RIKEN RESEARCH

SEPTEMBER
2006 Volume 1 Number 3

Quantum quirks in quarks revealed

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A new recipe for making neurons in a dish

A readily available human material supports neural differentiation of human embryonic stem cells

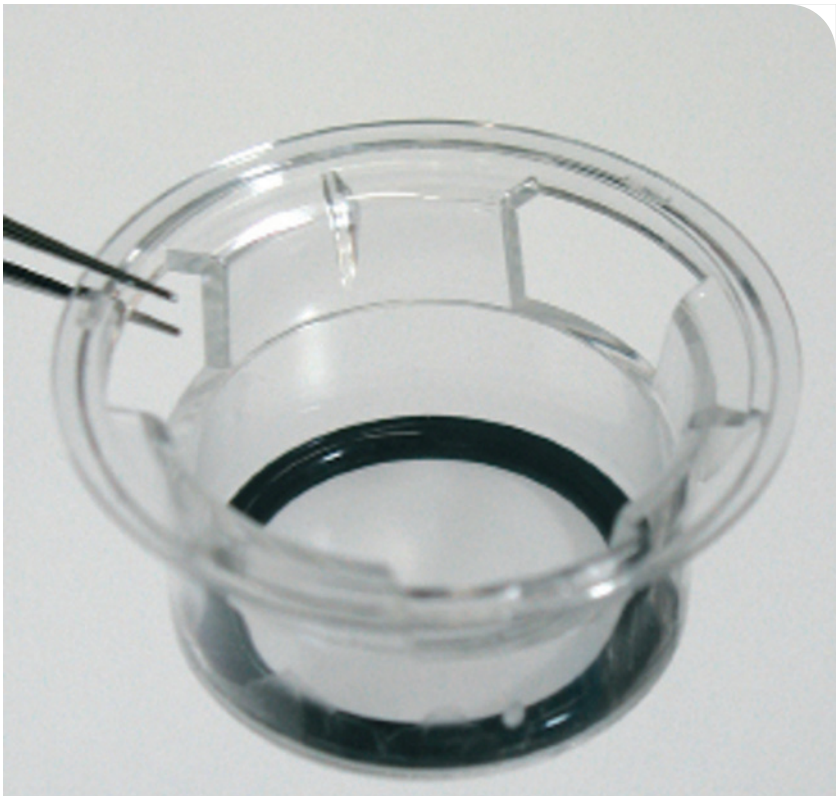

Figure 1: A culture dish in which matrix materials were coated.

Recently, the possibility of using cells differentiated from embryonic stem (ES) cells in the laboratory to ameliorate debilitating human diseases has garnered much media attention. Yoshiki Sasai and colleagues at the RIKEN Center for Developmental Biology, in Kobe, developed a new system to stimulate ES-to-neuron differentiation in a culture dish.

The therapeutic utility of ES cells stems from their 'pluripotency', or their ability to become any type of cell. Different tissues within the body are composed of distinct cell types; each specialized to perform the specific set of functions demanded in that tissue. Some diseases affect tissues that can be replaced by organs obtained from other human donors. However, other diseases result in damage not so easily undone. For example, Parkinson's disease causes progressive irreversible damage to neurons. Amelioration of the resultant devastating symptoms therefore requires a source of healthy replacement neurons.

Producing wholly human neurons

While neurobiologists know that embryonic pluripotent cells hold the potential to become neurons, they do not understand precisely how this occurs inside the body. This limited understanding renders the task of inducing and recapitulating this mysterious process outside of the body, in the artificial environment of a laboratory dish, or *in vitro*, all the more daunting.

Despite these obstacles, researchers have devised a number of systems capable of supporting human ES cell to neural cell differentiation *in vitro*. As demonstrated in preliminary studies, neurons generated using these systems exhibit therapeutic activity in a monkey model of Parkinson's disease.

The most popular system used for *in vitro* production of neurons involves ES cell culture on supportive mouse cells called stromal cells. Although capable of generating multiple types of neurons, one flaw inherent in this system—the use of non-human material—will likely preclude its clinical application. Human precursor cells differentiated on non-human stromal cells can 'pick up' bits of non-human material. The human immune system, in its perpetual patrol for 'non-self' material, recognizes these precursor cells as foreign and orchestrates their elimination.

Sasai and colleagues demonstrated that mouse and human ES cells cultured in dishes (Fig. 1) coated with matrix layers of human amniotic membrane (hAM) (Fig. 2)—the internal coating of the human placenta—gave rise to diverse types of neurons. These neurons displayed surface proteins characteristic of those decorating the surface of neurons located in multiple regions of the brain (Fig. 3). To ensure that this resemblance was more than superficial, Sasai and colleagues analyzed the spectrum of genes expressed within neural precursors differentiating in dishes coated with hAM; these neural precursors expressed genes found in *bona fide* neurons. In addition, neural precursor cells differentiating on the hAM matrix responded to external stimuli in a manner similar to neural precursor cells developing within a live mouse or human embryo.

Thought-provoking findings

In experiments using mouse stromal cells, a portion of ES cells incubated with hAM developed into what

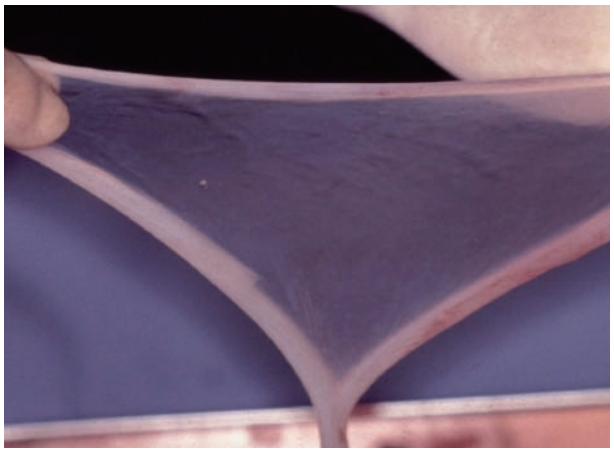

Figure 2: Amniotic membrane detached from the human placenta.

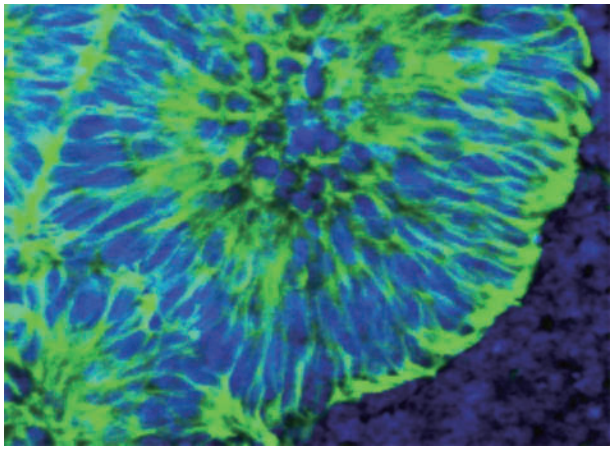

Figure 3: Neural cells generated from human ES cells using the hAM *in vitro* system. Green is a neural marker and blue is the nucleus. Neural cells make rosette-like structures.

appeared to be retinal pigment epithelial cells and lens cells, which are crucial components of eye tissue. Importantly, Sasai's team excluded the possibility that the observed neural differentiation was due to contamination with pre-committed neural cells, or to fusion between stromal cells and differentiating ES cells. Their work is reported in the *Proceedings of the National Academy of Sciences*[1].

Sasai and colleagues tested other matrix materials such as gelatin, collagen, and fibronectin, but none of these materials supported ES-to-neuron development as efficiently as hAM. These results highlight the unique, yet still-not-understood capabilities of hAM[1].

Of course, the ultimate test is to determine whether the neurons produced in this new system, which from every angle *look* like bona fide neurons, *act* like bona fide neurons. The team also needs to assess whether these neurons exhibit therapeutic activity in animal models of Parkinson's disease.

According to Sasai, the planning of these experiments is already under way. "In collaboration with Kyoto University Hospital, we plan to graft these cells into the basal ganglia of Parkinsonian model monkeys. This is an important and, in a sense, the ultimate step of preclinical studies of stem cell therapy for this disease," says Sasai. Because the neurons generated on hAM strongly resemble those generated on mouse stromal cells, which did exhibit therapeutic activity in a monkey model of Parkinson's disease, the researchers have reason to be optimistic.

The ready availability of hAM via informed consent during caesarean section is a plus for the team. Further, its biological safety has been proven after years of use in opthalmological and dermatological surgeries, and its neural differentiative capability was maintained even after six months of frozen storage. "How and why the amniotic membrane has such activity is a mystery, but, practically speaking, it works ideally for stem cell therapy," says Sasai.

Remaining questions

A remaining challenge for the team is to identify the cell type(s) and factor(s) derived from the hAM matrix layer that are responsible for inducing ES-to-neuron development. This information might help in gaining a more thorough understanding of the stimuli and signals that induce neural differentiation within the body.

Sasai and colleagues failed to identify an individual hAM component that could alone support ES-to-neuron differentiation. But as stem cell research continues to attract media attention globally, the team's findings represent another step forward in the clinical application of human cells differentiated in the laboratory. ■

1. Ueno, M., Matsumura, M., Watanabe, K., Nakamura, T., Osakada, F., Takahashi, M., Kawasaki, H., Kinoshita, S. & Sasai, Y. Neural conversion of ES cells by an inductive activity on human amniotic membrane matrix. *Proceedings of the National Academy of Sciences USA* **103,** 9554–9559 (2006).

About the author

Yoshiki Sasai was born in Hyogo, Japan, in 1962 and received his MD from Kyoto University School of Medicine in 1986. From 1986 to 1988, he performed an internship in general and emergency medicine. In 1993, he earned a PhD from the same university for work on neural specific transcriptional regulators. From 1993 to 1996, he was a visiting research fellow at UCLA School of Medicine, California, and then appointed as an associated professor at Kyoto University School of Medicine. From 1998 to 2003, he served as a professor at the Institute for Frontier Medical Sciences, Kyoto University. From 1998 to 2003, Sasai served as a professor at the Institute for Frontier Medical Sciences at Kyoto University. During that time, in 2002, he also became a group director at the RIKEN Center for Developmental Biology. Since 2003, Sasai has been concurrently serving as an affiliated professor at Kyoto University Graduate School of Medicine. http://www.cdb.riken.jp/sasai/index-e.html

Exposing the eye's 'turn-offs' and 'turn-ons'

A recent study has revealed an unusual 'double negative' regulatory system in fruit fly development and identified a key connection between two major signaling pathways

Most processes in embryonic development involve signaling from multiple pathways, with cross-talk between these circuits mediating the formation of different tissues and organs. For example, the development of light-sensitive photoreceptor cells in the eye of the fruit fly is governed in part by signaling from two receptors, Notch and epidermal growth factor receptor (EGFR), although the connection between these pathways is poorly understood.

"Involvement of multiple signaling pathways [in eye development] has been observed, but no previous work has identified the molecular process mediating the cross-talk between these two pathways," says Shigeo Hayashi, a developmental biologist at the RIKEN Center for Developmental Biology in Kobe.

EGFR signaling is known to trigger the formation of a multiprotein complex, Ebi/SMRTER/Su(H); this complex activates production of the protein Delta (Dl), which stimulates cone cell differentiation. The basis of this activation was a mystery, since the Ebi/SMRTER/Su(H) complex generally acts as a gene repressor. Hoping to clarify this process, Leo Tsuda from the Hayashi laboratory (now at the National Institute for Longevity Sciences) and colleagues generated large numbers of mutant flies in a screen to identify target genes for the complex, leading to the identification of a candidate gene encoding the transcription factor Charlatan (Chn).

Closer analysis of the *chn* gene revealed a binding site for one of the members of the repressor complex, Suppressor of Hairless [Su(H)], and Tsuda, Hayashi, and their colleagues, subsequently found evidence that Su(H) can mediate *chn* activity as either an activator or repressor depending on the proteins with which it is associated. EGFR signaling leads to formation of the repressor complex, blocking production of the Chn protein, while Notch signaling triggers formation of an Su(H)-containing activator complex, stimulating Chn production. Chn, in turn, appears to act as a direct repressor of Dl production, and therefore of subsequent photoreceptor differentiation and eye development (Fig. 1).

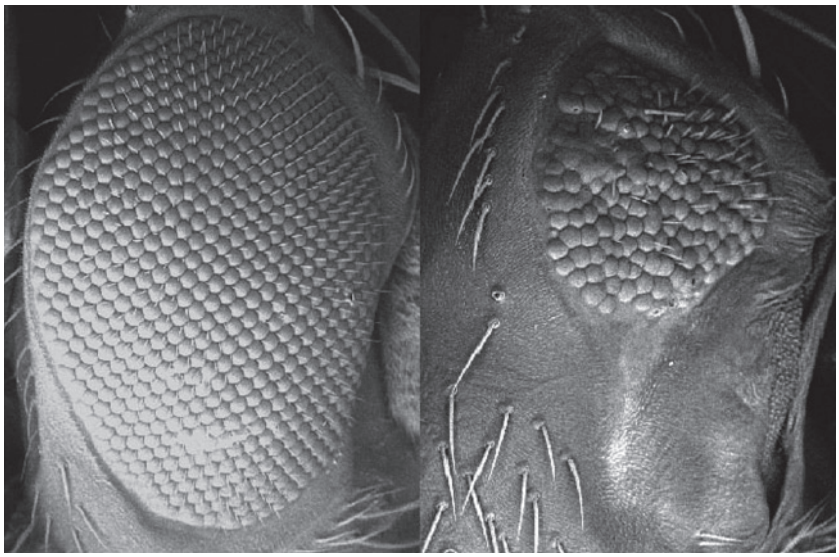

Figure 1: Compared to a normal eye (left panel), mutation of the *chn* gene leads to dramatic inhibition of proper eye formation (right panel).

This work, reported in *The EMBO Journal*[1], yielded several surprising findings, including Chn's role as an apparent 'missing link' between Notch and EGFR signaling. Most interesting to Hayashi, however, is the clarification of this 'double negative' regulatory process, in which repression of Chn by Ebi/SMRTER/Su(H) prevents repression of *Dl* by Chn, leading to net activation of the gene and subsequent photoreceptor differentiation. Chn also appears to regulate other genes responsible for neural development. "We're hopeful that these findings will lead to a clearer understanding of the cross-talk between EGFR and Notch signaling in neural differentiation," Hayashi concludes. ■

1. Tsuda, L., Kaido, M., Lim, Y.-M., Kato, K., Aigaki, T. & Hayashi, S. An NRSF/REST-like repressor downstream of Ebi/SMRTER/Su(H) regulates eye development in *Drosophila*. *EMBO Journal* **25** (13), 3191–3202 (2006).

Connecting loose ends

New research has identified a protein which may have a key role in organizing several functions essential to sexual reproduction

Cells from diploid eukaryotic organisms—such as humans and yeast—normally contain two copies of each chromosome, with the exception of reproductive cells, or gametes, which contain only a single copy. These copies, or homologs, are not identical, but contain numerous sequence variations that can affect the expression of heritable traits like hair colour or, less benignly, predisposition to certain diseases. This variability is enhanced by recombination—the routine swapping of information between homologs—during gamete production, which takes place via a process known as meiosis.

"Recombination between homologous chromosomes during meiosis is vital for the generation of genetic diversity and proper gamete formation in sexual reproduction in eukaryotes," explains Kouji Hirota, of the RIKEN Discovery Research Institute in Wako. Previous research has suggested that chromosomal DNA replication—an essential preparatory step for meiosis—is somehow linked with the subsequent process of recombination. But, Hirota adds, "there is little molecular evidence for such linkage."

Hirota and colleagues from RIKEN recently collaborated with Hisao Masai's group at the Tokyo Metropolitan Institute of Medical Science to investigate a protein that might tie these functions together. The protein Hsk1 from fission yeast has previously been associated with the regulation of DNA replication and DNA repair. Masai and Hirota's teams decided to further investigate its function with a mutant yeast strain that only produces functional Hsk1 at certain temperatures, allowing them to effectively turn the protein's activity on or off. Their findings are published in the *Proceedings of the National Academy of Sciences USA*[1].

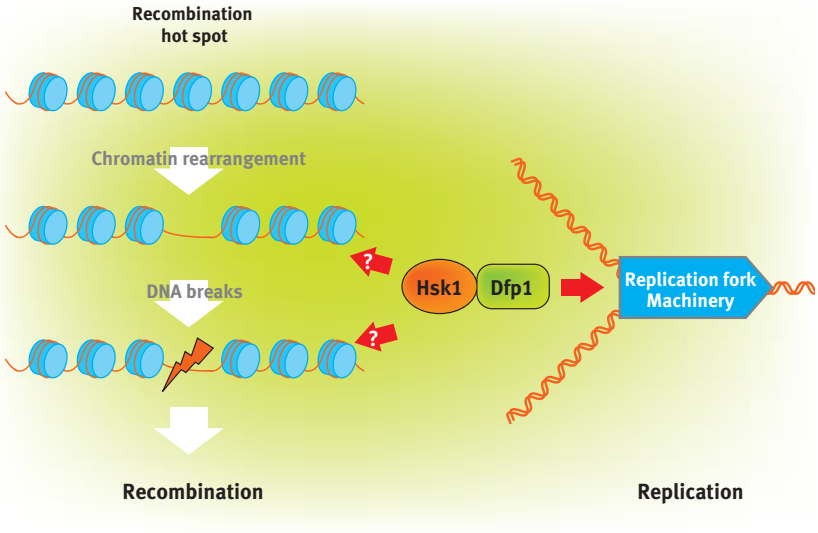

Figure 1: Hsk1—working with protein partners such as Dfp1—appears to participate in the regulation of both pre-meiotic DNA replication and subsequent physical chromosomal changes that allow recombination to take place.

Initial experiments showed that inactivation of Hsk1 delays, but doesn't halt, DNA replication, although subsequent cell division is stalled. More surprising, however, was the finding that Hsk1 inactivation appears to induce marked defects in chromosomal recombination.

Recombination is generally preceded by rearrangements of the proteins that organize and condense chromosomal DNA into chromatin, followed by the formation of breaks in the DNA itself. Disrupting the activity of Hsk1 appears to prevent either of these processes from taking place (Fig. 1).

"These findings provide us with knowledge of more direct molecular links between DNA replication and recombination initiation during meiosis," says Hirota. This work links Hsk1 with a number of important functions relating to meiosis, but it still remains unclear how these processes are connected. Hirota indicates that he and his colleagues are now exploring the function of Hsk1—and any potential protein partners—more closely. ■

1. Ogino, K., Hirota, K., Matsumoto, S., Takeda, K., Ohta, K., Arai, K. & Masai, H. Hsk1 kinase is required for induction of meiotic dsDNA breaks without involving checkpoint kinases in fission yeast. Proceedings of the *National Academy of Sciences USA* **103,** 8131–8136 (2006).

Molecular mimic sets the tone for calcium release

A new model of calcium release in cells provides insight into how intracellular communications are regulated

Cells constitute exquisitely fine-tuned systems whose development, function and death is determined by the well-orchestrated interplay of numerous cell processes. Maintaining these systems requires good communication between different cell components.

Cells respond to external and internal signals by transferring information from the 'receiving antennae' on a membrane, the so-called receptors, to appropriate targets using 'signaling' molecules.

Calcium is probably the most abundant of these signaling molecules. It can enter the cell or be released from storage compartments within the cell via specialized calcium-specific channels.

Katsuhiko Mikoshiba, a neurobiologist at RIKEN's Brain Science Institute in Wako, and colleagues from the University of Tokyo and the Japan Science and Technology Agency, now propose, in *Molecular Cell*[1], a model to explain the regulation of the activity of one family of internal calcium-specific channels, the inositol-trisphosphate receptors (IP_3Rs).

Working with mouse, monkey and human cells, the team determined how the activity of the natural trigger of calcium release by the IP_3Rs, inositol-trisphopshate (IP_3), is modulated by IRBIT, a previously described IP_3-binding protein[2]. Mikoshiba and colleagues show that at the molecular level, the interaction of IRBIT with the IP_3Rs is based on a similar structure and phosphorylation status of the components in IRBIT and IP_3 that interact with the receptor—in other words, IRBIT mimics and competes with IP_3 (Fig. 1).

IRBIT alone however has no function and does not trigger the release of calcium, which led the researchers to postulate that: "The physical competition between IRBIT and IP_3 for binding with the IP_3Rs primarily determines a threshold concentration above which IP_3 has to be present for calcium to be released into the cell. IRBIT thus regulates the oscillation in IP_3-dependent calcium concentrations, which in turn modulates gene expression and enzyme activity."

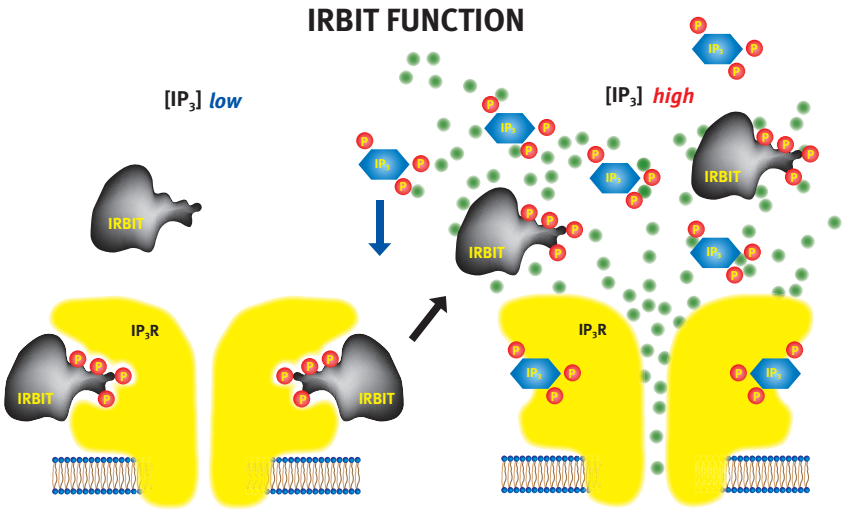

Figure 1: IRBIT regulates activity through direct competition for the binding site on the IP receptors. Once IP_3 reaches a threshold concentration, it displaces IRBIT from the binding site. (P = phosphate group indicating phosphorylation status; green dots = calcium ions)

While the team has previously identified the interaction of IRBIT with the IP_3Rs, no exact mechanism of interaction was known and no regulatory model had been proposed[2]. "Our current work sheds new light on how cells have evolved to regulate the complex task of intracellular communication by using seemingly simple, yet very sophisticated, molecular tricks," says Mikoshiba.

Final confirmation of the validity of the proposed model will come through crystallographic analysis of the IP_3Rs bound to IRBIT. And, further studies are required to determine the physiological importance of the interaction between IRBIT and IP_3R. ■

1. Ando, H., Mizutani, A., Kiefer, H., Tsuzurugi, D., Michikawa, T., & Mikoshiba K. IRBIT suppresses IP_3 receptor activity by competing with IP_3 for the common binding site on the IP_3 receptor. *Molecular Cell* **22,** 795–806 (2006).
2. Ando, H., Mizutani, A., Matsu-ura, T., & Mikoshiba, K. IRBIT, a novel inositol 1,4,5-trisphosphate (IP_3) receptor-binding protein, is released from the IP_3 receptor upon IP_3 binding to the receptor. *Journal of Biological Chemistry* **278,** 10602–10612 (2003).

More responsibilities for a busy pathway

New findings reveal a previously unknown link connecting a major cellular signaling pathway with the regulation of physiological pH levels

The release of calcium ions into the cytoplasm from storage organelles is mediated in part by the binding of inositol 1,4,5-trisphosphate (IP_3) to its receptor (IP_3R). Calcium release triggered by IP_3 is known to play an important role in a wide variety of essential cellular activities.

A team of neurobiologists led by Katsuhiko Mikoshiba of RIKEN's Brain Science Institute, in Wako, identified IP_3R binding protein called IRBIT. IRBIT binds to IP_3R under normal physiological conditions but dissociates from the receptor in the presence of elevated concentrations of IP_3[1,2]. This led them to believe that IRBIT could be mediating the transmission of IP_3-induced signals to other targets.

Now, Mikoshiba and his colleagues from RIKEN, the University of Tokyo and the Japan Science and Technology Corporation report in the *Proceedings of the National Academy of Sciences USA*[3] that they have identified a target for IRBIT binding and activation. The target is a protein called NBC1, which is involved in moving ions across the plasma membrane. NBC1 exists in two major forms: one found predominantly in the kidney (kNBC1), and the other expressed primarily in the pancreas (pNBC1). According to Mikoshiba, improper function of pNBC1 can have severe physiological consequences. "pNBC1 is involved in acid-base balance. If the activity is low, the balance shifts to acidosis, which results in cataracts and glaucoma," he says. "It is also expressed in the nervous system... [and] abnormality of pNBC1 results in mental retardation and low growth rate."

Protein binding experiments showed that IRBIT associates specifically with pNBC1 but not kNBC1, which differs only by a short stretch of amino acids at one end of the protein. Additional experiments performed in frog oocytes showed that pNBC1 appears to be dependent on coexpression of IRBIT in order to function properly, suggesting that the latter protein acts as an activator of pNBC1, directly linking cotransporter activity to IP_3 signaling (Fig. 1).

This finding came as somewhat of a surprise to Mikoshiba's group. "This is the first report to directly link IP_3 signaling to pNBC1 cotransporter activity," he says. "It is exciting to know that the role of IP_3 is not only to release calcium ions, but also to release IRBIT and work on pNBC1, which regulates pH balance." They believe that IRBIT regulation may play an important part in controlling proper pNBC1 function, and are now attempting to identify the detailed mechanism by which IRBIT is released from IP_3R and binds to pNBC1. ■

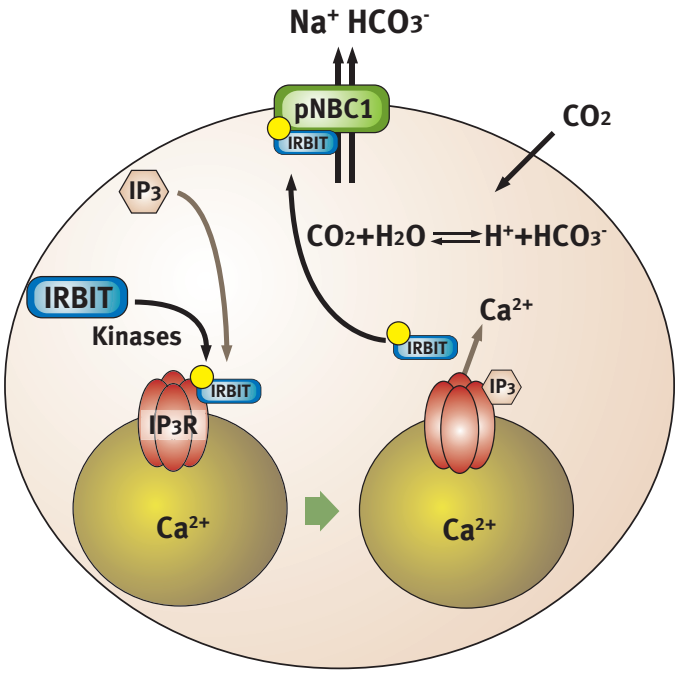

Figure 1: IRBIT is bound to the IP3 binding core of the cytoplasmic domain of IP3R under normal conditions (left). Binding of IP3 to the receptor causes it to release (right), after which IRBIT associates with pNBC1 to stimulate ion transport across the plasma membrane (top). (Ca^{2+} = calcium ion; CO_2 = carbon dioxide; H_2O = water; H^+ = hydrogen; HCO_3^- = hydrogen carbonate; yellow circle = phosphate).

1. Ando, H., Mizutani, A., Matsu-ura, T., & Mikoshiba, K. IRBIT, a novel inositol 1,4,5-trisphosphate (IP3) receptor-binding protein, is released from the IP3 receptor upon IP3 binding to the receptor. *Journal of Biological Chemistry* **278** (12), 10602–10612 (2003).
2. Ando, H., Mizutani, A., Tsuzurugi, D., Michikawa, T., & Mikoshiba, K. IRBIT suppresses IP3 receptor activity by competing with IP3 for the common binding site on IP3 receptor in a phosphorylation-dependent manner. *Molecular Cell* **22,** 1–12 (2006).
3. Shirakabe, K., Priori, G., Yamada, H., Ando, H., Horita, S., Fujita, T. Fujimoto I, Mizutani, A., Seki, G., & Mikoshiba, K. IRBIT, an inositol 1,4,5-trisphosphate receptor-binding protein, specifically binds to and activates pancreas-type Na^+/HCO_3^- cotransporter 1 (pNBC1). *Proceedings of the National Academy of Sciences USA* **103** (25), 9542–9547 (2006).

A DNA sequence not to be sneezed at

A sequence of DNA required for generating specialized lymphocytes regulates onset of allergy and asthma

In the June issue of *Immunity*[1], a team led by Masato Kubo, at the RIKEN Research Center for Allergy and Immunity in Yokohama, characterize a DNA sequence in lymphocytes responsible for controlling the development of a specific type of 'T helper lymphocyte' commonly associated with allergy and asthma.

Allergic diseases occur when the immune system is out of balance. Many of the mechanisms responsible for allergy and asthma are well-known and include over-production of immunity mediators such as interleukins, key signaling molecules in the immune system, and fast-acting histamine, which causes sneezing and constricted airways. T lymphocytes in particular are important producers of interleukins.

Inflammation leading to allergy and asthma can occur if too many specialized T lymphocytes called T helper type 2 (Th2) cells are generated. Th2 cells develop from naïve T cells, or T cells responding to newly encountered pathogens or allergens, after a program of differentiation that triggers the production of interleukins, such as IL-4, IL-5, IL-9 and IL-13. In large amounts these interleukins predispose people to allergy and asthma.

Kubo and team show that two other types of T lymphocytes, a subset of 'memory' $CD4^+$ T cells and 'natural killer T lymphocytes' (NKT cells), prime the development of Th2 cells. They determined that a specific DNA sequence in the region of the gene for interleukin 4 (IL-4) is active in both these cell types. The IL-4 produced, especially by the memory $CD4^+$ T cells, stimulates the generation of Th2 cells that then produce more IL-4 and other allergic mediators.

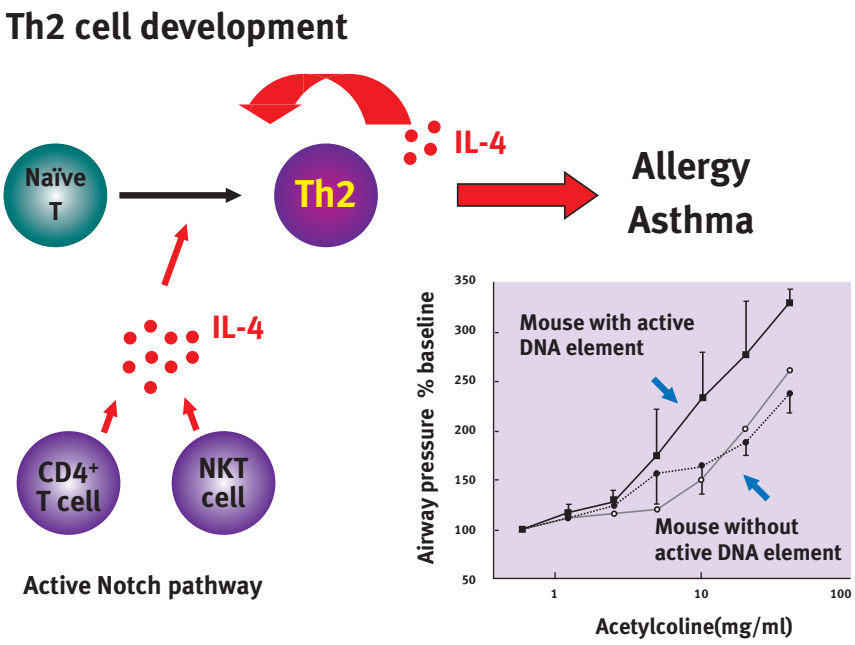

Figure 1: a) Notch signal regulates primary IL-4 production from $CD4^+$ and NKT cells through the unique DNA sequence in those cells. The IL-4 produced primes the differentiation of Th2 cells from naive T cells. The Th2 cells then produce IL-4 and other factors that mediate allergy and asthma.
b) The graph shows data from an experiment in which mice that have the IL-4-producing memory $CD4^+$ cells have more airway obstruction than mice that don't have the cells.

The critical finding by the team is that without the initial production of IL-4 by the memory $CD4^+$ T cells, the generation of Th2 cells does not occur. They also show that the specific DNA sequence required for IL-4 production in the memory $CD4^+$ T cells is regulated by the Notch pathway—a signaling pathway known to be important for development (Fig. 1).

Determining that the Notch pathway regulates the DNA sequence in the memory $CD4^+$ T cells required for generating Th2 cells may provide a target for therapeutically regulating the development of Th2 cells and allergic responses. According to Kubo, "the memory $CD4^+$ T cells uniquely use the Notch pathway for IL-4 production," which suggests that it may be possible to specifically target the cells therapeutically and develop treatments for debilitating forms of Th2-mediated diseases like asthma, the incidence of which continues to increase. ■

1. Tanaka, S., Tsukada, J., Suzuki, W., Hayashi, K., Tanigaki, K., Tsuji, M., Inoue, H., Honjo, T., & Kubo, M. The interleukin-4 enhancer CNS-2 is regulated by Notch signals and controls initial expression in NKT cells and memory-type $CD4$ T cells. *Immunity* **24,** 689–701 (2006).

Rare-earth elements show their mettle

A rare breed of metal clusters help make ethylene from carbon monoxide

A cornerstone of the chemical industry is the ability to convert one chemical compound into another. As well as making existing processes more efficient, researchers also work to develop completely new reactions. Efforts often focus on catalysts that can either speed up a known reaction or promote an otherwise unknown one. Organometallic compounds—substances containing both organic groups and metal atoms—often fill this role, but the potential of some metallic elements is only now being explored.

Zhaomin Hou from RIKEN's Discovery Research Institute in Wako is an advocate for the little-used rare-earth metals—a group of elements that comprises scandium, yttrium and the lanthanides. "The aim of our research is to search for new catalysts for more selective and efficient chemical transformations," says Hou, "or for new processes that cannot be achieved by previously known catalysts."

The reaction of carbon monoxide with hydrogen to give a mixture of liquid hydrocarbons and their oxygen-containing derivatives—the Fischer-Tropsch reaction—has been known for over 80 years. This process is industrially important because it is used to make a synthetic petroleum substitute from either coal or natural gas. However, as Hou points out, "the catalyst system is rather complicated, the reaction gives a mixture of different products and little is known about the reaction mechanism".

Now, Hou and coworkers have developed rare-earth metal complexes that can quickly and cleanly convert carbon monoxide into ethylene. This process is important because ethylene is a versatile precursor that is used in the manufacture of other chemicals such as polyethylene or polyvinyl chloride (PVC). "The formation of ethylene from this reaction shows, for the first time, that carbon monoxide can be hydrogenated selectively into ethylene under mild conditions," comments Hou.

The metal clusters contain either four yttrium or lutetium atoms that are held together with bridging hydrogen atoms. Carefully controlled studies using isotopically labeled carbon monoxide allowed Hou to identify intermediates in the reaction pathway and deduce the order in which the chemical bonds were being broken and formed. This insight into the reaction mechanism, which is reported in the *Journal of the American Chemical Society*[1], may shed light on how other similar reactions work.

This study demonstrates the unique reactivity of rare-earth metal clusters and highlights their potential as chemical catalysts. "This work will give us a better understanding of how carbon monoxide is converted into useful higher molecular weight chemicals," says Hou, "and may eventually lead us to make a better catalyst system."

1. Shima, Y. & Hou, Z. Hydrogenation of carbon monoxide by tetranuclear rare earth metal polyhydrido complexes. Selective formation of ethylene and isolation of well-defined polyoxo rare earth metal clusters. *Journal of the American Chemical Society* **128,** 8124–8125 (2006).

Superconducting circuit to test quantum theories

Device could form basis of powerful quantum computer

A simple circuit that tests the boundaries of quantum physics has been devised by RIKEN scientists. The proposed device could also be a key element of a future quantum computer, where information is stored and processed using the quantum properties of sub-atomic particles.

The circuit relies on three tiny superconducting devices that can carry electrical current, in the form of pairs of electrons, with virtually no resistance (Fig. 1). If trapped within the superconductor, odd or even numbers of electron pairs can represent the opposing states of binary logic that match the stream of 'ones' and 'zeros' used in conventional computers.

The data can be retrieved by counting the total number of electron pairs held in each superconducting 'box'.

But there's a catch. Although each box contains billions of electron pairs, making it far from sub-atomic, the behavior of the electrons is governed by the rules of the quantum world. This makes it possible for the overall quantum state of each box to become entangled with its neighbors so that they share the same information, as if they were part of a unified whole. Einstein himself dubbed this strange entanglement as 'spooky action at a distance', and it means that changing—or even measuring—the status of one of the superconducting electron-pair boxes can instantaneously affect the other two.

So each box essentially behaves as a unique quantum particle, and linking the three in this way is known as Greenberger-Horne-Zeilinger entanglement, named after the scientists who first described it in 1989.

"We propose that these phenomena can also be observed in the macroscopic world, using circuits, and not only in the microscopic realm," explains L. F. Wei of RIKEN's Frontier Research System in Wako, who devised the circuit with his colleagues Yu-xi Liu and Franco Nori, who is also at the University of Michigan, USA. Their proposal is published in *Physical Review Letters*[1].

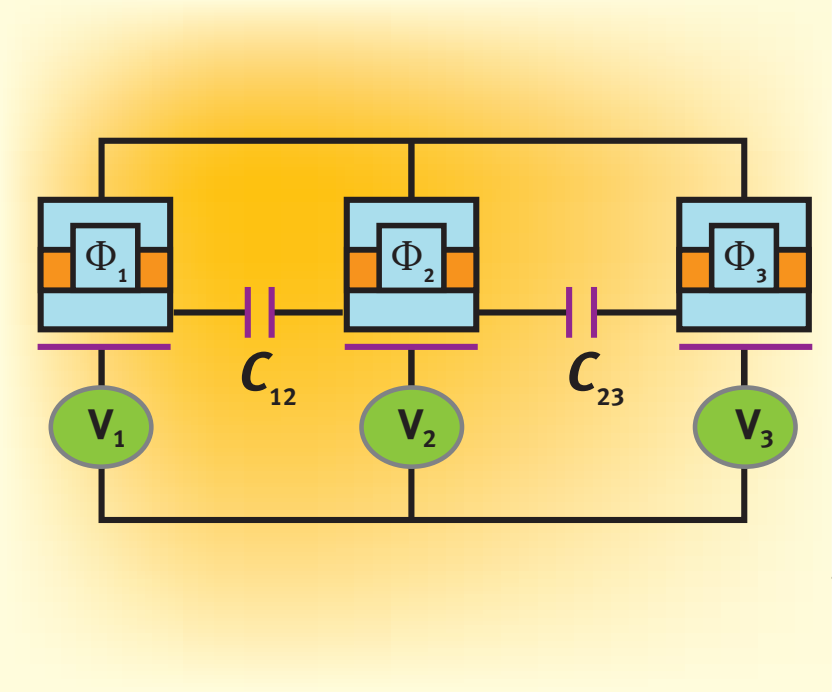

Figure 1: The three superconducting devices linked together in this circuit could form a key element of a future quantum computer.

The three superconducting boxes should be much easier to manipulate into specific quantum states than individual electrons, and controlling these 'macroscopic' quantum states provides a way to test some fundamental laws of quantum mechanics, such as entanglement, at the macroscopic level, says Nori. "But it is also a key step to building future quantum computers," he adds.

Since quantum states can exist in various combinations known as superpositions, there are many more configurations available to the three superconducting boxes than if they were a simple series of classical computer bits, which substantially increases the system's computing power. "We believe that the proposed system could be experimentally built in the near future," says Wei. ■

1. Wei, L. F., Liu, Y-X. & Nori, F. Generation and control of Greenberger-Horne-Zeilinger entanglement in superconducting circuits. *Physical Review Letters* **96,** 246803 (2006).

High-energy collision highlights quantum quirk

Uneven explosion of quarks spotted in particle accelerator

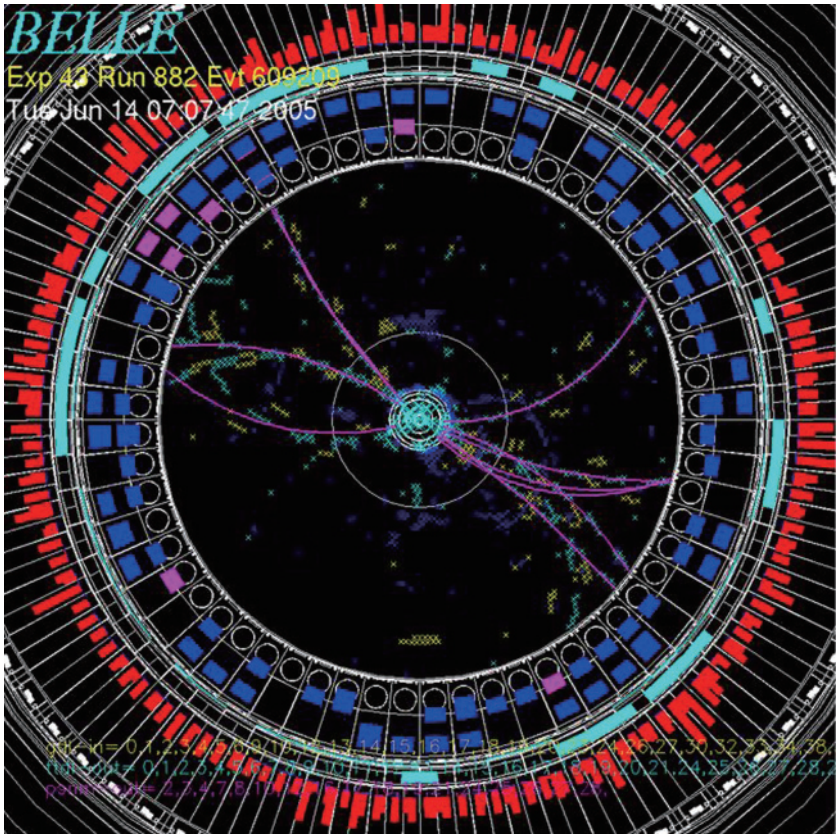

Figure 1: This computer-generated image shows the scatter of particles produced in an electron-positron collision.

The first experimental confirmation of a subtle effect predicted by quantum theory could lead to a better understanding of how the particles at the heart of every atom acquire properties such as spin, physicists say.

The protons inside each atomic nucleus were once thought to be indivisible, fundamental particles. But in the 1960s, physicists realized that protons were each composed of three particles called quarks, and that these constituents were bound together by a powerful short-range force, dubbed the 'strong' force.

Scientists can now generate and study quarks using facilities such as the Belle detector at the KEK-B particle accelerator in Tsukuba. KEK-B accelerates electrons and their antimatter counterparts, positrons, very close to the speed of light, before smashing them together. This creates two new particles—a quark and an antiquark—that fly in opposite directions away from the point of impact.

About 79 million of these collisions were recently analyzed by an international team of researchers led by Ralf Seidl of the RIKEN BNL Research Center, New York, US. The team reports their findings *Physical Review Letters*[1].

Quantum surprise

The quarks generated in the collisions cannot exist on their own for long. As they hurtle away from each other, each quark uses up some energy to create a partner antiquark. This stabilized quark–antiquark pair usually constitutes a particle known as a pion, whose violent birth jolts it into a different trajectory than its progenitor quark.

One might expect these pions to scatter evenly around the point of collision. But the laws of quantum mechanics had a surprise in store—on average, pions on one side of the collision tend to move along a slightly steeper trajectory.

Adding together the results from all 79 million collisions, it appears that the two sets of pions on either side of the impact point are actually moving asymmetrically, as though there were some intrinsic bias in this subatomic game of billiards (Fig. 1).

This was actually predicted by physicist John Collins in the early 1990s, and Seidl's team believes their experiment is the first confirmation of the so-called Collins effect. This underpins a key part of quantum chromodynamics (QCD), the theory that describes how quarks stick together. "It is really a very special probe to observe the nature of QCD," says Seidl.

Confirming this part of the theory, and precisely measuring the effect, could now lead to a deeper understanding of how the properties of protons are determined by their constituent quarks, he says. ■

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Sidonia Fagarasan

Happy accidents led to RIKEN

Sidonia Fagarasan made it from Romania to RIKEN through unrelenting efforts to discover the secrets of the gut's immune system – and a chance meeting in France

In her native Romania, Sidonia Fagarasan seemed set for a bright future. Graduating in 1990 from the country's top-class Iuliu Hatieganu University, she had become a gastroenterologist. But whenever she treated patients with inflammatory bowel diseases and other mucosal diseases, she felt frustrated: she thought she'd never know the fundamental causes of these diseases.

So Fagarasan gave up internal medicine and returned to her old university to research into bacteria and the immune system, and became an assistant professor of Microbiology Department in 1995. But lack of funding and the poor research environment in the former communist country limited her work mostly to reading. "I fed my brain with theoretical information. I realized I'd never understand how even one single bacterial cell lives its life," Fagarasan says.

Unfailing curiosity and a determination to seek answers eventually brought Fagarasan to Japan, a country about which she had known little other than classic literature, *ukiyoe* art painting and some history. During her eight years in Japan, Fagarasan's potential has blossomed and she is now being recognized as a specialist in the field of gut immunology. In 2004, she was appointed head of the Laboratory for Mucosal Immunity Laboratory at the RIKEN Research Center for Allergy and Immunology in Yokohama, near Tokyo, one of the few female leaders in the organization. Last year, she also won an award for promising young researchers from Japan's education minister.

A career-changing opportunity

While starting as a microbiologist in Romania, Fagarasan was already actively looking for greater opportunities to develop her research. One day in 1997, her career took a radically new direction. At a small conference in France, she heard a lecture about a mouse model of an autoimmune disease triggered by bacteria stimulation given by Tasuku Honjo, a renowned Japanese immunologist at Kyoto University Faculty of Medicine. Highly impressed, Fagarasan went to talk to Honjo during a coffee break. "I remember how that event impressed me and changed my direction," she says.

That conversation built a connection between them, and Fagarasan joined Honjo's lab in 1998, with a Japanese government scholarship she obtained partly owing to his recommendation.

'Happy every day'

During her first year in Japan, "I was happy every day," Fagarasan says, "and enjoying proving my ideas." Ever since her student days, she had been interested in the complex relationships among bacteria and between bacteria and our immune system. There are probably more than 1,000 species of bacteria in our gut, which help digestion, protect us against colonization with gut pathogens and even nurture the immune system. Fagarasan's work could help develop new vaccines and provide new approaches to treating immune and infectious diseases.

In Kyoto, she was trying to define cellular populations capable of generating a special type of immunoglobulin (IgA) in the gut, when she learned of the lab's breakthrough in discovering a protein called activation-induced cytidine deaminase (AID). For 20 years, Honjo had been investigating how IgM B cells switch to produce IgE, IgA and other Ig isotypes, but it was in 1999 that his group finally found the key molecule regulating this important genetic alteration. The team, including Fagarasan, were delighted to find that AID was essential not only for Ig isotype changes by class-switch recombination, but also for the generation of high affinity antibodies by somatic hypermutation, two processes that were believed to be regulated separately[1]. The finding contributed to developing the scope of Fagarasan's research.

Testing one idea after another

In mice that lack AID, the class-switch does not occur, and the mice do not produce IgA. Fagarasan started to address precisely how the gut and its immune cells respond to the lack of IgA. "Initially, I thought, like everybody else, that IgA was protecting against pathogen invasion. But by studying AID deficiency, we learned that IgA plays a subtler but probably more important role in controlling the composition of bacteria in the gut," she says.

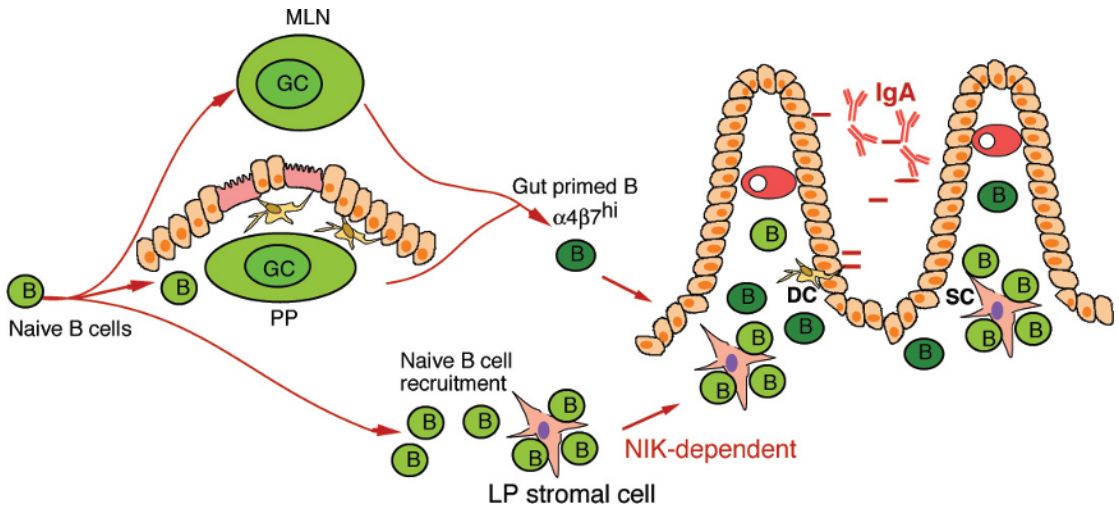

Figure 1: The model for B cells migration to gut lamina propria and IgA production
Immunoglobulin A (IgA) is the most abundant and critical isotype in mucosal secretions. Intestinal IgAs are generated from IgM B cells migrating to the gut by multiple pathways. Some B cells migrate first into organized structures, where they receive the 'gut flavor' or switch to IgA, and then they migrate to the lamina propria. Other IgM B cells migrate directly and switch to IgA in the lamina propria, with the help of local supportive, stromal cells (SC).

MLN = mesenteric lymph nodes
GC = germinal center
Gut primed B = B cells stimulated with antigens
α4β7hi = an integrin (adhesion molecule) for migration to gut
LP = lamina propria
DC = dendritic cells
NIK = NF-κB inducing kinase
PP = Peyer's patch (organized tissues)
SC = stromal cells

Fagarasan challenged the dogma that B cells producing IgA are generated only in the organized part of the gut-associated lymphoid tissue. Taking both cellular and molecular approaches, the team demonstrated that IgA B cells can be generated as well in non-organized gut tissue called lamina propria, suggesting that IgA production represents a primitive form of immune response[2].

Then, Fagarasan made her greatest finding to date. She showed that mice lacking IgA house as many as 100 times more bacteria in the small intestine[3]. What is more, this bacterial expansion in small intestine leads to over-stimulation of the whole body's immune system. Fagarasan's team continued on this line of research and demonstrated in 2004 that most of the bacteria expanded were uncharacterized species that can be controlled by IgA[4].

To RIKEN as a leader

After a few years in Kyoto, Honjo told Fagarasan "it was time to become independent." At first she thought it was too early to move on, but he recommended she apply to RIKEN, which had set up the Research Centre for Allergy and Immunology in 2001 and was accepting foreigners. Until that time, she confesses, "I didn't know about RIKEN." Fagarasan had thought about going to the US, but "I felt my mentality is much closer to the Japanese," says the soft-spoken researcher, who is fond of Japanese literature such as the *Tale of Genji*, a book on beauty and love written a thousand years ago.

At RIKEN, Fagarasan says she is learning a lot by managing a lab–albeit a small seven-member one. "This place is very good for my development at this stage," she says, adding that she tries her best to create a nice atmosphere in her group and keep the scientific standard high. Indeed, Keiichiro Suzuki, a colleague at Honjo's lab, left there to work under her at RIKEN. "She's very gentle and serious… reading her papers I was impressed that she kept her direction consistent," Suzuki says.

With Suzuki and other members, Fagarasan is tackling more challenging questions about IgA–especially how the antibody regulates the composition of the gut bacteria and how those bacteria maintain the fitness of the immune system.

Fagarasan says happy accidents are one of the important things in life. Honjo adds that fate brought her in contact with his breakthrough, but it can't be attributed only to luck. "Fortune falls to everyone, but you have to have the receptor to capture it. That fell to her because of her background and sincere approach towards cherishing curiosity, observing biological phenomena deeply, and thinking deeply," Honjo says. ■

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About the researcher

Sidonia Fagarasan was born in Brasov, central Romania in 1965. In 1990, she graduated from Iuliu Hatieganu University of Medicine and Pharmacy, Romania. As a student and soon after graduation she worked at the Gastroenterology Department of the University's Hospital. In 1993, Fagarasan received a specialty degree in microbiology, biochemistry and haematology and became an assistant at the university's microbiology department. In 1995, she became an assistant professor. In 1998, she came to Kyoto University under the Japanese government's scholarship program, and obtained a PhD in Immunology in 2000. Since 2002 she has been head of the Laboratory for Mucosal Immunity at the RIKEN Research Center for Allergy and Immunology.

Development of VCAD system; from intelligent manufacturing to cell modeling

Akitake Makinouchi

Program Director
VCAD System Research Program
Center for Intellectual Property Strategies
RIKEN Headquarters

Tracing the history of research into the design and manufacture of industrial products at RIKEN leads us finally to the source–the Okouchi Laboratory established in 1918. Akitake Makinouchi is Director of the VCAD System Research Program (established in April, 2006), which belongs partly to the school of the Okouchi Laboratory. Makinouchi joined RIKEN in 1969, and has been consistently engaged in research into manufacturing engineering. At present, he leads the VCAD System Research Program, which aims to provide computer-based assistance to manufacturing in Japanese style, that is closely related to job sites and actual products. Furthermore, he plans to apply this technology to medical science and research into bioscience. "Our target is to simulate an entire live cell in a computer. The VCAD system will serve as one of the most advanced tools for this," says Makinouchi. New developments on the continuing research into intelligent manufacturing at RIKEN are introduced in the following.

What is VCAD?

"It is really difficult to give people an understanding of Volume-CAD (VCAD)," says Makinouchi in an embarrassed tone. "VCAD is really hard to understand. However, it is a very important tool that holds the promise of significantly affecting not only intelligent manufacturing in the future, but also medical science and research into life science. Thus we think one of our major challenges is to win public acknowledgement of the VCAD system."

The CAD in VCAD refers to Computer Aided Design, that is, designing products with computer technology. Computers are indispensable at manufacturing job sites. Computer-assisted design, simulation, manufacturing, and measurement have contributed to shorter development periods and cost reduction. However, Makinouchi indicates that there are significant problems in practice.

"The reality is that programs that were developed separately are being combined just for the sake of connecting programs. Data is generally incompatible between programs, which may often result in having to create new data at each stage, or losing data during the conversion process. Tremendous amounts of manpower and time can be needed to cope with the problem. Thus we thought that we should develop a new kind of software system based on an original concept."

"In conventional CAD systems, the 'shape' came first," says Makinouchi. Current master stream CAD systems are solid CAD, which can represent three-

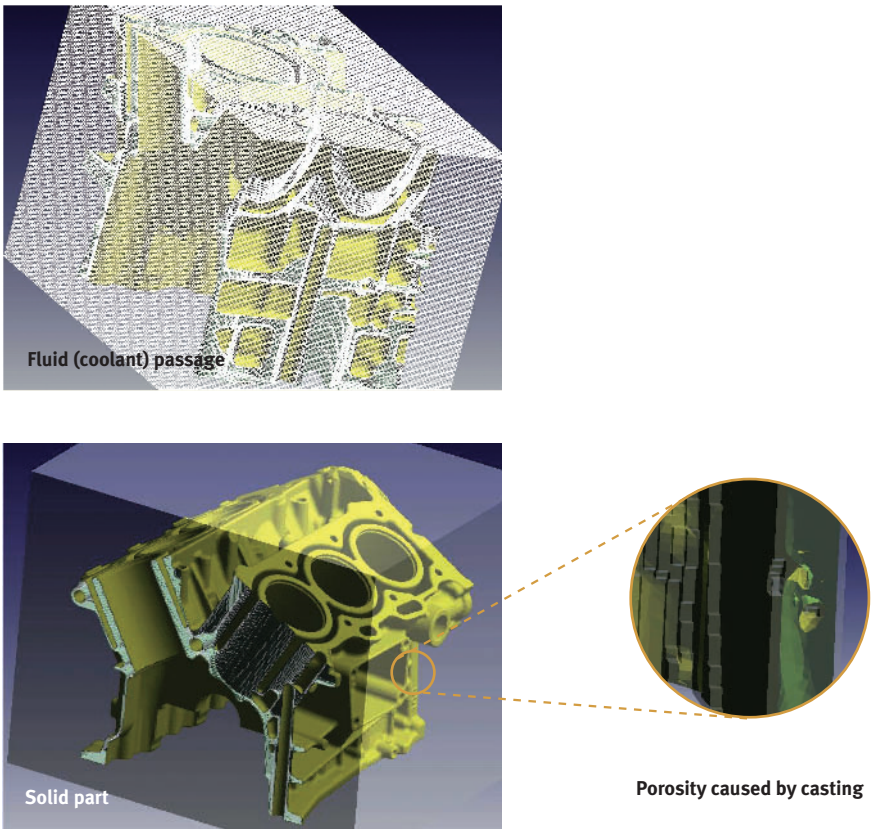

Figure 1: VCAD model of an aluminum engine
VCAD model generated from CT measurement data. Necessary parts or information can be picked out from a single model. In addition to solids, fluid can also be handled.

dimensional objects, but its capabilities are limited only to the surface of a three-dimensional volume. With solid CAD, we cannot represent the internal parts. However, actual objects are more complex, and have internal structures. Some have different physical properties in different portions. In other words, surface data is insufficient to represent an object precisely. This has been the primary reason preventing design, measurement, simulation, and manufacturing from being unified smoothly. "We thought that the 'content' should come first. The representation of an object as a three-dimensional structure with its internal parts allows us to express the data in one unified form from design to manufacturing. That is the principle behind Volume CAD (Fig. 1).

RIKEN started developing their VCAD system in April 2001, and in that year the Integrated Volume-CAD System Research Program was established (fiscal 2001-2005). What we aimed at is the construction of a next-generation infrastructure for intelligent manufacturing that can revolutionize conventional technology. However, a new infrastructure is not easily constructed. Even so, the VCAD system that we have developed this far features four basic and revolutionary techniques. This Volume-CAD System Research Program is implemented based on the results achieved during the last five years."

The VCAD System Research Program consists of seven teams, made up of around 30 research scientists (Fig. 2).

Connecting science with technology

The VCAD System Research Program has four research challenges: upgrading the VCAD system, popularizing it, finding applications in the medical field, and applying it to research into life science.

"One of the key phrases of Ryoji Noyori, President of RIKEN, is 'Build a RIKEN that is useful to the world.' I believe that what is directly useful to the world is technology rather than science. Science produces knowledge, and technology produces wealth. Science and technology are separated by a great gulf." Makinouchi thinks that the VCAD system is a very important tool that can connect science with technology (Fig. 3).

"Science brings knowledge. When a phenomenon is discovered, we want to understand the essence of

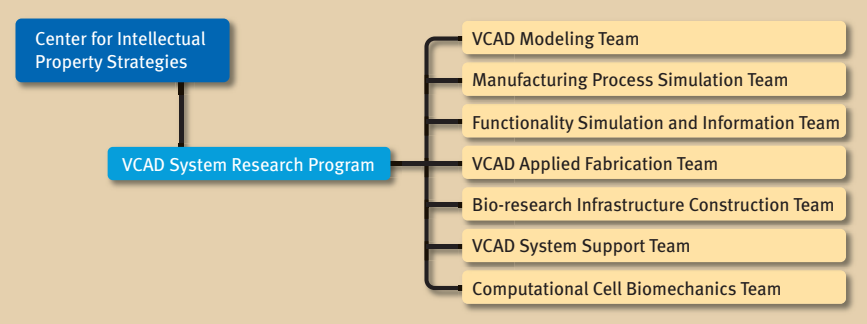

Figure 2: Organization of VCAD system research program

that phenomenon. When we have understood the phenomenon, we want to proceed to predicting and controlling the subsequent phenomena. This must be the basic nature of human beings, or an inherent aspiration of the intellect. The VCAD system supports the flow of intellectual activity, and can be used as a tool to connect science with technology."

Makinouichi has two methods in mind to popularize the VCAD system. One is the members-only VCAD System Study Group they have established. "We distribute developed programs to the members of the Study Group for evaluation and feedback, so that these programs can be improved to give higher functionality and better usability," he explains. At present, 33 company members and 21 individual researchers from universities are participating in the Study Group.

The other method is to open access to the software to the public through the web site so that more people can use it. In July, RIKEN made several programs available for download free of charge. "The VCAD system is a unique technology, and I am sure the system will attract the attention of overseas scientists. We are looking forward to their response," says Makinouchi with joyful expectation.

However, Makinouchi thinks that mere disclosure of the software does not necessarily lead to true popularization and practical application. Since free software is not guaranteed, many companies will hesitate to use it in the field. Thus popularization must extend to commercial versions of the software which incorporate after-sales care and user-friendly interface programs.

This commercialization requires close cooperation among the research teams, and software vendors including RIKEN venture companies. "I do not think that we can team up with companies unless we change our conventional ideas and methods. I hope that the VCAD system will become a technology transfer model, and an activity of the Center for Intellectual Property Strategies."

Modeling a live cell in a computer

Makinouchi talks about the research challenges of the VCAD System Research Program: "Application to the medical field and application to research into bioscience are two different challenges. Thus far we have focused on intelligent manufacturing. However from now on, we will conduct research into medical science and bioscience on the basis of the technology we have developed. The research will not end at the study phase. We would like to proceed to a stage where the technology offers real benefits to people."

One of the major features of the VCAD system is that it is capable of dealing, not only with artificial objects, but also with natural things including the living body. "Suppose you are trying to make an artificial hip joint. Wouldn't it be great if you could model the body of the patient on the basis of CT measurement data, use the model to design the artificial hip joint for the patient, and simulate movement with the model? The VCAD system is capable of dealing with artificial objects and natural things as a unified model using the same data format. I am sure that the day will come when the VCAD system finds applications in the medical field."

Makinouchi goes on: "What is becoming interesting is the cell. We will start conducting research on cells under the theme of 'modeling the living cell.' This is one of the challenges of the Strategic Research Project at RIKEN (President's Fund), which aims to assist cutting-edge research in various fields. Research scientists from six RIKEN research centers are participating in the project.

"In a cell, various minute organisms such as the nucleus, Golgi bodies and endoplasmic reticulum come together to form a system. In RIKEN, there are many laboratories where many scientists are engaged in research into cells, proudly presenting their profound findings that lead the world in terms of our understanding of the individual organisms and parts. However, nobody has studied how to treat the cell as one

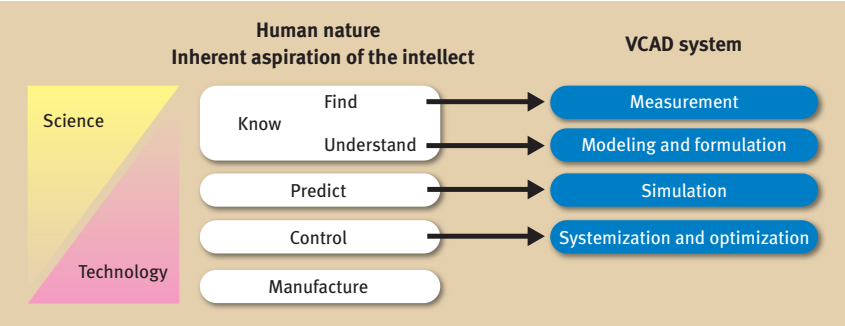

Figure 3: **VCAD System as a tool connecting science with technology**

complete cell system, because no tools were available." Makinouchi focuses on this point.

"We think that the VCAD system will provide us with the means to model the entire three-dimensional structure of a living cell with minute organisms in it, and life phenomena such as the transfer of material between these minute organisms. Of course, a host of challenges lie ahead. However, RIKEN has started developing a next-generation 10-petaflop supercomputer. This will provide us with an efficient tool. Now is the time to take on this challenge."

Modeling the structure of a cell in a computer is the first step toward our major goal. "We will create a model of a living cell in a computer, and the simulation model will be fully disclosed. Our next goal is to update the simulation model as a research infrastructure for researchers from around the world so that they can use the model to analyze and predict cell functions. We think that if we meet this goal, we will be able set a course toward our major target of functional control, or in other words, drug discovery."

Research into engineering at RIKEN

Makinouchi joined RIKEN in 1969. He looks back on those days: "In those days there were six engineering laboratories. The history of RIKEN shows that engineering has always been very important. However, I feel that engineering has recently been cast into the shade. Of course, any research can be caught up in the tide of the times. Recently many research scientists speak about the importance of developing their own measurement methods or instruments for scientific research. Thus I think engineering will become increasingly important again."

Makinouchi says emphatically, "I think continuity is power. To produce anything new, we need to build up individual items and to persevere until they mature. If you start on a new research project every five years, you can hardly open up the world's most advanced fields. Unless continuity is respected, research at RIKEN and in Japan as a whole will increasingly follow a trend of choosing only research projects that can produce results within a short period. I am concerned about that trend."

Finally, what is the future of research into engineering at RIKEN? Makinouchi answers this question clearly. "We have started five new years of research into VCAD systems on the basis of the previous five years. Highly-motivated and deserving researchers are now engaged in research activities under seven team leaders. They are experts from various fields such as mathematics, geometry, mechanics, measurement, software systems, manufacturing, and bioscience. Two-thirds of them are continuing their research projects and one-third are new participants from this April. Continuity is power. With the addition of this new power, I am sure that we can achieve significant results in the coming five years." ■

Background reading/information

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About the researcher

Akitake Makinouchi was born in Nagano, Japan in 1940. He graduated from the Department of Precision Engineering, the University of Tokyo in 1964 and earned his doctorate in engineering from the same university in 1969. In the same year, he joined RIKEN's Deformation Processing Laboratory as a research scientist and became the chief scientist at RIKEN's Materials Fabrication Laboratory in 1994. In 2001, he was appointed as the Director of RIKEN's Integrated VCAD System Research Program. He's concurrently serving as a visiting professor of the Engineering Department, Graduate School of Hokkaido University.

Brain states and state transitions: BSI's Summer Program

Dynamic. That's the only way to describe the people who recently spent two hot summer weeks listening to over sixty hours of lectures about the brain. It is an apt description. After all, RIKEN Brain Science Institute's eighth Summer Program Lecture Course explored experimental and theoretical approaches to "Dynamical states in the brain".

Thirty-one budding neuroscientists from twenty countries assembled in a nicely chilled room in the Ikenohata Research Building on RIKEN Wako Campus. The intensive study began July 25. By the time the last lecture ended at 5:50 pm on August 4, participants had toured a broad range of approaches to understanding the dynamic activities of the brain, guided by some of the best scientists in their fields.

"This is a perfect marriage of interests," said Canadian Ph. D student Elan Ohayon. He had come to Japan and BSI in search of possible post-doctoral work, and to gain deeper understanding of his field.

Boris Vladimirskiy, a Russian post-doc working at the Institute of Physiology at the University of Bern, is a computational neuroscientist who had a mission at the course. He came for the lectures. "To work with experimentalists and biology-based researchers, I need to speak their language, I came here to get the vocabulary of the field." Did he get it? "Yes."

Half of the lectures included detailed reviews of molecular and single-cell studies of neuron activity, as well as past and revolutionary approaches to imaging studies. The eight theoretical lectures were diverse. While John Rinzel of New York University attempted to give those with a fear of math a "love of the geometry", others presented and argued for models and robotic states of forgetting, learning, and cognition. Each speaker shed light on dynamic changes in the brain.

The first speaker, David McCormrick from Yale University spoke about observed activity in a signal neuron through state transitions and suggested that neural communication may use both digital and analogue means of transmitting information. His talk was overwhelmingly well received. "McCormrick's lecture balanced history, experimental data, and exciting speculation," explained another Russian post-doc, Mikhail Druzin.

Participants at the program (Ofer Tchernichovski of City College New York in the middle and Matthew Wilson of MIT furthest on the left)

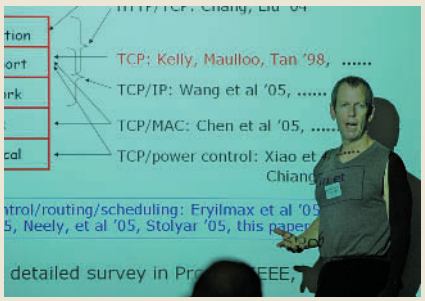
BSI's Summer Program is an annual event that invites promising young students and scientists to Japan for a two-week lecture course or a two-month internship (that includes the lectures). Participants attend fifteen lectures and poster sessions during the two weeks, and spend time interacting with BSI researchers in their labs.

This year, there were thirty-one lecture course participants, fourteen more here for a two-month internship. They represent 'the future of neuroscience' said Vice Director Keiji Tanaka. Judging from the number of participants who said they would like come back, they may also be part of BSI's future too.

International Workshop on Recent Advances in Biological Control

Research in the life sciences has recently been focusing on the concept of 'control.' Molecular biologists are studying how to control metabolism and genetic expression. Medical scientists are trying to control diseases by conducting examinations and tests on many parts of the body and combining all the information together. In bioengineering, researchers are studying how the brain controls behavior, with a view to building humanoid robots.

In July, RIKEN held an International Workshop on Recent Advances in Biological Control, at its Bio-Mimetic Control Research Center in Nagoya. The event was attended by more than 200 researchers from a wide range of fields, including control engineering and robotic engineering as well as biological control. This mix led to many lively and fruitful discussions.



John Doyle of the California Institute of Technology

At the workshop, scientists reported on a number of remarkable recent achievements in cell biology that use the idea of control. John Doyle of the California Institute of Technology claimed that control on the internet could lead to understanding of control at the cellular level—metabolism corresponds to TCP (the transmission control protocol), and genetic expression to IP (the internet protocol). Hiroaki Kitano of the Systems Biology Institute stated his view that insights into what control engineers call 'robustness' could help us understand complicated diseases like cancer, and that cancer treatment should try to deprive cancerous cells of their robustness. From RIKEN's Center for Developmental Biology, Hiroki Ueda talked about his explanation of the circadian rhythm in rats. The data analysis for this research used a system identification method from control theory.

Seminar for the public in Nishina's hometown

Yoshio Nishina (1890–1951), father of nuclear physics in Japan and one of RIKEN's most eminent scientists, was born in the town of Satosho, in Okayama prefecture in western Japan. Satosho is still very proud of its famous son, and places great emphasis on education. Each year it sends about ten children to RIKEN and to the Niels Bohr Institute in the Netherlands, to increase their interest in science.

Every year since 1992, RIKEN has been holding a seminar for the general public in Satosho as one of its outreach activities. This year's event was on Saturday August 19, in the Nishina Kaikan building. More than a hundred people came, including high-school students. First Hideo Kitamura gave a talk about the X-ray Free Electron Laser, a major national project that RIKEN is carrying out at its SPring-8 Center in Harima, and then Atsuko Yamashita spoke about analysis of protein structures using radiation beams. After the seminar, visitors were also able to visit the house where Nishina was born.

Powerful light derived from teamwork

The world's brightest and highest energy light beams are a product of close collaboration between RIKEN and external researchers

In the outskirts of Harima near Kobe, the world's biggest synchrotron radiation facility sits quietly on a green hill. The facility, called SPring-8, produces the most powerful synchrotron radiation on earth. It is also Japan's first large-scale and successful scientific project that involved more than one major research institute.

Synchrotron radiation is electromagnetic wave emitted when electrons at nearly the speed of light are bent by a magnetic field. It was fist observed in 1947 in the US. This newly invented light was much brighter and more directional than conventional light sources and its wave lengths were more diverse. This radiation has since contributed to a variety of advanced scientific research, including observation of the crystallized structure of proteins.

Japan led synchrotron radiation research from the beginning when only a few countries were involved, but this research boomed worldwide in the late 1970s. Europe started design study of a third-generation facility with energy of 6 Giga electron Volts (GeV) in the mid-1970s and decided to build it in 1987; the US also started research and development of a 7 GeV facility in 1987. By the mid-1980s RIKEN considered building its own small facility—with energy of 1.5 GeV, but decided to collaborate with a research group in Osaka proposing a 6 GeV synchrotron.

In 1986 researchers from RIKEN's cyclotron laboratory took the lead in calling for the construction of a large-scale synchrotron facility in Japan. As the project had to be internationally competitive and needed substantial funding, the government ordered it be an 'all Japan' project. In 1988, RIKEN and Japan Atomic Energy Research Institute, or JAERI (the current Japan Atomic Energy Agency) signed a cooperative agreement and joined forces as the project leads.

Despite potential hurdles, including the different cultures of RIKEN and JAERI and the inexperience of many of the team who were young researchers and engineers, the two organizations established a common goal and proposed to build an 8 GeV synchrotron radiation facility. The major objective was to achieve the world's most brilliant beams in X-rays. The Ministry of Finance approved construction of the facility in 1990.

Japan's synchrotron radiation facility was named SPring-8, meaning Super Photon Ring, 8 GeV. To realize the best light sources, the project team worked hard to develop a high-quality storage ring and superior insertion device called an in-vacuum undulator, a set of special permanent magnets. In March 1997, the first generation of synchrotron radiation was confirmed—two years ahead of schedule. Seven months later, use of the facility by RIKEN and JAERI started. At the same time, RIKEN established the RIKEN Harima Institute to conduct research using SPring-8. Initially, SPring-8 offered just 10 beam lines, but the number is now 48. A total of 10,000 researchers use SPring-8 for 1,500 research projects annually.

SPring-8's project team decided to preserve the mountain in Harima's science park and build a storage ring around it.

Researchers at RIKEN are now developing 'a light of the future' called the X-ray Free Electron Laser (XFEL), which would be one billion times more brilliant than the current SPring-8 light. If all goes to plan, the XFEL facility will be available at the site of SPring-8 by 2010. ■

A note about SPring-8

The SPring-8 facility consists of a linear accelerator, a synchrotron and a huge storage ring. Electrons are accelerated and stored in this accelerator complex. In general, compared to a cyclotron which can accelerate only ion particles, a synchrotron can accelerate both electrons and ions and the energies produced can be much higher.
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