RIKEN RESEARCH

AUGUST

2008 Volume 3 Number 8

Magnetic influences on quark pairs

www.rikenresearch.riken.jp

© 2008 RIKEN

Transfusable blood from a stem cell

A new technique for growing blood cells *in vitro* may reduce the need for blood donors

Researchers at the RIKEN BioResource Center in Tsukuba have established several cell lines that produce functional red blood cells (RBCs) from mouse embryonic stem cells[1]. The technique may pave the way for production of human donor red blood cells *in vitro*, lessening the need for blood donation.

According to team leader Yukio Nakamura, both embryonic and adult stem cells have been used in the past to establish red blood cell-like cell lines. But this is the first time, he says, that researchers have shown the feasibility of using stem-cell derived cell lines to efficiently produce red blood cells.

"To date, the use of hematopoietic cells produced *in vitro* has not proved practical for routine therapeutic applications," Nakamura says.

A step-wise approach

The researchers initially induced hematopoiesis—that is, differentiation from the stem cell into more mature blood and immune system cells—in mouse embryonic stem cells by culturing the stem cells on a layer of so-called feeder cells in the presence of several specific growth factors as well as the synthetic steroid drug dexamethasone.

Four consecutive phases of cell culture were used to induce differentiation (Fig. 1). Initially the cells were cultured on the feeder cells in the presence of vascular endothelial growth factor (VEGF) and insulin-like growth factor II (IGF-II). After four days the free-floating (or detached) cells were transferred to a new layer of feeder cells and cultured in the presence of a new set of growth factors including stem cell factor (SCF), erythropoietin (EPO) and interleukin-3 (IL-3). At this stage dexamethasone was also added to the culture.

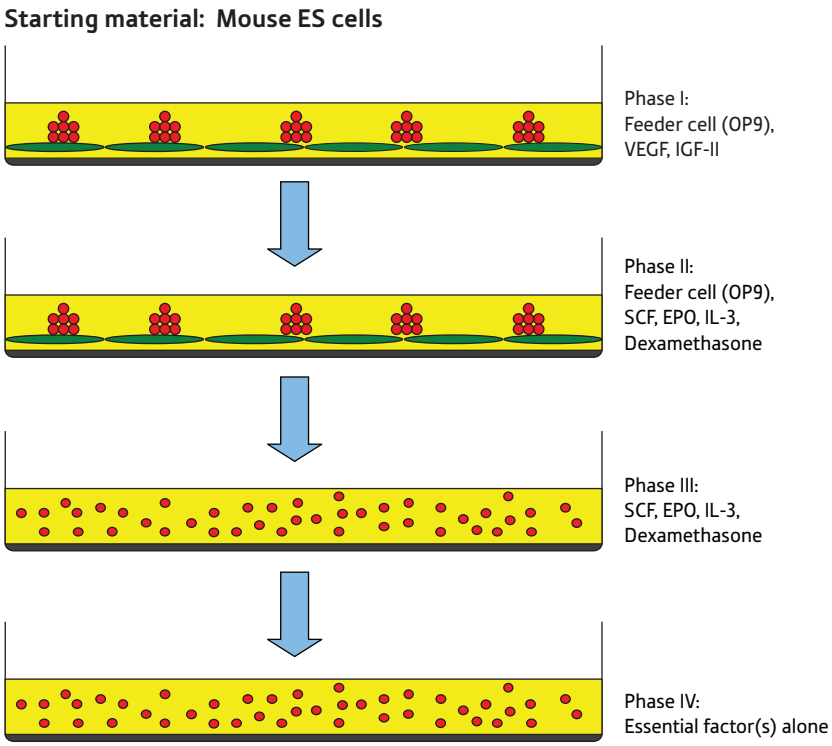


Figure 1: The four stages of cell culture required to generate red blood cell-producing cell lines from embryonic stem cells in mice. The green cells are feeder cells and the red cells are the embryonic stem cell-derived cell line.

This second phase of cell culture was maintained over a period of 60 days or more, at which point the researchers started to test the detached cells in the culture for the ability to grow in the absence of feeder cells. Once the cells were growing well in the absence of feeder cells, each cell line was tested to establish which cell growth factors were essential for continued growth.

The team reports they established a total of five cell lines by this method. Three cell lines exhibited characteristics of immature red blood cell, or progenitor erythroid, lineages. The other two lines exhibited the characteristics of mast cells, a type of immune system cell.

Cells function as expected

Analysis of the three erythroid cell lines demonstrated that the cells expressed genes specific for erythroid cells. Furthermore, the cells expressed α and β globin chains, which are only expressed by adult erythroid cells. But each cell line appeared to be at a slightly different stage of differentiation, demonstrating that the erythroid progenitor cells could be immortalized at different stages.

By altering the growth conditions, the team could induce each erythroid-like cell line to further differentiate *in vitro* producing more mature erythroid cells, including red blood cells (Fig. 2).

Next, the researchers examined the ability of the erythroid cell lines to

© 2008 RIKEN

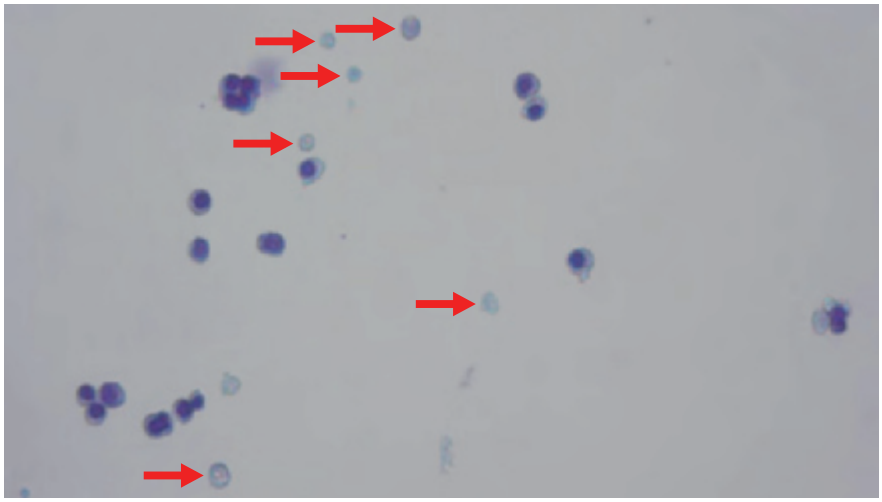


Figure 2: The erythroid cell line could be induced to further differentiate, generating mature red blood cells lacking nuclei (marked by arrows).

produce red blood cells *in vivo* in mice suffering from acute anemia. A subline of one of the erythroid cell lines was modified to express a green fluorescent protein marker and these cells were injected into the anemic mice. A transient proliferation of the marker-expressing cells was observed, but as differentiation of the cells occurred they lost the ability to express the marker making it more difficult to track the transplanted cells. However injection of the erythroid cell lines ameliorated the anemia, suggesting that differentiation of the injected cells occurred *in vivo* to produce red blood cells similar to those produced naturally by the host mouse.

Further investigation showed that the cell-line derived cells differentiated *in vivo* into much more mature lineages than seen *in vitro*.

Tumor-free transplants

The researchers also evaluated the potential for the cell lines to form tumors *in vivo* as some stem cell lines have been associated with tumorigenicity. The cell lines generated by the RIKEN group were shown to include some cells containing abnormal chromosomes, a common occurrence in long-term cell cultures. Mature red blood cells lack a nucleus, and hence lack DNA, so carry little risk of tumorigenesis, but the less mature cells produced by the cell line do contain DNA.

The team made two observations that imply that these cells are not tumorigenic. Cells expressing the fluorescent marker disappeared about 3 months after transplantation into the mice. And, no tumors were detected in other mice observed for a period of up to 6 months following transplantation with the cell lines. However, the researchers suggest that human cell lines generated for clinical use might need to be periodically recloned to maintain their genotype.

Future transfusions

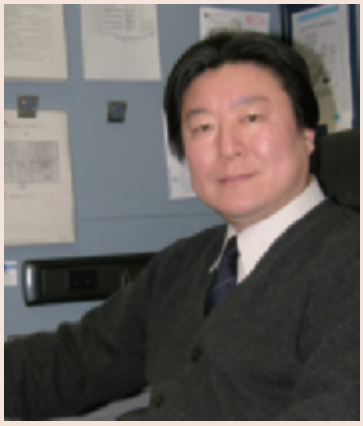
Nakamura says it should be possible to use the same method to produce human erythroid cell lines capable of producing red blood cells, platelets and other useful blood cells, which could reduce dependence on volunteer blood donations.

"There is little doubt that red blood cells, platelets, and neutrophils produced *in vitro* would be candidate materials to replace cells donated from such a large group of anonymous individuals," he says. ■

1. Hiroyama, T., Miharada, K., Sudo, K., Danjo, I., Aoki, N. & Nakamura, Y. Establishment of mouse embryonic stem cell-derived erythroid progenitor cell lines able to produce functional red blood cells. *PLoS ONE* [online] **3(2),** e1544 (2008) (doi:10.1371/journal.pone.0001544).

About the researcher

Yukio Nakamura was born in Nagano, Japan, in 1961. He graduated from the Niigata University (School of Medicine) in 1986, obtained his license as a medical doctor in 1986, and obtained his PhD in 1996 from Tsukuba University. After four years working as a medical doctor, he moved to RIKEN (Tsukuba Life Science Center) in 1990, where he started his career as a basic hematologist. He moved to Tsukuba University as an assistant professor in 1994 and then moved to the Walter and Eliza Hall Institute (Melbourne) as a visiting scientist. He was promoted to principal investigator of RIKEN in 2002 and then to division head of RIKEN in 2003. His research focuses on the establishment of useful cell lines and the *in vitro* production of blood cells that can be used in the clinic.



© 2008 RIKEN

The heart of the quark matter

The magnetic field may have a strong effect on the ground state of the matter in a neutron star

In a theoretical study on quarks investigating the ground state of matter at the extremely high densities found in neutron stars, physicists at Brookhaven National Laboratory (BNL), USA, have determined the importance of the magnetic field[1].

Quarks are usually found in groups of three, forming protons or neutrons—which in particle physics are known as baryons. However, when the density becomes high, it is more appropriate to describe quarks as forming a liquid. At extremely high densities, as present almost exclusively in neutron stars, quarks can pair and form a state known as color superconductivity (Fig. 1).

Analogous to carriers in solid-state superconductors, quarks form so-called Cooper pairs, and an amount of energy Δ is necessary to split the pair. But unlike carriers, there are several types of quarks, which are distinguished by two properties known as 'flavor' and 'color'. "Since there are nine quarks (three colors and flavors), there are many patterns of the Cooper pairing," says Kenji Fukushima of the RIKEN BNL Research Center. "Although we knew that the ground state is a color superconductor, we did not know which pairing pattern is the right one." The pairing strongly depends on factors including density, temperature, and external field.

Fukushima and his colleague, Harmen Warringa of BNL's physics department, estimated that the maximum magnetic field in a neutron star can reach 10^{18} gauss, which is enough to provide an energy comparable with the average Δ. "The effects of the density and temperature have been well investigated, but only little is known about the magnetic field, though the magnetic field exists in compact stars in general," says Fukushima.

Figure 1: A neutron star is possibly the only place in nature where color superconductivity can form.

The two scientists calculated the variation of three types of Δ—corresponding to different pairs of the up, down and strange quark flavors—with magnetic field. An important component of their calculations was that the system was electrically and color-neutral, which is realistic for a compact star. They found that all three types of Δ oscillate in a magnetic field, and for particularly high fields the color superconductor is formed only by down–strange pairs. "We found that the magnetic field has a significant effect on the ground state with neutrality imposed, which was surprising to us."

The results could also be important for predicting the life of magnetars, neutron stars with extremely powerful magnetic fields, as the oscillations in the Δ—due to a decaying magnetic field—could influence the cooling rate and therefore the time of their evolution. ■

1. Fukushima, K. & Warringa, H. Color superconducting matter in a magnetic field. *Physical Review Letters* **100**, 032008 (2008).

© 2008 RIKEN

Anti-matter of fact?

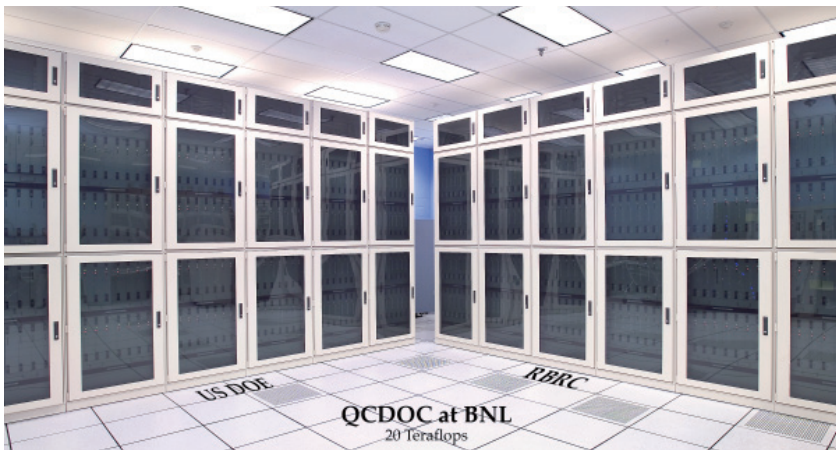
The theories that distinguish matter from anti-matter are surviving new tests in highly accurate supercomputer simulations

Very soon after the big bang our universe became dominated by matter rather than anti-matter, possibly because of small but crucial differences in the ways that matter and anti-matter behave. Scientists try to explain these differences using the Standard Model of Particle Physics which considers the interactions between quarks. Now Thomas Blum at the RIKEN-BNL Research Center in Upton, USA, and co-workers[1] have provided accurate new calculations linking quarks to anti-matter behavior.

The question being asked is: what happens to the fundamental forces of nature when we consider anti-matter instead of matter? The change does not affect the electromagnetic or strong nuclear forces, but alters the equations for the weak nuclear force. This anomaly was first discovered in 1964, and researchers eventually had to introduce new types of quarks to explain the effect[2], so that the current Standard Model requires six quark types in total.

Blum and co-workers studied the matter/anti-matter asymmetry in oscillations of a k-meson, or kaon, that are induced by the weak interaction. "The neutral kaons are made of 'down' and 'strange' quarks, which change into each other via the weak interaction," says Blum. "This leads to [kaon] oscillations. In other words, the weak interaction changes quark flavor, or type."

The researchers used supercomputers developed at Columbia University, RIKEN-BNL (Fig. 1) and the University of Edinburgh to simulate the kaon oscillations on a large lattice of points in space-time. To perform the calculations correctly, the researchers had to consider fermions—particles such as quarks or electrons—in an extra spatial dimension along with the three usual spatial dimensions and time. These 'domain-wall fermions' are confined to moving within the boundaries of a five-dimensional box.



Courtesy of Brookhaven National Laboratory

Figure 1: A photograph of the QCDOC supercomputer at Brookhaven National Laboratory that was used for the calculations.

"We don't know yet if nature really behaves this way," says Blum, "so for now we should think of domain-wall fermions as a very clever way to simulate four-dimensional … theories like QCD [Quantum Chromodynamics]." These techniques, combined with immense computing power, provide convincing evidence that the six-quark model correctly describes the differences between matter and anti-matter.

Blum looks forward to finding out whether new experiments such as the Large Hadron Collider opening this year at CERN in Switzerland could test his team's theories or even reveal new physics beyond the Standard Model. "It is crucial to have precise predictions [like ours] of the Standard Model, so we will know when nature tells us something new," he says. "That would be really exciting!" ■

1. Antonio, D.J., Boyle, P.A., Blum, T., Christ, N.H., Cohen, S.D., Dawson, C., Izubuchi, T., Kenway, R.D., Jung, C., Li., S., *et al.* Neutral-kaon mixing from (2 + 1)-flavor domain-wall QCD. *Physical Review Letters* **100,** 032001 (2008).
2. Kobayashi, M. & Maskawa, T. CP violation in the renormalizable theory of weak interaction. *Progress of Theoretical Physics* **49,** 652–657 (1973).

© 2008 RIKEN

Frustration yields results

Theoretical calculations elucidate the origin of unusual electronic behaviors recently observed in geometrically frustrated compounds

A study by researchers at the RIKEN Advanced Science Institute in Wako, in collaboration with scientists at the Universities of Tokyo and Kyoto, provides insight into the effects of geometrical frustration in strongly correlated electron systems[1].

Geometrical frustration occurs in materials in which the spatial arrangement of atoms creates ambiguity in the magnetic configuration that corresponds to the minimum energy, or ground state. For example, in a triangular lattice in which the magnetic moments, or dipoles, of the atoms are coupled antiferromagnetically—such that the spins of neighboring atoms point in opposite directions—there are two configurations that correspond to the same magnetic energy (Fig. 1).

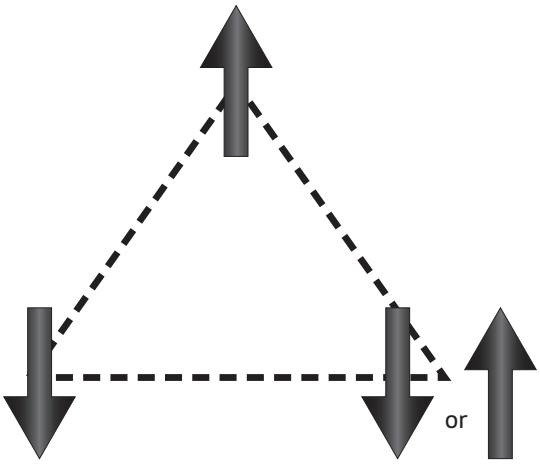


Figure 1: A classical example of geometrical frustration. Spins of neighboring atoms tend to point in opposite directions. This creates an ambiguity for the spin in the bottom right corner, which cannot point in the opposite direction of both its nearest neighbors.

Tsutomu Momoi of RIKEN and his colleagues focused on the effect of geometric frustration on the Mott transition, a phenomenon that occurs when metallic systems become insulators due to the strong repulsion between electrons. "Recent experiments on triangular lattice organic materials prompted us to consider the effect of magnetic frustration on this phase transition," says Momoi. Indeed, the organic material κ-(BEDT-TTF)$_2$Cu[N(CN)$_2$]Cl, which has an anisotropic triangular lattice, has recently been found to exhibit a so-called re-entrant Mott transition. In other words, by lowering the temperature the system changes from an insulator to a metal (as in a usual Mott transition), but becomes an insulator again at a lower temperature.

The researchers studied a generic triangular lattice with a Hubbard model—one of the most standard models used to describe metal–insulator transitions. For their calculations, they used an extension of the dynamical mean-field theory, which has already been used to explain Mott insulator transitions, but did not allow for re-entrant behavior.

The team's calculations have shown that a generic triangular lattice with a medium degree of anisotropy comparable to that of κ-(BEDT-TTF)$_2$Cu[N(CN)$_2$]Cl indeed exhibits re-entrant Mott insulator behavior.

The details of the theoretical study also suggest the mechanism behind the re-entrant behavior. "There are two energy scales in electron systems," explains Momoi. One comes from the electrical repulsion between electrons and the other from ordering of spin correlations. "In the frustrated systems, the second energy scale becomes very low, which makes two energy scales well separated in temperature and the reentrant behavior visible."

Because the results of the calculations are not specific to κ-(BEDT-TTF)$_2$Cu[N(CN)$_2$]Cl, it can be expected that the re-entrant behavior will also be observed in other geometrically frustrated systems. ■

1. Ohashi, T., Momoi, T., Tsunetsugu, H. & Kawakami, N. Finite temperature Mott transition in Hubbard model on anisotropic triangular lattice. *Physical Review Letters* **100**, 076402 (2008).

© 2008 RIKEN

Keeping cool for quantum clarity

A new theoretical method of cooling quantum computing components to provide clearer signals

Exploiting some of the bizarre features of the quantum world to process information could lead to computers much faster than current ones. The technology relies on scientists being able to clearly realize one unit of quantum information, known as a qubit, which can be encoded in 'artificial atoms' made from superconductors. Now researchers from the RIKEN Advanced Science Institute (formerly the Frontier Research System) in Wako have proposed a method to improve the coherence of a superconducting qubit by simultaneously cooling the qubit and its surroundings[1].

Conventional technologies can lower the temperature of a nanoscale device to a few hundredths of a degree above absolute zero. However this temperature is still not quite low enough for some quantum devices that require extremely quiet environments free from thermal agitations.

Recently scientists in the US[2] managed to lower the temperature of a superconducting qubit to two orders of magnitude lower than its surroundings. Their method involves cooling the qubit by transferring it between energy states.

"Thermal noise moves the system from its lowest-energy state to a higher-energy state. Then, additional energy (via microwaves) is added to drive the system to an even higher-energy state," explains Franco Nori of RIKEN and the University of Michigan, USA. "The higher-energy state is unstable, and allows the system to quickly decay to its lowest energy state; therefore lowering its energy and thus 'cooling' the qubit" (Fig. 1).

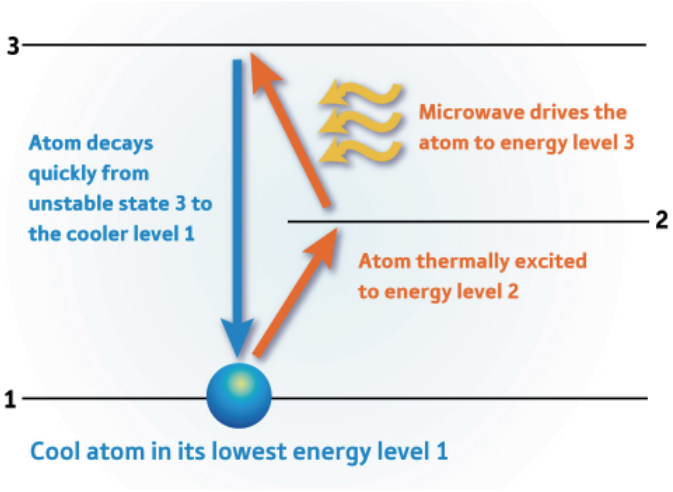


Figure 1: Cooling of an 'artificial atom'.

"The only problem with this method is that, while the superconducting qubit is greatly cooled, the noise sources surrounding the qubit are not, so the qubit will quickly warm up again," explains RIKEN visiting scientist Jianqiang You, also with Fudan University, Shanghai, China. "The new challenge is to maintain the qubit in the cooled state."

The proposed method also considers a tunable qubit that, for some time in each cooling cycle, resonantly interacts with the noise sources surrounding the qubit. Thereafter, both the qubit and its neighboring noise sources can be cooled simultaneously. This will significantly enhance the quantum coherence of the qubit because it will take a relatively long time for the cooled qubit to be thermally activated again.

In practice, there are different types of quantum noise. The team's theory gives similar results for two different noise sources, implying that the cooling could be robust and effective in many surrounding environments. The technique could be applied for cooling mechanical resonators at the nanoscale, providing opportunities to observe the transition between classical and quantum resonant behavior. ■

1. You, J.Q., Liu, Y.-X. & Nori, F. Simultaneous cooling of an artificial atom and its neighboring quantum system. *Physical Review Letters* **100**, 047001 (2008).
2. Valenzuela, S.O., Oliver, W.D., Berns, D. M., Berggren, K.K., Levitov, L.S. & Orlando, T.P. Microwave-induced cooling of a superconducting qubit. *Science* **314**, 1589–1550 (2006).

© 2008 RIKEN

Cold copper stops the spin

The performance of spintronic devices depends on several temperature-dependent scattering mechanisms

In the future, many electronic systems could be replaced by spintronic devices, which communicate information via the intrinsic angular momentum, or spin, of electrons. Now researchers at the RIKEN Advanced Science Institute (formerly the Frontier Research System) in Wako and the University of Tokyo have completed an important study into the effects that temperature can have on spintronic devices[1].

Spintronics relies on the effective transport of 'spin-polarized' currents, in which electrons all have the same spin. Spin-polarized currents flow well in magnetic materials, but when they enter non-magnetic materials the electrons begin to lose their spin polarization in a process called spin-flip scattering (Fig. 1). The length scale over which the electrons remain polarized, called the spin diffusion length, is particularly important for fabricating devices.

Spin-flip scattering is known to occur in two different ways. At high temperatures, most of the scattering is caused by electrons interacting with 'waves of heat' called phonons. Otherwise scattering is caused by impurities, defects and boundaries in the material.

To investigate the effects of temperature on spin-flip scattering, the researchers fabricated a 'lateral spin valve' consisting of two magnetic electrodes that inject a spin-polarized current through a copper wire. The distance between electrodes was altered in order to observe the spin diffusion length of the copper at different temperatures.

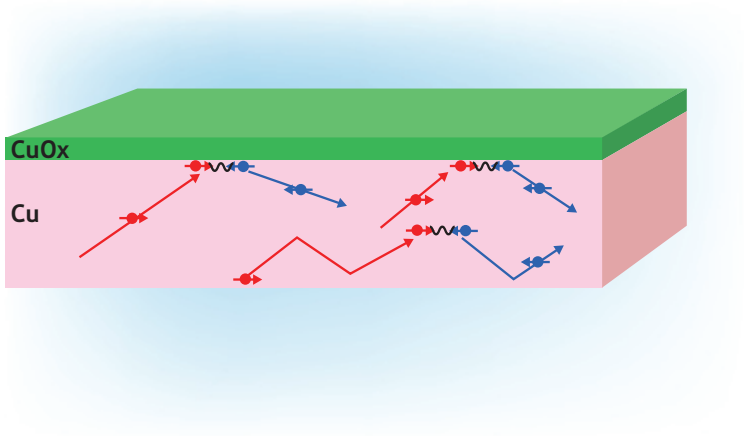


Figure 1: Electron scatterings inside copper (Cu) sometimes flip the spin directions. On the other hand, scatterings at the boundary between Cu and copper oxide (CuOx) flip the spin every time.

The researchers found that the spin diffusion length of the copper increased as temperature was decreased. This was expected, because the phonon scattering decreases with temperature. However, there was an unexpected maximum at around 30 K (-243.15 °C), below which the spin diffusion length decreased again.

The researchers explained this effect by considering the wire surfaces, which are oxidized by the surrounding air and cause strong spin-flip scattering. At very low temperatures, the polarized electrons travel further on average, so they are more likely to collide with the wire surfaces. This explanation was verified by tests with different thicknesses of wire, showing that thinner wires with greater surface-area-to-volume ratio experience a greater level of scattering at low temperatures.

In very small devices, the scattering by oxidized copper surfaces could cause problems for real, room-temperature applications. RIKEN team-member Takashi Kimura suggests making use of aluminum, which reflects electrons rather than scattering them.

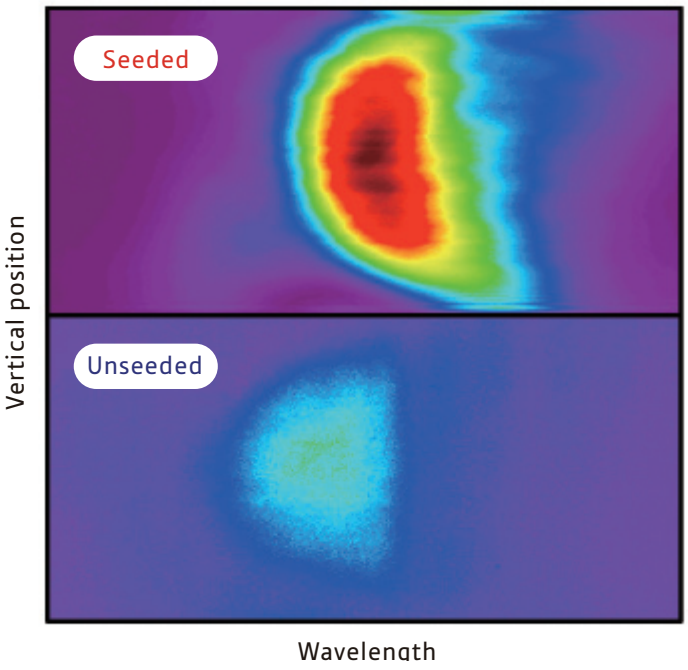
"We did not observe the spin signal maximum at low temperature in an aluminum lateral spin valve," he explains. "Therefore, if we use an aluminum capping layer on top of the copper wire, it may prevent the present problem." ■

1. Kimura, T., Sato, T. & Otani, Y. Temperature evolution of spin relaxation in a NiFe/Cu lateral spin valve. *Physical Review Letters* **100,** 066602 (2008).

© 2008 RIKEN

Sowing the seeds for improved lasers

The use of seed lasers significantly improves the emission characteristics of free-electron lasers



Modified from Ref. 1 © 2008 Nature Publishing Group

Figure 1: Comparison between seeded (top) and unseeded (bottom) FEL emission at a wavelength of 160 nm. The seeded FEL beam shows a much higher intensity and better beam profile. The slight distortion of the beams is an experimental artifact.

Free-electron lasers (FEL), where high-density electrons are accelerated so that they emit intense laser radiation in the so-called vacuum ultraviolet (VUV) and x-ray part of the spectrum, are an invaluable tool for materials research and the characterization of biological samples. Researchers from RIKEN's SPring-8 Center in Harima, in collaboration with scientists from the French technological research agency CEA and Synchrotron SOLEIL in Saclay, have now developed a method that enhances the coherence of the radiation generated by the FEL and thereby allows for the realization of powerful lasers.

In an FEL, the electrons follow a wiggling path in so-called undulators, analogous to a skier racing around slalom poles. This process creates strong light emission. To achieve lasing, the emission process needs to occur in a coordinated manner, a requirement that necessitates a long wiggling path where the laser action is slowly built up. However, owing to a lack of suitable materials for these short wavelengths, the FEL has no mirrors between which the light oscillates back and forth. Therefore, unlike conventional lasers, the light emitted is not synchronized by the repeated reflections from the mirrors and shows little temporal coherence. To compensate for this deficiency and achieve full temporal coherence, physicists have proposed feeding in an external 'seed' laser beam of the same frequency to the FEL. Furthermore, the seed would shorten the length of the wiggling path, resulting in a compact facility.

Reporting in the journal *Nature Physics*[1], the researchers demonstrate the realization of this concept. "This is the first time that this experiment has been done in a short-wavelength FEL," explains Toru Hara from the team. Indeed, impressive improvements in laser intensity of three orders of magnitude have been achieved (Fig. 1), whilst the laser spectra are now much more stable.

In the present study, the fundamental wavelength is 160 nm but the researchers have already demonstrated FEL laser output at wavelengths as short as 32 nm. Indeed, Hara explains that "in principle, this method can be extended down to wavelengths around 10 nm"—close to the important region of 2–3 nm, where water is transparent. This is particularly advantageous to biological studies as the laser can penetrate much farther into tissue. However, new seeding schemes may be required to produce these shorter wavelengths. Nevertheless, the improvements in light characteristics, such as temporal coherence, already offer significant advantages to researchers using free electron lasers in their work. ■

1. Lambert, G., Hara, T., Garzella, D., Tanikawa, T., Labat, M., Carre, B., Kitamura, H. Shintake, T., Bougeard, M., Inoue, S., *et al.* Injection of harmonics generated in a gas in a free-electron laser providing intense and coherent extreme-ultraviolet light. *Nature Physics* **4**, 296–300 (2008).

© 2008 RIKEN

A breath of fresh air for electronics

Oxygen significantly influences the electronic properties of an important material proposed for use in new electronic devices

In the emerging field of oxide electronics, electronic devices are based on oxide materials rather than conventional materials such as silicon. One of the most promising candidates for this application is the oxide semiconductor strontium titanate, $SrTiO_3$. Now, researchers from RIKEN's SPring-8 Center in Harima and their colleagues have uncovered fundamental properties of the electronic states in $SrTiO_3$ that may be crucial to understanding the unusual electronic properties of this material.

The strength of $SrTiO_3$'s candidacy in oxide electronics is its versatility: it can be integrated with a number of related oxide materials to form complex electronic devices. "[In] particular, the interface between layers of $SrTiO_3$ and other oxide materials has shown some novel properties, such as magnetism and superconductivity, whose precise origins are still under debate," comments team-member Yukiaki Ishida. These properties are attributed to the way the material reacts to impurities that are intentionally introduced to provide a surplus of electrons.

Writing in the journal *Physical Review Letters*[1], the researchers have uncovered the nature of the electronic states of $SrTiO_3$. Unlike regular semiconductors, where all surplus electrons contribute to conductivity and fill the electronic states of the so-called conduction band, some of the electrons in $SrTiO_3$ are not free to conduct and instead form localized electronic states within the band gap (Fig. 1).

To investigate the origin of these so-called in-gap states, the team used x-rays from the SPring-8 synchrotron to force electrons out of $SrTiO_3$ and measured their properties. Through fine-tuning of the x-ray energy, this emission is selective to a particular type of atoms, allowing for an unambiguous determination of the different atoms' contribution to the electronic states.

Indeed, significant differences were observed between the electrons in the conduction band and those from the in-gap states. The electrons in the conduction band predominantly originate from Ti atoms, whereas those in the gap consist of electronic contributions from Ti as well as O atoms. In effect, the electrons from the oxygen 'screen' those from Ti, lowering their energy to below that of valence band electrons.

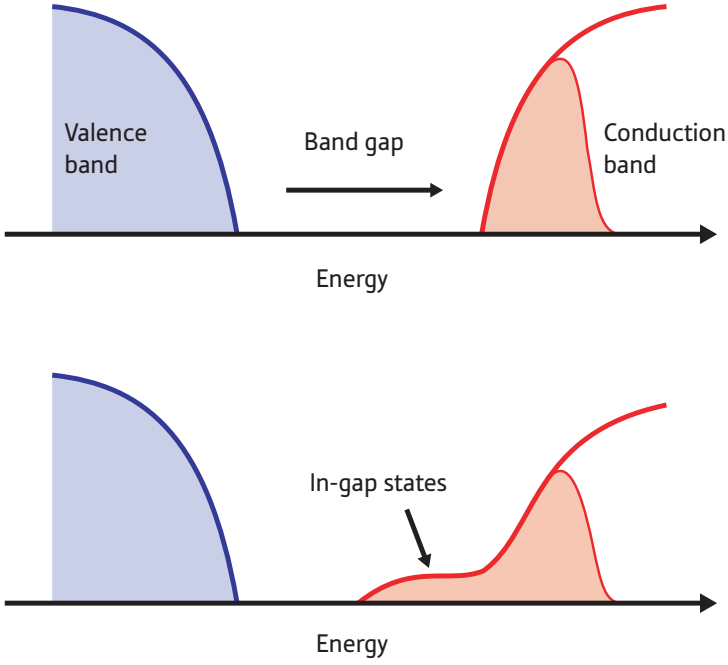


Figure 1: Electrons in $SrTiO_3$. In regular semiconductors, excess electrons fill the conduction band (top; red shaded region). In $SrTiO_3$, owing to an interplay between the electronic states of oxygen and titanium atoms, unusual electronic states form within the band gap region (bottom).

Modified with permission from Ref. 1 © 2008 by the American Physical Society

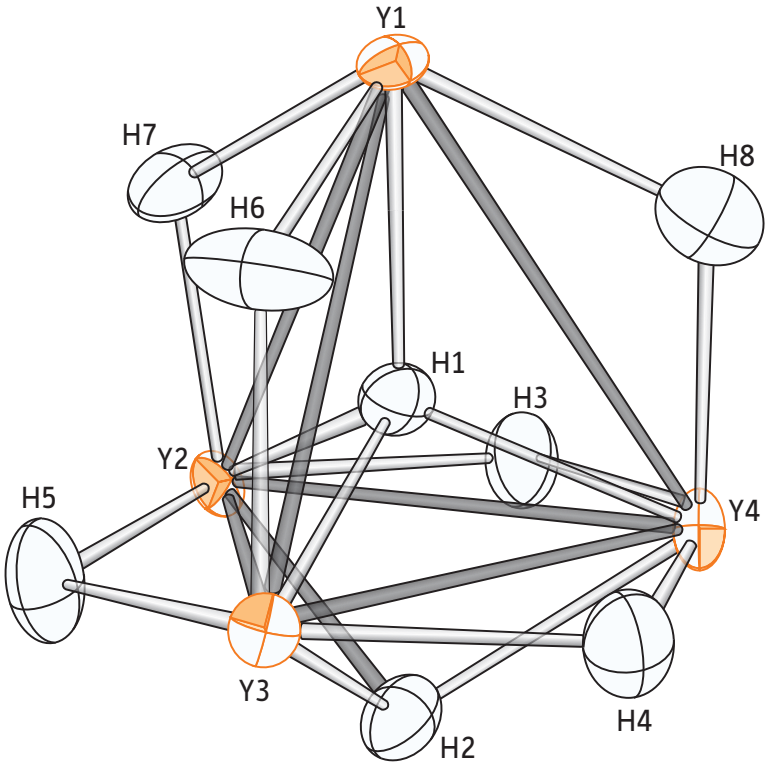
As Ishida asserts, this result is significant, as "previously the oxygen states were expected to play no role in the energetic states of $SrTiO_3$, and people looked only at titanium." The influence of oxygen on the electrons in $SrTiO_3$ may explain some of the unusual properties of $SrTiO_3$ so may lead to better control over these properties for enhanced oxide-electronic devices, for example in non-volatile information storage. ■

1. Ishida, Y., Eguchi, R., Matsunami, M., Horiba, K., Taguchi, M., Chainani, A., Senba, Y., Ohashi, H., Ohta, H. & Shin, S. Coherent and incoherent excitations of electron-doped $SrTiO_3$. *Physical Review Letters* **100**, 056401 (2008).

© 2008 RIKEN

Hydrogen atom trapped in unique cage

Unusual compound sees hydrogen bonded to four metal atoms



Reproduced with permission from Ref. 2 © 2008 American Chemical Society

Figure 1: The hydrogen atom (H1) nestles perfectly between four yttrium atoms (orange) in the unusual organometallic compound.

RIKEN scientists, along with an international team of co-workers based in the US, UK and France, have spotted a hydrogen atom simultaneously bonding to four metal atoms, a highly unusual arrangement in this particular class of chemical compounds. The research may help to understand the structure of materials that could store hydrogen more efficiently.

Hydrogen normally prefers to bond with just one other atom. However, it can be persuaded into polygamy by surrounding it with metal atoms that form a cage-like cluster.

Certain compounds of uranium or thorium are already known to host four-coordinate hydrogen atoms. But these compounds' structures and properties are usually difficult to control or modify.

Conversely, the behavior of organometallic compounds—which possess organic (carbon-based) molecules as supporting groups around the metal atoms—can be easily controlled by changing the organic groups, allowing the compound's properties to be fine-tuned.

Zhaomin Hou and colleagues from RIKEN's Advanced Science Institute in Wako had previously prepared a series of organometallic compounds containing four metal atoms with eight hydrogen atoms and studied their structures by x-ray diffraction experiments[1].

Now, in collaboration with the international team of co-workers, Hou and colleagues have studied a compound based on the metal yttrium using neutron diffraction[2], a more precise technique which fires a stream of the neutral particles through a crystal of the compound and uses their subsequent trajectory to calculate the precise arrangement of atoms (Fig. 1). Two crystals, both smaller than the head of a match, were analyzed at facilities in the UK and France.

The team found that hydrogen atoms in different parts of the same compound display a range of three different bonding modes—hooking up with either two, three or four other atoms. The distance between the four-coordinate hydrogen atom and its yttrium neighbors is also surprisingly small: strong evidence that hydrogen fits tightly into the cage made by the four metal atoms.

Hou says that "studies like this will increase our understanding and appreciation of the element hydrogen and its chemistry." But it may also have practical applications. "The increasing interest in hydrogen as a fuel warrants careful studies into the structural chemistry of this most ubiquitous element," he says, adding that there are very few high-precision studies on compounds containing multiply bonded hydrogen.

The team is now studying similar compounds containing two or more different types of metals, which are expected to have unique structures and properties of their own. ■

1. Hou, Z., Nishiura, M. & Shima, T. Synthesis and reactions of polynuclear polyhydrido rare earth metal complexes containing "$(C_5Me_4SiMe_3)LnH_2$" units: A new frontier in rare earth metal hydride chemistry. *European Journal of Inorganic Chemistry* **18,** 2535–2545 (2007).
2. Yousufuddin, M., Gutmann, M.J., Baldamus, J., Tardif, O., Hou, Z., Mason, S.A., McIntyre, G.J. & Bau, R. Neutron diffraction studies on a 4-coordinate hydrogen atom in an yttrium cluster. *Journal of the American Chemical Society* **130,** 3888–3891 (2008).

© 2008 RIKEN

Working well in a crowded cell

Understanding how glycoproteins are processed in cells may help scientists develop therapies for specific disorders

Cells within the body are packed with many different molecules. Many of these molecules play important biological roles. Glycoproteins—proteins that have short sugar chains attached to them—play crucial roles in protein folding, transport and subsequent degradation. Diseases can result when these roles are disrupted; consequently a full appreciation of their function could lead to medical advances.

Now, Yukishige Ito, Kiichiro Totani from the RIKEN Advanced Science Institute (formerly the Discovery Research Institute), Wako, and colleagues have analyzed three key enzymes involved in the processing of glycoproteins under conditions that mimic the crowded environment inside cells[1]. Although much research has been performed in this area, in most cases, the natural glycoproteins used are not homogenous, says Ito. "In addition, these studies have been conducted in dilute buffer solutions, the environment of which is quite different from that of the inside of living cells."

The team synthesized a series of glycoprotein sugar chains and studied their reactions as a single entity and bound to additional proteins. Three enzymatic reactions—using glucosidase, glucosyltransferase and mannosidase—were considered under cell-like conditions (Fig. 1). These reactions were compared to similar reactions under standard laboratory dilute conditions.

Surprisingly, the team found that the behavior of certain enzymatic reactions was significantly different under cell-like conditions compared to standard conditions. In particular, when glucosidase was used, the rate at which a specific part of the glycoprotein was trimmed (step 2 of Fig. 1) dramatically accelerated in the cell-like conditions.

When trying to understand how cells work closely matching in-cell conditions is very important. The team achieved this by using various biomacromolecules to crowd the reaction solutions. When they used bovine serum albumin—a protein commonly used in biochemical studies—the trimming rate was greatly enhanced. Similar effects were observed when they used ribonuclease A—another cell enzyme—and high molecular-weight polyethylene glycol. The effects seen are likely the result of conformational changes of the enzymes.

Overall, these latest results of the team have provided a valuable insight into how environment can dramatically alter the way reactions take place and emphasizes the need to mimic real conditions of the cell. Even though this study has taken five years so far, Ito is keen to continue the work. The next step, he says, is to try and prove the biological significance of the current work by studying a wider range of reactions under conditions similar to real cells. ■

1. Totani K., Ihara Y., Matsuo I., & Ito Y. Effects of macromolecular crowding on glycoprotein processing enzymes. *Journal of the American Chemical Society* **130,** 2101–2107 (2008).

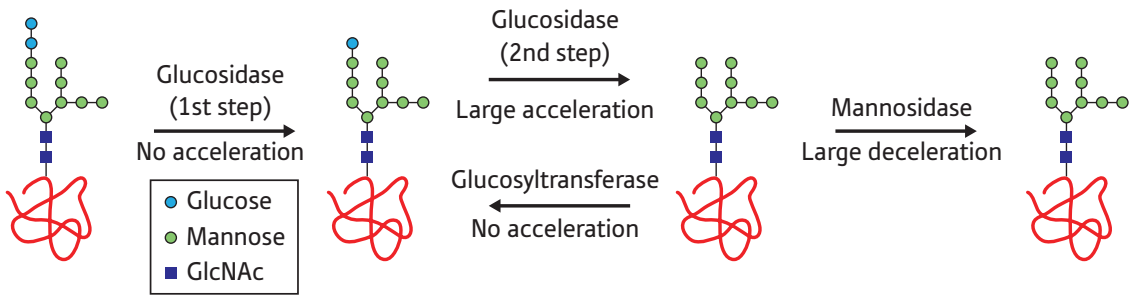


Figure 1: An illustration of the effects of cell-like conditions on glycoprotein processing reactions catalyzed by three enzymes: glucosidase, glucosyltransferase and mannosidase (GlcNAc, *N*-Acetyl-D-glucosamine).

Reproduced in part with permission from Ref.1 © 2008 American Chemical Society

© 2008 RIKEN

Keeping everything in order

Investigators may have uncovered a molecular 'switch' that ensures that processes relating to cell division occur in the proper sequence

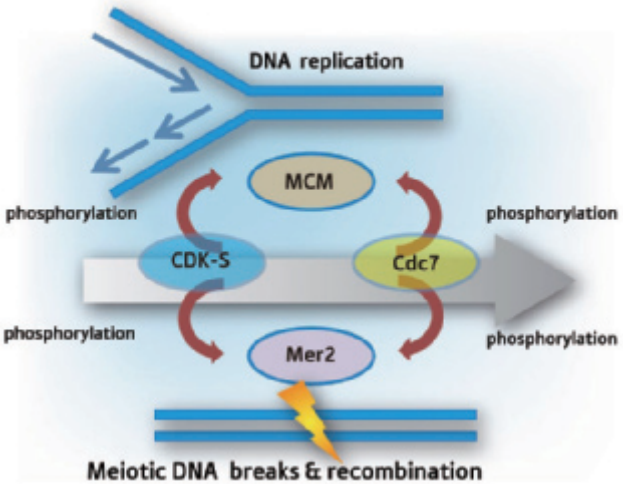


Figure 1: The protein kinases CDK-S and Cdc7 play an important role in regulating two key steps in meiotic cell division, mediating DNA replication through the phosphorylation of the MCM proteins, and controlling DSB formation and chromosomal recombination via phosphorylation of Mer2.

Meiosis is a complex multi-step process by which certain cells divide to yield specialized cells called gametes, which contain half the normal cellular complement of genetic material and act as the vehicles for sexual reproduction.

Prior to division, the chromosomes replicate and align in sets. At this stage, sister chromosomes will occasionally swap segments, a process called recombination that introduces an additional measure of genetic diversity prior to cell division. Recombination requires the introduction of double-stranded breaks (DSBs) in the DNA, a tightly regulated process mediated by a handful of specialized proteins.

Previous research in yeast has demonstrated that the protein kinase Cdc7/Hsk1, an important factor in DNA replication, is also involved in DSB formation[1]. Now, one author from this study, Kunihiro Ohta of the RIKEN Advanced Science Institute (formerly the Discovery Research Institute) in Wako, has followed up with a study that explores more closely the mechanism of Cdc7's involvement in this process[2].

Ohta's team worked with a mutant strain of the yeast species *Saccharomyces cerevisiae* in which Cdc7 expression is eliminated, but DNA replication is not affected. They observed a complete absence of meiotic DSBs in this strain, as well as altered expression in genes known to act in the middle and late stages of meiosis.

One component of the DSB formation complex, Mer2, is known to be phosphorylated by CDK, another cell-cycle-associated protein kinase. Based on this information, Ohta and colleagues investigated whether Cdc7 also phosphorylates Mer2, and identified several Cdc7-specific phosphorylation sites.

These modifications appear to be essential triggers for recombination, and yeast strains expressing Mer2 variants in which these phosphorylation sites had been eliminated exhibited defects in meiotic division and reduced spore viability. DSB formation and recombination were both sharply reduced in these mutant strains.

These findings are a valuable step toward understanding the regulatory mechanisms that ensure that the various steps of meiotic division occur in the proper sequence. "Many researchers have thought replication and recombination are tightly coupled in meiosis—our results suggest a molecular mechanism for such linkage via a master regulator," explains Ohta. In such a scenario, the Mer2 phosphorylation by Cdc7 and CDK would act as a switch, establishing a state in which DSB formation and recombination can take place once DNA replication is complete (Fig. 1).

Ohta's team is now investigating the details of this phosphorylation, and attempting to clarify the specific events in early meiosis that trigger CDK- and Cdc7-mediated activation of Mer2. ■

1. Ogino, K., Hirota, K., Matsumoto, S., Takeda, T., Ohta, K., Arai, K. & Masai, H. Hsk1 kinase is required for induction of meiotic dsDNA breaks without involving checkpoint kinases in fission yeast. *Proceedings of the National Academy of Sciences USA* **103,** 8131–8136 (2006).
2. Sasanuma, H., Hirota, K., Fukuda, T., Kakusho, N., Kugou, K., Kawasaki, Y., Shibata, T., Masai, H. & Ohta, K. Cdc7-dependent phosphorylation of Mer2 facilitates initiation of yeast meiotic recombination. *Genes & Development* **22,** 398–410 (2008).

© 2008 RIKEN

New potential to curb a neurodegenerative disease

Researchers pinpoint viable cellular targets for therapies to slow the progression of amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) is a neurodegenerative disease marked by a progressive, and eventually fatal, loss of motor neurons. Familial forms of the disease are associated with dominant mutations in the gene for the protein superoxide dismutase (SOD1). These mutations result in misfolding and aggregation of SOD1. The misfolded protein, in turn, causes motor neuron toxicity, though the mechanism for this effect is unknown.

ALS has been modeled in the mouse by expressing *SOD1* harboring a human mutation. However, it was not clear whether mutant SOD1 expression in non-neuronal cells in the central nervous system also plays a role in ALS; namely, in microglia, resident immune cells responsible for neuro-inflammation, and in astrocytes, a supporting cell type that plays a principal role in brain repair (Fig. 1).

To address this question, Koji Yamanaka at the RIKEN Brain Science Institute in Wako, along with colleagues in Japan and the United States, developed a new mouse model of ALS that expresses a mutant version of the human *SOD1* gene, but in such a way that the human gene can be deleted in specific cell types at will. When the team deleted the mutant human *SOD1* in motor neurons, a delay in disease onset was observed[1]; whereas, deletion in either microglia[1] or in astrocytes[2] did not delay the onset but it did slow the rate of progression. Thus, as compared to controls, the ALS mice with deletion of the human mutation in microglia survived for an average of 99 days longer, while mice with the deletion in astrocytes survived for an average of 60 days longer.

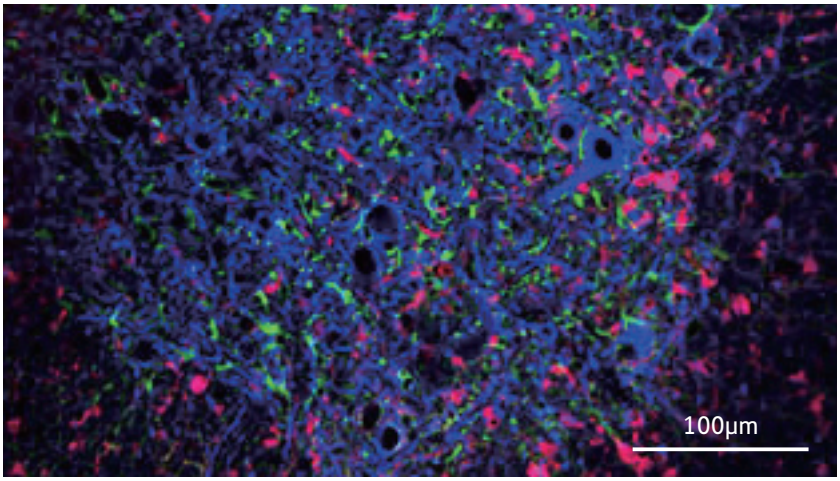


Figure 1: Labeled neuronal (blue), microglial (red), and astrocytic (green) cells in a spinal cord lesion of a mouse with ALS.

Modified from Ref. 2 © 2008 Nature Publishing Group

The team's findings suggest that onset of disease is due to motor neuron damage, but this damage in turn leads to a strong inflammation response by the microglia that further exacerbates the disease process. However, the team has found that mutant *SOD1* damage in the astrocytes resulted in more of the microglial-derived inflammation, which may then damage the motor neurons further and thus astrocytes also play a role in late disease progression.

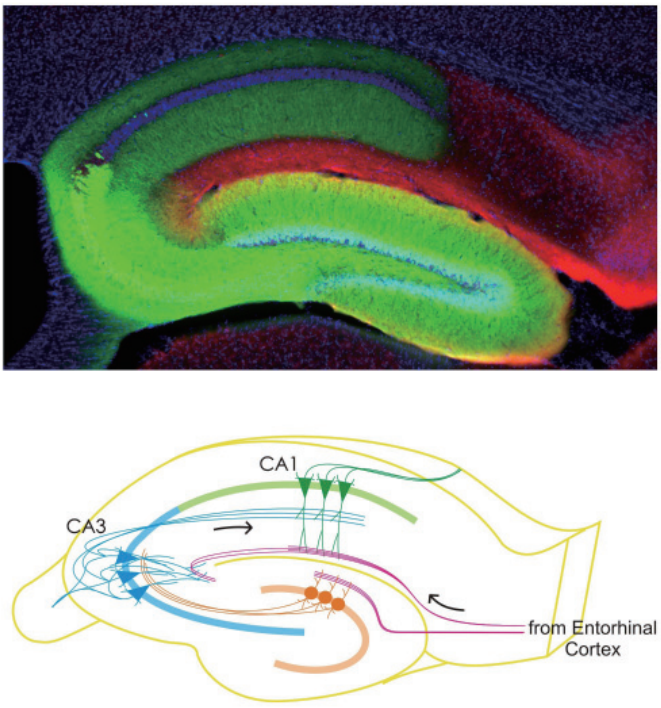
How the mutant astrocytes are affecting the neuro-inflammation response of the mutant microglia, however, remains unclear. Yamanaka plans to uncover this mechanism in a future study. And once identified he hopes that "the information could help target a therapy that can halt the inflammation response mediated by the astrocytes and microglia." This would ameliorate ALS by slowing disease progression, even if disease onset due to motor neuron dysfunction is not preventable, he says. ■

1. Boillée, S., Yamanaka, K., Lobsiger, C.S., Copeland, N.G., Jenkins, N.A., Kassiotis, G., Kollias, G. & Cleveland, D.W. Onset and progression in inherited ALS determined by motor neurons and microglia. *Science* **312,** 1389–1392 (2006).
2. Yamanaka, K., Chun, S.J., Boillée, S., Fujimori-Tonou, N., Yamashita, H., Gutmann, D.H., Takahashi, R., Misawa, H. & Cleveland, D.W. Astrocytes as determinants of disease progression in inherited amyotrophic lateral sclerosis. *Nature Neuroscience* **11,** 251–253 (2008).

© 2008 RIKEN

Longer circuit fast-tracks memory

A new way of blocking nerve transmissions allows more sophisticated studies of how the brain functions



From Ref. 1. Reprinted with permission from AAAS

Figure 1: An example of the DICE-K method used to interrupt the tri-synaptic pathway. In this slice through the mouse hippocampus, nerve transmission is blocked in the area stained green.

RIKEN researchers working in the US with American colleagues have developed a technique for switching individual nerve circuits on and off, and employed it to determine the role of an important pathway used in forming memories. In specially bred mice, the international research team found the tri-synaptic pathway (TSP) in the hippocampal region of the brain is integral to rapid formation of functional memory, but not necessary for incremental learning. Decline of the TSP is thought to be associated with ageing and neurodegenerative conditions such as Alzheimer's disease.

The TSP is one of two parallel nerve circuits known to be involved in learning and memory. It carries information from the entorhinal cortex (EC) through the three major processing regions of the hippocampus—the dentate gyrus, CA3 and CA1—before returning to the EC (Fig. 1). The other circuit, the monosynaptic pathway (MSP), simply takes information from the EC to the CA1 and back again. Previously, researchers studied what happened when cells in each of these regions are destroyed, and when specific nerve receptors are blocked. But these methods can only provide partial understanding of the role of each pathway.

In a recent paper in *Science*[1], the team of researchers from the RIKEN-MIT Neuroscience Research Center in Cambridge, Massachusetts, led by Susumu Tonegawa, outlines how they developed a technique to block and unblock the transmission of impulses across a specific nerve junction in the TSP by controlling the expression of the tetanus toxin gene using the antibiotic doxycycline. The team then used its technique—named DICE-K after a Japanese major league baseball pitcher—to study the ability of mice with or without a functional TSP to perform tasks involving different types of learning and memory.

The researchers found that the MSP alone is sufficient for the incremental acquisition and recall of spatial learning and memory associated with the Morris water maze, where over repeated trials mice learn to associate the position of an escape platform hidden underwater with landmarks placed outside the tank. But the TSP is crucial to the more sophisticated acquisition of memory in tasks where rapid learning is required—in novel environments, for instance.

"Using this technology, we can shut down communication between nerve cells whenever we want, during or after memory acquisition," says team member Toshiaki Nakashiba. "We can also apply it to circuits other than the TSP. It provides a level of experimental accuracy never achieved before." ■

1. Nakashiba, T., Young, J.Z., McHugh, T.J., Buhl, D.L. & Tonegawa, S. Transgenic inhibition of synaptic transmission reveals role of CA3 output in hippocampal learning. *Science* **319**, 1260–1264 (2008).

© 2008 RIKEN

Huntington's researchers chase a new lead

Study implicates the transcription factor for a key heat shock protein

wikipedia / Library of Congress Prints and Photographs

Figure 1: Huntington's disease affected the health and behavior of the celebrated American folk singer and philosopher, Woody Guthrie, whose son later founded a major charity to combat the disease.

RIKEN researchers have come up with a novel mechanism to explain the onset of Huntington's disease. They have found that mice carrying the mutation that leads to the degenerative nerve condition also have lower levels of the transcription factor known as nuclear factor Y (NF-Y). This transcription factor regulates the production of heat shock proteins (HSPs) 70 and 40 which control the folding, unfolding and assembling of proteins critical to proper nerve cell function. The researchers believe their work could lead to new treatments for the disease which involve boosting NF-Y.

Huntington's disease typically leads to abnormal body movements and affects behavior and mental abilities sometime after the age of 40 (Fig. 1). The direct cause—a mutation in the Huntingtin gene—has been known for about 15 years, but not how it leads to the observed degeneration of nerves in specific regions of the brain. What is known, however, is that protein made from the mutant gene forms aggregates in nerve cells and they subsequently degenerate. The aggregation process can be suppressed by heat shock proteins. Recent studies have shown that transcription factors are incorporated into the aggregates thus affecting the activity of the genes they control.

In a paper in *The EMBO Journal*[1], the researchers from RIKEN's Brain Science Institute in Wako detail their discovery that the transcription factor for HSP70 is among those caught up in the mutant Huntingtin aggregates. This leads to low levels of HSP70 which could not only affect the folding and assembly of a great many proteins, but could also decrease the suppression of aggregate formation.

The researchers initially discovered components of NF-Y in mutant Huntingtin aggregates using mass spectrometry. They then confirmed presence of the NF-Y components by tagging them. They subsequently found the same NF-Y components in aggregates in the brains of model mice with Huntington's disease, and showed that this was associated with decreased activity of the genes for making the heat shock proteins. Their work has allowed them to put together a hypothetical model of the progression of Huntington's disease.

"We now want to try to confirm our results using NF-Y knockout mice," says Nobuyuki Nukina, who leads the team. "We predict the expression of genes will change in a similar way to Huntington's disease.

"If so, NF-Y could become a target for treatment of the disease. It is very important to stop aggregation formation, and that could mean activating NF-Y." ■

1. Yamanaka, T., Miyazaki, H., Oyama, F., Kurosawa, M., Washizu, C., Doi, H. & Nukina, N. Mutant Huntingtin reduces HSP70 expression through the sequestration of NF-Y transcription factor. *The EMBO Journal* **27,** 827–839 (2008).

© 2008 RIKEN

Replacement rods and cones

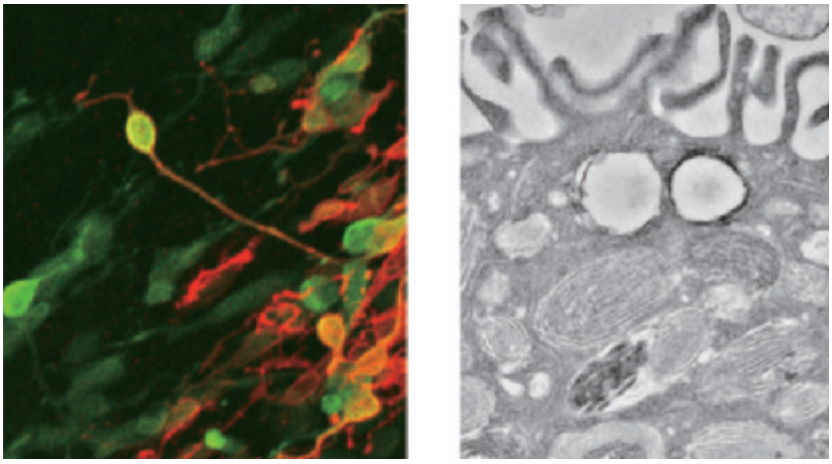
The generation of photoreceptors derived from embryonic stem cells may lead to new therapies for retinal diseases

Japanese researchers have succeeded in generating photoreceptor cells from mouse, monkey and human embryonic stem (ES) cells using specific *in vitro* cell culture conditions[1].

The team, led by Masayo Takahashi at the RIKEN Center for Developmental Biology in Kobe, initially developed a method for generating the rod and cone photoreceptors from mouse ES cells using a so-called 'floating culture' where the stem cells were induced to differentiate into retinal progenitor cells by aggregation into floating clumps of cells in a serum-containing growth medium.

By culturing these progenitor cells with an inhibitor blocking a specific signaling pathway, Takahashi and colleagues were able to significantly increase the number of photoreceptor precursor cells and generate both cone photoreceptor- and rod photoreceptor-like cells. But the proportion of rod photoreceptors was much lower than that of cone receptors—about 5% and 20% of the total cells respectively. The low proportion of rod photoreceptors could be significantly increased to nearly half of the total number of photoreceptors by culturing the cells in the presence of a number of developmental factors including fibroblast growth factors, the sonic hedgehog protein, taurine and retinoic acid (vitamin A).

The cell culture method developed for mouse ES cells, however, had one major drawback: the use of fetal bovine serum in the culture medium. Using monkey ES cells, the floating cell culture system was adapted for photoreceptor differentiation using a serum-free, defined culture medium. Culturing the cells in the presence of two inhibitors blocking separate signaling pathways resulted in generation of retinal pigment epithelial (RPE) cells as well as neural retinal progenitor cells. Subsequently, culture of the neural retinal progenitors in the presence of both taurine and retinoic acid resulted in differentiation into the two photoreceptor types.



Reproduced from Ref. 1 © 2008 Nature Publishing Group

Figure 1: Photoreceptor cells (left) and retinal pigment epithelial cells (right) differentiated from human ES cells.

The same method was successfully optimized to generate photoreceptors and RPE cells from human ES cells (Fig. 1). Importantly, Takahashi and her colleagues showed that the photoreceptors generated by this method are similar to their *in vivo* counterparts both in morphology and expression of the genes required for light responses. But it remains to be seen whether the cells will be functional.

"We need to purify photoreceptors from human ES cells and establish transplantation methods for integrating photoreceptors into the host retina," says Takahashi.

The technique holds promise for the development of clinical methods for transplantation therapies utilizing stem cell-derived photoreceptors or RPE cells for retinal disorders such as retinitis pigmentosa and age-related macular degeneration. ■

1. Osakada, F., Ikeda, H., Mandai, M., Wataya, T., Watanabe, K., Yoshimura, N., Akaike, A., Sasai, Y. & Takahashi, M. Toward the generation of rod and cone photoreceptors from mouse, monkey and human embryonic stem cells. *Nature Biotechnology* **26,** 215–224 (2008).

© 2008 RIKEN

A 'turn-off' that promotes reproduction

New research has revealed a tiny protein with huge responsibilities—regulating the formation of reproductive cells in the developing fly embryo

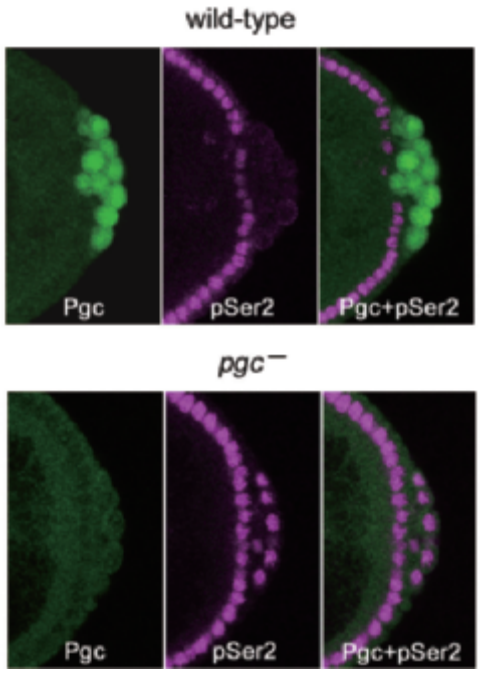


Figure 1: *Drosophila* embryos which have been fluorescently labeled to reveal expression of Pgc (Pgc, green) and CTD phosphorylation (pSer2, purple). In wild-type embryos (upper panels), CTD phosphorylation is eliminated in the Pgc-expressing germ cell progenitors. When *pgc* expression is eliminated (lower panels), CTD phosphorylation is detected throughout the embryo.

Reproduced from Ref. 1 © 2008 Nature Publishing Group

During embryonic development, somatic cells form the vast majority of the body's tissues and organs, while germ cells are the foundational cells for sexual reproduction. Germ cell formation requires the global blocking of transcriptional activity, to prevent the expression of the genes responsible for inducing somatic cell differentiation.

The enzyme RNA polymerase II is the primary engine of gene transcription, but proper operation of the enzyme requires phosphorylation—the addition of a phosphate group—to a region called the carboxy-terminal domain (CTD). In some organisms, the formation of germ cells from precursors is promoted in part by the blocking of CTD phosphorylation.

Over a decade ago, Akira Nakamura—now at the RIKEN Center for Developmental Biology in Kobe—identified the RNA of the *pgc* gene as an essential factor for germ cell formation in the fruit fly, *Drosophila melanogaster*[1]. Based on existing evidence, this RNA was thought to act as a noncoding RNA rather than being translated into protein, and this model has persisted since then.

However, more recent work from Nakamura and colleagues has now overturned this hypothesis[2]. Their careful analysis of the *pgc* RNA sequence revealed the potential to encode a relatively tiny protein, and they were subsequently able to detect this protein within *Drosophila* embryo germ cell progenitors.

When expression of *pgc*was eliminated, CTD phosphorylation was detectable in these progenitors (Fig. 1), preventing proper germ cell formation and resulting in the development of sterile adult flies.

Nakamura and colleagues found that the Pgc protein not only interacts with P-TEFb, the protein complex responsible for CTD phosphorylation, but also appears to actively sequester it. The result is that P-TEFb can no longer associate with normally active promoters, and transcription is thereby inhibited.

"Our study is the first to establish that inhibition of P-TEFb activity is essential for germ cell specification in an intact organism," says Nakamura. The significance of this finding is further reinforced by mounting evidence that the recruitment of P-TEFb to promoters may be one of the most important checkpoints for transcriptional regulation.

As such, the team is now actively engaged in better understanding how Pgc interacts with and sequesters P-TEFb—information that could also have valuable clinical consequences. "P-TEFb has been implicated in several serious diseases, including cardiac hypertrophy and cancer, and is therefore a potential target of therapeutic interventions," says Nakamura, "and Pgc may be an ideal archetype for developing potent and specific P-TEFb inhibitors." ■

1. Nakamura, A., Amikura, R., Mukai, M., Kobayashi, S. & Lasko, P.F. Requirement of a noncoding RNA in *Drosophila* polar granules for germ cell establishnment. *Science* **274,** 2075–2079 (1996).
2. Hanyu-Nakamura, K., Sonobe-Nojima, H., Tanigawa, A., Lasko, P. & Nakamura, A. *Drosophila* Pgc protein inhibits P-TEFb recruitment to chromatin in primordial germ cells. *Nature* **451,** 730–733 (2008).

© 2008 RIKEN

Mother's little helpers

Mammalian fertilized eggs can develop only with a nucleolus inherited from the mother

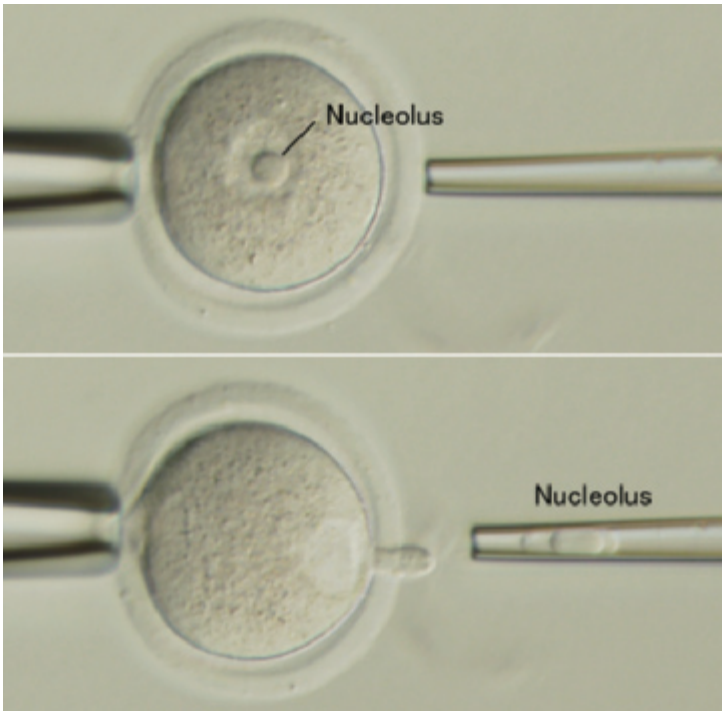
An international team led by RIKEN researchers has determined that the nucleolus—the most prominent structure in the nucleus where the cell's ribosomes, the protein factory organelles, are built—is passed down from the mother, and that it plays an essential role in early embryonic development in mammals.

The work adds to an understanding of the necessary components comprising the zygote, the truly totipotent cell which develops into every other kind of cell in an organism.

It has long been known that the nucleolus is responsible for assembling ribosomes, but that this activity ceases in fully-grown oocytes and fertilized eggs. In fact, until now the role of nucleolus during and after fertilization has been unclear.

In a series of experiments using pig and mouse oocytes from which only the nucleolus was microsurgically removed (Fig. 1), researchers from RIKEN's Center for Developmental Biology in Kobe in collaboration with colleagues from Kobe University, Italy and the Czech Republic have gained new understanding of its role. Their work is reported in a recent issue of *Science*[1].

Oocytes lacking a nucleolus matured normally, and were capable of further division and development when activated with or without fertilization. Early development stopped, however, at the two- or four-cell stage, and these embryos never assembled nucleoli. Control oocytes with intact nucleoli, but from which an equivalent amount of nucleoplasm or nuclear fluid had been removed, continued to divide quite normally, and assembled nucleoli. Interestingly, the cells without nucleoli could be induced to develop normally if the nucleolus were replaced, but only with the oocyte (maternal) nucleolus. Cells with nucleoli from other sources all failed to develop.



From Ref. 1. Reprinted with permission from AAAS.

Figure 1: Removal of the nucleolus from the oocytes using a very thin pipette.

The nucleolus must now be added to the list of organelles inherited solely from one parent, says Sugako Ogushi from RIKEN, along with mitochondria from the mother and centrioles from the father. "We still don't know the precise function of the nucleolus and its molecular components, but are now working to answer these questions by determining the proteins and RNAs present. We hope these studies will lead to a better understanding of how a totipotent zygote is constructed," she says. ■

1. Ogushi, S., Palmieri, C., Fulka, H., Saitou, M., Miyano, T. & Fulka Jr, J. The maternal nucleolus is essential for early embryonic development in mammals. *Science* **319,** 613–616 (2008).

© 2008 RIKEN

Sights set on plant tumor trigger

New insight into how a key enzyme causes plant tumors could ultimately reduce crop losses

Researchers at RIKEN's Plant Science Center in Yokohama have unraveled the structure, molecular operation and evolution of a key enzyme in the bacterial production of the plant growth hormones known as cytokinins. The work is important because bacterially produced cytokinins can trigger tumors (Fig. 1), which cause significant crop losses. The findings may be used to design plant growth regulators and to stop bacteria from generating tumors.

A critical step in synthesizing cytokinins is prenylation. The enzymes which control prenylation are called adenosine phosphate-isopentyltransferases (IPTs). From previous work it is known that the IPTs of plants and of bacteria, although catalyzing the same reaction, are structurally very different. Bacterial IPTs are more efficient and versatile in that they can use two different compounds as donors of the prenyl molecular group—one of which is hijacked from the plants they attack—whereas plants use only one.

In a recent paper published in the *Proceedings of the National Academy of Sciences*[1], the researchers detail how, using x-ray crystallography, they determined the structure of Tzs, an IPT of the important plant pathogen *Agrobacterium tumefaciens*. By solving four structures of Tzs bound to compounds or their analogues involved in prenylation, the researchers were able to uncover the reaction site of the enzyme and a probable mechanism.

They then substituted individual amino acids in the enzyme protein chain at the reaction site and discovered two specific amino acids were crucial to the catalyst's ability to use different donor compounds. The reaction involves an amino acid sequence known as a *p* loop, used in sulfate or phosphate transfer in many other enzymes.

Figure 1: A crown gall (tumor) caused by *Agrobacterium* infection.

Interestingly, however, when the researchers compared the proteins' structures with others in an electronic database, they found that, while it closely resembled a superfamily of *p* loop-containing enzymes, the bacterial IPT is the sole known example of *p* loop involvement in prenylation. They suggest the enzymes evolved from a common ancestor.

"The reaction center is very, very similar, but the function of the *p* loop is different between the IPT and the other enzymes," says project-leader Hitoshi Sakakibara. "Now, by modifying *Agrobacterium* genes, we are trying to find out why the bacteria use the second prenyl donor. Eventually, we hope to develop something to block bacterial cytokinin formation and reduce economic loss." ■

1. Sugawara, H., Ueda, N., Kojima, M., Makita, N., Yamaya, T. & Sakakibara, H. Structural insight into the reaction mechanism and evolution of cytokinin biosynthesis. *Proceedings of the National Academy of Sciences USA* **105,** 2734–2739 (2008).

© 2008 RIKEN

Interferon production mechanisms revealed

Researchers are a step closer to understanding the mechanisms underlying a major immune defense against viruses

Researchers based at the RIKEN Research Center for Allergy and Immunology in Yokohama have unraveled part of the mechanism for the production of type I interferons by immune system cells known as plasmacytoid dendritic cells (PDCs).

PDCs are specialized producers of type I interferons: proteins, produced in response to viral and other infections, which play an important role in the so-called innate immune response, which is the body's first line of defense against infection (Fig. 1). Type I interferons, including IFN-α and IFN-β, rapidly act to inhibit viral replication within infected cells, giving the infected host time to marshal a full immune response. But the mechanisms underlying interferon production are poorly understood.

Now, the research team, led by Masaru Taniguchi, has identified a protein on the surface of PDCs that is expressed after stimulation through the so-called toll-like receptor (TLR) pathway[1]. TLR is known to be required to activate interferon production in PDCs, but previous studies have shown that signaling through TLR is not the only trigger for interferon production.

The researchers demonstrated that the protein, known as PDC-TREM, was associated on the PDC cell surface with at least two other proteins, Plexin A1 and DAP12. Under the condition of limited TLR stimulation, PDC-TREM was expressed on PDCs, but interferon production was not triggered.

However, when TLR stimulation took place in the presence of a protein that binds to Plexin A1, known as Sema6D, interferon was produced. Further investigation revealed that PDC-TREM mediated the activation of a cascade of signaling molecules that ultimately up-regulated the production of IFN-α.

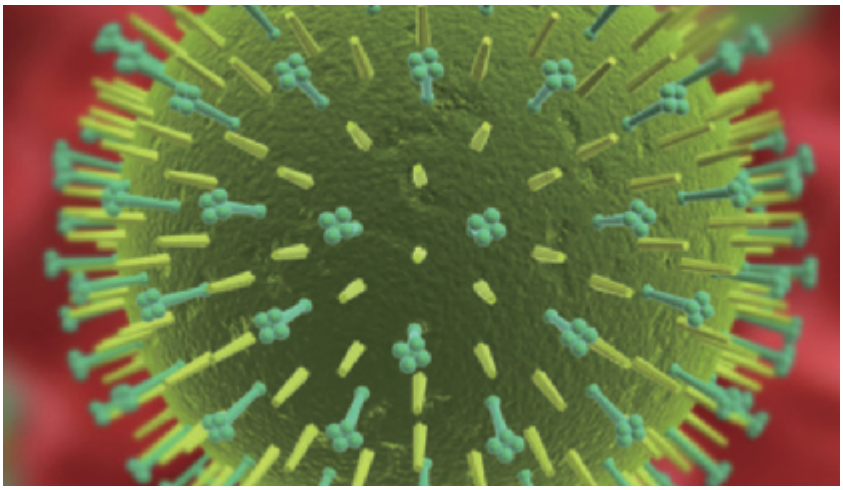


Figure 1: Image of a virus particle. Infection with a virus can trigger production of type I interferons in the body's first line of defence.

Finally, the team demonstrated that inhibition of PDC-TREM expression, blocking of its binding to Plexin A1, and DAP12 deficiency all resulted in significantly reduced activation of these signaling molecules and subsequent production of IFN-α.

According to team-member Hiroshi Watarai, the results clearly demonstrate that PDC-TREM plays a central role in inducing interferon production in PDCs, which may provide possibilities for treatment of viral infections and other diseases in which interferon plays a role.

"Serum in patients with autoimmune diseases such as systemic lupus erythmatosus and Crohn's disease contains high level of type I interferons," notes Watarai. "These results indicate that modulation of PDC-TREM signaling results in the regulation of type I interferon production from PDCs, so the PDC-TREM pathway may be a target for therapeutic use in anti-viral and autoimmune diseases." ■

1. Watarai, H., Sekine, E., Inoue, S., Nakagawa, R., Kaisho, T. & Taniguchi, M. PDC-TREM, a plasmacytoid dendritic cell-specific receptor, is responsible for augmented production of type I interferon. *Proceedings of the National Academy of Sciences USA* **105,** 2993–2998 (2008).

© 2008 RIKEN

Using the world's best x-ray spectrometer to detect atomic vibrations

Alfred Q. R. Baron

Associate Chief Scientist, Director of the Material Dynamics Laboratory
SPring-8 Center

"This is the world's best beamline," says Alfred Baron, Associate Chief Scientist, referring to the BL35XU beamline at SPring-8, RIKEN's large synchrotron radiation facility. The BL35XU beamline incorporates an 'inelastic x-ray scattering spectrometer,' which is a very large instrument used to study atomic vibrations in the ultra-micro world. The Materials Dynamics Laboratory makes use of both x-rays from SPring-8, the world's brightest synchrotron, and the world's best spectrometer for detecting atomic vibrations in superconductors, liquids, and substances under high pressure. This article looks at the forefront of the study of the dynamics of atoms guided by Baron.

Huge, ten-meter-long, five-ton spectrometer

A huge apparatus, 10 m in length and 5 metric tons in weight (Fig. 1), takes our eye when we enter the experimental hatch of the BL35XU beamline at SPring-8 in the RIKEN Harima Institute.

Baron joined the Japan Synchrotron Radiation Research Institute, which built and now administers SPring-8, in 1997 and shortly thereafter began work on a huge inelastic x-ray scattering spectrometer. "I intended to complete my work within three years and go back to the US, but I found myself staying longer than expected," says Baron with a smile. After a successful trial in 2001, in which x-rays were passed through the beamline for the first time, Baron began research with the instrument. Since 2006, he has been heading the Materials Dynamics Laboratory at RIKEN SPring-8 Center.

What kind of research does the laboratory do with this huge apparatus? "We use the inelastic x-ray scattering spectrometer to detect atomic vibrations in a substance," explains Baron.

When a substance is irradiated with x-rays, the x-rays are scattered by the electrons around the nuclei. In most cases, the direction and intensity of the scattered radiation are detected and then used to determine the atomic positions. "Analysis of crystals can clearly show how atoms are arranged in a regular pattern. Many may think that the atoms in crystals are stationary. However, individual atoms vibrate in a very complex manner," says Baron. A quantum of atomic vibration in a crystal is called a 'phonon' (lattice vibration).

"We measure not only the direction and intensity of the scattered radiation but also how much the energy has changed, by performing a spectrographic analysis of the scattered radiation. The electrons bound to vibrating atoms can interact with the incident x-rays to change the direction, intensity and energy of the scattered radiation, and this variation in energy and intensity is used to detect the atomic vibrations in a crystal."

Inelastic x-ray scattering refers to the phenomenon in which the incident x-rays interact with a substance to emit scattered x-rays with an energy different from that of the incident x-rays. When the energy is the same, the scattering is called 'elastic'.

Japan's only beamline, and the world's best

Detecting atomic vibrations is no easy job because the change in the energy of the scattered radiation due to the interaction between the electrons and the x-rays is very small. Baron explains, "The energy changes involved are of the order of 0.001 electronvolts, whereas typical x-ray energies are 10,000 eV, so the fractional change in energy that we can detect is about 0.001/10,000 or 10^{-7}, which is an extremely good resolution. We have made a huge effort to make this possible."

The following describes the mechanism of the inelastic x-ray scattering spectrometer. A group of electrons moves through the 1.5 km-long storage ring of SPring-8 at nearly the speed of light. The electrons emit radiation when their

© 2008 RIKEN

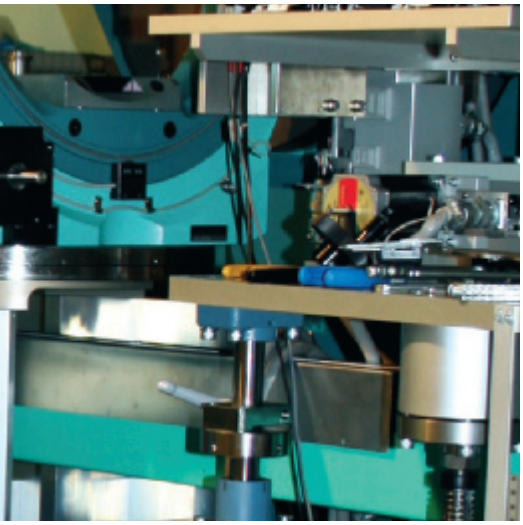


Figure 1 : The BL35XU and its inelastic x-ray scattering spectrometer.
The spectrometer is installed in the SPring-8 beamline (BL35XU). Its arm is 10 m long and weighs 5 metric tons. The arm can move up to 55° and is capable of observing the vibration of atoms in a specimen. The movement of the arm is controlled by a suspension mechanism on a highly polished granite base. The long arms of APS beamline in the US and the ESRF beamline in France move only up to 30°. Thus, the length and the rotation angle of the BL35XU are outstanding. The insets show an array of four (horizontal rows) by three (vertical columns) pieces of crystal installed at the top end of the 10 m-long arm. The array is used as a spectroscope for dispersing the scattered radiation from the specimen into its components. Each piece of the analyzer crystal, 10 cm in diameter, consists of 10,000 smaller pieces of perfect silicon single crystal, which are precisely arranged to form part of a sphere for the efficient collection of the scattered radiation.

orbit is bent by the field of a magnet. The BL35XU beamline uses a special array of magnets called an 'undulator' to selectively increase the number of x-rays emitted by the electrons in the storage ring. These x-rays cannot, however, be applied directly to specimens. "The energy change due to scattering will immediately fall below the noise level unless the incident x-rays are made sufficiently monochromatic," says Baron. Thus, a backscattering monochromator is used to select precisely those x-rays with the correct energy, which are applied to a specimen set at the rotational center of the arm.

The scattered radiation is collected by an analyzer crystal installed at the far end of the 10 m-long arm for spectrometric analysis. "The analyzer is an array of three (horizontal rows) by four (vertical columns) of crystals (Fig. 1, insets). The horizontal–vertical array structure is very useful because atomic vibrations usually occur in specific directions called longitudinal and transverse, and the array helps you see both of them." The radiation selected by the analyzer crystals is collected by a special detector.

The arm is very long (10 m). This is because the longer the distance between the specimen and the analyzer crystal, the better the resolution. In addition, the arm is designed to move up to 55° in the azimuth direction so that scattered x-rays coming from various directions can be detected and three-dimensional atomic vibrations can be investigated.

Around the world, there are only three facilities with an inelastic x-ray scattering spectrometer: SPring-8, the Advanced Photon Source (APS) in the US, and the European Synchrotron Radiation Facility (ESRF) in France. Baron asserts, "An analyzer array consisting of three (horizontal rows) by four (vertical columns) pieces of crystal is installed only in SPring-8. Our inelastic x-ray scattering spectrometer has the world's most comprehensive performance."

Pursuing the mechanism of superconductivity

Strongly correlated materials are one of the hottest topics in modern condensed matter physics. They are a wide class of materials that feature a strong interaction between electrons. The physical properties of strongly correlated materials are significantly affected by this strong interaction. "To understand the materials, we need to investigate the action of phonons." At the Materials Dynamics Laboratory, superconductors, which are one type of correlated material, are one subject of study. Superconductivity refers to a phenomenon occurring below a certain temperature (the superconducting transition temperature: T_c), characterized by exactly zero electrical resistance. "Superconductors exhibit zero electrical resistance because electrons interact with phonons and can then move with the help of phonons," explains Baron. "One of the things we do is to look for evidence of the interaction between phonons and electrons that causes superconductivity." New substances such as superconductors rarely form large crystals. However, the inelastic x-ray scattering spectrometer makes it possible to work with very small crystals—for example 0.1 mm in size, which is almost too small to see.

© 2008 RIKEN

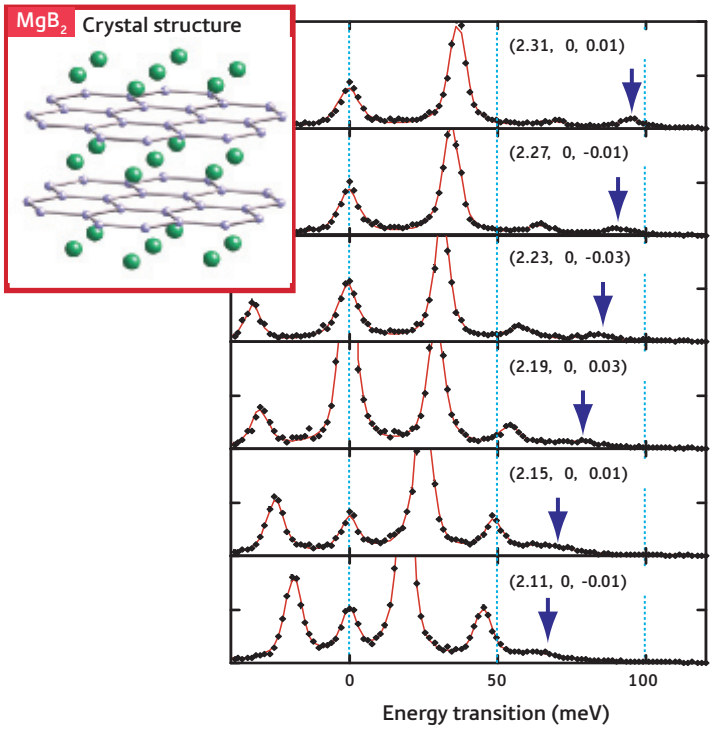


Figure 2 : Inelastic x-ray scattering spectra of superconductor MgB_2.
The spectra of six phonons with different kinetic moments are measured. The vertical line represents the intensity of inelastic scattering. Phonon energy is reduced at the arrowed positions, and the peak widths are broader. The reduction of phonon energy suggests that the force acting between atoms is screened (hindered) by electrons, whereas the broader widths indicate that the lifetime of the phonons has been shortened. In other words, these results show that phonons are interacting with electrons (Baron *et al., Physical Review Letters* **92,** 197004; 2004).

Figure 2 shows results obtained with the superconductor MgB_2 (magnesium diboride), which was discovered by Jun Akimitsu of Aoyama Gakuin University in 2001. The superconductor is attracting much attention because its superconducting transition temperature is 39 K (-234 °C), the highest temperature among metallic superconductors that has ever been discovered. "Take a look at the small peaks (Fig. 2, arrows) on the right side," says Baron. In normal materials these peaks, or phonons, would be narrow and at a higher energy. However, the energy of the phonons is reduced when interaction occurs between the electrons and phonons.

This achievement alone is a breakthrough, but the Laboratory looks beyond the present. Recently, new ceramic superconductors have been discovered one after another. They are superconductors with a transition temperature near or even above 100 K (-173 °C) and are therefore called 'high-temperature superconductors.' They are expected to be used in extremely low-loss power cables. "The mechanism of high-temperature superconductivity is, however, still debated. We are not sure whether high-temperature superconductivity occurs as a result of the 'conversation' between electrons and phonons, or by a different mechanism. Thus we are trying to investigate atomic vibrations to explore the mechanism of high-temperature superconductivity. That is one of our research targets."

At the Materials Dynamics Laboratory, other superconductors have also been investigated, including $HgBa_2CuO_{4+\delta}$, $YBa_2Cu_3O_{7-\delta}$, and $La_{2-x}Sr_xCuO_4$. "High-temperature superconductors normally show phonon anomalies that simple theories cannot explain. These anomalies may be related to more microscopic and complicated phonon structures, but no current instruments could easily be used to detect them." The lab has also begun work on a new Fe-As based superconductor recently discovered by Hideo Hosono at Tokyo Institute of Technology.

Observing the phase transition from metal to non-metal

Liquids are the second target of the Laboratory. "Daisuke Ishikawa, a contract researcher, is taking a leading role in conducting the research using mercury, which is a liquid metal," says Baron. "Liquid metals are good electrical conductors. When electrons are spatially close to each other and these electrons are in the same orbit, they can jump to a neighboring orbit, causing electricity to flow. As the temperature rises, however, these electrons are spatially separated as a result of thermal expansion. Then the orbits of electrons are also separated, preventing the electrons from jumping to their neighboring orbits. Thus a 'metal-to-non-metal transition' occurs, in which an electrical conductor turns into an electrical insulator. At the moment, however, the question of how the atomic vibrations change remains a mystery."

Fig. 3a shows measurements of atomic vibrations in mercury with increasing temperature and pressure. "The figure shows the world's first measured results of a change in the dynamics of atoms involved in the metal-to-non-metal transition of mercury."

In fact, the BL35XU beamline at SPring-8 is optimized for the measurement of solid crystals. Furthermore, the ESRF beamlines in Europe are said to be able to perform equivalent measurements. What, then, contributed to this world-first achievement? "The metal-to-non-metal transition of mercury occurs under conditions of high temperature and high pressure in the vicinity of the liquid–vapor critical point (Fig. 3b). Fortunately, in Japan we have Kozaburo Tamura of Kyoto University, and his collaborators (especially Masanori Inui of Hiroshima University), specialists in handling liquids at high temperatures and high pressures. We used a special

© 2008 RIKEN

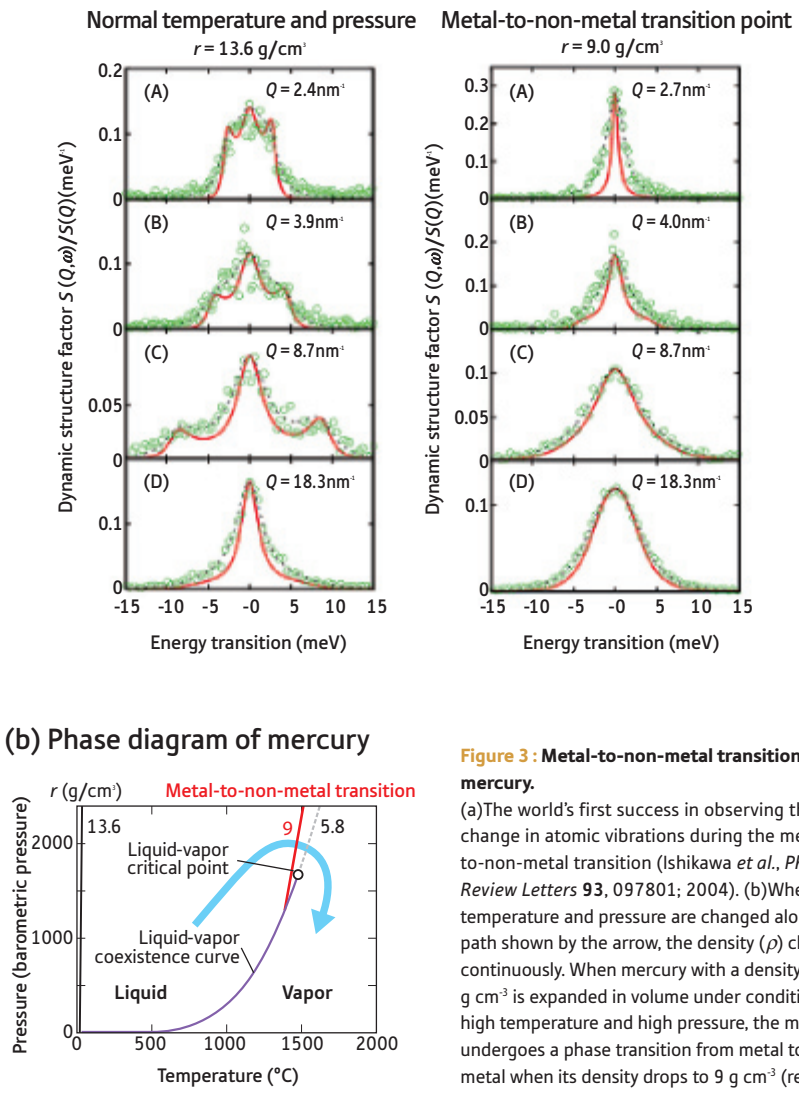


Figure 3 : Metal-to-non-metal transition of mercury.
(a)The world's first success in observing the change in atomic vibrations during the metal-to-non-metal transition (Ishikawa *et al.*, *Physical Review Letters* **93**, 097801; 2004). (b)When temperature and pressure are changed along the path shown by the arrow, the density (ρ) changes continuously. When mercury with a density of 13.6 g cm^{-3} is expanded in volume under conditions of high temperature and high pressure, the mercury undergoes a phase transition from metal to non-metal when its density drops to 9 g cm^{-3} (red line).

gas-compression specimen container made of sapphire, which was developed by Tamura and can be used under these conditions. This was a key factor in our success. "

Substances under very high pressure are also one of the targets of the Laboratory. "Hiroyuki Fukui, a contract researcher, is taking a leading role in conducting research into the dynamics of substances within the Earth. Although this study is only beginning, we look forward to future reports on our findings."

Looking forward to a new beamline

Many scientists are pouring in from all corners of the world because they want to use the world's best, beamline BL35XU, at SPring-8. Baron, however, is not content with the present situation. "I would like to construct a better beamline," says Baron with enthusiasm.

"SPring-8 has a potential that other synchrotron radiation facilities do not: it can accommodate a very long undulator. The longer the undulator, the brighter and stronger are the x-rays that can be produced. SPring-8 can accommodate an undulator with a length of up to 25 m, whereas at APS or ESRF it can only be up to 5 m. SPring-8 also has a very high electron energy, 8 GeV – the '8' in SPring-8, so that it can produce high-energy x-rays that are nearly perfect for this inelastic x-ray scattering work."

It is expected that introducing the very long undulator in combination with optimization of the other parts of the apparatus will improve the beamline performance up to 50-fold. Baron is anticipating that the improvement will enable researchers to do measurements in a single day that currently require a whole month, and will contribute to the exploration of new studies in physics. "For example, without the introduction of a new beamline, it seems almost impossible to observe how phonons act in detail in these strongly correlated materials, and how atoms move near the surface of a substance. Furthermore, the new beamline will help in using the high-resolution inelastic x-ray scattering technique for electronic excitation measurements. Although these are not related to atomic vibrations, such work will contribute to the exploration of the complex electronic structure of strongly correlated materials. Such high resolution studies will be the first such experiment in the world. I would really like to do it." ■

About the researcher

Alfred Baron was born in Manhattan, New York, in 1965. He attended Michigan State University on a full academic scholarship, receiving separate degrees in physics and mathematics. He then attended Stanford University, receiving a PhD from the Department of Applied Physics in 1995. In 1994 he moved to France, where he spent three years working at the European Synchrotron Radiation Facility, in Grenoble, before joining the Japan Synchrotron Radiation Research Institute (JASRI) at SPring-8 in Hyogo Prefecture, Japan, in 1997. At SPring-8, he changed fields and built Japan's first inelastic x-ray scattering beamline. This is arguably the largest, most complex, and highest-resolution end-station operating at SPring-8. He joined Harima RIKEN in 2006 where, as an Associate Chief Scientist, he heads the Materials Dynamics Laboratory in the RIKEN SPring-8 Center and continues research into atomic dynamics, especially phonons in superconductors. He presently hopes to extend the worldwide capability of measuring phonons by about an order of magnitude though building a new instrument at SPring-8, one matched to the challenges of modern-day materials synthesis.

© 2008 RIKEN

Third international MAXI workshop on astrophysics

The Cosmic Radiation Laboratory (CRL) of the RIKEN Advanced Science Institute held the third international MAXI workshop on June 10–12, focusing on astrophysics using all-sky X-ray observations. The workshop was held under the auspices of RIKEN, the Japan Society for the Promotion of Science, the Japan Aerospace Exploration Agency (JAXA), the Physical Society of Japan and the Astronomical Society of Japan.

The MAXI (Monitor of All-sky X-ray Image) instrument, which the CRL has been developing for 10 years, will be finally be launched on a space shuttle in May 2009. It will then be attached to the Japan Experimental Module 'Kibo', which was launched earlier this year and installed by a Japanese astronaut on the International Space Station on June 4, just before this MAXI workshop.

The purpose of the workshop was to determine ways to fully utilize the MAXI. Participants heard reports on the final tests of the completed instrument, summaries of scientific objectives, and plans for international collaborations.

The workshop had 180 participants this year, including 33 from 10 different foreign countries (the USA, the European Union, Russia and Asia), who gave 41 oral presentations and 42 poster sessions. Masaru Matsuoka of JAXA, the MAXI team leader, and others on his team gave the introductory presentations. Kazuo Makishima of the CRL and Andrzei Zdziarski of the Copernicus Center in Poland gave presentations on possible new aspects of black-hole physics to be explored with the MAXI. David Thompson of NASA's Goddard Space Flight Center and Grzegorz Madejski of Stanford University gave an enthusiastic talk on collaborative observations with the gamma-ray observatory GLAST, which was launched on June 12. "We will have a dream team of MAXI, GLAST and Swift missions," he said.

The participants also heard about the high international expectations for the instrument, which realizes an all-sky X-ray monitoring capability that is 10 times more sensitive than can be achieved by a similar instrument that NASA is operating. One of the ground-based astronomers said, "We would highly appreciate MAXI alerts issued within a few hours of any new findings, because such a prompt notice is essential for detecting outbursts from active galaxies in other wavelengths."

RIKEN, JASRI host 3rd International Workshop on Diamonds for Modern Light Sources

The 3rd International Workshop on Diamonds for Modern Light Sources (DMLS2008) was held on May 20–23 at the Awaji Yumebutai International Conference Center on the island of Awaji, Hyogo Prefecture. The meeting was co-hosted by the RIKEN Harima Institute and the Japan Synchrotron Radiation Research Institute (JASRI), and was supported by the Hyogo International Association and several private companies.

The meeting brought together researchers who grow diamond crystals, use them in modern (3rd and 4th generation) X-ray sources, and characterize them. The participants discussed the quantitative and qualitative characteristics of diamonds, the status of and future trends in the development of diamond-growth technologies, the characterization of diamonds to promote the improvement of crystal-growth technologies, and how the industry might satisfy future needs for high-quality diamonds.

Tetsuya Ishikawa of RIKEN made the opening remarks. Shunji Goto of JASRI gave one of the two keynote addresses, presenting recent results in characterizing high-quality diamond crystals and providing examples of the use of diamonds at SPring-8, the most advanced facility in the world for diamond usage.

In addition, the participants decided that the Stanford Linear Accelerator Center (SLAC) in the US would host the group's next meeting in 2010.

After the meeting, the participants visited the construction site of the X-ray free-electron laser (XFEL) and the prototype FEL at the RIKEN Harima Institute at SPring-8, followed by Himeji castle, a beautiful site near Hiroshima that has been designated a World Heritage site by UNESCO. When the event was over, the foreign participants received colorful yukatas (Japanese bathrobes) as souvenirs.

Japan–Korea symposium on plant growth and signal transduction

This year's Japan–Korea Symposium on 'Plant Growth and Signal Transduction' was held in Koryuto Hall at the RIKEN Yokohama Institute. The event, sponsored by RIKEN Plant Sciences Center and co-hosted by the Japan Plant Science Foundation and the Kao Foundation for Arts and Sciences, took place over the course of two days beginning on June 9, 2008.

Eight scientists from South Korea and eight from Japan attended the symposium, all of them researchers at the forefront of plant science. Kazuo Shinozaki, director of the PSC, gave the opening remarks, along with Masaaki Umeda of the Nara Institute of Science and Technology. The South Korean and the Japanese researchers at the symposium engaged in a lively exchange of ideas.

Two presentations in particular were especially well received. Ohkmae K. Park, along with his colleagues Sun Jae Kwon, Hak Chul Jin and Soon Il Kwon at Korea University's School of Life Sciences and Biotechnology, gave a presentation on their research into the systemic response of plants to infection, in particular the activation of a systemic response by GDSL lipase 1 (GLIP1). The study of GLIP1 is regarded to be important for applications, since Arabidopsis with excess expression acquires resistance against various pathogens.

Yoshikatsu Matsubayashi from Nagoya University's Graduate School of Bio-Agricultural Sciences, and his team members Kentaro Ohyama and Mari Ogawa, gave a talk on their research into the biologically active small secreted peptide hormone PSY and CEP in Arabidopsis, which they investigated using in silico gene screening followed by LC-MS-based structural analysis. Many researchers are of the opinion that identification of new small secreted peptide hormones will broaden the study of plant hormones and open up a host of new possibilities.

It has been agreed that such symposia on plant growth and signal transduction will be held every two years, with hosting duties alternating between the two countries. It is hoped that such events, as well as exchanges of young scientists and joint research, will help further relations between the science communities in the two countries.

© 2008 RIKEN

Dr. Maki Kawai
Chief Scientist
Surface Chemistry Laboratory
RIKEN Advanced Science Institute
Wako, Saitama, Japan.

Dear Kawai Sensei,

I wish to thank you very much indeed for all you have done for me: for the opportunity to use the top research facilities offered by RIKEN, and for your stimulus, encouragement and interest in my work.

Thanks to the extremely high scientific level and friendly atmosphere at the Surface Chemistry Laboratory, my stay at RIKEN was even more enjoyable than I had ever dreamed, —from both an intellectual and social point of view.

I have been trying not to keep the unique experience acquired at RIKEN to myself, but to share it daily with the PhD and MSc students here at the University of Waterloo, Canada. I enjoyed the experience immensely and have many pleasant memories to revisit.

The lectures given by world-leading scientists that I could attend remain among the most memorable events of my stay at RIKEN. The Friday seminars during which the 'Kawai Ken' team members introduced and discussed the status of their work can be also counted among the unforgettable moments that I spent at the Surface Chemistry Laboratory. The very free and friendly atmosphere, in which the discussions were led, helped everyone to get a deeper understanding of the research work being carried out by others in your laboratory.

My research activities here at the University of Waterloo, though still related to the physical chemistry of ice nanolayers, are more focused on the interaction of amino acids with those nanolayers. In particular, I have studied in detail the interaction of one of the most important biological compounds (a multifunctional molecule), namely the amino acid glycine (NH_2CH_2COOH), with low-density amorphous (LDA) ice nanolayers. This is an ideal model system since it constitutes a first step in understanding the adsorption of proteins, the constituent of the so-called primary film, which enables the further growth of biofilms.

I have obtained very important results which will be submitted for publication soon.
This work and my other ongoing projects (concerning alanine and cysteine) have been made possible via the construction of a high-flux cryogenic beam doser, which I designed and built.

I am very grateful for the scientific experience I acquired at your laboratory, which stimulated and helped me in my further research activities.
With my best regards,

Michel Malick Thiam
Research Associate
Department of Chemistry
University of Waterloo
Canada

© 2008 RIKEN

RIKEN

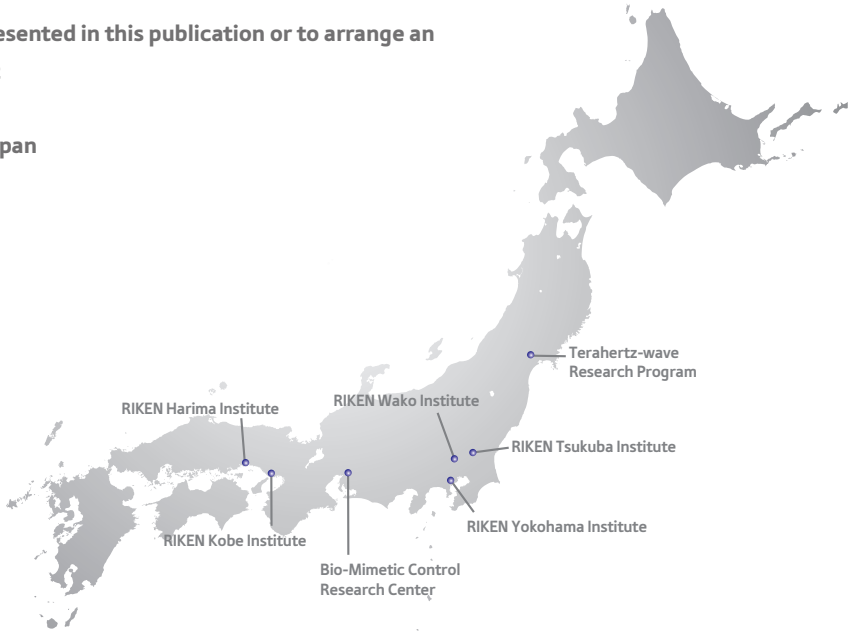
www.riken.jp

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 48 467 9443
FAX: +81 48 462 4715
E-Mail: rikenresearch@riken.jp

www.rikenresearch.riken.jp



© 2008 RIKEN