eye derived from human embryonic stem cells.

Producing retinal tissue from human embryonic stem cells is now possible thanks to a team of researchers led by Yoshiki Sasai of the RIKEN Center for Developmental Biology in Kobe[1].

Sasai and his colleagues have developed a novel cell culture method in which embryonic stem (ES) cells are grown in suspension instead of on a flat surface. ES cells grown under these conditions can organize themselves into complex three-dimensional structures when they are treated with the appropriate combination of growth factors.

Last year, Sasai's team reported that mouse ES cells cultured in this way recapitulate developmental mechanisms and self-organize into a cupped, layered structure that resembles the embryonic eye and contains all the cell types found in the mature retina, including photoreceptor cells[2].

In their latest study, the team repeated these experiments using human ES cells, and found major differences in how they form eye-like structures. The structures derived from human ES cells were substantially larger and thicker than those formed by mouse cells, reflecting the differences in size between the two species (Fig. 1). And unlike the structures formed from mouse cells, the human-based structures also had a tendency to curve more at the edges.

Importantly, the human ES cells took significantly longer to form embryonic eyes—more than 100 days compared to just 20 days for mouse cells, presumably reflecting the differences in normal gestation times. This made the experiments technically challenging, because it is difficult to maintain stable cell cultures for periods of longer several weeks.

Sasai and his colleagues noticed, however, that the cell cultures that grew well during the first month tended to generate well-formed retinal tissue. To keep the cultures stable at this critical stage, they developed a novel cryonic preservation method for storing the tissue at this critical intermediate stage.

The cryopreservation method involves cutting the retinal tissue from the cupped structures after 18 days in culture and then leaving it to continue growing in suspension for another 12 days. The tissue is then briefly cooled on ice before being submerged in liquid nitrogen. Crucially, the tissue can be stored in this state for long periods of time, but remains healthy and continues to grow when thawed later on.

"We now plan to test the functionality by grafting these tissues into animal eyes," says Sasai. "The most straightforward application would be for transplantation to patients suffering from retinitis pigmentosa, in which photoreceptors gradually degenerate, leading to blindness." ■

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YOSHIHIRO ITO

Chief Scientist
Nano Medical Engineering Laboratory
RIKEN Advanced Science Institute

Creating new products through 'bio-fabrication'

Yoshihiro Ito, chief scientist at the RIKEN Advanced Science Institute's Nano Medical Engineering Laboratory, is at the forefront of 'bio-fabrication'—a new approach to fabricating products through the integration of more traditional chemical and biotechnological methods. Ito's team are working on establishing bio-fabrication techniques and developing sophisticated new functional materials. Recently the team developed a groundbreaking cell culture substrate that enables convenient cultivation of induced pluripotent stem cells (iPS cells). "We also employ molecular evolution engineering with the aim of advancing bio-fabrication to better contribute to medicine and society," says Ito. A wide variety of new materials and technologies are expected to emerge from the laboratory.

iPS cells: great hope, big challenge

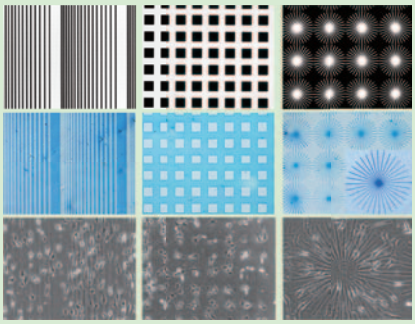
Pluripotent cells, which are cells with the ability to develop into a variety of specific cell types, offer the potential for major advances in regenerative medicine and the repair of tissues and organs that have been injured or have lost functionality. Human embryonic stem cells (ES cells) are pluripotent, but pose ethical problems because they are derived from cells taken from embryos in the early stages of development. Their use in therapies also carries increased risk of graft rejection because they originate from a foreign donor. Thus, iPS cells—created by reprogramming differentiated somatic cells, such as skin cells, by transferring defined genes which confer pluripotency—are stimulating increasing interest.

When human iPS cells were first produced in 2007 by Shinya Yamanaka at Kyoto University, their applicability to medicine was obvious: iPS cells could be generated from a patient's own cells, avoiding the ethical problems of ES cells and reducing the likelihood of graft rejection. "However, iPS cells cannot actually be used in clinical settings until many problems are solved, including how to culture them," points out Ito. Then, in March 2012, Ito announced that his team had developed a new cell culture material for an improved iPS cell culture substrate.

Fixing cells

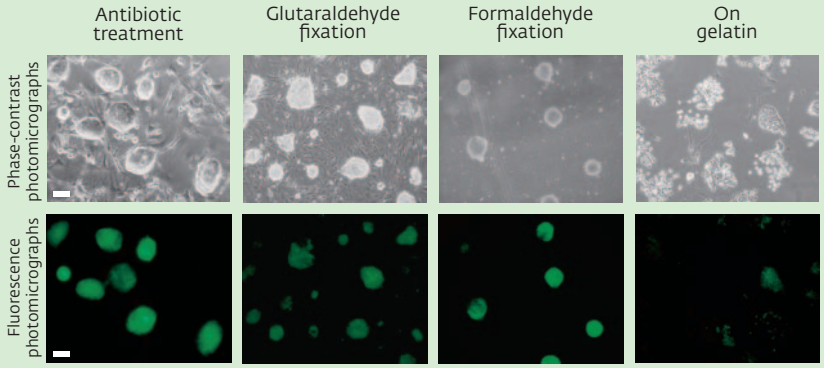
"My laboratory is promoting the concept of bio-fabrication," says Ito. "'Bio-fabrication' refers to creating a new material using new technology established by integrating chemistry and biotechnology. We are aiming to produce novel materials that will contribute greatly to medical practice. For example, we were the first in the world to develop a cell culture material that allows biomolecules to be fixed in a micropattern by ultraviolet light stimulation (Fig. 1(A)). This material will be useful in regenerative medicine because it allows us to control cell growth, differentiation and migration"—and controlling cell growth, differentiation and movement is key to the effective therapeutic use of iPS cells.

It is common practice to use feeder cells when culturing iPS cells. Feeder cells supply nutrients to iPS cells in culture, allowing iPS cells to propagate and producing an environment suitable for the maintenance of iPS cell pluripotency. However, the use of live feeder



A: Using ultraviolet light to control biomolecule micropatterns and cells in culture

A biomolecular species such as a growth factor is applied over a cell culture substrate. After drying, the substrate is covered with an optical micropattern mask (upper images). Upon ultraviolet exposure, the biomolecules respond to the light and become fixed on the micropattern (middle images). When culturing cells on the substrate, the cells propagate on the micropattern of biomolecules (lower images).



B: Culturing iPS cells using chemically fixed feeder cells

Mouse iPS cells were genetically modified to express labeled Nanog, a protein serving as an index of pluripotency, and cultured. Thus, the cells emitted green light in proportion to the amount of Nanog they expressed. The cells were visualized using two types of microscopes: a phase-contrast microscope (upper panels) and a fluorescence microscope (lower panels). The Nanog expression observed after cell culture using antibiotic-treated feeder cells (a method for reducing feeder cell propagation) demonstrates the maintenance of iPS cell pluripotency. Nanog was also expressed by iPS cells when the feeder cells had been chemically fixed in glutaraldehyde or formaldehyde; this finding further demonstrates the maintenance of the iPS cells' pluripotency. Meanwhile, when the iPS cells were cultured on gelatin, they lost pluripotency. Scale bar is 100 μm.

Figure 1: A new cell culture material developed via bio-fabrication

cells can also create complications.

"It is painstaking to prepare confluent feeder cells to synchronize the passage of stem cells," explains Ito. "It is also necessary to prevent feeder cells from propagating by themselves. But, if the feeder cells become incorporated into the iPS graft and are still present when the graft is removed from culture and prepared for transplantation, the graft is useless. Many researchers are trying to pursue alternative safe and convenient methods of culturing iPS cells."

Ito conceived a bold method of cell culture: "I decided to fix the feeder cells by chemical treatment."

A new approach to cell culture

Fixing the feeder cells in the cell culture substrate would stop their growth and movement, allowing the iPS cells to grow separately and undisturbed. Ito chose two chemicals commonly used to fix cells and tissues, glutaraldehyde and formaldehyde.

"If feeder cells are fixed in glutaraldehyde or formaldehyde, they will die. According to conventional knowledge, iPS cell culture using dead feeder cells is unlikely to go well," says Ito. "However, feeder cell fixation is an attractive method of increasing the therapeutic usability of iPS cells by reducing the work involved in culturing them and preventing the co-presence of feeder cells in the iPS cell graft. I had the courage to try it at least once."

Ito seeded glutaraldehyde- or formaldehyde-fixed feeder cells over a Petri dish to obtain a culture substrate and attempted to culture iPS cells on the substrate. He succeeded in proliferating iPS cells on the substrate while maintaining the cells' pluripotency (Fig. 1(B)). Furthermore, he was able to stimulate the cultured iPS cells to differentiate into neurons, confirming that the cells were not only pluripotent but also able to complete the process of differentiation, which is important if the graft is intended for therapeutic use. "Feeder cells have been believed to be necessary for supplying nutrients in iPS cell culture, and therefore it was necessary that they were alive," says Ito. "In fact, feeder cells may only be needed as a scaffold."

Ito's method offers some great advantages over conventional, live feeder cell culture techniques. For example, fixed feeder cells can be preserved in a freeze-dried state for a long time and can be used after thawing whenever needed. Fixed feeder cells are also reusable: even when glutaraldehyde-fixed feeder cells are used three times, approximately 95% of the cultured iPS cells maintain their pluripotency. "Because cost is important in clinical settings, this reusability is a major advantage. To obtain these results, we used mouse iPS cells. I am continuing to research whether chemically fixed feeder cells can be used to cultivate human iPS cells."

"Human iPS cells are more difficult to culture than mouse iPS cells because they are much more susceptible to ambient conditions. Very small environmental changes can make human iPS cells unable to propagate or maintain their pluripotency, so there is strong demand for a safe, convenient and inexpensive method of iPS cell culture. I look forward to making a major contribution to the development of regenerative medicine by creating a culture substrate of chemically fixed feeder cells that can be used to culture human iPS cells."

Reprogramming of somatic cells by cell fusion

Ito has long been researching somatic cell reprogramming to confer pluripotency. "Professor Yamanaka successfully reprogrammed mouse somatic cells by transferring four defined genes into them in 2006. But even before then, somatic cells had been known to be reprogrammable by fusion with ES cells. I was aiming to reprogram somatic cells using this method."

The cytoplasm of ES cells contains factors essential for cell reprogramming. It is hypothesized that when an ES cell and a somatic cell are fused together, the somatic cell becomes reprogrammed to acquire pluripotency. However, this method has a major drawback: the chromosome number becomes doubled when the cells fuse. To solve this problem, Ito first devised a method in

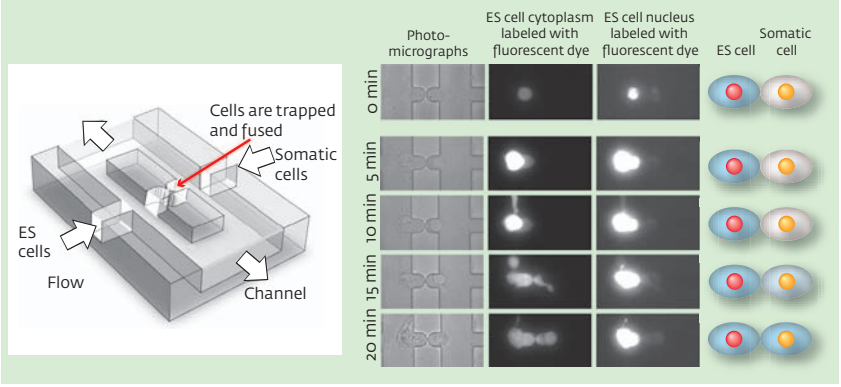


Figure 2: Fusion of an ES cell and a somatic cell using a microchannel

ES cells are put in the apparatus from one end and somatic cells are put in from the other end; the cells are fused in the hollow at the center of the apparatus. The channel width at the point of contact between the ES cells and the somatic cells is 2 μm, too narrow for cell nuclei to pass through. As a result, only the cytoplasm of the cells fuses through the channel.

which the ES cell nucleus is destroyed by laser exposure following cell fusion, but this technique was unsuccessful. After trying numerous other approaches, he devised another method for cell fusion involving the use of a microchannel.

"What is needed for somatic cell reprogramming are the factors contained in the cytoplasm of ES cells. I thought that optimizing the width of the microchannel—narrowing it to allow only the cytoplasm but not the nucleus of the ES cells to fuse with the somatic cells—would achieve the reprogramming of the somatic cells without the doubling of the chromosomes. Since our laboratory lacks the technology for fabricating microchannels, we have been conducting joint research with Senior Research Scientist Kazuo Hosokawa and Chief Scientist Mizuo Maeda at the Bioengineering Laboratory in the RIKEN Advanced Science Institute."

In February 2012, they unveiled their new technique. Cell fusion takes place in a small, carefully designed chamber (Fig. 2). "ES cells are put in the apparatus from one end, while somatic cells are put in from the other end, and the cells are fused at the center of the apparatus. The opening which allows contact between the ES cell and somatic cell is only 2 μm wide, so the nucleus of the ES cell cannot pass through it but the cytoplasm can," explains Ito. "Using this apparatus, I succeeded in fusing only the cytoplasm of the ES cells with the somatic cells. I'm planning to examine whether the thus-fused cells will become reprogrammed to acquire pluripotency."

Controlling the differentiation of iPS cells

Regenerative medicine requires not only the ability to create pluripotent cells, but also to control how they differentiate: for example, making repair tissue for the heart requires a technique for differentiating iPS cells into heart muscle cells. "They say that in the lineage determination for iPS cells, the environment around the cells is critical in controlling into which cell types the reprogrammed cells differentiate," Ito affirms. "The next problem is how to create the desired environments using artificial materials."

Ito already has a good idea. "Progress is being made toward determining the types of cells into which iPS cells differentiate and identifying the specific reprogramming factors involved. I'm planning to fix the necessary factors onto a Petri dish and culture iPS cells there. The main feature of this approach is that the factors are not added to the culture broth but are fixed to the Petri dish. If the factors are added to the culture broth, they will immediately be absorbed in the cells and soon exhausted. However, if they are used in a fixed state, they will be able to transmit the directions for proper differentiation for a long time without being absorbed in the cells."

Ito's experimental technique—reprogramming somatic cells using his purpose-built microchannel device, culturing and propagating the cells while maintaining their pluripotency using a culture substrate of chemically fixed feeder cells, and then further culturing and differentiating the cells on Petri dishes with the factors essential for controlling their differentiation fixed thereon—has the potential to dramatically increase the practicality of regenerative medicine.

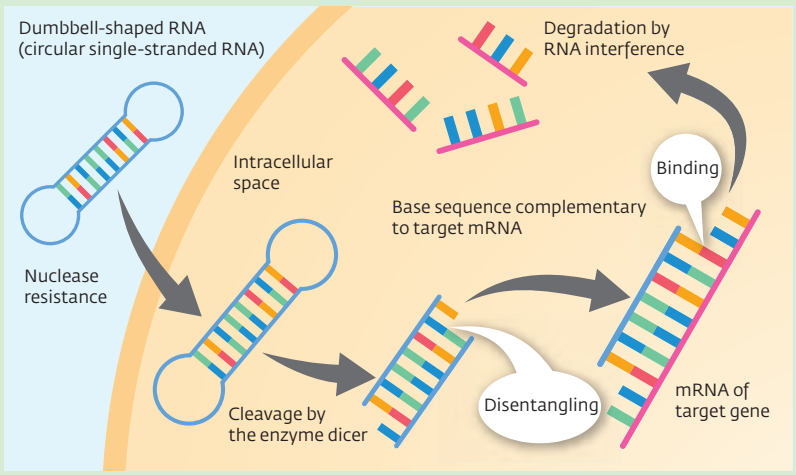
Creating RNA drugs using dumbbell-shaped RNAs

Ito's ideas for therapeutics are not limited to iPS cells. He is also very excited about his 'dumbbell-shaped RNA' project which he announced in November 2007. "The RNA looks like a dumbbell used for weight training," says Ito (see Fig. 3, upper panel). "This technology will help identify practical applications of RNA drugs."

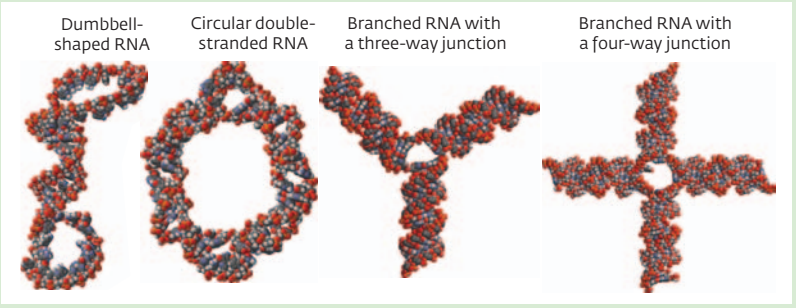
RNA drugs are a new type of therapeutics that act by making harmful genes nonfunctional using RNA interference. In living cells, genes' DNA sequences are translated into messenger RNA (mRNA) and, based on the information contained in the mRNA, specific proteins with a variety of functions can be synthesized. Andrew Fire at Stanford University and Craig Mello at the University of Massachusetts discovered that when double-stranded RNA is put in cells, only the mRNAs having a base sequence complementary to the double-stranded RNA are degraded—a phenomenon now known as RNA interference, and a discovery for which Andrew and Mello received the 2006 Nobel Prize in Physiology or Medicine. For RNA drugs, double-stranded RNA having the same base sequence as the mRNA of a harmful gene are artificially synthesized and delivered into the body, leading to the degradation of the target mRNA and the suppression of its function.

"RNA drugs are expected to provide an ideal treatment that enables us to suppress the expression of the targeted gene alone. However, because double-stranded RNA is highly unstable, it degrades immediately after being placed in the body and so does not reach the cells in the diseased area. To solve this intractable problem, dumbbell-shaped RNA was developed under the initiative of Hiroshi Abe, senior research scientist at our laboratory," says Ito.

Dumbbell-shaped RNA is prepared by joining both ends of a double-stranded RNA by means of a ligase enzyme to make the RNA circular (Fig. 3). Circular RNA is highly stable in living



RNA interference by dumbbell-shaped RNA
Double-stranded RNA is quickly degraded by nuclease in the body. However, circular and dumbbell-shaped RNA (RNA whose ends are joined using ligase, a joining enzyme) is protected from degradation outside of cells. Upon entering a cell, the circular portion is cleaved by the enzyme dicer, initiating RNA interference and resulting in the degradation of target mRNA.



Computer modeling of various nanostructured RNAs

Figure 3: Nanostructured RNA for RNA interference

organisms and can be delivered to the cells located in the diseased part of the body without being degraded. Upon entering the cells, an enzyme known as dicer cleaves the circular portion between the two ends, enabling the process of RNA interference. "It is a very chemistry-oriented idea to use an enzyme to increase stability. In addition to dumbbell-shaped ones, we succeeded in synthesizing circular double-stranded RNA and the like, and have confirmed their respective functions. I hope that the nanostructured RNAs that have emerged using an integration of chemical and biotechnological approaches will accelerate the development of RNA drugs."

Adding molecular evolution engineering

"In recent years, I have also been conducting research which is unrelated to medicine," continues Ito. "In a joint research project with the Advanced Device Laboratory and the Yu Initiative Research Unit in the Advanced Science Institute, we are working on binding peptides to carbon nanotubes to create new sensors and photodielectric materials. These studies are ongoing and use a new approach which we have developed by adding molecular evolution engineering to bio-fabrication—a combination of chemistry and biotechnology."

"The body of an organism consists of a wide variety of molecules. All of them are the result of the long process of evolution throughout the history of life, which spans more than three billion years. The essence of molecular evolution engineering is to accelerate molecular evolution *in vitro* and create a wide variety of molecules that do not exist in nature. It is a way to discover molecules with novel functions and molecules that bind specifically and selectively to desired substances," explains Ito.

There has been active research into molecular evolution engineering since the late twentieth century, but once again Ito is doing something unique. "In the conventional approach to molecular evolution engineering, new molecules have been created by introducing selected substances of biological origin. I want to establish a new approach that will create unique molecules by introducing artificial chemical substances and develop new functional materials."

Ito's group is currently screening a wide variety of molecules, created by introducing artificial chemical substances in this new approach, for new molecules that bind specifically to carbon nanotubes, and is also developing sensors and photodielectric materials with novel functions.

"I love the term 'molecular evolution engineering'. It conjures up visions of something great, doesn't it?" Ito looks happy. "I have long been troubled by the delay in yielding significant advancements due to operational complexity, but we are about to announce an achievement. Please wait just a little longer!" ■

ABOUT THE RESEARCHER

Yoshihiro Ito was born in Gifu, Japan, in 1959. He received his Bachelor's (1981) and Master's (1983) degrees in polymer chemistry at Kyoto University and was awarded a Doctorate in Engineering from the same university in 1987. Since then he has held a number of posts at various institutions including research fellow of the Japan Society for the Promotion of Science (1987), assistant (1988) and associate (1996) professor at Kyoto University, research fellow at the University of California, Irvine (1992–1993), professor of the University of Tokushima (1999), and Project Leader at the Kanagawa Academy of Science and Technology (2002). Now he is chief scientist and director of the Nano Medical Engineering Laboratory at the RIKEN Institute (from 2004). His research focuses on biomaterial science, regenerative medical engineering, combinatorial bioengineering for the creation of functional polymers, and soft nanotechnology.

MASAMICHI KAWASAKI

Manager
RIKEN Canteen
Tokyo Catering

Serving up a quality dining experience at RIKEN

What do you do at RIKEN?

Commissioned by the RIKEN Welfare Section, I have worked at the canteen since October 1996 and currently work as manager. Approximately 350 people use our canteen daily, including the lunch delivery service. Our food service is available throughout the day and our pub is open in the evenings three days a week. I contribute to RIKEN by ensuring that workers can relax during their breaks. My job is not just to provide meals, but also to maintain a high quality of food and a welcoming atmosphere.

Please tell us about how you manage the canteen.

As manager, my most important responsibility is to create a relaxing atmosphere; therefore, I pay attention to details and have implemented effective methods and policies. With so many people using our canteen every day, it is crucial that they are able to access fresh food as quickly as possible. To help our customers, I work to locate accessible food stations within the canteen. When diners come into the canteen I guide them to where they can find their food of choice and I carefully control the number of people in the hall so that there is no one waiting for seats, which could disturb the relaxing atmosphere.

How has the canteen changed in recent years?

In June 2012, the Welfare Section refurbished the canteen. This means that our canteen is more versatile, and we are now able to present food in more effective ways. The new counter table is the best option for those who visit the canteen on their own, while our terrace offers a great chance to dine *al fresco* in a relaxing natural setting.

How do you support people with different dietary requirements?

RIKEN has many workers with different religions and different dietary preferences. We offer vegetarian meals and other options for people with specific requirements. It may seem hard for non-Japanese people to understand what is available at the canteen due to the language barrier. However, once they visit us, they find our canteen has good options and start using our services regularly.

How does your service change during the day?

The work patterns of the staff at RIKEN are quite varied and this has an impact on the profile of visitors to the canteen throughout the day. For example, there tends to be more administrative staff using our facilities during lunch time, while more researchers, who often work until late, visit during the evening dinner time. We strive to ensure that no matter what their schedules, all of our diners can enjoy their meals in a relaxed and sociable atmosphere.

What do you enjoy about working at RIKEN?

I am proud that we have gained the trust of employees at RIKEN. I also enjoy getting feedback from visitors praising our attention to detail, including the queue management system as I mentioned earlier.

Serving food is not only about feeding people, but also providing visitors a relaxing and enjoyable experience with both delicious and nutritious meals. We will continue to contribute to the development of RIKEN by maximizing our strength in terms of good food and quality service.

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

The First Global Summit of Research Institute Leaders

Participants from research institutes around the world gathered in Kyoto, Japan on 6 October 2012 for the First Global Summit of Research Institute Leaders. The summit was held within the framework of the annual Science and Technology in Society (STS) Forum and was based on a proposal by STS Forum Chair, Koji Omi. Leaders from 16 organizations in 12 countries—Australia, France, Germany, Indonesia, Italy, Japan, Korea, Russia, Singapore, Thailand, Turkey, and the United States—joined the one-day event.

Co-chaired by RIKEN President Ryoji Noyori and Alain Fuchs, the president of the National Centre for Scientific Research (CNRS) in France, the summit began with presentations by participants who introduced their organizations and shared their ideas on how they could best contribute to the achievement of a sustainable society.

Following a brief congratulatory address by Koji Omi and a photo session, the participants discussed some of the common issues confronting research institutes around the world. Major topics of the summit included a discussion of 'brain drain', where skilled labor moves to other countries, versus 'brain circulation', a broader concept that looks at both the outflow and inflow of researchers from their home countries.

Leaders from 16 research institutes came together to discuss current issues facing the international research community.

RIKEN President Ryoji Noyori (1st row, 4th from left), CNRS President Alain Fuchs (1st row, 3rd from right), STS Forum Chair Koji Omi (1st row, 4th from right) and participants gathered for the First Global Summit of Research Institute Leaders in Kyoto, Japan.

Other issues discussed at the summit included the proper balance between basic and applied research, how to quantify the return from investments into R&D in order to justify funding for basic research, how to integrate researchers from different cultures into a single team, and the need for collaboration between research centers and universities in order to nurture new generations of researchers.

In closing, the participants agreed to a joint statement that called for enhanced international collaborations that transcend national and regional boundaries in order to address global concerns, such as changing population demographics, diminishing natural resources, and the spread of contagious diseases. The summit participants reaffirmed the role that basic science has played in history and called for the securing of scientific freedom, and concluded by agreeing to hold the summit on a yearly basis. The next summit is scheduled to be held in Kyoto on 5 October 2013, with the agenda focusing on specific topics of interest common to research institutions. ■

K computer opens for shared use

On 28 September 2012, the K computer—RIKEN's award-winning supercomputer based at the RIKEN Advanced Institute for Computational Science—was for the first time made available for shared use to members of academia and industry.

Jointly developed by RIKEN and Fujitsu since 2006, the K computer has collected top industry accolades in supercomputing performance including its No. 1 ranking both in June and November 2011 as the world's fastest supercomputer in the TOP500, a renowned international ranking of the most powerful computer systems. The K computer was also awarded top honors in the HPC Challenge and the Gordon Bell Prize, proof of its distinguished performance in real-world applications.

Proposals for using the K computer by researchers and industry bodies were evaluated by the Research Organization for Information Science and Technology (RIST), a non-profit public-service organization that promotes the development and utilization of computational science and technology to support a highly information-oriented society. On 3 September 2012, RIST announced the first selection of research proposals for 62 projects, including 29 general use projects, 8 young researcher projects and 25 industry-related projects, as well as selected projects for HPCI strategic programs.

In the coming years RIKEN and RIST in cooperation with users of the K computer will work together to translate the K computer's exceptional simulation precision and computational speed into world-class technological and research advancements. RIKEN will set about forging links between computational science and computer science fields and strive to provide a user-friendly computational environment for users of the K computer, while RIST will manage user support and program improvement. ■

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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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