RIKEN RESEARCH

DECEMBER
2007 Volume 2 Number 12

A profitable pest

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Signaling simplified

Japanese immunologists find differential usage of essential components of signal pathways in innate and acquired immune responses

Threats to our health from attacking microbes are combated by the immune system; an intricate web of molecules that detect invasion, communicate emergency messages and activate the defense reaction. Immunity is vital to life, but when the system breaks down, debilitating conditions such as autoimmune disease and inflammatory illnesses can result. For all of these reasons, it is of particular interest that immunologists deconstruct the immune system and lay bare its component parts so that its mechanisms can be better understood and future therapies developed.

Now a team of researchers, led by Takashi Saito from the RIKEN Research Center for Allergy and Immunology in Yokohama, has given clear insights into the way constituent parts of the immune system communicate with each other. In their study recently published in *Nature Immunology*[1], the team describes a key factor through which urgent chemical messages are routed when the immune response is triggered.

Figure 1: The function of the adaptor proteins CARD9 and CARMA1 in innate and acquired immune responses was studied in mice deficient in these proteins.

Types of immune response

The body mounts an immune response when invading pathogens are recognized by a variety of receptors found on the surface of white blood cells, namely myeloid and lymphoid cells. Each cell type is involved in one of two lines of defense against infection: innate and acquired immunity. The innate immune system is our first barrier against invading microbes; it recognizes and responds to pathogens in a generic way. The acquired immune system acts as a second barrier, and also provides protection against re-exposure to previously encountered pathogens as 'memory' responses. Myeloid cells are implicated in innate immunity and are the main subject of the RIKEN study.

Myeloid cells have a plethora of microbe-responsive receptors including toll-like receptors (TLR), c-type lectins (e.g. Dectin-1), Nod and Nod-like receptors, among others. Urgent chemical signals from activated receptors are routed through specific pathways within the cell. The constitutive components of these pathways include molecules known as adaptor proteins, which mediate the signaling process. Although adaptor proteins lack any intrinsic catalytic activity themselves, they enable the formation of protein complexes and allow a rich diversity of coordinated molecular interactions to occur within the cell during signal transduction.

Adaptor proteins CARD9 and CARMA1

Saito and colleagues have concentrated on the adaptor CARD9 by studying a population of mice lacking this protein (Fig. 1). They found that CARD9 is active in myeloid cells and is intrinsic to the signal pathway that results in the innate immune reaction. Many receptors in myeloid cells mediate signals through protein molecules that contain a module called an ITAM (immunoreceptor tyrosine-based activation motif) and one of the myeloid cell receptors for fungus, Dectin-1, contains an ITAM-like motif as part of its structure.

Using the mouse population, the RIKEN team has provided genetic evidence that all myeloid receptors that initiate signals through an ITAM-containing protein need CARD9 and two other adaptor proteins, Bcl-10 and MALT1, to activate the innate immune response. Toll-like receptors do not involve the ITAM motif in their signal pathways. However, the team has demonstrated that toll-like receptor-dependent signaling pathways do converge on CARD9, but then are routed elsewhere.

ITAM recruits an enzyme, Syk, known as a kinase to start a signal cascade leading to gene activation, a procedure that is promoted by molecules known as transcription factors, such as NF-κB (nuclear factor-kappa B). CARD9 has disparate functions in the ITAM-related and TLR pathways; it links ITAM-related receptors to NF-κB activation and toll-like receptors to another gene-activating molecule MAPK (mitogen-activated protein kinase).

In addition to their study of myeloid cells, the researchers have provided evidence that another adaptor protein, known as CARMA1, acts like CARD9, but in the adaptive immune response in lymphocytes (Fig. 2). They concluded this after studying a population of mice lacking CARMA1. The team found that it is essential in lymphocytes but dispensable in the myeloid receptor pathway and thus CARMA1 seems to be the CARD9 counterpart in lymphoid cells. Similarly to CARD9, CARMA1 functions in combination with the adaptors Bcl-10 and MALT1.

Cytokine response

The information that passes along these cellular pathways ultimately leads to activation of genes that produce cytokine molecules. Cytokines are a group of proteins that are particularly important in both innate and adaptive immune responses as they signal immune cells to travel to the site of infection and also stimulate them to produce more cytokines.

It is not yet apparent how CARD9 selectively activates NF-κB and MAPK. These discrete CARD9 mediated pathways modify gene expression in unique ways resulting in distinct cytokine responses. The fact that these responses are unique may provide an opportunity to fine-tune cytokine production in reaction to infection.

Immune signal routes

The team has provided genetic evidence for the essential role played by CARD9 in innate immunity. This gives us a simplified picture of the way information is directed through myeloid cells. ITAM-associated receptors transfer their chemical messages through CARD9 to stimulate transcription factor NF-κB activation and TLRs route their signals through CARD9 to trigger MAPK. Both avenues lead ultimately to gene activation and the production of cytokine molecules which promote resistance to and security against infection.

"Therapeutic approaches targeting either the lymphoid CARMA1 complex (L-CBM) or the myeloid CARD9 complex (M-CBM) might provide a strategy for specifically modulating lymphoid versus myeloid cells for the activation or inhibition of their functional responses," Saito says. Such control would ultimately benefit the treatment of devastating, but unfortunately common, illnesses such as rheumatoid arthritis and harmful infectious diseases. ■

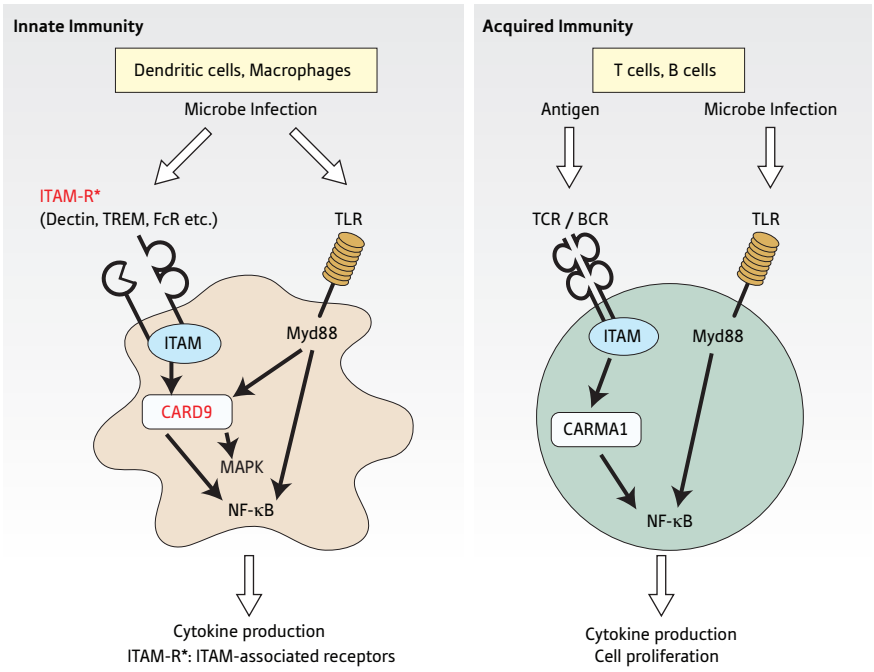


Figure 2: Activation of immune cells through ITAM-receptors. Receptors on the surface of lymphocytes induce signal transduction pathways resulting in the production of cytokines.

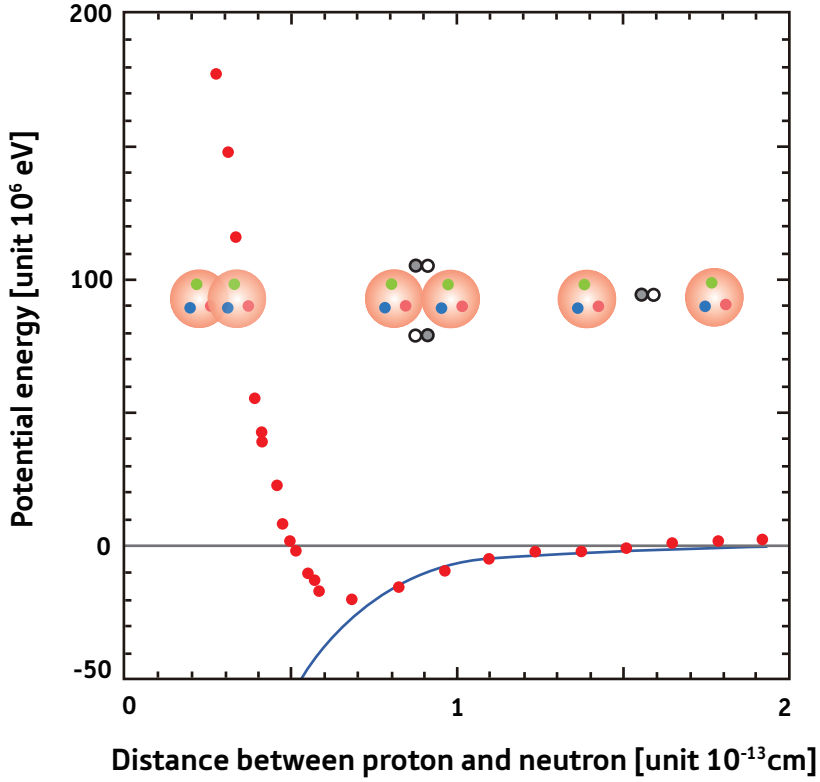
1. Hara, H., Ishihara C., Takeuchi, A., Imanishi, T., Xue, L., Morris, S.W., Inui, M., Takai, T., Shibuya, A., Saijo, S., Iwakura, Y., Ohno, N., Koseki, H., Yoshida, H., Penninger, J., Saito, T. The adaptor protein CARD9 is essential for the activation of myeloid cells through ITAM-associated and Toll-like receptors. *Nature Immunology* **8**, 619–629 (2007).

About the researcher

Takashi Saito was born in Tokyo, Japan, in 1950. He graduated from the Tokyo Institute of Technology in 1975. He was a graduate student majoring in chemistry at the Tokyo Institute of Technology when he became deeply fascinated by the life sciences, especially immunology. He changed his major and received his PhD under the supervision of Tomio Tada and Masaru Taniguchi at Chiba University School of Medicine in 1982. As a postdoctoral fellow, he started his academic career in the laboratory of Klaus Rajewsky, University of Cologne, Germany from 1982, before working with Ronald Germain at the National Institutes of Health in the USA from 1985. He returned to Japan as an assistant professor at Chiba University in 1988. He was promoted to Professor of the Division of Molecular Genetics, Center for Biomedical Sciences, Chiba University School of Medicine in 1989. When the RIKEN Research Center for Allergy and Immunology was established in 2001, he was assigned as a group director of the Laboratory for Cell Signaling. In 2004, he became Deputy Director of the center. He has been focusing on analyzing the mechanisms of immune responses, in particular, T cell activation and regulation.

Don't get too close

A new approach proves that the nuclear force is strongly repulsive at close distances



Aoki, Hatsuda and Ishii

Figure 1: The nuclear potential between a proton and a neutron as a function of separation distance. The blue line represents the predictions of Yukawa's original one-pion exchange potential, and the red dots are the predictions of the present study that shows strong repulsion at short range.

The force that holds atomic nuclei together is a complicated residual effect of the strong force between quarks and gluons—elementary particles that make up protons and neutrons. RIKEN researchers at the University of Tsukuba are explaining the nuclear force by extending quantum chromodynamics (QCD), the theory of the strong force[1].

The nuclear force involves the exchange of particles such as pions, first predicted by Nobel laureate Hideki Yukawa over 70 years ago. The force is thought to consist of three distinct regions (Fig. 1).

At separations greater than two femtometers (quadrillionths of a meter), the nuclear force falls off exponentially with distance and is mainly communicated by one-pion exchange. Closer in is a potential well that traps the nucleons at an average separation of about one femtometer—and where the exchange consists of multipions and heavy mesons. Closer still, the nucleons interact directly and the force is strongly repulsive.

The repulsive core explains scattering experiments, the stability of nuclei, and even supernova explosions. It is probably caused by the structures of quarks and gluons in the overlapping nucleons, but this remains an open question. The RIKEN researchers made use of lattice QCD—a theory restricting quarks and gluons to a discrete space-time lattice—to investigate the repulsive core in numerical simulations.

"Previous studies have tried to extract the nuclear force from the energy of two nucleons whose separation is kept fixed, but this is difficult because they move around," says team-member Sinya Aoki. "In our study, we calculated the wave-function of two nucleon systems—which is very similar to experimentally measured quantities—and derived the potential from it."

The potential obtained from the wave-function is plotted in Figure 1 as red dots. This result reproduces the nuclear potential observed in experiments, with repulsion at short distances and attraction at long distances. In particular, data at long distances are consistent with Yukawa's original one-pion exchange potential, represented by the blue line.

"At this moment, we can only say that QCD reproduces the qualitative behavior of the nuclear potential," says Aoki, "however our study opens the possibility of studying the repulsive core from its first principle—the dynamics of quarks and gluons."

In future, QCD could be extended to study interactions between hyperons. These three-quark particles (baryons) include the third type of quark, 'strange quarks', whereas nucleons only contain up and down quarks. Hyperons play important roles in neutron stars, but their interactions are not fully understood. ■

1. Ishii N., Aoki, S. & Hatsuda, T. Nuclear force from lattice QCD. *Physical Review Letters* **99**, 022001 (2007).

Looking forward at proton collisions

Asymmetry in neutrons produced by proton collisions makes a good detector for spin-polarized protons

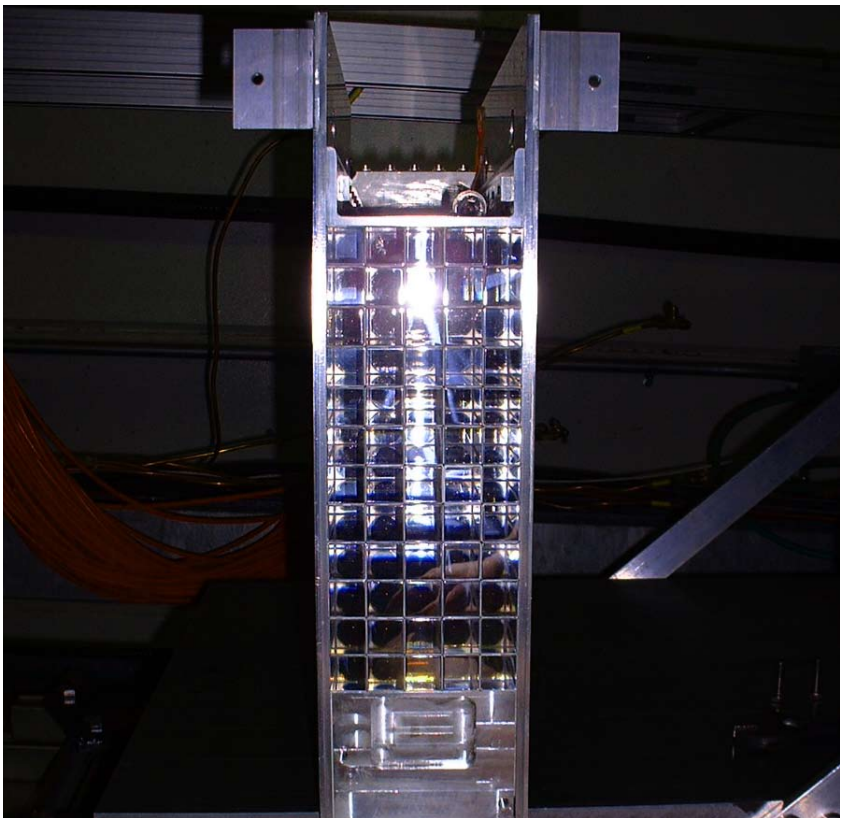


Figure 1: Photo of the calorimeter used to measure the asymmetry in neutron production of high-energy proton collisions.

An international team of researchers at the Relativistic Heavy Ion Collider (RHIC) of Brookhaven National Laboratory, in the US, has developed a new particle detector and used it to observe a large asymmetry in the distribution of neutrons produced during the collision of protons.

At RHIC, high-energy collisions of protons are studied to understand the fundamental physics governing subatomic particles like protons and neutrons. In these collisions, energy is converted to matter that generates a large number of particles as a result.

Of particular interest to particle physicists is the role of the quantum-mechanical property known as 'spin' in these collisions. Just as the needle of a compass points in a certain direction, so does the spin of protons and neutrons. The researchers have now studied collisions where the spins of the protons in the two colliding beams of the RHIC point in the same direction.

As the direction of the spin polarization is predetermined, any asymmetries in the direction at which the generated particles are scattered provide valuable clues on the influence of spin. "Such results are not only important to understand the fundamental physics of the collisions, but also to eventually use [these] asymmetries as a monitor for RHIC beam polarization," explains Yuji Goto from the RIKEN team.

In their study, published in *Physics Letters B*[1], the researchers have observed a large asymmetry in the number of neutrons that are produced in the left compared with the right side of the polarized proton beams. Their detector (Fig. 1), which is relatively compact for such complex tasks, consists of a calorimeter that measures the energy that is deposited in one of the beam directions. It also contains position and timing sensors for the necessary detailed analysis.

The asymmetry was found to be surprisingly large and Goto is convinced that "this is one of the most important results so far in the collision of spin-polarized protons at the RHIC". Already, these findings provide important clues towards the fundamental processes leading to this asymmetry.

Moreover, the large asymmetry in neutron production can be used as a sensitive tool to measure the spin polarization and direction in the original proton beam. Indeed, the calorimeter has already been implemented at RHIC as a monitor of the polarization of the proton beams. The fundamental importance of these results aside, the detector developed by the researchers will play an important role in the other fundamental investigations performed at RHIC. ■

1. Fukao, Y., Togawa, M., Bazilevsky, A., Bland, L. C., Bogdanov, A., Bunce, G., Deshpande, A., En′yo, H., Fox, B.D. & Goto, Y. *et al.* Single transverse-spin asymmetry in very forward and very backward neutral particle production for polarized proton collisions at $\sqrt{s}$=200 GeV. *Physics Letters B* **650**, 325–330 (2007).

Core structures

Japanese scientists describe crystal structures at the heart of antitumor compound synthesis

Japanese biochemists have brought the design of anticancer compounds a step closer in a study published recently in the *Proceedings of the National Academy of Sciences USA*[1]. Shingo Nagano, Yoshitsugu Shiro and their colleagues from the RIKEN SPring-8 Center, the University of Hyogo and Toyama Prefectural University have studied the biosynthesis of a natural product called staurosporine. This molecule is isolated from bacteria of the genus *Streptomyces* and is of interest because it exhibits antitumor activity. Staurosporine has been identified as a potent inhibitor of enzymes that regulate cell growth and death, known as protein kinases.

Staurosporine is a member of a family of compounds whose biosynthesis involves the formation of a base unit called an indolocarbazole core. Because of their potential as therapeutic agents for cancer and neurodegenerative diseases, indolocarbazole compounds have attracted scientists' attention.

The formation of the indolocarbazole core in part involves binding a molecule of chromopyrrolic acid with an enzyme known as cytochrome P450 StaP. StaP is a member of the cytochrome P450 family of compounds which includes enzymes involved in steroid hormone biosynthesis, drug metabolism and many other physiologically important reactions.

Nagano and co-workers presents the first report of the precise arrangement of atoms during a key stage in the formation of the core structure. The configuration of atoms they describe is known as its crystal structure and is elucidated using the technology of x-ray crystallography, a method of determining the arrangement of atoms in a molecule by analyzing the reflection patterns of x-rays directed at it.

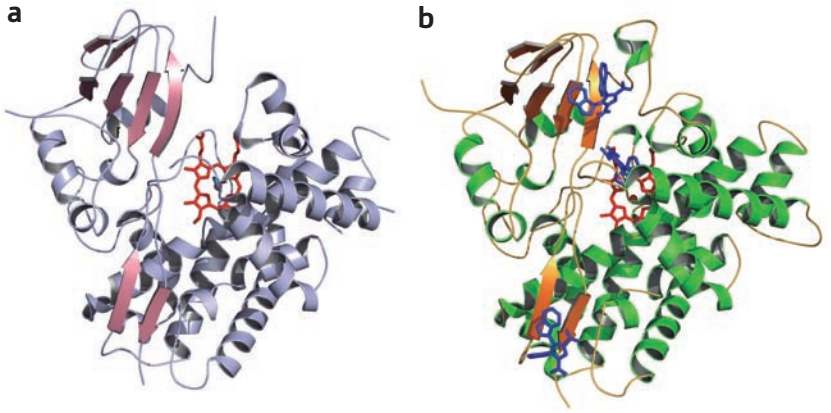


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Figure 1: Indolocarbazole core formation showing high resolution crystal structure of cytochrome P450 StaP in the absence (a) and presence (b) of the substrate chromopyrrolic acid.

The study provides high resolution crystal structures of StaP in the presence and absence of the substrate chromopyrrolic acid (Fig. 1). The structure of the complex with the substrate StaP in place provides structural insights into the process of enzyme-substrate recognition and the molecular mechanism of indolocarbazole core formation.

This crystallographic study provides valuable insights into the process of staurosporine biosynthesis, the mechanism of indolocarbazole synthesis, and the diverse chemistry performed by cytochrome P450s.

"The ultimate goal of our project on indolocarbazole is structure-based design of enzymes that produce 'unnatural' indolocarbazole which have improved antitumor activity or new bioactivities," says Nagano. Moving forward, in a study to be published shortly, the group has described the structure of an enzyme involved in another similar reaction. The ultimate aim is to synthesize a variety of indolocarbazole compounds that could have important therapeutic use in the fight against cancer. ■

1. Makino, M., Sugimoto, H., Shiro, Y., Asamizu, S., Onaka, H., & Nagano, S. Crystal structures and catalytic mechanism of cytochrome P450 StaP that produces the indolocarbazole skeleton. *Proceedings of the National Academy of Sciences USA* **104**, 11591–11596 (2007).

Lanthanide as leading light for display technology

Innovative use of existing film technology may lead to a new type of thin-film display

A promising new way to make thin-film displays is being developed by a team of Japanese scientists led by Masaki Takata from the RIKEN SPring-8 Center, Harima.

Liquid crystal, thin-film displays are now commonplace in our daily lives; however, their manufacture is complex requiring a number of expensive and error-prone techniques to be used to produce each one. The result is a high-cost product. Consequently there is much interest in developing a new, lower-cost technique; a technique that Takata believes could be possible using their latest research findings.

The technique uses Langmuir–Blodgett films that are usually comprised of layers of organic molecules. The films are built-up one layer at a time until the desired number of layers is obtained. For this system, the team used two different layers. One layer contains the compound melem, which is capable of emitting light at specific wavelengths. The other layer contains a metal ion from the lanthanide group, praseodymium (Fig. 1).

Takata and colleagues explain in their latest paper published in *Photochemical & Photobiological Sciences*[1] that in the films, the orientation and density of the molecules can be controlled. The exact positioning of these molecules then has a profound effect on their behavior. The emission spectra of the films were then studied in detail.

Two distinct emission bands were observed and the polarity of these bands was also different. The first band was seen at 375 nm and polarized through 0°; the second was seen at 410 nm and had polarized by 30°. This important finding means that if this film was used in optical fiber cables, two different streams of information could run down a single fiber simultaneously.

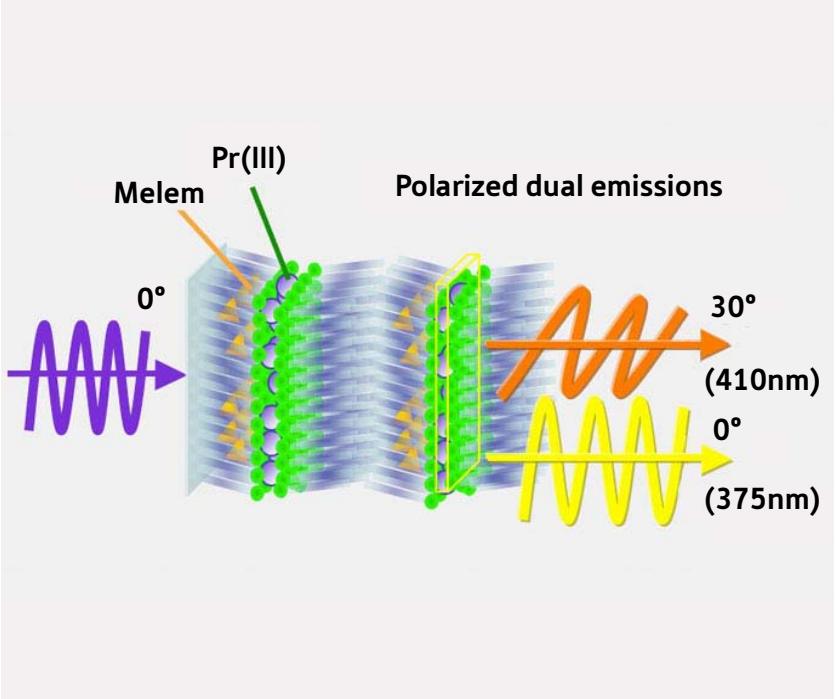


Figure 1: Illustration of the interactions between the metal, praseodymium, and chromophore, melem.

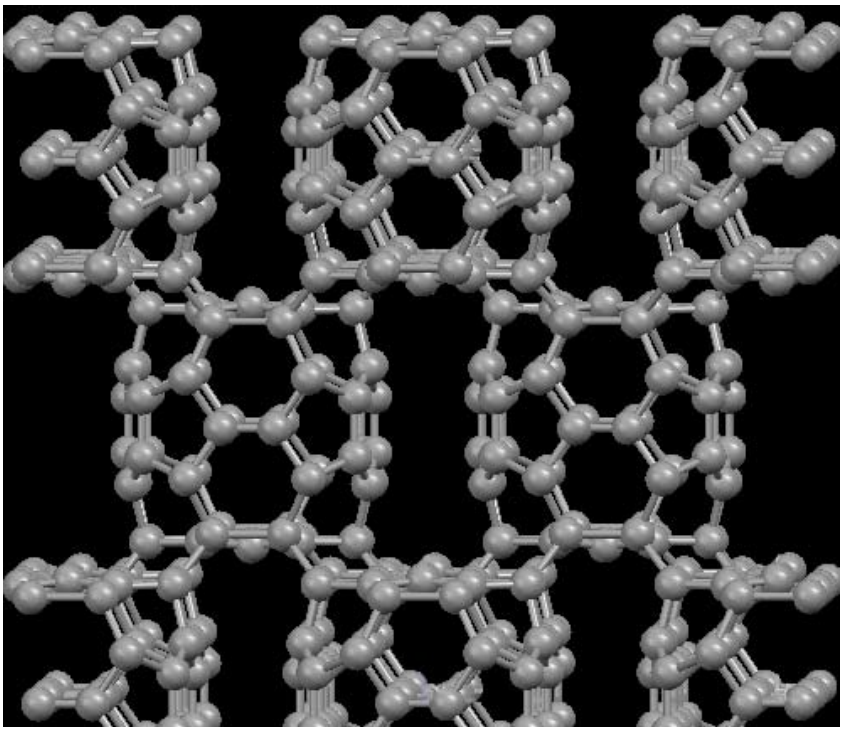
Interestingly, the results obtained from the thin-film are markedly different from what would be obtained from either a mixed solid or liquid of the two compounds. In the solid state, melem can bind in several ways with lanthanide metal ions through its nitrogen atoms forming a polymer-like complex. The resulting emission of praseodymium is then very weak and difficult to detect, which is the same as in a standard praseodymium complex with melem.

Even though scientists first started using Langmuir–Blodgett film techniques in the 1930s, Takata and a team member, Miki Hasegawa from Aoyama-Gakuin University in Tokyo, are confident that their team's investigations into metal complexes and molecular interactions will uncover new optical properties. "Finally, we have found a new possibility by using [an] 'old' method with coordination chemistry," they say. ■

1. Ishii, A., Habu, K., Kishi S., Ohtsu, H., Komatsu, T., Osaka, K., Kato, K., Kimura, S., Takata, M., Hasegawa, M. & Shigesato, Y. Novel emission properties of melem caused by the heavy metal effect of lanthanides(III) in a LB film. *Photochemical & Photobiological Sciences* **6**, 804–809 (2007).

Just add barium

Squashed carbon balls show promising electronic properties



Angew. Chem. Int. Ed.

Figure 1: A graphical representation of clathrate–C_{60}.

Theoretical calculations have shown that an exciting new material—made by squashing together latticework balls of carbon atoms—could be a superconductor.

Such superconductors are widely sought, since they carry electricity with no resistance and could be used to make extremely efficient energy transfer and storage systems.

Materials containing a cage-like structure of atoms, known as clathrates, have shown promise as superconductors. Scientists led by Shoji Yamanaka from Hiroshima University recently made a new clathrate[1] based on buckminsterfullerene (C_{60})—a hollow molecule made of sixty carbon atoms arranged into a soccer ball shape. High temperatures and pressures were used to squeeze the balls together until they became interconnected cubes of carbon, dubbed clathrate-C_{60} (Fig. 1).

Toshiaki Iitaka of RIKEN's Discovery Research Institute in Wako and colleagues from the University of Saskatchewan in Saskatoon, Canada, led by John Sak Tse, have now calculated the structural and electronic properties of this material, and report their results in the international edition of *Angewandte Chemie*[2].

They found that pure clathrate-C_{60} is metallic, and suggest that it could be a superconductor. Recent experiments have confirmed that clathrate-C_{60} is weakly metallic, but found no superconductivity even at the low temperature of –269 °C: just four degrees above the coldest temperature possible, known as absolute zero. Colder temperatures even closer to absolute zero may be needed to uncover the predicted superconductivity, the team suggests.

The structure of clathrate-C_{60} allows individual metal atoms to sit either inside, or between, each of the carbon cages. The team looked at how adding barium—just the right size to fit in either space—would alter the material's properties.

The team also found that in both cases, adding barium would release heat energy from the material, making the overall structure more stable. Although the compounds have not been made, this result means that the compounds should be achievable experimentally, the team says.

Further calculations revealed that if the barium atoms sit inside the carbon cages, they lose an electron—this does not change the overall structure by much, but it turns the material into a semiconductor. Conversely, adding barium atoms into the spaces between the carbon cages distorts the overall structure. The metal atoms also lose less charge, and the material remains metallic.

These changes in electronic properties suggest that clathrate-C_{60} "may potentially be an important electronic material for technology applications," the scientists predict. ■

1. Yamanaka, S., Kubo, A., Inumaru, K., Komaguchi, K., Kini, N.S., Inoue, T. & Irifune, T. Electron conductive three-dimensional polymer of cuboidal C_{60}. *Physical Review Letters* **96**, 076602 (2006).
2. Yang, J., Tse, J. S., Yao, Y. & Iitaka, T. Structural and electronic properties of pristine and Ba-doped clathrate-like carbon fullerenes. *Angewandte Chemie International Edition* **46**, 6275–6277 (2007).

Unlocking the mysteries of a molecular motor

A combination of experimental and theoretical approaches may help explain the molecular mechanics underlying each muscle contraction

Flexing a muscle might seem like a smooth motion, but each contraction actually consists of several staged movements, as thin actin filaments slide along thick myosin filaments. Each thick filament consists of numerous myosin molecules that interact directly with actin. During contraction, these myosins consume adenosine triphosphate (ATP)—the fundamental energy currency of the cell—to generate a ratcheting motion that leads to direct mechanical movement of neighboring actin filaments.

The specific points of interaction between myosin and actin and the process by which myosin turns energy into movement have remained unclear, but Hirofumi Onishi of the RIKEN SPring-8 Center in Harima has made considerable progress in resolving some of these uncertainties. In recent studies conducted with Manuel Morales at the University of the Pacific in San Francisco, US—a former mentor and a longtime collaborator—Onishi's group generated myosin mutants that revealed essential regions of the molecule. "Functional tests of these mutants allowed us to determine which residues are really responsible for the interaction between actin and myosin," Onishi explains.

Now, Onishi and Morales have combined their findings with work from other researchers to develop a model that could help resolve the mysteries of myosin movement[1]. The two investigators compared two sets of structural data from different stages of actin–myosin interaction. The first was developed by Onishi and Morales to model the initial 'weak' association between myosin and actin, while the second was based on a structure representing the 'strong' interaction state observed after myosin has completed its movement.

Integrating these data with their mutational findings enabled Onishi and Morales to identify amino acids from myosin and actin involved in each step of the contraction process. This in turn led to a promising model for how physical movements triggered in the myosin head by ATP metabolism and changing interactions with the actin molecule in the transition from weak to strong binding might trigger mechanical activity elsewhere in the myosin molecule (Fig. 1).

"Comparison between these models was informative in clarifying the detailed mechanism of how influences initiated at the interface transmit to other functional sites," says Onishi. This remains a theoretical model, and Onishi and Morales are planning to follow up with more sophisticated computer modeling and experimental strategies. "We have to investigate not only the actin-binding site," he says, "but also other functional sites, in order to understand how myosin catalyzes ATP hydrolysis and delivers a mechanical impulse." ■

1. Onishi, H. & Morales, M.F. A closer look at energy transduction in muscle. *Proceedings of the National Academy of Sciences USA* **104**, 12714–12719 (2007).

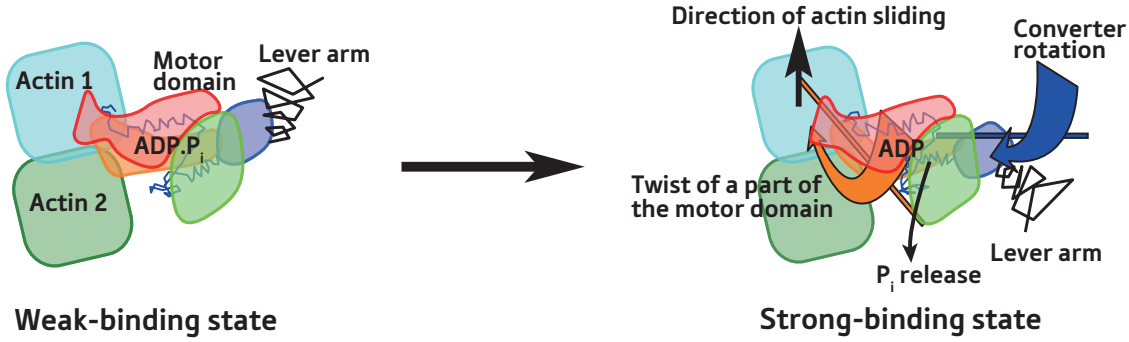


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Figure 1: A proposed model for how changes in myosin's interaction with actin filaments in the transition from the weakly bound state to the strongly bound state might translate into the mechanical movement necessary for muscle contraction. The breakdown of ATP and release of resulting byproducts at the motor domain (red, ocher and green regions) is translated to ratcheting of the lever arm (black) via a 'converter' domain (blue).

Identification of a novel cellular messenger

Zinc acts as second messenger in the cell to propagate extracellular signals

Researchers from Japan have shown that zinc can be used by the cell to transduce extracellular signals into cellular responses by propagating intracellular signaling pathways.

Cells that comprise the tissues of many different systems in the body must respond to extracellular molecular signals, such as hormones, toxins, cytokines, and metabolic by-products, in order to generate an appropriate and coordinated response. These external stimuli are often blocked by the plasma membrane that surrounds these cells, so they rely on so-called 'second messengers' within the cell to propagate the signaling cascade from the cell's exterior. Numerous reports indicate that certain small molecules play this role, the best studied being calcium.

Now Toshio Hirano at the RIKEN Research Center for Allergy and Immunology in Yokohama and his colleagues have added zinc to this list of second messengers[1]. The team's findings elevate our understanding of the biological importance of zinc beyond its previously identified role as a neurotransmitter and a co-factor for protein folding and function.

Working with mast cells, which are immune cells involved in the allergic response, Hirano's group showed that when they mimicked the immune activation of these cells by stimulating a membrane-bound receptor on their surface, a wave of zinc was generated that washed across the cell a few minutes after the stimulation (Fig. 1). They then showed that a rapid influx of calcium from outside the cell was required before this zinc-wave occurred. According to Hirano and his team, the zinc-wave seemed to originate from the endoplasmic reticulum, but they could not rule out other intracellular sources, such as the nucleus.

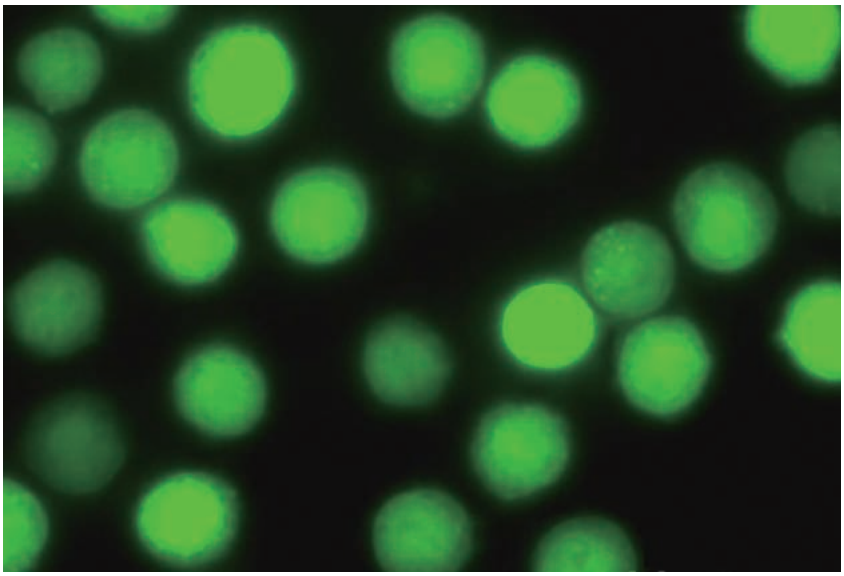


Figure 1: Bone-marrow derived mast cells were stimulated, and intracellular fluorescence to measure zinc levels was assessed every 30 seconds for 15 minutes.

Investigating further, the researchers showed that one role of the zinc-wave, at least, is to inhibit an important class of enzymes that remove the activation signals from other signaling proteins. This inhibition extends the activation time of these signaling proteins and therefore allows the continuation of the cellular signaling cascade. In the case of the mast cells, this resulted in further expression of IL-6 and TNFα—two key immunoregulatory cytokines that, in turn, can influence the behavior of a number of other cell types.

Hirano hopes to perform future experiments that will determine the molecular mechanisms that coordinate calcium influx with intracellular zinc flow. Also in his sights is identifying other cell types that use zinc as a second messenger and the targets within those cells. ■

1. Yamasaki, S., Sakata-Sagawa, K., Hasegawa, A., Suzuki, T., Kabu, K., Sato, E., Kurosaki, T., Yamashita, S., Tokunaga, M., Nishida, K. & Hirano, T. Zinc is a novel intracellular second messenger. *Journal of Cell Biology* **177**, 637–645 (2007).

Getting out of a jam with jellies

The isolation of a promising new protein could help reverse the economic damage being done by exploding jellyfish populations

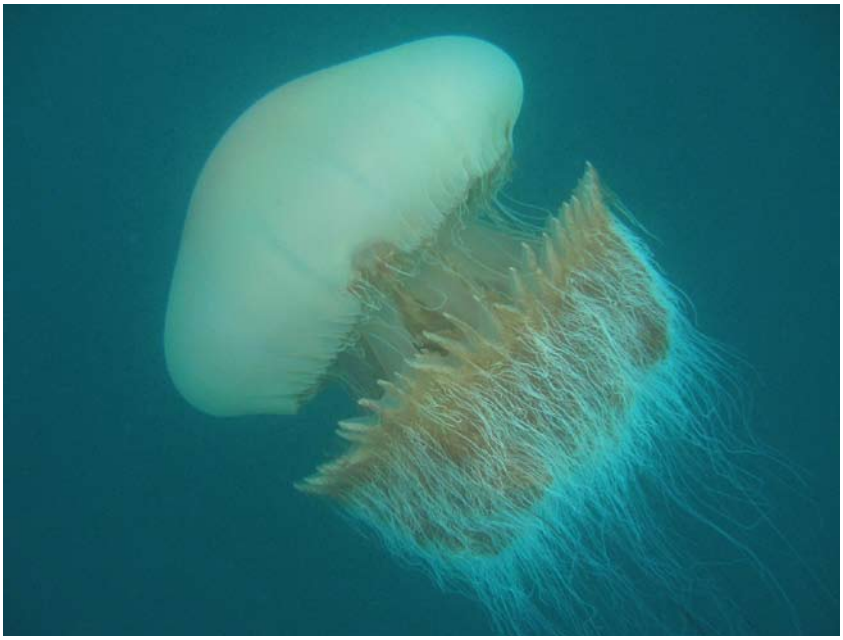


Figure 1: Nomura's jellyfish (*Nemopilema nomurai*)—one of the species now plaguing the Japanese coast—can grow as large as two meters in diameter.

One jellyfish can throw a swimmer into a panic, but relentless swarms can disrupt entire economies. Recent, dramatic increases in jellyfish populations—for reasons ranging from overfishing to the impact of global warming on coastal ecosystems—have had equally dramatic effects on human communities.

Several coastal power plants in Japan have been damaged or shut down entirely by the accumulation of tons of jellyfish bodies within their cooling systems, and fishermen in the Sea of Japan now find themselves confronted by nets full of jellyfish—including one particularly massive species (Fig. 1). Removing and disposing of these jellyfish bodies in an economically feasible way represents a major challenge, but a recent discovery by Kiminori Ushida and colleagues at the RIKEN Discovery Research Institute, Wako, and Shinwa Chemical Industries, Kyoto, may offer new hope.

"I know a lot about the economic situation with waste that requires compensation for the cost of collection, transportation and disposal," Ushida explains. "I felt that figuring out how to make money from jellyfish waste is essential for cleaning up and protecting the environment." Ushida's group set about performing a series of extractions on different jellyfish species, and identified a novel protein that consistently appeared in every sample[1]. It turned out to be a glycoprotein—a class of proteins naturally linked to sugar molecules—from a family known as mucins.

Mucins are found in many plant and animal species, and are currently used as additives for a number of commercial applications, ranging from cosmetics to medicines. Ushida's team named their protein 'qniumucin', a play on the word '*kuniumi*'; this term from Japanese history refers to the early government that arose to provide stability to a once-disorganized country. "I am worried about the terrible situation of people living in the districts where the ancient Japanese government originated, who are suffering because of these giant jellyfish," says Ushida, "and I hope that this material will generate new industry in the district, like the 'rebirth of the countryside'."

Indeed, qniumucin shows a great deal of promise—its structure is simple and well-understood, making it a candidate for further engineering to enhance particular characteristics. For example, some mucins have proven to be effective as antibiotics. Accordingly, Ushida's top priority is to make qniumucin extraction as profitable as possible. "We are developing designer mucins to enhance certain functions of our protein," he says, "and many companies are interested in finding effective commercial uses for qniumucin." ■

1. Masuda, A., Baba, T., Dohmae, N., Yamamura, M., Wada, H. & Ushida, K. Mucin (Qniumucin), a glycoprotein from jellyfish, and determination of its main chain structure. *Journal of Natural Products* **70**, 1089–1092 (2007).

Sweet synthesis to aid understanding of bacteria

A new route to synthesize an antibiotic may also lead to new drugs

A team of Japanese scientists led by Shino Manabe from the RIKEN Discovery Research Institute, Wako, has synthesized an oligosaccharide with antibiotic activity.

Helicobacter pylori is a very common bacterium that infects nearly half the human population and can lead to diseases such as gastric ulcers, carcinoma and cancer. The infection takes hold in the lining of the stomach and can be treated using a combination of antibiotics; however resistance can be a problem and many people suffer allergic reactions to them. Therefore, the development of new, more effective antibiotics is crucial.

A few years ago, it was discovered that, although the bacterium prospers on the surface of the stomach lining, deeper down in the membrane its growth is suppressed. It was proposed that a glycoprotein, a protein with saccharide side chains, was responsible by effectively inhibiting the synthesis of a compound needed by the bacterium to form cell membranes (Fig. 1). Upon investigation this glycoprotein was shown to consist of an unusually branched hexasaccharide believed crucial for this behavior.

With existing methods to synthesize this molecule producing only small amounts of material, Manabe realized the importance of being able to make larger quantities to allow for more detailed studies. Therefore, her team set about designing and preparing an efficient strategy to produce the hexasaccharide as presented in a recent paper published in the *Journal of Organic Chemistry*[1]. The structure proved a challenge because a particular part of the saccharide needs to be arranged in an uncommon way where two adjoining groups are on the same side of the molecule instead of on opposite sides, known as a 1,2-*cis* linkage.

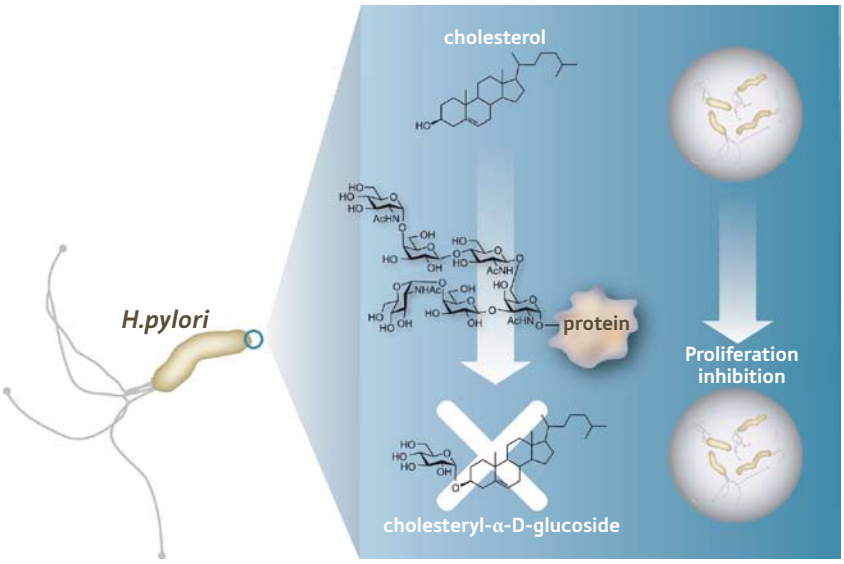


Figure 1: An illustration of how the hexasaccharide antibiotic prevents bacterial growth of *Helicobacter pylori*.

Overall the synthetic route developed by the team gave good yields in an efficient way allowing for greater quantities of material to be obtained. Manabe's strategy has an additional benefit: the way in which the researchers have synthesized the compound means making derivatives will be straightforward. Following the success of this project, the team is now focusing on using their approach to synthesize various oligosaccharides and investigate their potential biological activity.

This planned study should provide the team with the opportunity to fully investigate and understand the inhibition mechanism and consequently develop suitable drugs. "It might be possible to develop a novel drug candidate that produces minimal side effects and is specific against *Helicobacter pylori*. The mechanism of growth inhibition is different from the currently used antibiotics," explains Manabe. ■

1. Manabe, S., Ishii, K. & Ito, Y. Synthesis of a natural oligosaccharide antibiotic active against *Helicobacter pylori*. *Journal of Organic Chemistry* **72**, 6107–6115 (2007).

Stem cell precursors of ovarian support cells

Researchers isolate and devise a way to produce progenitors of cells essential for ovarian follicle maturation

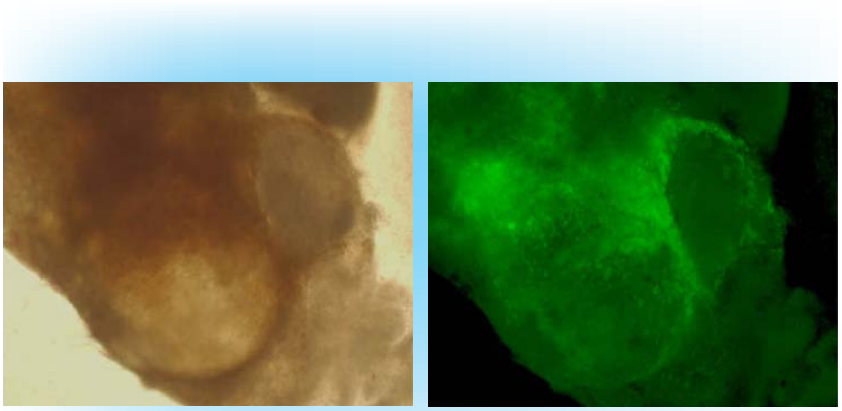
New work pinpoints stem cells that give rise to ovarian thecal cells, which together with granulosa cells and oocytes, form ovarian follicles. Thecal cells secrete steroid substrates required for production of the hormone estrogen, and aggregate in layers that ensheath and structurally support ovarian follicles, the growth of which is referred to as folliculogenesis.

Although much is known about the factors regulating mature thecal cell function, immature 'ancestors' of thecal cells have not been isolated, and the processes influencing thecal cell development and localization within the ovary remain uncharacterized.

Although originally intending to isolate elusive stem cells capable of giving rise to oocytes, a team led by Atsuo Ogura, a scientist at the RIKEN BioResource Center in Tsukuba, instead identified, and managed to produce in a dish, thecal stem cells[1].

The researchers cultured cells from ovaries of newborn mice in a medium containing growth factors but lacking serum. In just a few days, cellular 'colonies' appeared, grew rapidly and released oocytes. However, unlike stem cells, which undergo continuous cell division, these oocytes did not replicate their DNA and thus likely arose from pre-existing immature oocytes, rather than from oocyte stem cells.

However, further analysis of proliferating colonies revealed the existence of a stem cell-like population that expressed genes specific to thecal cells. To determine whether these cells could give rise to thecal cells, the researchers added serum and/or the hormones to which thecal cells in follicles are normally exposed.



PNAS

Figure 1: Thecal stem cells isolated from culture media are transplantable and localize correctly around developing follicles (green fluorescence).

When confronted with serum and hormones, this population underwent morphological changes associated with steroid production, released steroids into the culture medium, and activated genes expressed exclusively in mature thecal cells. Co-culture with granulosa cells further enhanced thecal cell differentiation of this population.

Lastly, the researchers subjected these putative thecal stem cells to the ultimate test—the ability to localize in layers surrounding actual mouse ovarian follicles. Remarkably, within two weeks of intra-ovarian transplantation, fluorescently labelled culture-derived thecal stem cells were incorporated, like *bona fide* thecal cells, within thecal layers of ovarian follicles (Fig. 1).

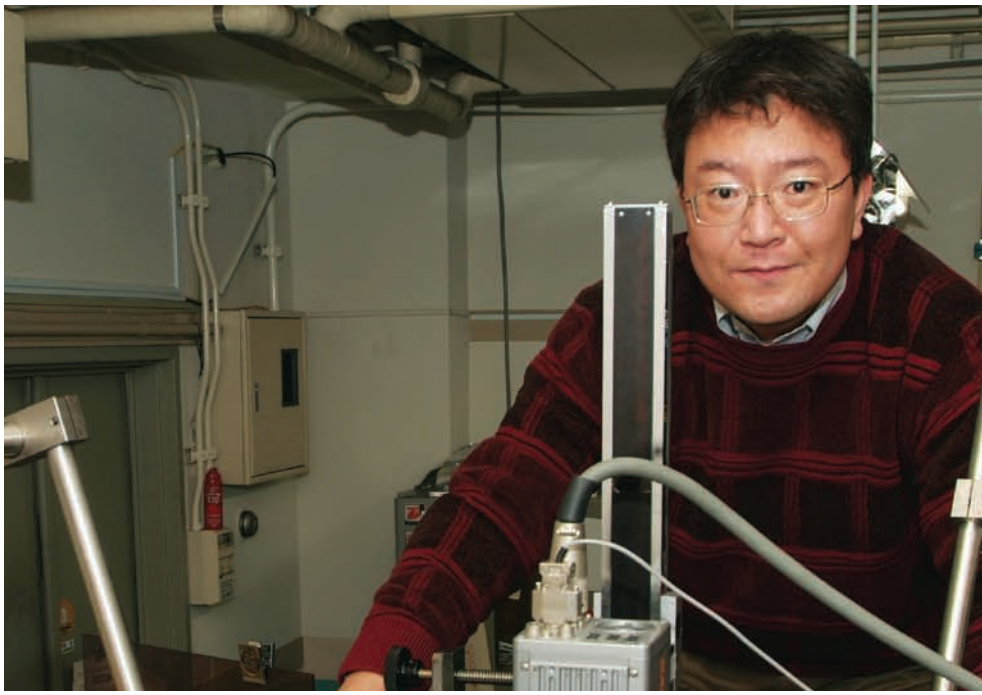
This tractable method for the production of large populations of thecal cells and their precursors will likely aid future experiments investigating thecal cell biology. "By using thecal stem cells isolated in this way, we will be able to reproduce the entire process of folliculogenesis in a dish. These studies may lead to a new treatment for folliculogenesis failure," says Ogura. ■

1. Honda, A., Hirose, M., Hara, K., Matoba, S., Inoue, K., Miki, H., Hiura, H., Kanatsu-Shinohara, M., Kanai, Y., Kono, T., Shinohara, T. & Ogura, A. Isolation, characterization and *in vitro* and *in vivo* differentiation of putative thecal stem cells. *Proceedings of the National Academy of Sciences USA* **104**, 12389–12394 (2007).

Computational living cell modeling

Hideo Yokota

Laboratory Head
Bio-Research Infrastructure
Construction Team
VCAD System Research Program
Center for Intellectual Property
Strategies (CIPS)



The VCAD System Research Program at RIKEN is now conducting 'live-cell modeling', an innovative research project that has never been attempted before. "Live-cell modeling is computational modeling of a cell as it really is in a living organism," says Hideo Yokota, Team Leader. "Nobody has conducted this kind of modeling project or feels inclined to take on such a challenge. I think live-cell modeling holds an important clue to leading life science to the next step." Yokota, who is a proponent of live-cell modeling, explained how living cells can be simulated with a computer and what lies ahead.

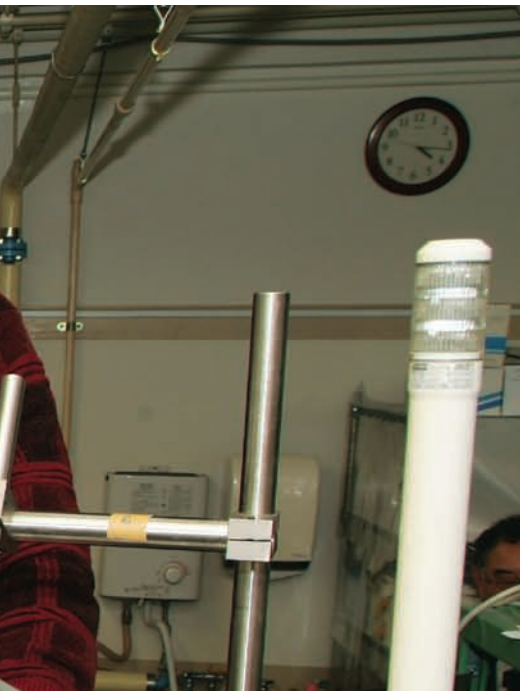
The world's first live-cell modeling

There are many pictures of natural life forms posted around in various places in the laboratory of the Bio-research Infrastructure Construction Team headed by Yokota. These pictures include crawfish (Figure 1), beetles, stag beetles, and mice. Some pictures show whole bodies, whereas others, cross-sectional views. The interview with Yokota was conducted in a corner of this laboratory.

"The greatest challenge we are addressing now is live-cell modeling (Figure 2)," says Yokota. "Live-cell modeling is computational modeling of a cell as it really is in a living organism. RIKEN has many laboratories related to cell biology. In collaboration with these laboratories, we are advancing our own research for the fiscal 2006 and 2007 periods." Six research institutes and centers at RIKEN are now participating in the live-cell modeling project.

However, why is Yokota focusing on live-cell modeling now? Yokota explains that conventional biology is mainly based on observing phenomena, taking photos for data, and expressing an interpretation in the form of sentences. Understanding how living organisms work, however, requires the step of simulation in order to analyze the mechanism of the phenomena. "We first need to create a numerically expressed digitized model of a cell so that the model can be used for computer simulation."

However, cell models created in a computer have also been reported in some other studies. What are the differences between the new and conventional models? Yokota explains that the E-CELL system built by the Institute of Advanced Biosciences, Keio University, was created assuming the cell to be a closed bag filled with homogeneous material so that the system could be used for metabolism simulation. In the E-CELL system, however, the concept of cell organelles such as mitochondria and Golgi bodies is not taken into account, although cell organelles in a real cell exchange such materials with the environment. The Virtual Cell in the US is no more than an



extremely simplified model, which has a nucleus in a round cell. "What we want to create," says Yokota, "Is a complex model of a cell as it really is in a living organism. Science is generally based on a simplified version of a complex system. In that sense, we are not following a smart strategy in this modeling process," says Yokota with a smile.

Yokota, however, has the odds in his favor. His confidence is based on the techniques he and his team members have accumulated through the VCAD System Research Program. The acronym CAD stands for Computer Aided/Assisted Design. In the place of today's skilled manufacturing, computers are actively used in each phase of design, simulation, and processing. These CAD systems, however, are still suffering defects such as conversion data loss owing to data format incompatibilities. In contrast, VCAD, the innovative software program developed by the team headed by Program Director Akitake Makinouchi, allows us to deal with the same data consistently across the design, simulation, and processing stages. The V in VCAD stands for volume because VCAD allows us to consider internal data whereas conventional CAD programs consider only external data.

The VCAD System Research Program is now in its second phase (fiscal 2006-2010). In the first phase (2001-2005), Yokota was the leader of the VCAT (volume CAD system's computer-aided testing) Development Team. "VCAD allows us to deal with not only artifacts but also natural things." However, he adds that there is a big difference between artifacts and natural things. Since most artifacts are accompanied by detailed drawings, researchers can use the data of the artifacts for VCAD simulation. In contrast, researchers firstly have to use tomographic techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) to acquire internal and structural data of biological specimens. VCAT is a pre-processor program for the acquired data, and can convert the data to make it ready for the VCAD system. "Thus, VCAD in cooperation with VCAT enables us to reproduce and simulate natural things in a computer, something that has never been achieved before."

For example, the VCAD data processed by VCAT from the data set of a whole human body acquired by MRI, enables the dynamic simulation of a human body. Researchers in the Computational Biomechanics Unit at the Discovery Research Institute, where Yokota holds an additional post, are using the VCAT system to establish a human-body model. The research is expected to help diagnose diseases and injuries, determine how systems operate, and develop medical apparatus, by acquiring a greater understanding of how a human body is deformed under external forces.

The three-dimensional internal structure microscope (3D-ISM) that has been developed by the Computational Biomechanics Unit at the Discovery Research Institute is also very helpful when acquiring data from biological samples. This 3D-ISM can freeze a sample at −80°C, and takes cross-sectional pictures of the sample continuously while slicing it. The microscope can be used for a sample of up to 18 × 13.5 × 20 cm^3. The upper pictures in Fig. 1 show some of the cross-sectional pictures of 30 μm-thick crawfish slices taken by the three-dimensional internal-structure microscope. Yokota and his team took 3,000 pictures in 30 minutes continuously. These slices can be thinned to 1 μm, which is smaller than the size of a cell. "A picture of a whole crawfish can be reproduced by VCAT when the acquired image data are piled up," says Yokota. (See lower-left in Fig. 1.) "When these VCAT data are fed into the VCAD system, we can not only view cross-sectional pictures at any given location, but also, for example, simulate the air flow around a heated crawfish (lower-right in Fig. 1)."

It is safe to say that VCAT, which can deal with three-dimensional space, has been completed. "Thus in the second phase, we changed the name of our team to the Bio-research Infrastructure Construction Team, and decided to work on research into live-cell modeling," says Yokota. So this is how the pictures of natural life forms posted all over the laboratory have been produced.

A bird's-eye view of cells

Yokota explains how in-depth research into local phenomena of individual organelles has advanced, and says that the mechanisms of organelles have been considerably clarified on an individual

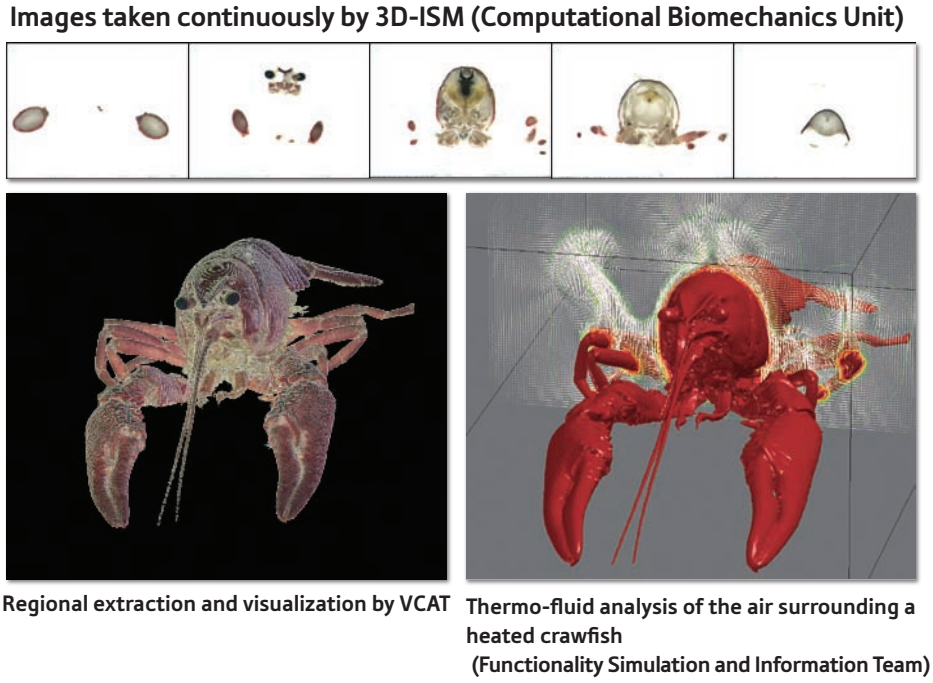


Figure 1 : Sample images taken and processed by 3D-ISM, VCAT, and VCAD.

object basis. However, researchers still have problems clarifying the cell as one whole body. For example, in regard to the positional relationship of organelles and how they are transferred. "Thus, we are trying to look at cells from a bird's-eye view to understand them on a unified platform."

Then, how can a living cell be reproduced in a computer? Yokota points out that there are already established techniques for acquiring the data of natural things for VCAT, such as CT, as long as they are large enough for data collection. For a cell, however, no means were available. "Just when we are looking for a new data-acquisition technique, the live-cell imaging technique advanced to the point of practical use." High-resolution observation of a cell has necessarily involved using chemicals for sample fixing, and placing samples in a vacuum environment. In other words, observation has been of dead cells. Recently, however, the use of laser microscopes and fluorescent proteins has enabled the observation of living cells. Furthermore, RIKEN has some world-leading laboratories for live-cell imaging technology such as the Laboratory for Cell Function Dynamics headed by Atsushi Miyawaki, Laboratory Head at the RIKEN Brain Science Institute.

The live-cell modeling procedure starts with culturing HeLa cells stored at the Riken Bioresource Center, which are then given to the cell biology laboratories participating in the live-cell modeling project. HeLa cells are human cancer cells often used in life science experiments. In each laboratory, researchers observe organelles in their specialized genre of choice, and record images of the positions, shapes, and movement of materials in a cell. Finally, Yokota and his team members extract the necessary information, which is then integrated into a set of data.

Although the same HeLa cells are used, different organelles of different cells are observed by each laboratory. So, how is the extracted data integrated? "RIKEN Bioengineering Laboratory at the Discovery Research Institute is developing a new culture substrate that can transform the outer shape of a cell into a triangle," says Yokota. He adds that transforming the outer shape of a cell essentially allows control over the arrangement of large organelles and the nucleus in the cell, making it possible to obtain unified data even though different cells are used. "This is a benchmark technique often used in engineering fields for performance measurement."

This is the world's first attempt. Of course, there are many challenges to overcome. Recently, live-cell imaging technology has greatly advanced, but the current level is not good enough to acquire four-dimensional information on a cell over a long period of time. Living cells will die if the laser light is intensified to give a brighter fluorescent response. In contrast, if the laser light is weakened to give a longer observation period, image data processing will become difficult due to a weakened fluorescent response. "Thus," says Yokota, "I think, both biologists and engineering researchers should jointly develop new technologies."

VCAT should also be upgraded to the four-dimensional version, which can deal with time-varying parameters. Researchers definitely need to develop a new technique that can automatically extract the boundary or specific portions of an organelle. Yokota, however, had no hesitation in making the following optimistic statement: "By the last year of the two-year plan, namely, by around March 2008, we will have established a simulation model in a computer that enables us to reproduce the positions

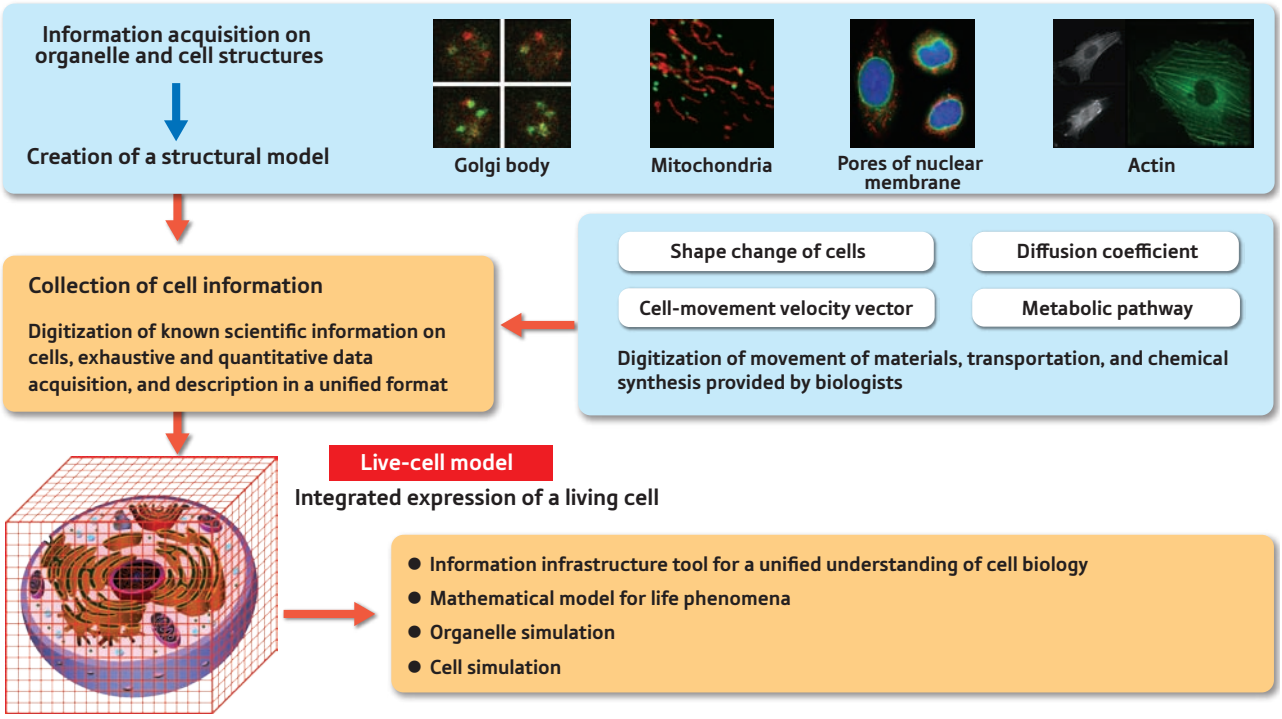


Figure 2 : **Live-cell modeling.**

and shapes of organelles, and the exchange of materials."

Toward simulation

The live-cell model will be widely disclosed to the world as a basic research tool for living organisms. However, this is not the final target. "Objects that can be visualized by imaging technology are limited. There is always something beyond the range of our imaging techniques working behind the scenes. Creating a live-cell model in a computer and simulating a cell using that live-cell modeling will allow us to imagine what is going on in a cell, and in this way we can truly understand living organisms."

However, Yokota is quick to point out that the simulation is very hard. "It may take 10 or more years because we still do not know the equations that describe the cell phenomena. In the end, we have no choice but to try."

Now, RIKEN is taking the leading role in developing the next-generation supercomputer, which is scheduled for completion in 2012. Yokota and team members are planning to use the supercomputer for the difficult challenge of cell simulation. Yokota has an idea he has been thinking about. "I want to simulate the mechanism of development. I also want to observe how a single fertilized egg changes into an individual organism."

Then, what can we expect after the completion of the simulation? "We will be able to control and improve the functions of cells, thus advancing engineering technology. Development of these techniques could lead to the creation of tissues for regenerative medicine, or it could be applied to other areas of medicine."

Yokota studied biology until he had obtained his Master's degree. However, he changed his area of expertise from biology to precision engineering because he realized the limitations of the imaging technology at the time, and wanted to develop the necessary tools for himself. His current area of expertise is information engineering. "I have long been interested in creating and simulating cell models. Finally, I have returned to the starting point," says Yokota with confidence and a smile.

He concludes, "I am interested in dealing with complex shapes of cells. That is why I want to create an accurate model of a cell as it really is in a living organism." ■

1. Japanese Patent No. 2003-025277
2. Japanese Patent No. 2002-057963
3. Japanese Patent No. 2000-347398

About the researcher

Hideo Yokota was born in Yokosuka, Japan, in 1969. He received his MS from the Graduate School of Agriculture, Nihon University, in 1993. After six years research working at the Higuchi Ultimate Mechatronics project, Kanagawa Academy of Science and Technology, he obtained his PhD from the Department of Precision Engineering at the University of Tokyo. He obtained a post as contract researcher of computational biomechanics at RIKEN, in April 1999. He was then promoted to team leader of the VCAT development team, VCAD Integrated V-CAD System Research in 2003. Since then, he has been director of his own research group at the same time as serving the computational biomechanics unit. Now, he is Bio-research Infrastructure Construction Team Leader for the V-CAD System Research Program. His research focuses on the construction of a biological computer simulation model and the development of these techniques.

'*Nishina Zao*,' a yellow sakura cherry tree born in the RIBF

Researchers at the RIKEN Nishina Center for Accelerator-Based Science, collaborating with the Japan Flower Culture (JFC) Ishii Farm, have for the first time created a new variety of sakura cherry tree using heavy-ion beams. The new strain is a tree with pale yellow flowers that has been named '*Nishina Zao*'.

Using the RIKEN Ring Cyclotron (RRC) at the RI Beam Factory (RIBF) in the Nishina Center, the group, led by Tomoko Abe, induced mutations at a high rate compared with conventional breeding techniques that use gamma rays, X-rays, or chemicals.

The high energy and penetrating power of the RRC's heavy-ion beams yielded a high mutation rate. The number of genes damaged by the radiation is much lower, and the mutations stabilize much more quickly.

The RIKEN group took cuttings from *Gyoikou* cherry trees from Zao in Yamagata Prefecture, which have a mixture of yellow and green blossoms. They irradiated the cuttings with heavy-ion beams from the RRC, and the resulting plants were taken back to Zao to be grown, where they blossomed in the spring.

RIKEN, jointly with JFC Ishii Farm, registered the *Nishina Zao* with the Ministry of Agriculture, Forestry and Fisheries as a new variety of sakura on October 16, 2007.

Nishina Zao (left) and *Gyoikou*, the original species (right).

Robotic surgeon's assistant could be the solution to nurse shortages

The RIKEN Bio-Mimetic Control Research Center has developed a robotic assistant for surgical specialists who use endoscopes. The robot does the tasks performed by surgical nurses and can be operated via spoken commands or by remote control using a cell-phone monitor and keypad.

A team led by Toshiharu Mukai at the Bio-Mimetic Control Center, along with researchers from Nagoya University and NTT DoCoMo Tokai, developed the robot, on the basis of a prototype made by Tokai region companies (Aska, ChunichiDenshi, and Miwa Electric Medical) with support from Tokai Monodukuri Council.

Endoscopes minimize the incisions needed, thereby reducing the patient's pain, shortening the recovery time, and greatly reducing medical costs. An endoscopist may need 10 to 20 different sets of forceps and other instruments in an operation, which must be handed over by a nurse. A serious shortage of nurses qualified to do this work prompted the development of the surgical-assistant robot.

The robot loads the instruments into a magazine, and hands them via a robotic arm to the surgeon, who gives orders using audio commands by means of a headset fitted with a microphone and earphones. The robot identifies the instruments by means of attached barcodes. Once the surgeon has finished using an instrument, the robot takes it from him and returns it to the magazine automatically.

Instruments can be added or removed by pushing buttons on a cell-phone keypad. With this function, an experienced surgeon in a remote location, for example, can support an operation by a less experienced specialist by watching the operation on a video monitor and operating the robot via the cell-phone keypad. The selected tool is displayed on the cell-phone screen for verification by the remote operator.

The team demonstrated the results at the Chukeiren Techno Fair 2007 in Nagoya on October 11, operating the robot from a remote location via cell phone.

RIKEN and the IMGS host 21st International Mammalian Genome Conference

RIKEN and the International Mammalian Genome Society (IMGS) hosted a joint conference from October 28 to November 1, called the 21st International Mammalian Genome Conference (IMGC)—a five-day event held in Kyoto at the Kyoto Terrsa conference center.

Project Director Yoshihide Hayashizaki of the RIKEN Genomic Sciences Center (GSC) Genome Exploration Research Group presided as chairman of the IMGC organizing committee. The event featured keynote speeches by several first-class researchers from around the world, including John Quackenbush from the Dana-Farber Cancer Institute and Harvard School of Public Health in the USA, who is an authority on bioinformatics. In addition to the talks and the poster presentations given by the attendees, three unique sessions were held, namely: 'The RIKEN symposium—The Transcriptome World', 'Mutagenesis', and 'A Journal Panel Discussion'.

In the RIKEN symposium 'The Transcriptome World' held on October 31, Thomas Gingeras from the Biotechnology Section of the US firm Affymetrics and project director Yoshihide Hayashizaki gave presentations on their transcriptome research. They introduced the latest analytical results on RNA, such as ncRNA (non-coding RNA and non-protein-code RNA), which is becoming a keyword in research leading to the development of new drugs.

One session was on trends in mouse mutagenesis, based on the findings of the large-scale International Knockout Mouse Consortium (IKMC), which has focused on genome function clarification for nearly 20 years.

Toshihiko Shiroishi from the Mammalian Genetics Laboratory at the National Institute of Genetics and project director of the GSC Functional Genomics Research Group, and Yoichi Gondo, the vice-director of the GSC Functional Genomics Research Group, organized this session. Topics included ENU (*N*-ethyl-*N*-nitrosourea, a highly potent mutagen) mouse mutagenesis, in a project by scientists from Japan, the USA and Europe. Monica Justice, an associate professor at the Baylor College of Medicine in Houston, Texas, and a representative of the Knockout Mouse Project (KOMP) in the USA and the European Conditional Mouse Mutagenesis (EuCOMM) program, gave a lecture full of cutting-edge information. Communication was helped along by simultaneous interpretation at the session.

On the final day, editors and representatives of 10 prestigious international science magazines, including *Nature* and *Science*, participated in a panel discussion, in which they exchanged views on the rapidly changing conditions in publishing and the future of scientific journals, especially pertaining to the handling of large-scale datasets and online and electronic publications. Many scientists and students in the audience made use of the unique opportunity to ask the editors questions directly.

RIKEN's ongoing quest to become an ideal research organization

RIKEN's future hinges upon the long-lasting success of the Discovery Research Institute that was founded as a core center for cutting-edge researchers from diverse disciplines

The foundation of RIKEN's research structure is its 'chief scientist' system. Introduced by Masatoshi Okochi, RIKEN's third president until after World War II, the system guaranteed independent and creative research activities by letting chief scientists run laboratories largely at their discretion. After growing to become Japan's flagship institute with more than 3,000 researchers from various backgrounds, RIKEN established the Discovery Research Institute as its comprehensive research center in Wako in 2002.

The idea to create the new research center stems back to 1958, when RIKEN made a fresh start as a public corporation after suffering through tough times as an incorporated company in the postwar period. One of the organization's most difficult challenges was effectively managing its research structure, including decision-making on budgets, personnel and research themes.

At that time, RIKEN consisted of 37 'Institute Laboratories' (ILs), a traditional system in which tenured chief scientists were given great responsibilities to run their laboratories. As these laboratories were deemed to last for 'one-generation' only, this system generated highly competitive researchers. Important decisions were discussed at meetings called the 'Chief Scientist Assembly.' RIKEN decided to retain the traditional IL system but made the assembly an advisory body to the president.

These 37 ILs were initially specialized in physics, engineering, chemistry or biochemistry, but new research fields were gradually added including electronics, agricultural chemicals and laser science. The ILs were located in three regions— Tsukuba, Harima and Wako.

The breadth of RIKEN's research continued to expand, and 1997 heralded the beginning of a new era when the Brain Science Institute was created and initiated the establishment of several life science centers. By that time, RIKEN had introduced a 'Research Advisory Council,' consisting of top external scientists from Japan and abroad to evaluate the RIKEN president's work (see History of RIKEN, *RIKEN RESEARCH* **2 (11)**, p.18). Each of these new centers introduced their own advisory council, as did the ILs.

When the first Institute Laboratories Advisory Council met in 2000, chief scientists suggested ILs should be 'the Heart of RIKEN.' The council proposed that a 'Chief Scientist Assembly' be organized as an official research center to enhance their potential and creativity (Fig.1). In the same year, RIKEN's top management categorized RIKEN's research into a group free to select their own research themes and a group working on projects related to an overall theme.

Figure 1: Chief scientists at the Discovery Research Institute take advantage of its liberal spirit to tackle unique research themes.

Because the ultimate goal to set up a new center was to increase the visibility of ILs, RIKEN decided to locate the new center in Wako and control existing laboratories in Harima remotely (most Tsukuba-based laboratories were moved to Wako).

In April 2002, the Discovery Research Institute was inaugurated, and Yorinao Inoue, an executive in charge of research activities, was appointed as the first director. Later that year, Shunichi Kobayashi, RIKEN's then president, gave IL chief scientists much-awaited approval to select their own director. The Chief Scientist Assembly unanimously chose Hiromichi Kamitsubo, an executive director and former IL chief scientist of nuclear physics, as their second director.

Currently, the six-year-old Discovery Research Institute has more than 30 laboratories, in addition to research groups and research units. It houses most of the 400 tenured scientists employed by RIKEN. Their representatives, selected by internal voting, run the institute along with the approval of the director. The management policy suits the open nature of this institute, and new research projects are often generated through active interactions between researchers. To meet the high internal and external expectations of RIKEN, the institute is forging ahead to further improve its research structure under the leadership of the third director Koji Kaya. ■

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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.

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

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