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Tapping the cosmic pulse

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RIKEN

Gaining strength from change

RIKEN has implemented significant changes since the previous external evaluation in 2006 by the RIKEN Advisory Council (RAC). At the seventh meeting, held in April 2009, the RAC made several new recommendations. RIKEN President Ryoji Noyori and RAC Chair Zach Hall discuss RIKEN's progress and future directions.

Hall: RIKEN has been very responsive to many of the recommendations we have made. Many of the important changes have been substantive. We were also very pleased that RIKEN has internalized the view that it should become more international; not just in the sense of having collaborators from other countries, but in having people from other countries come to RIKEN at all levels.

Noyori: We are already nurturing the careers of talented young [Japanese] scientists, and many of them go to work overseas. We now need to ensure that RIKEN is also a destination for scientists from outside Japan.

In that sense, I think inviting Susumu Tonegawa from MIT to the Director of RIKEN Brain Science Institute (BSI) will have an enormous impact, not only for RIKEN, but for all of Japan. I consider this one of the most important events in my presidency.

Acting on worthy advice

RIKEN clearly takes the RAC's recommendations seriously. What are the main advantages of receiving this advice?

Noyori: RAC is our asset. Hearing the opinions and suggestions of this most able and experienced group of scientists and scientific administrators contributes to our ability to manage RIKEN as effectively as possible.

Hall: It is to RIKEN's credit that it invites such an extraordinarily talented group to comment constructively. The fact that this group comes to Japan serves as recognition of what a great institution this is.

Noyori: Importantly, when they return to their own countries, they talk about RIKEN with their colleagues. It is a mechanism bringing us into contact with the whole scientific world.

It is evident that the RAC also takes its charge very seriously.

Hall: I have to say it's very gratifying. I have been involved in visiting committees where recommendations are just shelved. There are situations in which one can't just apply a simple fix, walk away and be done with it. We understand that. We encourage persistent attempts to find solutions that will take many years, partly because some of them involve changes in culture, which can be very hard and very slow.

Out of the many recommendations, were any particularly urgent or salient?

Hall: It cannot be done overnight, but one of the most straightforward involves the administration that supports science at RIKEN. We've come to realize that RIKEN is restrained by an administrative structure that has not changed as the institute has expanded and gotten more complex. We hope that RIKEN will now begin to apply the most modern management ideas and methodologies to streamline its administration, and improve its efficiency and performance. The ground needs to be prepared for a culture and structure that promotes the kind of creativity and scientific advances that RIKEN has achieved in the past, and to which it continues to aspire. For an institution of this size, good administration is a necessity.

Noyori: Scientists are used to having their work evaluated in many ways, but management, in Japan at least, is never subjected to these same kinds of assessments. We are very proud that our organization will be able to pioneer that reform. The operation of the Japan's flagship institute is open worldwide and is totally transparent.

Addressing current challenges

Given RIKEN's current strengths in the physical and life sciences, and its significant large-scale infrastructure facilities, how will it address the critical challenges of food, environment, energy and health?

Noyori: We have many strong individual research programs, so the key will be finding ways of integrating and building linkages between them. But, we will still need to work together with many

external stakeholders. Building such networks is very important and already underway. We have many excellent scientists, but individual efforts will not be enough to address the many serious challenges the world now faces. RIKEN must fulfill our responsibility to future generations.

The global economic crisis has struck particularly hard in Japan. How should RIKEN reconcile its new directives and ambitions with inevitable constraints?

Hall: RIKEN must have a rigorous process of priority setting. Downsizing or bringing something to a close is hard to do in an academic—or government—setting because activities tend to develop a constituency. No one is going to admit, "This institution has done its job, but our field is no longer as important as it used to be." Advisory committees tend to act as boosters for their fields. The president of RIKEN should have the very best [independent] scientific advice. If these tough decisions are not made, it becomes impossible to take advantage of new opportunities and eventually leads to stagnancy.

Noyori: Both administrators and scientists worry about shrinking budgets, but this is not always a bad thing. It provides us with an opportunity to think very carefully about which fields to pursue, and for collaboration and the integration of knowledge. The interdisciplinary and international collaboration is crucial. Only by working together can we generate new fields. We don't need more clones, we need hybrids.

Hall: I like that analogy. Hard times can force you to evaluate what you're doing, and ask, "What are we doing that is really important?" That can be a valuable exercise.

RAC members were strongly in favor of making women 25% of all new hires, not only to ensure diversity, but to maintain Japan's scientific and economic competitiveness. What prompted this bold call?

Hall: This was not an entirely new recommendation, but the sense of urgency was. It is too important an issue to be satisfied with incremental progress. Women scientists represent a very large pool of underutilized talent. Using only half of a population foregoes a great opportunity that is important in competitive situations. Rita Colwell questioned the source of the next generation of scientists given factors such as the shrinking population in Japan, and the decline of interest in science among the young. Importing them is one solution, and such exchange is healthy, but using existing talent is another wonderful solution. Anecdotal evidence indicates that talented Japanese woman scientists cannot get positions here, so they move overseas. The remedy may require not just placing ads for open positions, but actively learning about the existing pool of female scientists.

In the US, a growing number of university presidents are women. RIKEN should make a conscious effort to enlist this talent on evaluation committees, which would also provide a visible role model for young scientists.

Best foot forward

Adapting and evolving to rapid change is challenging. Can you offer encouragement to RIKEN's scientific and administrative staff about the value of transformation?

Hall: RIKEN has reinvented itself several times and maintained its scientific excellence throughout, so I have great confidence in its ability to continue to adapt and be successful.

Noyori: The most important thing, I think, is for the researchers and the administration to share a common vision for the future of RIKEN.

Hall: Many people get nervous when they hear 'administrative reform'. These are reforms intended to help people to do their best by empowering people to acquire new skills and grow, which is in RIKEN's best interest.

Noyori: Our administrative staff has always worked internally to support the scientists, but it is not enough. I'd like to ask them also to serve as an interface with society. That is very important and I would like to see them take a lead in that. ■

Box1: Members of the seventh RIKEN Advisory Council

Name	Title and affiliation
Zach W. Hall, Chair	Emeritus Vice Chancellor, University California, USA Founding President, California Institute for Regenerative Medicine, USA
Yuan Tseh Lee, Vice-chair	President Emeritus, Distinguished Research Fellow, Academia Sinica, Taiwan 1986 Nobel Laureate
Hiroo Imura, Vice-chair	Chair, Foundation for Biomedical Research and Innovation, Japan Principal Fellow (Chair), Center for Research Development Strategy, Japan Science and Technology Agency, Japan Professor Emeritus, Kyoto University, Japan
Howard Alper	Distinguished University Professor, University of Ottawa, Canada Chair, Government of Canada Science, Technology and Innovation Council, Canada
Teruhiko Beppu	Professor, Advanced Research Institute for the Sciences and Humanities, Nihon University, Japan Professor Emeritus, University of Tokyo, Japan Former Chair, Japan Bioindustry Association, Japan
Colin Blakemore	Professor of Neuroscience, University of Oxford, UK Former Chief Executive, UK Medical Research Council, UK
Rita R. Colwell	Distinguished University Professor, University of Maryland at College Park, USA 11th Director, National Science Foundation, USA
Mitiko Go	Executive Director, Research Organization of Information and Systems, Japan Former President, Ochanomizu University, Japan
Toshiaki Ikoma	Executive Vice President and CTO, Canon Inc., Japan Professor Emeritus, University of Tokyo, Japan
Biao Jiang	Director, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, China
Paul Kienle	Professor Emeritus, Department of Physics, Munich University of Technology, Germany Former Director, GSI Darmstadt, Germany
Karin Markides	President, Chalmers University of Technology, Sweden
Rainer E. Metternich	Vice President of Basic Research and Site Head, West Point, Merck & Co., USA
Hans L. R. Wigzell	Senior Strategic Advisor and Professor, MTC, Karolinska Institutet, Sweden Former President, Karolinska Institutet, Sweden
Allan Bradley	Director, Wellcome Trust Sanger Institute, UK
Max D. Cooper	Professor, Department of Pathology and Laboratory Medicine, Emory University, USA
Hidetoshi Fukuyama	Professor, Tokyo University of Science, Japan Professor Emeritus, University of Tokyo, Japan
Sydney Gales	Director, Grand Acceleraeur National D'Ions Lourds, France
Sten Grillner	Professor and Director, Nobel Institute for Neurophysiology, Karolinska Institutet, Sweden
Wilhelm Gruissem	Professor, ETH Zurich, Institute of Plant Sciences, Switzerland
Jean-Louis Guenét	Director, Unite de Genetique des Mammiferes, Institut Pasteur, France
Jerome Hastings	Professor, Photon Science, SLAC National Accelerator Laboratory, USA
Bengt Långström	Professor, Uppsala University, Sweden
Mark Lathrop	Director General, Centre National de Genogypage, France
Austin Smith	MRC Professor and Director, Wellcome Trust Centre for Stem Cell Research, University of Cambridge, UK

How it all begins

Germ cell development depends on a complex regulatory process in the embryo, but can be initiated by a single signal in the test tube

In the process of exploring the formation of primordial germ cells (PGCs), the precursors to both sperm and ova, RIKEN researchers have uncovered an effective means for cultivating functioning germ cells. The findings could have a profound effect on fertility research and help scientists to better understand the earliest stages of reproductive development.

At the start of the second week of embryonic development, certain cells in the proximal posterior epiblast region of the mouse embryo begin to undergo radical changes that enable their transformation into PGCs. "Our studies have identified that germ cell specification involves at least three key events: repression of the somatic [gene expression] program, re-acquisition of potential pluripotency and ensuing epigenetic reprogramming," says Mitinori Saitou, an investigator at the RIKEN Center for Developmental Biology in Kobe.

In previous work, Saitou's team identified the protein Blimp1 as a key factor controlling all of these processes, demonstrating that it is specifically expressed at exactly the right time and place to kick off PGC development[1]. However, it has remained unclear which factors are the top-level triggers for expression of PGC 'master switch' genes like Blimp1 and Prdm14, which is another important regulator of germ cell development. To address this question, Saitou and colleagues embarked on a new study to characterize the involvement of a variety of other signaling factors previously linked to the PGC formation process[2].

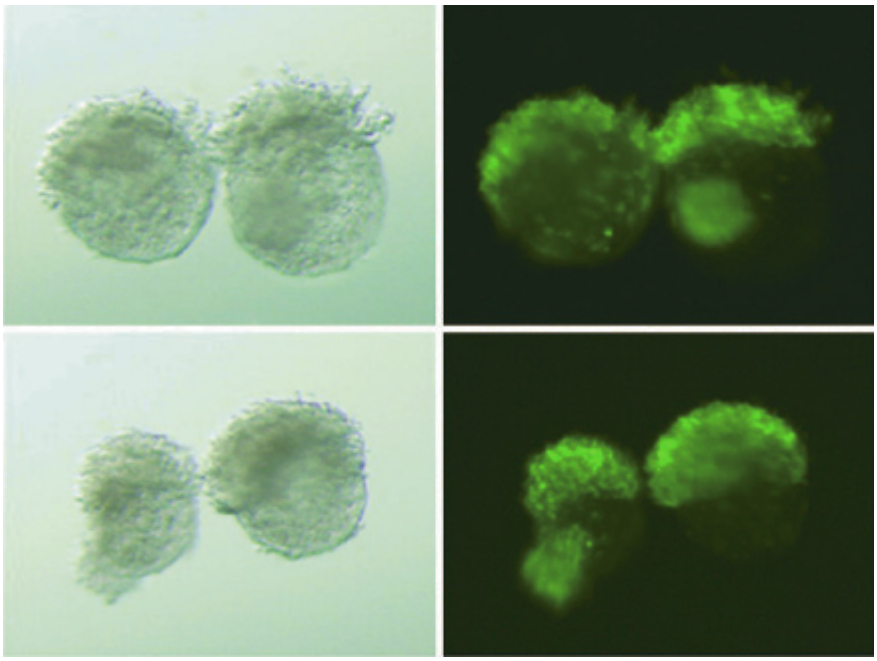


Figure 1: epiPGCs exhibiting expression of genes specific to PGCs. The fluorescent protein Venus was used to label either Blimp1 (top row) or Prdm14 (bottom row), and both proteins are abundantly expressed (right column) in Bmp4-induced epiblasts.

Bmps in the road

The team began by looking at Bmp4 and Bmp8b, two factors secreted by a region known as the extraembryonic ectoderm (ExE), which borders the posterior epiblast. Both proteins proved essential to Blimp1 expression, although both are also expressed in a far broader swathe of the embryo than Blimp1, suggesting that Bmp4 and Bmp8b are being blocked by an inhibitory factor that restricts their activity in the anterior portion of the embryo.

In order to directly observe the effects of various factors at different stages of PGC development, the researchers cultured whole embryos and embryonic fragments under serum-free conditions in the presence of different signaling molecules. These experiments confirmed that the ExE is needed to induce Blimp1 expression and that signals from the anterior visceral endoderm serve to keep Blimp1 expression in check. Unexpectedly, however, they also indicated that the presence of Bmp4 alone is sufficient to drive the development of PGC-like cells that express both Blimp1 and Prdm14.

This finding raised questions about why embryos lacking Bmp8b fail to undergo proper germ cell development, but subsequent experiments made the answer clear: Bmp8b restricts the development of the anterior visceral endoderm, keeping in check the Blimp1 inhibitory signals produced by this extraembryonic region. Only through the combined effects of both Bmp8b and Bmp4 will proper Blimp1 expression—and therefore PGC development—take place.

Figure 2: The offspring. Healthy spermatozoa derived from epiPGCs containing the gene for green fluorescent protein (GFP) were used to fertilize oocytes. The resulting litter of mice represents a 50:50 mix of GFP-expressing and non-GFP-expressing animals (left), as can be observed when the mice are subjected to GFP-exciting ultraviolet light (right).

Playing the part

Although the cells derived in these experiments bore several of the hallmarks of naturally occurring PGCs, Saitou and colleagues performed another battery of experiments to confirm that these PGC-like cells also resembled their naturally occurring counterparts at a functional level.

After nearly a week of culture, cells derived from Bmp4-treated epiblasts—which the authors termed epiPGCs—continued to express not only Blimp1 and Prdm14 (Fig. 1), but also expressed a number of other key genes specific to PGCs, such as stella and SSEA1. More importantly, however, they also proved capable of producing viable sperm following transplantation into mice; this was demonstrated both with implantation of *in vitro* reconstructed gonads as well as direct injection of epiPGCs into the testes of neonatal recipients. In both models, the resulting spermatozoa were healthy and suitable for fertilization of oocytes, producing healthy offspring (Fig. 2).

In addition to the raw information encoded within the genomic sequence, reproduction also involves the transmission of parent-specific epigenetic 'imprinting': patterns of chemical modification on the chromosomes that provide an additional level of gene regulation. Parental epigenetic marks are normally wiped clean in PGCs, and then subsequently restored during spermatogenesis. Similar behavior was observed in spermatozoa generated from transplanted epiPGCs, providing further evidence that BMP4-induction is sufficient to yield cells that are apparently interchangeable with natural PGCs.

"It's surprising that Bmp4 is sufficient to drive epiblast cells to undergo PGC specification and subsequent further differentiation, including epigenetic reprogramming and erasure of imprints," says Saitou. "This indicates that this specification signal is sufficient to promote PGC development ... autonomously to a certain extent."

Reconstructing reproduction

This study has enabled Saitou's team to identify the essential factors involved in germ cell formation, and thereby reconstruct a spatial and temporal map of these various activation and inhibition signals that achieves an unprecedented level of detail.

Importantly, this work also represents the first time that fertilization-ready gametes have been successfully derived from cultured embryonic cells—a breakthrough with potential implications for both the laboratory and the clinic. This technology could provide the means for scientists to introduce genetic modifications in animal models for which suitable stem cells are not available. Moreover, Saitou sees this method as a powerful tool for studying—and addressing—human infertility, and he indicates that a long-term objective of his team involves using these epiPGCs to recapitulate the entire process of germ cell development *in vitro*. "Application of these findings to human embryonic stem cells or induced pluripotent stem cells may provide a way to find critical mutations regarding human infertility," he concludes. ■

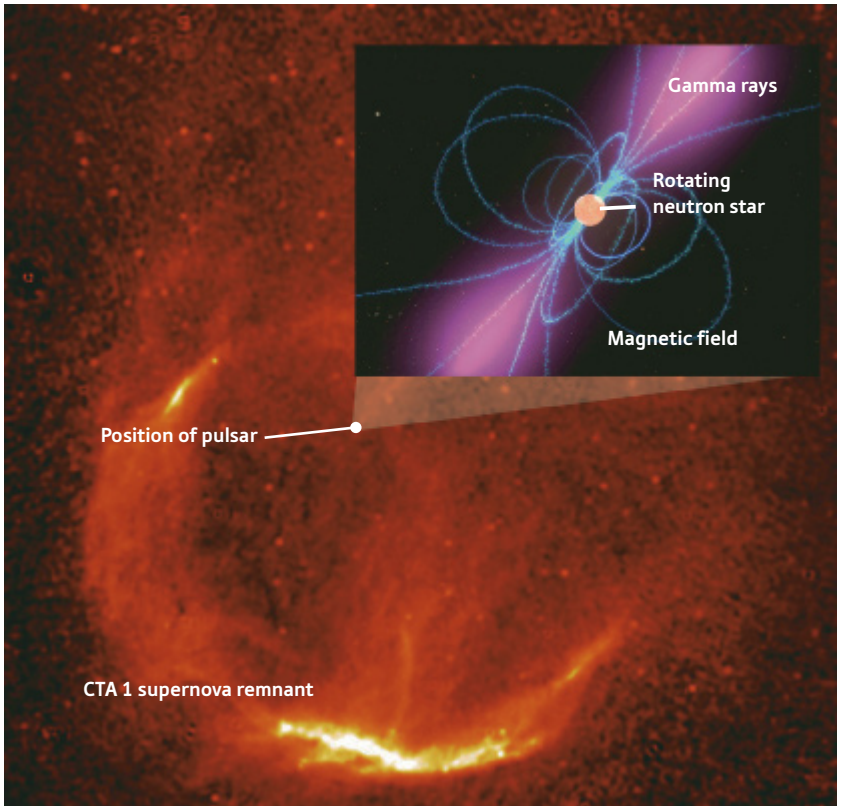
1. Kurimoto, K., Yabuta, Y., Ohinata, Y., Shigeta, M., Yamanaka, K. & Saitou, M. Complex genome-wide transcription dynamics orchestrated by Blimp1 for the specification of the germ cell lineage in mice. *Genes & Development* **22,** 1617–1635 (2008).
2. Ohinata, Y., Ohta, H., Shigeta, M., Yamanaka, K., Wakayama, T. & Saitou, M. A signaling principle for the specification of the germ cell lineage in mice. *Cell* **137,** 571–584 (2009).

About the researcher

Mitinori Saitou received his M.D. from the Kyoto University Faculty of Medicine in 1995, and was award a Ph.D. in 1999 for his study of the structure and function of tight junctions under Shoichiro Tsukita at the Kyoto University Graduate School of Medicine. He then moved to the Wellcome Trust/Cancer Research UK Institute, where he worked as a postdoctoral research associate in Azim Surani's laboratory, focusing on his long-term interest in the origin of the germ line in the mouse. He was appointed team leader at the CDB in 2003, and received a three-year grant from the Japan Science and Technology (JST) Corporation under the PRESTO program for the development of a single-cell microarray technology. In 2004 he became Associate Professor at the Kyoto University Graduate School of Biostudies, and was subsequently appointed Professor of the Kyoto University Graduate School of Medicine in 2009. He continues to investigate the origin, properties, and regulation of the mammalian germ cell lineage with the aim of reconstituting the lineage *in vitro*.

Pinpointing pulsars

The new Fermi Gamma-Ray Space Telescope has identified a new pulsar by detecting its gamma-ray emission



NASA/S. Pineault, DRAO

Figure 1: A pulsar (inset) that lies in the CTA 1 supernova remnant and beams only in gamma rays. This pulsar was discovered by NASA's Gamma-ray Space Telescope.

A massive star can die when its core collapses in on itself, causing an explosion called a supernova. Some of the most important remnants of supernovae are pulsars—extremely dense stars composed mainly of neutrons.

Now, a new pulsar has been discovered by an international collaboration of researchers using the Fermi Gamma-Ray Space Telescope[1], which was launched in June 2008. The researchers, including Nobuyuki Kawai at RIKEN Advanced Science Institute in Wako, hope that this new pulsar could help to explain several unidentified gamma ray sources throughout the galaxy.

Pulsars get their name because they are highly magnetized and rotate at great speeds to emit beams of electromagnetic radiation in pulses. These pulses are so regular they have been compared to the accuracy of an atomic clock.

Many pulsars are associated with supernovae remnants; for example the famous Crab nebula is fed by a wind of relativistic particles from an energetic pulsar at its center.

Kawai and co-workers discovered their new pulsar in a supernova remnant called CTA 1 (Fig. 1), which is relatively young having exploded between 5,000 and 15,000 years ago. CTA 1 was previously studied using the EGRET telescope on NASA's Compton Gamma Ray Observatory satellite, but this device was not capable of proving the existence of a pulsar.

The Large Area Telescope on the new Fermi satellite is more sensitive and can probe much higher energies than EGRET. The researchers were able to record just over 900 gamma-ray photons from CTA 1 before the Fermi telescope was even fully calibrated. They observed significant pulsations in the gamma radiation, occurring at intervals of 317 milliseconds.

The researchers calculated that the pulsar is roughly 14,000 years old, by assuming that it has been losing speed over its lifetime by emitting radiation. They also found that it has the second-highest magnetic field of known gamma-ray pulsars.

In the past, most pulsars were identified by observing pulsations in their radio-frequency emissions. However the researchers recorded no radio signal from the pulsar in CTA 1, probably because it emits a narrow beam of radio waves that is not in the line of sight of the telescope. This implies that there are many other 'gamma-ray-loud but radio-quiet' pulsars that could now be verified by recording gamma rays with the Fermi telescope.

In their paper, published in *Science,* the researchers say: "This pulsar detection implies that many of the yet-unidentified low latitude Galactic gamma-ray sources also could be pulsars." ■

1. Abdo, A.A., Ackermann, M., Atwood, W.B., Baldini, L., Ballet, J., Barbiellini, G., Baring, M.G., Bastieri, D., Baughman, B.M., Bechtol, K., *et al.* The Fermi Gamma-Ray Space Telescope discovers the pulsar in the young galactic supernova remnant CTA 1. *Science* **322,** 1218–1221 (2008).

Magnetic x-ray vision

Enhancements to an experimental technique reveal novel magnetic materials

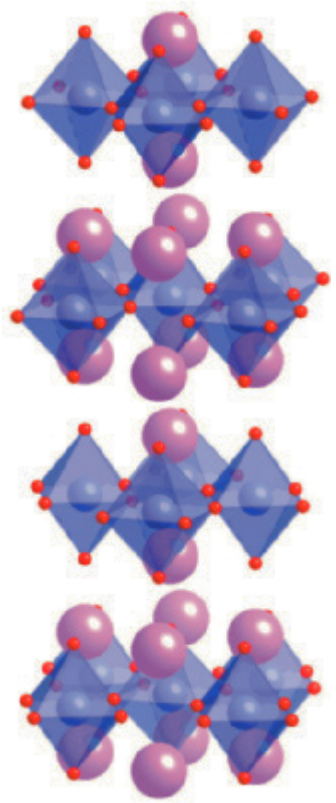


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Figure 1: The crystal structure of Sr_2IrO_4 (pink, Sr; red, O; blue, Ir).

Electrons orbiting the nucleus of an atom act like waves, rather than particles. To study these electrons, particularly the important outer electrons, researchers from the RIKEN Advanced Science Institute, Wako, in collaboration with colleagues from the SPring-8 Center, Harima, have advanced an x-ray spectroscopy technique that exploits this wave-like behavior[1]. They then found unique magnetic and electronic properties in experiments on a recently synthesized oxide of iridium, Sr_2IrO_4.

Normally, the outer electrons of atoms stop orbiting freely around the nucleus, as they are used in the chemical bonds of a material. In the so-called 5*d* heavier elements such as iridium, however, the motion of an electron and its spin are strongly coupled properties. This coupling allows the electrons to regain some of the freedom of motion lost to the chemical bonds. As a consequence, an unexpected insulating behavior had been predicted for 5*d* oxides such as Sr_2IrO_4.

In conventional neutron diffraction spectroscopy, the study of the often complex crystal structure of 5*d* oxides (Fig. 1) has been problematic. However, enhancements by the researchers to the resonant x-ray scattering (RXS) technique have enabled them to probe the complete magnetic structure of a compound using this technique alone. "In the past, RXS has only been used to enhance the x-ray signal, whereas we have now opened up a completely new opportunity," explains Hidenori Takagi who led the research team.

Using interference effects between the different x-ray beams scattered by the crystal, the researchers can obtain the precise details of the electron waves. 5*d* transition metal oxides such as Sr_2IrO_4 are particularly amenable to RXS, as their atomic resonances occur at short wavelengths and therefore produce more complete data. In their study of Sr_2IrO_4, the researchers determined its full magnetic structure and, more importantly, confirmed the full recovery of the electron's freedom and hence the predicted unique insulating state.

This insulating state interests physicists because, in combination with certain properties of the crystal structure of some 5*d* oxides, an even more unusual insulting state—a so-called topological insulator—could develop. Topological insulators are rare but important since they could be used in novel electronic applications that exploit the electron's spin properties. "Experimentally, identifying a topological insulator amongst these compounds, particularly at room temperature, would be the realization of a big dream," says Takagi. In the search for topological insulators and other unusual magnetic properties of 5*d* elements, Takagi and colleagues have established RXS as an ideal method of choice. ■

1. Kim, B. J., Ohsumi, H., Komesu, T., Sakai, S., Morita, T., Takagi, H & Arima, T. Phase-sensitive observation of a spin-orbital Mott state in Sr_2IrO_4. *Science* **323**, 1329–1332 (2009).

Green catalysis makes a splash

Efficient synthesis of 'mirror-image' molecules is now possible in water

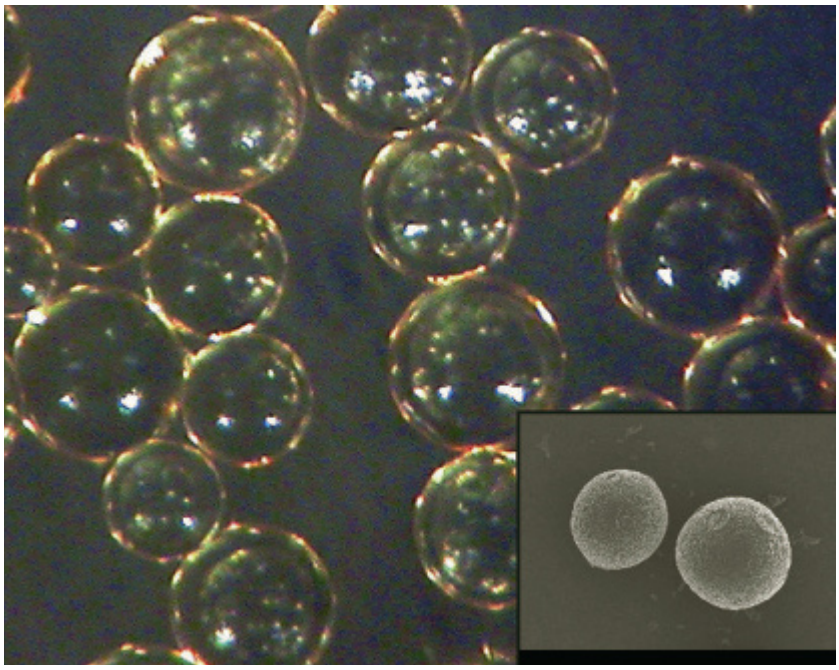


Figure 1: Optical microscopy and electron microscopy (inset) images of the polystyrene–polyethylene catalyst beads.

Replacing hazardous solvents with water and improving efficiencies are ways that chemists can reduce the environmental impact of their reactions—a central goal of the 'green chemistry' movement. Now, Yasuhiro Uozumi and colleagues from the RIKEN Advanced Science Institute in Wako have developed recyclable catalysts that selectively generate chiral organic molecules in water[1]—a nearly ideal green chemical process.

Chiral compounds are molecules that contain an asymmetric site in their structure. This asymmetry means that two enantiomers, molecules that are chemically identical but organized so that they are mirror images of each other, are found for each chiral substance. Because enantiomers can have drastically different properties—one may be therapeutic while the other is toxic, for example—it is crucial for chemists to be able to control the chirality of their reactions.

Uozumi's group specializes in the technique of asymmetric catalysis, in which a chiral metal catalyst is used to generate specific enantiomers with high yields and little waste. In their latest work, the researchers have discovered how to couple two naphthalene-based molecules into a single chiral compound by using a specially designed palladium catalyst.

The catalyst developed by Uozumi contained a large chiral molecule, named imidazoindole phosphine, which forms a complex around the palladium metal. The geometry of this catalyst allows only one enantiomer type to emerge from the coupling reaction. The researchers found that the catalyzed reaction was up to 94% selective, and could be performed with a wide range of starting materials.

"High enantiomer selectivity is seen because the imidazoindole ligands provide a rigid and effective chiral environment," says Uozumi. "And, the catalyst has high activity because of the bulky and basic phosphine substituents attached to palladium."

Next, Uozumi's team attached the palladium catalysts to very small polystyrene–polyethylene beads (Fig. 1) so that they could perform the chiral coupling in a water medium. The solid polymer supports made the catalysts easily recyclable and preserved the catalyst activity in an aqueous environment.

"The polymer support helps the catalyst become water-compatible, which is the key to driving the catalysis in water," says Uozumi. The researchers found that the catalytic coupling performed just as well in water as in a traditional organic solvent.

According to Uozumi, tightening regulatory environments make the development of sustainable chemical reactions, like his water-based catalysis, a true necessity. "Meeting 'green' and safe chemical requirements is rapidly becoming very important in the field of chemical processes," he says. ■

1. Uozumi, Y., Matsuura, Y., Arakawa, T. & Yamada, Y.M.A. Asymmetric Suzuki–Miyaura coupling in water with a chiral palladium catalyst supported on an amphiphilic resin. *Angewandte Chemie International Edition* **48**, 2708–2710 (2009).

Mastering motion

The signaling protein G-substrate modulates motor learning of the eyes during different stages of postnatal development

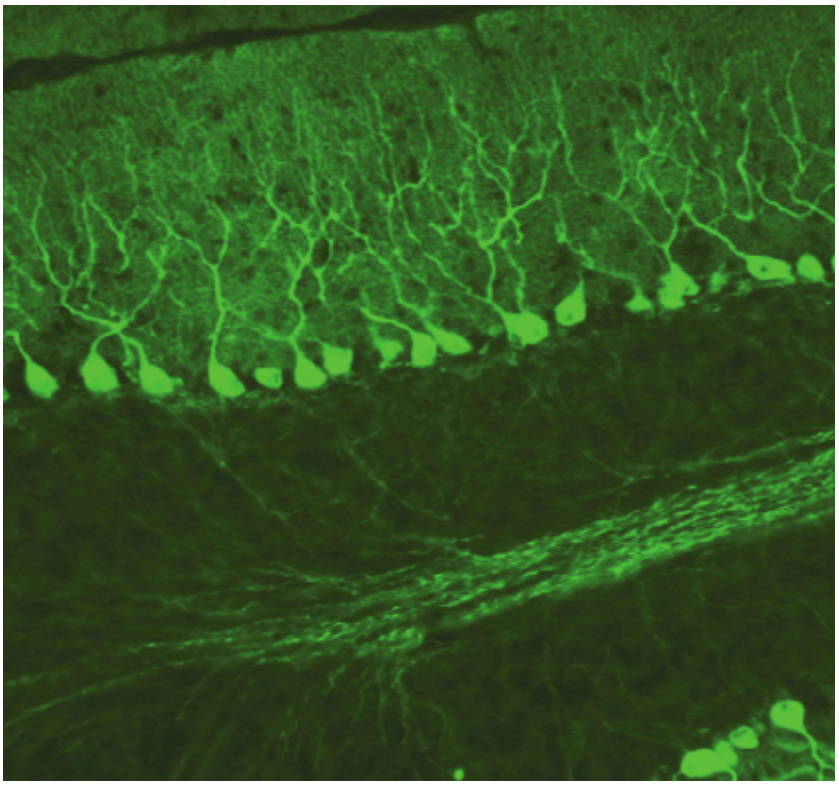


Figure 1: Picture of the cerebellum expressing a fluorescent protein in Purkinje neurons. G-substrate is expressed within these neurons, and mice lacking this protein have specific deficits in long-term motor memory.

An international team of scientists, led by Shogo Endo at the Okinawa Institute of Science and Technology and Masao Ito at the RIKEN Brain Science Institute in Wako, has shown that deletion of the G-substrate gene in mice causes motor learning deficits during particular periods of postnatal development[1]. According to Ito, this research "required ten years of collaboration between ten different laboratories."

Purkinje neurons, found in the part of the brain known as the cerebellum, contribute to regulating the learning of motor skills, such as riding a bicycle (Fig. 1). G-substrate is a signaling protein found within cerebellar Purkinje neurons. Previous work by these researchers had shown that G-substrate, when activated, inhibits enzymes called phosphatases, which remove phosphate groups from a variety of proteins in the cell. However, the functional role of G-substrate in behavior in living animals was unknown.

Endo, Ito and colleagues found that animals lacking the G-substrate gene had normal brain structure and overall locomotor behavior, but had deficits in a type of motor learning called the optokinetic eye movement response (OKR).

In the OKR test, the researchers tracked the eye movements of a mouse as it observes a checkered screen that is oscillating. After an hour of exposure to the screen, normal six-week-old mice have an increased eye movement response. However, this 'short-term OKR adaptation' was absent in six-week-old mice missing the G-substrate gene.

Surprisingly, at earlier and later developmental stages, this short-term OKR adaptation was equivalent in normal mice and in mice lacking the G-substrate gene. This specific motor learning deficit observed at six weeks of age in mice missing the G-substrate gene corresponds to the developmental stage during which these mice also had deficits in synaptic plasticity within the cerebellum. This suggests that synaptic plasticity plays a key role in regulating short-term OKR adaptation.

In twelve-week-old mice lacking the G-substrate gene, short-term adaptation was normal but there were deficits in long-term OKR adaptation. These mice were exposed to the oscillating screen for an hour per day over five days, and the eye movement responses were measured at the end of that period. In spite of this particular deficit, other types of motor learning seemed normal in the mice missing the gene for G-substrate.

These findings suggest that multiple signaling pathways are operating during development to regulate different types of motor learning. Ito says the data also "provide strong support for the hypothesis that synaptic plasticity is causally linked to motor learning." ■

1. Endo, S., Shutoh, F., Dinh, T.L., Okamoto, T., Ikeda, T., Suzuki, M., Kawahara, S., Yanagihara, D., Sato, Y., Yamada, K., *et al.*, Dual involvement of G-substrate in motor learning revealed by gene deletion. *Proceedings of the National Academy of Sciences USA* **106,** 3525–3530 (2009).

Shortening the generation of generations

Immature mice father faster medical research via an assisted reproduction technique that speeds up the production of mouse models

Japanese researchers have developed a breeding strategy to produce strains of genetically modified mice with precise genetic backgrounds in about six months. This compares to three to four years using conventional breeding strategies and is more than twice as fast as now possible with the latest 'speed' methods. The new strategy, based on existing assisted reproduction techniques, should accelerate the genetic analysis integral to biomedical research using mouse models.

After decades of experience in engineering laboratory mice, geneticists can now alter mouse genomes with the precision of a single nucleotide change, and create mice with specific genetic modifications. The biological function of genes, however, can vary depending on their genetic background, and the easiest genomes to alter often result in unexpected or irreproducible individuals. So an engineered change must typically be back-crossed into a standard inbred strain.

Using classical breeding techniques it takes 10 generations, or three to four years, to produce strains that differ by less than 1%, including the desired genetic change. This is time consuming and expensive. Recently, employing markers associated with particular groups of genes, this process has been accelerated to four to five generations or one to two years.

Geneticists then began to wonder whether the process could be accelerated further by using hormones to mature and ovulate the eggs of immature female mice to shorten the generation time. But the number of eggs able to be treated this way is limited and the response to hormones is variable.

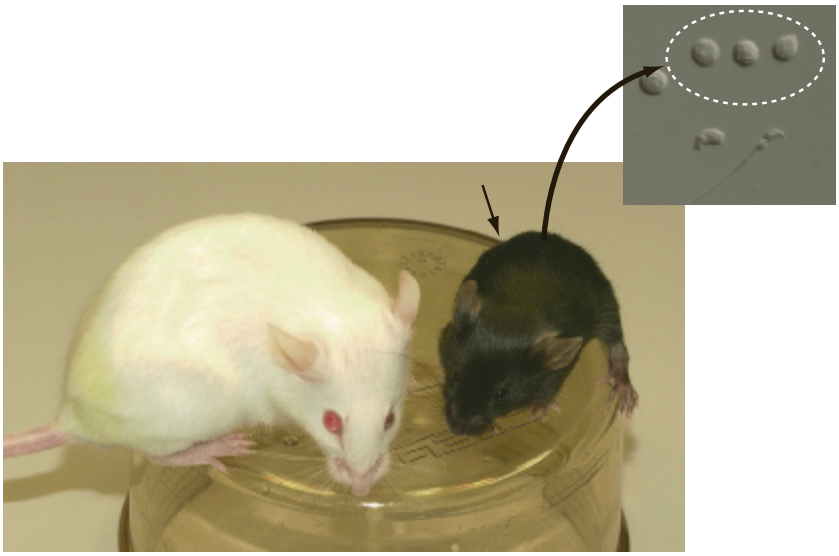


Figure 1: Germ cells (dotted circle, right) collected from a 22-day old male (black mouse) can be used in high-speed breeding of genetically engineered mouse models.

So Atsuo Ogura and colleagues from the RIKEN BioResource Center and the universities of Tokyo and Tsukuba tried the reverse. In a recent paper published in the journal *PLoS ONE*[1], they detail how they used a technique known as round spermatid injection (ROSI) to extract the first wave of round spermatids—the earliest stage of maturing spermatozoa—from immature male mice and inject them into the eggs of mature females producing healthy offspring (Fig. 1).

The optimum age of male mice used was 22 days old, shortening the generation time to about 40 days, and the establishment of genetically specific strains to less than 200 days. They have applied their technique to generate separate strains of genetically modified mice: transgenic mice; 'knock-in' mice with a DNA sequence added; and mutant mice that were produced using the chemical N-ethyl-N-nitrosourea. "Our next goal is to make the technique easier," Ogura says, "in the hope that it will become more popular." ■

1. Ogonuki, N., Inoue, K., Hirose, M., Miura, I., Mochida, K., Sato, T., Mise, N., Mekada, K., Yoshiki, A., Abe, K., Kurihara, H., Wakana, S. & Ogura, A. A high-speed congenic strategy using first-wave male germ cells. *PLoS ONE* **4 (3),** e4943 (2009).

Fungal recognition

Mincle, a protein expressed on immune cells, is a receptor that recognizes Malassezia fungal species and mediates inflammatory responses

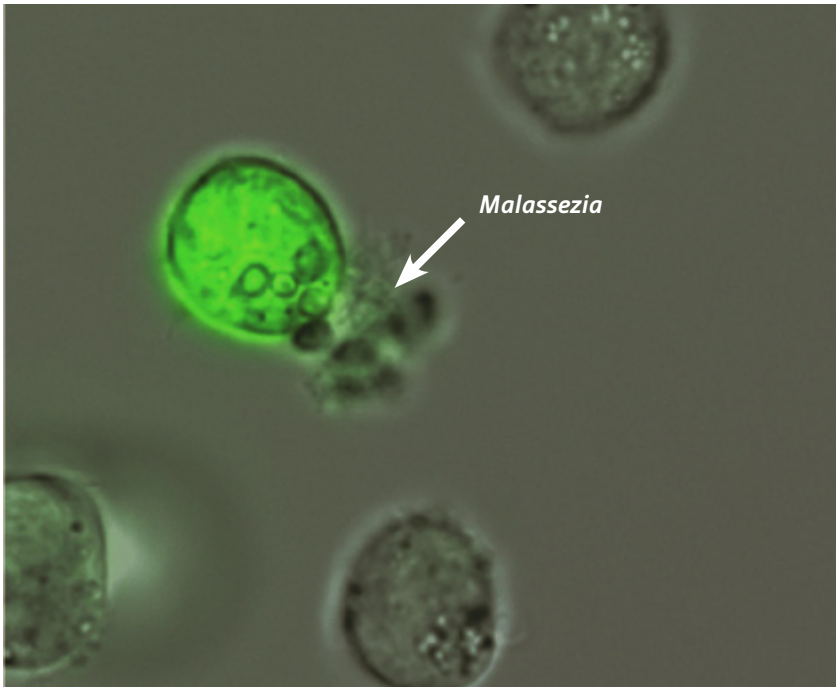


Figure 1: Activation of Mincle signaling causes a specially engineered reporter cell to fluoresce green when it binds to *Malassezia* fungal species (arrow).

Malassezia fungi live on human skin. These organisms have been linked to some human skin diseases—including atopic dermatitis, which is a type of eczema induced by allergies—and to a deadly infection if they invade the bodies of premature infants. Discovering how the immune system senses and reacts to these fungal species could pave the way for the development of new treatments for the diseases caused by these organisms.

Now, a team of researchers, led by Takashi Saito at the RIKEN Research Center for Allergy and Immunology in Yokohama, has found that an immune cell protein called Mincle binds to and recognizes *Malassezia* species, and controls the body's inflammatory reaction against these fungi[1].

The researchers began looking at Mincle because its gene is located on the mouse and human chromosome near other fungal receptor genes, and because the Mincle protein has some structural characteristics that are also found within these other fungal receptor proteins. Expressing Mincle protein on cells that were engineered to fluoresce green when Mincle signaling was activated, Saito and colleagues found that all nine of the *Malassezia* species they tested—but not 42 other fungal species—are able to activate Mincle signaling (Fig. 1).

The Mincle protein seems to recognize a carbohydrate on the fungi, because Mincle mutations that alter its carbohydrate-binding domain block Mincle signaling when the *Malassezia* fungi are present. "We have previously found that Mincle recognizes dead cells upon tissue damage and induces inflammatory responses, but this type of recognition was not mediated by carbohydrate binding," says Saito. "Mincle thus alerts the body to different types of danger—danger originating from inside or outside the body—using differing mechanisms."

Immune cells increase their expression of Mincle protein and secreted inflammatory proteins called cytokines when treated with *Malassezia* fungi, suggesting that Mincle is required for driving immune responses to these organisms. Indeed, immune cells lacking the Mincle gene were not able to efficiently increase inflammatory responses when exposed to the fungi. When one species of *Malassezia* was injected into mice, normal mice produced inflammatory cytokines, and had marked immune cell infiltration. These responses were blunted in mice lacking the Mincle gene.

These findings suggest that drugs that target Mincle signaling could treat diseases caused by *Malassezia* fungal infections on the skin or within the body. "In future work," says Saito, "we plan to analyze if there is also a link between the Mincle protein and autoimmune disorders in humans." ■

1. Yamasaki, S., Matsumoto, M., Takeuchi, O., Matsuzawa, T., Ishikawa, E., Sakuma, M., Tateno, H., Uno, J., Hirabayashi, J., Mikami, Y., Takeda, K., Akira, S. & Saito, T. C-type lectin Mincle is an activating receptor for pathogenic fungus, *Malassezia*. *Proceedings of the National Academy of Sciences USA* **106**, 1897–1902 (2009).

Plotting a career change

Cells normally responsible for keeping the immune response in check can transform into stimulators of immune activity if placed in the proper environment

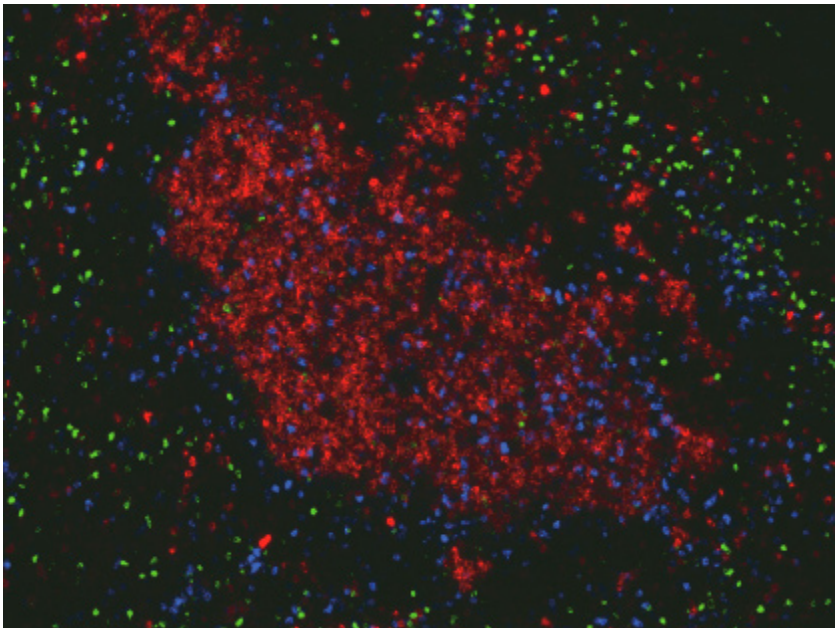


Figure 1: An image of a germinal center in a Peyer's patch, showing fluorescently tagged cells Foxp3$^+$ T cells (green), TFH cells derived from Foxp3$^+$ T cells (blue), and activated B cells (red) capable of producing IgA.

Many animals benefit from the presence and support of a diverse community of microorganisms within their gut. However, it is also important that these bacteria be kept in their place, and prevented from invading the intestinal lining and thereby causing harm to their host.

Research by Sidonia Fagarasan and colleagues at the RIKEN Research Center for Allergy and Immunology (RCAI) in Yokohama has revealed that maintenance of this ecosystem depends on production of immunoglobulin A (IgA) within clumps of immune cells known as Peyer's patches. IgA is generated specifically by B cells within sites known as germinal centers (GCs), a process that also requires participation of specialized T cells known as T_{FH} cells. However, the nature and origin of these T_{FH} cells has remained enigmatic. Fagarasan says that she and her team realized that very little is actually known about the T cells that are involved in this process.

Fortunately, an ongoing collaboration between her laboratory and that of RCAI colleague Shohei Hori has proven fruitful in illuminating this mystery[1]. Since T cell-deficient mice fail to develop functional GCs, the researchers began by investigating whether transplantation of different T cell types restores their formation. Hori's group is particularly interested in regulatory T cells (T_{reg}), which inhibit the immune system to prevent it from 'overreacting' or triggering an autoimmune response. Hori's team has demonstrated that these cells are characterized by strong expression of the *Foxp3* gene, which encodes a protein essential to their development and function, but also found that some Treg cells show greatly reduced Foxp3 expression and capacity for immune suppression when introduced into T cell-deficient mice. When Hori and Fagarasan examined the Peyer's patches of these mice, they found—surprisingly—that many of these cells had adopted the characteristics of T_{FH} cells.

Most importantly, transplantation of these cells was sufficient to drive proper GC formation and activation of IgA-producing B cells (Fig. 1). "It was most surprising to us that these T cells, considered 'professional suppressor cells', were the most efficient helpers of immune responses in the gut," says Hori. "Our findings thus require immunologists to reconsider the concept of T_{reg} cells."

This unexpected capacity for immune cell adaptation raises many questions, and Hori and Fagarasan are looking to dissect the mechanism underlying this T_{reg}-to-T_{FH} transition. "The final goal is to understand how the immune system converts and adapts its cells to be able to maintain the homeostasis—especially the delicate balance of the intestine," says Fagarasan. ■

1. Tsuji, M., Komatsu, N., Kawamoto, S., Suzuki, K., Kanagawa, O., Honjo, T., Hori, S. & Fagarasan, S. Preferential generation of follicular B helper T cells from Foxp3$^+$ T cells in gut Peyer's patches. *Science* **323**, 1488–1492 (2009).

Many ways to grow

Environmental conditions may determine which particular process plants will use to build an essential hormone

Figure 1: Effects of disrupting the CYP79B pathway. In comparison to normal *Arabidopsis* plants (left), plants with a disrupted CYP79B pathway show reduced growth at higher temperatures (middle). However, treating mutant plants with indole-3-acetamide (IAM), an intermediate between IAOx and IAA, restores normal growth (right).

For the better part of a century, scientists have recognized indole-3-acetic acid (IAA), one of several hormones known as auxins, as one of the most important drivers of plant growth and development. However, it remains unclear exactly how IAA is synthesized. Previous research has identified at least four different enzymatic 'assembly lines' that may be involved in its production, and each of these pathways generates chemical compounds that are potential precursors to IAA, as well as a number of other biologically important molecules involved in protecting plants against predators and pathogens.

In the thale cress plant, *Arabidopsis thaliana,* indole-3-actaldoxime (IAOx) is thought to represent a likely intermediate compound in IAA production via two of these candidate pathways, CYP79B and YUC. In order to clarify which of these contribute primarily to production of IAOx and IAA, Hiroyuki Kasahara of the RIKEN Plant Science Center in Yokohama and colleagues generated several mutant *Arabidopsis* strains in which key enzymes in either pathway had been ablated.

From the data, the team consistently identified an exclusive role for the CYP79B pathway in IAOx production and—by extension—IAA synthesis, and demonstrated no effect on levels of either compound resulting from interference with YUC-associated enzymes[1]. They also identified two compounds, indole-3-acetamide and indole-3-acetonitrile, as likely intermediates in the conversion of IAOx to IAA (Fig. 1). Many plant species, including tobacco and rice, lack the CYP79B pathway altogether and do not produce detectable IAOx. However, these plants do produce these other IAA intermediates, suggesting the existence of yet-unidentified, parallel biosynthetic pathways in these species.

These findings indicate the need for a considerable reorganization of existing models of plant hormone synthesis. "Before this research, three proposed pathways were thought to converge at IAOx or its metabolites," says Kasahara. "We have clearly separated these pathways." Interestingly, their data also revealed that even in *Arabidopsis,* CYP79B does not represent the primary pathway of IAA production; instead, it is simply one of several that appear to contribute under different, specific conditions—in this case, cultivation at higher than room temperature.

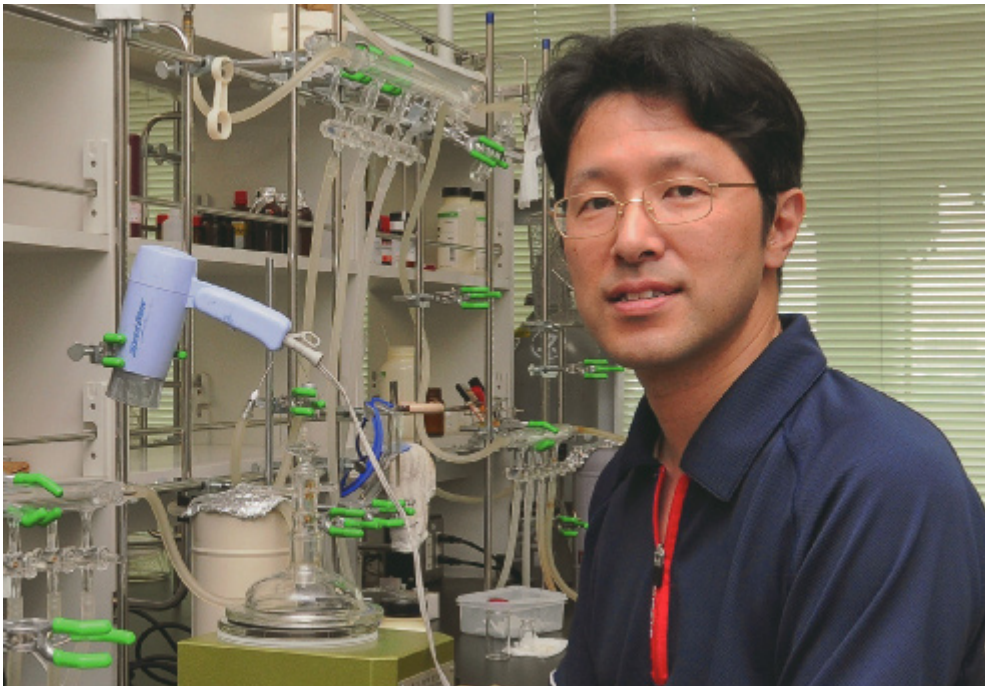
Other non-IAOx biosynthetic pathways appear to be common to most plant species and Kasahara and colleagues now hope to clarify their independent contributions to overall IAA production. "We do not know why plants have so many biosynthetic pathways for IAA," he says. "Here we showed that the IAOx pathway contributes to IAA generation under high temperature conditions, and now we are studying the physiological roles of other IAA biosynthetic pathways." ■

1. Sugawara, S., Hishiyama, S., Jikumaru, Y., Hanada, A., Nishimura, T., Koshiba, T., Zhao, Y., Kamiya, Y. & Kasahara, H. Biochemical analyses of indole-3-acetaldoxime-dependent auxin biosynthesis in *Arabidopsis*. *Proceedings of the National Academy of Sciences USA* **106,** 5430–5435 (2009).

Using 'pinpoint' catalysts to innovate chemical synthesis

Kei Manabe

Initiative Research Scientist
Manabe Initiative Research Unit
RIKEN Advanced Science Institute



Our life is supported by a multitude of chemical substances, including medicines, detergents, chemical fibers and plastics. However, these many useful chemical substances require many synthetic processes, and the larger the number of synthetic processes, the higher the energy consumption and the greater the generation of waste. Furthermore, many potentially useful chemical substances may not be synthesized because of the time and expense required to complete the large number of processes.

Kei Manabe, Initiative Research Scientist, has developed an innovative 'pinpoint' catalyst, which can drastically reduce the number of synthetic processes required for the production of chemical substances, bringing innovation to chemical synthesis.

Aiming at an 'engine of creation'

"When I was a college student, I did not think that chemical synthesis was an attractive subject," says Manabe, looking back on his college days. "A synthetic process for a complex chemical substance requires as many as dozens of synthetic processes because it starts with a simple, easily available compound, which is gradually transformed through many synthetic processes into the target substance. I wondered why the process required so many processes, and what method would allow us to synthesize a complex compound more flexibly."

It was when he was a graduate student that he happened to read *Engines of Creation: The Coming Era of Nanotechnology*, in which K. E. Drexler, the author, described a future world of nanotechnology as early as the 1980s. In this book, Manabe was greatly impressed by an imaginary machine called an 'assembler' that could connect a molecule to any specific site of another molecule. Experts in this field would have found what was written in this book difficult to understand, and the book itself to be only a work of science fiction. However, it made Manabe think of carrying out the research needed to build engines of creation like that assembler.

Using 'pinpoint' catalysts to drastically shorten the time required for synthetic processes

Why do conventional methods require so many synthetic processes? When we try to attach an object molecule to a target molecule at a particular molecular site, the object molecule tends to bind

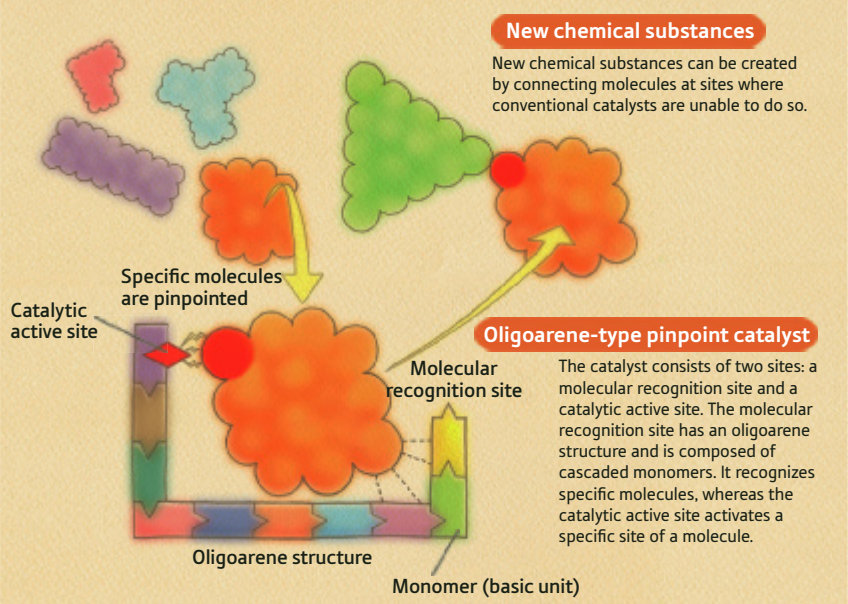


Figure 1: 'Pinpoint' catalysts reduce the number of processes required in chemicial synthesis. By designing a catalyst that specifically targets a certain site on a target molecule, the number of processes required for the synthesis of many chemical compounds can be reduced.

to the target molecule at the site where the target reacts most readily with other molecules—its reactive site.

A typical method of connecting an object molecule to a target molecule at a specific site requires multiple synthetic processes. It starts with a process to attach a molecule to the target's reactive site in order to prevent that site from binding in subsequent steps. The target molecule is then processed such that the intended site on the target can react readily with other molecules. Finally, the site is activated by a catalyst to bind to the object and target molecules.

The greater the number of synthetic processes used, the longer the synthesis takes, the more energy is consumed and the more waste materials are produced. Many approaches have therefore been taken to reduce the number of synthetic processes and waste materials. "Various chemical reactions and techniques have been developed. Combining these accumulated methods has allowed chemists to gradually reduce the number of synthetic processes used. There are still, however, too many synthetic processes."

To reduce the number of synthetic processes, Manabe came up with the concept of a completely new type of catalyst. He called this a 'pinpoint' catalyst: it is able to activate the target molecule exactly at its intended site and force an object molecule to bind to the target at the site in much the same way as the assembler in *Engines of Creation*.

"Conventional catalysts can also activate molecules. However, they only activate the site that can react readily with other molecules because they cannot activate the intended site of a target molecule. The pinpoint catalyst requires two factors: a structure that allows the catalyst to discriminate a target molecule and to move towards the intended site of the target, and a strong catalyst that activates the intended site of the target molecule."

With current techniques it is difficult to design a structure that can discriminate a target molecule. "The best method is to form structures of various shapes, and to select from them some special structures that can exactly discriminate the target molecule."

To form these kinds of structures, we can consider the enzymes in our bodies. Enzymes are proteins that serve as catalysts, and they are sensitive enough to act on specific molecules from among the many molecules within an organism.

Proteins are a folded chain of amino acids linked together. There are 20 amino acids that constitute proteins, linked in various orders and in different lengths on the basis of genetic information, which results in many protein structures. Some of these proteins serve as catalysts with exquisite specificity for their target molecules.

Why, then, should we not use our knowledge of genetic engineering to develop enzymes that can be used as

pinpoint catalysts? "There are only a limited number of chemical reactions in which enzymes serve as catalysts," explains Manabe.

"In addition, their catalytic power is not strong, and enzymes are inactivated at high temperatures because they are proteins. We have only a limited number of practical enzyme-based chemical reactions. I am therefore planning to create a catalyst that can be used for a number of chemical reactions."

Structure formation with oligoarenes

Manabe came up with the idea of using a molecular unit called an 'oligoarene' as the structure. Just as a protein is a chain of amino acids, an oligoarene is a chain of benzene ring units (monomers). "We thought the oligoarene would be the best molecule from the following viewpoints: (1) it is stable and resistant to various chemical reactions, (2) it can be designed into various stable shapes, (3) its monomers are easily connected, and (4) various kinds of monomer are available."

The oligoarene-type pinpoint catalysts currently under development consist of an oligoarene structure and two characteristic sites: a molecular recognition site that pinpoints a specific molecule, and a catalytic active site that activates a specific site of a molecule (Fig. 1).

In 2005 Manabe started a research unit at RIKEN called the Manabe Initiative Research Unit, which is one of RIKEN's fixed-term five-year projects that provide young, excellent researchers with independent research opportunities. Manabe dared to take the fixed-term post, sacrificing his tenured associate professorship at the University of Tokyo.

"It seemed reckless," said Manabe with a laugh. "I thought this was the right time for me to take the post because I was already 40 years old and I knew that I did not have enough time to spend on studying." At the interview with RIKEN, he relied only on the idea of the pinpoint catalyst because he had previously had no chance to conduct research on it. Some selection committee members wondered about the idea because he had no experimental data.

Developing catalysts that can drive new reactions

To begin with, Manabe tried to develop a method for connecting the monomers that constitute the basic unit of an oligoarene-type pinpoint catalyst (Fig. 2). "Various kinds of catalyst can be created by combining different monomers with different shapes. However, there were no known methods that could effectively connect the monomers and easily produce various kinds of catalyst. So we focused on developing a new method, and successfully created several oligoarene-type pinpoint catalysts."

Among these materials, Manabe fortunately found a special catalyst that connected molecules at a specific site where conventional catalysts could not (Fig. 3). "The catalyst has a simple structure, but it caused a special chemical reaction that had not been possible with conventional catalysts. I believe that if we continue to advance our own research, we will be able to find more useful oligoarene-type pinpoint catalysts."

Expectations for drug discovery

When asked, "Who are your rival researchers?" Manabe replied, "I don't know of any."

There is no other research in the world that is based on pinpoint catalysts. What innovation can this unique research bring to the world of chemical synthesis?

Manabe says he will be happy if his pinpoint catalyst is used to develop new drugs, because he graduated from a Faculty of Pharmaceutical Sciences. "Development of medicinal products starts with creating many candidate agents, from which only the effective ones are selected as drugs and medicines. In this process, however, chemical scientists focus on chemical substances that can be easily manufactured, or that require fewer synthetic processes. They avoid manufacturing chemical substances that require many synthetic processes due to the immense amount of time and money involved. However, chemical

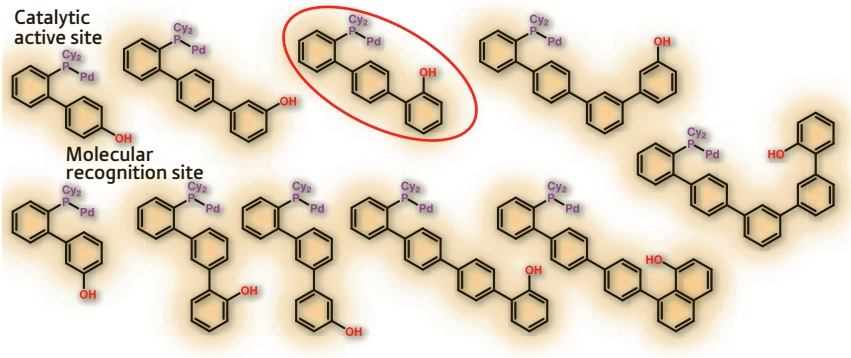


Figure 2: Oligoarene-type pinpoint catalysts.
Various oligoarene-type pinpoint catalysts have been developed. One of the catalysts (circled) enables the new chemical reaction illustrated in Fig. 3.

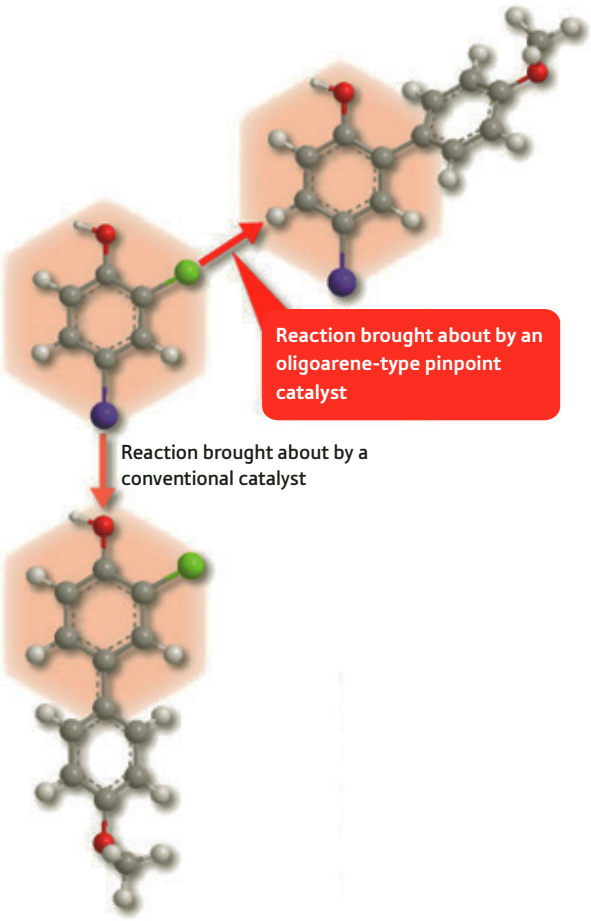


Figure 3: A new reaction brought about by an oligoarene-type pinpoint catalyst. Conventional catalysts are used to connect an object molecule to a target molecule at the most reactive site (purple). The newly developed oligoarene-type pinpoint catalyst enables the target molecule to bind to the object molecule at a specific site (green) that cannot be accessed usign conventional catalysts.

substances requiring many synthetic processes may include effective drugs and medicines. If these can be easily manufactured using pinpoint catalysts, chemical scientists will surely be able to find unconventionally effective drugs and medicines among them."

It goes without saying that the application of pinpoint catalysts is not limited to the development of drugs and medicines. They will also bring about substantial innovation in the methods used for developing any chemical substance.

Study giving great encouragement

One of the important targets in developing oligoarene-type pinpoint catalysts is how to increase variations in its oligoarene structure. If Manabe succeeds in finding a method of connecting the monomers more effectively, he will be able to increase the variations further in about five years.

Another major target is to enhance the activation capability of oligoarene-type pinpoint catalysts. "Even though the structure of the catalysts recognizes a target molecule and pinpoints the specific site of the molecule that reacts with an object molecule, the target molecule sometimes fails to bind to the object molecule because of the weak activation capability of the catalyst." He has so far targeted the same active site for his new catalysts as for conventional catalysts. In the future, Manabe intends to incorporate a new catalyst, recently developed by another research group, with strong activation capability. The structure of the oligoarene has the ability to incorporate various catalysts and make them function as required. "We also plan to develop new catalysts with strong activation capability. However, it takes a lot of time to develop these sorts of active catalyst."

The Manabe Initiative Research Unit held its interim appraisal and research achievement report meeting in July 2008, halfway through its fixed-term five-year project.

"Our research received a high evaluation from the selection committee members. I was very happy when some young researchers at RIKEN said, 'We are very encouraged by your research activities.'" Many young researchers are in an environment where they are asked to achieve good results in a short time. However, Manabe's research into pinpoint catalysts received a high evaluation even though research of this kind should be evaluated from a medium- to long-term viewpoint, not from a short-term perspective. This fact may have encouraged the young researchers. "I was also encouraged by young researchers who, in expressing their interest in our research activities, embrace their dreams for the future of chemical synthesis."

The Manabe Initiative Research Unit will end in 2010, but Manabe is determined to continue the research and development into pinpoint catalysts as his life's work. ■

About the researcher

Kei Manabe was born in Kanagawa, Japan, in 1965. He completed his doctoral studies at the University of Tokyo in 1993, and after working as a postdoctoral fellow at Columbia University, New York, US, he returned to the University of Tokyo as Assistant Professor, and later as Lecturer and Associate Professor. He joined RIKEN in 2005 as Initiative Research Scientist, and also now holds the position of Professor at the School of Pharmaceutical Sciences, University of Shizuoka.

Second A*STAR–RIKEN Joint Symposium held in Singapore

The RIKEN Advanced Science Institute (ASI), together with the Science and Engineering Research Council (SERC) of the Agency for Science, Technology and Research (A*STAR), Singapore, organized the 2nd A*STAR–RIKEN Joint Symposium at the Biopolis international research and development center on May 18 and 19, 2009. A total of around 200 people, including 24 members of RIKEN, attended the event, which showcased cutting-edge research and technology in chemical and materials science.

The two-day symposium was divided into four sessions. The sessions on the first day covered the topics of Physical Materials and Devices, and Photonics and Nano-Optics; and those on the second day covered the topics of Synthesis and Catalysis, and Biomaterials and Devices. In all, 21 speakers (11 from RIKEN, 10 from A*STAR) gave presentations at the symposium, each followed by active question-and-answer periods. Poster presentations by young and mid-career researchers (7 from RIKEN, 20 from A*STAR) also triggered lively discussions.

The symposium also provided an opportunity for Executive Director Yoshiharu Doi and other top management at RIKEN ASI to meet with Chairman Lim Chuan Poh and other members of A*STAR to discuss future cooperation. The two institutions came to an agreement on plans to establish a program for providing financial support to outstanding joint collaboration projects between the ASI and SERC.

Following the joint A*STAR–RIKEN symposium, a seminar jointly organized by RIKEN, Nanyang Technological University (NTU) and the National University of Singapore (NUS) was held on May 20 at NTU at the behest of the two universities. Thirteen speakers (7 from RIKEN, 3 each from NTU/NUS) gave oral presentations, and 34 researchers (4 from RIKEN, 30 from NTU/NUS) gave poster presentations, addressing the topic of the 'Frontier of Chemical and Material Sciences'.

By strengthening ties between the RIKEN ASI and top-level research institutions in Singapore, the A*STAR–RIKEN symposium and RIKEN–NTU–NUS seminar provided valuable opportunities for attendees, in particular young scientists, to exchange ideas for future collaboration. In so doing, the meetings have laid the groundwork for important new discoveries to come in chemical and material science. ■

RIKEN and Keio University hold kickoff symposium to launch Research Center for Human Cognition

RIKEN and Keio University signed a comprehensive agreement in December 2008 with a long-term view to the future, aiming toward the creation of 'intelligence to lead the world'. The agreement sets the groundwork for interdisciplinary collaboration between the organizations across diverse areas of research and study through the shared development of human resources and coordination between administrative departments.

As an important element of this partnership, Keio University have formed a new Research Center for Human Cognition, officially launched at a kickoff symposium held on May 23, 2009. The new center, one of the Keio Advanced Research Centers (KARCs), will act as a space for joint collaboration among researchers attempting to understand the intelligence that makes us human. Drawing on wide-ranging perspectives from science and the humanities, this research will strive toward the creation of knowledge that is useful in solving the diverse problems humans face in today's complex world.

One of the speakers at the symposium was Atsushi Iriki, head of the Laboratory for Symbolic Cognitive Development at the RIKEN Brain Science Institute. Iriki reflected on the link between the physical growth of the human brain and the development of high-level human cognition. At the basis of all other intellectual functions carried out by the brain, Iriki described the neural mechanisms for language and concept formation as the most highly developed of all human faculties.

Another speaker at the symposium was Hideaki Kawabata of Keio University's Department of Letters, who discussed the possibilities of Neuroaesthetics, a field that attempts to reveal the relationships between art and the brain. Professor Kawabata described research findings on the functional role of frontal cortex rewards in aesthetic evaluation, and presented his thoughts on future prospects for the field.

The symposium also featured a special talk by Toru Shimizu from the University of Florida's Department of Psychology, who spoke about the application of comparative neuroanatomy to understanding the evolution of human intelligence. In total, six researchers presented at the event, which was followed by a spirited debate on the future path of research in human intelligence. ■

Atsushi Iriki, head of the Laboratory for Symbolic Cognitive Development at the RIKEN Brain Science Institute

Detecting H1N1 faster than ever using Omics SmartAmp technology

With the number of novel influenza A (H1N1) cases increasing in countries around the world, the rapid spread of the virus has triggered worldwide alarm. There is a pressing need at medical institutions for methods to detect whether individuals are infected with the virus in order to effectively slow its spread. As a part of emergency government research aimed at addressing this need, the RIKEN Omics Science Center (OSC), in cooperation with the Institute of Medical Science at the University of Tokyo, is developing an H1N1 detection technique based on its SmartAmp technology.

The SmartAmp (Smart Amplification Process) reduces the time required for single nucleotide polymorphism (SNP) analysis to just half an hour, and the precise results thus produced allow genetic diagnosis to be carried out immediately upon initial consultation. Using this technology, OSC has developed methods for detecting the regular seasonal influenza A virus, the H3N2 virus, and the susceptibility of these viruses to Tamiflu treatment. Most laboratories continue to use the RT-PCR system, which for H1N1 necessitates reverse transcription in order to convert RNA into DNA (H1N1 is an RNA virus). The SmartAmp approach carries out this step in parallel with DNA amplification. The time and effort required for the new technique is thus roughly the same as in the conventional SmartAmp process.

OSC researchers are currently applying SmartAmp for diagnosis of the H1N1 virus, as well as developing reagents for virus detection and optimizing the conditions for the reagents. Once optimization is complete, tests will be performed on actual samples from patients at the Osaka Prefectural Institute of Public Health. In cooperation with the Infectious Disease Surveillance Center and the International Medical Center of Japan, the goal is to deploy the technique to clinics within the next six months. ■

Dr Kathleen Rockland
Laboratory Head
Cortical Organization and Systematics
RIKEN Brain Science Institute
Wako, Saitama, Japan

Dear Kathy,

It's been only a few months since my return to Italy, and I still have a very fresh impression of the year I spent in your lab. I think I'll never forget that very important experience. In your laboratory, I found a comfortable, stimulating, professional environment where I could grow as a scientist and as a person.

I came to your laboratory to learn more about the visual areas of the cerebral cortex and the cortical microcircuitry, topics in which you and your collaborators are authorities. At the end, my learning, however, was not limited to visual areas but extended to many other aspects of neurosciences.

I spent many weeks at the microscope collecting observations by 'old style' but reliable neuroscientific methods, and I also had the opportunity to use and learn new powerful methods. The observations and data we collected always gained additional depth and interest through discussions with you, and with Dr Noritaka Ichinohe and Dr Manabu Tanifuji.

I really enjoyed also the great variety of seminars, lectures and journal club presentations offered at the RIKEN Brain Science Institute. For me, as I was a senior PhD student at the time, it was a great opportunity to learn more about various topics from top-level scientists from almost all fields of neuroscience. I had the opportunity to have discussions with people from all over the world, including well-known scientists, young researchers and other PhD students.

Furthermore, before going to Japan I was very curious about the Japanese culture, but also a bit worried about the difficulties that I would have to face, with the language for instance. The reality was different: I didn't have any great difficulty because in RIKEN many people help foreigners to overcome almost any kind of problem.

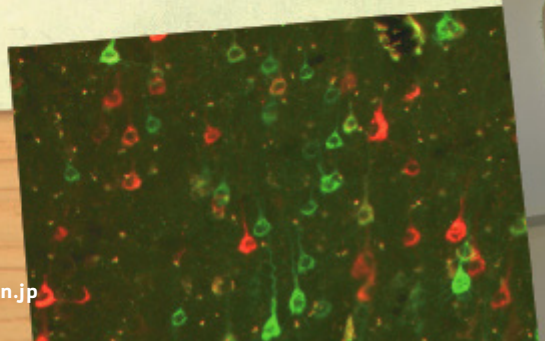
In my leisure time, I enjoyed exploring various aspects of the Japanese culture, like martial arts, theater and cuisine. I was pleased to know that RIKEN itself, through 'RIKEN clubs', is promoting the Japanese culture. A real must for foreigners! Japanese people have a great culture.

Now, we are writing the papers from the results of the work we did together, and I'm looking forward to delivering these papers. I'm also looking forward to future work together.

I want to thank you for your consideration and help, and to thank all the people at the Cortical Organization and Systematics laboratory for the very friendly atmosphere. My experience at RIKEN is now a source of inspiration for my work and professional life.

With my best regards,

Elena Borra
Dipartimento di Neuroscienze
Università di Parma
Parma, Italy



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