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Focus on phosphate

Researchers provide the first large-scale identification of protein control sites from the model plant *Arabidopsis*

A team of Japanese biologists, including Ken Shirasu from the RIKEN Plant Science Center in Yokohama, has provided a snap-shot of the proteins regulated by phosphate, collectively known as the ‘phospho-proteome’, in living plant cells. This is the first time such a large-scale comprehensive analysis has been performed in plants.

In plants, protein modification by the introduction of a phosphate group, a process known as phosphorylation, regulates cell signaling in response to a wide range of external and internal stimuli such as pathogen attack or hormone release (Fig. 1). Nearly all cellular processes are controlled by switching proteins on and off using phosphate, a molecule containing phosphorous and oxygen atoms. Phosphate modulates protein functions by bonding to an amino acid residue, such as serine, threonine or, less commonly, tyrosine.

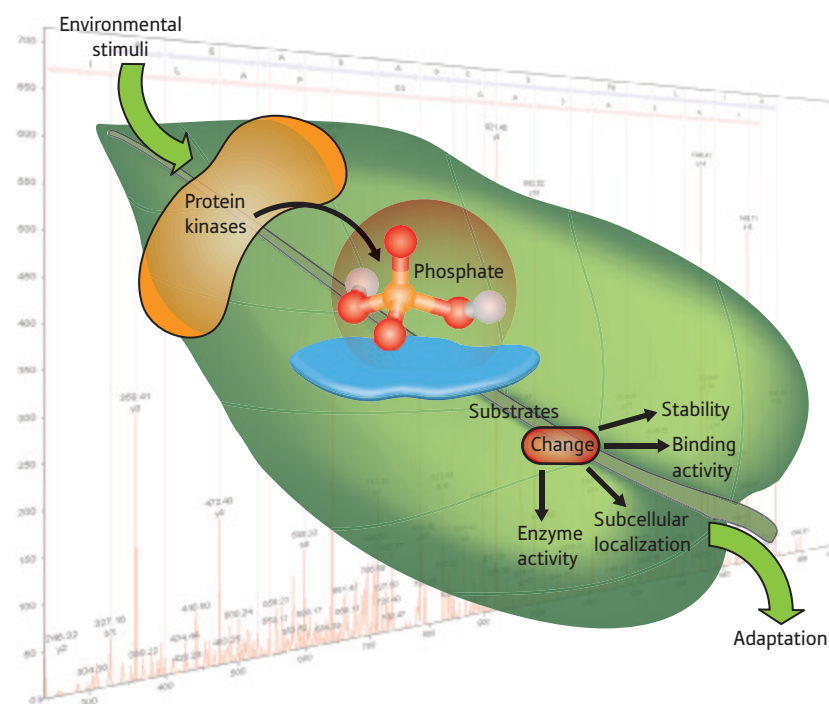


Figure 1: Phosphorylation of proteins occurs in response to signals from the environment and enables plant cells to react to changes in the surroundings and perform basic biological functions. Enzymes known as protein kinases attach a phosphate group onto an amino acid residue of substrate proteins. The background shows a mass spectrometry scan which identifies phosphorylated peptides by mass.

The whole-cell approach

In previous studies of phosphorylation in plants, only parts of the cell such as the plasmamembranewereassessed. Uniquely, the team, led by Shirasu and Yasushi Ishihama from Keio University, Tsuruoka, used unfractionated, whole cells to provide an overall view of phosphorylation in all the cellular components of the model plant *Arabidopsis thaliana* (Fig. 2). The team employed six procedures to isolate phosphorylated peptides—ensuring a wide variety of peptides were captured—and analyzed them using mass spectrometry, a technique that identifies the chemical composition of molecules.

Their approach identified 2,172 unique phosphorylation sites on 1,346 proteins from *Arabidopsis* cells. Over 85% of the identified phosphoproteins were novel, establishing

this data-set—published recently in *Molecular Systems Biology*¹—as the largest available to date. “This work is just the beginning of a long journey to understand the ‘complete map’ of phosphorylation sites in plants,” says Shirasu.

Firstly, the researchers surveyed the characteristics of phosphoproteins and phosphorylation sites in *Arabidopsis*. Then they analyzed the abundance, distribution, molecular and biological functions and cellular localization of identified phosphoproteins and compared these traits with those of all proteins encoded by the *Arabidopsis* genome. The distributions of the molecular functions of the phosphoproteins were aligned to those of all genome-encoded proteins,

suggesting that most cellular processes in *Arabidopsis* are likely to be regulated at least in part by various phosphorylation events. They also showed that all sub-cellular compartments of the plant cells investigated contained phosphorylated proteins, but that nuclear proteins were the most popular targets for phosphate groups with approximately 40% of phosphorylation events taking place in the cells’ headquarters.

An unexpected similarity between plants and humans

Shirasu, Ishihama and colleagues found phosphorylation to be focused mainly on serine and threonine; 85.0 and 10.7% of all phosphate introductions took place



Figure 2: Proteins modified by the addition of a phosphate group were isolated from the model plant *Arabidopsis thaliana* in a large-scale study.

on these amino acid residues. Surprise came when 94 of the 2,172 identified sites of phosphorylation were found to occur on tyrosine residues. This level of phosphotyrosine was much higher than expected, explains Shirasu, indicating that the extent of tyrosine phosphorylation has been largely underestimated in plants. At 4.3%, the level of phosphorylation events that occur on tyrosine is similar to that found in humans, where the range is between 1.8 and 6%.

Intriguingly, humans employ over 90 enzymes, collectively known as tyrosine kinases, that work specifically to phosphorylate tyrosine residues, but these enzymes do not exist in *Arabidopsis*. The researchers investigated the mechanism that might be used by plants to attain this high level of tyrosine phosphorylation by comparing patterns of amino acids around tyrosine phosphorylation sites in *Arabidopsis* and humans. They found most of the plant-based motifs to be novel and distinct from those in humans, indicating that tyrosine phosphorylation in *Arabidopsis* is carried out by a novel class of kinases that are specific to plants. Candidates for the role could include multi-specific serine/threonine/tyrosine protein kinases or enzymes called tyrosine-specific protein kinase-like kinases (TKLs), which are especially abundant in plants.

The function of TKLs remains unclear, but their plentitude in plants suggests that they are significant in catalyzing molecular reactions. It will be of particular interest to investigate whether plant TKLs possesses tyrosine phosphorylation activity, according to Shirasu.

Elucidating the roles of key players

Tyrosine phosphorylation plays a central role in a variety of signal transduction pathways regulating animal cell growth and differentiation, but its relevance in plants is still largely unknown. Shirasu, Ishihama and colleagues found that many tyrosine phosphorylated proteins are involved in cellular signaling and are likely to be crucial players in the regulation of cellular processes.

Trends in the protein-based position of phosphorylation sites can provide clues to their functions. The research team investigated whether the phosphorylation sites identified in this study are located in important areas known as conserved domains. These domains are conserved through evolutionary time and contain essential features that perform vital protein functions. Phosphorylation sites involving serine and threonine were found to be located mainly outside conserved domains, but, strikingly, nearly half of the phosphorylated tyrosine residues were located on conserved domains. These data indicate that tyrosine phosphorylation

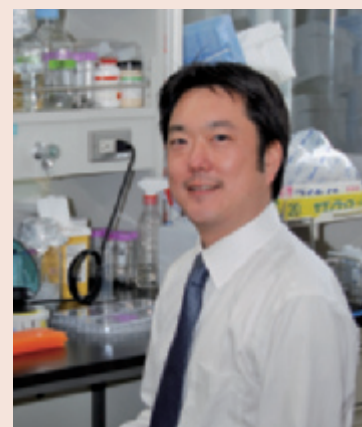
may have more impact on key regulatory processes compared to serine and threonine phosphorylation.

To further enrich the map of phosphorylated proteins, the researchers will need to extract proteins from different cell types over various developmental stages and under different environmental cues such as light, temperature, humidity and pathogen exposure. A future goal of the team is to determine the role of phosphorylation in plant immunity by isolating proteins that are phosphorylated when plants encounter pathogens. According to Shirasu, “we show here that the technology is ready and the next stage is to ‘just do it’”

1. Sugiyama, N., Nakagami, H., Mochida, K., Daudi, A., Tomita, M., Shirasu, K. & Ishihama, Y. Large-scale phosphorylation mapping reveals the extent of tyrosine phosphorylation in *Arabidopsis*. *Molecular Systems Biology* **4**, 193 (2008).

About the researcher

Ken Shirasu graduated from the Department of Agricultural Chemistry at the University of Tokyo in 1988. He moved to the USA and earned his PhD in genetics at the University of California, Davis, in 1993. He then obtained a Salk/Noble postdoctoral fellowship to study plant immunity at the Salk Institute in the USA. In 1996 Shirasu moved to the Sainsbury Laboratory in the UK as a researcher, where he later became a group leader in 2000. In 2006 he returned to Japan and became a group director at RIKEN Plant Science Center. He has also been a visiting professor in the Department of Biological Sciences in the University of Tokyo since 2008. His research focuses on molecular elucidation of the mechanism for plant immunity.



Generating new information from the web

Development of a new search engine allows statistical analysis of numerous databases containing scientific papers and omics data

Researchers from the RIKEN Bioinformatics And Systems Engineering (BASE) division (formerly the Genomic Sciences Center) in Yokohama have developed a search engine that can find statistically significant information from integrated published scientific papers and omics data. They have applied it to various problems such as using the externally observable or phenotypic characteristics of mice to estimate the location of genes in which mutations have been chemically induced.

At present, pages on the World Wide Web and the information they contain are designed to be read and handled by humans, not machines. Computer scientists hope one day to generate a Semantic Web, within which information will be understandable by machines that can then automate the process of finding, sharing and combining data, as well as analyzing it statistically. However, this demands structuring information in a

form capable of being read by machine, and has led to much work on developing such datasets together with computer languages able to handle them.

But even in fields such as molecular biology, where there is an awareness of the value of producing structured machine-readable datasets, the overwhelming majority of information is still published in a non-structured form. And the most highly used programming language for manipulating structured data, SPARQL, does not support statistical evaluation of the links between data.

In a recent paper in *Bioinformatics*¹, Norio Kobayashi and Tetsuro Toyoda, at BASE have detailed a practical advance in dealing with this problem (Fig. 1). They have developed a new computer language, General and Rapid Association Study Query Language (GRASQL), in which they have added to SPARQL procedures for associating entities using statistical measures. Based on their new language they

have generated a prototype rapid search engine that can be used to make statistical inferences in non-structured data.

In order to test the power of their computer language and its search engine, Kobayashi and Toyoda used it to evaluate links between keywords statistically, and applied it to problems such as ranking researchers in a particular field on the basis of their number of publications in that field. "It has also been applied to the PosMed system that is used to estimate those genes responsible for the phenotypes generated by N-ethyl-N-nitrosourea (ENU), which causes random mutations in genomes," says Toyoda. "The system has contributed to more than 50 discoveries in the ENU mutant mice project."

1. Kobayashi, N. & Toyoda, T. Statistical search on the Semantic Web. *Bioinformatics* **24**, 1002–1010 (2008).



Figure 1: Researchers at the RIKEN BASE division have developed a new search engine that allows machines to analyze statistically the semantic web of numerous databases containing scientific papers and omics data.

Easy multiferroics

The control of electric polarization using small magnetic fields augurs well for novel electronic devices

A rare class of materials, known as multiferroics, holds great promise for future applications, for example as data storage devices or sensors. However, progress has been hampered by the low operation temperatures and high magnetic fields required to control a property of the materials known as electric polarization. A solution to this problem may have been found by researchers from RIKEN's Advanced Science Institute in Wako and from the Japan Science and Technology Agency (JST), who have synthesized a multiferroic material in which electric polarization can be easily controlled by small magnetic fields.

In a ferromagnetic material, the individual magnetic moments of its atoms are aligned in one direction. In a ferroelectric material, if the positive and negative electric charges are uniformly separated electric polarization is generated. In multiferroic materials, magnetism and ferroelectricity occur simultaneously and both properties are coupled to each other.

Hexaferrites, compounds based on iron oxide, comprise a particularly interesting class of multiferroic materials and hold promise as novel high-temperature multiferroics. "Hexaferrites at present may be the best candidates for room-temperature multiferroics, as at least their magnetism exists up to room-temperature," comments team-member Shintaro Ishiwata.

In the journal *Science*¹, the researchers now report low-magnetic-field control over the electric polarization in the hexaferrite $\text{Ba}_2\text{Mg}_2\text{Fe}_{12}\text{O}_{22}$. This compound is part of a class of multiferroics

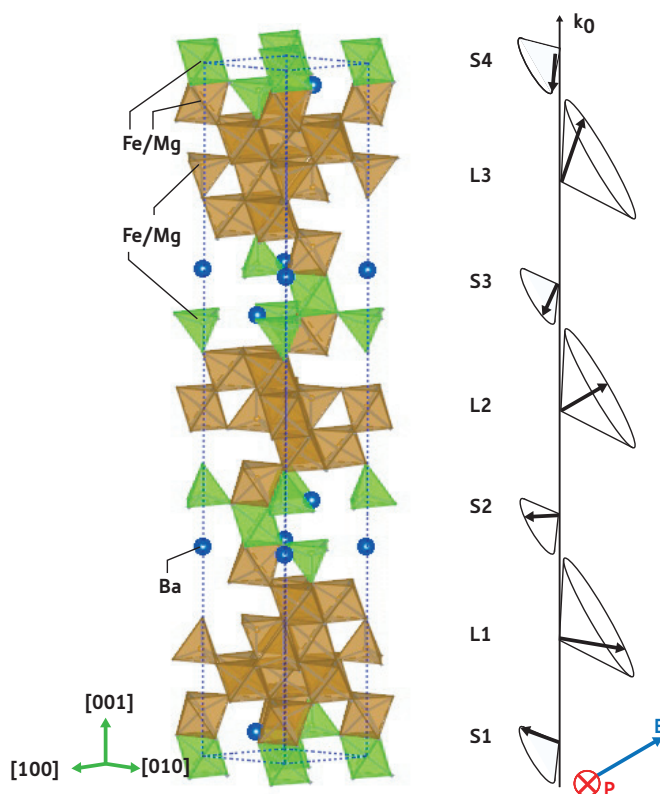


Figure 1: Multiferroic $\text{Ba}_2\text{Mg}_2\text{Fe}_{12}\text{O}_{22}$. The left panel shows the schematic crystal structure, and the right shows the corresponding magnetic moments. The magnetic moments show a periodic variation along the crystal axis, a so-called spin spiral. The spin spiral creates an electronic polarization P . As each individual magnetic moment rotates like a spinning top, small magnetic fields B significantly influence the spin spiral.

in which the ferroelectric polarization is generated by its unusual magnetic structure. The electric polarization is induced by so-called spin spirals, or cyclic variations in the orientation of the different magnetic moments along the crystal (Fig. 1).

The conical spiral structure found in $\text{Ba}_2\text{Mg}_2\text{Fe}_{12}\text{O}_{22}$ is particularly interesting, as the magnetic moments additionally rotate around their axis like small spinning tops. Just as spinning tops can be easily pushed off balance by a horizontal force, a small external magnetic field can significantly alter the properties of the spin spiral. This strongly influences the electric polarization through the magnetoelectric coupling.

For conical spin spirals, the sensitivity of the magnetic moments to external fields is

so strong that the ferroelectric polarization can be switched by magnetic fields that are almost two orders of magnitude lower than in other multiferroic compounds. "This provides an exciting avenue of exploring new multiferroic materials for novel electronic devices," says Ishiwata. However, as this effect remains confined to relatively low temperatures of 50 K (-223.15°C), the researchers now aim to develop multiferroic materials with similar properties for high-temperature operation, possibly up to room-temperature. ■

1. Ishiwata, S., Taguchi, Y., Murakawa, H., Onose, Y. & Tokura, Y. Low-magnetic-field control of electric polarization vector in a helimagnet. *Science* **319**, 1643–1646 (2008).

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New clues on organic superconductors

The transport properties of organic conductors are strictly connected to the internal geometry of crystals

Recent findings by a team of researchers from Japan and the United Kingdom could prove essential in explaining the origin of superconductivity in organic materials¹, and pave the way for the development of new organic materials. The origin of superconductivity has been attributed to magnetic interactions, but this has never been fully accepted because some non-magnetic insulators can become superconducting.

Takashi Yamamoto from RIKEN's Advanced Science Institute (now at Osaka University) and his colleagues have studied the charge states of β'' -type ET salts, which are a type of molecular charge-transfer salt. Until now, κ -type ET salts have been studied intensively as organic superconductors. Their crystal structure consists typically of two-dimensional molecular sheets intercalated by counter ions.

Yamamoto and colleagues focused on the β'' -type ET salts because they were convinced of the necessity to study how molecular charges and crystal structures are connected to the insulating, metallic and superconducting states of organic materials.

The team considered that the geometric arrangement of the molecules was the key element in determining the type of conducting state. If only one counter ion is present per every two molecules, then half of the molecules are charged and the other half are neutral. In this case, only a geometrical pattern that minimizes the interaction between charged molecules occurs. The charges are localized in a so-called charge-ordered state, and the material is insulating.

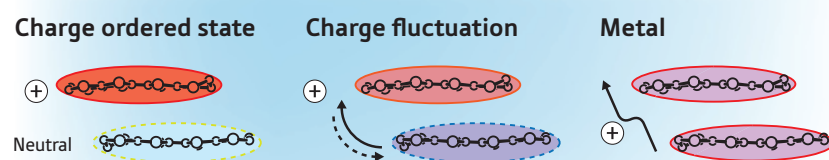


Figure 1: Sketch of the patterns corresponding to the three types of charge transport in ET salts.

Crystal structures, however, are not always that simple: when two counter ions are present per every three molecules, there is not always a single preferred configuration, and several geometrical patterns with different formation energies can occur. Most importantly, the charges are not necessarily localized to specific sites.

The technique used by Yamamoto and colleagues—vibrational spectroscopy—allowed them to investigate both the geometry of the molecular arrangement and the average time charges spend on specific sites. They confirmed that when the system is in an insulating state, the formation energy of one geometrical pattern is much lower than all other possibilities. In the case of a metal, several patterns had the same formation energy. Finally, superconductivity occurs when different patterns have different but close energies (Fig. 1). In this case, the

measurements also showed that charges fluctuate among sites within the crystal.

The observation is a breakthrough in understanding the pairing mechanism that yields superconductivity, according to Yamamoto. “The correlation between conducting behavior and the crystal structure will open the door to new organic materials, including superconductors, by using the crystal engineering method or organic synthesis.” ■

1. Yamamoto, T., Yamamoto, H.M., Kato, R., Uruichi, M., Yakushi, K., Akutsu, H., Sato-Akutsu, A., Kawamoto, A., Turner, S.S. & Day, P. Inhomogeneous site charges at the boundary between the insulating, superconducting, and metallic phases of β'' -type bis-ethylenedithio-tetrathiafulvalene molecular charge-transfer salts. *Physical Review B* **77**, 205120 (2008).

Lasers pushing the limits

The dissociation of nitrogen molecules by a free-electron laser signals a departure for more extreme light-matter interactions

When matter is hit by a laser-beam, the effects on the molecules can be dramatic, particularly for short pulses of high-intensity radiation. In a quest to push the limits of intensity to achieve extreme light-matter interactions in large molecules, a team of researchers from RIKEN's Advanced Science Institute in Wako, the SPring-8 Center in Harima, and the University of Tokyo, has demonstrated the ionisation and consequently the dissociation of nitrogen molecules using a free-electron laser.

Laser radiation is an electromagnetic wave that oscillates along a laser beam. These oscillating electromagnetic fields can exert strong forces on the electrons in a molecule, particularly at the very short wavelengths in the extreme ultraviolet (XUV) part of the spectrum. At high laser intensities, the influence on molecules increases, leading to a so-called Coulomb explosion (Fig. 1).

A Coulomb explosion is a process where the force exerted by the laser field is so strong on electrons in a molecule that an electron gets ejected and leaves positively charged ions. These ions strongly repel each other and the molecule quickly dissociates. However, few experimental studies on this process have been reported and "little is understood concerning the interaction of intense high-frequency light in the XUV with atoms and molecules," comments Katsumi Midorikawa from the research team.

So far, Coulomb explosions have been observed in hydrogen, deuterium and even in the much heavier nitrogen molecules using so-called higher harmonic laser sources. Experiments using these laser

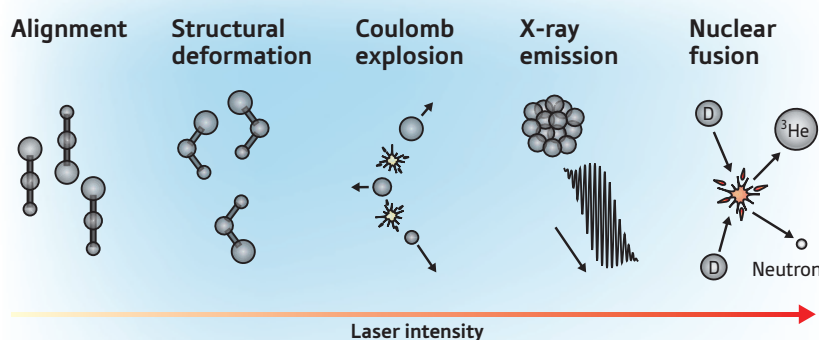


Figure 1: Various phenomena observed in molecules with increasingly intense optical laser fields.

sources reach the limits available with such technology owing to the amount of laser power that is required. Now, the team has demonstrated a Coulomb explosion of nitrogen molecules using the XUV free electron laser (XUV-FEL) at the SPring-8 site¹.

The researchers focused laser light of extremely short wavelengths of only 50 nm on nitrogen gas. They found that each nitrogen atom absorbs two light particles from the beam, providing sufficient energy to eject an electron, so that N_2 is transformed into the highly unstable N_2^{2+} molecule. Because of the strong repulsive forces, the two nitrogen ions separated. The detection of individual N^+ atoms provides conclusive evidence that a Coulomb explosion occurred.

Achieving a Coulomb explosion in this way is significant because, as Midorikawa comments, "the XUV-FEL laser has the potential to produce much higher beam intensities that will allow a much better study of the interaction of matter with strong electromagnetic fields." Indeed, experiments on larger molecules will commence once the XUV-FEL facility reaches full capacity. ■

1. Sato, T., Okino, T., Yamanouchi, K., Yagishita, A., Kannari, F., Yamakawa, K., Midorikawa, K., Nakano, H., Yabashi, M., Nagasono, M. & Ishikawa, T. Dissociative two-photon ionization of N_2 in extreme ultraviolet by intense self-amplified spontaneous emission free electron laser light. *Applied Physics Letters* **92**, 154103 (2008).

X-rays play the right hand

Circularly polarized x-rays of the proper energy can distinguish ‘left-’ and ‘right-handed’ structures of quartz

Many proteins, sugars and pharmaceuticals crystallize into two forms that are mirror images of one another—similar to the way a left and right hand mirror each other. Often, the two structures of these so-called enantiomers can have very different chemical properties.

The polarization of light typically changes depending on whether it passes through a ‘left-’ or ‘right-handed’ form of an enantiomer, providing a convenient means to tell them apart. X-rays, which are normally useful in determining the structure of materials and biomolecules, are much less sensitive to the ‘handedness’ of an enantiomer. Now, a team of scientists from Japan and the UK have shown that circularly polarized x-rays of the right energy can distinguish ‘left’ from ‘right’ α -quartz¹.

In the left and right forms of single-crystal α -quartz (SiO_2), the Si-O tetrahedra spiral in opposite directions, but conventional x-rays cannot tell them apart (Fig. 1). Team-member Yoshikazu Tanaka, an expert in x-ray diffraction at the RIKEN SPring-8 Center in Harima, says he found a way to separate these two forms of quartz essentially “by chance”. His colleagues were testing an x-ray diffractometer with a quartz crystal when they observed that the intensity of a diffraction peak from the quartz varied with the energy of the x-ray beam. This variation occurred particularly when the x-ray energy was near the atomic absorption edge of Si that occurs at 1.85 keV.

Tanaka suggested using the same x-ray energy to look for a reflection in α -quartz that is normally forbidden by the

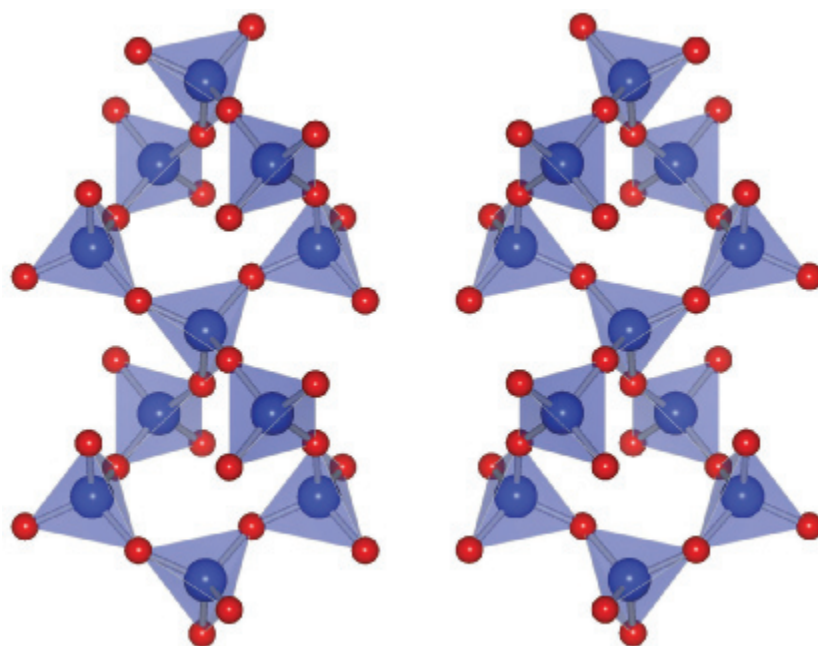


Figure 1: α -quartz (SiO_2) forms two crystal structures that are mirror images of one another. With circularly polarized x-rays that are tuned to the Si absorption edge, it is possible to tell the ‘left quartz’ (left) from the ‘right quartz’ (right).

symmetry of the crystal. Such a reflection could, he thought, be used to distinguish left from right if it became visible.

The idea worked: the team found the reflection and saw that at the ‘resonant’ energy of 1.85 keV, the intensity of the reflection depended on whether the crystal was of the left or right form. The fact that the x-rays were circularly polarized, as opposed to linearly polarized, was also essential to observe the large difference.

Much is already known about α -quartz but physicists would benefit from understanding how the handedness (also known as chirality) of a crystal develops as it grows. The team’s x-ray

technique has a clear advantage over optical techniques when applied to non-transparent materials such as metals or oxides, says Tanaka.

Tanaka is ultimately interested in using this technique to explore the role of chirality in a broad range of materials, including liquid crystals, biochemicals, magnets and multiferroics. ■

1. Tanaka, Y., Takeuchi, T., Lovesey, S. W., Knight, K. S., Chainani, A., Takata, Y., Oura, M., Senba, Y., Ohashi, H. & Shin, S. Right handed or left handed? Forbidden x-ray diffraction reveals chirality. *Physical Review Letters* **100**, 145502 (2008).

An open-and-shut case

The adsorption of gases onto the surface of flexible porous networks is a critical stage in the transformation of the porous structures

Researchers in Japan have revealed important information about why the threshold of gas pressure required for the structural transformation of flexible, three-dimensional molecular networks known as porous coordination polymers (PCPs) varies for different gases. The ability of PCPs to reversibly change their structure and properties on adsorption of 'guest' gas molecules has received considerable attention in recent years owing to their commercial potential in gas separation and sensing applications.

Flexible PCPs exist in two forms: a closed phase, in which guests, such as oxygen molecules, are unable to penetrate the structure; and an adsorbed phase that allows sorption of oxygen into the structure. Transformation from the closed to the adsorbed phase, which results in opening the 'gates' to structural channels, is guest-induced and occurs when the pressure of the gas—defined as P_{go} —is sufficient.

The research team, led by Susumu Kitagawa and including researchers from the RIKEN SPring-8 Center in Harima and from Kyoto, Okayama and Osaka-Prefecture universities, has used a kinetic study to show why the value of the threshold pressure required for the initially closed structure to become accessible is different for similar gases¹. Much of the commercial interest sparked in these materials has arisen from the difference of sorption behavior, that is, the difference in P_{go} for similar gases.

The flexible PCP synthesized by the team is formed from cadmium ions and organic ligands and shows that the value of P_{go} increases in the order of oxygen, argon

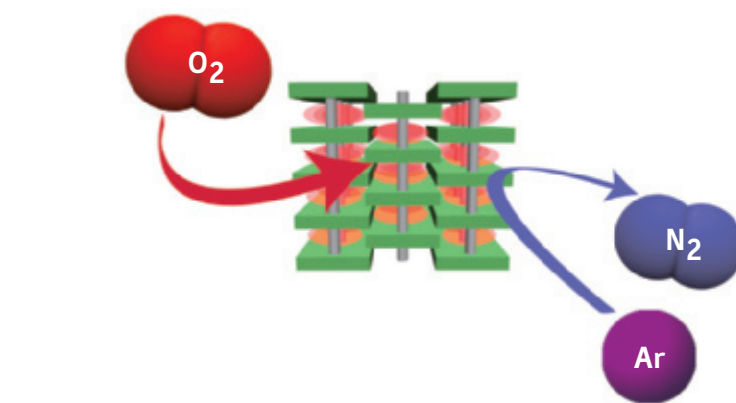


Figure 1: Selective gas adsorption of flexible PCPs. The onset pressure for the gate-opening process is lower for oxygen (O_2) than for nitrogen (N_2) and argon (Ar). As a result, within a certain pressure range, only oxygen adsorbs.

and nitrogen and so, at low pressures, only oxygen is adsorbed (Fig. 1).

The researchers believe that their kinetic investigation of the structural transformation should further our knowledge and hence, allow the gas adsorption performance of PCPs to be fine-tuned.

According to RIKEN team-member Masakazu Higuchi, an 'intermediate phase' exists at the point of gate-opening and, it is the formation kinetics of this intermediate that determines P_{go} . Moreover, the kinetic behavior suggests that the gate-opening process is attributable to condensation of the adsorbate on the surface of the crystal, indicating that surface chemistry, rather

than crystal structure analysis, needs to be probed to fully understand the gate-opening process.

The team hopes to investigate the process further by observing the surface using microscopic techniques and, in the long-term future, it may be possible to modify the crystal surface and hence, create a new mechanism for adsorption.

1. Tanaka, D., Nakagawa, K., Higuchi, M., Horike, S., Kubota, Y., Kobayashi, T. C., Takata, M. & Kitagawa, S. Kinetic gate-opening process in a flexible porous coordination polymer. *Angewandte Chemie International Edition* **47**, 3914–3918 (2008).

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Miniscule nuclear molecules

A theoretical study of a beryllium isotope shows the formation of several molecular states between subunits of the nucleus

Researchers at the RIKEN Nishina Center for Accelerator-Based Science in Wako, and the University of Tokyo, have demonstrated theoretically the formation of different molecular states in nuclei at the femtometer scale¹. A femtometer is one quadrillionth of a meter.

Makoto Ito of RIKEN and colleagues were interested in the similarities between nuclei and atoms. The interactions between the elementary particles in these systems are very different. In atoms, the electrons repel each other but are kept together by an attractive interaction with the protons in the nucleus. In nuclei, the nucleons—protons and neutrons—are kept together by a strong, attractive nuclear interaction. In both systems, however, the result is the formation of a shell structure. “We [therefore] expected the formation of molecule-like configurations in nuclear systems, which are an analogue to molecules in atomic physics,” explains Ito. These molecules would be only a few femtometers wide, which is the typical size of nuclei.

The existence of such molecular states would be particularly favored in neutron-rich nuclei, that is, those with more neutrons than protons. In these nuclei, some of the excited states could result from the nucleus dividing into sub-nuclei that are bound together by the extra neutrons.

The researchers focused on the beryllium isotope ^{12}Be , which has two alpha particles—Helium nuclei—and four extra neutrons. Their calculations show that ^{12}Be does indeed exhibit molecular states with the alpha particles as subunits. Depending on the level of excitation

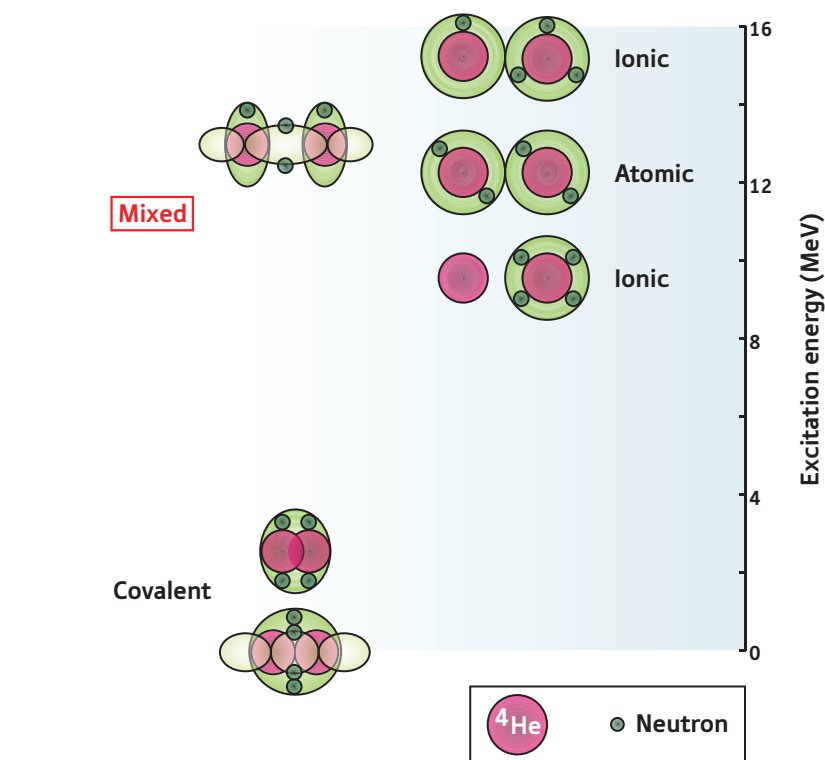


Figure 1: Miniscule nuclear molecules. Excited states of a ^{12}Be nucleus exhibit several types of femtoscale molecular states.

energy in the nucleus, different types of bonds hold these molecules together (Fig. 1). In the case of ionic or valence bonding, the two subunits do not mix and effectively create the analogue of a diatomic molecule. In the case of covalent bonding of the two alpha particles through the valence neutrons, the system is not really divided into two sub-nuclei.

Apart from confirming the existence of the molecular states, Ito believes that their most important result is finding the co-existence of different types of bonding in the same system. “In molecular physics, there is a one-to-one correspondence

between the type of bonding (covalent or valence) and the chemical system. Namely, the form of bonding is unique for each molecule,” he explains. “In marked contrast, both valence and covalent bonding coexist in a nuclear system. This is a characteristic property which arises in a nuclear system governed by a strong nuclear interaction.” ■

1. Ito, M., Itagaki, N., Sakurai, H. & Ikeda, K.

Coexistence of covalent superdeformation and molecular resonance in an unbound region of ^{12}Be . *Physical Review Letters* **100**, 182502 (2008).

Right on target

Short-lived nuclei can be efficiently trapped for study in the electron beam of a high-energy electron storage ring

A team of Japanese researchers has developed a technique that will enable the study of the internal structure of unstable (radioactive) nuclei with electron scattering¹.

In an electron scattering measurement an electron is accelerated up to several hundreds of MeV (106 eV) and scatters from a charged nucleus. “This technique is the only way to determine precisely—and model independently—the proton distribution in a nucleus,” explains Masanori Wakasugi from the RIKEN Nishina Center for Accelerator-Based Science in Wako. “Electron scattering measurements have greatly contributed to the establishment of nuclear structure models that are written in current textbooks.”

It has not been possible, however, to use this technique to study short-lived nuclei because of the difficulty in confining a sufficiently large number of such nuclei in a target. What this means in practice is that the collision luminosity—a measure of how likely an electron is to scatter from a nucleus—for unstable nuclei has to be quite high.

The team designed a high-luminosity target in the *Kaken* electron storage ring at Kyoto University that takes advantage of the ion-trapping potential of the circulating electron beam (Fig. 1). Cesium (Cs^{1+}) ions were accelerated up to 4.05 keV and injected into the electron beam in a region that forms the target. The target, named SCRIT (self-confining radioactive isotope ion target), is about 200 mm long and made up of 40 longitudinally stacked, thin electrodes that can trap the ions in an electrostatic potential. Because the target ions are confined within a region that is

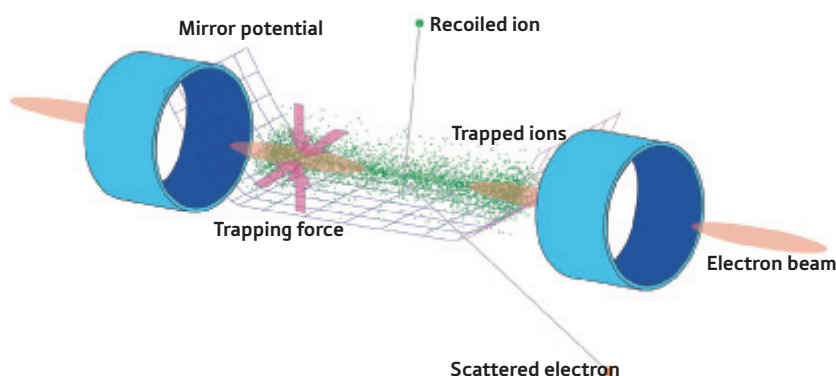


Figure 1: The SCRIT nuclear target permits electron scattering measurements to be performed on short-lived (radioactive) nuclei. The trap makes use of the electron beam in a high-energy electron storage ring. Cesium ions are confined transversely by the electron beam (green dots) and longitudinally by an electrostatic potential (indicated by the grey grid).

the same size as the electron beam, it is possible to achieve a high luminosity even with a small number of ions.

Specially designed detectors determine the ionization state of the Cs ions and the energy and trajectory of the scattered electrons. The team determined that the Cs ions remain trapped for about 85 ms and that the electrons have a high probability of interaction with the trapped ions indicating a high luminosity. Although the experimentally measured luminosity is about 40 times lower than would be needed to perform electron scattering on unstable nuclei, a higher electron beam current could make up the difference.

The study of nuclei far from stability may ultimately help in developing a general theory of nuclei, according to Wakasugi. In addition, unstable nuclei play an important role in nucleosynthesis. The SCRIT would enable radioactive nuclei with a half-life of as little as 100 ms to be studied. ■

1. Wakasugi, M., Emoto, T., Furukawa, Y., Ishii, K., Ito, S., Koseki, T., Kurita, K., Kuwajima, A., Masuda, T., Morikawa, A., *et al.* Novel internal target for electron scattering off unstable nuclei. *Physical Review Letters* **100**, 164801 (2008).

A four-dimensional picture of our three-dimensional world

Scientists use a theory that exists in higher dimensions to better understand the process by which a neutron decays into a proton

An international team of scientists from RIKEN at Brookhaven National Laboratory (BNL) and elsewhere in the USA, Japan and the UK are testing the Standard Model—the foundation of high-energy physics that unifies three of the four known forces found in nature—by calculating a well-known nuclear decay process¹.

Summarizing the work, Thomas Blum, a member of the team, says: “We want to understand the structure of the particles in the nucleus from the standpoint of the Standard Model, in general, and quantum-chromodynamics (QCD), in particular. QCD is the theoretical basis for the strong force between quarks, the particles that make up neutrons, protons and other particles that are the building blocks of matter in our universe.”

Most of the predictions of the Standard Model, which was developed in the 1960s, can only be tested at high-energy particle accelerators, such as CERN in Switzerland, or the Relativistic Heavy Ion Collider (RHIC) at BNL in the USA. In contrast, beta decay in radioactive nuclei is a well-known process that can be measured, extremely accurately, with a simple experimental set-up. Beta-decay occurs when a neutron emits an electron and a massless particle called a neutrino (Fig. 1). In so doing, the neutron turns into a proton.

Blum and colleagues calculated the part of the decay rate of the neutron that depends on QCD, using a numerical method called ‘lattice gauge theory’ in which each point on a grid corresponds to a point in space-time. By solving the problem on successively finer grids,

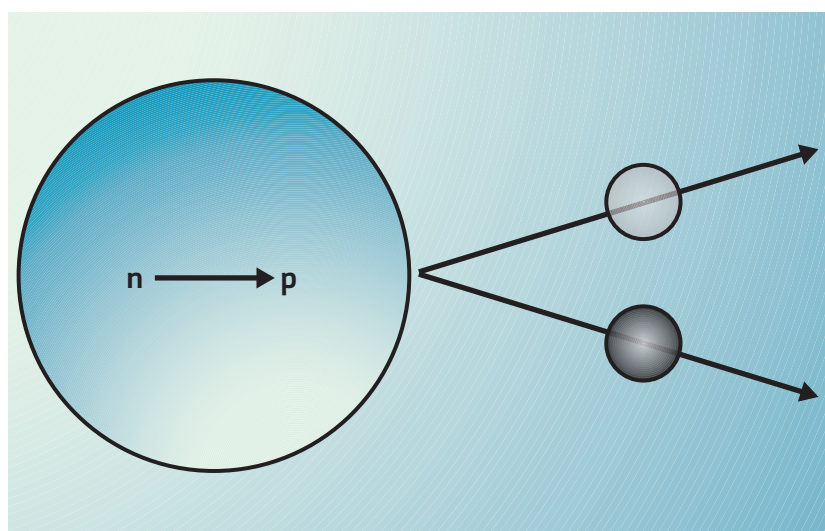


Figure 1: In nuclear beta decay, a neutron (blue sphere) emits an electron (light grey) and a massless particle called a neutrino (dark grey). In so doing, the neutron turns into a proton.

the calculations approach the true ‘continuum limit’ of the real world. The state-of-the-art calculations were made possible through the use of the QCDOC supercomputers at Columbia University, the RIKEN BNL Research Center, and the University of Edinburgh.

Most implementations of lattice gauge theory correspond to three spatial dimensions and one time dimension, but Blum and his colleagues use a ‘mathematical trick’ called ‘domain wall fermions’. They perform their calculations in four space dimensions—only reducing their answer back to the three-dimensional world at the end. The trick allows the group to capture important

physics that most three-dimensional theories cannot.

An important aspect of the work lies in being able to test a sophisticated numerical technique that is consistent with the Standard Model and QCD against a simple result—neutron beta-decay. Confirmation that their results are accurate gives theorists the confidence to pursue increasingly complex problems in particle and nuclear physics. ■

1. Yamazaki, T., Aoki, Y., Blum, T., Lin, H.W., Lin, M. F., Ohta, S., Sasaki, S., Tweedie, R.J. & Zanotti, J.M. Nucleon axial charge in (2+1)-flavor dynamical-lattice QCD with domain-wall fermions. *Physical Review Letters* **100**, 171602 (2008).

Closing the gap in understanding a broken symmetry

A 'toy' theoretical model may advance our understanding of a fundamental concept in particle physics

From a recent theoretical study, Japanese high-energy particle physicists have provided an important new method to apply to a fundamental concept known as supersymmetry.

Particle physicists have long struggled with what is known as the 'hierarchy problem': the relative weakness of the gravitational force compared with the other known forces in nature. The world we live in—and can measure—exists at energy scales up to about 100 GeV. Yet, there is a fundamental length scale—the Planck scale—at which gravitational interactions become so strong, they cannot be handled by existing quantum theory. At the Planck scale, energies reach 10^{19} GeV.

To deal with this huge discrepancy in energy scales, theorists developed the supersymmetry concept, which predicts that every fermion—particles like electrons and protons—has a 'supersymmetric' partner that is a boson—particles like photons or helium atoms—of equal mass. The existence of these partner states provides a framework in which theorists can naturally connect our low-energy world with the Planck scale.

"What this means is that there must be, in nature, a boson that has precisely equal mass to the electron. That boson is termed the 'selectron,'" explains Hiroshi Suzuki of RIKEN's Nishina Center for Accelerator-Based Science, Wako. But, no such particle has been observed in nature. According to Suzuki, this shows that although the underlying theory might be supersymmetric; supersymmetry must somehow break spontaneously in nature.



Figure 1: In 'lattice gauge theory', space and time are represented by discrete points on a grid. This allows theorists to perform calculations numerically, using state-of-the-art computational methods.

But how does supersymmetry break? Most efforts to understand this from first principles are restricted to models that can be studied without taking quantum fluctuations—energy fluctuations consistent with a principle known as the Heisenberg uncertainty principle—into account. However, as reported in the journal *Physical Review D*, Suzuki and co-authors have developed the computational tools that allow them to treat symmetry breaking that occurs only through quantum fluctuations¹.

The calculations were performed using so-called 'lattice gauge theory' (Fig. 1). However, even with advancements in their computational tools, the group must use a simplified, or 'toy', model. Although

the results of their calculations using this model are not immediately applicable to a real experimental situation in particle physics, Suzuki and colleagues believe that their study provides an important clue for subsequent computational approaches to understanding supersymmetry breaking.

Advancements in understanding supersymmetry are particularly timely as one objective for the new Large Hadron Collider at CERN in Switzerland will be the detection of superpartner particles. ■

1. Kanamori, I., Suzuki, H. & Sugino, F. Euclidean lattice simulation for dynamical supersymmetry breaking. *Physical Review D* **77**, 091502(R) (2008).

Twisting around the palladium

A metal catalyst teaches an old chemical reaction new tricks

A new twist on a common chemical reaction has enabled RIKEN scientists to create molecules that are useful building blocks for making new pharmaceuticals.

The aldol reaction is a very reliable way to stitch together two carbon-based organic molecules that each contain a carbonyl group—a carbon atom doubly bonded to an oxygen atom.

Organic chemists have devoted enormous effort to developing asymmetric forms of this reaction. The products of these reactions cannot be superimposed on their ‘mirror image’ molecule—just as your left hand cannot be superimposed on your right.

Nature often selects molecules of a particular handedness; so many pharmaceuticals must be the correct mirror image form. But it is often difficult to synthesize a chemical of one handedness without also producing an equal amount of its twin.

Pilot molecules are often added to these reactions to steer their progress, ensuring that the correct form of the desired chemical is produced. Ideally, these molecules should speed up the reaction even though they are present in only trace amounts, and should not be consumed by the reaction. Chemists call them asymmetric catalysts.

Mikiko Sodeoka and colleagues at RIKEN’s Advanced Science Institute in Wako have now developed an asymmetric catalyst that connects two different types of molecular building blocks— β -ketoesters and acetals—in an aldol reaction to form new compounds of a single handedness (Fig.1)¹. “This type of aldol reaction has long been recognized

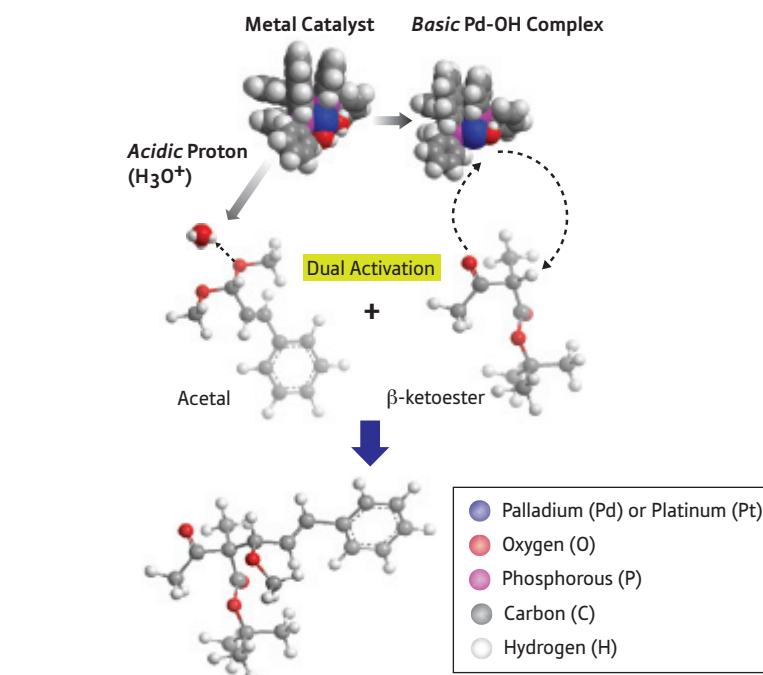


Figure 1: An asymmetric aldol-type reaction catalyzed by a palladium acid-base catalyst.

to be notoriously difficult, and the key to success is the double activation by the Pd complex as an acid-base catalyst,” says Sodeoka.

The catalyst is made from the metal palladium, attached to a bulky molecule called binap which has a twist in its structure. This twist ensures that the β -ketoester molecule sticks to the central palladium metal atom in a specific way—which, in turn, determines the orientation of the acetal connecting to it.

Sodeoka and her team tried a range of different β -ketoester and acetal combinations, and found that in most cases the catalyst helped to form the product in almost entirely the correct handedness. The compounds can in

principle be converted into important building blocks for many drugs, which would otherwise be difficult to make catalytically using conventional methods.

The team also developed an alternative catalyst, which used platinum in place of palladium, and found that it was more resistant to decomposition in those reactions which took a long time to complete. They now hope to refine the catalysts’ design, and use them to create more complex, bioactive molecules. ■

1. Umebayashi, N., Hamashima, Y., Hashizume, D. & Sodeoka, M. Catalytic enantioselective aldol-type reaction of β -ketoesters with acetals. *Angewandte Chemie International Edition* **47**, 4196-4199 (2008).

Zirconium takes the strain from carbon rings

‘Impossible’ molecule undergoes improbable chemistry

An unusual molecule once thought to be too strained to exist has been transformed into another contorted compound by RIKEN chemists, testing the limits of how far carbon-based molecules can be distorted by combining them with metal atoms.

The complexity of organic chemistry is largely due to the tendency of carbon atoms to join together into chains and rings. Yet carbon–carbon triple bonds ($\text{C}\equiv\text{C}$ –, also known as alkynes) are relatively rare in ring systems, because they prefer to connect to other atoms in straight lines.

It’s just about possible to bend this alkyne group so that it will fit into a ring of seven carbon atoms. But smaller rings are extremely reactive, due to the strain put on that triple bond, explains Noriyuki Suzuki of RIKEN’s Advanced Science Institute in Wako. “It was believed that it was impossible to isolate them in a pure form,” he says.

However, in 2002 Suzuki’s team reported that they had made a ring of just five atoms which included an alkyne group, yet was extremely stable and could be isolated as crystals. Their secret was that one of the atoms in the ring was a zirconium atom¹.

The researchers are now exploring how this molecule behaves. Recently, they have used it to create another ring system containing two carbon–carbon double bonds sitting side by side ($\text{C}=\text{C}=\text{C}$ –), also known as an allene. Under normal circumstances a five-membered ring containing an allene would be too strained to exist for long—but with the zirconium atom in place, the team found that the cycloallene compound could be isolated (Fig. 1).

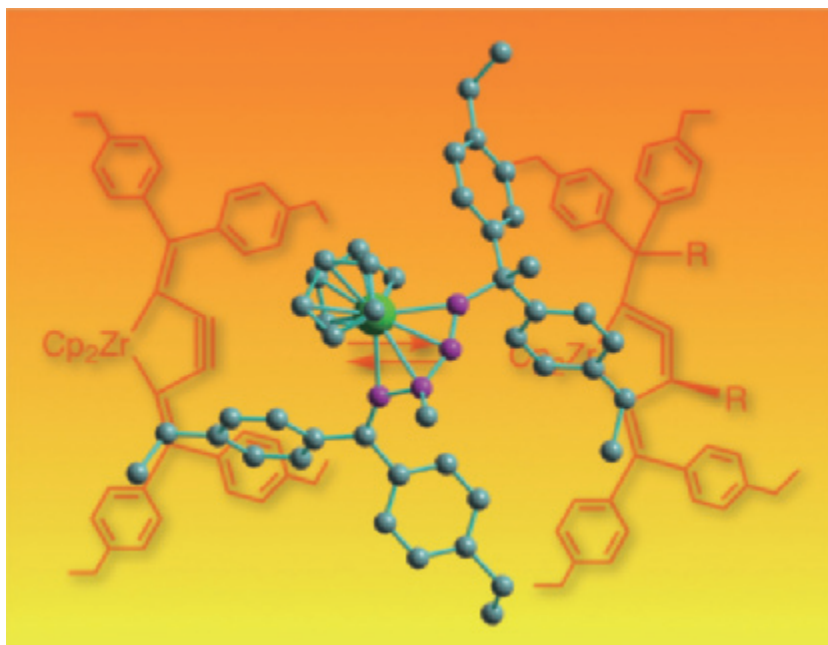


Figure 1: Pushing back the boundaries of chemistry. This molecular structure shows a zirconium atom (green) sitting in a ring with four other carbon atoms (purple) in the new cycloallene compound. In the background, the chemical reaction shows the interconversion between alkyne and allene.

The team made the compound by mixing lithium or potassium into a solution of their zirconium–alkyne ring, which gave it a negative charge and a deep blue color. Adding a reagent such as iodomethane then formed the cycloallene—although the team was surprised that adding a source of hydrogen atoms formed a mixture of a cycloallene and a cycloalkene, which contained just a single carbon–carbon double bond².

Suzuki says that these compounds are unlikely to have any practical uses. Instead, the research pushes back the boundaries of chemistry that would once have been thought impossible. Suzuki notes that another group recently made a similar compound which included a hafnium atom³.

The team is now testing the physical and chemical properties of the new compounds, and trying to clarify exactly why these molecules are so stable. ■

1. Suzuki, N., Nishiura, M. & Wakatsuki, Y. Isolation and structural characterization of 1-zirconacyclopent-3-yne, five-membered cyclic alkynes. *Science* **295**, 660–663 (2002).
2. Suzuki, N., Hashizume, D., Koshino, H. & Chihara, T. Transformation of a 1-zirconacyclopent-3-yne, a five-membered cycloalkyne, into a 1-zirconacyclopent-3-ene and formal “1-zirconacyclopenta-2,3-dienes”. *Angewandte Chemie International Edition* **47**, 5198–5202 (2008).
3. Ugoletti, J., Dierker, G., Kehr, G., Fröhlich, R., Grimme, S. & Erker, G. Five-membered metallacyclic allenoids: synthesis and structure of remarkably stable strongly distorted cyclic allene derivatives. *Angewandte Chemie International Edition* **47**, 2622–2625 (2008).

New route to specific sugars

A new method to selectively synthesize unusual linkages for sugar derivatives allows scientists access to important biological compounds

Glycoconjugates—carbohydrates that are chemically linked to another compound—constitute biologically important molecules. The two parts of the glycoconjugate are joined by what is known as a glycosidic linkage of which there are several types. Each type of linkage results in a different spatial arrangement of the two components but it is the selection of the linkage and the resulting spatial configuration that is critical for a glycoconjugate's biological activity within a larger molecule.

Yukishige Ito, Yong Joo Lee and Akihiro Ishiwata from the RIKEN Advanced Science Institute (formerly the Discovery Research Institute), in Wako, have now developed a method to selectively synthesize a glycoconjugate, β -L-rhamnopyranoside, an important constituent of polysaccharides in bacteria, such as *Sphaerotilus natans*, that stimulate an immune response¹.

Although a number of new methods for glycosidic linkages exist, they are often

unselective or able only to link a limited range of compounds, aglycons, to the carbohydrates. In addition, the synthesis of one specific linkage, known as a 1,2-*cis* linkage has been particularly challenging. It is this 1,2-*cis* linkage that is present in β -L-rhamnopyranoside.

Ito and colleagues proposed a new approach to the synthesis of β -L-rhamnopyranoside. The approach exploits the use of 2-naphthylmethyl (NAP) ether to form a temporary linkage between the carbohydrate and the aglycon as a bridge compound. This bridge brings the two components into close proximity and then an intramolecular reaction forms the desired glycoconjugate (Fig. 1). Similar methods have been applied to the synthesis of other complex saccharides.

"This approach had been expected to be a promising method to get 1,2-*cis* isomer, however, there were some problems to overcome," explains Ito. The technique, known as intramolecular aglycon delivery (IAD), is necessarily a two-step reaction

and so the yield of each step needed to be optimized. Also, the bridge compound could link two carbohydrate compounds or two aglycons together giving an unproductive intermediate.

Following optimization of the reaction, the team successfully used the IAD technique to selectively form the 1,2-*cis* linkage to produce β -L-rhamnopyranoside without using an excess of the substrates. They also found that a wide range of aglycons could be used demonstrating a general use for this reaction.

Overall, Ito and colleagues' study to improve synthetic methods for unusual glycoside linkages has been ongoing for over a decade. This latest advance means that the team can now go on to synthesize other important polysaccharides, that also include the important 1,2-*cis* linkages, and further investigate their biological significance. ■

1. Lee, Y.J., Ishiwata, A. & Ito, Y. Stereoselective synthesis of β -L-rhamnopyranosides. *Journal of the American Chemical Society* **130**, 6330–6331 (2008).

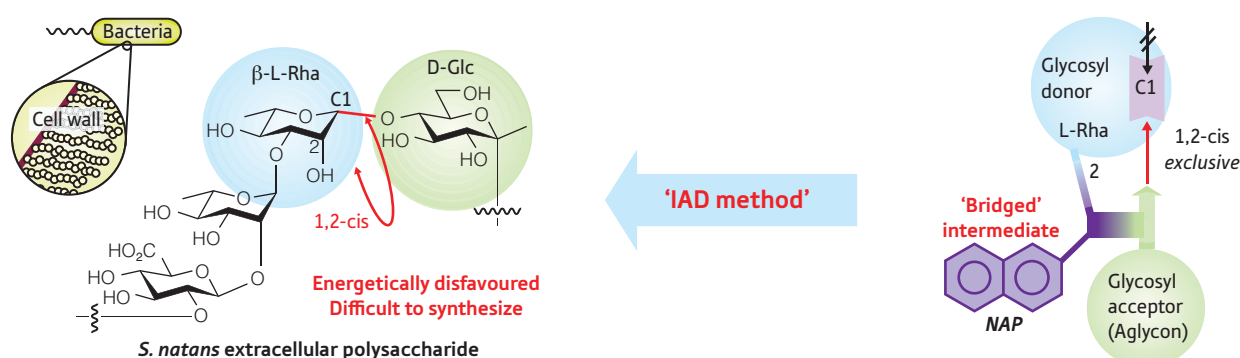


Figure 1: An illustration of the intramolecular aglycon delivery (IAD) method that links together two component parts of a polysaccharide through a temporary bridge. This temporary bridge guarantees exclusive formation of the desired isomer.

What's in a whiff

Mice have different ways of processing the smell of gender and relatedness

Mice use only a small number of smell or olfactory receptor cells—which respond exclusively to the urine of males or of females—to discriminate gender, an international research team led by Ron Yu has found. In contrast, information distinguishing strains and individuals is encoded in the combinations or patterns of the cells which are stimulated.

The team worked on sensors in the mouse vomeronasal organ (VNO) at the base of nose to produce the first report of how mice extract such information from smell. It is a step towards understanding how smell impacts behavior, knowledge that could be applied to controlling pest animals.

Previous studies have determined that the chemicals known as pheromones, released by animals into the external environment, play an important role in social communication in rodents (Fig. 1). They trigger hormonal changes and a range of aggression and mating behaviors, and are detected in the VNO by more than 250 individual cell types, each of which carries only one kind of odorant receptor.

In a recent paper in *Science*¹, the team, including Junichi Nakai from the RIKEN Brain Science Institute in Wako, details its studies on how information on gender and individuals is encoded in smell.

Calcium increases in the cell when a receptor is activated by a pheromone. So the researchers engineered mice which produce a biosensor molecule in VNO receptors that fluoresces when binding calcium. The level of fluorescence detected is proportional to the excitation level of cells activated.



Figure 1: Much of rodent social communication hinges on the pheromones they secrete.

The researchers then exposed thousands of olfactory receptors contained in sections of the VNO of several different individuals to urine of male and female mice. They found that while the urine activated many receptors, less than 1% responded only to male mouse urine and about 2.6% responded exclusively to female urine. When the information from these few cells was removed from the analysis, the urine samples could not be discriminated in terms of gender.

Information on strain and individual identity, however, was encoded in the patterns of cells activated. Littermates, for instance, stimulated about 87.5% of

the same receptors as each other; non-littermates only about 36%. Information on the strain of mouse and the stage of the estrus cycle in females is also provided by the combinations of receptors activated.

“We are interested in determining how pheromones relate to behavior,” Nakai says. “We began with the primary sensory neuron, the receptor. Our next target is the accessory olfactory bulb, the next center of information processing.” ■

1. He, J., Ma, L., Kim, S-S., Nakai, J. & Yu, C.R. Encoding gender and individual information in the mouse vomeronasal organ. *Science* **320**, 535–538 (2008).

Synaptic protein coupling

Electrical activity between neurons can regulate protein interactions at the synapse

Changes in protein interactions at the synapse—or junction between neurons—play a key role in many important processes during brain development, such as synapse maturation, learning and memory formation. A team of scientists, led by Katsuhiko Mikoshiba at the RIKEN Brain Science Institute in Wako, has identified how synaptic activity can regulate the binding of an adaptor protein, Homer3, to one of its targets, a membrane receptor for the neurotransmitter glutamate called metabotropic glutamate receptor 1 α (mGluR1 α)¹.

Synaptic activity results in an influx of calcium ions into the neuron, which turns on an enzyme called calcium/calmodulin-dependent protein kinase II (CaMKII). The researchers showed that active CaMKII chemically modifies Homer3 by adding phosphate groups onto the protein in a type of neuron known as the Purkinje cell (Fig. 1). This phosphorylation reaction causes Homer3 to be expelled from the synapse and into the cytoplasm of the neuron, which may serve to communicate the activation state of that synapse to the rest of the cell.

Akihiro Mizutani, the first author of the paper, believes that Homer3 phosphorylation “triggers the reorganization of the molecular architecture at the synapse, which can be a synaptic tag for long-lasting synaptic plasticity.”

Homer3 usually binds to mGluR1 α at the membrane, coupling this glutamate receptor to another protein that regulates intracellular calcium stores. Mikoshiba and his colleagues found that phosphorylation of Homer3 inhibits

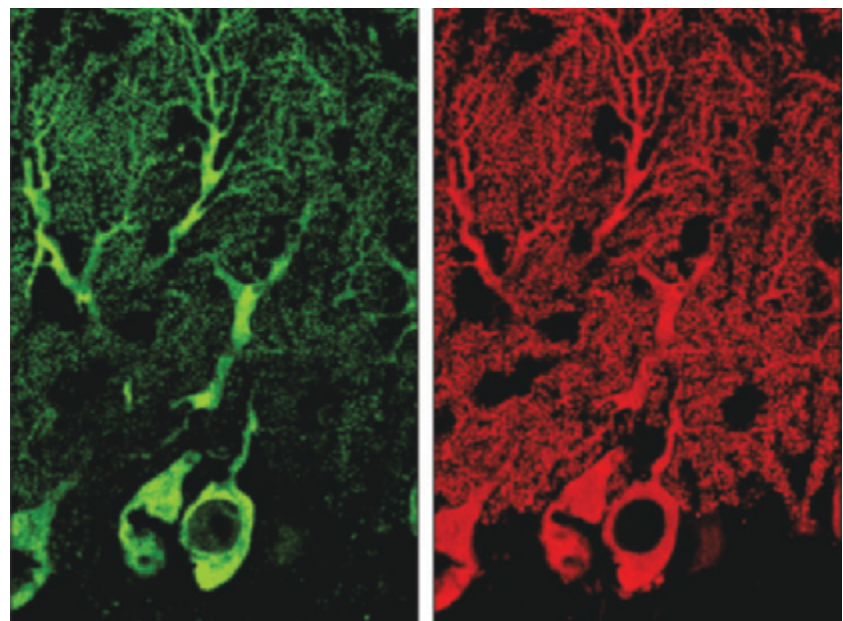


Figure 1: Phosphorylation alters Homer3 distribution in Purkinje cells of young mice. Homer3 protein (red) is distributed throughout Purkinje cells. By contrast, phosphorylated Homer3 (green) is preferentially distributed in soma, proximal dendrites, and some parts of postsynaptic regions in Purkinje cells.

its binding to mGluR1 α . This switch in the Homer3-mGluR1 α interaction was functionally important, because cells in which this switch was activated had a different pattern of calcium release from intracellular stores in response to glutamate than cells in which the switch was turned off.

One important message from this work is that synaptic activity can very quickly induce changes in molecular interactions, which can translate to changes in calcium signaling inside the cell. An increase in intracellular calcium at the synapse is a key step in altering the strength of synaptic connections, which is thought to be necessary for the formation of new memories.

Because the work was performed in Purkinje cells from young mice within the cerebellum, the part of the brain involved in motor learning, the findings suggest that the regulation of Homer3 phosphorylation may be involved in this important process during development.

If this mechanism is also operating in other areas of the brain and in older animals as well, the findings may also be more widely relevant to other forms of learning. ■

1. Mizutani, A., Kuroda, Y., Futatsugi, A., Furuichi, T. & Mikoshiba, K. Phosphorylation of Homer3 by calcium/calmodulin-dependent kinase II regulates a coupling state of its target molecules in Purkinje cells. *The Journal of Neuroscience* **28**, 5369–5382 (2008).

Global genetic risk for osteoarthritis

A gene mutation and susceptibility to arthritis are linked in two highly divergent ethnic groups

An international team of scientists, including Shiro Ikegawa and colleagues at the RIKEN Center for Genomic Medicine (formerly the SNP Research Center) in Yokohama, has reported in the journal *Human Molecular Genetics*¹ a 'global' role for a specific variant, or polymorphism, of a gene in the susceptibility to osteoarthritis (OA). A large-scale statistical analysis of new data shows that mutation of a gene called *GDF5* (growth differentiation factor 5) and susceptibility to OA is wide-spread among European and Asian populations.

OA, also known as idiopathic degenerative arthritis, is the most common type of arthritis worldwide, affecting hundreds of millions of people every year. Like many human diseases, OA has several causes, including non-genetic (environment, trauma) factors; however, an underlying genetic component of OA has been clearly established by many studies.

Examining data from the UK and the Netherlands combined with three published European and Asian studies that were previously inconclusive, the researchers used a statistical analysis called meta-analysis to look for evidence of an association between the *GDF5* risk gene and susceptibility to OA. Meta-analysis combines data from several individual studies into a single dataset, which can increase the statistical power over that of the individual studies.

Analysis of the combined data—representing more than 11,000 individuals—revealed a significant association of the *GDF5* polymorphism and OA susceptibility. However, differences were noted in the risk of

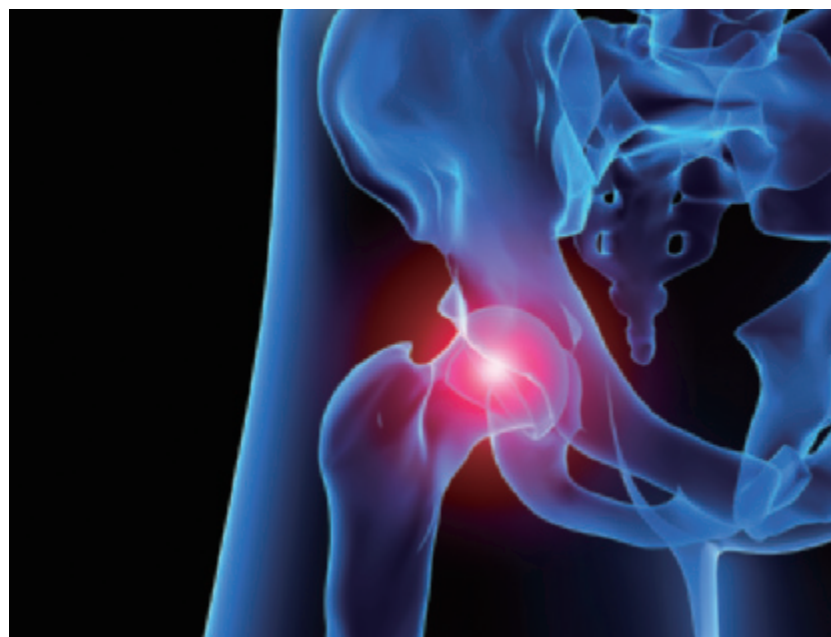


Figure 1: A pictorial representation of an inflamed hip as in OA.

developing OA in the hip or the knee: European and Asia individuals in fact have a similar risk for knee OA. But the meta-analysis helped to reveal the significant risk for hip OA in Europeans.

Ikegawa's team has studied *GDF5* for several years, initially linking the specific polymorphism in *GDF5* to OA in Asians, and producing mice with the *GDF5* mutation. The protein produced by the *GDF5* gene is normally involved in joint formation and especially important for development and regeneration of cartilage, the dense but pliable connective tissue on the surface of joints most susceptible to OA, such as the hip (Fig. 1).

Commenting on number of other genes that are known to be associated with genetic risk for OA, Ikegawa says: "In a strict sense, there are none. Only *GDF5* and asporin [a second gene Ikegawa's team previously linked to OA²] have definite functional data supporting

the causality of OA, and replication in different ethnic groups." The paucity of other known genetic factors highlights the importance of the present study for estimating risk for OA.

1. Chapman, K., Takahashi, A., Meulenbelt, I., Watson, C., Rodriguez-Lopez, J., Egli, R., Tsezou, A., Malizos, K.N., Kloppenburg, M., Shi, D., *et al.* A meta-analysis of European and Asian cohorts reveals a global role of a functional SNP in the 5' UTR of *GDF5* with osteoarthritis susceptibility. *Human Molecular Genetics* **17**, 1497–1504 (2008).
2. Nakamura, T., Shi, D., Tzetis, M., Rodriguez-Lopez, J., Miyamoto, Y., Tsezou, A., Gonzalez, A., Jiang, Q., Kamatani, N., Loughlin, J. & Ikegawa, S. Meta-analysis of association between the ASPN D-repeat and osteoarthritis. *Human Molecular Genetics* **14**, 1676–1681 (2007).

Getting to the bottom of lower-back pain

Genetic analysis reveals a biochemical pathway involved in the pathology of a painful spinal disorder

Lumbar-disc herniation (LDH), in which the cushioning discs that separate and protect the vertebrae of the lower back become deformed or ruptured (Fig. 1), can cause profound discomfort in patients. In severe cases, surgery is required to relieve the resulting back and leg pain.

Accumulating evidence suggests a genetic component to LDH, and most candidate genes identified to date have been involved in maintaining the extracellular matrix (ECM)—the protein scaffolding that serves as infrastructure for the connective tissue that composes the spinal discs.

Now, new work from a group led by Shiro Ikegawa of the Center for Genomic Medicine in Yokohama has revealed the involvement of a novel ECM-related biochemical pathway in hereditary LDH¹. Previous studies have suggested that *THBS1* and *THBS2*, two genes encoding proteins from a family known as thrombospondins, might be associated with LDH, and Ikegawa's group began their study by performing genomic analyses on Japanese LDH patients to see if this condition could potentially be linked to mutations in either of these genes.

Their analysis led to the identification of a single-nucleotide sequence variation in the *THBS2* gene that showed significant association with LDH. This mutation appears to lead to altered processing of the RNA transcribed from *THBS2*, producing a variant of the protein that lacks a domain involved in mediating protein–protein interactions.

In this case, the relevant interacting proteins are matrix metalloproteinases (MMPs), enzymes that break down the



Figure 1: A magnetic resonance image (MRI) of herniated discs in the lower back.

ECM and play a role in tissue remodeling and repair. The mutation identified by Ikegawa's group was found to impair the interaction of THBS2 with certain MMPs, suggesting that these enzymes—and their regulation by THBS2—may play an important role in LDH.

In a follow-up genetic study, this hypothesis gained support after an additional LDH-associated mutation was discovered in *MMP9*, a gene encoding one of the MMPs specifically known to interact with THBS2. In fact, these two mutations in combination were found to associate especially strongly with the occurrence of LDH.

These data suggest a novel mode of regulation for *MMP9* via *THBS2*,

and Ikegawa believes that the resulting insights into LDH pathology may yield valuable clinical advances in the treatment or prevention of this disorder. “We are now characterizing the binding sites of THBS2 and MMPs and the control mechanism of THBS2 on MMPs,” he says, “which could lead to the development of innovative drugs.” ■

1. Hirose, Y., Chiba, K., Karasugi, T., Nakajima, M., Kawaguchi, Y., Mikami, Y., Furuichi, T., Mio, F., Miyake, A., Miyamoto, T. *et al.* A functional polymorphism in *THBS2* that affects alternative splicing and MMP binding is associated with lumbar-disc herniation. *The American Journal of Human Genetics* **82**, 1122–1129 (2008).

Why plants can resist their own deadly toxins

Resistance to self-produced anticancer toxins could help the study of drug resistance in cancer patients

Japanese researchers have explained the mechanism of self-resistance in plants to their own lethal toxins. This new information will help medical researchers to tackle resistance in humans to anticancer drugs that are often based on these plant toxins.

Camptothecin (CPT) is a plant-derived anticancer drug that kills cancerous cells by disrupting the action of an enzyme called topoisomerase 1 (Top1) (Fig. 1), which is essential to DNA maintenance in almost all living organisms. Although CPT is deadly to most life forms, resistance to the toxin is found in its source plants and in some CPT-treated human cancer cells.

Now Kazuki Saito of the RIKEN Plant Science Center in Yokohama and his team from Chiba University and the Japan Science and Technology Agency in Chiba, have shown for the first time how plant self-resistance works at a molecular level. Understanding these processes is becoming increasingly important because of the expanding use of plant-derived compounds as medicines and the evolving drug resistance in the human cells they are used to target.

By comparing Top1 genes from CPT-producing and non-producing plants, the team found three mutations in the toxin producers that cause amino acid changes in the resulting enzyme and make it immune to the drug's poisonous attack. Remarkably, one of the amino acid substitutions found by Saito and his colleagues in plants is identical to one that has been found previously in CPT-resistant human cancer cells.

The team's genetic comparisons, reported recently in the *Proceedings of the*

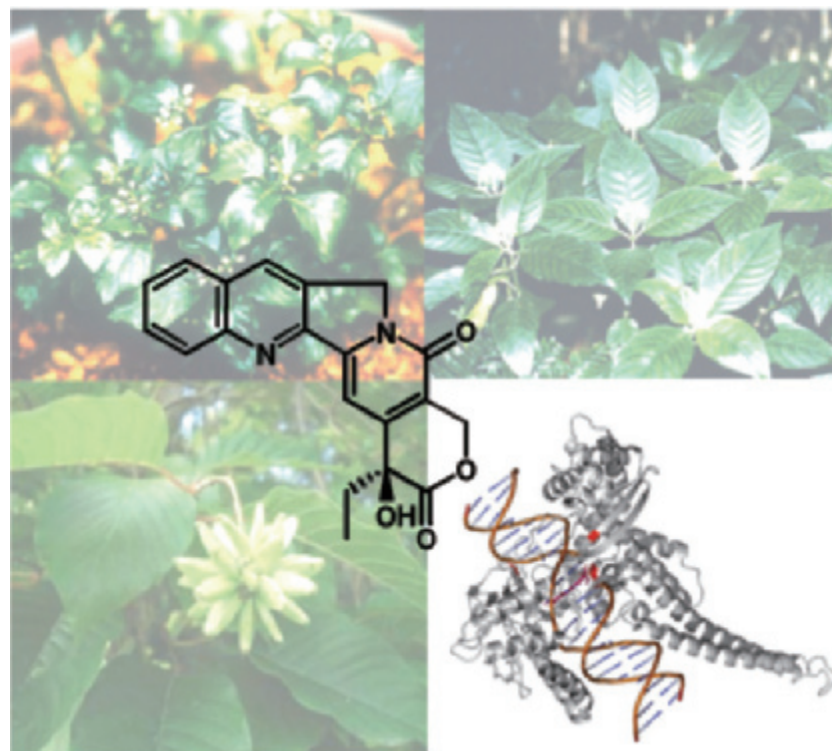


Figure 1: Three plant species producing camptothecin and its interaction with DNA and topoisomerase I.

*National Academy of Sciences*¹, suggest that CPT resistance in the source plant has developed gradually in parallel with the ability to produce the drug. Consequently, the team proposes that low-level CPT production may have triggered the resistance-giving mutation to occur in Top1. The importance of this suggestion is exemplified by the observation that continuous exposure of human cancer cells to CPT results in a Top1 mutation conferring CPT resistance.

The team's findings will help to uncover similar self-resistance mechanisms in other plants and for different toxins. Furthermore, understanding the molecular interaction between cancer drugs and their target molecules will

facilitate the design of drug therapies that prevent resistance in their human targets. Saito's team intends to explore CPT biosynthesis with a view to the feasible production of anticancer compounds. They also "look forward to establishing the evolutionary genomic basis of chemical diversity in plants through the study of plant toxins," says Saito. ■

1. Sirikantaramas, S., Yamazaki, M. & Saito, K. Mutations in topoisomerase I as a self-resistance mechanism coevolved with the production of the anticancer alkaloid camptothecin in plants. *Proceedings of the National Academy of Sciences USA* **105**, 6782–6786 (2008).

Image courtesy of Supart Sirikantaramas and Hiroshi Sudo

How do cells read genetic information?

Haruhiko Koseki

Group Director
Laboratory for Developmental Genetics
Research Center for Allergy and
Immunology

Induced pluripotent stem cells (iPS cells) generated from human skin cells are attracting considerable attention. These cells are universal cells, capable of differentiating into types of cells of any tissue. What, then, is the difference between skin cells and iPS cells?

Although different types of cells share the same genetic information, how it is read differs. In skin cells, only the genetic information required by that cell is read, and the reading of information carried by other genes is suppressed. Induced pluripotent stem cells have many genes in an immediately readable state; on stimulation, only the desired genes are read, one after another, resulting in the cell's differentiation into a particular type. Haruhiko Koseki, Group Director of the Laboratory for Developmental Genetics at the RIKEN Research Center for Allergy and Immunology, is working to elucidate the mechanisms by which cells read genetic information in this process.



How to play music

Our body originates from a single fertilized egg. The fertilized egg undergoes repeated cell division to differentiate into a variety of cell types, including skin cells, muscle cells, and nerve cells. The differentiated cells carry exactly the same design life plan as the fertilized egg, known as the genome (all genetic information).

In a sense the genome can be compared to a piece of music. Although the notes in a piece of music are not re-written, different musicians will render different interpretations when they play the piece. Likewise, the genome essentially cannot be re-written. "A wide variety of cell types are produced and maintained depending on the way the genetic information being carried by the genome is read," says Koseki.

For example, the reason why skin cells do not suddenly turn into other types of cells, such as muscle cells, is that only the genes for producing the proteins necessary for skin cells are read in the

genome, and the reading of other genes is suppressed.

A form of this suppression is DNA methylation. When a methyl group attaches to a particular site in DNA, gene expression is in principle suppressed. Essentially, the regions carrying information for producing the proteins necessary for the cells account for only about 1% of the entire genome. The remaining 99% of the genome is strongly suppressed, mainly by this process of DNA methylation.

However, if the 1% of the genome that has the protein information is also strongly suppressed, the cells are no longer able to differentiate or maintain themselves as entities. For example, in the course of cell differentiation, various genes are read one after another, resulting in the synthesis of the desired proteins. Koseki explains, "In this process, genes to be read subsequently must be suppressed into a state that cannot yet be read. The major theme in our research is to elucidate the mechanisms for suppression of the readable state."

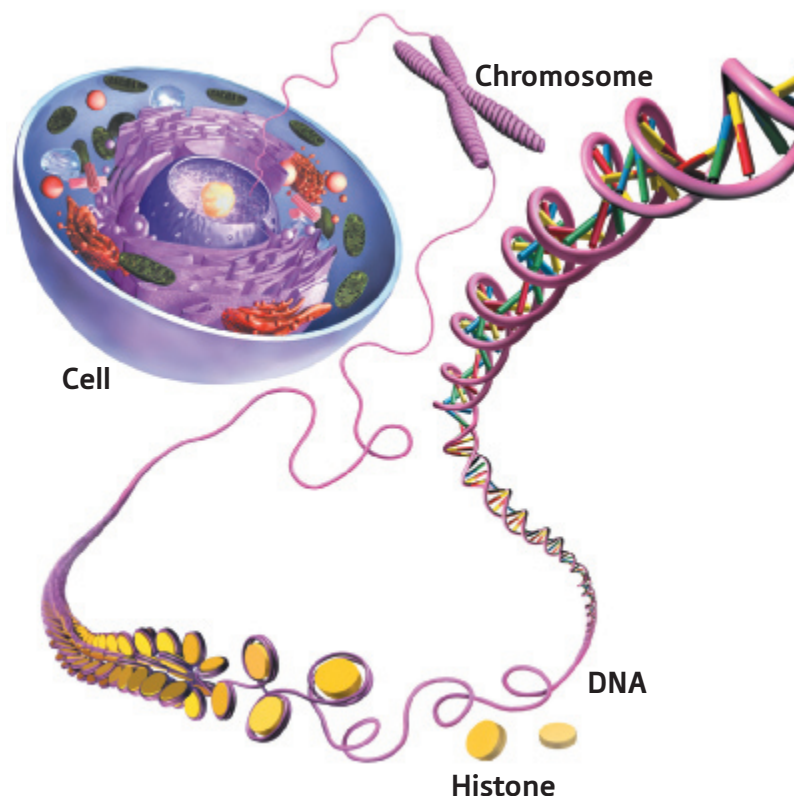


Figure 1: Histone and DNA

Histone winds up the long DNA into a compact state. When a gene is expressed, the DNA double strand gets untied by histone detachment or shifting, resulting in the reading of the genetic information and protein generation.

The Polycomb group protein complex

In readable-state suppression, histone modification plays a key role. The human DNA in each cell measures about 1.8 meters in length. Histone is a protein that winds up the long DNA into a compact state (Fig. 1).

When a gene is expressed, the DNA double strand gets untied by histone detachment or shifting, resulting in the reading of the genetic information. Histone undergoes a variety of modifications with various attachments, including methylation, acetylation, phosphorylation, and ubiquitination. Now the leading hypothesis is that combinations of these modifications serve as ciphers for the directions of gene-expression control.

Since the second half of the 1990s, Koseki has been investigating a class of enzymes, known as the Polycomb group protein complex (hereinafter the Polycomb group), which plays a key role in histone modifications. The Polycomb group was discovered in

Drosophila more than 30 years ago, and acts as a suppressor of the expression of particular genes by methylating histone. If this function is impaired, the manifestation of the characters of the posterior side of the body will shift to the anterior side (head side); for example, ribs are formed in cervical vertebrae. These ribs emerge because the suppression of rib gene expression is eliminated at sites where the cervical vertebral gene is, in all other respects, expressed.

“The Polycomb group suppresses gene expression as an assembly of proteins,” Koseki explains. “For example, if one of them is lacking, their suppressive action will weaken, and if two are lacking, the Polycomb group is no longer suppressive.”

Meanwhile, another class of enzymes, known as the trithorax group protein complex (hereinafter, the trithorax group), promote gene expression.

Regarding the suppression and promotion of gene expression, it is

hypothesized that gene expression is suppressed at sites where the Polycomb group is dominant, and that if the Polycomb group becomes less dominant, the trithorax group soon comes to the site to promote gene expression (Fig. 2). “Two systems with opposite functions, namely the Polycomb group and the trithorax group, antagonize each other to achieve suppression or immediate reading whenever necessary. However, it remains unclear how this balance between the two systems is determined to control the expression of a variety of genes.”

In 1990, proteins in the Polycomb group and the trithorax group were discovered in mammals. “I had been interested in the theme of how the body is built up in the morphogenetic process, and more than 10 years ago, I became aware of the unique function of the Polycomb group in mammals while looking for a research theme that had not been investigated by anyone else.”

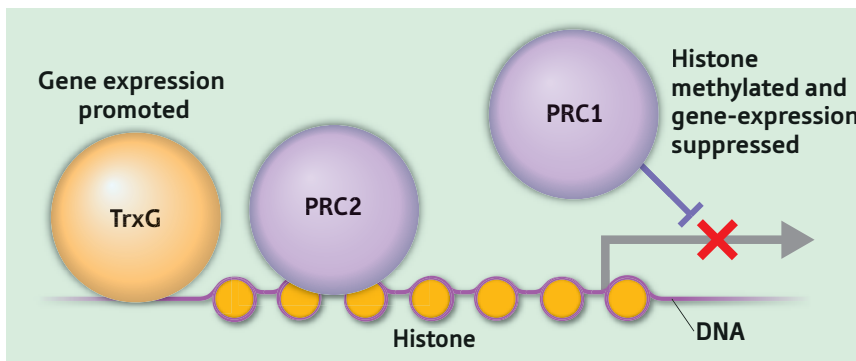


Figure 2 : The mechanism for gene-expression suppression and promotion by the Polycomb group and the trithorax group.

Regarding the suppression and promotion of gene expression, the following is hypothesized. The Polycomb group comprises two major components: PRC1 and PRC2. First, PRC2 binds to the target region to methylate a particular site of histone. The PRC1 component is then attracted there to suppress gene expression. If the Polycomb group becomes less dominant, the trithorax group (TrxG) soon comes to promote gene expression.

Toward progress in various fields of medicine

In 1996, Koseki became the second person to succeed in generating knockout mice lacking the function of the gene for the Polycomb group. These mice exhibit morphological anomalies (Fig. 3), immune deficiency, and alterations that lead to a lower likelihood of carcinogenesis. The cells of the mice devoid of the function of the Polycomb group are less likely to transform than those of normal mice. Meanwhile, the cells of the mice devoid of the function of the trithorax group undergo indefinite and repeated cell division like cancer cells. “The Polycomb group and the trithorax group control the expression of genes that promote or suppress carcinogenesis.”

These systems play important roles, particularly in stem cells. Somatic stem cells, a type of stem cell, are capable of differentiating into cells of particular tissues. It is thought that in the DNA of somatic stem cells, the readable state of many genes necessary for differentiation is suppressed by the Polycomb group. For example, if the somatic stem cells that produce immune cells are functionally impaired, the necessary immune cells are no longer produced, resulting in an

immunodeficient state.

In culture, embryonic stem cells (ES cells), derived from a blastocyst after several divisions of a fertilized egg, are universal cells that have the ability to differentiate into any type of cell. “If the function of the Polycomb group is lacking, however, these ES cells will no longer be capable of functioning as ES cells; for example, they will begin to differentiate into a particular type of cell.”

The iPS cells created by Shinya Yamanaka and others, at the Institute for Frontier Medical Sciences at Kyoto University in 2007, is attracting major attention. They succeeded in reprogramming skin and other cells into a pluripotent state by transducing several kinds of genes. Why do the once-

differentiated cells become pluripotent? The mechanism remains unknown, but it is thought that gene transduction may alter histone and other modifications to allow many genes to be in a suppressed readable state, hence restoring pluripotency.

At present, active investigations in regenerative medicine are being undertaken to produce desired types of cells from ES cells or iPS cells, and to transplant them to diseased or injured tissues with the expectation of functional regeneration. To realize successful regenerative medicine, techniques are necessary for examining DNA methylation and histone modification states, and for differentiating target cells into desired types of cells by altering the states.

Research into mechanisms by which cells read genetic information represents a key to success in unravelling the mechanisms for various diseases, such as cancer and immune deficiency, the development of effective and safe therapies, and the realization of regenerative medicine.

The mechanism of replication of DNA methylation

Koseki and his colleagues are now in search of proteins that bind to the Polycomb group, and are examining the functions of these proteins to clarify the functions of the Polycomb group. Among them is Np95, which served to solve a major riddle. This protein is associated

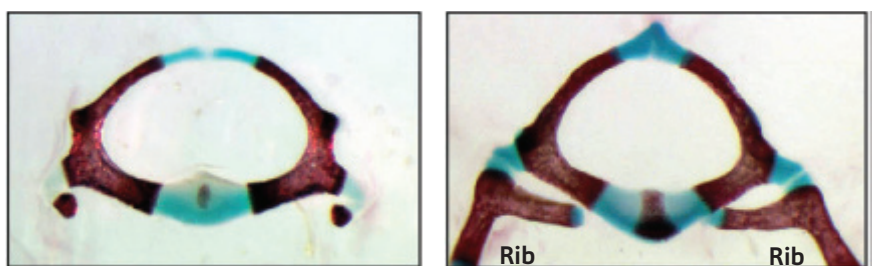


Figure 3: A morphological anomaly in knockout mice lacking Polycomb group function

No ribs are seen in the cervical vertebrae of normal mice (left panel), whereas ribs are formed in knockout mice (right panel).

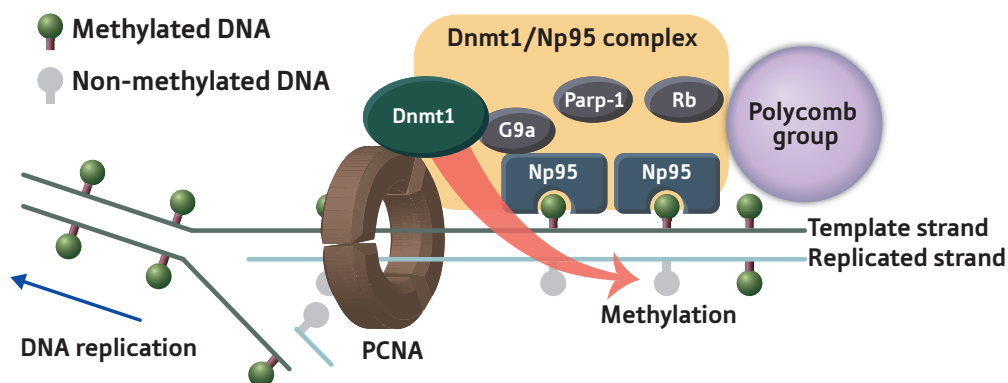


Figure 4: Replication of the DNA methylation pattern

When DNA is replicated at cell division, Np95 detects the site of methylation in the template strand, and this is followed by the binding of the Dnmt1 enzyme to Np95 to methylate the replicated strand. Thus exactly the same methylation pattern as the template strand is reproduced on the DNA.

with DNA methylation. Depending on the type of cell, DNA undergoes methylation at particular sites. But how the pattern of DNA methylation is passed on in cell division was a major riddle.

When a cell divides, the DNA double helix is untied, and DNA is replicated with each strand serving as a template. In this process, the DNA in the template strand is methylated in a certain pattern, whereas the strand that has just been replicated is not methylated at all. In 2007, Koseki and his colleagues demonstrated that Np95 detects the sites of methylation in the template strand and induces methylation in the corresponding portion of the replicated strand, so as to allow the DNA methylation pattern to be passed on (Fig. 4).

“However, the reason why the Polycomb group, which functions in readable-state suppression, and Np95, which mediates DNA methylation for stable suppression, bind together remains unknown,” says Koseki. “We are highly interested in the question of how strong suppression and suppression of the readable state are utilized in distinct ways, and we are working to clarify the mechanism behind this process.”

Interactions between the Polycomb group and RNAs

Furthermore, Koseki and his colleagues found that the Polycomb group, which

suppresses gene expression, also binds to a protein that functions in gene expression. Hence, they demonstrated the binding of the Polycomb group to the enzyme responsible for RNA splicing.

When a gene is expressed, DNA information is read by RNA, and the unwanted portion of the DNA is cut away in the splicing process; the desired protein is produced on the basis of the RNA information. Additionally, Yoshihide Hayashizaki, a project director at the RIKEN Genomic Sciences Center, and his colleagues discovered that there are many RNAs that do not carry any information for protein biosynthesis, and the team is investigating ways to demonstrate their action in controlling gene expression. “Gene expression may be controlled by an unknown mechanism that involves interactions between the Polycomb group and RNAs,” adds Koseki.

Toward elucidation of the entire scheme

“In recent years, competition has been heating up and we have been encountering a dramatic increase in the number of rivals,” says Koseki. “However, many riddles remain to be solved.” He adds that current research will only reveal part of the mechanism by which cells read genes, and that there are certainly many more mechanisms than expected.

“In the context of histone modification, methylation is overemphasized, but other forms of modification, such as ubiquitination and phosphorylation, must also be highlighted. Now is a very important time in elucidating the entire scheme of mechanisms.”

Finally, Koseki talks about his determination. “I think that at the very least, it is our responsibility to elucidate the mechanisms involved in the Polycomb group. How do cells read genes? Research to solve this question is about to have a major impact on the life sciences and medicine in the future.” ■

About the researcher

Haruhiko Koseki was born in Chiba, Japan, in 1961. He graduated from the School of Medicine, Chiba University, in 1986, and obtained his PhD in 1990 from the same university. After three years postdoctoral training at the Max Planck Institute of Immunobiology in Freiburg, Germany, he returned to Japan as an assistant professor at Chiba University. He was promoted to a professor in 1998. Since 2004, he has been a group director at the RIKEN Center for Allergy and Immunology. His research focuses on the epigenetic regulation of mammalian development.

International Symposium on Immunology

The fourth RCAI-JSI International Symposium on Immunology 2008 took place on June 26-27 in Yokohama. This annual symposium is jointly organized by the RIKEN Research Center for Allergy and Immunology (RCAI) and the Japanese Society for Immunology (JSI). Four hundred people, including 89 from outside of Japan, attended this year's symposium entitled 'Regulation of Immune Homeostasis and Diseases'. There were 25 prominent invited speakers who gave talks about the hottest topics related to immune regulation.

In the first session 'Regulation of lymphocyte activation: Molecular events and imaging', Arup Chakraborty from Massachusetts Institute of Technology presented his unique computational approach to analyzing the biological

experimental data on molecular signaling in T cells. Related to imaging analysis, Takashi Saito of RCAI presented his recent data on T-cell activation, and Facundo Batista of Cancer Research UK reported his research on B-cell activation. In the second session 'Molecular basis of innate immunity', Tadatsugu Taniguchi of the University of Tokyo nicely summarized his tremendous body of work on the interferon regulatory factor (IRF) family, and Shizuo Akira of Osaka University introduced the function of Toll-like-receptor 5 for host defense in the intestine. On the second day, a session 'Signal transduction pathways regulating cell fates' focused on the cytoskeletal proteins and apoptosis. Shigekazu Nagata of Kyoto University showed several movies

to explain the variety of molecules used by different macrophages for recognition of apoptotic cells. The final session 'Molecular mechanisms of immunological diseases and future direction' focused on disease-related approaches. Michael Lenardo from the National Institutes of Health in the USA introduced a human genetic approach to understanding abnormalities of immunological tolerance. Alain Fischer of Hospital Necker introduced genetic disorders resulting in T-cell immunodeficiencies.

The various approaches introduced in this symposium gave a clear impression that research on immune regulation is moving toward the successful integration of multidisciplinary fields. ■

RIKEN researchers take home the Simon Prize

Two RIKEN researchers, Yasunobu Nakamura and Jaw-Shen Tsai, have jointly won the prestigious 2008 Simon Memorial Prize for their ground-breaking contributions to the development of low-temperature physics, in particular quantum computing. Both scientists work at the RIKEN Advanced Science Institute in Wako and are currently key members of NEC's Nano Electronics Research Laboratories.

The two scientists were rewarded for their work investigating the behaviour of superconducting electronic devices and applying their findings to creating quantum bits (qubits), the building blocks of quantum computers. With their massive processing power, quantum computers will be able to solve a variety of problems that conventional computers cannot.

One prize committee spokesman noted that Nakamura and Tsai "were the first to show that quantum coherence could be displayed in a superconducting device, opening the way to a completely new solid-state quantum-computer architecture and a new regime in which to test quantum mechanics."

The prizes were awarded at the opening ceremonies of the 25th International Conference on Low Temperature Physics in Amsterdam in August.

The Simon Prize recognizes outstanding contributions to experimental or theoretical low-temperature physics. It is awarded by the Institute of Physics, based in London. ■

The RIKEN Brain Science Institute and Harvard continue their summer internship program

The RIKEN Brain Science Institute (BSI) and Harvard University continued their collaboration in the RIKEN BSI-Harvard University Undergraduate Student Internship Program this year. Five Harvard students took part, with BSI's Hessler, Saido, Leeuwen, Hosoya, and Okanoya labs all accepting one each. The internship ran from June 10 to August 16.

In addition to their work doing experiments in the labs, the five students attended Japanese classes twice a week. They also attended lectures in BSI's Brain Science Immersion Program series, 'Developmental Foundations of Brain Function and Dysfunction' for two weeks.

The students had nothing but good things to say about their experience. "Overall, I believe the internship was a positive experience. Comparing techniques and ways of thinking across labs and cultures provided room for growth and improvement in both the host laboratories and the interns' individual scientific pursuits," said Jannis Brea, one of the students who took part. He added, "It was also a great way to meet researchers in neuroscience from all over the globe and sowed the seeds for potential future collaborations." Joseph Stujenske, another student, agreed, adding, "BSI is well-organized and does a lot of great work."

Kunal Raygor, who also took part in the



Keiji Tanaka, acting director, and the students.

internship, noted, "I was able to learn many techniques and really grasp the scientific process." Joseph Stujenske was similarly impressed, saying, "Many researchers are true experts in their field and are doing innovative work."

Some of the students took the opportunity to explore Tokyo, which included trips to the famous Tsukiji fish market, Asakusa and Ueno Park, and to get insights from their co-workers on some of the finer points of Japanese culture, such as dressing in yukata (cotton summer kimono), the different types of sake, and performing a tea ceremony. The students also took a day to visit four labs at the University of Tokyo, and spent some time discussing research with young postgraduate students.

The internship program is supported by the Edwin O. Reischauer Institute of Japanese Studies. ■



Dr Masahiko Hara
Group Director
Global Collaboration Research Group
Corporate & International Relations Division
RIKEN Advanced Science Institute
Wako, Saitama, Japan.

Dear Professor Hara,

I was thinking back to my time at your laboratory recently and realized that studying at RIKEN can be really fun. I was there in 1996, more than ten years ago, but I am still influenced by that time.

RIKEN is located in a beautiful park, with green space and sports facilities: tennis, soccer, golf, swimming ... you name it! All these facilities can really help in research life because if your body is fit, and your mind is clear, then you are ready to do research at full strength and give the best of your abilities.

When I joined your and Professor Knoll's "Exotic Nano-material Group" I had never seen a more international, multicultural and multidisciplinary environment. We had staff from all around the world and the official language of the lab was English! When you showed me around your labs, I noticed an old printout of a graph on your wall. You told me that it was your very first data. I thought you must be very fond of that for some reason...

As you will remember, we became friends quickly and you gave me the responsibility to build a new system, a photon-scanning tunneling optical microscope, called SNOM in short. Thrilled at the challenge, I had to purchase a lot of expensive stuff to make it. After about 6 months of work I was able set it up and we had our first images from the nanometer world.

We had several people working in quite different fields; I was involved in optics, and one colleague, Morgan Denyer from Great Britain, was working with biocells. We chatted a lot and decided to try and measure the life dynamics of living cells under the photon tunnel effect.

After few months of effort, we succeeded: we could detect—for the first time in the world with extremely high resolution—tiny movements of biocells. Our report was published in major international journals; I was interviewed and ended up even on the cover (yes, my full picture in the cover) of a technology magazine!

Still now I enjoy the success of that work back at RIKEN, and I think even my current position as laboratory director and professor here in Yokohama is due to that experience.

And, now I understand the old printout on your wall. I have my first data on my wall, the first SNOM data I took at RIKEN! That's the place where I had a great experience, met great people and where I have my best memories.

Best regards,

Ruggero Micheletto, PhD
Nano-Sensory Laboratory's Director
Sensory Information Science Course
International College of Science
Yokohama City University
Japan





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

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For further information on the research presented in this publication or to arrange an interview with a researcher, please contact

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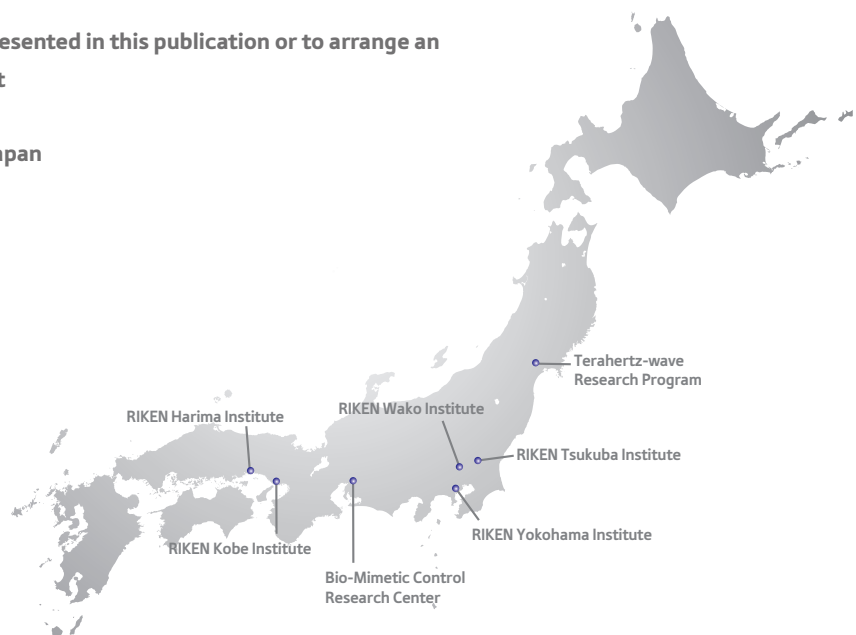
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