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The cell link that goes with the flow

Researchers find proteins that bind cells can move

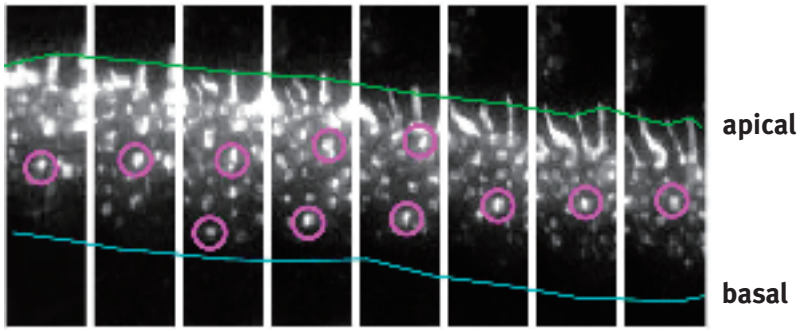
RIKEN researchers have discovered that protein molecules directly involved in binding cells into tissues can move in a coordinated, unidirectional flow. This flow is linked with the flexible actin-filament network responsible for cellular movement, and may play a significant role in cell migration and tissue remodeling.

The discovery could have clinical application as both cellular adhesion and movement where cells slide across one another without losing contact are important in physiological development, wound healing and the spread of cancer cells.

Membranes of neighboring cells in tissues are anchored to each other by means of flexible junctions involving complexes formed from three families of proteins—cadherins, catenins and actin filaments. The name cadherin is a combination of the English words 'calcium' and 'adhere' and was coined by a student of Masatoshi Takeichi, the Director of the RIKEN Center for Developmental Biology in Kobe.

The cadherin molecules extend across the membrane itself. Outside the cell, the long tails of these molecules link with cadherins of like type from an adjoining cell. Within the cell, cadherins bond with catenin molecules and through them become associated with actin filaments, though details of how this happens remain unclear. The association with actin is important, however, as its loss disrupts cell junctions.

In a paper published recently in *Nature Cell Biology*[1], Takeichi and Yoshiko Kametani, also from the Center for Developmental Biology, describe how Kametani attached green fluorescent protein to cadherin. This allowed her to trace the movement of cadherin in epithelial cancer cells in the laboratory under the microscope.



Nature Cell Biology

Figure 1: Time-lapse images of the movement of cadherin clusters acquired at 4-minute intervals (left to right). Two cadherin clusters are marked with magenta circles. They move up the cell junction from the basal (blue line) to the apical (green line) region.

These cells organize themselves into sheets. The zones where adjacent cells join are oblique from the lower or basal region to the upper or apical region, as if one cell were creeping under another. Kametani observed cadherin clusters forming in the basal area and moving up this incline (Fig. 1) in an organized flow along restricted routes.

When the researchers studied the molecular details of this flow, they found that the cadherin molecules in adjacent cells remained linked both to each other and to their associated catenin molecules. The whole complex moved as a unit. What's more, by introducing mutations which disrupted the structure of the molecules in the complex, the researchers showed that the flow depended on the connection with actin (Fig. 2).

Staining studies showed that during flow the cadherin clusters maintained their association with actin filaments, which were also moving (Fig. 3). In some cases, the clusters even jumped between actin filaments. In fact, it was the actin filaments that were providing the driving force. When the researchers introduced biochemical inhibitors to stop the actin movement, the cadherin flow ceased as well.

The fact that the cadherin complex across two cells is moving as a single unit and is motivated by actin seems to suggest that the actin filaments in the two adjacent cells are coordinated in some way. But when the researchers investigated this under the microscope, they found that actin filaments were organized and integral to the flow on one side only. The association with actin was not symmetrical.

So cadherins are present in a wide variety of cells, and therefore Kametani investigated whether cadherin flow was related to cell type. Similar directional cadherin flow was detected in some, but not all, the cell lines she observed in the laboratory. Directional, as opposed to random, flow was associated particularly with those cells that were actively moving

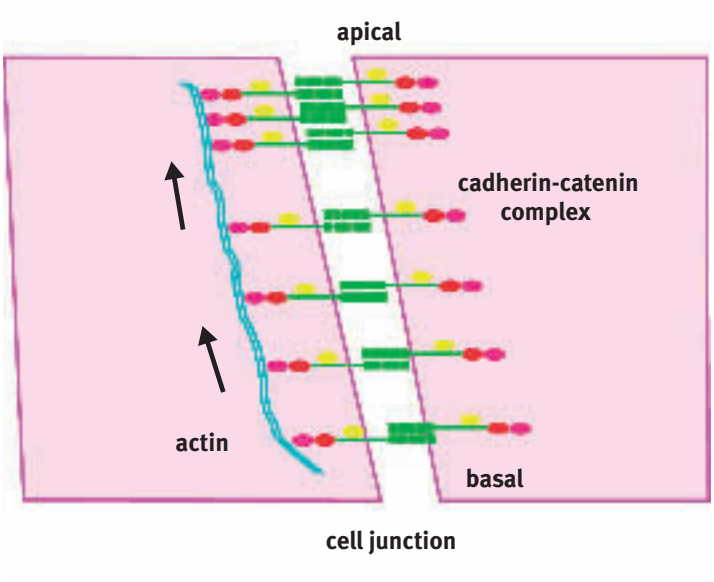
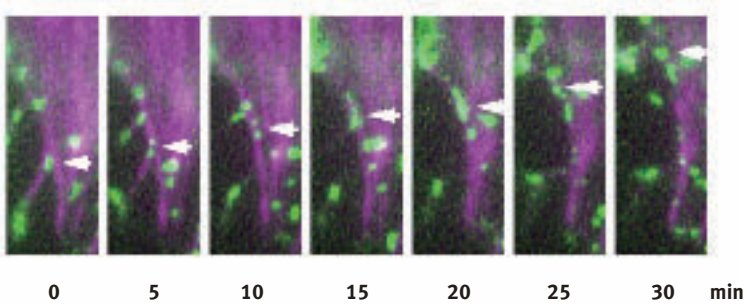


Figure 2: A schematic illustration of cadherin flow at a cell junction.



Nature Cell Biology

Figure 3: Time-lapse images showing the movement of cadherin clusters along actin fibers. A cell with green fluorescence protein-labeled cadherin was injected with phalloidin (tagged with a magenta fluorescence dye), which is known to bind actin. Cadherin clusters, an example of which is shown by the arrow, move along the magenta-labeled actin filament.

across one another. In cells where directional flow was normally absent, it could be induced by simulating a wound in the tissue. As cell migration towards the wound began at its edges, cadherin flow commenced in the direction of the migration.

So the researchers suggest that cadherin flow may enable cells in a continuous layer to move under or over each other while retaining the ability to switch this function off once migration is no longer needed. "It seems," Kametani says, "that cadherins may be working as a kind of clutch during cell migration that uses actin flow to provide the impetus."

"We now want to test these ideas and uncover the biological role of this phenomenon in tissues in living organisms," adds Takeichi, a pioneer in applying the techniques of cell biology to developmental biology. In fact, he was the first to recognize two distinct mechanisms in cell linkage, one dependent on calcium and the other not. But he is perhaps best known for his discovery and continuing work on cadherins. In addition to the research reported here, Takeichi recently turned his attention to the role of cadherins in the formation of links between neighboring nerve cells. ■

1. Kametani, Y. & Takeichi, M. Basal-to-apical cadherin flow at cell junctions. *Nature Cell Biology* **9**, 92–98 (2006).

About the researchers

Masatoshi Takeichi is director of the RIKEN Center for Developmental Biology in Kobe, Japan. He completed M.S. programs in biology at Nagoya University before receiving a doctorate in biophysics from Kyoto University. After attaining his PhD, he took a research fellowship at the Carnegie Institute Department of Embryology under Dr. Richard Pagano. He then returned to Kyoto University, attaining a full professorship in the Department of Biophysics, before becoming professor in the Graduate School of Biostudies at the same university. He assumed his current positions in 2000.

Yoshiko Kametani was born in 1977 in Japan, and graduated in 2001 from the Tokyo Institute of Technology, with a major in bioscience. In 2007, she received her PhD in life science from Kyoto University, under the supervision of Masatoshi Takeichi. In 2006, she joined Takeichi's laboratory at the RIKEN Center for Developmental Biology as a research associate/scientist. In May, she moves to the Department of Biochemistry and Biophysics at the University of California, San Francisco.

Subatomic particles lighten up

Fundamental particles lose mass in the presence of dense atomic nuclei

Some of the most fundamental particles in nature are protons and neutrons. These particles themselves are composed of elementary particles, the quarks. Three quarks make up each proton and neutron. Another class of particles, the mesons, consists of only two quarks. Different types of mesons are classified according to their constituent quarks. The force that holds protons, neutrons and mesons together is the 'strong interaction' between the quarks, which essentially determines the mass of particles.

Researchers at the RIKEN Nishina Center for Accelerator-Based Science in Wako, in collaboration with other Japanese researchers, have now studied the change in mass when a φ meson travels through an atom's nucleus. The nucleus, full of protons and neutrons, is a place where the forces of the strong interaction are particularly intense. As the strong interaction controls the meson mass, it is expected to change in an atomic nucleus compared to its value in vacuum.

Indeed, such a change has previously been observed for two other meson types, ρ and ω. However, according to Ryotaro Muto from the RIKEN team, "Changes in ρ and φ mesons are very difficult to be distinguished from each other in experiments, whereas the φ meson shows as a narrow resonance that can be examined more clearly".

Writing in the journal *Physical Review Letters*[1], the researchers report on changes in φ meson mass they detected in experiments conducted at the 12-GeV Proton-Synchrotron of the KEK-PS facility in Tsukuba. In the experiment, protons collide with nucleons and generate φ mesons. Then, to determine the meson mass, the researchers analyzed the energy released by the meson's radioactive decay. This mass varies according to where the decay takes place: in vacuum or in a large target nucleus such as copper (Fig. 1). The team found that the mass of the φ meson is actually lighter in the copper nucleus.

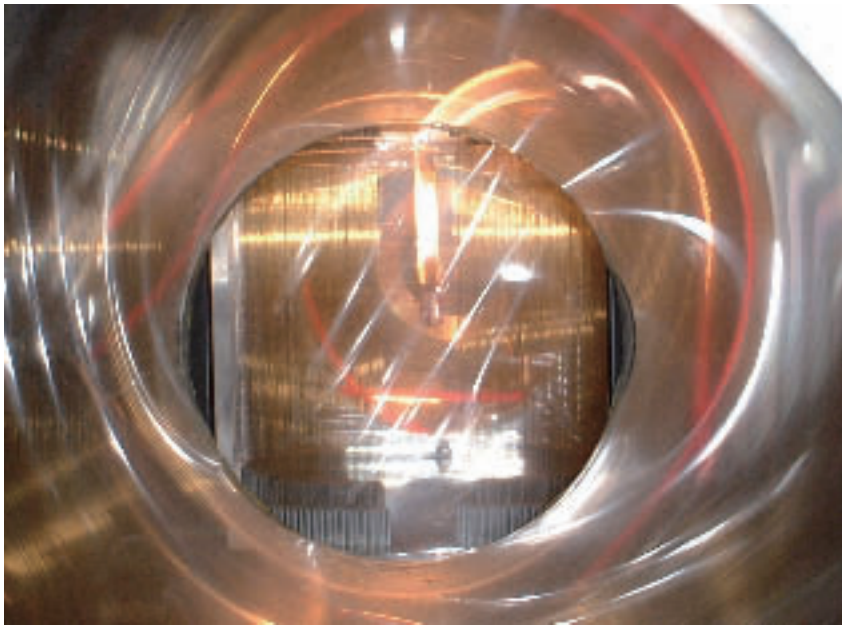


Figure 1: A view inside the spectrometer to detect the decay products of vector mesons. The centre of the image shows the small copper target where the φ mesons are produced by incident protons. The structures around the target are the detectors for the meson decay products.

What is needed now, explains Muto, is "to obtain a clearer picture on the origin of the meson mass and the role of the strong interaction". This requires further experiments using heavy ion collisions instead of protons. The team already has plans to carry out such experiments in facilities such as the Japan Proton Accelerator Research Complex (J-PARC). These studies could provide important details to one of the most fundamental questions in nature—the origins of the mass of fundamental particles. ■

1. Muto, R., Chiba, J., En'yo, H., Fukao, Y., Funahashi, H., Hamagaki, H., Ieiri, M., Ishino, M., Kanda, H., Kitaguchi, M. *et al.* Evidence for in-medium modification of the φ meson at normal nuclear density. *Physical Review Letters* **98,** 042501 (2007).

The anti-trap

First milestone achieved in building a suitable trap for antimatter

When chemists study the different electronic excitations of atoms, the only equipment they need is a Bunsen burner. Sodium, for example, emits a very characteristic yellow light when heated by the flame of the burner. Unfortunately, when physicists study similar properties of antimatter they face much more of a challenge.

Antimatter, the counterpart of normal matter, is extremely rare to find in nature. To study whole antimatter atoms such as antihydrogen, which is composed of an antiproton and a positron (the positively charged opposite to the electron), these atoms need to be artificially created. For this, RIKEN has partnered with eleven other international institutions to form the ALPHA collaboration at the European Organization for Nuclear Research CERN in Switzerland.

The aim of ALPHA is to examine the electronic excitations in antihydrogen, similar to sodium's yellow light. "Our purpose is to detect any tiny difference between antihydrogen atoms and hydrogen atoms," explains Yasunori Yamazaki, the RIKEN project leader from the Discovery Research Institute in Wako.

To create and trap antihydrogen, antiprotons produced by particle accelerators and positrons from a radioactive source (^{22}Na) are injected into the trap at the heart of the ALPHA apparatus (Fig. 1). As antimatter would be violently destroyed when brought into contact with normal matter, the trap consists of intricate magnetic force fields rather than a material such as steel. In an improvement on previous designs, "the magnetic field developed here has a much more uniform distribution near the axis of the magnet, while still maintaining the strong non-uniformity outside the trap that is necessary to trap neutral as well as charged particles," says Yamazaki.

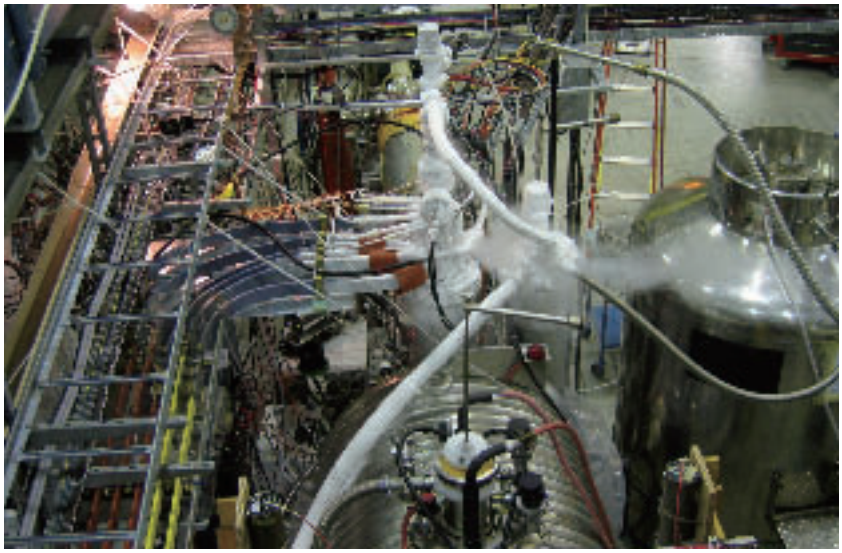


Figure 1: A view of the ALPHA apparatus in operation. The iced cyrostat that holds the magnetic field trap for the antiparticles is visible in the center of the photograph. The vacuum tubes that deliver the positrons and antiprotons to the trap come in from the top and bottom of the image, respectively.

The teams' first experimental results, now published in the journal *Physical Review Letters*[1], are very encouraging. Antiprotons as well as positrons were stored simultaneously in the trap for almost 10 minutes. However, researchers need to synthesize antihydrogen before they can start studying its fundamental properties. Then they need to develop a mechanism to continuously cool the atoms down to temperatures less than a degree above absolute zero so that they remain trapped.

Once this is achieved, the scientists can embark on their investigation into the differences between matter and antimatter. The implications of their work could be profound, as the slightest differences would mean the violation of one of the most fundamental symmetries of nature that predicts antimatter to be an exact mirror image of matter. ■

1. Andresen, G. Bertsche, W., Boston, A., Bowe, P., Cesar, C., Chapman S., Charlton, M., Chartier, M. Deutsch, A. Fajans, J. *et al.* Antimatter plasmas in a multipole trap for antihydrogen. *Physical Review Letters* **98**, 023402 (2007).

Inheriting a defective genome

Researchers begin to solve a genetic puzzle

Using yeast, molecular biologists at RIKEN have put forward a new model of how a normal genome is inherited in mitochondria, and thus how a faulty genome can be preferentially passed on to future generations. The research provides insight into the mechanics of mitochondrial genetics in yeast, and may have relevance to mammals.

Mitochondria provide energy for all cell functions, and contain their own double-stranded DNA which encodes several of the enzymes and other components critical to their role. This mitochondrial DNA (mtDNA) is separate from the nucleus, and comes packaged in a circular chromosome typical of micro-organisms, such as bacteria. Thus, when the mitochondria divide asexually in cells, the method of replication differs from that of nuclear DNA.

Generally, all the thousands of copies of the mtDNA within cells are the same. Sometimes, however, defective copies of mtDNA with large deletions arise and can accumulate in specific tissues, with disastrous health results in humans. The team from RIKEN's Discovery Research Institute in Wako studied how this happens in yeast.

In earlier work, the researchers demonstrated that replication of mtDNA in yeast involves the formation of concatemers, multiple copies of the genomic DNA linked head to tail in a line. The concatemers were shown to be produced by a process known as rolling-circle replication (Fig. 1). When passed on to the next generation, the concatemers are broken into individual copies each of which forms into a circular chromosome.

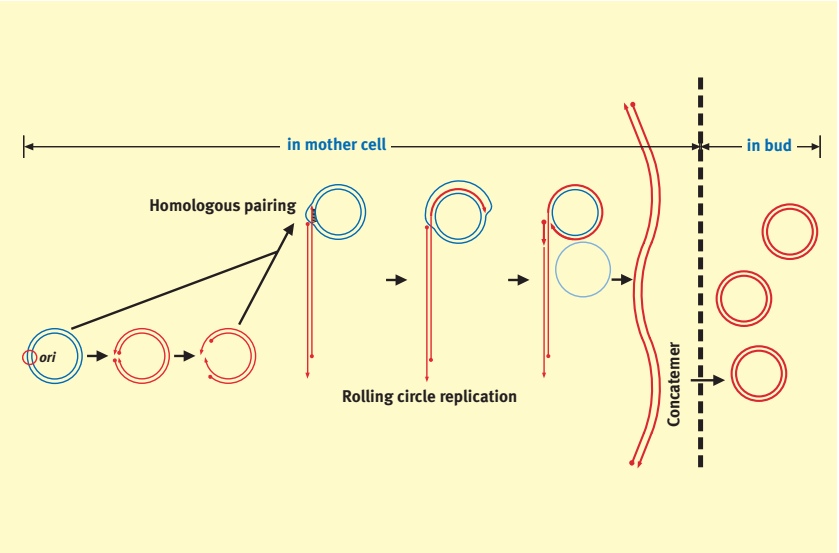


Figure 1: The proposed model of rolling-circle replication that produces the linear head-to-tail array of multiple mitochondrial genomic units known as concatemers.

In the conventional scheme of replication, an RNA primer is synthesized and initiates the unidirectional process at a particular sequence called a replication origin. In the latest work reported in *Molecular and Cellular Biology*[1] the team found that both DNA strands are cut at the replication origin known as *ori5*. One of the cut strands serves as a primer onto which connected copies are synthesized using intact circular mtDNA as a template (Fig. 1).

The researchers suggest that the mutant genomes contain greater numbers than usual of the replication origin sequence. The resulting mutant concatemers contain more copies of the smaller defective genome than is the case with the normal mtDNA chromosome. Hence, greater numbers of the mutant genome are passed on to the next generation, and almost all progeny contain mitochondria with the mutant genome.

"We hope our work will cause people cation," say team members, Feng Ling and Takehiko Shibata. "We now want to extend our work into mammalian systems." ■

1. Ling, F., Hori, A. & Shibata, T. DNA recombination-initiation plays a role in the extremely biased inheritance of yeast [*rho*⁻] mitochondrial DNA that contains the replication origin *ori5*. *Molecular and Cellular Biology* **27**, 1133–1145 (2007).

A better way to produce proteins

Perfected—a new cell-free system for synthesizing glycoproteins *in vitro*

Cell biologists at the RIKEN Genomic Sciences Center in Yokohama have developed a highly efficient cell-free system to derive important proteins.

These 'cell-free protein translation systems', as they are formally known, lack messenger RNA (mRNA) and therefore can be programmed by adding the gene encoding the protein of interest. As such, all the energy of the system is devoted to producing a single protein from the gene, thus yielding relatively pure samples of that protein.

Typically, bacteria or plants are the source of these cell-free systems as they are cheaper and more reliable in quality than animal-based systems. However, unlike animal-based systems, they lack the ability to add sugar residues to newly synthesized proteins, a process called glycosylation. This modification is vital for the normal folding and function of most animal proteins, and for certain proteins it allows their secretion.

The team at RIKEN, led by Shigeyuki Yokoyama, has now developed a cell-free system that combines the best of both worlds. When searching for a cell that would give them all the features they were looking for—ease of use, low-cost, and a well-developed protein translation/glycosylation system—they hit upon the idea of basing it on a hybridoma cell line, which are immortalized B cells that secrete large quantities of antibodies. Immortalization allows for easy and cost-effective growth in the laboratory, while their animal nature means they are capable of glycosylation. And the fact that they pump out so much protein indicates that they have a very strong protein translation/glycosylation system.

The team shows, in separate experiments, successful programming of extracts from this cell line with mRNA for the HIV-encoded surface protein gp120 and a hormone involved in human reproduction called choriogonadotropin[1]. Besides actual synthesis they also show that these proteins are correctly glycosylated. But more importantly, for human choriogonadotropin the protein from their cell-free system has biological activity.

The clear advantage of this system is that the hybridoma cell line is quite easy to maintain and grow, so researchers can easily use this system in their laboratory on a cost-effective basis, the team notes. It can also be adapted to bioreactors for pharmaceutical use, and thus scaled up. Also, since the hybridoma cell line is clonal in nature, there will be little batch-to-batch variability that plagues other animal-based cell free systems. Finally, the system is quite robust, so many different types of glycoproteins could be synthesized successfully and in quantity. ■

1. Mikami, S., Kobayashi, T., Yokoyama, S. & Imataka, H. A hybridoma-based *in vitro* translation system that efficiently synthesizes glycoproteins. *Journal of Biotechnology* **127**, 65–78 (2006).

Proteins pumping protons

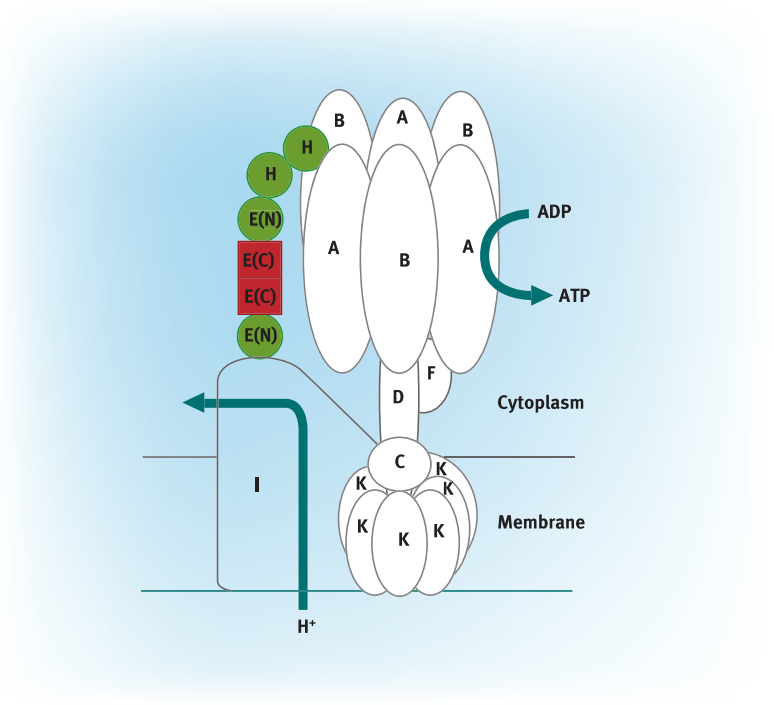
Researchers unlock the secret of an important enzyme

A RIKEN research team has uncovered significant details of the internal structure of a protein complex which actively transports protons across membranes in cells.

The complex on which the team worked is an H^+-ATPase found in primitive, single-celled organisms known as archaea. But it is closely related to a similar enzyme of the internal cell membranes in higher animals, where it is responsible for maintaining the acidic environment required for many cellular processes, and plays an important role in the spread of cancer and in bone resorption, hence osteoporosis.

H^+-ATPases use the energy released in breaking the chemical bond to the terminal phosphate in the universal energy molecule adenosine triphosphate (ATP) to power the transfer of a proton (H^+) across a membrane. They are constructed out of many different protein-chain subunits—nine in the archaeal version (A-ATPase) studied. The proton transport part of the complex spans the membrane, and the ATP-ase is attached to it by means of a protein spike, known as a stator (Fig. 1). It is through this stator that the energy of ATP-breakdown is linked to proton transport. Until now, neither the structure, nor even the numbers of stators per A-ATPase complex were known.

From previous work, the heart of the stator was known to be a protein chain called subunit E. In a recent paper in the *Journal of Molecular Biology*[1], researchers from the RIKEN SPring-8 Center in Harima reported the first crystal structure of subunit E. They also studied the relationship of subunit E with another stator protein chain, subunit H, using electrophoresis, mass spectrometry, amino acid sequencing and circular dichroism spectroscopy, which measures the coiling of proteins.



J. Mol. Biol./Elsevier

Figure 1: A model of the stator part of A-ATPase is shown with its dimeric core (red) and a modular architecture (red and green).

They found that the ends of two subunit E chains bind together to form a two-part or dimeric working core of the stator structure (Fig. 1). The two other ends of subunit E bond either with subunit H or directly to the proton transfer part of the complex. The group suggests that subunit E, subunit H, and at least two other subunits in other H^+-ATPases fit together like modular building blocks, and can be used to make stators longer or shorter to match the other structures of the complex.

"We now want to clarify the situation with other H^+-ATPases, as they are all related evolutionarily," says research team leader, Naoki Kunishima. ■

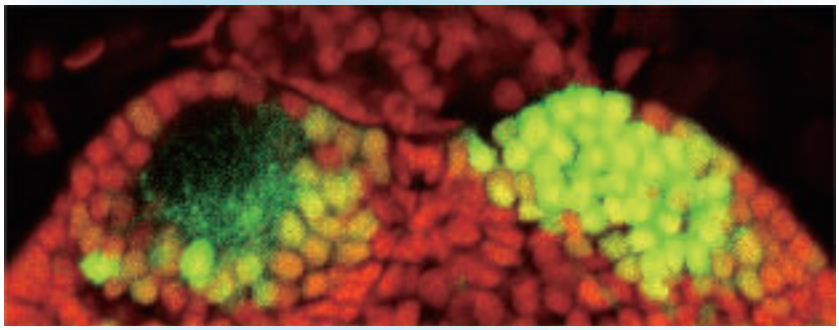
1. Lokanath, N.K., Matsuura, Y., Kuroishi, C., Takahashi, N. & Kunishima, N. Dimeric core structure of modular stator subunit E of archaeal H^+-ATPase. *Journal of Molecular Biology* **336**, 933–944 (2007).

Timing is everything

New work sheds light on the processes determining brain asymmetry

A recent study identifies one way in which brain asymmetry is generated. No one knows why many vertebrates contain asymmetrical brains. Some think it might allow multi-tasking. For example, while the left side is processing speech, the right side could be recognizing a face. Regardless, even less is known about the events responsible for this asymmetry.

A team led by Hitoshi Okamoto, a scientist at the RIKEN Brain Science Institute in Wako, uncovered one factor influencing asymmetrical formation of a region of the brain called the habenulae, which influences behaviors such as smell, appetite, and mating. The team's work was recently published in *Developmental Cell*[1].



Devel. Cell/Elsevier

Figure 1: TCross-section of the habenulae of a zebrafish larva.

The habenulae contain left and right nuclei, each of which can be populated by one of two types of subnuclei, lateral or medial. Each of these subnuclei contains nerve cells displaying distinct characteristics. Lateral subnuclei in the left side of the habenulae contain larger numbers of nerve cells than those on the right side, and vice versa for the medial subnuclei (Fig. 1). Thus, the researchers hypothesized that habenular asymmetry might be caused by asymmetries in the way these distinct varieties of nerve cells develop.

The researchers tracked nerve cell development in zebrafish, which have simpler brains than mammals and are easy to manipulate. Nerve cells exhibiting features of those in lateral subnuclei were 'born' earlier during development than medial subnuclei type nerve cells.

To determine whether birth date influences lateral versus medial nerve cell fate, the researchers manipulated signaling through a receptor called Notch, which regulates nerve cell development. Early Notch hyperactivity, which permitted only a quick burst of early nerve cell development, resulted in an increase in the number of lateral nerve cells on both sides of the habenulae. Likewise, Notch inhibition, which delayed nerve cell development until a late stage, favored development of medial nerve cells.

These data suggest that the left habenulae might provide nerve cell differentiation cues earlier than the right habenulae. Identification of these putative cues remains for future investigation.

"The nerve cells of the medial and lateral subnuclei are separately and indirectly connected with the region of the brain that regulates various states of mind, such as motivation, attention, awareness and fear," explains Okamoto. "Therefore, this new information about the asymmetry in the sizes of the habenular subnuclei may shed light on the biological basis for functional brain asymmetry in the process of emotion and behavior." ■

1. Aizawa, H., Goto, M., Sato, T. & Okamoto, H. Temporally regulated asymmetric neurogenesis causes left-right difference in the zebrafish habenular structures. *Developmental Cell* **12**, 87–98 (2007).

How one domain makes life or death decisions

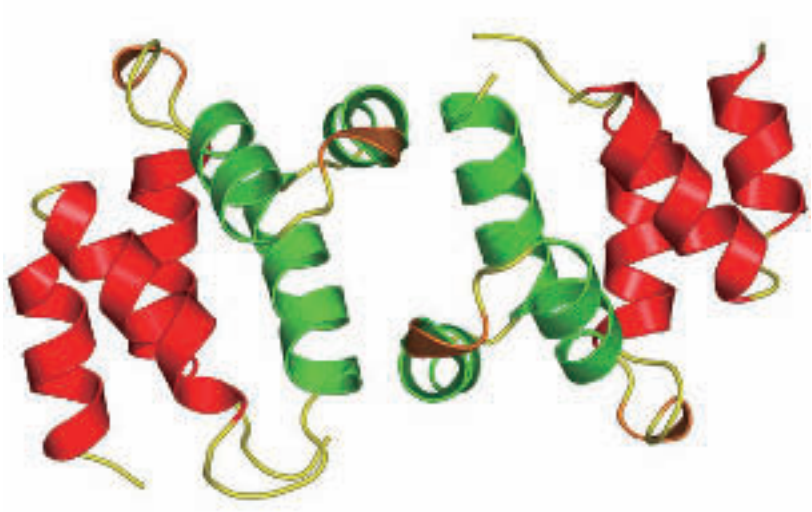
Structural analysis has revealed how some neurons choose between growth or death in response to different cues

A key component of nervous system development and maturation is the directed growth and extension of the axonal processes through which neuronal signals are transmitted. This is partly mediated by secreted axonal guidance factors such as the protein netrin-1, which can trigger either an 'attractive' or 'repulsive' effect on a target neuron depending on which receptor it binds.

One of the target receptors of netrin-1, UNC5H2, is what is known as a 'dependence receptor', meaning that its function is dependent on the presence or absence of its binding partner, or ligand. The binding of netrin-1 causes the receptor molecules to pair off forming complexes known as homodimers, which consist of two identical molecules each. This triggers a 'repulsion' signal for target axons expressing the receptor. Without netrin-1, UNC5H2 fails to dimerize and instead induces cell death, mediated by the enzyme caspase.

Previous research has shown that the UNC5H2 'death domain' may mediate these receptor activities, and Shigeyuki Yokoyama and his colleagues at the RIKEN Genomic Sciences Center in Yokohama recently set out to investigate this possibility more closely. "We thought that the 3-D structure of the UNC5H2 death domain would provide clues to these mechanisms," he explains.

Caspase cleaves the death domain from UNC5H2, which then binds to the death domain of another protein, death-associated protein (DAP) kinase, to induce programmed cell death, or apoptosis. This has led some investigators to believe that when the receptor dimerizes in the presence of netrin-1, the two matching death domains may also come together to form a homodimer, blocking enzymatic cleavage and thus preventing cell death.



Acta Cryst./International Union of Crystallography

Figure 1: Structural analysis of the UNC5H2 receptor 'death domain' has revealed how this segment of the receptor forms homodimers in solution.

In a recent article published in *Acta Crystallographica*, Yokoyama and colleagues present crystallographic data that confirm this hypothesis. They also reveal that the UNC5H2 death domain forms dimers (Fig. 1) and identify the mechanism underlying this pairing[1]. Such experimental confirmation is essential, as death domains can vary widely in sequence and the specific nature of their interactions may be difficult to predict. "Death domains have no conserved interaction surface, although their overall folds are very similar," notes Yokoyama.

Having clarified this aspect of receptor function, Yokoyama indicates that he is now interested in applying similar structural biology techniques to analyze the other important functional interactions of this domain. "We are planning to crystallize the complex between the UNC5H2 death domain and the DAP kinase death domain," he says. "Comparisons of the structures will reveal the molecular mechanism of these proteins." ■

1. Handa, H., Kukimoto-Niino, M., Akasaka, R., Murayama, K., Terada, T., Inoue, M., Yabuki, T., Aoki, M., Seki, E., Matsuda, T. *et al*. Structure of the UNC5H2 death domain. *Acta Crystallographica* **D62**, 1502–1509 (2006).graded to biphasic response for cell differentiation. *The Journal of Biological Chemistry* **282**, 4045–4056 (2007).

Balance in the sway

Nerve control keeps humans upright

Researchers from RIKEN Frontier Research System in Nagoya have devised a mathematical model of the control system of sensory cells, nerves and muscles that keeps humans upright and balanced, and is essential to standing and walking.

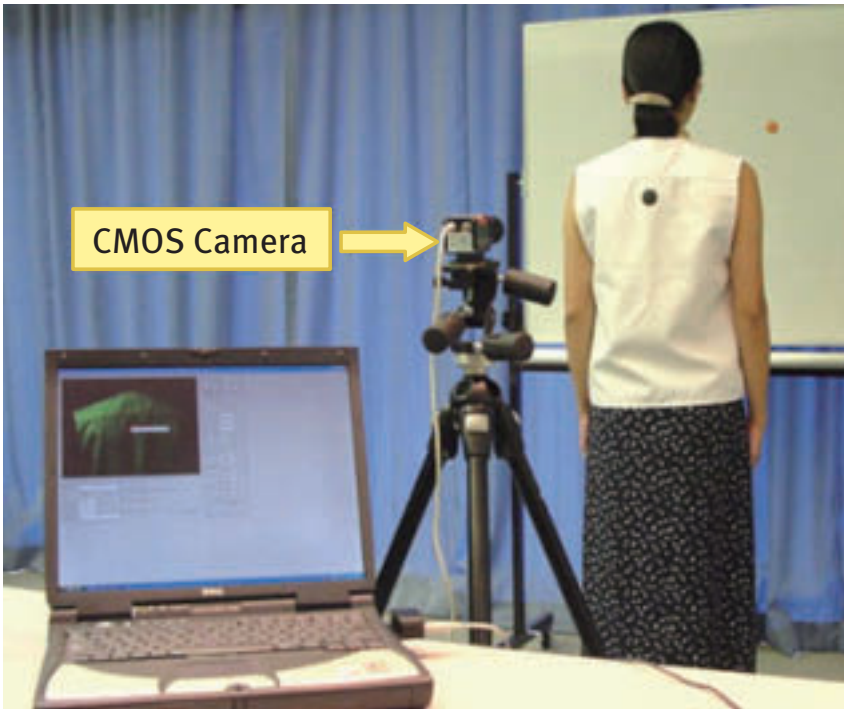
They hope to use their model to develop measurements to aid diagnosis and treatment of balance disorders in elderly people, and to examine the link between deterioration of the balance control system and susceptibility to falls—a serious problem for the aged.

Maintaining balance is an active process which minimizes body movement. The researchers were able to use data on body sway to show that both ageing and closing of the eyes decreases stability.

In a recent paper in *IEEE Control Systems Magazine*[1], the researchers detail the development of their model based on the theory behind standard proportional-integral-derivative (PID) industrial controllers. A controller typically consists of a feedback loop. It takes the value of a measured output from a process, and compares it to a reference setpoint value. It then adjusts the process inputs to minimize the difference or 'error' between the output and the setpoint.

Typically such feedback controllers lead to an oscillation around the setpoint, because of the time lag between measurement and action. In PID controllers, that oscillation is damped because the input adjustment is made not only based on the size of the error, but also on its history and rate of change.

In order to examine their model of balance in humans, the researchers gathered experimental data on body sway.



IEEE Control Syst. Mag./IEEE trol Systems Society

Figure 1: The experimental setup to measure and record body sway.

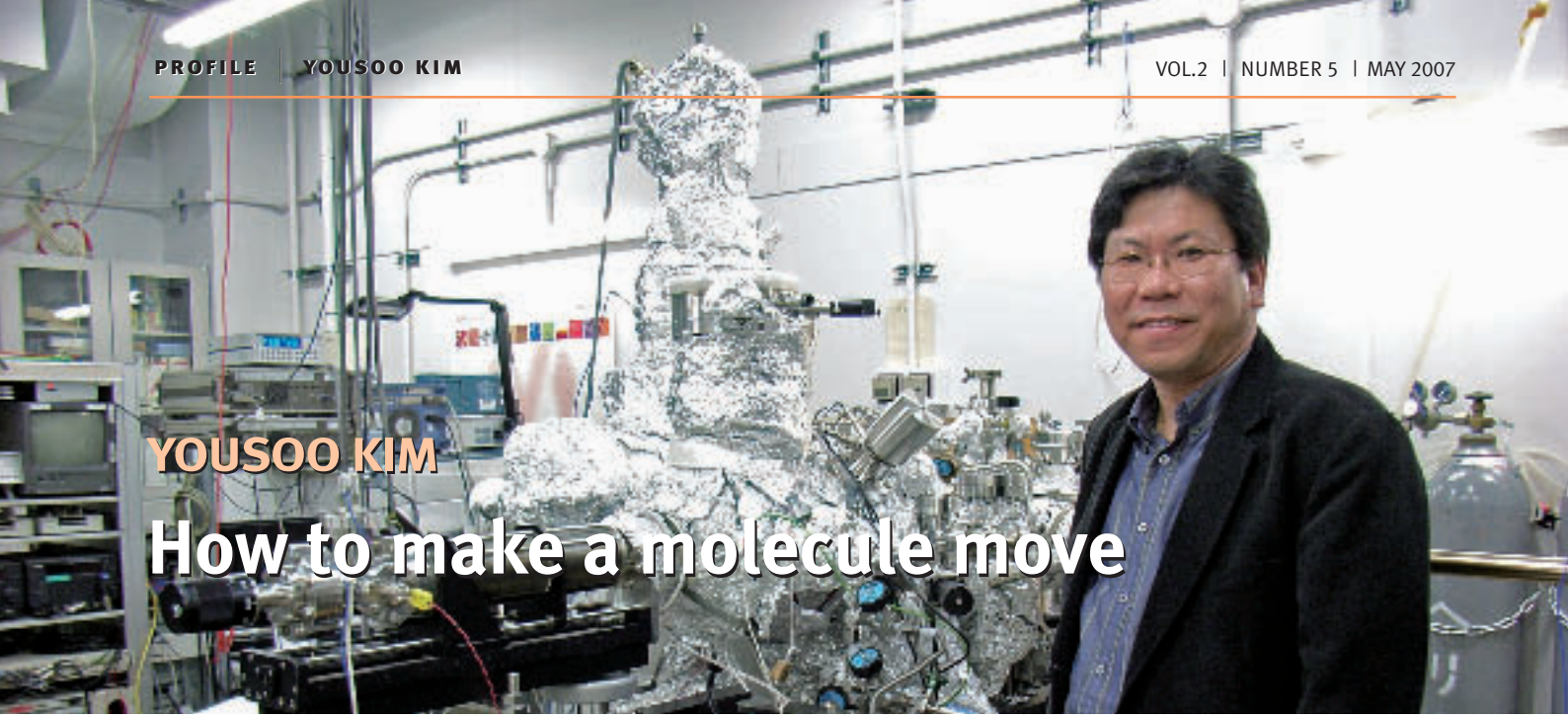
They placed a circular black marker, 30 millimeters in diameter, between the shoulder blades of a subject's back (Fig. 1). Using a digital video camera, the marker's movement was recorded over 30 or 60 seconds, while the subject was standing still. More than 100 people of a range of ages were recorded with their eyes open and closed.

The researchers found that the elderly displayed greater body sway, suggesting a deteriorating ability to balance. They also showed that balance is vision related, as body sway increases when the eyes are closed compared with open.

The data also allowed the researchers to calculate values for the gain or sensitivity to the rate of change of the error measurement. This value decreases with ageing and when eyes are closed, suggesting it is balance- and stability-related.

"Our research clearly showed nerve control, not weakening muscles or deteriorating sense organs, is the decisive factor in fall vulnerability," says team leader Hidenori Kimura. ■

1. Kimura, H. & Jiang, Y. A PID model of human balance keeping. *IEEE Control Systems Magazine* **26**, 18–23 (2006).



YOUSOO KIM

How to make a molecule move

A chemist at RIKEN opens a new field in nanoscience by manipulating a single-molecule formation using electrons

In 1990, researchers at IBM surprised the world by spelling the letters 'I-B-M' with individual atoms on a metal surface. The work was achieved with a high-tech scanning tunneling microscope (STM), which can not only visualize an atom but move it around and position it accurately (Fig.1).

Now, scientists like Yousoo Kim are taking the STM even further. The Korean chemist at RIKEN places a single molecule—a group of two or more atoms—on a solid surface and looks at how it changes its properties when electrons thrown from the spectroscope's tiny tip push it around or even cut the bonds between atoms.

Kim's work is opening a new realm in nanoscience, especially in surface chemistry, which looks at the chemical and physical reactions at interfaces between particles and a solid surface. Kim's team is one of the few that have achieved such sophisticated molecular manipulation. His research helps to deepen our knowledge about how molecules come together, and could eventually lead to new catalysts or materials.

"We can't create an atom, but I think we can design and use a molecule properly if we understand its nature," says Kim, a senior research scientist of the Surface Chemistry Laboratory at the RIKEN Discovery Research Institute in Wako.

Against the grain

The 38-year-old Kim has taken an unusual career path for a Korean scientist. When he was a student at Seoul National University, the conservative chemistry community held that people aiming for an advanced career should go to the US for their doctorate.

But Kim believed in going to the best group regardless of country. At that time, Kim wanted to study photocatalysts, and the front-runner was a Japanese researcher, Akira Fujishima at the University of Tokyo. In 1994, Kim met Fujishima at a conference in Seoul, and was invited to join his lab.

South Korea is Japan's nearest country, but until recently historical disputes meant that each country had complex feelings about the other—so people around Kim were against his idea to go to Japan. "But I thought it would be interesting to explore an undeveloped path," Kim says.

A photocatalyst is a substance that accelerates a chemical reaction when irradiated by light, as in a plant's photosynthesis. Fujishima was renowned for his 1968 finding that the surface of a titanium oxide electrode acts as a photocatalyst and accelerates the dissolution of water into hydrogen and oxygen. It was thought that the finding would help create clean energy sources, which Kim was highly interested in.

But when Kim joined his lab in 1996, Fujishima didn't let him take on photocatalyst research. Given his electrochemical background, Kim was sent to one of Fujishima's other projects, newly launched at the Kanagawa Academy of Science and Technology near Tokyo. "I even didn't touch a photocatalyst," Kim says with laugh, adding that he thought tackling a new theme sounded more enjoyable.

Tomokazu Iyoda, a polymer chemist who supervised Kim, remembers he made a fluent speech in Japanese and made people laugh at a welcome party for newcomers. "He's very friendly, cheerful and good at making jokes," says Iyoda, now a professor at the Tokyo Institute of Technology.

In 1999, Kim earned his PhD by studying how individual fullerene molecules gather to form nanometer-scaled structure when light is shone on them surface. After that, Kim thought about taking the orthodox path to the US, but on Fujishima's recommendation joined RIKEN's Surface Chemistry Laboratory, which was run by Maki Kawai.

The world of the surface chemistry

Kim was once again sent to a different laboratory, and spent his first six months learning how to use the STM. It was a time when the STM was becoming a hot device after researchers in the US achieved a breakthrough by obtaining vibrational spectra for a single molecule absorbed onto a solid surface[1].

The chemical bonds that bind atoms into a molecule vibrate constantly provided it is at the right temperature. Depending on the energy of the electrons given to a molecule, its bonds can be

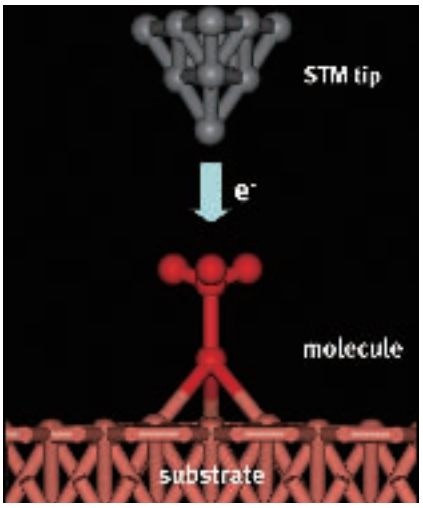


Figure 1 : Schematic model of a scanning tunneling microscope (STM).

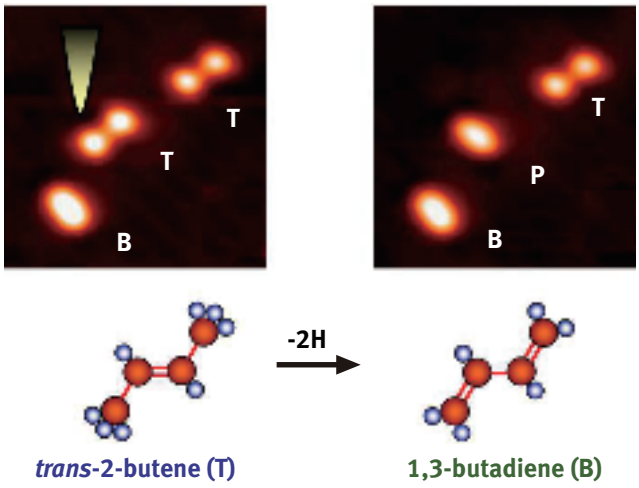


Figure 2 : C-H dissociation of trans-2-butene to 1,3-butadiene by vibrational excitation of C-H stretching mode.

disbanded to change the molecule's properties, and researchers can also stimulate the vibrating electronic state between a molecule and the surface, instead of cutting bonds, and then see how this affects the molecule.

At Kim's lab, two huge metallic STMs are wrapped in aluminum foil to control the temperature. Inside the machine is an ultra-high vacuum, and the temperature is cooled to a superconducting level. "We create the Universe in the chamber," Kim says. One molecule is placed on a metal plate inside the chamber. Kim then injects billions of electrons onto the target site in a molecule from a micron-sized tip. The idea of using electrons to induce a chemical reaction was not new, but Kim was the first to control the position of a single molecule and induce excitation of vibrational modes selectively.

Making a molecule hop

In 2002, Kim made a carbon monoxide molecule hop in only one direction on a palladium plate[2]. Later that year came his greatest achievement so far[3] (Fig.2). Using an unsaturated hydrocarbon absorbed onto a palladium plate, he cut the bond between carbon and hydrogen and made the molecule more responsive by meticulously adjusting the energy of electrons to match the frequency of vibration. Other researchers had shown only the dissociation of bonds—Kim was the first to suggest that the process is controllable.

Later, Kim has made an unsaturated hydrocarbon molecule rotate[4]. Earlier this year, his team also observed how an achiral carbon molecule, adamantine, becomes chiral in the process of self-assembling to form a monolayer[5]. More recently, they succeeded in the reversible bond rearrangement of a single molecule-metal contact through the combination of catalytic surface chemistry and an STM-tip induced reaction[6].

So far, Kim has used molecules and metals that are known for an effective catalytic reaction. Kim is now trying new molecules, and also moving beyond cutting bonds to creating them. Although he admits cutting bonds is much more difficult and still has a long way to go, he is experimenting with combining a nanotube with an organic molecule. Kim is also keen to develop a library for nanotech researchers worldwide about molecules and the energy levels that electrons need for particular chemical reactions.

Kim says RIKEN is the best place for him to work. There is still room to improve the environment, such as support for the family, but the benefits far outweigh the disadvantages, he says. As a senior scientist at RIKEN, Kim often organizes drinks and karaoke with young researchers, takes care of temporary overseas researchers, and promotes friendship between Korea and Japan outside work. "Kim's presence is important for RIKEN's internationalization," says Kawai. ■

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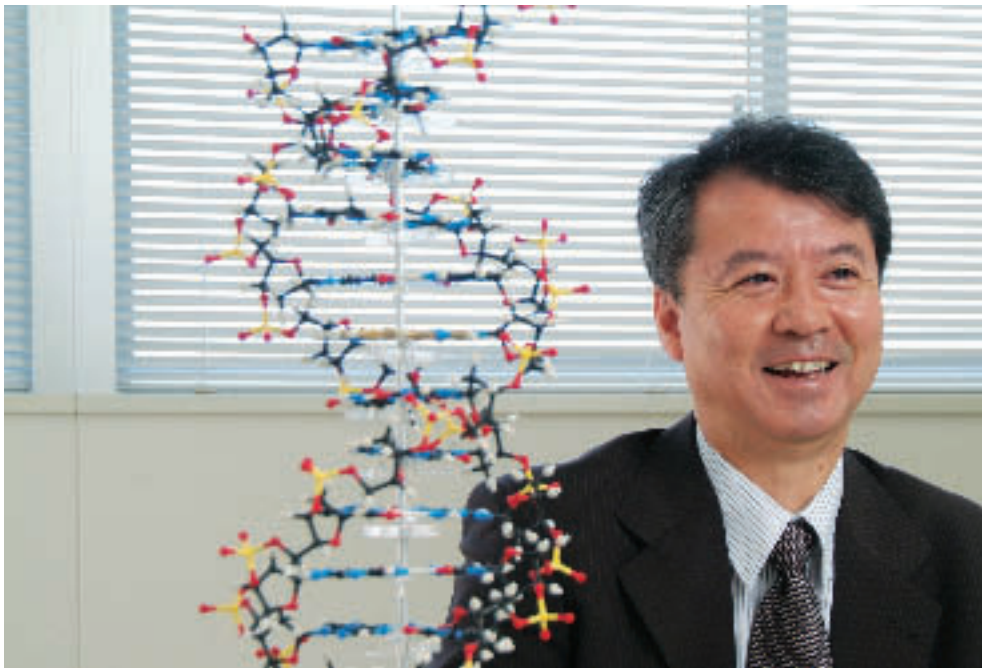
About the researcher

Yousoo Kim was born in South Korea's capital, Seoul, in 1968. In 1991, he graduated from the Department of Chemistry, Seoul National University, and obtained his masters at the same university in 1993. In 1999, he earned his doctorate in applied chemistry at the University of Tokyo. In the same year, he joined the Surface Chemistry Laboratory at the RIKEN Discovery Research Institute as a research associate, and six months later became a special postdoctoral researcher. In 2002, he was promoted to research scientist. Since 2006, he has been serving as a senior research scientist at the same laboratory.

Expanding the DNA alphabet

Ichiro Hirao

Team Leader
Protein-Regulating Macromolecules Research Team
Protein Research Group
Genomic Sciences Center
RIKEN Yokohama Institute



Protein-Regulating Macromolecules Research Team Leader, Ichiro Hirao, succeeded in incorporating an unnatural base pair (Ds–Pa) created by chemical synthesis, into DNA, precisely replicating it and transcribing its genetic information to RNA. His success is a remarkable achievement that rewrites the fundamental rule common to all organisms living on Earth, 'DNA consists of four different bases named adenine (A), thymine (T), guanine (G), and cytosine (C)'. The technology of unnatural base pairs expands the genetic alphabet, enabling the incorporation of extra components, such as unnatural bases or amino-acid analogs with increased functionality, into DNA, RNA, and proteins. Several research teams in the world have been competitively tackling the development of unnatural base pairs. What enabled the Protein-Regulating Macromolecules Research Team to lead the race? Team Leader Hirao thinks that the team's 'Japaneseness' may be one of the reasons.

Challenging research

During the interview, team Leader Ichiro Hirao frequently takes up the DNA model and looks at it with a smile. "The appeal of DNA comes down to its double helix structure," he says, and continues to explain how not only can DNA replicate itself, but it can also transmit information to RNA and proteins. "There is no substance comparable to DNA on the Earth. DNA is my favorite substance."

DNA has a structure in which two strands made up of sugar and phosphate form a helix and the four different bases (ATGC) arranged in a ladder form are held between the two strands. The bases A–T and G–C always form pairs and the base sequences represent the genetic information. This is common to all of the Earth's organisms.

DNA has two main functions; one is to replicate itself. The double helix unwinds and the bases arranged along each of the original strands are paired with their complementary bases in newly replicated strands. In this manner, DNA with the same base sequence can be replicated. The accuracy of pairing among the bases in replication exceeds 99.99%. The other function is to make proteins via RNA. Base sequences of DNA are transcribed to RNA and the transcribed base sequence is translated to amino-acid sequences of proteins.

Team Leader Hirao was first attracted to DNA when he was 19 years old. "While I was a student at a technical college, my teacher recommended me to read James Watson's 'The Double Helix', which clarified the conformation of DNA," he reminisces. "I was so impressed by the beautiful double helix that I wondered how the four different bases were combined together and whether other substances could be added into DNA. I was really interested in the double helix." Since then, he has had a strong desire to study the double helix and solve this puzzle. "The study of unnatural base pairs is my life work."

According to Hirao, the unnatural base pair is a considerably challenging scientific theme because the ability of the scientist is tested in both chemical and biological fields. Because of this, research groups engaged in the development of

unnatural base pairs in biological systems are limited to Hirao's team and some teams in the US.

Beyond the limitation of recombinant DNA technology

The study of unnatural base pairs has been promoted by scientists' intellectual interest in the possibility of artificial modification of bases, and high hopes have been placed on practical applications.

The Nobel Prize in Physiology or Medicine for 2006 was awarded to Andrew Z. Fire and Craig C. Mello for their discovery of RNA interference. RNA interference is a phenomenon that suppresses translation from RNA into protein by a specific RNA action. Although RNA has been regarded simply as a substance that transmits DNA information to protein, according to recent findings, there are many RNAs that are not translated into protein. RNA, which has a large variety of functions, seems to be involved in various life phenomena. Researchers are making efforts to use recombinant DNA technology to create RNA that suppresses translation of the proteins responsible for pathogenesis and utilize such RNA in medical treatment.

Hirao, however, points out the limitation of the current recombinant DNA technology and says that further progress is needed before it can contribute to the development of functional RNA. RNA consists of A, G, C, and U (uracil) instead of T, but the number of bases is limited to only four. Because of this limitation, RNAs with significantly different functions cannot be created. "If we succeed in inserting new base components into RNA, we can create RNAs with new functions," he continues (Fig. 1). "Since we can bind the functional molecules including fluorescent dyes to an unnatural base, we can create RNAs, which detect specific proteins or viruses."

In addition, the study of unnatural base pairs is linked to the study of protein. Actually, Hirao and his colleagues have promoted the study of unnatural base pairs as a part of the Protein 3000 Project—a national project (2002–2006) aimed at clarifying the three-dimensional structure of proteins and understanding their functions. "The project will not come to an end when we have determined their structures alone," says Hirao. The researchers are expected to modify the structure of proteins, design the chemical compounds that bind to the proteins associated with pathogenesis and enhance or weaken their effects. "The next goal is to control the functions of proteins by taking such an approach," continues Hirao. "One of the technologies that may enable control of protein function is the use of unnatural base pairs."

A protein is a folded chain of amino acids. Each amino acid is coded by a particular sequence of three nucleotides (called a 'codon') arranged on the RNA. The four bases in a codon can generate 64 (that is, 4×4×4) possible combinations. Twenty amino acids are assigned to each codon. If the bases are increased to six, the number of possible combinations of codons is increased to 216 (6×6×6). Thus, we can create proteins with new functions that are different from those of natural proteins by assigning unnatural amino acids to the increased codons (Fig. 1). Although researchers have already created more than 80 unnatural amino acids, only one or two unnatural amino acids can be incorporated into protein by using the current recombinant DNA technology. "We are sure that we will be able to extensively modified protein functions by using unnatural base pairs," says Hirao.

The development of a 'replicable' unnatural base pair

The year 2002 marked a milestone in the progress of Hirao's research project. He succeeded in developing an unnatural base pair, s–y, and the transcription and translation of DNA in which the unnatural base pair worked, for the first time in the world. Following his success, his peers made comments such as "You succeeded in transcription and translation, but how about replication?" Actually, the unnatural base pair developed by Benner's research team in the US could be replicated to some degree. Hirao says, "All the team members have devoted themselves to

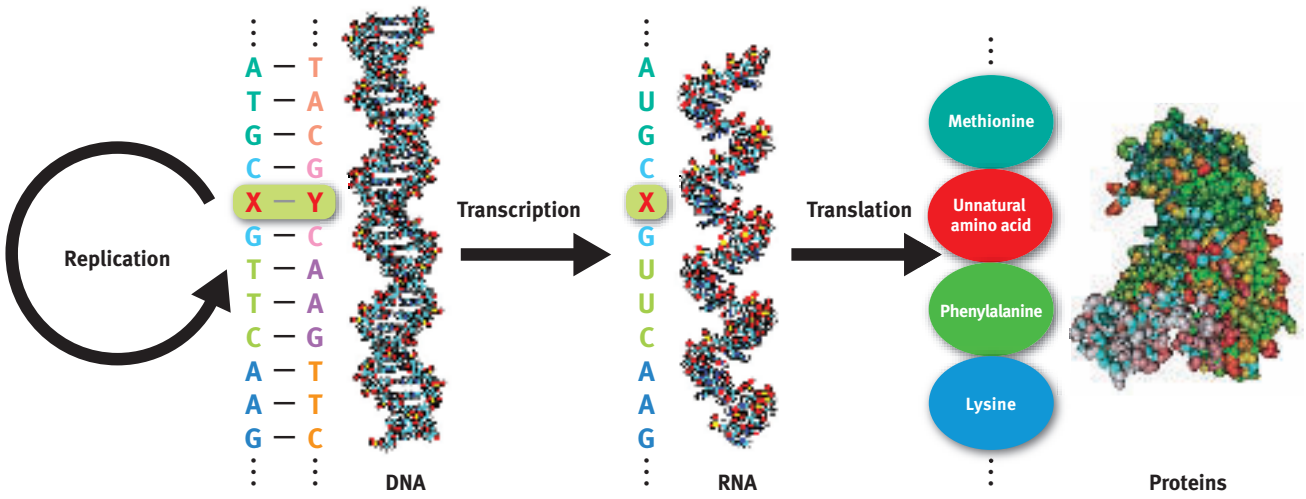


Figure 1 : Genetic information extension system using the unnatural base pair. An unnatural base pair (X-Y) in DNA mediates the site-specific incorporation of extra components into RNA and protein by transcription and translation, producing novel functional biopolymers.

the study and made concerted efforts to develop an unnatural base pair that can replicate itself." He explains that to achieve the biotechnology of unnatural base pairs, mass replication of DNA by PCR (Polymerase Chain Reaction, a method for replication in a test tube) is necessary. However, the performance of the s–y pair is still insufficient in replication.

In August 2006, Hirao and his colleagues succeeded in developing an unnatural base pair, Ds–Pa, which can be replicated and transcribed (Fig. 2). The accuracy of replication was more than 99.8%, which indicated a remarkable improvement on the accuracy reported by Benner *et al.* (96%). Ds–Pa is characterized by its higher level of selectivity. There are several points that contributed to achieving this excellent selectivity.

First of all, let's look at the structure of the naturally occurring base pairs. The bases A and G are large, whereas T and C are small bases. If we try to prepare a double helix with the same width, we should combine a large base with a small base. If the partner is selected according to the size of the base alone, combinations, such as A–C or G–T, are also possible. The hydrogen bond that binds one base to the other plays an important role in selecting the combinations. According to the combination of the hydrogen bond, only two combinations, A–T and G–C, can be selected.

How can Ds–Pa be selected? The width of Ds–Pa is the same as that of the naturally occurring base pairs. However, Ds is larger than A and G, whereas Pa is smaller than T and C. "The trouble was the hydrogen bond," explains Hirao. He adds that because of its hydrogen-bonding property, unnatural bases with hydrogen bonds also pair with some of the natural bases. "So we dared to eliminate the hydrogen bonds between the unnatural bases, Ds and Pa, and found that this elimination worked effectively," he continues. "We faced another problem with pairing between Ds bases, but we fortunately overcame it by accidental findings in the experiment." He smiles.

In the process of chemical synthesis of the materials for the unnatural bases, the researchers accidentally produced a unique product, which was slightly different from what they needed. They were so interested in the product, they could not simply discard it, and so they attempted to use the product in their experiment. The attempt was successful. "My experience can be expressed by the word, 'serendipity'. I always take particular care to notice what I encounter incidentally. In life and in scientific experiments, something that attracts my attention by chance or something that I find incidentally may have the potential to bring about something significant."

The trouble is that the unnatural base pair, Ds–Pa, is not as efficient in translation from RNA into protein as in replication and transcription. However, as Hirao says, this experimental result shed more light on the roles of the base pair in translation. "I have already thought of a solution," he says. Team Leader Hirao is clearly confident about the development of an unnatural base pair that functions in all three aspects, including replication, transcription, and translation.

He goes on to explain his next goal. "Currently, I conduct all my experiments in test tubes." He says that the unnatural base pair will find practical application in wider fields if it can function in cells. "I have confidence in such an application but it is hard to predict what may happen when I consider the intracellular system, which functions to remove foreign matter." He says that in the experiment that he is preparing now, he is attempting to incorporate a plasmid DNA containing Ds–Pa into Escherichia coli and examine whether the unnatural base pair can be replicated. "Because this experiment may result in creating a new organism, this project should be pursued with special care," he cautions. The materials for the unnatural base pair do not exist in nature, and an organism with DNA containing an unnatural base pair cannot grow without externally adding raw materials for the unnatural base pair.

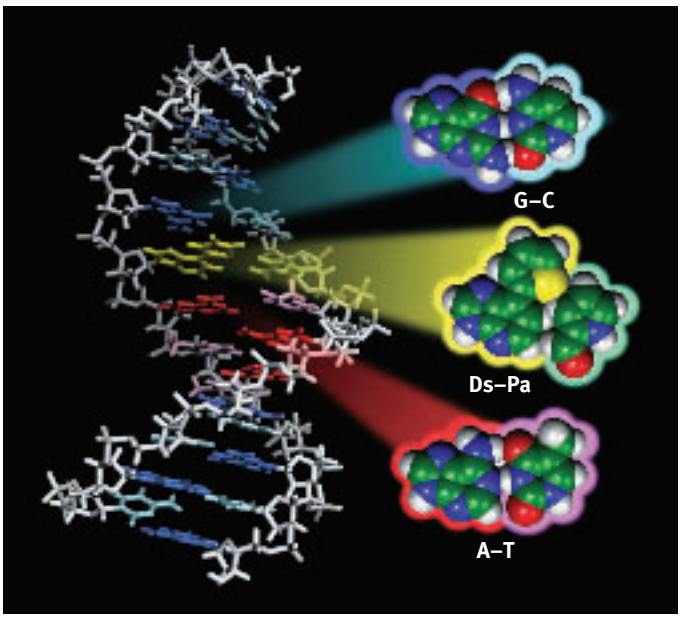


Figure 2: DNA double-helix-structure model containing the unnatural Ds–Pa pair. Ds and Pa, which are different in form from the naturally occurring base pairs, can produce a base pair selectively. Because the width of Ds–Pa is the same as that of the naturally occurring base pairs, the Ds–Pa pair can spatially fit in the double helix without any distortion. Although hydrogen bonds are used to form the natural A–T and G–C pairs, Ds–Pa is hydrophobic.

Regarding his future research project, Hirao says, "A complete change in our concept of DNA and the possibility of the production of genetic information with different substances has attracted my attention. This will involve me in more challenging studies."

Plans for a RIKEN venture company

Hirao is planning to establish a RIKEN venture company in the near future. "It is important for a scientist to make efforts to achieve outstanding results," he says. "However, I think that if my achievements have industrial applications, even though they may need further improvement from the scientific aspect, they should be utilized by society."

The new venture company is to be involved in licensing the technology of the unnatural base pair and developing detection and diagnostic products and inhibitors for proteins and viruses that may serve as treatment drugs. Hirao expresses his hopes as follows: "Since the unnatural base pair is a newly developed technology, I would like to show concretely what we can do with it." Because Hirao specialized in engineering at university, he is making efforts to apply the new technology in fields other than biological science. The new technology has contributed to the development and commercialization of biometric authentication systems using fingerprints and veins. An authentication system using DNA is currently in the process of testing. We can expect improvements in the specificity and diversity of authentication by using the unnatural base pair, as the amount of information increases.

The Importance of Japaneseness

What enabled Hirao and his colleagues to take over the lead in the challenging race to develop an unnatural base pair? He analyzed his success and commented as follows: "It is true that the presence of rivals has contributed to the progress of the study because of the friendly competition. However, what lies behind our remarkable success seems to owe something to the difference in the way of thinking between Japanese researchers and European and American researchers." He says that European and American researchers embark on a research project rigidly following a main concept. In contrast, Japanese researchers take up various concepts and take the middle course, proceeding with their research using this approach. "At first, we also used the concept of the hydrogen bond, but we gave it up in the course of our research," he explains. "Then we introduced a different concept based on a combination of forms. The attitude of not sticking to one concept—characterized as fuzziness—is an advantage that Japanese people have when they create new products." Recently, the European and American research style is becoming increasingly prevalent in Japan, but Hirao believes that Japanese researchers can also contribute to the progress of science with a different approach—making the most of their 'Japaneseness'. ■

About the researcher

Ichiro Hirao was born in 1956 in Shizuoka, Japan. In 1978, he graduated from the Department of Industrial Chemistry, Shizuoka University, and obtained his doctorate in chemistry from the Tokyo Institute of Technology in 1983. From 1984 to 1992, he served as an assistant professor at the University of Tokyo and then as an associate professor at the Tokyo College of Pharmacy from 1992 to 1996. After stints at Indiana University in the US, and the Japan Science and Technology Corporation, he became, in 2001, the leader of the Protein Synthesis Technology Team at the RIKEN Genomic Sciences Center (GSC). In 2002, he became a senior visiting scientist at the same center following his appointment as a professor at the University of Tokyo. Since 2006, he has been serving as the leader of the Protein-Regulating Macromolecules Research Team at the GSC. In March, he also set up a company called TagCyx Biotechnologies.

Advanced school for young Asian neuroscientists held at RIKEN Brain Science Institute

From February 26 to March 9, Asia-Pacific Regional Committee (APRC) of the International Brain Research Organization (IBRO) and RIKEN BSI held two weeks Advanced School. This school was designed for senior postdoctoral fellows and junior faculties. According to the Chair of IBRO APRC, Ying-Shing Chan, APRC IBRO chose RIKEN BSI as the partner for the First APRC IBRO Advanced School because of their state-of-the-art infrastructure for neuroscience research and excellent track record in organizing training programs.

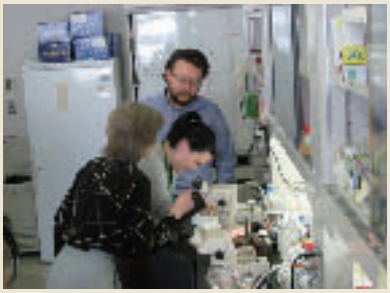


Figure 1: Esther Stoeckli intsructs an Australian student

Eleven selected participants gathered from such countries as Korea, India, Taiwan and Australia. The program consisted of lectures and experiments, which were executed by ten principle investigators (PIs) of BSI and an invited lecturer. For example, at the laboratory of Hiroyuki Kamiguchi, the invited lecturer, Esther Stoeckli from Zurich University instructed an experiment to observe the growth of neuronal circuit after injecting an antibody into the spinal cord in a chicken embryo at a very early stage in its generation (Fig.1). The experiment was very delicate, using a glass tube of just 5μm in diameter and fine tungsten scalpel. At the laboratory of Hajime Hirase, a student learned to use two-photon imaging for the study of cortical structures, including neurons and glia, and observation of *in vivo* intracellular and multi-channel recording (Fig.2).

The participants were all pleased to have the opportunity to learn the most advanced techniques in neuroscience. Nana Sunn from Australia, who was learning

Figure 2: A Taiwanese student and Hajime Hirase

immunohistochemistry of mouse brain tissue at the laboratory of Masaharu Ogawa, commented, "Even though well-known, the hosting PIs at BSI are very modest, patient and generous with the advise." She continued saying that at BSI, laboratories are interactive and there are fewer restrictions on experiments. "As opportunities permits, I want to come here to do my research." One of the PIs, Alexey Semyanov, said that the participants were qualified and gratifying to teach. He added, "It is also a good chance for our laboratory staff to teach them."

International conference on plant hormones held at RIKEN PSC

On March 1 and 2, an international symposium named 'Trends in Plant Hormones' was held at the Yokohama institute.

It has long been accepted that plant hormones are substances with a low molecular weight. However, recently it has been reported that some peptides or mRNA have a plant-hormone-like function, which has attracted a lot of interest. In this symposium, such newly discovered substances as the novel peptide hormone that regulates vascular-bundle differentiation (Hiroo Fukuda, the University of Tokyo) or identification of branching-control hormones, named MAX, whose chemical structure is yet unknown (Thomas Moritz, Umea Plant Science Centre, Germany) were reported.

There were also some presentations about an insight into the metabolic regulation mechanism of well known plant hormones. In particular, the discovery of gibberellin methyl transferase by Shinjiro Yamaguchi of RIKEN PSC and Eran Pichersky of the University of Michigan, and the quality-control function of a novel cytokinin synthesase, found by Hitoshi Sakakibara of RIKEN PSC, gave rise to several comments.

A new method invented by Yuji Kamiya to analyze various trace plant hormones simultaneously using liquid chromatography and mass spectroscopy attracted considerable attention.

More than half of the 150 participants were gathered from outside RIKEN, and there were a number of discussions among students, young researchers, participants outside, and guest speakers, not only in the sessions but also at the poster presentations.

2007 CDB Symposium: 'Germline versus Soma: Towards Generating Totipotency'

The RIKEN Centre for Developmental Biology (CDB) in Kobe, Japan held its fifth annual symposium on the theme 'Germline versus Soma: Towards Generating Totipotency', from 26 to 28 March in the CDB auditorium. The annual symposium series, which was launched in 2002, was established as a forum for addressing diverse aspects of developmental biology and the mechanisms of regeneration, and it aims to promote the free, timely and borderless exchange of research achievements. This year's event was co-organized by Akira Nakamura, Mitinori Saitou, and Fumio Matsuzaki from the CDB, along with Azim Surani of the Gurdon Institute, University of Cambridge in the UK.

This fifth CDB symposium focused on themes that have attracted intense scientific interest for more than 100 years, as the cells of the germline are unique in their ability to transmit genetic information across generations, and are characterized by the expression of numerous molecular factors involved in the maintenance of genomic continuity, diversity, and cellular totipotency. With a broad spectrum of presentations covering germline biology and related fields, such as pluripotency in embryonic stem cells and epigenetic reprogramming, this year's symposium featured unusually lively discussions and poster sessions, as well as numerous presenters and participants from abroad.

Next year's CDB symposium will be held on March 24 to 26, on the theme, 'Turning Neurons into a Nervous System'.

Nanoscience research heralds big changes

A pioneer of nanoscience and nanotechnology research, RIKEN is set to expand its exploration of this infinitesimal world

Recent and significant advances in nanotechnology research are soon expected to boost our quality life. By manipulating tiny objects that are 10,000 times smaller than the diameter of a human hair, scientists are creating novel materials and devices that can contribute to improvements in medicine, IT and the environment. RIKEN has been at the world's forefront in this hot research field for the past 30 years, and is strengthening its technological and research prowess.

RIKEN's history in nanotechnology research dates back to 1976, when laser physicist Susumu Namba successfully obtained crucial synchrotron radiation data for application to lithography, a technique to write circuit patterns on a semiconductor surface. A few years later, physicist Yoshiyuki Kawamura became the world's first to publish a paper on the excimer laser ablation.

Then in 1982, the Japanese government began promoting nanoresearch nationwide through a project called Nanometer Structure Electronics.

By that time, scientists at RIKEN had been working on nanoresearch individually, but in 1986 RIKEN established the Frontier Material Research Program—its first large-scale research project in this field. Project sub-teams looked mainly at quantum, molecular and biological devices. From 1991, the project's themes became more complex and included research into nano-electronic materials, nano-organic photonics materials and exotic-nano materials.

In 1993, RIKEN established a strategic research program based on the concept of 'atomic scale sci-engineering' (coined from the words 'science' and 'engineering'). The aim was to combine sophisticated nanotechnologies with fundamental research to better understand the nano-properties of materials and electron behavior. Concurrently, RIKEN's research focus on semiconductor development shifted to nanoscale manipulation, measurement and observation of atoms and molecules. These efforts provided the impetus for the launch of nanoscience research at other institutes and universities.

In 2000, seven years after RIKEN initiated this strategic research, the US announced its National Nanotechnology Initiative. The US plan garnered enormous attention as it portrayed nanotechnology as a promising research field in the early 20th century.

Amid intensifying competition, the Japanese government in 2001 launched national strategic nanotechnology programs. Following this move, in 2002 RIKEN established the Nanoscience Research Program that was structured to facilitate cross-disciplinarily projects. Then in 2003, RIKEN built a cutting-edge Nanoscience Joint Laboratory in Wako (Fig. 1), which accommodates 21 sub-teams of researchers.

Figure 1: Researchers at RIKEN use a clean room of the Nanoscience Joint Laboratory, opened at Wako in 2003, to conduct nanotechnology research into microfabrication.

Over the past few decades, researchers at RIKEN have accomplished a variety of impressive research and development achievements. One laboratory, conducting laser science research, demonstrated how to freely attach or remove atomic layers one-by-one, while another laboratory developed a novel ion-scattering spectroscopy technique and investigated the position and alignment of surface atoms. Meanwhile, biological polymer researchers produced a material capable of self-controlling the level of light transmission. They also invented a technique called 'nanofishing' to make detailed observations of protein structures by stretching individual polymer chains. Another research team found a way to form quantum dots under unusual conditions.

In addition, a research group investigating atomic-scale mechanisms developed an innovative scanning tunneling microscope (STM) equipped with multiple tips, instead of the conventional single tip. This made it possible to observe and control the behaviors of individual atoms and molecules effectively. Using a different type of STM, a team of atomic-scale materials researchers successfully made a carbon oxide molecule hop from one place to another on a metal surface by introducing electrons onto it (see Profiles, *RIKEN RESEARCH* **2(5)**, 11–12).

Researchers at RIKEN foresee that nano-photonics will become a key research area in the near future. The research focus is already shifting from inorganic materials to carbon-based and biological materials, among many others. RIKEN is well positioned to build on its accumulated technological and research expertise in this rapidly expanding field. ■

For further information, please visit:
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