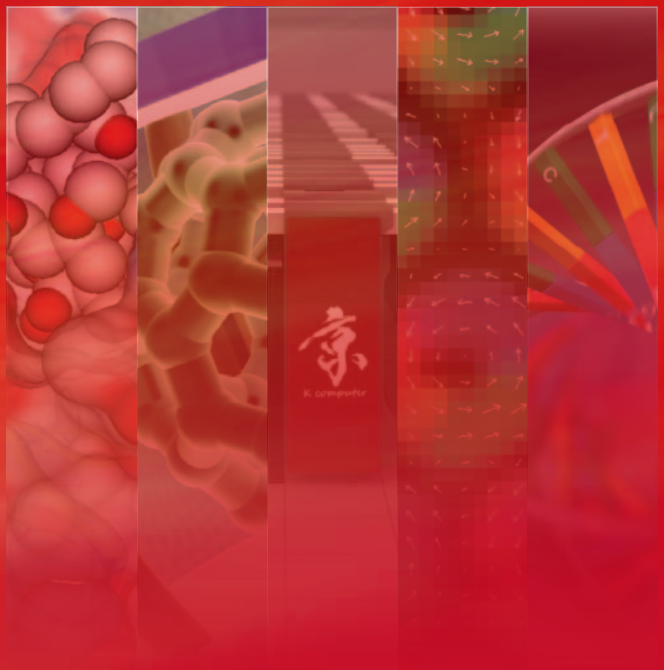
RIKEN
ANNUAL REPORT
2011-2012
Science Serving Society



RIKEN ANNUAL REPORT 2011-2012

Science Serving Society

Message from the President

It is over a year now since the tragedy of the Great East Japan Earthquake of 11 March 2011, but there is still much work to be done in the disaster-hit areas. Japan must not only recover from the calamity, but move forward to new heights of development.

Even as Japan undertakes its own reconstruction, the whole of humanity is confronted by increasingly complicated issues, and the science and technology community needs to change if it is to help resolve these issues. With the rapid globalization that is taking place today, no nation can stand alone. We must tackle global-scale problems—the population explosion, climate change, the depletion of natural resources, and the emergence and re-emergence of infectious diseases—that threaten the very existence of humanity. Nations, societies, and all sectors of human endeavor must join together to find creative solutions of high public value. It is not enough that we sustain contemporary civilization; we must forge the way to an affluent future society for our descendants.

Our values are changing. We are moving away from science purely for the sake of knowledge to science in society and for society. Science has already made major contributions to solving many problems confronting society. This Annual Report offers a view of RIKEN's endeavors to help build a shining future for humanity. RIKEN's objective is not only to push forward the frontiers of science, but also to become an essential and contributing member of society. We will never cease in our self-scrutiny and efforts to improve. I ask for your support as we move forward in the company of researchers sharing the same high ideals.

NOYORI Ryoji (DEng)
President, RIKEN

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

RIKEN Global Relations Office
2-1 Hirosawa, Wako, Saitama 351-0198, Japan
TEL: +81-48-462-1225
FAX: +81-48-463-3687
gro-pr@riken.jp

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Taking the lead

The 2011–2012 fiscal year was one of many firsts for RIKEN—the first lasing of the new SACLA X-ray free electron laser, the K computer taking first place in the global supercomputer rankings, and the opening of a string of new collaborative centers and agreements around the world.

Major achievements in science and technology

Defining the 2011–2012 fiscal period was the unveiling of two new major research facilities—the SACLA X-ray free electron laser (XFEL) located next to the SPring-8 synchrotron radiation facility in Harima, and the K computer in Kobe. The SPring-8 Angstrom Compact Free Electron Laser (SACLA) is the first of its kind in Japan and the most advanced example of XFEL technology in the world. A joint National Critical Technology project of the Japanese government developed by RIKEN and the Japan Synchrotron Radiation Research Institute (JASRI), SACLA generates a coherent X-ray laser beam over one billion times brighter than the synchrotron radiation from SPring-8 and with pulse lengths thousands of times shorter, allowing researchers to observe moving individual atoms and molecules directly for the first time.

In June 2011, SACLA produced its first X-ray laser beam, achieving a laser wavelength of 1.2 angstroms or 0.12 nanometers, matching the wavelength produced by the only other operational XFEL facility in the world, the Linac Coherent Light Source (LCLS) in the United States. This remarkable light source makes it possible to observe what was previously unobservable, such as the structures of uncrystallized proteins, the ultrafast movement of electrons and atoms during chemical reactions, or even the atomic and molecular mechanisms in living cells.

The RIBA (Robot for Interactive Body Assistance) II, unveiled in September 2011

The K computer in Kobe is another project of strategic national importance, developed by RIKEN and Fujistu with the support of the Japanese government. When it becomes fully operational in mid-2012, the world's newest supercomputer will have computational power of 10 petaflops, or 10^{16} operations per second. In June 2011, with only three-quarters of its processing nodes installed, the K computer surprised the international community by easily taking the number one position in the TOP500 global supercomputer rankings. In the next round of rankings in November 2011, the K computer cemented its leading position with 10.51 petaflops performance in its full configuration and secured four top accolades at the High Performance Computing Challenge Class 1 Awards. This new supercomputing resource will provide researchers with unprecedented computing power, opening up opportunities for simulations at scales and complexities never before attempted. The K computer will be used for research in many areas, including life sciences, medicine and drug discovery, materials and energy, climate and natural disasters, industrial innovation and the origin of matter and the universe.

The second version of the patient care support robot RIBA-II was also unveiled in September 2011 by researchers from the RIKEN–TRI Collaboration Center for Human-Interactive Robot Research—a joint project undertaken in partnership with Tokai Rubber Industries (TRI). The new robot expands the abilities of the original Robot for Interactive Body Assistance (RIBA) developed in 2009, and can now lift heavier loads of up to 80 kg and crouch to lift from floor level. RIBA-II is also fitted with new travel guidance controls and all-rubber capacitance tactile sensors—the first of their kind. The robot is currently being trialed in nursing care facilities to further tailor the robot's abilities to the needs of care-givers and patients.

Regional outreach

In the 2011–2012 fiscal year, RIKEN president, Ryoji Noyori, made a number of visits to collaborating institutes in Asia as part of RIKEN's commitment to expanding its regional ties. President Noyori presented lectures at the opening of the RIKEN–XJTU Joint Research Center in China in February 2012, and also at an event commemorating the opening of the RIKEN Beijing Representative Office in June 2011. The president's visits—which also took in Malaysia and Singapore in September 2011, coinciding with the opening of the RIKEN–USM Joint Laboratory for Bioprobe Discovery at USM—reaffirmed ties between RIKEN and its fellow research institutions in Asia.

Research institutes, centers and facilities

A national network

Since relocating its original campus from central Tokyo to Wako on the city's northern outskirts in 1967, RIKEN has expanded its domestic network of centers and facilities. It now supports five major institutes and two research facility sites across Japan, and in early 2011 established the new Quantitative Biology Center (QBiC) and the HPCI Program for Computational Life Sciences at the RIKEN Kobe Institute. RIKEN also maintains two major research facilities: the K computer on Kobe Port Island and the SPring-8 Synchrotron Radiation and SACLA X-ray Free Electron Laser (XFEL) facilities in Harima.

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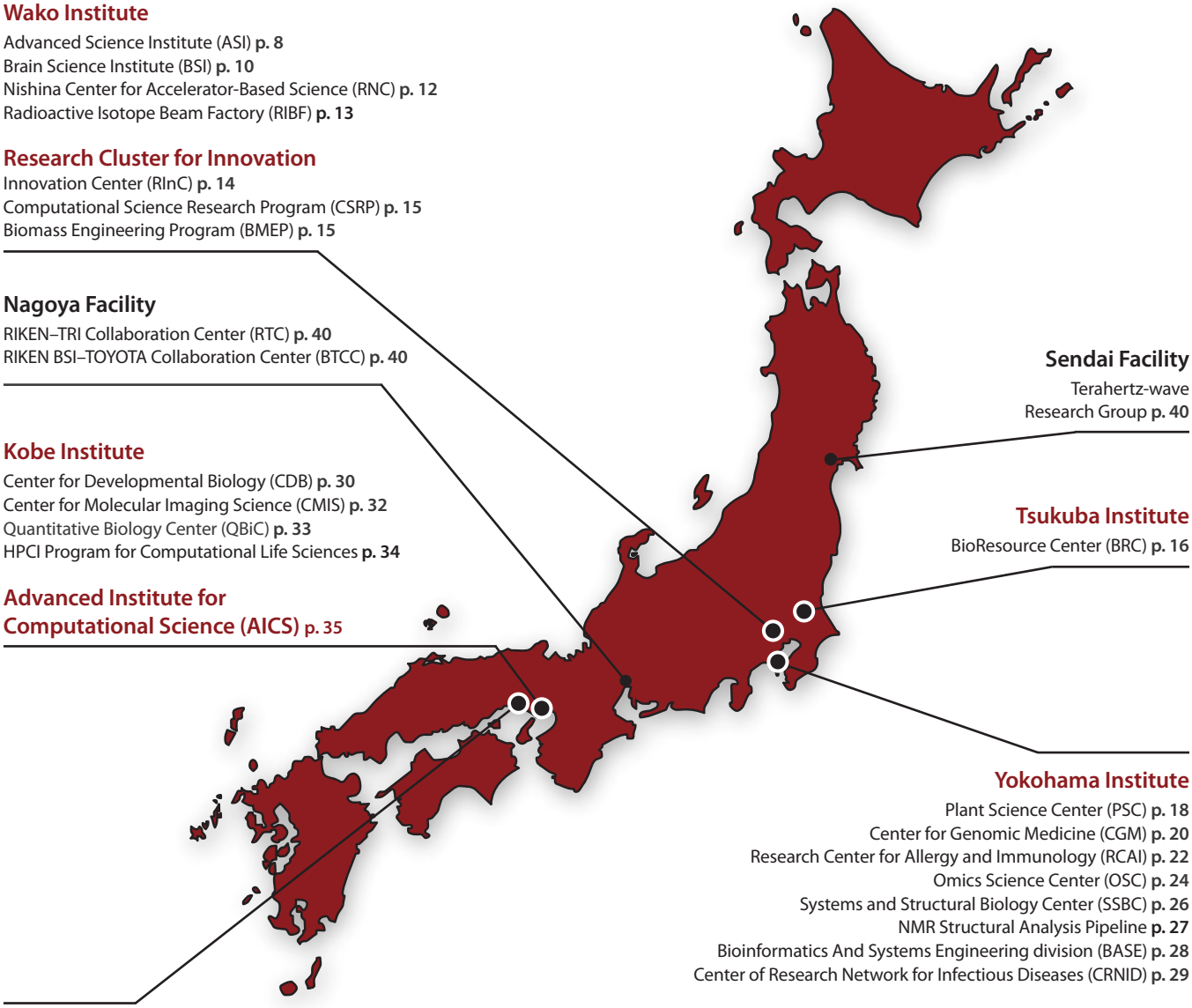

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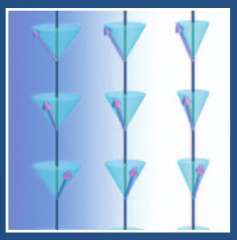
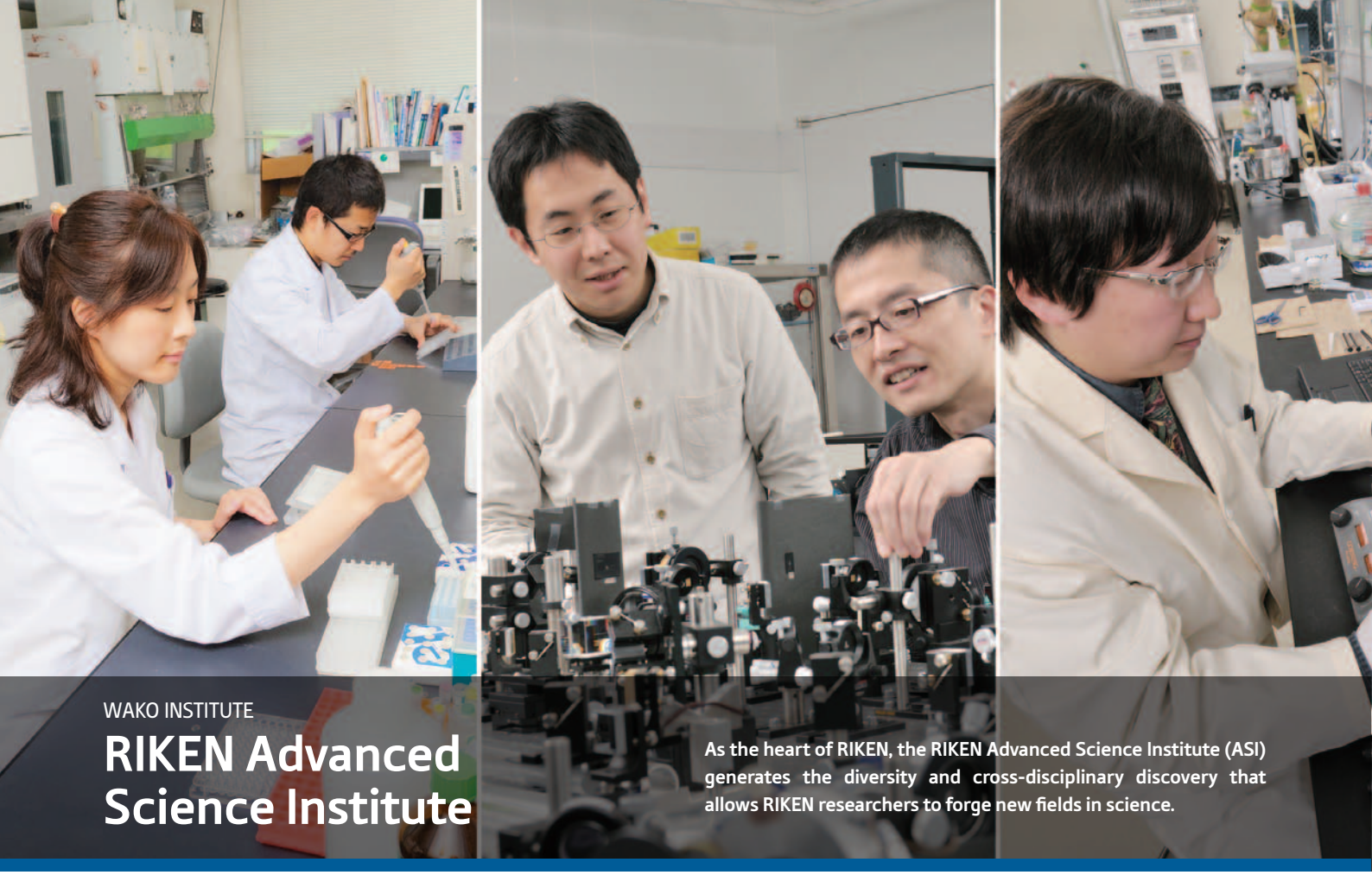
INSIDE RIKEN



A look inside the research institutes, centers, programs and state-of-the-art facilities that make RIKEN one of the world's leading research institutions.



WAKO INSTITUTE

RIKEN Advanced Science Institute

As the heart of RIKEN, the RIKEN Advanced Science Institute (ASI) generates the diversity and cross-disciplinary discovery that allows RIKEN researchers to forge new fields in science.

Located alongside RIKEN's administrative headquarters in Wako north of Tokyo, the RIKEN Advanced Science Institute (ASI) is the core and foundation of RIKEN's research culture. The ASI was established in 2008 through the merger of two former systems, the chief scientist system established in 1922, under which permanent chief scientists performed long-term curiosity-driven basic research, and the frontier research system introduced in 1986, which allowed fixed-term researchers to pursue term-limited field-specific project research. The ASI thus brings together scientists from diverse fields to collaborate on emerging and imaginative research that transcends the traditional disciplinary boundaries in science and technology.

The ASI has a systematic three-layered research structure for cultivating new fields in science. First, the ASI establishes laboratories under the leadership of permanent chief scientists to germinate new research areas through long-term basic research and the integration of diverse fields of science and technology. Second, interdisciplinary basic science research projects are created to cultivate promising research seeds through novel, bottom-up approaches and integrated collaborative research. This can eventually lead to a third stage—the establishment of a research 'department' for incubating the new field, involving field-specific projects that integrate both bottom-up and strategic top-down research. The ASI's aim is to develop some of these departments into independent, world-class research centers within RIKEN. The institute thus has the capacity to create fixed-term, goal-oriented strategic research centers to target specific topical fields or urgent needs.

"It is important to foresee the potential of research—to see which seeds will grow into new research fields and eventually guide national science and technology strategies," says Institute Director Kohei Tamao. Acknowledging the continued cross-disciplinary diversification of global research, the ASI is active in pursuing new research that spans multiple fields. For example, under the 'Extreme Photonics Department' theme, researchers are working on challenging projects at the boundary of multiple disciplines such as physics, chemistry, engineering and biology. This is one of the ASI's four current research departments, which also include 'Green-forefront Materials', 'Emergent Materials' and 'Chemical Biology'—all of which are of interest to international researchers.

Tamao believes that this innovative approach to research has given the ASI an edge in the highly competitive world of research funding, allowing it to secure more than 20% of the total external funding brought in by RIKEN. "I am confident that it is our research competitiveness that has led to our ability to acquire various research resources," he says.

The institute's impressive list of research achievements in 2011 and 2012 is testament to the effectiveness of the ASI's approach to research. These achievements include work by Yasuhiro Uozumi and colleagues, who constructed a range of polymeric palladium-nanoparticle membrane-installed microflow devices which facilitate the rapid dehalogenation of arylhalides and triflates using sodium formate, a safe, non-explosive hydrogen source (*ChemSusChem* **5**, 293–299, 2012). In biological chemistry, Naoyuki Taniguchi and co-workers investigated the expression mechanism of

brain-specific glycosyltransferase, GnT-IX, one of the factors controlling *O*-mannose glycan biosynthesis. The team found that neural glycosyltransferase genes are controlled by epigenetic histone modifications in the first report to illustrate a molecular mechanism and glycan expression at the chromatin level (*The Journal of Biological Chemistry* **286**, 31875–31884, 2011).

ASI researchers Tahei Tahara and his team have discovered through a combination of molecular dynamic simulations and high-level spectroscopy that water molecules are positioned at air–water interfaces in bonded water pairs linked by hydrogen bonds, which overturns the previous theory of "ice-like" structures at the air–water interface (*American Chemical Society* **133**, 16875–16880, 2011).

Recent strides in multiferroic research could lead to the improvement of electronic memory technology. Yasujiro Taguchi and his team have demonstrated that the material strontium barium manganite holds a unique combination of magnetic and ferroelectric properties. Essential to the development of multiferroic materials devices, these properties could play an important role in improving memory devices (*Physical Review Letters* **107**, 137601, 2011).

Satoshi Wada's team and collaborators have developed a device that is capable of decontaminating cesium from contaminated water in tandem with the growth process of algae. The team supplied CO_2 to a sample of cesium-contaminated water containing algal culture plants, and also used a large lens to supply solar light to the sample, resulting in enhanced efficiency of photosynthesis and cesium absorption in the plants. Ninety percent of cesium was removed from three liters of contaminated water over three days. Wada and his team are currently conducting demonstration tests in paddy fields in Fukushima, the area affected by the nuclear accident which followed the 2011 Great East Japan Earthquake and tsunami. This device could be instrumental in future decontamination procedures in the Tohoku region.

The ASI has also seen the inception of other projects, including the 'Green-forefront Materials' department. "In 2011 we launched a new team within that department to develop thin-film organic photovoltaic devices for next-generation solar-energy conversion," says Tamao. "That's the great thing about the ASI, we can bring together the best researchers to develop new science."

Embracing superficial imperfections

Numerical simulations reveal that deliberately engineering defects into ultrathin oxide films enhances catalytic water-splitting reactions

Chemists normally work rigorously to exclude impurities from their reactions. This is especially true for scanning tunneling microscopy (STM) experiments that can produce atomic-scale images of surfaces. Using STM to investigate processes such as catalysis usually requires pristine substrates—any flaws or foreign particles in the surface can critically interfere with the test study. Preconceptions about interface defects and catalysis are about to change, however, thanks to recently published research led by Yousoo Kim and Maki Kawai at the ASI in Wako[1].

Through a series of high-level computer simulations, the researchers found that the catalytic splitting of water molecules occurs faster on an ultrathin insulating film containing misplaced atoms than on a non-defective surface. Because water splitting reactions are one of the easiest ways to generate hydrogen fuel, this finding could be a boon to future fleets of hybrid vehicles.

Recently, Kim, Kawai, and colleagues discovered that depositing insulating magnesium oxide (MgO) onto a silver (Ag) substrate enabled extraordinary control over water dissociation reactions[2]. By injecting electrons into the MgO/Ag surface with an STM tip, they were able to excite absorbed water molecules and cause them to sever hydrogen and hydroxide ions. Optimizing the MgO film thickness was a key part of this approach; only ultrathin layers could direct water splitting owing to its enhanced electronic interaction strength[3].

This relationship between insulator thickness and chemical reactivity suggested to the researchers that the oxide–metal interface plays a crucial role in directing catalytic reactions. Engineering specific flaws into the ultrathin interface could be one way to heighten the electronic control over the water-splitting process. However, since artificially manipulating oxide atoms is a difficult experimental procedure, they used density functional theory simulations, based on quantum mechanics, to analyze the role of structural imperfections in MgO.

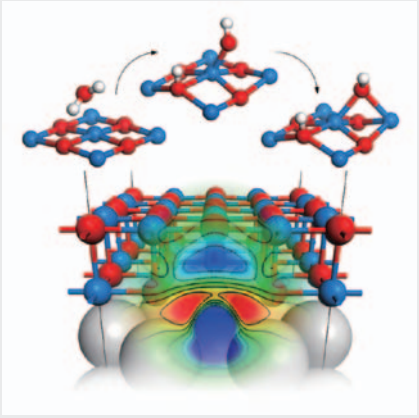


Figure 1. Defects inside an ultrathin magnesium oxide film (red and blue spheres, bottom) accumulate electronic charges (red and blue contour map) and enhance the catalytic dissociation of water molecules (top).

Surprisingly, the researchers found that three different types of defects—oxygen and magnesium impurities, as well as an oxygen vacancy—improved water adsorption and substantially lowered dissociation energy barriers compared to an ideal MgO film. Further analysis revealed that the oxide defects accumulate charges injected into the substrate (Fig. 1), creating an electronic environment that speeds up the catalytic water splitting. "In the presence of these defects, the film's chemical reactivity can be greatly enhanced," says Kim.

The next goal for the researchers is to find systematic techniques to control interface imperfections on these novel catalytic films—an objective best achieved by the team's unique combined experimental–theoretical approach, notes Kim.

1. Jung, J., Shin, H.-J., Kim, Y. & Kawai, M. Activation of ultrathin oxide films for chemical reaction by interface defects. *Journal of the American Chemical Society* **133,** 6142–6145 (2011).

2. Shin, H.-J., Jung, J., Motobayashi, K., Yanagisawa, S., Morikawa, Y., Kim, Y. & Kawai, M. State-selective dissociation of a single water molecule on an ultrathin MgO film. *Nature Materials* **9,** 442–447 (2010).

3. Jung, J., Shin, H.-J., Kim, Y. & Kawai, M. Controlling water dissociation on an ultrathin MgO film by tuning film thickness. *Physical Review B* **82,** 085413 (2010).

WAKO INSTITUTE

RIKEN Brain Science Institute

Research on the most enigmatic of human organs—the brain—promises to unlock the secrets of the human condition and lead to better treatments for neurological disease. Through cross-disciplinary innovation, the RIKEN Brain Science Institute (BSI) has emerged as a global leader in the field.

Susumu Tonegawa

The human brain, beyond controlling mere physiological functions such as our heartbeat and breathing, provides the remarkable functions that make humans 'human'—our sensations and the ability to make decisions, have abstract thought, store memories and use language. "The brain, like the Universe, is one of humanity's last great mysteries," says Susumu Tonegawa, director of the RIKEN Brain Science Institute (BSI).

Since its founding in 1997, the BSI has enjoyed a distinguished international reputation for innovation in brain science. The institute's interdisciplinary and integrative research structure ensures collaboration and integration among diverse research fields, from molecular and cellular biology, genetics and physiology, to engineering, informatics, mathematical sciences, medical science and psychology.

Over the past year, researchers from the BSI have made several notable findings across the spectrum of brain science research. In a recent study, the BSI's Adrian Moore and colleagues investigated the mechanisms of neuronal subtypes in the olfactory system of the fruit fly. Moore's team demonstrated that particular neuronal precursors experience two rounds of division which result in different cellular subtypes. The researchers found that the identity of these subtypes is determined by the presence or absence of the Notch and Hamlet proteins. The study also casts light on the role of Hamlet in defining subsets of target genes and the part this protein plays in the process of neuronal diversification (see *Hamlet sets the stage for neuronal development*, p. 11).

The BSI's Soichi Nagao and his team recently reported a study on an improved model of motor learning in mice. When examining the area of the brain responsible for motor function, the researchers detected a shift in activity from the cerebellum to another population of cells in the brain after the mice underwent approximately four days of training sessions. In order to study this shift more efficiently, Nagao and his team trained their mice within a series of spaced intervals instead of longer, amassed training sessions. They found that memory trace occurred within two-and-a-half hours after the spaced training regime commenced, and established that protein synthesis during this period plays a key part in memory transfer, thus providing a refined model for better understanding the construction of memory (*The Journal of Neuroscience* **31**, 8958–8966, 2011).

In neuropsychiatry, Jun Aruga and colleagues identified a protein which is related to the development of brain disorders. In conditions such as autism and schizophrenia, an imbalance between the excitatory synapses and the inhibitory synapses exists in the brain. Aruga and his team showed that a molecular signal between neighboring neurons is key to the development of inhibitory synapses, highlighting that the interaction between the Slitrk3 protein on dendrites and PTPδ on axons of neighboring cells is essential for the full development of inhibitory synapses and for inhibitory neurotransmission in the brain (*Nature Neuroscience* **15**, 389–398, 2012).

A recent study in neuroscience by Takaomi Saido and his team has illuminated a specific fragment of the amyloid precursor protein (APP), which is involved in the formation of plaques in the brain found in Alzheimer's disease. These plaques disrupt

communication between nerve cells which result in the deterioration of learning ability and memory. Saido and his team focused on the 43 amino acid-long fragment called $A\beta_{43}$ and showed that mice bred from *presenilin-1* mutant mice and APP mutant mice had an increased formation of $A\beta_{43}$ and experienced early plaque growth and memory deterioration. The team's results highlight that $A\beta_{43}$ plays a part in escalating the development of Alzheimer's disease (*Nature Neuroscience* **14**, 1023–1032, 2011).

In the area of cell function dynamics, Atsushi Miyawaki and Hiroshi Hama and colleagues have developed a treatment which transforms brain tissue into a reversible state of transparency, giving neuroscientists an unimpeded view of neural circuitry. The transparency induced by the mixture Sca*l*eA2 enabled the team to visualize deeper than ever before within the brain, even when using standard microscopy (*Nature Neuroscience* **14**, 1481–1488, 2011).

In another recent study, Justin Gardner and his team have demonstrated how the brain is capable of responding to some stimuli but not others during a specific visual task. The researchers found that visual cortex responses to stimuli influenced the observer's choice of focus, which resulted in greater performance on the visual task (*Neuron* **72**, 832–846, 2011).

These discoveries and others by BSI laboratories represent groundbreaking achievements today, yet the BSI realizes that fostering the next generation of young researchers is essential for the development of neuroscience. As part of this mission, the BSI's Brain Science Training Program provides basic training for a select group of graduate students from Japanese universities. The BSI also organizes the BSI Seminar Series, where young researchers can meet world-class scientists from across the globe. In addition, the BSI Summer Program for graduate students offers an internship in a BSI laboratory, or an intensive two-week lecture course featuring distinguished international faculty. The 2012 BSI Summer Program probes the collective interaction of neurons under the theme, "The Collective Brain."

A key collaborator with major academic institutions overseas, the BSI conducts research with the Massachusetts Institute of Technology (MIT), where the BSI supports a joint research center with the MIT's Picower Institute for Learning and Memory—the RIKEN–MIT Center for Neural Circuit Genetics. The BSI also has two major collaborative centers—the RIKEN BSI–TOYOTA Collaboration Center and the RIKEN BSI–OLYMPUS Collaboration Center.

As expectations for brain science grow, the role played by the BSI in basic and translational brain research is taking on a greater level of significance. One key area of basic research being developed at the BSI is the elucidation of neural circuit functions. In 2011, the Neural Circuit Genetics Research Building was established in the campus and serves as a beacon for the recruitment of talented young scientists from all over the world to energize the important mission of the BSI. "With an eye toward the future of brain science, the BSI aims to train the next generation of scientists, and has devoted significant energy toward supporting young researchers," says Tonegawa.

Hamlet sets the stage for neuronal development

A genetic 'reset switch' enables a signaling pathway to induce multiple developmental outcomes for olfactory neurons

Within the nervous system, a handful of signaling pathways modulate development of a cornucopia of different neuronal subtypes. "Even small alterations in neuron differentiation pathways can disrupt subsequent circuit organization and catalyze the genesis of neurological disorders," explains Adrian Moore of the BSI in Wako.

Recent work from Moore's team, which includes Keita Endo of the University of Tokyo, has revealed mechanisms governing this complexity in the fruit fly olfactory system[1]. Within the antennae—the fly equivalent of the nose—it was known that cells called neuronal precursors undergo multiple rounds of 'asymmetric division', wherein each resulting daughter cell follows a distinct developmental path, yielding different combinations of olfactory receptor neurons (ORNs). Moore's team showed specifically that ORN precursors undergo two rounds of division, yielding four different cellular subtypes, three of which will typically mature into ORNs.

Earlier work from Endo showed that the activation or suppression of signaling by the Notch protein helps differentiate these cellular fates[2], but other factors were clearly involved. Their joint research demonstrated that a second protein, Hamlet, modulates the effects of Notch.

"This [process] provides an important foundation for all future studies of odorant receptor expression and axon targeting control on the olfactory system," says Moore. The researchers found that presence or absence of Notch and Hamlet activity plays a central role in establishing the identity of these subtypes, and this in turn determines both the connections formed by the resulting ORNs as well as the subset of olfactory receptor proteins that will be expressed.

Moore and Endo's study also revealed a surprising mode of action for Hamlet. Chromosomal DNA is wrapped around clusters of protein, and chemical changes to those proteins profoundly alter local gene activity—a mechanism called 'epigenetic regulation'. They found that Hamlet selectively deactivates genes activated by Notch by triggering such changes. This means that immature ORNs produced by division of a Notch-activated cell can essentially be 'reset' by Hamlet. The ultimate developmental fate of those cells is then determined, in part, by whether or not they subsequently undergo a new round of Notch activation.

Moore and colleagues also observed that, beyond simply switching off active Notch genes, Hamlet may define subsets of target genes that can subsequently be reactivated by Notch signaling. "The modifications induced by Hamlet may help establish cell fate by marking gene promoters for use later during differentiation," says Moore. "This could prove fundamental to understanding the process of neuronal diversification."

1. Endo, K., Karim, M. R., Taniguchi, H., Krejci, A., Kinameri, E., Siebert, M., Ito, K., Bray, S. J. & Moore, A. W. Chromatin modification of Notch targets in olfactory receptor neuron diversification. *Nature Neuroscience* **15**, 224–233 (2011).
2. Endo, K., Aoki, T., Yoda, Y., Kimura, K. & Hama, C. Notch signal organizes the *Drosophila* olfactory circuitry by diversifying the sensory neuronal lineages. *Nature Neuroscience* **10**, 153–160 (2007).

WAKO INSTITUTE

RIKEN Nishina Center for Accelerator-Based Science

Researchers at the RIKEN Nishina Center for Accelerator-Based Science (RNC), with the world-class Radioactive Isotope Beam Factory (RIBF) at their disposal, are working not only to unravel the mysteries of the Universe but also to address practical issues closer to home.

Eighty years ago, Yoshio Nishina, hailed as the founding father of modern physics research in Japan, established a laboratory at RIKEN. That laboratory would eventually become the RIKEN Nishina Center for Accelerator-Based Science (RNC). Epitomizing the pioneering spirit for which Nishina is renowned, the center continues to play a leading role in promoting accelerator-based science in Japan and throughout the world.

"The primary mission of the center is to unravel the mystery of the genesis of the elements by investigating the nature of nuclei," says the center's director, Hideto En'yo.

In 2006, the RNC's research facilities were given a huge boost with the introduction of the Radioactive Isotope Beam Factory (RIBF), a next-generation heavy-ion research facility, which researchers are using to shed some light on the ultimate picture of nuclei and thus propel forward our understanding of how heavy elements were first formed in the Universe. Although other facilities with comparable capabilities are under construction at other leading nuclear physics laboratories around the world, such facilities take many years to bring online. "The RIBF will probably maintain its unrivalled position in the world for another ten years," says En'yo.

Results published in 2011 by the RNC reflect the significant and central role of the RIBF in the center's research. In a recent study at the RIBF, Hiroyoshi Sakurai and colleagues investigated the effects of adding neutrons to synthetic atoms. The researchers found that the addition transformed the shape of the atoms' nuclei from a spherical to oblate shape, as well as changing the nuclei's stability. The results help to determine the amount of neutrons required to achieve maximized nuclei stability (see *Out-of-shape nuclei*, p. 13).

In 2012, the RIBF Research Division plays a pivotal role in two exciting new international projects. The Euroball–RIKEN–Cluster Array (EURICA) Project brings together 51 institutions from 16 countries in Europe, Asia and North America to explore the structure of nuclei and to unravel the puzzle of nucleosynthesis in the supernova explosion. The EURICA project will utilize the high-intensity RIBF, RIKEN's beta-ray counting system, and the largest in gamma-ray detector technology, the Euroball Germanium Cluster detector. A central component of the EURICA project, the cluster detector allows

Hideto En'yo

researchers to efficiently detect gamma rays emitted from radioactive isotopes (RI). By coupling the cluster detector with the beta-ray counting system and the range of radioactive beams at the RIBF, researchers will be able to undertake the spectroscopy of rare RIs in a mere 40 minutes, a dramatic improvement from the current time frame of one month. The experimental stages of the project commence in June 2012 and will run through to June 2013.

Another landmark project for the RIBF Research Division is the newly constructed large-acceptance multi-particle spectrometer, the Superconducting Analyzer for Multi-particles from Radio Isotope Beams (SAMURAI). The

SAMURAI comprises a large superconducting dipole magnet and a range of detectors for charged particles and neutrons. The large acceptance facilitates a variety of radioactive beam experiments that require multi-particle coincidence measurements, such as invariant-mass spectroscopy for the study of neutron/proton halo or skin structure, which appears uniquely in extremely neutron-rich/-deficient systems. This instrument will also be used to study radiative-capture reactions, which play a key role in stellar nucleosynthesis. Initial building of the instrument commenced in 2008, and the construction of experimental devices was completed in 2011. The first experiments were conducted at the facility in May 2012.

Other unique instruments at the RIBF include the DALI2 gamma-ray detector, which Tohru Motobayashi and his colleagues have built and been using to conduct a series of experiments on the exotic deformation of neutron-rich nuclei. Those experiments are soon expected to yield an answer to a question that has been debated for many years about the nucleus ^{42}Si—and in so doing demonstrate the possible existence of a new region of nuclei with unexpected deformation.

It is En'yo's hope that the RNC will continue to act as a core facility for researchers all over the world. And research at the RNC is not confined to solving the big questions about the creation of the Universe. En'yo believes that the future bodes well with regard to practical applications of the discoveries made at the RNC. "One of our featured methods for applied research is to use a heavy-ion beam to develop new plant strains. I feel that in the future we will be able to produce research results that lead to ways to solve food shortage and energy issues."

Radioactive Isotope Beam Factory

The Radioactive Isotope Beam Factory (RIBF) in Wako is RIKEN's next-generation heavy-ion research facility, providing researchers with the most intense ion beams in the world. At its heart lies the superconducting ring cyclotron, the world's largest at 18 meters in diameter and weighing in at 8,300 tons—more than twice the weight of Tokyo Tower. Recent upgrades to the RIBF allow for the generation of intense beams of about 4,000 unstable nuclei, ranging from hydrogen to uranium, making it possible to probe beyond the limits of the known nuclei.

Out-of-shape nuclei

Adding neutrons to synthetic atoms can drastically alter the shape of their nuclei and affect their stability

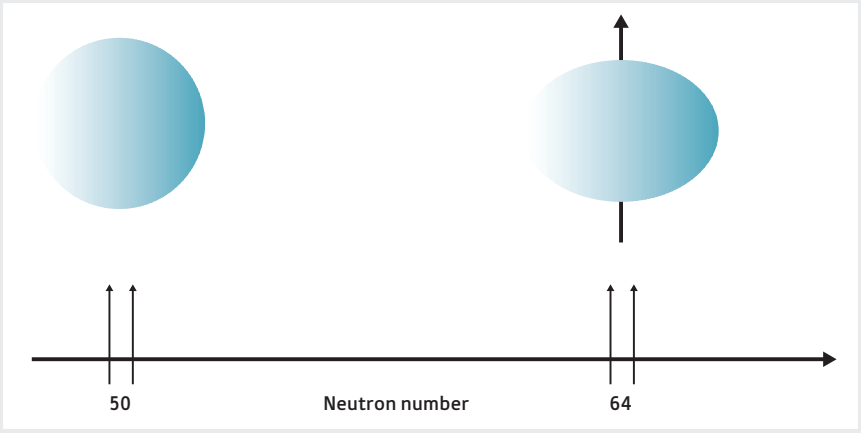


Figure 1. A zirconium atom changes its shape from spherical to oblate after the addition of neurons.

To probe the evolution of atomic nuclei with different shape —a factor which affects atomic stability—a large team of international researchers has added neutrons to zirconium atoms and revealed the possibility of very unusual shapes[1]. "The shape of a nucleus reflects the symmetry of its quantum state," explains team member Hiroyoshi Sakurai from the RNC in Wako. This result helps us to understand how many neutrons are needed for the most stable nuclei.

Most atoms can exist in one of several alternative forms called isotopes, depending on the number of neutrons in their core. Naturally occurring, stable atoms tend to have between 1 and 1.5 neutrons per proton. However, synthetically generated atoms with higher neutron–proton ratios can reveal much about changes within an atomic nucleus.

The protons and neutrons in a nucleus usually form arrangements of concentric spherical shells. In some cases, however, the outermost particles exist further from the center than normal. This can lead to nuclei that are wider than they are long. Just as atoms with a specific number of protons can exist as different isotopes, atoms with a specific number of protons and neutrons can exist as different nuclear isomers—nuclei with different shapes. "By measuring the shape of nuclei, we are probing the internal symmetry in the nucleus—the so-called shell structure," explains Sakurai.

At the Radioactive Isotope Beam Factory, operated jointly by RIKEN and the University of Tokyo, the researchers experimented with zirconium atoms that have 40 protons and, in their stable form, between 50 and 52 neutrons. They created zirconium atoms with as many as 68 neutrons through collisions between uranium and beryllium atoms. After filtering isotopes from the remnants of the collision, they measured the rate of decay of beta and gamma radiation emitted by the quickly decaying, unstable synthetic atoms. The measurements showed that these nuclei changed shape from spherical to oblate (Fig. 1).

The degree of deformation of the zirconium nuclei increased as Sakurai and colleagues added more neutrons, but this trend stopped when they reached 64 neutrons. This result raises the intriguing prospect of a tetrahedral-shaped isomer of zirconium-108—an isotope with 68 neutrons—which has been predicted previously by other researchers. However, further work is needed to verify this. "We next hope to gain further insight into the evolution of nuclear isomers by extending our study to strontium atoms," Sakurai says.

1. Sumikama, T., Yoshinaga, K., Watanabe, H., Nishimura, S., Miyashita, Y., Yamaguchi, K., Sugimoto, K., Chiba, J., Li, Z., Baba, H. *et al.* Structural evolution in the neutron-rich nuclei ^{106}Zr and ^{108}Zr. *Physical Review Letters* **106**, 202501 (2011).

FEATURED INITIATIVE

Research Cluster for Innovation

The Research Cluster for Innovation provides a systematic framework for the transformation of RIKEN discoveries into applications that contribute to a better society by focusing RIKEN's diverse and interdisciplinary capabilities on solution-finding research.

RIKEN Innovation Center

'Science for the sake of science' certainly has many merits but creating practical results that will benefit society is not necessarily one of them. Based on RIKEN's 'baton zone' model (see p. 55) for efficient technology transfer, the RIKEN Innovation Center (RInC) links researchers at RIKEN to counterparts in private companies to promote more effective technology transfer. The RInC supports this collaboration by providing a location and framework for these researchers to advance their research rapidly. The RInC's motto for meeting the needs of industry is 'from challenge to achievement.'

The RInC was created in 2010 through reorganization of its predecessor, the Center for Intellectual Property Strategies, based on RIKEN President Ryoji Noyori's initiative that RIKEN should carry out research that is useful to society.

Collaborations with private companies are initiated when the companies discover that RIKEN's researchers are working on themes that are relevant to them. The company may propose joint research based on a three- to five-year time frame. Once a confidentiality agreement is signed, RIKEN will establish a project team in which the private company will take the lead in research. RIKEN has already been approached by some leading companies seeking to develop novel methods and materials based on RIKEN's cutting-edge science and technology.

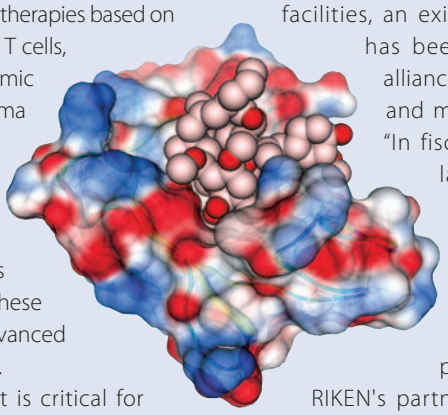
On 22 September 2011, Yutaka Arimoto—RIKEN Invited Senior Scientist for the Sponsored Laboratories in the Innovation Center—was presented with the SCJ President Award for his work on "EdibleSaFE Pesticide" at a presentation ceremony held in Tokyo. The award is one of the 9th Industry-Academia-Government Collaboration Contribution Awards, which commends innovations that address the challenges of an environment with reduced resources through collaborations with industry, academia and the government.

"One of the most important things is to increase the number of researchers who can work with industry. Earning trust from the scientific community and creating jobs that contribute to industry can be achieved simultaneously," says Yoshiharu Doi, director of the Research Cluster for Innovation.

RIKEN Program for Drug Discovery and Medical Technology Platforms

In Japan, basic research in the life sciences produces high-quality results, but the process of translating basic research results from universities and research institutions into drug discovery and medical technology is relatively inefficient and time-consuming. A bridging role is needed to improve the process. In the United States, this bridging role is carried out by bioventure companies, but there are few such companies in Japan. This has hampered drug development.

The RIKEN Program for Drug Discovery and Medical Technology Platforms was launched in April 2010 to play this bridging role, as well as putting to optimal use medical technology and drug discovery platforms cultivated at RIKEN. Today, ten drug discovery units, organized into five centers, have been established within RIKEN under the program, comprising 22 drug discovery projects selected from RIKEN, universities and research institutes. The projects focus on the development of drugs to treat illnesses that pharmaceutical companies find difficult to approach, as well as rare (orphan) diseases. Examples of these projects include cancer therapies based on the use of natural killer T cells, drugs that target leukemic stem cells, neuroblastoma treatment antibodies, and drugs for the rare connective-tissue disease fibrodysplasia ossificans progressiva. Some of these projects have even advanced to the clinical trial stage.



Good management is critical for competing in innovation on a global level. The program is operated based on a matrix management system, under the leadership of a steering committee. In concrete terms, members of each RIKEN center's drug development unit forms a team that goes beyond traditional organizational bounds, supported by a manager who is well-versed in portfolios, clinical development, regulations and business development.

As RIKEN does not have its own hospital facilities, an exit for the program has been established via alliances with companies and medical institutions. "In fiscal 2011, relatively late-stage projects were carried out," says program director Toshio Goto. "In our Alzheimer disease project, Pharma8, RIKEN's partnering venture, received capital from the Innovation Network Corporation of Japan, a public-private provider, and leads the project as an independent entity. In our natural killer T cells project, we formulated an agreement under the National Hospitals Organization to conduct clinical trials with Chiba University. For our regenerative medicine project, we have launched preclinical research to develop therapies using iPS cells."

Japan's new 10 petaflops supercomputer—the 'K computer,' located at Kobe Port Island and due to be opened for use in the second half of 2012—is part of the Japanese government's strategic policy of maintaining and improving Japan's international competitiveness in science and technology.

Computational Science Research Program

As the operating partner, RIKEN has been working closely with academia and industry to develop this key piece of national technology. Supercomputers like this new facility are becoming increasingly important for research, providing a research tool for a wide range of fields, making a significant contribution to the design and development of a variety of products, and forming an indispensable part of the continuing advancement of science and technology. Since 2006, the Computational Science Research Program (CSRP) has been responsible for the development and distribution of software to make maximum use of the supercomputer, as well as the construction of a world-class supercomputing research and education hub at the new facility.

The main task of the CSRP has been to develop software for the 'Next-Generation Integrated Simulation of Living Matter'—an ambitious project aimed at simulating the entirety of organisms, from the molecular and cellular level through to organs, the brain and the body itself. This project will not only establish computational science as a new methodology for life sciences, but will also establish methods that allow simulations to be carried out using the full potential of the K computer.

Program Director Koji Kaya plans to distribute the software to industry in the hope that they will be used in real-world applications, such as in genetic medicine and protein analysis for drug design. "Before the era of the K computer, people didn't believe that computation could make precise predictions for use in drug development, but with largescale computers like the K computer, we will be able to simulate drugs with high accuracy," says Kaya.

RIKEN Biomass Engineering Program

In the twenty-first century, it is hoped that biomass will become a viable renewable energy source to help address the problem of global warming. The RIKEN Biomass Engineering Program (BMEP) was established in April 2010 in order to take the lead in this field of green biotechnology by establishing innovative bioprocesses that produce biomaterials and bioplastics from plant biomass.

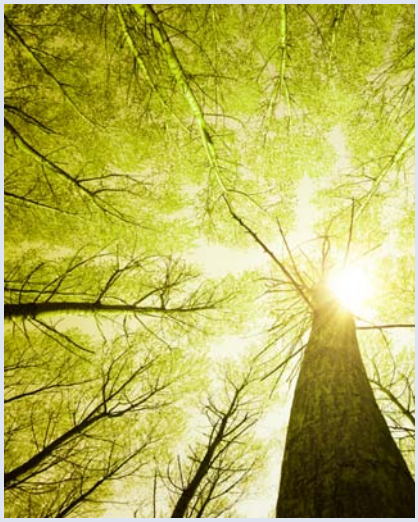
The BMEP aims to develop a system that converts basic research findings into practical applications through collaboration among various research fields. "The BMEP is an interdisciplinary research and development program that links together plant science, microbial science, enzyme research and bioresource research to create non-foodstuff biomass that can be broken down by microbes, then fermented to create new biomaterials and bioplastics," says Kazuo Shinozaki, the program's director.

In order to fulfill its specific goals, the BMEP will adopt three separate strategies over a fixed time frame of 10 years. One strategy is to establish a technology that can introduce 'super plants' that offer higher levels of woody biomass production and degradability. The second research goal is to establish efficient, direct bioprocesses for biotechnology-related products, and the third strategic thrust is to pursue the development of environmentally friendly 'bioplastics' that can be created from biomass.

Environmental issues such as climate change are strong drivers of research at the BMEP. "We need to use alternative resources such as biomass to decrease carbon dioxide levels," says Shinozaki. "It would be ideal to be able to achieve this use of biomass from non-food sources in areas where crops cannot be grown."

The program consists of five research teams working in the areas of cellulose production, synthetic genomics, enzymes, bioplastics, and biomass itself. "With the BMEP, there is much cooperation with outside fields, which allows, for example, the possibility of creating new biomaterials," says Shinozaki.

In order to expand the scope of research conducted under the BMEP, collaboration with other fields and organization is crucial. To this end, the program has signed accords with the Forestry and Forest Products Research University in China and the Forest Science Institute of Vietnam to further develop the research undertaken at the BMEP.



Shinozaki has much that he wants to achieve in the future. "We are not going to just focus on creating environmentally friendly bioplastics—we also aim to produce non-food cellulose in the easiest-to-use form possible, as well as design and discover new enzymes and create new super plants. Our aim is to use our findings from basic research to make a contribution to society," he says.

TSUKUBA INSTITUTE

RIKEN BioResource Center

Marking its tenth anniversary milestone in 2011, the RIKEN BioResource Center (BRC) has much to celebrate, having risen from humble beginnings to become one of the world's top repositories for biological resources.

Research in the life sciences and biotechnology relies on having the right biological experimental materials, whether plant cell lines, stem cells or mice with mutant genetic profiles that allow them to be used in studies of the function of genes and human diseases. Such bioresources have become essential for both academic research and industry, and research and development is accelerated by the sharing of bioresources among researchers. Since its establishment in 2001, the RIKEN BioResource Center (BRC) has acted as a bioresource core facility for researchers through the collection, preservation and distribution of bioresources. Through these activities, the BRC supports studies in a range of fields, from basic research to the treatment of disease, health promotion, food production and even environmental conservation. The BRC is guided in this mission by its founding principles of 'Trust', 'Sustainability', and 'Leadership'.

A key characteristic of the BRC is that it handles a variety of bioresources, including human specimens, model mice, experimental plants such as *Arabidopsis*, cell lines, genes and microorganisms, as well as extensive information on all of these materials. "There are a number of important bioresource repositories in the world, such as the Jackson Laboratory and American Type Culture Collection in the US and the Nottingham Arabidopsis Stock Centre in the UK," says BRC Director Yuichi Obata. "But, in our ability to handle many different types of bioresources, we are unique in the world."

Yuichi Obata

Along with other centers, the BRC was affected by the unprecedented disaster of the Great East Japan Earthquake and Tsunami on 11 March 2011. Based in Tsukuba city, the center experienced significant damage to its facilities. As a result, the BRC was forced to halt the shipping operation of resources for

The BRC participated in the 3rd conference of the Asian Network of Research Resource Centers (ANRRC), hosted by the Institute of Microbiology at the Chinese Academy of Sciences in Beijing, China from 24–25 November 2011. The ANRRC was established in 2009 to act as an information hub for Research Resource Centers across Asia and to promote cooperation and networking between centers. The BRC's director, Yuichi Obata, currently serves as vice president of the ANRRC.

two weeks. Fortunately, the center did not lose any of its bioresources, and its services have remained unchanged. With the aim of accelerating the early recovery of research and development in the disaster areas, the BRC has so far provided 240 replacement bioresources at no cost to those scientists and researchers at universities, research institutes, and companies where resources were destroyed. The disaster underlined to the BRC the importance of maintaining bioresources and emergency planning.

After the earthquake, the BRC acquired governmental funding to build new water supplies, as well as enlarging the center's fuel capacity for emergency electricity and setting up liquid nitrogen generation machines.

The BRC also decided to upgrade their backup facility at the Harima Institute. In this way, the BRC have improved the risk management system of the center's bioresources — the BRC's most precious assets.

In efforts to support world-leading research on regenerative medicine involving stem cell resources, such as iPS cells, the BRC established the BioResource Building for Cell Research in March 2011 which aims to collect, preserve, and distribute such stem cell resources.

By providing iPS and other types of stem cells to researchers both inside and outside Japan, the BRC is promoting research not only in regenerative medicine but also in drug design by facilitating a better understanding of disease mechanisms, and thus contributing to advances in medical sciences in general.

The 4th Science and Technology Basic Plan legislated by the Japanese government in August 2011 is based on science, technology, innovation, and reconstruction. In line with this plan, the BRC aims to move forward with renewed passion to promote the research and development of life sciences and to create novel values by facilitating their bioresources not only for academic use, but as a foundation for innovation and reconstruction.

"Over the next ten years, there will be dramatic progress in the life sciences through the many novel bioresources derived from genomics research," says Obata.

"We are preparing to manage new bioresources in an international framework, such as handling bioresource-related information, and how to best disseminate bioresources."

Long-term benefits from a 'moment of silence'

By temporarily silencing a hyperactive gene, scientists dramatically boost the efficiency of mouse cloning

In principle, somatic cell nuclear transfer (SCNT) is a potent tool for scientists looking to produce exact genetic replicas of a particular animal. By injecting a nucleus from an adult cell into an oocyte from which the nucleus has been removed, one can initiate the embryonic development process and derive a clone of the 'donor' animal.

Figure 1: By briefly silencing the hyperactive *Xist* gene, scientists can more efficiently generate litters of healthy cloned mice.

Unfortunately, this technique is terribly inefficient, with a success rate of 1–2% in mice. "This must be due to some errors in the reprogramming of the donor genome into the 'totipotent' state, which is equivalent to the state observed in conventionally fertilized embryos," explains Atsuo Ogura of the BRC. However, Ogura and colleagues have now made significant progress in clearing a major roadblock thwarting SCNT success[1].

During development of female mammalian embryos, one of the two X chromosomes is targeted for inactivation, thereby ensuring that both males and females achieve equivalent expression of X-linked genes. This inactivation depends on RNA produced by the *Xist* gene, which blankets the selected chromosome and sets the inactivation process in motion.

Ogura and his team previously determined that *Xist* is inappropriately activated in SCNT embryos[2], impairing expression of essential genes, and have now set about correcting this defect. Irreversibly inactivating this gene is not an option, so the researchers injected molecules called 'short interfering RNAs' (siRNAs) that directly inhibited *Xist* activity in early stage male SCNT embryos, which must maintain their single X chromosome in order to survive.

This treatment markedly boosted expression of X chromosomal genes relative to untreated controls, and although the direct effects of siRNA injection were fleeting, the benefits lingered. "The siRNA was effective for only 72 hours," says Ogura, "but it had long-term effects not only on the birth rate but also on the health status of the offspring." Indeed, his team achieved a success rate of nearly 20%—ten-fold better than previous efforts—and generated mouse pups that were apparently normal and healthy (Fig. 1).

The implications for this improved efficiency extend beyond mass-produced mice, and this approach could represent a step toward improving the economics of cloning other species such as pigs and sheep, which are harder to genetically manipulate but nevertheless of considerable agricultural and scientific interest. "Our goal is to increase the birth rate of healthy cloned offspring not only in mice but also other mammals," says Ogura, "and to understand the mechanisms by which the genome is drastically altered during the life cycle."

1. Matoba, S., Inoue, K., Kohda, T., Sugimoto, M., Mizutani, E., Ogonuki, N., Nakamura, T., Abe, K., Nakano, T., Ishino, F. & Ogura, A. RNAi-mediated knockdown of *Xist* can rescue the impaired postimplantation development of cloned mouse embryos. *Proceedings of the National Academy of Sciences USA* published online 7 November 2011 (doi: 10.1073/pnas.1112664108).

2. Inoue, K., Kohda, T., Sugimoto, M., Sado, T., Ogonuki, N., Matoba, S., Shiura, H., Ikeda, R., Mochida, K., Fujii, T., *et al.* Impeding *Xist* expression from the active X chromosome improves mouse somatic cell nuclear transfer. *Science* **330,** 496–499 (2010).

YOKOHAMA INSTITUTE

RIKEN Plant Science Center

The RIKEN Plant Science Center (PSC) conducts research that is helping to build a healthier and more sustainable society by improving food security and developing renewable plant-based sources of energy.

Food security is of vital importance to Japan, which ranks 28th among the 30 member countries of the Organisation for Economic Co-operation and Development (OECD) in terms of self-sufficiency of food supply. The RIKEN Plant Science Center (PSC) in Yokohama—the only research center in Japan dedicated to plant science—is playing a crucial role in utilizing plants to help develop foodstuffs to tackle this issue, as well as developing new plant-based sources of energy and producing plant-derived therapeutics. And in doing so the PSC has established an international reputation as one of the world's leading research centers in plant science.

"Our overall aim is to improve plant growth, metabolic pathways, environmental resistance, and plant immunity to contribute solutions to food problems and environmental issues, and to advance collective health through the discovery and production of new plant substances," says PSC Director Kazuo Shinozaki.

The PSC was established in 2000 as part of the Japanese government's five-year Millennium Project, one of the main thrusts of which was to promote plant science for the discovery of useful genes for food and energy supply. During this phase, the PSC was able to achieve a high level of basic research in the areas of plant hormone metabolism and the signaling, morphology, development and metabolism of model plants.

Kazuo Shinozaki

Since 2005, the PSC has been working on the second phase that aims to quantitatively and qualitatively improve plant production based on functional genomics in model plants with known genomic sequences, such as *Arabidopsis* and rice. Research on metabolic systems is a particular focus of the research. In collaboration with various universities and international organizations, as well as various companies, the PSC is using its research findings on model plants to improve the production of crops and trees and thus hopefully ensure a reliable supply of food and energy from plants.

In 2011, the PSC's Hiroyuki Kasahara and colleagues conducted experiments on *Arabidopsis* plants which revealed the main pathway for production of the phytohormone auxin. This pathway is likely to exist in a wide variety of plants, and Kasahara and colleagues believe that this study is a major leap forward in further understanding the biochemical processes influencing plant growth (see *A shorter road to growth*, p. 19).

In the area of gene discovery, a recent study by Takashi Kuromori and colleagues has identified a key gene that enables plants to conserve water in extreme drought conditions. Takashi Kuromori and colleagues analyzed the plant *Arabidopsis thaliana* and uncovered the gene called *AtABCG22*. This finding will enhance biologists' understanding of plant survival in drought-stricken environments, and it is hoped this research will bring plant biologists one step closer toward making drought-tolerant plants a reality (*The Plant Journal* **67**, 885–894, 2011).

A recent achievement in the study of plant pathogens at the PSC is that of Ken Shirasu and colleagues, who have investigated the molecular structure of a disease effector from *P. infestans*, causing the crop-destroying blight disease in potato plants. Through understanding the effector's molecular structure and function, plant biologists will be able to better combat the disease through the development of improved control measures (*Proceedings of the National Academy of Sciences USA* **108**, 14682–14687, 2011).

In 2012, a team led by Kazuki Saito and Toshiyuki Muranaka explored the complex array of enzymes in the plant genus *Glycyrrhiza*, which is most renowned as the key ingredient of licorice and a component of traditional medicines. The researchers identified a new enzyme, CYP72A154, which plays a role in the process of glycyrrhizin biosynthesis. The partial glycyrrhizin biosynthesis demonstrated by the researchers is a significant finding: even though this valuable molecule is simply purified from licorice plants, scientists may have to resort to laboratory production methods in future due to an impending shortage of natural resources (*The Plant Cell* **23**, 4112–4123, 2011).

Also in 2012, inroads have been made in the development of a genetic alternative to fertilizer. Takatoshi Kiba and his colleagues have illuminated how the nitrate transporter gene, *NRT2.4*, benefits nitrogen-deprived plants. Kiba and colleagues found *NRT2.4* expression in the roots and shoots of *Arabidopsis* seedlings, and observed that the gene is essential to increasing nitrate absorption by *Arabidopsis* plants at very low concentrations. The introduction of the *NRT2.4* gene to crops could in future advance nitrogen uptake efficiency, and eventually lead to the reduction of nitrogen fertilizer usage (*The Plant Cell* **24**, 245–258, 2012).

Collaborations are also necessary to achieve all of the PSC's goals. This is where the PSC makes use of its strong connections with the Ministry of Agriculture, Forestry and Fisheries in Japan on rice genomics, the Max Planck Institute on metabolomics and UC San Diego on hormone research overseas.

Looking back, Shinozaki is proud of what the center has achieved since 2005. "We have been conducting research on how to improve the production of plants, and having achieved many results, we have established our position internationally as one of the world's leading plant science centers," he says.

A shorter road to growth

New insights into a plant hormone synthesis pathway could prove fruitful for improving crop robustness and productivity

By promoting cell expansion, division and differentiation, and regulating developmental events and environmental responses, the family of plant hormones known as auxins is central to a wide variety of growth and behavioral processes in a plant's life cycle. Discovered more than 70 years ago, indole-3-acetic acid (IAA) is the most abundant and potent auxin and plays a fundamental role in plant growth and development. Surprisingly, however, little is known about how it is synthesized.

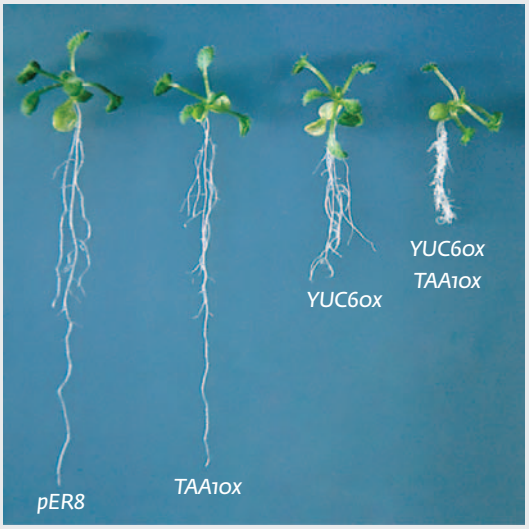


Figure 1: When overexpressed in *Arabidopsis*, TAA1 (*TAA1ox*) and YUC6 (*YUC6ox*) act synergistically to stimulate denser lateral root growth (right) relative to plants that overexpress either gene alone (middle) or negative control plants (*pER8*; left).

In a recent study, PSC researcher Hiroyuki Kasahara and his collaborators, including Yunde Zhao of University of California San Diego, sought to clarify the pathways via which this synthesis occurs. Earlier research showed that plants synthesize IAA from tryptophan, an amino acid, via a set of four such pathways, and the team's own research in 2009 indicated that IAA biosynthesis may vary among plant species. The overall picture of these pathways, however, remained unclear.

One point of contention with existing hypotheses concerns two families of enzymes named TAA (TRYPTOPHAN AMINOTRANSFERASE OF ARABIDOPSIS) and YUC (YUCCA), each of which is required for IAA biosynthesis. While earlier research had placed these two families on distinct biosynthesis pathways, mutants deficient in TAA and YUC have very similar phenotypes, suggesting a linear relationship between the two.

Through a series of experiments on *Arabidopsis* using advanced mass spectroscopy techniques and enzyme assays, the research team confirmed for the first time this linear relationship (Fig. 1)[1]. Their findings show that the TAA and YUC families are not on separate pathways, as earlier believed, but on the same pathway, with YUC catalyzing a rate-limiting step in the synthesis of IAA from indole-3-pyruvic acid (IPA).

By clarifying this key step, the discovery unravels the 70-year old mystery of how auxins are synthesized, a major step towards understanding the biochemical processes that ultimately govern plant growth. "By identifying this main auxin biosynthesis pathway, it becomes possible to study in detail when and where plants make IAA by analyzing the expression of YUC family genes," Kasahara explains.

Applications of the discovery in agriculture promise increased plant robustness and productivity. "One recent study has demonstrated that one can increase IAA levels during ovule development to increase the yield and quality of cotton," says Kasahara. "We may be able to increase the production of crops by modulating expression levels of YUC and TAA genes, and the IPA pathway offers a novel target for the development of herbicides."

1. Mashiguchi, K., Tanaka, K., Sakai, T., Sugawara, S., Kawaide, H., Natsume, M., Hanada, A., Yaeno, T., Shirasu, K., Yao, H. *et al.* The main auxin biosynthesis pathway in *Arabidopsis*. *Proceedings of the National Academy of Sciences USA* **108**, 18512–18517 (2011).

YOKOHAMA INSTITUTE

RIKEN Center for Genomic Medicine

Scientists at the RIKEN Center for Genomic Medicine (CGM) are using powerful, sophisticated approaches to identify gene variations linked to various diseases in discoveries that could lead to personalized medicine.

Major genetics research projects, such as the International Hapmap Project, have uncovered single nucleotide polymorphisms (SNPs) that further illuminate our understanding of genetic variability in individuals. SNPs are key to unlocking the links between genes and phenotypes, such as an individual's susceptibility to disease, and new technological processes have the ability to determine genotypes at a rapid rate. The RIKEN Center for Genomic Medicine's (CGM) expertise and achievements in gene identification and genotyping techniques place it firmly at the forefront of human genetics research today.

An accurate and sensitive SNP-typing method developed by the CGM has helped to identify genes involved in the onset of various diseases, and has made an invaluable contribution to high-profile research projects, including the International HapMap Project (contributing 24.3%), and the creation of the Japanese SNP (JSNP) Database. Drawing from these achievements, the CGM is now generating a large amount of SNP-genotyping data for the genome-wide association study (GWAS) of common diseases in close collaboration with the BioBank Japan Project.

Michiaki Kubo

The GWAS method itself has its roots in the SNP Research Center (renamed the CGM in 2008), which revolutionized biological research with the development of the GWAS method in 2002. This approach allows researchers to seek genes linked to diseases or drug responses by examining more than 500,000 markers of the genome in thousands of people. Today the methodology is widely applied in international genetics research.

The CGM aims to fully utilize the results of its genetic approaches for personalized medicine—a relatively new concept—to develop optimal treatment tailored to suit each patient based on his or her specific genetic makeup. Through further investigation of genes that give rise to various diseases, the CGM also plans to innovate preventive techniques which are capable of detecting if a patient is at higher risk of specific diseases.

The 12 research teams that comprise the CGM are engaged in research themes ranging from genotyping development, statistical analysis and biomarker development, to pharmacogenomics and the analysis of disease.

The center's recent major achievements well illustrate its cutting-edge position in the field, and underline the CGM's aim to expand the focus of GWAS investigations to hone in on the genetic variation of Asian individuals. As many international GWASs focus primarily on populations of European descent, risk markers for other ethnic groups remain relatively unexplored. The CGM has aimed to address this imbalance by seeking out genomic factors which may influence disease in East Asian populations.

Mayumi Tamari and her team identified five gene regions which are linked to asthma susceptibility in Japanese adults. With more

than 300 million asthma sufferers around the world, the CGM's findings serve to enhance biologists' understanding of asthma pathogenesis and the bearing of genetics on asthma susceptibility, which will in turn innovate new therapeutic treatments to combat the disease (see *Pinpointing asthma susceptibility in Japanese adults*, p. 21).

Researchers at the CGM have also investigated the genomic regions linked to age-related macular degeneration (AMD). Resulting in blindness, AMD develops due to cell death in the retina of the eye, and a type of AMD known as exudative AMD is prevalent among Asian populations. Michiaki Kubo and his colleagues have now determined the four genomic areas that elevate the risk of exudative AMD in Japanese individuals, and these findings will help to spearhead new therapies to treat the disease (*Nature Genetics* **43**, 1001–1004, 2011).

In a large-scale GWAS of Japanese individuals, Yukinori Okada and colleagues uncovered previously overlooked genetic variants associated with metabolic diseases such as diabetes, hyperlipidemia and chronic renal disease. These findings underline the importance of expanding the focus populations of GWAS analyses to include the entire spread of ethnic diversity (*Nature Genetics* **43**, 990–995, 2011).

Shiro Ikegawa and colleagues have also discovered a genomic variant in the newly identified gene, *FONG*, which is connected to a heightened risk of developing osteoporosis in Japanese individuals, paving the way to the development of new treatments for this debilitating condition (*PLoS ONE* **6**, e19641, 2011).

In 2012, Yukinori Okada and colleagues conducted a meta-analysis between body mass index (BMI) and 2.4 million SNPs in a population of 27, 715 East Asian individuals. The study identified ten BMI-associated loci, of which three were novel. It is anticipated the findings of this research will underscore the importance of GWASs conducted in non-European populations, and further illuminate new pathways associated with obesity (*Nature Genetics* **44**, 307–311, 2012).

Acting center director Michiaki Kubo is planning to translate these results into clinical practice as part of the CGM's aim to make personalized medicine a reality.

"Many people think that the identification of genetic factors can easily apply to clinical practice, but it's not so easy," says Kubo. "We need to uncover the impact of individual genetic risk on the development and progression of disease, and how to prevent it."

Pinpointing asthma susceptibility in Japanese adults

Identification of genetic variations that increase the risk of adult asthma will lead to better understanding of this disease

A team of geneticists has identified five specific gene regions associated with asthma susceptibility among Japanese adults[1]. Mayumi Tamari of the CGM, led the research.

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Figure 1: The respiratory disease asthma, although controllable, affects millions of people worldwide and can be fatal.

Asthma is a chronic inflammatory disease affecting the airways and lung (Fig. 1). With an estimated 300 million sufferers worldwide, symptoms include recurrent wheezing and coughing, and shortness of breath. Although controllable in most cases, serious asthma attacks can be fatal.

"Asthma is caused by a combination of genetic and environmental factors," explains Tamari. "By identifying asthma genes and studying their function, biologists hope to elucidate mechanisms underlying asthma development and progression, leading to more effective treatments."

Other researchers have identified regions of the human genome containing genes associated with asthma. For example, one recent large-scale, consortium-based study identified nine of these so-called susceptibly loci in European populations. "Little is known about genetic differences contributing to asthma susceptibility among other ethnic groups such as Asians," says Tamari.

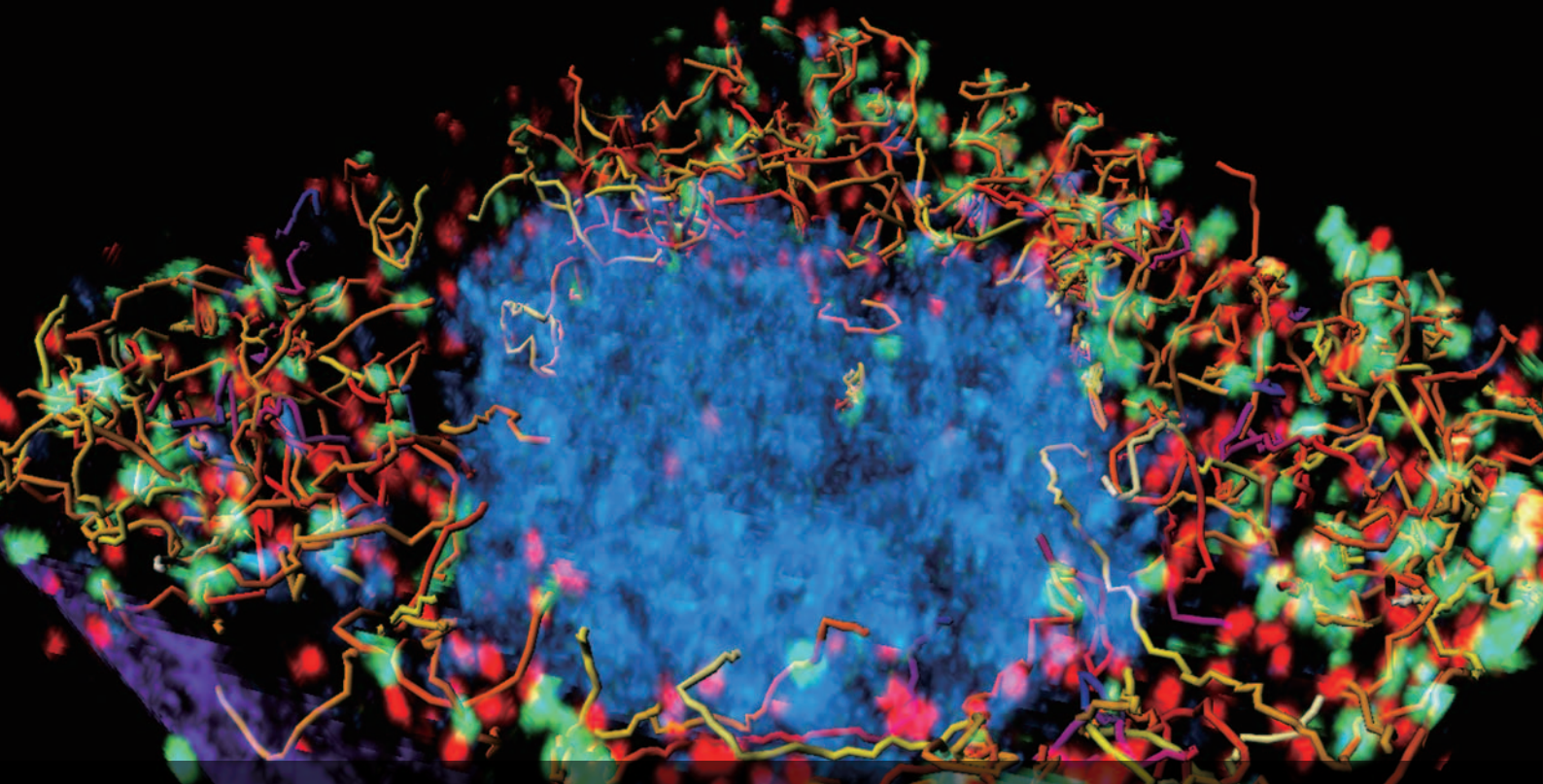
With this in mind, Tamari and her colleagues conducted a genome-wide association study involving a total of more than 7,000 adult Japanese asthma sufferers and around 28,000 unaffected individuals from the same population. By statistically analyzing nearly half a million genetic markers called single nucleotide polymorphisms (SNPs) distributed across the human genome, they identified five susceptibility loci in the Japanese population.

Two loci identified by the researchers were reported previously in Europeans. One was found in the vicinity of the major histocompatibility complex (MHC) on chromosome 6, which contains genes encoding molecules important for the functioning of the immune system. The other previously reported locus spans a region containing two genes, *TSLP* and *WDR36*. *TSLP* is already known to play a role in allergies.

In addition, Tamari and colleagues found three chromosomal regions significantly associated with asthma susceptibility in the Japanese population. They identified a locus on chromosome 10, a gene-rich region on chromosome 12, and a region on chromosome 4 spanning two known genes, *USP38* and *GAB1*. These two genes encode, respectively, an enzyme called ubiquitin-specific peptidase 38, the biological function of which is unknown, and a protein involved in signaling within the immune system. Interestingly, they found that the strongest association with asthma among Japanese adults was close to a SNP in a gene called *AGER* within the MHC previously shown to be important for lung function.

"Our findings contribute to a better understanding of the genetic contribution to asthma susceptibility, opening the way to further functional studies," concludes Tamari.

1. Hirota, T., Takahashi, A., Kubo, M., Tsunoda, T., Tomita, K., Doi, S., Fujita, K., Miyatake, A., Enomoto, T., Miyagawa, T., *et al.* Genome-wide association study identifies three new susceptibility loci for adult asthma in the Japanese population. *Nature Genetics* **43**, 893–896 (2011).



YOKOHAMA INSTITUTE

RIKEN Research Center for Allergy and Immunology

Findings from the RIKEN Research Center for Allergy and Immunology (RCAI) are creating innovation in the field of immunology with the ultimate aim of giving something back to society.

For a few months every year, from February to May, the lives of millions of people in Japan are made unbearable by their allergic reaction to cedar pollen. However, much sought-after, lasting relief for the condition, known as cedar pollinosis, may become a reality thanks to research conducted by RIKEN's Research Center for Allergy and Immunology (RCAI), which has developed a hay fever vaccine it hopes will improve people's quality of life. Research to develop this vaccine is currently being carried out in collaboration with Torii Pharmaceutical Company.

The RCAI's scope of research extends far and wide, including identifying and regulating the mechanisms of autoimmune disease, clarifying regulatory mechanisms in the immune system, developing immune cell therapies to regulate organ transplant rejection by the immune system and to protect against cancer, and developing basic treatments and preventive methods for allergies like cedar pollinosis.

In the eyes of Masaru Taniguchi, director of the RCAI, the reason for the center's success is clear: "RCAI makes use of RIKEN's unique standing to undertake the kind of research that universities or companies cannot."

Masaru Taniguchi

This field-leading stance is achieved by advancing research on immune control through a combination of approaches: developing a new paradigm in life sciences, utilizing new discoveries to establish an infrastructure that innovates technology and medicine, and offering the infrastructure to universities, companies and outside researchers. In this way, the RCAI can achieve its ultimate goal of giving back to society.

Findings published by the RCAI over 2011 and 2012 demonstrate the RCAI's position at the forefront of immunology research. In 2011, Takaharu Okada and his team have monitored the process of cell development in the germinal centers of mice by tracking the expression of the protein Bcl6, which helps regulate the expression of developmental genes. They observed that Bcl6 expression changes *in vivo* migration patterns of B cells, and also noted that plasticity of Bcl6 expression is significant to Tfh cells (see *Ensuring the persistence of immune memory*, p. 23).

In other research, Masato Kubo and colleagues have identified a transcription factor that regulates the protein, E4BP4. The team found that this protein is important in preventing the immune system from attacking the body's own organs, and could play a key role in the fight against autoimmune disease (*Nature Immunology* **12**, 450–459, 2011).

Takashi Saito and colleagues have uncovered new insights into the accumulation of microclusters at the interface between T cells and immune cells, where specialized

motor proteins shuttle microclusters of signaling receptors to a central area for later disposal, helping to control immune activation (*Immunity* **34,** 919–931, 2011).

Katsuaki Sato and his team have recently conducted a detailed analysis on a subset of immune cells in mice. Their results reveal that pDC immune cells take center stage in responding to infection, controlling the inflammatory response pathway and producing pathogen-destroying white blood cells. pDCs were also found to help prevent the immune system from overreacting to non-threatening antigens (*Immunity* **35**, 958–971, 2011).

A 2012 study on immune cells conducted by Shohei Hori and his team has shed light on the expression of the Foxp3 protein, which is used to identify a variety of immune cells. The team developed a labeling technique that enables them to differentiate cells which are currently expressing the protein from those that previously expressed the protein (*Immunity* **36**, 262–275, 2012).

The RCAI understands the importance of developing young immunology researchers and postgraduate students with an international mindset. As part of this endeavor, the RCAI conducts its annual International Summer Program. The RCAI has also developed the role of Young Chief Investigator, a new program that will provide a career path for researchers aged 40 or younger. Those chosen for the program run independent research laboratories on multidisciplinary research that bridges immunology with other research fields, while being mentored by specialists outside the RCAI in related fields.

The RCAI also collaborates with Harvard University in the US through the annual Harvard Summer School, which is held at the RCAI and attended by visiting students from Harvard. The two-week basic immunology course and the two-month internship provided at the RCAI are officially recognized as a credit course at Harvard University.

Looking to the future, a great deal of emphasis is being placed on nurturing young researchers based on RIKEN's strong belief that new areas of study must be continuously developed.

"The only way to have fresh areas of interdisciplinary study is by developing young blood," says Taniguchi. "I am looking forward to the day when these young talented researchers become the leaders in the field of integrative immunology."

Ensuring the persistence of immune memory

A gene regulatory factor promotes long-term protection against infectious threats by effecting the maturation of a variety of immune cells

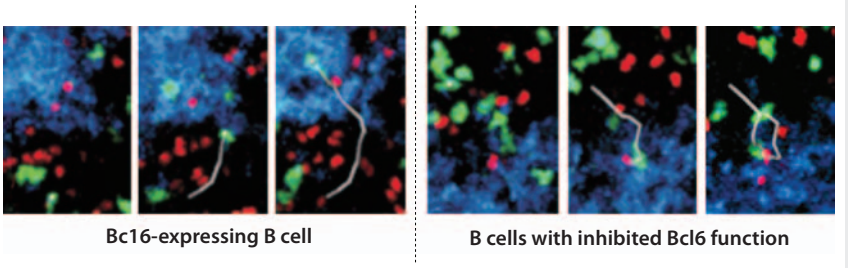


Figure 1: Time-lapse photography at four-minute intervals shows the migration (white trail) of a Bcl6-expressing B cell (green) into the GC (blue) following induction of an immune response. By comparison, B cells with inhibited Bcl6 function fail to migrate to the GC.

Structures within the lymph nodes known as germinal centers (GCs) help the body to maintain long-term immune defense against foreign threats. The GCs essentially act as sites where antibody-producing B cells undergo a process of 'evolution' to generate higher-quality antibodies. This evolutionary mechanism is in turn supported by a class of T cells known as follicular helper T (Tfh) cells.

Takaharu Okada and colleagues at the RCAI in Yokohama recently tracked the process of B cell development in mouse GCs by monitoring expression of Bcl6[1]. This protein facilitates B cell evolution by regulating expression of key developmental genes.

The researchers were surprised to note a broader scope of Bcl6 activity than expected. "It became apparent that Bcl6 is important for Tfh cells as well," says Okada, "and I felt that we should track [the levels of] Bcl6 expression in both B and T cells at the same time."

They quantified Bcl6 levels by generating transgenic mice in which a DNA fragment encoding a fluorescent protein had been inserted into one copy of the Bcl6 gene. Since this insertion partially disrupted Bcl6 function, this reporter system enabled the researchers to examine the effects of inhibiting this protein.

Following the induction of an immune response in the animals, Okada and colleagues observed an increase of Bcl6 expression in antigen-specific B cells within peripheral regions of the lymph node; these subsequently migrated to the GC, where they continued to strongly express Bcl6 (Fig. 1).

This migration and maturation process is dependent upon interaction with Bcl6-expressing helper T cells. All T cells expressing high levels of Bcl6 became Tfh cells, but many Tfh cells subsequently reduced Bcl6 production to varying degrees. Okada was surprised that the dynamics of Bcl6 expression differed between B and T cells. "This suggests that they employ different mechanisms for regulating expression of this important transcription factor," he says.

Okada and his team also recorded observations suggesting that Tfh cells expressing low levels of Bcl6 may give rise to 'memory cells', which enable the immune system to react quickly to recurring threats. However, this will require further investigation.

Understanding how these various cells employ this shared regulatory factor will also be a top priority moving forward. "We would like to learn the molecular mechanisms of Bcl6 expression in B and T cells by setting up collaborations with experts in the field of gene and protein expression control," says Okada.

1. Kitano, M., Moriyama, S., Ando, Y., Hikida, M., Mori, Y., Kurosaki, T. & Okada, T. Bcl6 protein expression shapes pre-germinal center B cell dynamics and follicular helper T cell heterogeneity. *Immunity* **34,** 961–972 (2011).

YOKOHAMA INSTITUTE

RIKEN Omics Science Center

Focused on the comprehensive study of molecules in living organisms, the RIKEN Omics Science Center (OSC) has a domestic and international presence that makes it one of the leaders in its field.

The core of research carried out at the Omics Science Center (OSC) is the in-depth study of molecules in living organisms. To achieve this, the center is faced with two challenges. One is to conduct research that elucidates mutual-effect gene networks in cells through the development of original technology based on next-generation sequencers. This technology is being promoted as basic research leading to regenerative medicine. The other challenge is to offer the technologies developed at the center in the course of research as a pipeline for external researchers to help bolster life sciences in Japan.

"Our research activities at the OSC are clearly carried out with medical research being the ultimate goal," says OSC Director Yoshihide Hayashizaki. Through joint efforts with industry, the OSC aims to carry out basic research that leads to practical applications.

As part of its mission to conduct research leading to regenerative medicine, the OSC plays a vital role in FANTOM5, the fifth phase of the Functional Annotation of Mammalian Genome (FANTOM) project. An international research consortium founded in 2000 by Hayashizaki and his colleagues, FANTOM assigns functional annotations to the full-length complementary DNA collected during the Mouse Encyclopedia Project at RIKEN. The aim of the FANTOM5 project—the biggest consortium in the world in life sciences—is to comprehensively elucidate the control mechanisms that regulate the behavior of various cells and clarify the differences in gene networks among different types of cells. Network data derived from the FANTOM5 project will be applied in cell conversion technology, bringing us one step closer to the realization of regenerative medicine.

Yoshihide Hayashizaki

In February 2011, RIKEN hosted an international symposium for FANTOM5 that was attended by 180 researchers from 51 institutions in 19 countries. The strong connections forged with researchers from around the world through such events is one of the key factors that allows the OSC to convert basic research results into actual applications for medical use.

In recognition of Hayashizaki's invaluable work in the FANTOM project and his vital contributions to key technologies in the field of RNA research, as well as to studies conducted by the Karolinska Institutet, he was appointed Honorary Doctor of Medicine at the Karolinska Institutet, Sweden, in 2012. The honorary doctorate is awarded to researchers who have made an important contribution to research at the Karolinska Institutet.

The OSC has gone from strength to strength in its research achievements. In genetic research, Charles Plessy and colleagues have mapped the genomic structure of odorant receptor repertoire in mice, which are associated with sense of smell. The study reveals important findings about how the start points and promoter regions play a part in controlling the expression of the broad majority of this type of gene, and how the promoter sequences are closely similar between olfactory receptors. These results help to enhance

scientists' understanding of gene expression which controls our sense of smell (see *On the scent of olfactory control*, p. 25).

In other research, Piero Carninci and colleagues investigated the role of mobile genetic elements known as retrotransposons in ordering the genetic circuitry governing neurobiological processes. They examined mutations in germline and somatic cells to show that retrotransposons move to active protein-coding genes differentially expressed in the brain (*Nature* **479**, 534–537, 2011).

Researchers from the same group have investigated the role of RNAi components in transcription processes in animal multicellular organisms. They showed that central RNAi components such as DCR2 and AGO2 associate with chromatin and interact with key transcriptional machinery, thus playing a vital role in transcriptional regulation by controlling the efficiency of RNA polymerase (*Nature* **480**, 391–397, 2011). In other studies, Takahiro Suzuki and his team explored the mechanisms that underpin cellular functions controlled by transcriptional regulatory networks (*PLoS One* **7**, e33474, 2012), and Yuki Hasegawa and her team also probed the factors associated with maintaining the pluripotency of mouse embryonic stem cells and induced pluripotent cells (*Stem Cells* **29**, 1196–1205, 2011).

The OSC is also making key contributions to the rebuilding of research communities in Tohoku affected by the Great East Japan Earthquake on 11 March 2011. In collaboration with bioinformatics solution provider, CLC bio Japan, the OSC provided researchers in affected areas with advanced software tools for DNA/RNA/protein analysis as well as dedicated servers and IT support. Such provisions allowed bioinformatics researchers in the Tohoku region to continue their research and bolster Japan's scientific output.

"Compared to all the troubles that people faced after 11 March in the affected areas, continuity of research may not seem like the highest priority," says Hayashizaki. "However, we feel that it is our duty to assist our colleagues in any way we can to help them get through this difficult time."

In the coming years, the OSC aims to further expand its contribution to society. "We would like to build upon the basic research carried out on intracellular gene networks and utilize the knowledge that we have obtained to work closely with companies and hence act as a foundation for life sciences in Japan," says Hayashizaki.

On the scent of olfactory control

Gene mapping reveals the architecture that controls the expression of the genes responsible for our sense of smell

Within the nasal cavity, millions of sensory neurons in a postage-stamp-sized patch of tissue called the olfactory epithelium control our sense of smell. Thanks to the exquisitely controlled expression of some 300 different olfactory receptor genes, each neuron can detect a small number of distinct volatile odorants. How these genes are regulated, however, has long been a mystery.

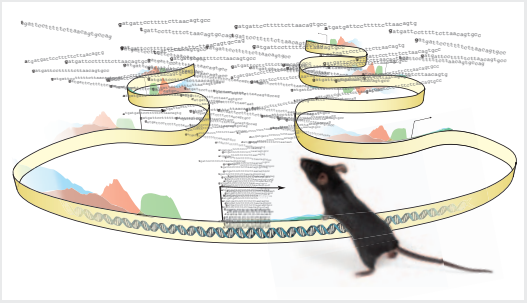


Figure 1: An artistic representation of how the nanoCAGE technique flags the gene promoters for the vast majority of mouse olfactory genes.

Now, an international team led by RIKEN researchers has mapped the genomic architecture of the odorant receptor repertoire in mice, revealing the start points and promoter regions involved in controlling the expression of the vast majority of these genes[1]. "Our study shows that these promoter sequences are strikingly similar between all the olfactory receptors," says Charles Plessy of the OSC, who led the study.

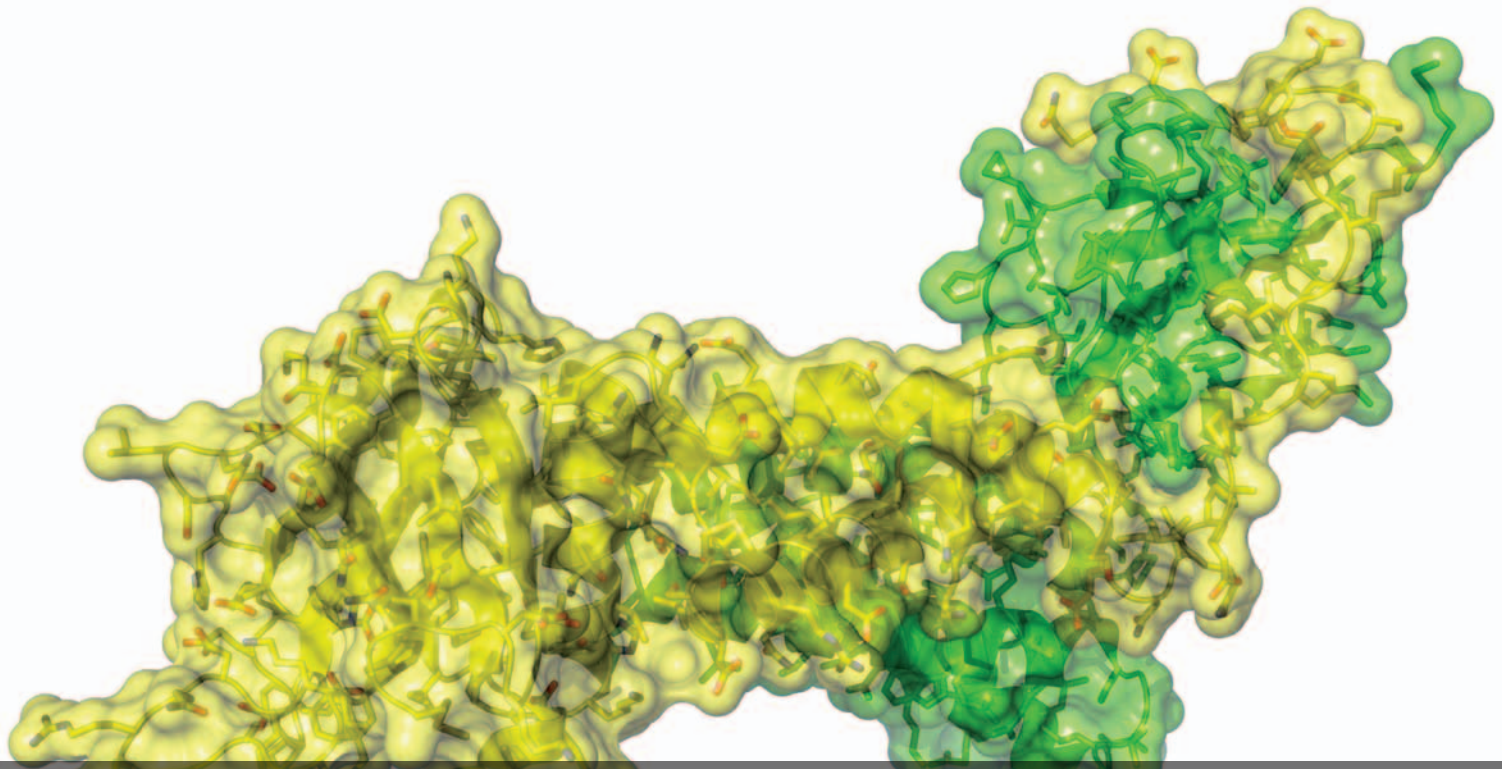
To chart all the promoters, Plessy and colleagues first had to devise an appropriate technique. Plessy's collaborator, Piero Carninci also from the OSC, had previously developed a method called cap-analysis gene expression (CAGE) that determines the location of transcription start sites across the whole genome[2]. But CAGE requires large quantities of RNA, which are not always obtainable from particular types of tissues, including the olfactory epithelium. The researchers therefore modified CAGE to nanoCAGE, which requires as little as 10 nanograms of RNA of biological material per sample[3].

Both CAGE and nanoCAGE work by taking all the messenger RNA transcripts in a given sample, converting them into DNA tags and then comparing the output against a reference genome to find all the transcription start sites. The investigators can then decipher the conserved DNA regulatory sequences in the immediate vicinity of the starting points that form the core promoters.

Using this approach on the minute quantities of RNA found in the olfactory epithelium of mice, Plessy's team plotted the promoters of almost 90% of the mouse olfactory receptor genes, as well as the expression of many non-coding regulatory RNAs (Fig. 1). Further bioinformatic analysis of the DNA surrounding the mapped promoters revealed a number of candidate transcription factor binding sites that help control gene expression, some of which the researchers also validated in mouse experiments.

Plessy and colleagues are now adapting the CAGE technique for even smaller biological samples: single cells. "Such a method would have wide applications in biology and medicine, and, of course, in the biology of olfactory receptors," says Plessy. "With a single-cell technology we will have the potential to make a significant contribution to the field."

1. Plessy, C., Pascarella, G., Bertin, N., Akalin, A., Carrieri, C., Vassalli, A.,Lazarevic, D., Severin, J., Vlachouli, C., Simone, R., *et al.* Promoter architecture of mouse olfactory receptor genes. *Genome Research* advance online publication, 22 December 2011 (doi: 10.1101/gr.126201.111).
2. Shiraki, T., Kondo, S., Katayama, S., Waki, K., Kasukawa, T., Kawaji, H. Kodzius, R., Watahiki, A., Nakamura, M. *et. al.* Cap analysis gene expression for high-throughput analysis of transcriptional starting point and identification of promoter usage. *Proceedings of the National Academy of Sciences USA* **100,** 15776–15781 (2003).
3. Plessy, C., Bertin, N., Takahashi, H., Simone, R., Salimullah, M., Lassmann, T., Vitezic, M., Severin, J., Olivarius, S., Lazarevic, D., *et al.* Linking promoters to functional transcripts in small samples with nanoCAGE and CAGEscan. *Nature Methods* **7,** 528–534 (2010).



YOKOHAMA INSTITUTE

RIKEN Systems and Structural Biology Center

Research spanning different scientific fields at the RIKEN Systems and Structural Biology Center (SSBC) takes life sciences to a new dimension and provides answers to why certain life phenomena exist.

How life works is a question that has been asked from time immemorial. The RIKEN Systems and Structural Biology Center (SSBC) aims to provide some answers to this question by building a bridge between the life sciences and material science, expanding the rational design of biomolecular mechanisms and increasing predictability in the life sciences.

"Our center's mission involves focusing on life phenomena that cover a wide range of research fields," says Shigeyuki Yokoyama, director of the SSBC. "We aim to clarify complicated biological phenomena using the laws of physics and chemistry that regulate molecular behavior, as well as creating a platform for the life sciences."

Initially established in 1998 as the Genomic Sciences Center, the SSBC has elucidated the structures and functions of many important analysis-defying proteins. The period between 2002 and 2007 was a particularly productive time for the center in terms of three-dimensional structure analyses and its associated novel technology development, when it determined around 2,700 protein structures and functions through the National Project on Protein Structural and Functional Analyses.

Using these fruitful results, the SSBC carries out structural analyses on even more challenging proteins to elucidate the mechanisms of interactions in biomolecular systems at an atomic resolution. The center also develops innovative elemental technologies to better understand the functions and structures of proteins that are difficult to tackle, and uses the results to find the mechanisms of and treatments for various diseases.

"We work on illnesses such as cancer that affect a large number of people. This not only improves people's health but ends up having a positive effect on the economy," says Yokoyama. Since 2010, the SSBC has taken part in the Program for Drug Discovery and Medical Technology Platforms under the Research Cluster for Innovation, being responsible for four of the nine drug discovery platform units currently supported by the program.

Recent results achieved by the SSBC make a vital contribution to drug development and the treatment of disease. In a recent study, Toru Sengoku and Shigeyuki Yokoyama investigated the elusive mechanism by which a histone-demethylating enzyme selectively regulates the methylation state of histone H3K27. The researchers obtained the H3 bound and unbound crystal structures of the demethylase UTX/KDM6A protein and used mutational analysis to show that many amino acid residues are vital to the process of histone demethylation (*Genes and Development* **25**, 2266–2277, 2011). The results pave the way for the development of novel inhibitors targeting the histone demethylase.

Shigeyuki Yokoyama

In other research, a team led by Shigeyuki Yokoyama and colleagues established the structural basis governing the autoinhibition of the proteins DOCK2 and ELMO1, whose

complex is a key intermediate in cell signaling in lymphocytes. The team used X-ray crystallography to identify residues at the termini of DOCK2 and ELMO1, which bind together to disrupt each other's autoinhibited state (*Proceedings of the National Academy of Sciences of the USA* **109**, 3305–3310, 2012).

Shigeyuki Yokoyama, along with Naoki Kamo's group at Matsuyama University, has revealed the characterization and function of the gene *ARII*—which encodes a rhodopsin from the algae *Acetabularia acetabulum*. Through structural analysis of the protein, researchers observed an amino acid network, which is central to the uptake and release of individual protons, as well as other concealed disparities in structure (*Journal of Molecular Biology* **411**, 986–998, 2011).

Beyond its own research, the SSBC maintains close ties with researchers throughout Japan, and researchers at other universities and institutions benefit from the SSBC's policy to provide its equipment for external use. The nuclear magnetic resonance (NMR) facility operates 24 NMR instruments which provides a valuable resource for external researchers, especially young scientists who do not have the budget to purchase their own equipment.

With the center now well established, Yokoyama is setting new goals for the SSBC. "It is my earnest desire to create a paradigm shift in how life science research is carried out. The more I discover about nature, the more I feel there is a need to understand and not look down upon it. Our goal is to comprehend biomolecular systems, and we would like to further contribute to society through our activities and our drug discovery research," he says.

NMR Research Network

The Nuclear Magnetic Resonance (NMR) Research Network between the SSBC and other institutions enables researchers outside of RIKEN to utilize RIKEN NMR instruments in their research. Already in operation at seven collaborative institutions in Japan, the instruments are critical tools for collaborative research activities in various fields. The SSBC has also extended this network to Tohoku University's medical school, where research infrastructure was severely damaged by the Great East Japan Earthquake in 2011.

Finding a tumor suppressor's groove

By piecing together the interactions between a pair of proteins involved in colorectal cancer, researchers may have identified suitable targets for drug development

The tumor suppressor protein called adenomatous polyposis coli (APC) is a central genetic risk factor for colorectal cancer. In fact, mutations that potentially alter the structure or function of this protein are found in an estimated 85% of human colorectal tumors, which are currently the third highest-ranked cause of cancer-related death worldwide.

Unfortunately, APC is a very large protein with numerous interacting partners, making it a challenge to determine the direct impact of a given mutation. "The mechanisms by which these mutations lead to cancer is still poorly understood," says Shigeyuki Yokoyama, director of the SSBC.

Structural analysis offers helpful insights into protein function, but obtaining these data can be difficult with such massive target proteins. Yokoyama and colleagues therefore decided to focus on one particular segment of APC, known as the armadillo repeat (Arm) domain[1]. In particular, they were interested in understanding how Arm interacts with and inhibits Sam68, an APC-binding protein that is believed to contribute to the activation of genes involved with tumorigenesis.

The researchers determined that the Arm domain forms a helical structure, with an L-shaped groove for the recognition of binding partners. The Arm-interacting domain of Sam68, on the other hand, appears to be relatively disordered until it binds this groove, an association stabilized by a number of interactions between specific amino acid residues on the two proteins (Fig. 1). Yokoyama and colleagues were subsequently able to confirm the contributions of these residues by systematically introducing mutations and determining their impact on these proteins' affinity for each other.

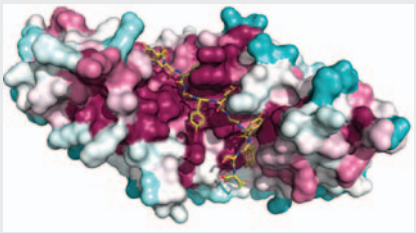


Figure 1: Crystal structure of the complex of the Arm domain of APC and Sam68. The groove on the Arm domain of APC contains highly conserved residues (magenta) that form numerous specific interactions with Sam68 residues (yellow).

With this information in hand, the researchers assessed the potential significance of real-life mutations at these points of interaction. "We were able to map cancer-related APC mutations within this domain and analyze their effects on the structure of APC and on the binding of proteins to APC," says Yokoyama. Indeed, some of the amino acid changes introduced by these mutations appeared to be directly detrimental to complex formation between APC and Sam68.

Arm interacts with several other important proteins, and Yokoyama's group plans to perform equally in-depth analyses to characterize the structural bases for these associations. However, he notes that the present findings—in conjunction with data obtained by co-author Tetsu Akiyama at the University of Tokyo—may already offer direct clinical utility. "We think that targeted disruption of the interaction between mutated APCs and Sam68 might be a good strategy to prevent the development of cancer," says Yokoyama.

1. Morishita, E.C., Murayama, K., Kato-Murayama, M., Ishizuka-Katsura, Y., Tomabechi, Y., Hayashi, T., Terada, T., Handa, N., Shirouzu, M., Akiyama, T. & Yokoyama, S. Crystal structures of the armadillo repeat domain of adenomatous polyposis coli and its complex with the tyrosine-rich domain of Sam68. *Structure* **19**, 1496–1508 (2011).

YOKOHAMA INSTITUTE

RIKEN Bioinformatics and Systems Engineering Division

An ingenious database infrastructure developed by the RIKEN Bioinformatics And Systems Engineering division (BASE) connects many of RIKEN's open databases to provide easy access to data by researchers both in-house and around the world.

Data are a precious commodity, and companies around the world spend millions of dollars in constructing intricate in-house systems to collect and protect the data produced by research. RIKEN, however, is different: it aims to make data available to the public.

"In five years' time, we want to have comprehensively analyzed the data produced by each of RIKEN's centers. We then plan to use that analysis as a means of making the database public so that each center's activities are connected independently and data are circulated from RIKEN to external communities," says Tetsuro Toyoda, director of the Bioinformatics And Systems Engineering division (BASE).

Established in 2008, BASE analyzes the vast amounts of life science data generated in RIKEN, and promotes information technology research strategically directed at making higher-level scientific discoveries.

In order to achieve this, BASE has constructed a new type of technical database infrastructure called SciNetS, a scalable system based on structured content known as the semantic web. SciNetS can host hundreds of different databases simultaneously in its cloud system, which allows every user to access all data using a common interface. "SciNetS aims to allow data from each of RIKEN's separate centers to be used more easily and permanently, by both in-house and external researchers, and to ensure that data will not be lost from the 400 database projects stored within SciNetS, even after the laboratory that originally generated the database is closed," says Toyoda.

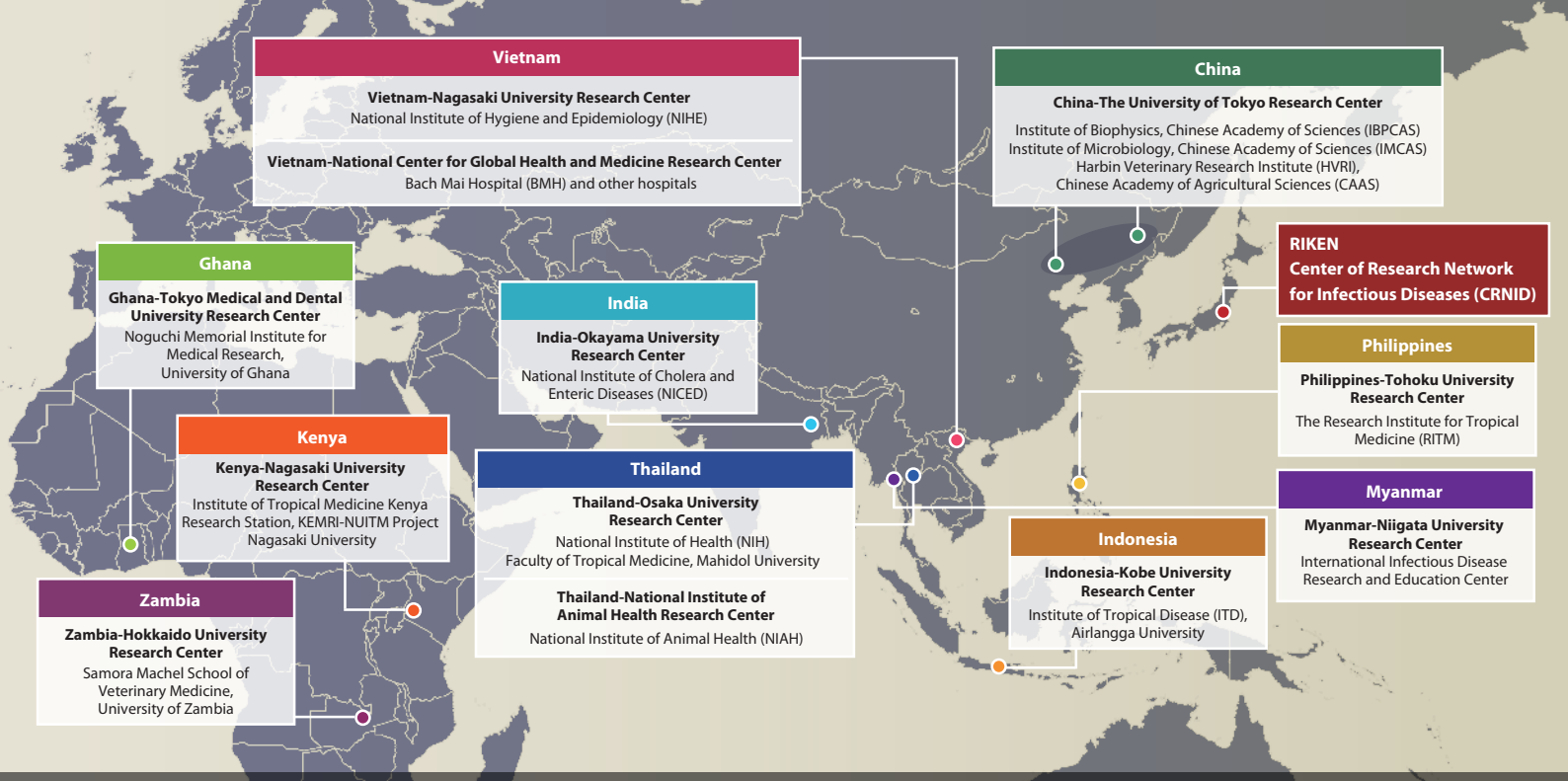
Tetsuro Toyoda

The infrastructure connects different 'clouds' or local user networks on the internet. This means that virtual laboratories can be created, allowing collaborative research to be carried out in a conceptual laboratory in the SciNetS cloud. Using this framework, data generated anywhere within RIKEN should be made available to all in-house scientists.

The SciNetS infrastructure is designed such that when a set of data is selected, life science data from different related semantic layers can also be extracted. This sharing of data brings researchers and individual scopes of research together to facilitate a higher level of scientific discovery.

SciNetS plays a central role on both domestic and international levels. Internationally, it acts as Japan's hub node by connecting with international databases of phenomes for mice and *Arabidopsis*, while on a domestic level it supplements the Integrated Database Project, funded by the Japan Science and Technology Agency promoting the National Bioscience Database Center project.

BASE's activities do not stop there. In 2012, BASE researchers developed key improvements to a technique of full-length RNA transcript reconstruction. Usual problems with this technique include noises and biases which interfere with correct reconstruction. BASE's new method, however, is robust against noise and bias, enabling accurate transcript reconstruction using any kind of equipment (*Bioinformatics* doi: 10.1093/bioinformatics/bts065, 2012).



YOKOHAMA INSTITUTE

RIKEN Center of Research Network for Infectious Diseases

The RIKEN Center of Research Network for Infectious Diseases (CRNID) plays a crucial role in coordinating research activities for J-GRID—an international network that aims to mitigate infectious diseases and make the world a safer place.

The RIKEN Center of Research Network for Infectious Diseases (CRNID) was established in 2005 as the headquarters of the Japan Initiative for Global Research on Infectious Diseases (J-GRID). "Infectious diseases heed no national borders," says Yoshiyuki Nagai, director of the CRNID. "Sharing information and research materials, however, is not always easy. Therefore, international collaboration across borders must be enhanced. This is the conceptual basis for launching the J-GRID program."

Since 2005, J-GRID has expanded to include 13 overseas collaboration centers in 8 countries (6 in Asia and 2 in Africa). In addition, J-GRID invited two associate members, Kenya and Myanmar, in 2011. These research collaboration centers were each established on a bilateral basis between a Japanese university/institution and a counterpart in the host country.

The aims of J-GRID include conducting research on infectious diseases of regional and global importance, and advancing technologies and developing human resources in the field in collaboration with the counterpart organizations. "In that way, we can contribute to the public health of the host country, our own country and the world," says Nagai.

K. Okada receiving a plaque in Thailand in 2012

After completion of the first start-up phase (2005–2009), J-GRID has stepped up its activity for the second phase (2010–2014).

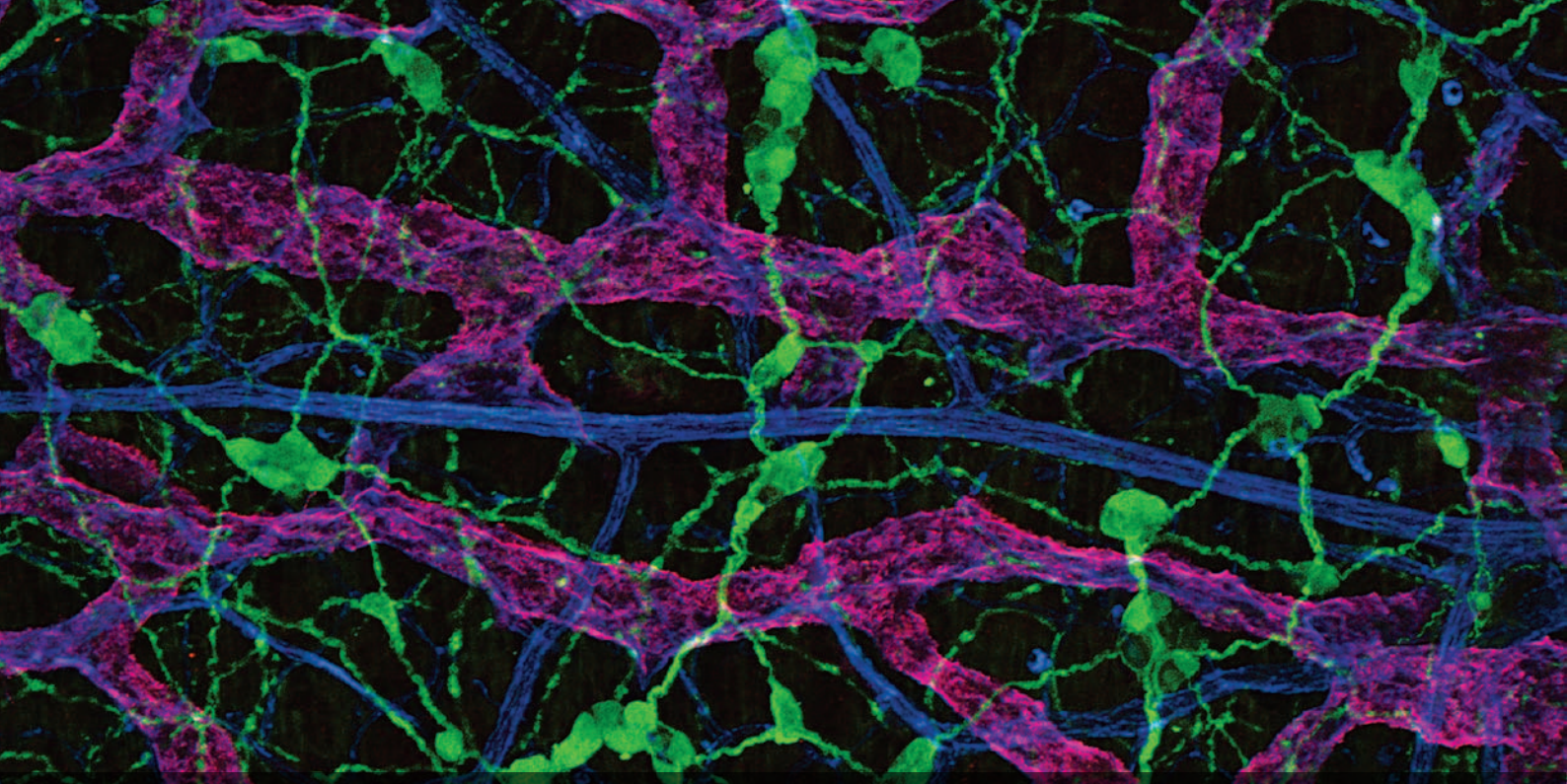
"While the first phase was just like an incubation period, the second phase should be the exponential growth phase, maximizing our research activities," says Nagai. In the initial two years (2010 and 2011) of this phase, J-GRID published a total of 379 papers. "We can see a lot of remarkable research outcomes from J-GRID. I am also quite proud of the fact that J-GRID's achievements have become highly recognized by our host countries," says Nagai.

Nagai cited the study conducted by Kerdsin and colleagues (*Lancet* **378**, 960, 2011), which reported two cases of *Streptococcus suis* infections with previously unreported serotypes in Thailand. In addition, Kazunori Oishi, the PI of this research, was awarded a commendation from the Thai government in April 2012 for his contribution to public health with his research on *S. suis*.

Kasuhisa Okada, who is based at a research center in Thailand, received a plaque in honor of his contribution to public health in Thailand through the development of a rapid detection method for cholera outbreaks. This method is based on loop-mediated isothermal amplification (LAMP) technology.

The CRNID's role is to ensure sustainability of the J-GRID network and to promote the network's activities on both the domestic and international stage. The CRNID plays a key role in publicizing J-GRID by developing and improving the project website, publishing e-mail newsletters, booklets and leaflets, and organizing public seminars. The CRNID is also making efforts to strengthen the interaction of J-GRID with national and international networks sharing similar missions.

"I think all efforts should converge on making J-GRID sustainable for many years to come," says Nagai.



KOBE INSTITUTE

RIKEN Center for Developmental Biology

The RIKEN Center for Developmental Biology (CDB) carries out basic research into the mechanisms of embryonic development, regeneration and stem cell biology with the aim to develop a deeper understanding of the formation of multicellular bodies, as well as possible future applications in regenerative medicine.

The RIKEN Center for Developmental Biology (CDB) was established in 2000 to serve as a national core institute focused on the study of embryogenesis—the processes that allow a single cell, the fertilized egg, to divide and differentiate into a body composed of enormous numbers of cells of many different types. This work relies on a very broad range of approaches from molecular and cell biology to comparative anatomy and evolutionary studies to help develop insights into how our bodies form. Such fundamental research may have the added potential of contributing to the development of cell-based approaches in the emerging field of regenerative medicine.

"One of our missions is to study biological development from various perspectives; another is stem cell research," says CDB Director Masatoshi Takeichi. "As the concept of stem cells becomes clearer, this opens up the potential for applications in medicine. But in order to achieve this, we need to know their fundamental mechanisms. It is important to implement these two missions simultaneously, which is why this institute was established."

Masatoshi Takeichi

At the time when the CDB came into existence, the city of Kobe was deemed an ideal location because of the recently created Kobe Medical Industry Development Project—which has developed into a cluster of 11 core research facilities as well as over 200 private companies.

Takeichi believes that due to the collaboration that exists between public, academic and corporate research organizations, the complex sets up an environment that is conducive to producing excellent research results.

The year 2011 was yet another in which the CDB made many important achievements. In two recent ground-breaking stem cell studies, Yoshiki Sasai and colleagues discovered that laboratory-grown embryonic stem cells can arrange themselves into a partial pituitary gland, and in another study, into a developed, properly organized retina. In the first study, the partial pituitary gland is able to completely function when transplanted into mice. Sasai and his team designed a unique cell-culture technique in order to grow stem cells in floating clusters, and findings could lead to new stem-cell therapeutic treatments for hormonal disorders (see *Great leap forward for regenerative medicine*, p. 31).

In the second study, Sasai and colleagues probed a new understanding of retinal development, in which the retina can form in the absence of external guidance. They reveal that cells destined to become the retina have a latent order that enables structural formation through the guidance of an internal program (*Nature* **472**, 51–56, 2011). The results of both studies represent an important stepping stone on the path to the

development of fully functioning laboratory-grown organs and transplantation material.

In other research, Shigeo Hayashi and his colleagues have discovered a surprising role for the power houses of cells, known as mitochondria, in the sperm of fruit fly. The researchers investigated the underlying mechanism of sperm cell elongation, and showed that sperm tail growth is influenced by the giant mitochondria and microtubules that form around the tails. The study demonstrated that the mitochondria acts as a structural platform for the rearrangement of microtubules, and supports the elongation of the sperm tails (*Current Biology* **21**, 805–814, 2011).

Kazuo Yamagata and colleagues have developed a new time-lapse imaging technique of animal embryos which has uncovered complications that adversely affect cloning efficiency. The researchers used a specially designed microscope to gather imaging data during the course of embryo development. The imaging showed that embryos were likely to experience disruptions to their genetic material during cell division. The results help scientists to better understand the connections between abnormalities and genetic instability, connections which could potentially contribute to human infertility problems (*Development Biology* **364**, 56–65, 2012).

New findings by Takashi Nishimura and colleagues show that insulin-producing cells (IPCs) in both fruit flies and humans apply similar molecular mechanisms through which hormone production is controlled. Using the process of gene expression analysis, Nishimura and his team found that numerous proteins associated with eye development also help determine IPC differentiation and gene expression (*Proceedings of the National Academy of Sciences USA* **109**, 2406–2411, 2012).

Researchers at the CDB are fortunate in that the center enables great freedom of choice in terms of how to pursue scientific goals. The center takes a balanced approach between trying to understand the mechanisms of animal development and applying such findings to the development of medical applications.

"Technological advances such as next-generation sequencers allow us to study genetic conditions in more detail than was previously possible, which will lead to more in-depth research on complex mechanisms in the future," says Takeichi.

Great leap forward for regenerative medicine

Recent success in growing a functional pituitary gland in a laboratory culture will advance regenerative medicine and stem-cell therapies for hormonal disorders

Embryonic stem cells grown in a laboratory culture can organize themselves into a partial pituitary gland that is fully functional when transplanted into mice, a team of researchers led by Yoshiki Sasai of the CDB reports[1]. These researchers developed a novel cell-culture technique for growing stem cells in three-dimensional floating clusters. They had previously shown that stem cells grown in this way can organize themselves into functional eye and brain tissue[2,3].

In their study on the pituitary gland, the researchers used their technique to grow mouse stem cells, and then altered the culture conditions to recapitulate the embryonic environment that gives rise to the anterior pituitary, or adenohypophysis.

The adenohypophysis contains cells that synthesize and secrete five hormones under the control of the hypothalamus. After release into the blood stream, these hormones play multiple roles in the body, including regulation of growth, blood pressure, metabolism and sex-organ function. Development of the adenohypophysis requires interaction between two types of tissue, leading to the formation of a small pouch that pinches off from the area of the embryo and forms the mucosa in the mouth.

When the researchers stimulated stem-cell clusters with specific signaling molecules, they generated both tissue types that separated naturally into layers. Cells at the interface between the two layers then spontaneously formed oval-shaped pouch-like structures (Fig. 1), before differentiating into four types of precursors, each of which began to synthesize and secrete a different hormone.

Sasai and colleagues transplanted the clusters into the kidneys of mice whose pituitaries had been surgically removed. Normally these mice would die two months post-surgery, but the transplanted cells rescued the animals by normalizing the levels of hormones in the bloodstream.

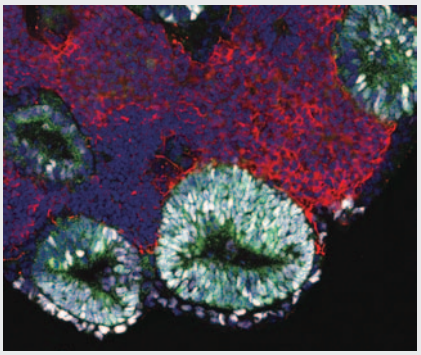


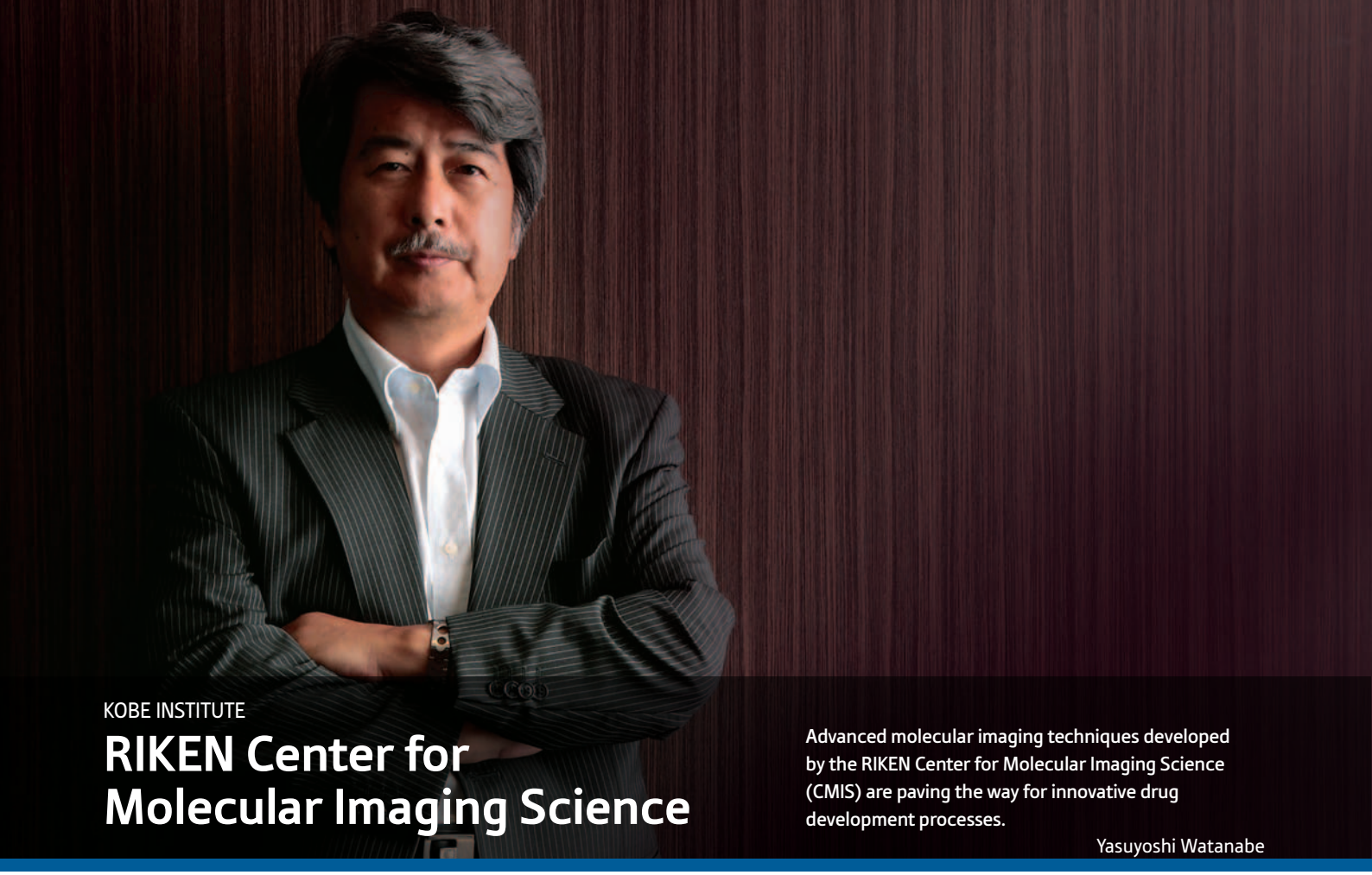
Figure 1: A micrograph of an embryonic pituitary gland that self-formed in an embryonic stem-cell aggregate on day 13 of culture.

The research could open new avenues for stem-cell therapies to treat hormonal disorders. It also represents a significant advance in using stem cells to generate complex three-dimensional structures: it represents a step towards growing fully functional organs in the laboratory.

This technique has a straightforward medical application in treating human patients with pituitary deficiencies. "Growth hormone deficiency could be also targets of the cell therapy," Sasai notes. Eventually, it could be possible to grow functional neural tissue for transplantation into the human brain. For example, the ability to grow cerebellar tissue containing Purkinje cells could be useful for treating cerebellar atrophy.

"Regenerative medicine is surely proceeding in this direction," says Sasai. "We are now developing computer-based models and simulations to facilitate the design of more complex organs."

1. Suga, H., Kadoshima, T., Minaguchi, M., Ohgushi, M., Soen, M., Nakano, T., Takata, N., Wataya, T., Muguruma, K., Miyoshi, H., *et al.* Self-formation of functional adenohypophysis in three-dimensional culture. *Nature* **480,** 57–62 (2011).
2. Eiraku, M., Takata, N., Ishibashi, H., Kawada, M., Sakakura, E., Okura, S., Sekiguchi, K., Adachi, T. & Sasai, Y. Self-organizing optic-cup morphogenesis in three-dimensional culture. *Nature* **472,** 51–56 (2011).
3. Eiraku, M., Watanabe, K., Matsuo-Takasaki, M., Kawada, M., Yonemura. S., Matsumura, M., Wataya, T., Nishiyama, A., Muguruma K. & Sasai, Y. Self-organized formation of polarized cortical tissues from ESCs and its active manipulation by extrinsic signals. *Cell Stem Cell* **3,** 519–532 (2008).



KOBE INSTITUTE

RIKEN Center for Molecular Imaging Science

Advanced molecular imaging techniques developed by the RIKEN Center for Molecular Imaging Science (CMIS) are paving the way for innovative drug development processes.

Yasuyoshi Watanabe

The rapid advance in molecular and genomic studies has opened a new realm of scientific research on humans, but the difficulty in observing samples in natural conditions remains a major obstacle. "We want to look into how they behave in the body. That is molecular imaging. Our objective is to elevate 'life science' to 'live science' in humans," says Yasuyoshi Watanabe, director of the RIKEN Center for Molecular Imaging Science (CMIS).

Molecular imaging refers to methods to visualize and track the dynamic behavior of genes, proteins and other biological molecules in the body using sophisticated technologies such as positron emission tomography (PET). Currently, less than 10% of compounds pass clinical trials due partly to the differences in targeted deliverability and pharmacokinetics of drug molecules between humans and small laboratory animals. PET allows such pharmacokinetics to be observed directly in humans noninvasively, providing an extra level of certainty prior to making the decision to take a drug to clinical trials. These are called 'micro-dose' clinical trials, in which pharmacokinetics can be observed using less than 1% of the normal dosage, well below the threshold of side-effect occurrence. "One thing we are aiming at is to conduct micro-dose trials and drop unpromising compounds before entering actual clinical phase trials. Another is to build an interface between animals and humans," Watanabe says.

The CMIS aim to use molecular imaging to diagnose illnesses such as dementia, cancer, diabetes and even fatigue. RIKEN researchers have been at the forefront of molecular imaging research, and their efforts accelerated in 2005 with the launch of the national Molecular Imaging Research Program. The base for the program in Kobe was reorganized as the CMIS in 2008. Since April 2010 and continuing in 2012, the CMIS has been playing a central role in the government's new initiative, the Japan Advanced Molecular Imaging Program (J-AMP). In 2011, the CMIS and Watanabe hosted and chaired the 6th Japanese Society for Molecular Imaging Congress in Kobe.

The CMIS has continued to unveil impressive research achievements. In recent studies, the high level technique of labeling chemistry has enabled for the first time in the world live imaging of ketoprofen-methyl ester and uric acid in living rats, which can be applied to diagnose neurodegenerative disorders such as dementia, and urate-related life-style diseases such as gout (*J. Nucl. Med.* **52**, 1094–101, 2011 and *Bioorg. Med. Chem. Lett.* **22**, 115–119, 2011).

Today, pre-clinical research for regenerative medicine with ES cells or iPSCs is rapidly progressing. One target is Parkinson's disease, which can be treated with dopaminergic neurons transplants. CMIS researchers have developed an evaluation system to verify the efficacy of transplanted human neurons in the center's primate model for Parkinson's disease. Non-invasive molecular imaging techniques proved useful for post-operative observations of transplantation therapy (*J. Parkinson's Disease* **1**, 395–412, 2012 and *Stem Cells* **30**, 935–945, 2012).

An expanding aim of the CMIS is to elucidate the mechanisms of fatigue or pain. The center is conducting research into chronic fatigue syndrome, while in another project the CMIS have developed a tool to record a person's feelings using touch panel devices. The CMIS is now uncovering the linkages between molecular dynamics in the human body and health.

"We want to create a center where we can test molecules or compounds in humans quickly and safely," Watanabe says. "Clinical institutions cannot afford such tasks. This has become another role of a basic research center like the CMIS."

KOBE INSTITUTE

RIKEN Quantitative Biology Center

The new RIKEN Quantitative Biology Center (QBiC) consolidates more than 15 cellular biology laboratories in cell dynamics, computational biology and synthetic biology research in Japan.

Led by director Toshio Yanagida, the RIKEN Quantitative Biology Center (QBiC) is a newly established research center that brings together several existing laboratories of cellular biology from the RIKEN Kobe Institute, the RIKEN Yokohama Institute, and newly recruited young researchers from outside RIKEN. Established in early 2011, QBiC aims to advance research into whole cell modeling by studying cell properties and the principles behind the interactions that form complicated biological systems. The center aims to replicate the dynamics of a cell through new innovative modeling technologies, developed by the center's three core research groups: Cell Dynamics, Computational Biology, and Cell Design.

"These days the words 'inter-disciplinary' or 'exchange' seem to be over-used," says Yanagida. "What this center is seeking is not simply cooperation between researchers with different disciplinary backgrounds, but cooperation in which researchers or students can learn, teach or exchange their special skills with each other, so they can eventually merge what they have learned into their own research methodologies."

The main role of the Cell Dynamics Research Core is to create techniques that enable quantitative measurement of intracellular molecular dynamics in order to better understand the attributes of biological molecules. The Cell Dynamics Core is generating key technologies including single molecule imaging techniques, such as 3D and multicolor imaging and single cell molecular detection techniques, such as nanospray mass spectroscopy.

The Computational Biology Research Core uses measurements produced by the Cell Dynamics Core coupled with experimental methods to mathematically analyze complex biological systems in detail. Through the development of unique modeling technologies that are able to predict and control cell systems, the Computational Biology Core will simulate three factors which underpin complex biological processes: millisecond-scale simulations of molecular behavior, intracellular particle simulation, and cell behavior simulation.

An emerging area of biology which fuses science with engineering, synthetic biology focuses on the creation of new biological systems and devices which provide models to explore cellular responses and functions. With three laboratories specializing in synthetic biology, cell-free protein synthesis and integrated biodevices respectively, the Cell Design Research Core will pursue new innovations that will enhance our understanding of and capability to manipulate biological systems.

Since its inception in 2011, QBiC has already made significant research achievements. A recent study by Tsutomu Masujima and colleagues using video-mass spectrometry detected drug metabolites in a live single cell, which has useful applications for drug metabolite monitoring in biopsied tissues and for accelerating drug discovery and development (*Anal. Sci.* **28**, 201–203, 2012), while Yuji Sugita and colleagues highlighted the importance of variable interactions between protein crowders and biomolecular solutes in the understanding of cellular crowding (*J. Phys. Chem. B* **116**, 599–605, 2012).

Through the development of key technologies and techniques, QBiC is on course to bring about greater advances in cognitive science, regenerative medicine, patient care, drug design and engineering in the years to come.

KOBE INSTITUTE

HPCI Program for Computational Life Sciences

Utilizing the most powerful supercomputer in the world, the RIKEN HPCI Program for Computational Life Sciences is preparing to embark on research in the most challenging of computational fields.

Toshio Yanagida

With the K computer, Japan can once again claim the most powerful supercomputer in the world. It last held that honor in 2004 with the Earth Simulator, but this time the circumstances surrounding the development of the latest ten-petaflops-class supercomputer are different—there is unprecedented pressure on the supercomputer program to both deliver tangible results and tackle ever-larger and improbably complex problems.

To ensure that not a spare computational cycle is left to waste, the Japanese government established the High-Performance Computing Infrastructure (HPCI) Program to promote strategic research using the country's impressive supercomputing resources—including the new K computer—in five key areas: the life sciences, materials and energy, climate and natural disasters, industrial innovation and the origin of matter and the universe. The RIKEN HPCI Program for Computational Life Sciences was established in April 2011 to pursue and develop a new generation of supercomputer-supported research in the first of these five strategic fields.

The use of computational approaches in biology and the life sciences is a recent and largely uncharted realm of research. Biological systems do not lend themselves well to computational simulation. The massive number of possible variables, heterogeneity and complexity of life systems have meant that progress in computational methods for the life sciences has been difficult and limited. Yet it is clear that computational modeling of complex interactions among biomolecules or large-scale analysis of genetic data being produced by the latest DNA sequencing technologies could have major and revolutionary impacts on life sciences research with applications in medicine and drug discovery.

Establishing a framework and systematic approach for developing the capacity for life science simulations using the unparalleled computational power of the K computer is the goal of the RIKEN HPCI Program. Program Director Toshio Yanagida is the first to admit that achieving that goal will be challenging. "Unlike other sciences, the life sciences do not have fundamental equations," he notes. "Life systems instead involve 'hyper-degrees of freedom'. Previously, we have attempted to understand life systems by making assumptions to limit the degrees of freedom to a manageable level. Even with the K computer, however, we can't leap directly to simulations with hyper-degrees of freedom, but what we can do is to perform more simulations of larger systems to lead to the next hypothesis, which we can then confirm through experiments and further modeling."

Research and development at the RIKEN HPCI Program is already underway with the aim of having a series of well-structured research programs ready to deploy when the K computer officially launches later in 2012. Research will focus on the simulation of biomolecules in cellular environments, simulations applicable to drug design, integrated hierarchical simulation of life systems such as the human body, and large-scale analysis of genomic and other life data.

"Our dream is to reproduce life phenomena representing highly complex, non-linear and dynamic systems using computational methods," says Yanagida.

"If we clear the many obstacles and can advance our research to a level comparable to that of other fields, computer simulation has the potential to contribute significantly to biology and medicine."

FEATURED INSTITUTE

Advanced Institute for Computational Science

The RIKEN Advanced Institute for Computational Science (AICS) acts as an international center of excellence in computer science and computational sciences, bringing together researchers and supercomputer developers to establish a new paradigm of prediction science.

Supercomputers have become indispensable for research and development in many fields of science and engineering, where high-order computational simulations can be pivotal in unearthing leads to the next scientific breakthroughs. The potential of computer simulations is broad-ranging, with applications in fields as diverse as drug discovery, genetic medicine, climate prediction and even our understanding of the universe and matter itself. Yet researchers in computationally intensive fields face twin challenges of developing the advanced computational methods needed to handle increased complexity and problem scale, and scheduling sufficient simulation time on high-demand supercomputing resources — both of which limit the pace of progress in computationally supported science.

Japan's new supercomputer, the K computer, is set to provide an unprecedented level of computing power to researchers in Japan. The facility recently topped the global supercomputer rankings with a benchmark performance of over ten petaflops, or 10^{16} operations per second, making it 250 times faster than the first-generation Earth Simulator and ten times more powerful than any operational supercomputer in the United States.

The K computer is scheduled to begin full operation in the second half of 2012, and RIKEN has been entrusted with the management and ongoing development of this shared resource of strategic national importance. The AICS was established in 2010 with the aim to pioneer the science of forecasting which uses simulation, and to act as an international center of excellence for both computer science and computational sciences.

"Our goal is to take full advantage of the K computer's capabilities to push Japan to the forefront of computational science and enhance our nation's competitiveness by creating a converging point of global knowledge that will attract scientists from around the world," says center director Kimihiko Hirao. "We have already astonished the world by introducing the number-one supercomputer; the AICS is now committed to amazing the world once again by producing exciting results in computer science."

The Japanese government has established five key fields for research based around the K computer: life sciences, materials and energy, global climate and natural disasters, industrial innovation and the origin of matter and the universe. Applying the incredible computing power of the K computer for such research, however, requires extensive planning and development before even a single simulation can be run. Researchers must turn their conceptual scientific models into programs and code, which is then tailored to the architecture of the supercomputer, verified, refined, tested and reverified in an iterative process that relies on a close working relationship between the computational scientists and the computer scientists and engineers responsible for the development of the supercomputer itself.

The AICS actively promotes close collaboration between the supercomputer developers and the researchers who will be using the computing resources toward achieving the institute's goal of establishing the field of 'prediction science' — the use of supercomputers to perform highly complex, large-scale simulations in a way that generates predictions of previously unknown fundamental relationships in nature. "The AICS is committed to producing exciting results in computer science that will bring intellectual contributions to humankind," says Hirao.

HARIMA INSTITUTE

RIKEN SPring-8 Center

Located on the same site as the world-class SPring-8 synchrotron radiation facility in Harima west of Kobe, the RIKEN SPring-8 Center (RSC) is fostering frontier research in a wide range of sciences, from structural biology to materials and the science of light itself.

With the completion of the 8 GeV super photon ring (SPring-8) in 1997 at the RIKEN SPring-8 Center (RSC), Japan joined an elite group of countries offering high-energy photon sources for research. Such facilities can cost billions of dollars and take decades to plan and commission—but can fall into obsolescence over a similar time frame. Although 15 years old, SPring-8 remains the largest third-generation synchrotron in the world, and thanks to ongoing joint development by the Japan Synchrotron Radiation Research Institute (JASRI) and RIKEN, continues to maintain its world-leading status.

"The world's most advanced facilities generally become second- and third-class technologies over a period of 15 years," says Tetsuya Ishikawa, director of the RSC. "Our mission at RIKEN has been to keep SPring-8 in the top position. That position was reinforced in 2005 when RIKEN founded the RSC. We are improving the brightness and stability of the light, and are always searching for new ideas."

JASRI has worked to facilitate public use of the SPring-8 facility by both domestic and international researchers, while RIKEN has worked to add new instrumentation and beamlines under its mandate from the Japanese government to enhance this large-scale research facility. "We are working to improve what we have. For example, we have developed long undulators and a one-kilometer beamline. RIKEN initiated these developments," says Ishikawa.

The SPring-8 synchrotron is a high-brightness source of X-rays, which are extracted into a series of beamlines equipped with instruments for a wide range of analyses. At the core of the facility is the storage ring, which circulates high-energy electrons around a 1.4-kilometer path. The intense X-ray beams produced by the facility are particularly suitable for determining crystal structures at ultrahigh resolution, and for this reason the SPring-8's beamlines are in high demand among researchers in both structural biology and materials science. "Using X-rays, we can achieve atomic resolution. By making the X-ray beam coherent, like a laser, we can also use it to determine the structure of non-periodic materials at the atomic scale."

In March 2011, a major addition was made to the SPring-8 facility. Coherent light, in which all of the light waves are in-phase, has been around for a long time in the form of lasers. It can be used to probe surface structures because the light has a wavefront that can be reflected and analyzed. However, such light sources have not been available at the X-ray wavelengths needed for resolving atoms and molecules. RIKEN began developing the X-ray Free Electron Laser (XFEL) concept over a decade ago, and in March 2011 the new light source, called the SPring-8 Angstrom Compact Free Electron Laser (SACLA), went into operation.

"An XFEL requires a long linear undulator. We realized that by using the in-vacuum type undulator developed at SPring-8, we could construct an XFEL a quarter of the length of similar facilities proposed in Europe or the US."

In June 2011, the XFEL successfully achieved "first light" and in autumn 2011, the SACLA team succeeded in producing an X-ray laser with a target value wavelength of 0.06 angstroms. Fifty-five proposals were submitted to apply for the use of the SACLA public beamlines, 25 of which—including seven from overseas—were accepted, and user operation commenced in March 2012.

The SACLA XFEL—the second of its kind in the world following LCLS in the US—promises

to open entirely new areas of research. "When light is not coherent, molecules need to be crystallized in order to determine their structure," says Ishikawa. Many molecules such as protein complexes, however, are very difficult to crystallize. The XFEL is expected to allow such targets to be characterized without crystallization, and this could lead to a revolution in structural biology research and drug development. But it is the unknown that excites Ishikawa.

"SACLA will also be able to produce ultrashort pulses of light that could be used to analyze ultrafast processes and chemical reactions we know very little about, like catalysis or even photosynthesis. We really don't know what we will see or what will be possible with this light. When light is this strong, one plus one will equal more than two. We will need to rewrite the textbooks as we did when visible lasers appeared."

The range of science that can be conducted using SPring-8 can be gleaned from findings published by RSC researchers in 2011. In a recent study, Kunio Hirata and colleagues investigated the structure of a protein powered by specific wavelengths of light, which could boost the effectiveness of tools used in the analysis of brain function (see *Algal proteins light the way*, p. 37).

In other research, Shik Shin and his team have identified a previously unexplored mechanism which causes superconductivity in a class of materials known as pnictides, bringing researchers a step closer towards realizing room-temperature superconductivity (*Science* **332**, 564–567, 2011).

Kenji Tamasaku and colleagues have developed an advanced imaging technique which can zoom in on objects the size of atoms with a resolution so precise, it overtakes all of its competitors to date (*Nature Physics* **7**, 705–708, 2011).

Susumu Kitagawa and his team have developed a gas sensor that is able to detect and identify air-borne gases and has the capability to differentiate between gases with the same chemical and physical properties, enabling regular tracking of gas type and its relative concentration in the air (*Nature Materials* **10**, 787–793, 2011).

The fields of science utilizing SPring-8 are ever-expanding, and with the new XFEL facility, there is no shortage of possibilities. "RIKEN keeps breaking frontiers," says Ishikawa. "No other facility can offer such a variety of premier light sources in one place."

Algal proteins light the way

Recently published insight into the structure of a light-powered protein may lead to more effective tools for probing brain function

Channelrhodopsins (ChRs) are remarkable proteins that respond to specific wavelengths of light by allowing ions to cross the cell membrane, a mechanism that makes them useful for manipulating ion-driven processes in the brain. Akin to cellular-scale power switches, ChRs allow scientists to selectively switch on individual neurons or neural circuits with a flash of laser light, even in live and alert animals. These valuable tools could soon become even more useful thanks to an international collaboration at the RSC in Harima that has unveiled the fundamental structure of these proteins[1].

"Researchers have engineered ChR variants with improved properties, including ion selectivity, kinetics and absorption spectrum, but these approaches were limited by the lack of the structural information about ChR," explains lead author Hideaki Kato, a researcher in senior author Osamu Nureki's laboratory at the University of Tokyo. X-ray crystallography is a powerful tool for mapping the three-dimensional structure of proteins, but ChRs had proved a tricky target. Since they are difficult to produce in useful quantities and hard to crystallize, Kato and colleagues engineered a more stable hybrid chimera protein composed of parts from the closely related ChR1 and ChR2 proteins from the alga *Chlamydomonas reinhardtii*.

The researchers used the powerful x-ray source at the RSC to generate a high-quality structure of the entire light-responsive segment of ChR (Fig. 1). "The RIKEN beamline, which started operation in May 2010, is highly effective for structure determination from tiny protein crystals," says SPring-8 scientist and co-author Kunio Hirata. "The manuscript [on our results] is the evidence."

The resulting structure revealed the path through which positively charged ions are transferred across the cell membrane, resolving an ongoing debate among molecular biologists. A large outer

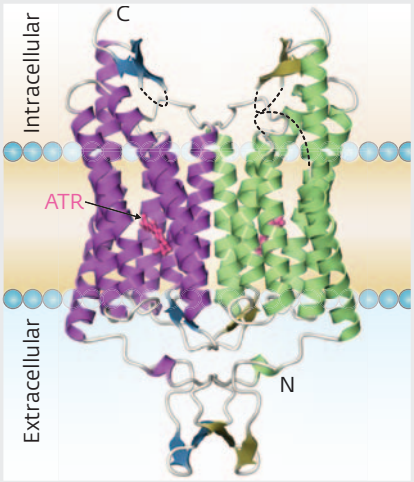


Figure 1: The structure of a chimeric channelrhodopsin protein (C1C2), a combination of elements of ChR1 and ChR2 from *C. reinhardtii*. The small pink structure represents all-*trans* retinal (ATR), a light-reactive molecule bound to C1C2 that plays an essential role in this protein's activation.

'vestibule' structure at the cellular exterior gives way to a pore lined with negatively charged surfaces, which favor the entry of positively charged ions. This pore is blocked when ChR is inactive, but illumination at the proper wavelength triggers a series of proton transfer events within the protein that eliminate these obstructions, enabling ions to pass. A series of mutation experiments provided additional support for this mechanism.

"[Further] detailed structural information around this pathway should provide useful insights for the precise and principled design of ChR variants with altered ion selectivity and absorption spectra," says Kato. He and his colleagues now plan to pursue such targeted protein engineering efforts, while also working to obtain additional ChR structures that provide further confirmation for their functional model.

1. Kato, H. E., Zhang, F., Yizhar, O., Ramakrishnan, C., Nishizawa, T., Hirata, K., Ito, J., Aita, Y., Tsukazaki, T., Hayashi, S. *et al.* Crystal structure of the channelrhodopsin light-gated cation channel. *Nature* **482,** 369–374 (2012).

RIKEN—A global presence

RIKEN Facility Office at RAL 1

Rutherford Appleton Laboratory (RAL)
Oxfordshire, UK

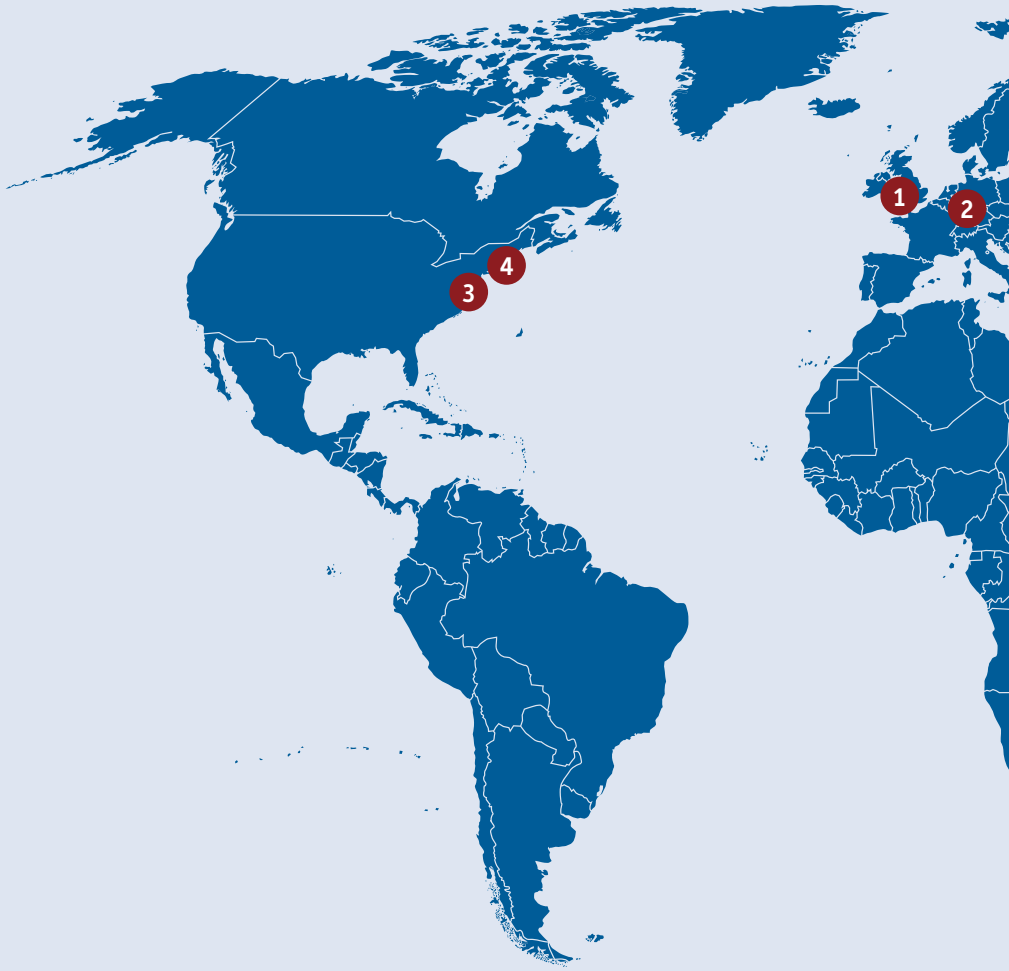
riken.nd.rl.ac.uk/ral.html

The RIKEN-RAL Muon Facility, based at the Rutherford Appleton Laboratory (RAL) located in Oxfordshire, UK, is the strongest pulsed source of muons in the world and a hub for international muon research. Under an agreement signed in 1990, RIKEN builds, operates and maintains the muon facility using a high-intensity proton beam provided by RAL. The RIKEN team at the RIKEN–RAL Muon Facility includes RIKEN scientists based at RAL and colleagues from the RIKEN Nishina Center for Accelerator-Based Science in Wako, Japan.

RIKEN–Max Planck Joint Research Center 2

Dortmund and Potsdam, Germany, and Wako, Japan

The RIKEN–Max Planck Joint Research Center was established in 2011 in Dortmund and Potsdam, Germany to conduct collaborative research in systems chemical biology, and brings together the natural chemical compounds bank (NPDepo) of the RIKEN Advanced Science Institute (ASI) and the biology-oriented synthesis (BIOS) library of the Department of Chemical Biology to create one of the world's leading banks of natural and synthetic compounds.



RIKEN BNL Research Center 3

Brookhaven National Laboratory (BNL)
Upton, New York, USA

www.bnl.gov/riken

The RIKEN BNL Center, run in collaboration with the Brookhaven National Laboratory (BNL) in New York, was established in 1997. The facility makes use of the BNL 2.4 mile Relativistic Heavy Ion Collider (RHIC) to conduct fundamental research fields of spin physics, quark gluon plasma and lattice quantum chromodynamics. Around 45 scientists divided into theoretical, computing and experimental groups work at the center where they also develop and maintain the Pioneering High Energy Nuclear Interaction Experiment (PHENIX).

RIKEN–MIT Center for Neural Circuit Genetics 4

Massachusetts Institute of Technology (MIT)
Cambridge, Massachusetts, USA

web.mit.edu/picower/about/rikenmit.html

Located in Cambridge Massachusetts, the RIKEN–MIT Center for Neural Circuit Genetics (CNCG) was established in 2008 as a joint initiative between the RIKEN Brain Science Institute (BSI) and the MIT's Picower Institute for Learning and Memory. Work at the CNCG is focused on the investigation of the molecular, cellular and brain system mechanisms that underpin learning and memory as well as other cognitive functions.

RIKEN–XJTU Joint Research Center 5

Xi'an, China

The RIKEN–XJTU Joint Research Center was established in February 2012 at Xi'an Jiaotong University (XJTU) in Xi'an, China. The center aims to carry out collaborative research activities between RIKEN and XJTU in environmental fluids, ubiquitous intelligence systems, and biomaterials. The center will enable RIKEN and XJTU to expand their collaboration to include other research areas that will enhance the globalization of the two institutions.

RIKEN–KRIBB Collaboration Research Center for Chemical Biology 10

Ochang, South Korea

The RIKEN–KRIBB Collaboration Research Center for Chemical Biology was launched in June 2011 and is based at the Korea Research Institute for Bioscience and Biotechnology (KRIBB). The center carries out joint research in the field of chemical biology, focusing on bioactive compounds derived from microorganisms with the aim to uncover new drug candidate compounds. The center also currently hosts researcher exchange programs.

RIKEN–USM Joint Laboratory for Bioprobe Discovery 9

Penang, Malaysia

The RIKEN–USM Joint Laboratory for Bioprobe Discovery was launched in September 2011 and is located at the Universiti Sains Malaysia (USM) in Penang, Malaysia. The laboratory undertakes joint research aiming to isolate novel biological active compounds from tropical plants in Southeast Asia, particularly in Malaysia. By utilizing RIKEN's chemical library, the laboratory aims to determine target molecules and develop drugs for tropical diseases.

RIKEN Beijing Representative Office 6

Beijing, China

china.riken.jp

Formally registered in December 2010, the RIKEN Beijing Representative Office was officially opened in June 2011 to provide a focal point for RIKEN'S activities in China. The office acts as a central information hub for scientific exchange between RIKEN and its Chinese partner research institutes, and aspires to become a center for 'brain circulation' of top-level research talent by encouraging international mobility of Chinese researchers and attracting them from overseas and back to their home country later in their careers.

RIKEN Singapore Representative Office 7

Biopolis, Singapore

www.riken.sg

The RIKEN Singapore Representative Office located at the Biopolis biomedical research and development hub was opened in 2006 as RIKEN's first overseas representative office, and coordinates collaborative research between RIKEN and Singaporean research institutes such as the Agency for Science, Technology and Research (A*STAR), Nanyang Technological University and the National University of Singapore. The office also promotes research exchange and collaborations with other institutes in Southeast Asia.

RIKEN–HYU Collaboration Research Center 8

Flucto-Order Functions Research Team

Fusion Tech Center
Hanyang University (HYU)
Seoul, South Korea

The RIKEN-HYU is a joint research program carried out in collaboration with Hanyang University in Seoul, Korea. The center undertakes an array of research, which includes the development of functional materials by combining nanoscience and nanotechnology with various other fields, such as bioengineering and information technology.

RIKEN in Asia

RIKEN has developed research ties with many countries in Asia. In Korea, RIKEN conducts collaborative research with a number of institutions including Seoul National University and Hanyang University (HYU) both based in the capital. RIKEN maintains a joint research program with the latter via the RIKEN–HYU Collaboration Research Center which supports interdisciplinary research by the Asian Research Network in nanoscience and functional materials. RIKEN has also pursued joint research with the Korea Research Institute of Bioscience and Biotechnology (KRIBB) since 2006. These ties were further strengthened in June 2011 with the opening of the RIKEN-KRIBB Collaboration Research Center for Chemical Biology which will see the RIKEN Advanced Science Institute and KRIBB carry out joint research in topics at the interface of chemistry and the life sciences.

In China, RIKEN maintains a presence in the country through the RIKEN Beijing Representative Office, which was founded in late 2010 and formally opened in June 2011. The office acts as a hub for scientific exchange between RIKEN and Chinese partner research institutes and is instrumental in expanding RIKEN's

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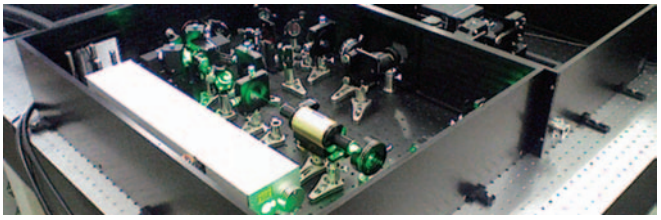
research network in the country, which already includes joint graduate school agreements with 15 Chinese institutions of higher education including Peking University, Zhejiang University, Fudan University and Shanghai Jiao Tong University. RIKEN's presence in China was extended in February 2012 with the opening of the RIKEN-XJTU Joint Research Center at the Xi'an Jiaotong University located in the central province of Shaanxi. The establishment of the center comes on the back of previous research initiatives in a diverse array of fields including environmental fluids, ubiquitous intelligence systems and biomaterials.

RIKEN is proactive in establishing research ties with countries in Southeast Asia via the RIKEN Singapore Representative Office. Opened in 2006, the office not only coordinates collaborative research between RIKEN and Singaporean research institutes such as the National University of Singapore, the Agency for Science, Technology and Research (A*STAR) and Nanyang Technological University, but also serves as a base for the promotion of scientific exchange and research collaborations with institutes and universities in other Southeast Asian countries.

In Malaysia, the opening of the USM-RIKEN Joint Laboratory for Bioprobe Discovery at the Institute of Research in Molecular Medicine of Universiti Sains Malaysia (USM) in September 2011 marked a culmination of existing research collaborations between RIKEN and USM. The center, which aims to isolate and investigate novel biological active compounds from tropical plants found in Southeast Asia is supported by a RIKEN-USM Joint Research Team based at the Chemical Biology Department of the RIKEN ASI in Japan. RIKEN's research portfolio in Southeast Asia also includes joint research agreements with the Thailand National Science and Technology Development Agency, and Indonesia's Padjadjaran University.

Sendai



The Terahertz-wave Research Group is a RIKEN Advanced Science Institute project based at RIKEN's Sendai Facility in northern Japan. Work in the group focuses on how light in the terahertz (THz) frequency spectrum, the region between microwaves and infrared, can be used for the non-contact analysis of molecules, with potential uses from medical imaging to security screening.

Under the THz program, research encompasses the technology for generating and detecting THz waves as well as the possible uses of the technology and the responses of different compounds and media to THz signals. Recent research themes include the development of an organic nonlinear optical crystal for high-sensitivity detection of THz waves at room temperature, and the investigation of mechanisms responsible for the characteristic 'fingerprint' THz absorption signature for biodegradable polymers. The Terahertz Quantum Device Team develops THz quantum cascade lasers (THz-QCLs) and THz photodetectors to establish new application fields for THz light. The team recently developed a THz-QCL with high operating temperature and reduced threshold current.

Nagoya

The RIKEN-TRI Collaboration Center for Human-Interactive Robot Research was established at RIKEN's Nagoya Facility in 2007 jointly by RIKEN and Tokai Rubber Industries to develop a human interactive robot for use in care-facilities and hospitals. The prototype Robot for Interactive Body Assistance (RIBA) was developed in 2009 and a second generation robot, dubbed RIBA-II, with improved sensors and guidance controls capable of lifting a person weighing over 80 kilograms, was unveiled in 2011. Also located at the Nagoya Facility and with a second site at the RIKEN Wako campus, the RIKEN BSI–TOYOTA Collaboration Center (BTCC) was opened in 2007 as a partnership between the RIKEN Brain Science Institute (BSI) and the TOYOTA Motor Company. Work at the center focuses on the integration of brain science and engineering for neuro-driving, neuro-robotics and health protection. Research themes include studies of rhythm-based brain computation and non-invasive brain–machine interfaces. In 2009, the BTCC successfully developed a wheelchair that can be maneuvered by the user's brain waves.

OPPORTUNITIES FOR INTERNATIONAL SCIENTISTS

Increasing scientific knowledge while promoting international cooperation and understanding are among the core principles of RIKEN. Whether a doctoral candidate or an experienced researcher, there are many opportunities—and no national boundaries—at RIKEN.

OPPORTUNITIES FOR INTERNATIONAL SCIENTISTS

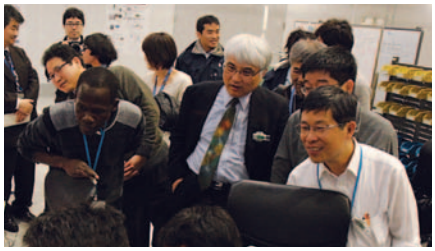
Life at RIKEN

www.lifeatriken.com

The success of RIKEN as a research organization arises from the quality of its people. Since its inception, RIKEN has always strived to recruit the best and the brightest Japanese scientists into its ranks, but in recent years it has begun to attract the cream of international research talent, both younger and more senior, to the RIKEN family. Believing that science knows no borders, RIKEN is actively pursuing ever greater internationalization and is currently home to over 550 scientists from more than 50 different countries on all five continents.

In order to better engage with its growing international audience, RIKEN launched www.lifeatriken.com, a website dedicated to attracting international scientists to RIKEN. The website contains a wealth of useful information about RIKEN's history, facilities and award-winning alumni as well as descriptions of the many research opportunities and programs open to international researchers including details on housing, support services, and other benefits available to international researchers who may be considering furthering their career at RIKEN. For scientists already working at RIKEN, www.lifeatriken.com acts as a one-stop shop for information to help international researchers make the most of their time in Japan, from details of the many sports and cultural societies operating at RIKEN to advice on general topics of interest to international staff while in Japan, such as lifestyle, customs, immigration issues, legal services, healthcare and education systems. Links to other support available at RIKEN such as staff counseling services, Japanese language programs at RIKEN and advice for researchers with families and working partners can also be found on the website.

RIKEN is committed to ensuring that all of its people enjoy the best possible working environment and encourages them to maintain a healthy work-life balance. The www.lifeatriken.com website carries advice about vacation and paid leave for RIKEN staff and details of recreational facilities available at RIKEN.



Initiative Research Unit Program

The Initiative Research Unit Program is targeted at early-career scientists and offers them the chance to fully realize their potential by granting them a high degree of independence and flexibility.

RIKEN places a high value on supporting non-Japanese researchers at its facilities and nowhere is this more evident than in the Initiative Research Unit (IRU) program. Commenced in 2001, the program offers ambitious early-career scientists in their 30s and 40s the independence and flexibility they need to realize their potential. As of March 2010 there are six IRU leaders engaged in a variety of research across RIKEN.

Hye Ryung Byon from South Korea is a chemist who joined RIKEN on the IRU program in February 2011 having previously been a postdoctoral researcher at the Massachusetts Institute of Technology (MIT). "I worked at RIKEN for a short time in 2007 and knew their high reputation. So when I had the chance to apply to become a unit leader of an IRU, I didn't hesitate," she says.

Byon specializes in the development of next-generation high-power and long-life batteries based on lithium oxides (Li_2O_2) formed by a chemical reaction between lithium (Li) and oxygen (O_2) drawn in from the air. Batteries constructed from this material have a theoretical energy density up to 11 times that of conventional lithium ion batteries and are comparable with that of gasoline. "The lack of basic knowledge of Li_2O_2 chemistry hinders the development of batteries based on these materials," explains Byon. "The main goal of our research is therefore focused on understanding the fundamental electrochemical reactions of Li_2O_2 systems."

Researchers at the IRU are able to make full use of RIKEN's comprehensive array of research equipment and facilities, a point which Byon cites as a major attraction to working at RIKEN.

Eligible applicants must hold a doctoral degree in physics, engineering, chemistry, medicine or the life sciences, and be able to propose and implement an ambitious research plan. Unit leaders select their own research staff, comprising three researchers or technical staff, and lead the research effort of the unit. "One important point about the IRU program is that I can recruit highly-educated researchers due to RIKEN's high reputation," says Byon.

Successful applicants are given a one-year contract renewable for up to five years. The IRUs are provided with an annual grant of about 50 million yen, which covers a yearly salary of 10 million yen and research and personnel expenses.

After three-and-a-half years, IRUs are subjected to mid-term evaluation by a committee. Unit leaders employed after the system was reviewed in FY2009 and whose IRU has demonstrated exceptional achievement will be recommended for a limited-term or permanent principal investigator position to continue research after completing their five-year term.

Although there are many challenges to building your career in a foreign country, Byon is in no doubt that she has made the right career choice. "I am very happy to work at RIKEN. I have been given a suitably-sized laboratory and five-year budget which allows me to concentrate on my research," she says. "Furthermore, RIKEN encourages collaborative research and I work alongside committed, passionate and experienced colleagues. The administrative assistants are also very helpful in assisting non-Japanese researchers with language and procedures."

Further information
Web: www.riken.jp/iru/
E-mail: iru@riken.jp

Foreign Postdoctoral Researcher Program

The Foreign Postdoctoral Researcher Program is an opportunity for young, non-Japanese postdoctoral researchers to contribute to the outstanding achievements of RIKEN's ongoing projects.

Even the most gifted of researchers needs assistance to advance their scientific career. For postdoctoral researchers, this often comes when they have completed their graduate studies and are looking for placements at scientific establishments where they can put their knowledge and experience to use. RIKEN's Foreign Postdoctoral Researcher (FPR) program offers a unique way for talented young non-Japanese researchers to gain a foothold in their chosen field and provides an opportunity for postdoctoral researchers in fields such as physics, chemistry, biology, medical science and engineering to contribute to the outstanding achievements of RIKEN's ongoing projects.

Stefan Ulmer is one of the 52 FPRs currently participating in the program. He joined RIKEN in July 2011 from the Max Planck Institute for Nuclear Research in Heidelberg in his native Germany and now works in the group of Yasunori Yamazaki of the RIKEN Atomic Physics Laboratory. Ulmer is based at the CERN Antiproton Decelerator in Geneva, Switzerland where he is investigating antimatter with high precision. "I was attracted to RIKEN by the reputation of my supervisor as an outstanding expert on antimatter," says Ulmer. "The MUSASHI/CUSP experiment that he has developed is of extreme importance. We anticipate that our work into the hyperfine structure of antihydrogen will help answer fundamental questions about the structure of the universe such as why it is composed of matter rather than antimatter," he explains.

To be eligible to apply for the FPR program, applicants need to have a doctoral degree, and usually less than five years' postdoctoral research experience. Initially researchers are offered a contract for one year that can be renewed for up to three years. A generous remuneration package is supplemented with an annual research budget of one million yen for the host laboratory.

Although Ulmer is located overseas, most participants on the FPR program join RIKEN at one of its many centers in Japan. RIKEN realizes that moving from one's home country to Japan to conduct research is not always a smooth transition. Foreign researchers at RIKEN are encouraged to join various sports and recreational clubs so that they can achieve a better work-life balance and develop relationships with their Japanese counterparts.

Life for non-Japanese researchers is facilitated by the many people at RIKEN who speak English and the people working full-time to help with any issues that may arise, from making phone calls to finding accommodation.

"Working for RIKEN at CERN is quite an unusual arrangement," says Ulmer. "But I received a great deal of support from staff in the Global Relations Office which helped me obtain this position. RIKEN puts high-quality research above everything else, including administrative issues, and I am very thankful for the opportunity to work here."

The Foreign Postdoctoral Researcher program provides an excellent chance for young, non-Japanese postdoctoral researchers to play an active role in shaping RIKEN's projects and contributing to RIKEN's top-class achievements.

Further information
Web: www.riken.jp/fpr/
E-mail: fpr@riken.jp

International Program Associate

RIKEN offers doctoral students the opportunity to further their studies as International Program Associates under the supervision of a senior RIKEN scientist.

Launched in 2006, the International Program Associate (IPA) offers non-Japanese nationals enrolled, or about to enroll in PhD programs at one of the many universities participating in RIKEN's Joint Graduate School Program, the opportunity to complete their doctoral studies under the supervision of a senior RIKEN scientist.

To date, 78 IPAs have been accepted and the aim is to increase the number to 100 in the near future. In March 2012, IPAs hailed from 48 universities located on four continents, including Peking University and Shanghai Jiao Tong University in China, Pohang University of Science and Technology in Korea, the Indian Institute of Technology Bombay in India, and the Karolinska Institutet in Sweden.

Tong Bu, a master's graduate of the Chinese Academy of Sciences and the École Normale Supérieure de Cachan, joined the bioengineering laboratory of Mizuo Maeda at RIKEN as an IPA in October 2011 after originally coming to RIKEN for a six-month internship. "After a few months I decided to stay on to do a collaborative doctoral course between RIKEN and the University of Tokyo. Being an IPA provides me with the opportunity to conduct research at a prestigious research institute while also being educated at one of the top universities in the world."

Bu, who is also a PhD candidate at the University of Tokyo researching the bio-applications of metallic nano-materials, relishes the open approach to research collaboration and free discussion at RIKEN.

"As a junior researcher I have the valuable chance to work with top scientists and learn from them. The free research environment here allows me to think independently. It gives me a great sense of accomplishment when I feel my ideas are respected and supported here."

Another attraction is the ability to make use of the advanced research infrastructure at RIKEN, a point which Bu singles out as an important reason for her becoming an IPA. "RIKEN has outstanding resources for carrying out research," she comments. "Not only does it have the most advanced experimental apparatus, it also has the best science administration system I've ever seen. As a researcher at RIKEN, you do not have to worry about anything else except your own studies."

IPAs can participate in the program for a maximum of three years. Benefits include living expenses, a housing allowance and airfare for one round trip between Japan and the student's home country.

However, the advantages to the participant far exceed financial gain. In addition to raising the next generation of scientists of the future, the program also aims to break down barriers between different nationalities, and foster international cooperation and mutual understanding and respect for different countries' cultures among individuals.

"As a foreigner I feel that RIKEN provides a very friendly living and working environment. There are free Japanese language classes, announcements are made available in English, and there are many English-speaking support staff. I would encourage anyone considering studying for a PhD in Japan to think seriously about applying to become an IPA," says Bu.

Further information
Web: www.riken.jp/ipa/
E-mail: ipa-info@riken.jp

Visiting Scholar Programs

In addition to the FPR and IRU programs, there are many other possibilities for visiting researchers at RIKEN, including the Associate Chief Scientist Program, the Special Postdoctoral Researcher Program and collaborative research and exchange programs. Through its many summer schools, RIKEN also gives visiting researchers and students the opportunity to learn from eminent researchers at one of the world's leading research institutions.

BSI Summer Program

The BSI Summer Program, hosted by the RIKEN Brain Science Institute (BSI), provides graduate students the opportunity to conduct research at the world-renowned BSI through either a two-month laboratory internship at a BSI laboratory, or an intensive two-week lecture course featuring a list of distinguished international speakers. It is a rare and stimulating opportunity for young people to get together in Japan to advance their scientific knowledge, and applications are received from around the world. Nearly 85% of the roughly 50 students who are selected for the program each year come from prestigious overseas universities.

The BSI Summer Program was initiated over a decade ago by Takao Hensch, a professor of Harvard University and former laboratory head at the BSI, at a time when such programs were still a novelty in Japan.

There have been growing numbers of summer school attendees who have returned later to the BSI as laboratory heads and researchers. In 2010, the BSI held a meeting entitled 'How to come back to RIKEN' where participants of the summer program got to hear the experiences of some of these 'returnees'.

Due to the Great East Japan Earthquake, the BSI Summer Program was cancelled in 2011; however the internship course was rescheduled from summer to autumn. The Summer Program resumes in 2012 under the theme, "The Collective Brain: How does the dynamics of collective interaction of neurons make our mind work?". For this program, the BSI had a record 300 applications for the 45 available positions, including internship placements and lecture courses. The surge in applications highlights the growing popularity of this program, in which participants are encouraged to take full advantage of the opportunities offered to broaden the horizons of their research.

Nishina School

The Nishina School, initiated as part of an agreement between RIKEN and China's Peking University in 2008, offers undergraduate students and selected doctoral students from Peking University a unique opportunity to acquire hands-on experience in theoretical and experimental nuclear physics at the RIKEN Nishina Center for Accelerator-Based Science in Wako. The fourth Nishina School was held from 4 to 14 October 2011, and included lectures and practical training for eight exceptional participants.

Through the Nishina School, RIKEN is fostering an interest in physics research among undergraduate students and strengthening research and educational ties with China.

RCAI International Summer Program

Each year, the RIKEN Research Center for Allergy and Immunology (RCAI) in Yokohama holds an International Summer Program for selected graduate students and young postdoctoral researchers from around the world. The program aims to teach young scientists about recent research in immunology and to promote RIKEN and the RCAI as a rewarding research destination. It is hoped that some of the participants will return to work at RIKEN in the future.

Participants at the summer program attend lectures by eminent immunologists from around the world, and some of the attendees get the opportunity to stay on at the RCAI for another month as summer interns to experience research at the center.

Cheiron School

The Cheiron School is a program offered under the Asia-Oceania Forum for Synchrotron Radiation Research (AOFSRR) to promote synchrotron radiation science by introducing participants to SPring-8, the world's largest third-generation synchrotron radiation facility. The Cheiron School's main aim is to give graduate students, postdoctoral fellows, young scientists and engineers first-hand experience with the science and technology of synchrotron radiation—a valuable opportunity for those wishing to pursue a career in fields where it is used.

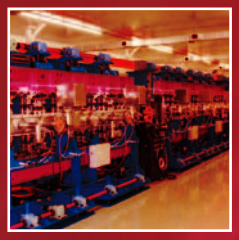
The school is co-sponsored by RIKEN, the Japan Synchrotron Radiation Research Institute (JASRI), the High Energy Accelerator Research Organization (KEK) and AOFSRR. The curriculum includes lectures and practical demonstrations on synchrotron radiation science and technology, covering a wide-range of topics from accelerator science to X-ray physics as well as applications to materials science and biology.

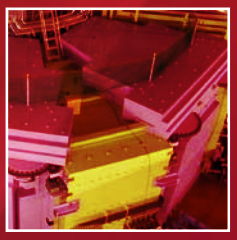
Other programs

RIKEN offers many exchange and visiting scholar programs, and is active in developing new programs and agreements with research institutions around the world. Some additions include an exchange program between RIKEN and the Université de Strasbourg in France, and an agreement between RIKEN and the German National Academic Foundation (RIKEN–SDV) to accept undergraduate and graduate students. RIKEN is accepting postdoctoral researchers and graduate students through the Japan Society for the Promotion of Science. RIKEN also maintains programs to accept undergraduate and graduate students from the Massachusetts Institute of Technology (MIT) in the US and with Korean universities through the JISTEC Winter Institute.

Further information
Visit the host center's website or contact the Global Relations Office.
E-mail: gro-pr@riken.jp

PERFORMANCE AND ORGANIZATION





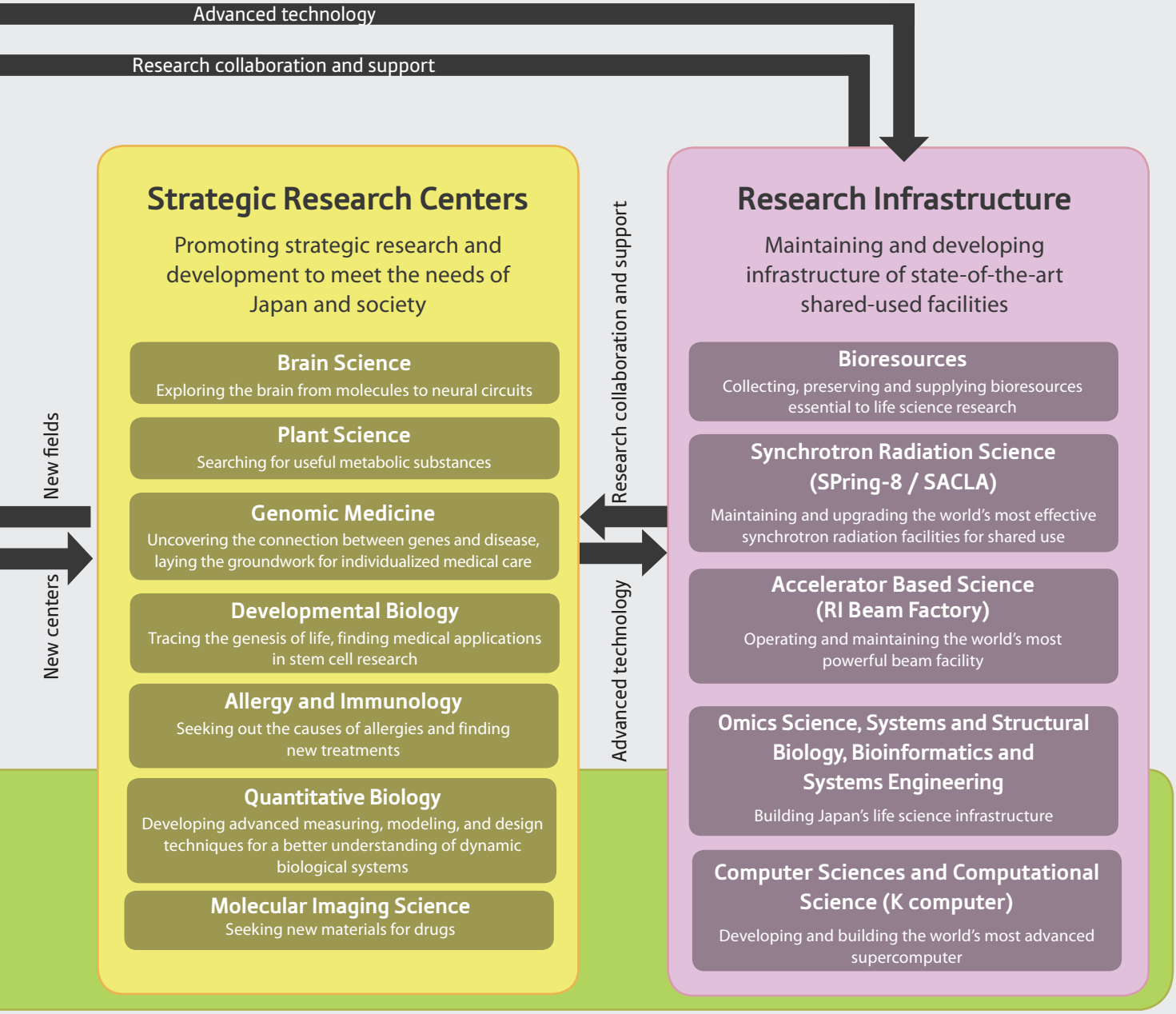
As an independent administrative institution, RIKEN is primarily funded by the Japanese government, and in return is responsible for securing additional revenue streams, implementing strategic administrative reforms, promoting international collaboration and serving society through the application of research outcomes.

PERFORMANCE AND ORGANIZATION

RIKEN—A research overview

At the forefront of scientific research and innovation

RIKEN is a high-profile research institute at the heart of scientific research in Japan, and a distinguished world leader in a diverse array of scientific disciplines. Central to RIKEN's success as a top-class research hub is the collaboration and support between its four groups of centers and institutes: Advanced Basic Research, Research Infrastructure, Strategic Research, and the Research Cluster for Innovation. These four groupings interact within an integrated research system, bringing together pioneering science and state-of-the-art research facilities to meet national and social needs, and are further enhanced by active collaborations both within and outside RIKEN. In the group of Advanced Basic Research, the Advanced Science Institute (ASI) aims to further key fields in science and technology such as chemical biology, photonics and materials science through an integrated research approach. RIKEN's numerous strategic centers, including the Brain Science Institute and the newly established Quantitative Biology Center, strive to promote and enhance strategic research. Cutting-edge research infrastructure including SPring-8/SACLA, the K computer and the RI Beam Factory support RIKEN's wider research efforts and enable researchers from around the world to conduct advanced scientific investigation. The Research Cluster for Innovation further disseminates RIKEN researchers' knowledge and discoveries to wider society through collaborations with other institutions. Together, these vital components of RIKEN's research structure form the very foundation of RIKEN's achievements today.



Research Network for Infectious Diseases

Focal point of a national network of centers researching emerging and re-emerging infectious diseases

HPCI Computational Life Sciences

HPCI Strategic Program: Computational Life Sciences and Application in Drug Discovery and Medical Development

History of RIKEN

In pursuit of science

Founded in 1917, RIKEN has a long and successful history of progressive and innovative scientific endeavor. From its beginnings as a private research foundation in Tokyo, RIKEN has grown to encompass five world-class campuses across Japan, as well as numerous research facilities and centers in Japan and around the world, including the new Quantitative Biology Center (QBiC) established in 2011 at the RIKEN Kobe Institute. A look back on the rich history of RIKEN provides insights into RIKEN's position in Japanese society and in the international research community as a whole.

1917 RIKEN Foundation established in Tokyo with funding from an imperial donation, governmental subsidies and private contributions following a decree in 1915 by the 37th Imperial Diet of Japan

1937 RIKEN's Yoshio Nishina constructs Japan's first cyclotron

1948 RIKEN Foundation dissolved and replaced by KAKEN (*Kagaku Kenkyusho*) corporation

1949 RIKEN's Hideki Yukawa awarded Nobel Prize in Physics

1958 KAKEN reorganized as RIKEN, a public corporation operated by the Japanese government

1965 RIKEN's Shinichiro Tomonaga awarded Nobel Prize in Physics

1967 Yamato Laboratory (now Wako Institute) established

1984 Tsukuba Life Science Center established in Ibaraki

1987 RIKEN's ring cyclotron completed

1995 RIKEN facility office established at the Rutherford Appleton Laboratory Muon Research Facility in the UK

1997 Harima Institute established in Hyogo to support shared use of the SPring-8 synchrotron radiation facility

Brain Science Institute established in Wako

RIKEN BNL Research Center established at Brookhaven National Laboratory, USA

1998 Genomic Sciences Center established in Yokohama

2000 Yokohama Institute established, including the Plant Science Center and the SNP Research Center

Center for Developmental Biology established in Kobe

2001 BioResource Center established in Tsukuba

Research Center for Allergy and Immunology established in Yokohama

2002 Discovery Research Institute established in Wako

Kobe Institute established

PRIVATE RESEARCH FOUNDATION AND CORPORATION PERIOD (1917–1958)

PUBLIC CORPORATION PERIOD (1958–2003)

1913

The birth of the RIKEN Spirit

The idea of establishing a national research institute for the study of pure science in Japan can be traced back to a famous speech by Jokichi Takamine at a gathering of 120 leading businessmen and government officials in Tokyo in 1913. Takamine, renowned for his success in the industrial production of adrenalin in the US, asserted that the world was moving away from mechanical industry and toward scientific industry. It was a turning point in Japanese history, and the idea of establishing an Institute of Physical and Chemical Research soon took hold.

2001

Ten years of achievement in bioresource management

More than ten years on since its establishment in 2001, the BioResource Center (BRC) based at the RIKEN Tsukuba Institute continues to be one of the foremost repositories for biological resources in the world. A driving force behind the National BioResource Project (NBRP) since 2002, and incorporating the Japan Collection of Microorganisms (JCM) into its repository in 2004, the BRC today is one of the world's top three bioresource repositories in the areas of model mice, model plant *Arabidopsis*, cell lines, genes, and microorganisms. The center is renowned for the diversity and quality of its bioresources and worldwide distribution to over 60 countries, and its ongoing success ensures Japan's future as a leading light in bioresource preservation and distribution.

Cryopresevation vat at the BRC

2003
- RIKEN reorganized as an Independent Administrative Institution

2005
- Center for Intellectual Property Strategies established in Wako
- Center of Research Network for Infectious Diseases established in Yokohama
- SPring-8 Center established in Harima

2007
- Molecular Imaging Research Program established in Kobe

2010
- Research Cluster for Innovation established in Wako
- Advanced Institute for Computational Science established in Kobe
- Beijing Representative Office registered in China

2011
- SACLA X-ray Free Electron Laser (XFEL) facility completed in Harima
- Quantitative Biology Center established in Kobe
- HPCI Program for Computational Life Sciences established in Kobe
- RIKEN–Max Planck Joint Research Center established
- Beijing Representative Office opened
- RIKEN–KRIBB Collaboration Research Center for Chemical Biology established
- RIKEN–USM Joint Laboratory for Bioprobe Discovery established

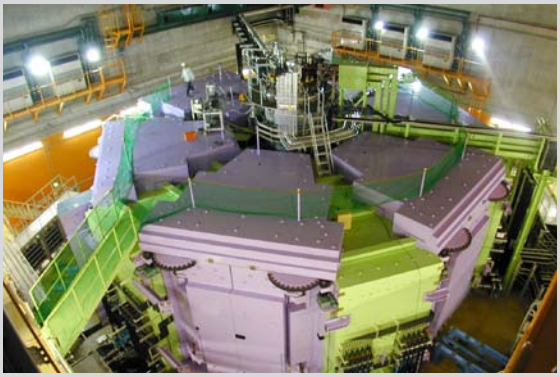
INDEPENDENT ADMINISTRATIVE INSTITUTION PERIOD (2003–)

2004
- Discovery of element 113 by RIKEN researchers

2006
- Next-Generation Supercomputer R&D Center established
- Singapore Representative Office opened
- Nishina Center for Accelerator-Based Science established in Wako
- Superconducting Ring Cyclotron completed in Wako

2008
- Advanced Science Institute inaugurated in Wako
- Omics Science Center, Systems and Structural Biology Center and Bioinformatics And Systems Engineering division (BASE) established in Yokohama
- RIKEN Center for Genomic Medicine established in Yokohama (integrating the SNP Research Center)
- Center for Molecular Imaging Science established in Kobe

2012
- RIKEN–XJTU Joint Research Center established



Superconducting Ring Cyclotron at the RIBF

2004

The discovery of element 113

One of the most spectacular of RIKEN's achievements came in 2004 when a team led by Senior Research Scientist Kosuke Morita succeeded in creating a new element using the RILAC ion accelerator at the Radioactive Isotope Beam Factory (RIBF) in Wako. For 80 days the team irradiated bismuth with a beam of zinc ions, and on the 80th day they were rewarded with the creation of a single atom of a new element—element 113, later known as ununtrium. The new element lasted just a fraction of a millisecond, but with its creation the reputation of Morita and his team was assured.

Governance and Advisory Council

In pursuit of excellence

Since 2003, when RIKEN embarked on a significant overhaul of its operational framework as an independent administrative institution, the organization has actively pursued a program to strengthen its research and administrative systems toward achieving greater internationalization and competitiveness amidst a more global and society-oriented research environment.

Organizational governance

RIKEN's highest policy-making body is the Board of Executive Directors, composed of the president and executive directors. The administration of affairs at the institute level is the domain of institute directors, who each oversee and manage the operations of an entire RIKEN campus.

Within each RIKEN campus, individual research centers and institutes are managed by a director who exercises strong leadership in the strategic management of the research center or institute. In making decisions on the direction of research and administration, RIKEN strives to strike a balance between top-down and bottom-up approaches by seeking the advice and cooperation of committees and councils established with the aim of achieving optimal scientific governance.

The **Committee for Research Strategy** is chaired by the President and is composed of members of the Executive Board, outside experts from diverse fields and full-time Committee members. The committee examines a wide range of research activities in RIKEN and discusses plans for research promotions strategies.

The **Institute and Center Directors' meeting**, composed of the president, executive directors, institute directors and center directors, provides a forum for directors responsible for research to exchange information and opinions and share common knowledge on research and management.

The **RIKEN Science Council** is an advisory body that reports directly to the RIKEN president and is charged with the task of examining suggestions on which research fields to pursue and determining the policies required to promote research with a long-term, broad-based outlook incorporating the perspectives of scientists.

Advisory Councils

RIKEN regularly evaluates its own research themes and the performance of its scientists based on governmental guidelines. In carrying out this important work, RIKEN is guided by the RIKEN Advisory Council (RAC) and the Center and Institute Advisory Councils.

The **RIKEN Advisory Council** is composed of world-famous scientists, both Japanese and international, as well as individuals with experience in managing research institutes. The RAC meeting, held twice as part of every five-year plan, provides recommendations on both general research activities and the overall management of RIKEN, and provides guidance on future research strategies and improvements to management structures.

The eighth RAC meeting was held from 25 to 28 October 2011 in Tokyo and chaired by Dr. Rita R. Colwell of the Center for Bioinformatics and Computational Biology at the University of Maryland. Attended by a top-class panel of scientists from around the world, the meeting gave the council an opportunity to discuss at length the future direction of RIKEN (see the opposite page for the full RAC members' list).

At the meeting, members endorsed RIKEN's next Five-Year Plan (2013–2018), which focuses on fundamental scientific research with innovative and translational approaches, as well as collaborations between problem-oriented and cross-disciplinary research. The RAC also highlighted at the meeting the importance of maintaining RIKEN's proud tradition of basic science, so that RIKEN can further bolster fundamental science and technology as well as innovation, reconstruction and reform.

The RAC members also commended RIKEN's fulfillment of goals set out in the recommendations of the last RAC meeting in 2009. Such major achievements include the establishment of the Research Cluster for Innovation (see pp. 14–15), the opening of the Quantitative Biology Center (QBiC) (see p. 33) in 2011, and the inception of the Administrative Advisory Council.

The **Center and Institute Advisory Councils** are bodies set up in each research center and institute to receive recommendations from eminent Japanese and international scientists in their respective fields of research. The council recommendations form an integral part of the ongoing appraisal of RIKEN's performance as a scientific research organization.

Members of the 2011 RIKEN Advisory Council

Rita R. Colwell
Chair
Oceanography
Distinguished University Professor, Center for Bioinformatics & Computational Biology, University of Maryland, USA

Howard Alper
Vice Chair
Chemistry
Distinguished University Professor, University of Ottawa, Canada
Chair, Science, Technology and Innovation Council, Canada

Colin Blakemore
Vice Chair
Neuroscience
Professor, Department of Physiology, Anatomy and Genetics, University of Oxford, UK

Hiroo Imura
Vice Chair
Medicine: Endocrinology
President, Foundation for Biomedical Research and Innovation, Japan

Yuichiro Anzai
Informatics/Cognitive Science
Executive Advisor for Academic Affairs at Keio University, Japan
Professor, Faculty of Science and Technology, Keio University, Japan

Teruhiko Beppu
Applied Microbiology
Professor, Advanced Research Institute for the Sciences and Humanities, Nihon University, Japan

Hidetoshi Fukuyama
Basic Solid States Science
Professor, Department of Applied Physics, Faculty of Science, Tokyo University of Science, Japan

Mitiko Go
Bioinfomatics
Executive Director, Research Organization of Information and Systems, Japan

Jean-Louis Guénet
Genetics
Emeritus Scientist, Unité de Génétique des Mammifères, Institut Pasteur, France

Zach W. Hall
Neuroscience
Emeritus Vice Chancellor, University of California, San Francisco, USA

Jerome Hastings
Applied Physics
Professor, Photon Science, SLAC National Accelerator Laboratory, USA

Stephen F. Heinemann
Molecular Neurobiology
Professor, Molecular Neurobiology, Salk Institute, USA

Biao Jiang
Chemistry
Vice President, Shanghai Advanced Research Institute, Chinese Academy of Sciences, China

Paul Kienle
Physics
Professor Emeritus, Department of Physics, Munich University of Technology, Germany

Bengt Långström
Biochemistry
Professor, Department of Biochemistry and Organic Chemistry, Uppsala University, Sweden

Mark Lathrop
Gene Science
Director General, Center National de Genotypage, France

Karin Markides
Chemistry
President, Chalmers University of Technology, Sweden

Rainer E. Metternich
Drug Discovery/Medical Chemistry
Managing Director, Chief Scientific Officer and Chief Business Officer, caprotec bioanalytics GmbH, Germany

Takehiko Sasazuki
Medicine: Immunology
Emeritus President, National Center for Global Health and Medicine, Japan

Raymond Stevens
Structural Biology
Professor, Department of Molecular Biology, The Scripps Research Institute, USA

Sukekatsu Ushioda
Surface Properties
President, National Institute for Materials Science, Japan

Chi-Huey Wong
Chemical Biology
President, Academia Sinica, Taiwan

(as of May 2011)

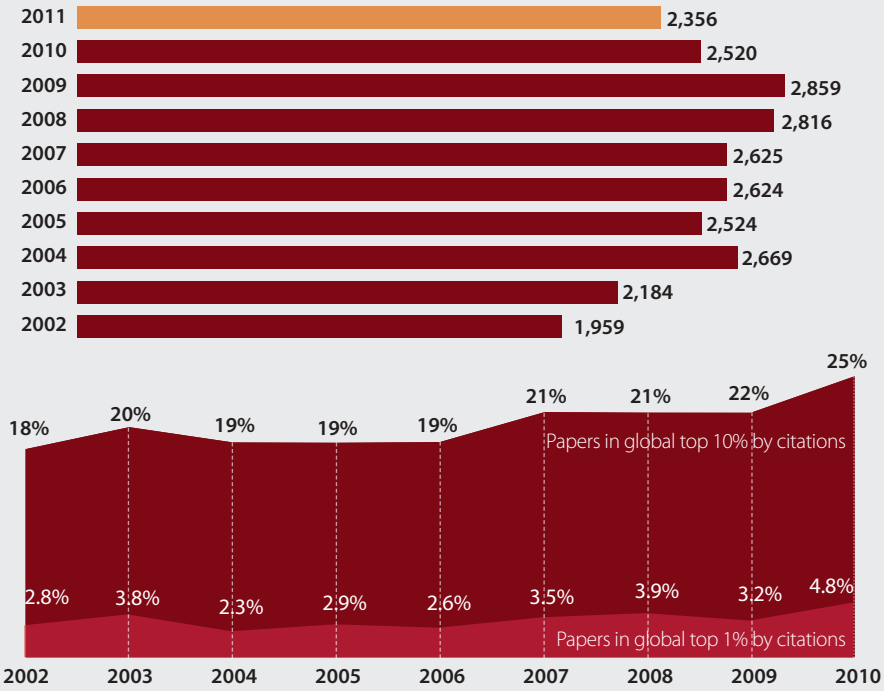
Research output

World-class research

Cutting-edge, first-class research is at the heart of RIKEN's activities. The institute has seen a steady rise in research publications over the past decade. Testifying to the exceptional quality of research carried out at RIKEN, the citation rates for articles published by RIKEN researchers exceed the international standard—the proportion of RIKEN papers rated in the top 10% of all articles published globally based on citations remains above 20%, and the proportion of papers in the top 1% of most highly cited articles is steady at more than 3% since 2007.

More than
20%
of papers by RIKEN ranked in the top 10% of all papers published worldwide

Papers published 2002–2011



Source: Thomson Reuters Web of Science/Science Citation Index Expanded, April 2012

RIKEN made a splash in the 2011 Thomson Reuters Hottest Researcher top-ten listing with the inclusion of Dr. Kazuo Shinozaki at fifth place—the only Japanese researcher selected in 2011. The listing compiles the top ten researchers with the most highly cited papers—known as 'Hot Papers'—which are derived from the world's top-class database of citation data, Thomson Reuters' Web of Science®. Shinozaki was ranked at number five for his 11 highly cited papers in the areas of functional genomics, stress responses, acquired resistance and other regulatory functions in *Arabidopsis* and other plants.

Kazuo Shinozaki

RIKEN RESEARCH

www.rikenresearch.riken.jp

Showcasing the best of RIKEN

Bringing the best of research from RIKEN to the international community and raising awareness of RIKEN as a global brand are at the core of RIKEN's science communication strategy. Two key tools for the realization of these aims are the bilingual *RIKEN RESEARCH* website—published in English and Japanese—and the associated English-language monthly magazine, which is distributed both in printed form and as a free download. Together these present the very best of the research published by RIKEN every year in an accessible, easy-to-read format. The publication also provides regular insights into the people, facilities and programs that make up daily life at RIKEN. In fiscal 2011, the website was visited by readers from 180 countries and registered 20% more visits than the previous year, whilst the number of people registering for the e-mail alert service rose by 22%. Over the same period, issues of the *RIKEN RESEARCH* monthly print magazine featuring research highlights covering over 120 carefully selected papers published by RIKEN scientists were distributed to top-flight researchers and institutions around the world.

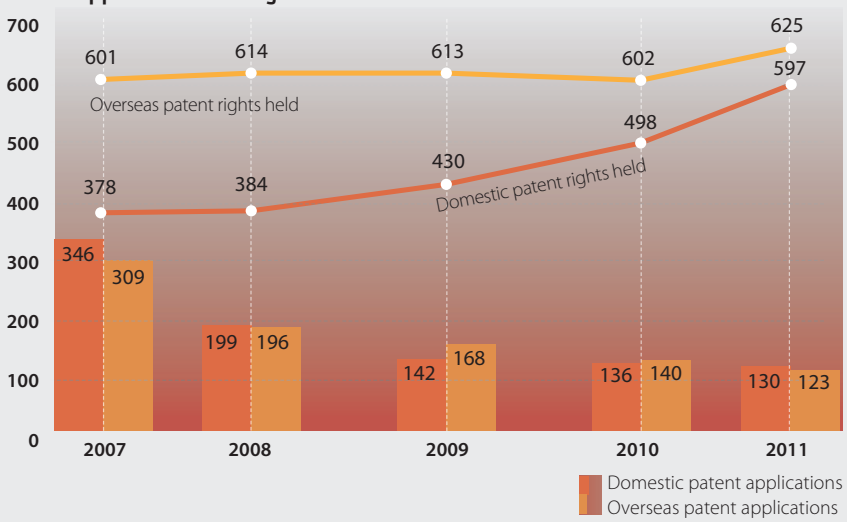
Technology transfer

Patent activity in 2011

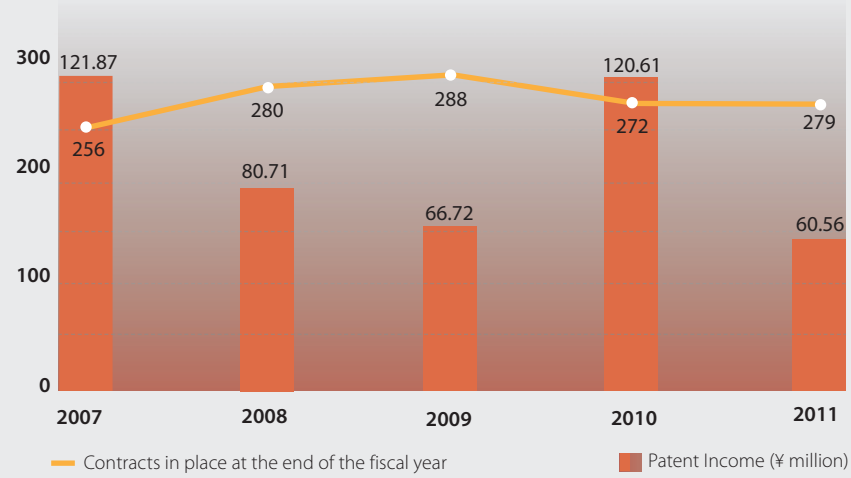
RIKEN not only disseminates its research results each year in top-tier science journals, it actively harnesses those discoveries and inventions with commercial potential and secures legal protection for its research achievements by registering many patents every year. The Technology Transfer Office (TTO) manages the RIKEN technology transfer portfolio and acts as a conduit between RIKEN and the private sector. Responsible for intellectual property patent applications, registrations, licenses and contracts, the TTO also collaborates with industry, acquires external and competitive funding, and supports RIKEN scientists in developing practical applications for their research.

RIKEN licensed a total of
733
patents in 2011

Patent applications and registrations



Patent income and contracts



RIKEN 'baton zone'

Bringing RIKEN and industry together

RIKEN actively promotes the transfer of its scientific achievements into commercial products through partnerships with private companies. Taking its name from the place in a relay race where the first runner hands off the baton to the next runner, both running in the same direction and at the same speed, RIKEN has created the concept of a 'baton zone' of innovative programs in which science and business work together to focus their energy on efficient technology transfer. According to the baton zone concept, RIKEN operates the following two programs:

Integrated Collaborative Research Program with Industry

Projects on themes suggested by private companies are carried out in RIKEN to integrate the two parties' expertise. An ad hoc collaborative research team, headed by an expert sent from the commercial partner, is formed to construct a technology platform and commercialize research outcomes in a timely fashion. As of March 2012, there were eleven active collaborative teams.

Industry–RIKEN Collaboration Centers

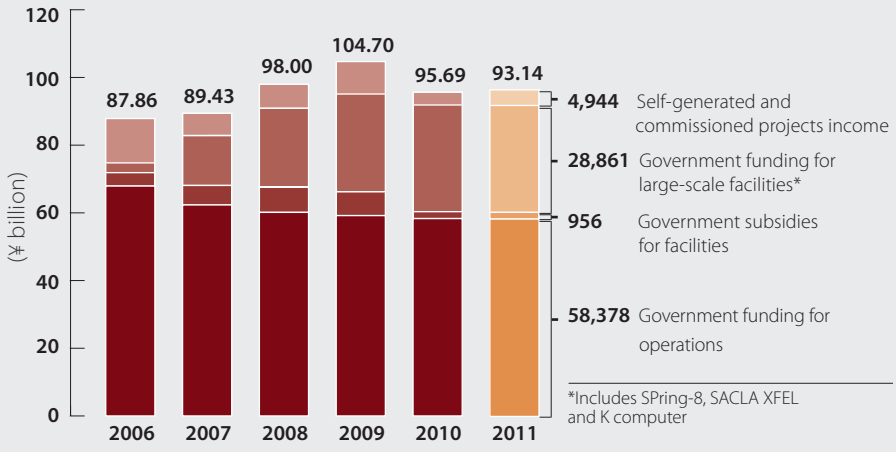
Based on proposals made by private companies, collaboration centers are set up in RIKEN institutes and centers to provide a research environment where a comprehensive relationship between the two parties accelerates the realization of medium- to long-term projects. As of March 2012, there were four centers in operation.

Budget profile

Income

Due to its status as an independent administrative institution, RIKEN derives most of its funding from the Japanese government. However, always aware of the need to diversify its funding resources, RIKEN strives to seek out alternative funding from other bodies.

The largest proportion of RIKEN's income is derived from government grants that fund RIKEN's general operations and facility maintenance. Government subsidies for the operation and construction of major facilities, such as the SPring-8 Synchrotron Radiation and the SACLA X-ray Free Electron Laser (XFEL) facilities in Harima and the K computer in Kobe, constitute a significant proportion of total income over the past several years.



RIKEN's total income for 2011 was

¥93.14 billion

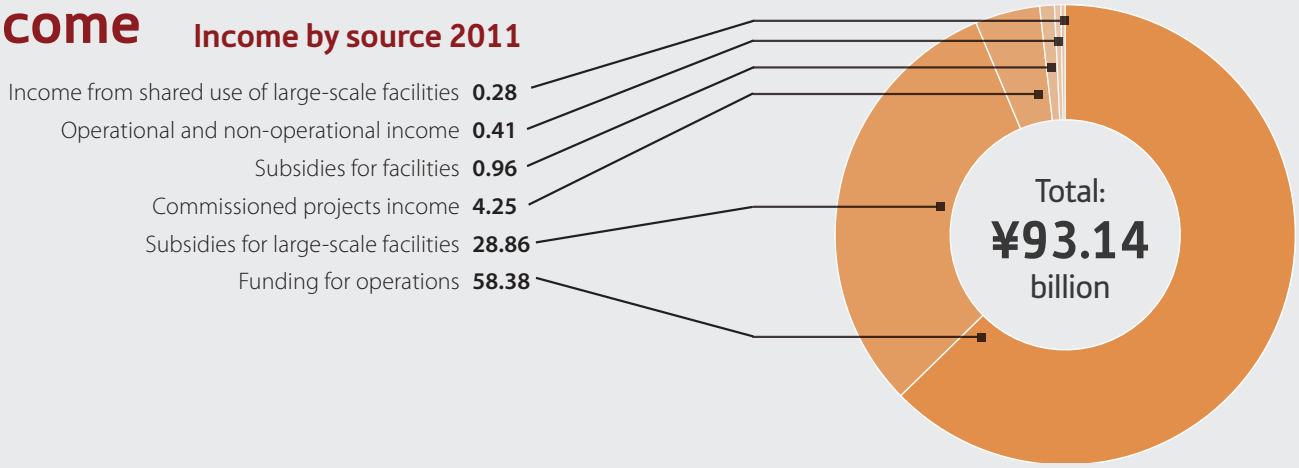
Additional revenue streams

In addition to its funding from the central government, RIKEN also obtains financing from a range of other governmental bodies, including the Ministry of Education, Culture, Sports, Science and Technology (MEXT), the Ministry of Health, Labor and Welfare (MHLW), the Japan Science and Technology Agency (JST), the Funding Program for World-Leading Innovative Research and Development on Science and Technology (FIRST), as well as other public and private organizations.

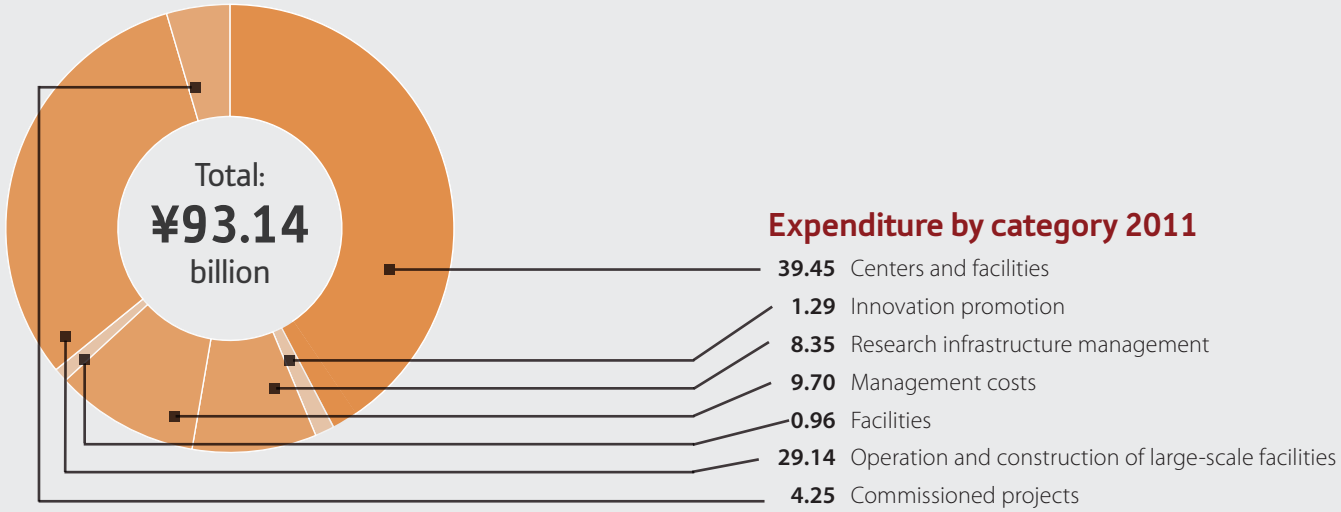
Category		FY2009	FY2010	FY2011
				¥ million
Competitive funds	Grants-in-Aid for Scientific Research	3,790	4,015	4,129
	Grants-in-Aid for Scientific Research (MHLW, MOE)	229	109	85
	Special Coordination Funds for the Promotion of Science and Technology	65	210	0
	Projects funded by organizations that fund science and technology	2,535	2,325	2,343
	Basic Research Programs	6,193	2,257	1,376
	Other publicly supported projects	484	556	552
	Leading-edge Research Promotion Fund	565	1,777	1,840
Sub-total		**13,861**	**11,249**	**10,325**
Non-competitive funds	Government-commissioned research	2,685	2,178	1,787
	Government-related commissioned research	246	254	492
	Government grants	539	3,714	2,420
	Contributions	152	65	52
Sub-total		**3,622**	**6,211**	**4,751**
International grants and domestic foundation grants		273	330	231
Private commissioned research		968	1,047	1,562
Total		**18,725**	**18,838**	**16,869**

Income

Income by source 2011



Expenditure



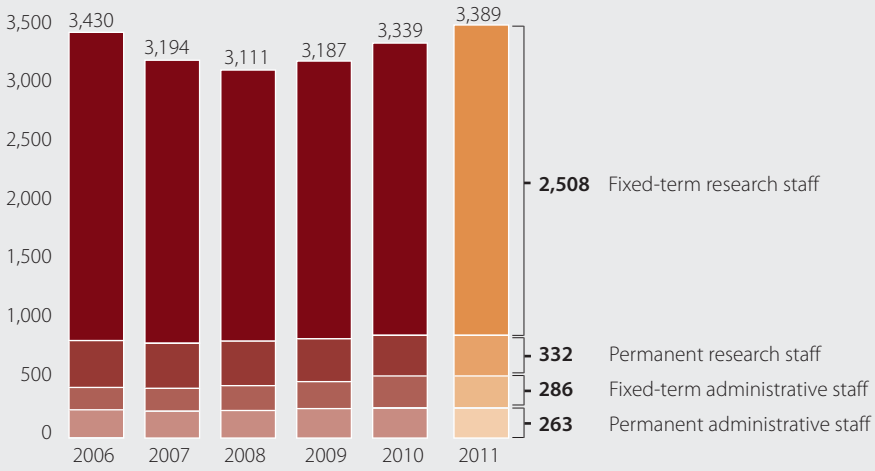
Expenditure by research center	FY2011 (¥ billion)
Advanced Science Institute	3.96
Brain Science Institute	8.36
Plant Science Center	1.13
Research Center for Allergy and Immunology	3.11
Center for Genomic Medicine	1.34
Center for Developmental Biology	3.82
Center for Molecular Imaging Science	1.35
Nishina Center for Accelerator-Based Science	3.55
BioResource Center	2.99
SPring-8 Center	1.96
Life science platforms*	2.90
Yokohama Institute shared research funds	1.70
Research programs for green innovation	1.21
Quantitative Biology Center	2.09
Total	**39.45**

*The life science platforms include the Omics Science Center, the Systems and Structural Biology Center, and the Bioinformatics And Systems Engineering division (BASE).

Personnel

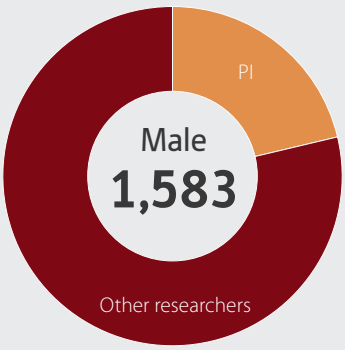
RIKEN endeavors to cultivate a first-class international research hub by bringing together top-quality researchers and administrative staff from Japan and around the world, regardless of nationality or gender. RIKEN personnel are employed as either permanent or fixed-term research or administrative staff. Diversity is at the heart of RIKEN's research environment, and this is no better illustrated than in the strong numbers of international and female staff who play a vital role in RIKEN's success today.

Research and administrative employees

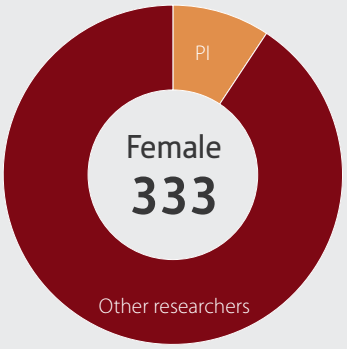


In 2011 RIKEN employed
3,389
research and administrative staff

Diversity of RIKEN scientists

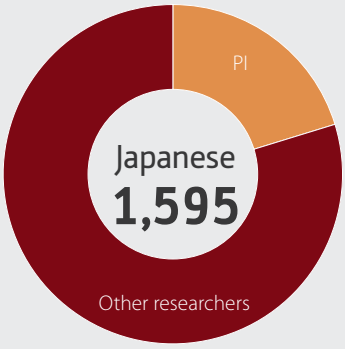


337 Principal Investigators
1,246 Other researchers

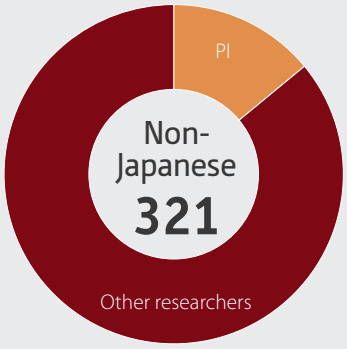


31 Principal Investigators
302 Other researchers

1,916
scientists work for RIKEN



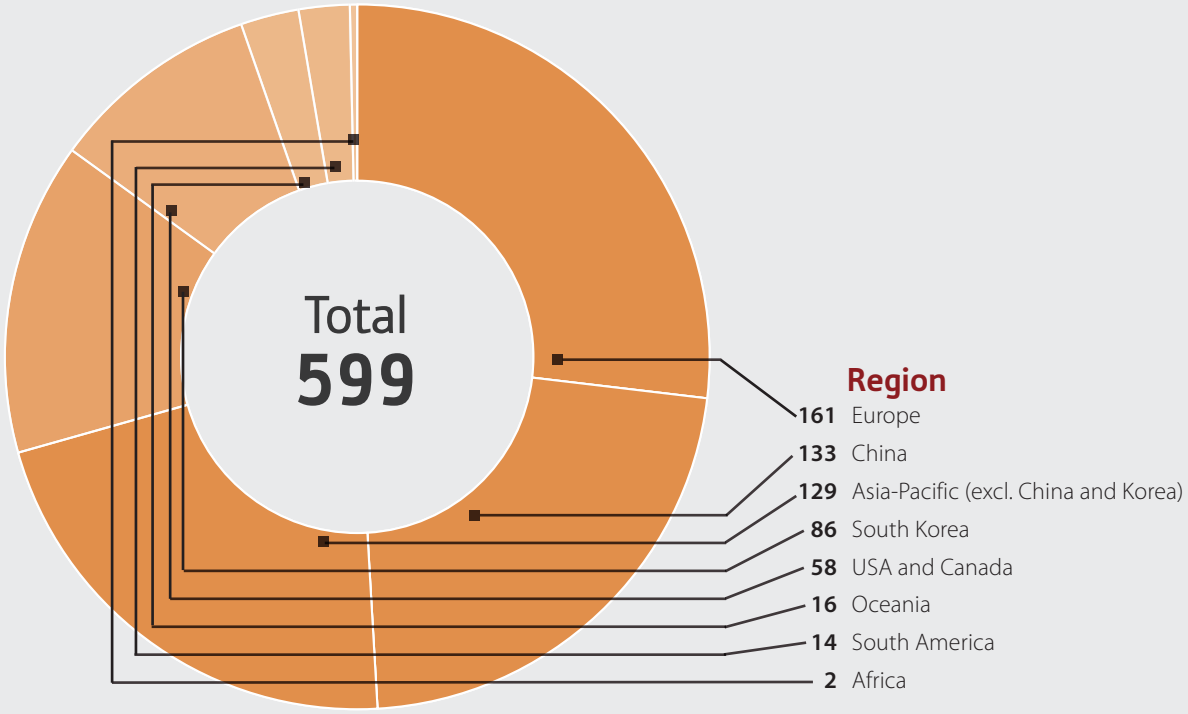
323 Principal Investigators
1,272 Other researchers



45 Principal Investigators
276 Other researchers

(as of March 2012)

International staff, visiting scientists and students at RIKEN



Europe
Austria, Belarus, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Denmark, Finland, France, Georgia, Germany, Greece, Italy, Lithuania, Netherlands, Poland, Romania, Russia, Slovakia, Spain, Sweden, Switzerland, Turkey, U. K.

Asia
Bangladesh, China, Hong Kong, India, Indonesia, Iran, South Korea, Malaysia, Nepal, North Korea, Pakistan, Philippines, Singapore, the Palestinian Territories, Taiwan, Thailand, Vietnam

North America
Canada, U.S.A.

South America
Chile, Colombia, Brazil, Mexico, Peru, Venezuela

Oceania
Australia

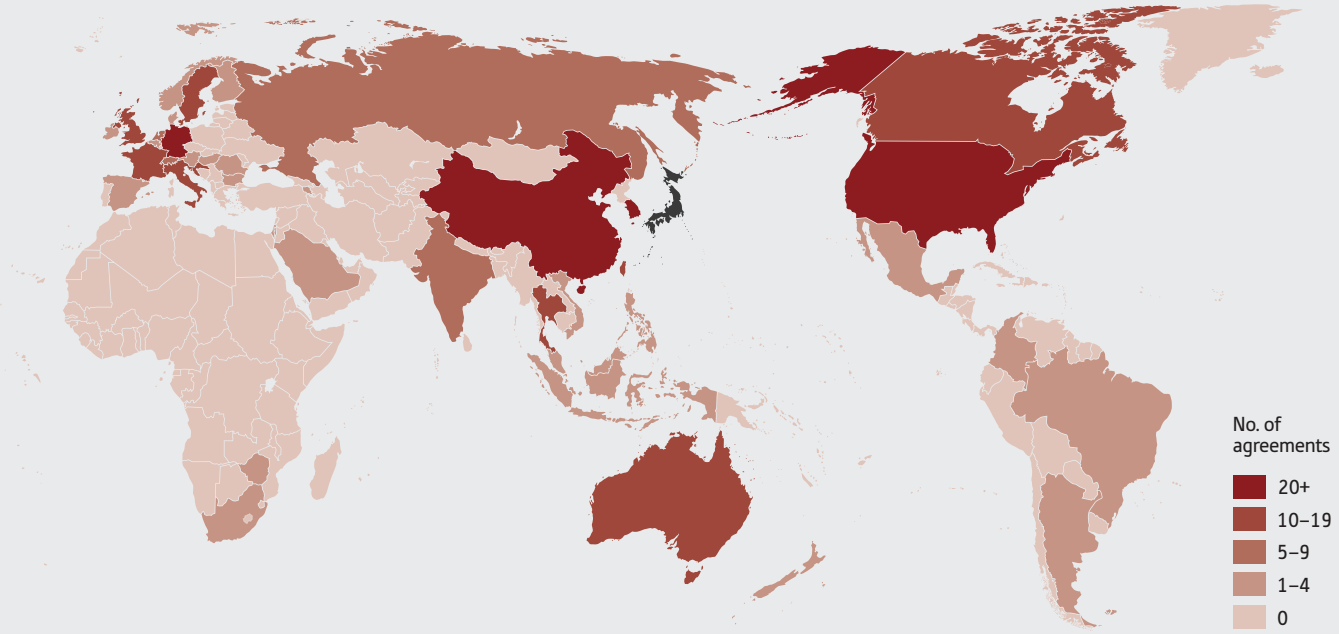
Africa
Egypt

In 2011 RIKEN employed **352** non-Japanese researchers and technical staff from **51** countries and regions around the world

Top 7 overseas countries and regions represented at RIKEN		
1	China	133
2	South Korea	86
3	U.S.A	44
4	India	37
5	Germany	29
6	U.K.	26
7	France	25

(as of October 2011)

International collaboration



Region	No. of partner countries in each region	No. of collaboration agreements
North America	2	67
South America	4	9
Oceania	2	18
Asia	10	150
Middle East	2	3
Europe	20	153
Africa	2	5
Total	**42**	**405**

(as of March 2012)

As RIKEN continues to grow, so does its network of collaborators at research institutions around the world. RIKEN actively supports research collaborations and the exchange of researchers, students and staff with universities and institutions all across the globe. The map above outlines the distribution of these reciprocal research arrangements, including the major institutions and universities that have a General Collaborative Agreement or Memorandum of Understanding (MoU) with RIKEN.

ASIA	
China	Chinese Academy of Sciences (CAS)
	The Shanghai Branch of the Chinese Academy of Sciences (CAS Shanghai Branch)
	Shanghai Jiao Tong University (SJTU)
	Xi'an Jiaotong University (XJTU)
Korea	Korea Institute of Science and Technology (KIST)
	Korea Research Institute of Chemical Technology (KRICT)
	Korea Research Institute of Bioscience and Biotechnology (KRIBB)
	Seoul National University (SNU)
Taiwan	Academia Sinica (Taiwan)
Malaysia	University of Malaya (UM)
Singapore	Agency for Science, Technology and Research (A*STAR)
	Nanyang Technological University (NTU)
	National University of Singapore (NUS)
Indonesia	The Agency for the Assessment and Application of Technology
India	Department of Science and Technology (DST)

NORTH AMERICA	
Canada	National Research Council Canada (NRC)
	McGill University
OCEANIA	
Australia	Australian Commonwealth Scientific and Industrial Research Organisation (CSIRO)
MIDDLE EAST	
Israel	Weizmann Institute of Science
EUROPE	
Sweden	Karolinska Institutet (KI)
England	University of Liverpool (UoL)
Germany	Max Planck Society (MPG)
	Technische Universität München (TUM)
France	Institut Pasteur
	Centre National de la Recherche Scientifique (CNRS)
	Université de Strasbourg (Unistra)
Switzerland	Swiss Federal Institute of Technology Zurich (ETH Zurich)

(as of March 2012)

RIKEN directory

Japan

RIKEN Headquarters
2-1 Hirosawa, Wako, Saitama 351-0198, Japan
Tel: +81-(0)48-462-1111; Fax: +81-(0)48-462-1554

RIKEN Wako Institute
RIKEN Advanced Science Institute
2-1 Hirosawa, Wako, Saitama 351-0198, Japan
Fax: +81-(0)48-465-8048
E-mail: asi@riken.jp

RIKEN Brain Science Institute
2-1 Hirosawa, Wako, Saitama 351-0198, Japan
Tel: +81-(0)48-467-9757; Fax: +81-(0)48-462-4914
E-mail: infobsi@brain.riken.jp

RIKEN Nishina Center for Accelerator-Based Science
2-1 Hirosawa, Wako, Saitama 351-0198, Japan
Tel: +81-(0)48-467-9451; Fax: +81-(0)48-461-5301
E-mail: nishina-center@riken.jp

RIKEN Research Cluster for Innovation
RIKEN Innovation Center
2-1 Hirosawa, Wako, Saitama 351-0198, Japan
Tel: +81-(0)48-462-5475; Fax: +81-(0)48-462-4718
E-mail: cips-kikaku@riken.jp

RIKEN Program for Drug Discovery and Medical Technology Platforms
1-7-22 Suehiro-cho, Tsurumi-ku, Yokohama, Kanagawa 230-0045, Japan
Tel: +81-(0)45-503-9658; Fax: +81-(0)45-503-9150

RIKEN Biomass Engineering Program
2-1 Hirosawa, Wako, Saitama 351-0198, Japan
Tel: +81-(0)48-462-1481; Fax: +81-(0)48-462-1220

Computational Science Research Program
2-1 Hirosawa, Wako, Saitama 351-0198, Japan
Tel: +81-(0)48-462-1488; Fax: +81-(0)48-462-1220

RIKEN Tsukuba Institute
RIKEN BioResource Center
3-1-1 Koyadai, Tsukuba, Ibaraki 305-0074, Japan
Tel: +81-(0)29-836-9111; Fax: +81-(0)29-836-9109
E-mail: webadmin@brc.riken.jp

RIKEN Harima Institute
1-1-1 Kouto, Sayo-cho, Sayo-gun,
Hyogo 679-5148, Japan
Tel: +81-(0)791-58-0808; Fax: +81-(0)791-58-0800

RIKEN SPring-8 Center
1-1-1 Kouto, Sayo-cho, Sayo-gun,
Hyogo 679-5148, Japan
Tel: +81-(0)791-58-2800; Fax: +81-(0)791-58-2898
E-mail: riken@spring8.or.jp

RIKEN Yokohama Institute
RIKEN Plant Science Center
RIKEN Center for Genomic Medicine
RIKEN Research Center for Allergy and Immunology
RIKEN Omics Science Center
RIKEN Systems and Structural Biology Center
RIKEN Bioinformatics And Systems Engineering division (BASE)
1-7-22 Suehiro-cho, Tsurumi-ku, Yokohama,
Kanagawa 230-0045, Japan
Tel: +81-(0)45-503-9111; Fax: +81-(0)45-503-9113
E-mail: yokohama-web@riken.jp

RIKEN Center of Research Network for Infectious Diseases
Jimbocho 101 Bldg., 1-101 Kanda-Jimbocho,
Chiyoda-ku, Tokyo 101-0051, Japan
Tel: +81-(0)3-3518-2952; Fax: +81-(0)3-3219-1061
E-mail: crnid-mado@riken.jp

RIKEN Kobe Institute
2-2-3 Minatojima-minamimachi, Chuo-ku, Kobe,
Hyogo 650-0047, Japan
Tel: +81-(0)78-306-0111; Fax: +81-(0)78-306-0101
E-mail: contact-kobe@riken.jp

RIKEN Center for Developmental Biology
2-2-3 Minatojima-minamimachi, Chuo-ku, Kobe,
Hyogo 650-0047, Japan
Tel: +81-(0)78-306-0111; Fax: +81-(0)78-306-0101
E-mail: cdb@cdb.riken.jp

RIKEN Center for Molecular Imaging Science
6-7-3 Minatojima-minamimachi, Chuo-ku, Kobe,
Hyogo 650-0047, Japan
Tel: +81-(0)78-304-7111; Fax: +81-(0)78-304-7112
E-mail: cmis_info@riken.jp

RIKEN Quantitative Biology Center
2-2-3 Minatojima-minamimachi, Chuo-ku, Kobe,
Hyogo 650-0047, Japan
Tel: +81-(0)78-306-0111; Fax: +81-(0)78-306-0101
E-mail: qbic_info@riken.jp

RIKEN HPCI Program for Computational Life Sciences
2-2-3 Minatojima-minamimachi, Chuo-ku, Kobe,
Hyogo 650-0047, Japan
Tel: +81-(0)78-306-0111; Fax: +81-(0)78-306-0101
E-mail: stpr1-life@riken.jp

RIKEN Advanced Institute for Computational Science
7-1-26 Minatojima-minamimachi, Chuo-ku, Kobe,
Hyogo 650-0047, Japan
Tel: +81-(0)78-940-5555; Fax: +81-(0)78-304-4956

Sendai Facility
519-1399 Aoba, Aramaki, Aoba-ku, Sendai,
Miyagi 980-0845, Japan
Tel: +81-(0)22-228-2111; Fax: +81-(0)22-228-2122

Nagoya Facility
(In the Nagoya Science Park Research and Development Center)
2271-130 Anagahora, Shimoshidami, Moriyama-ku,
Nagoya, Aichi 463-0003, Japan
Tel: +81-(0)52-736-5850;
Fax: +81-(0)52-736-5854

Itabashi Branch
1-7-13 Kaga, Itabashi, Tokyo 173-0003, Japan
Tel: +81-(0)3-3963-1611; Fax: +81-(0)3-3579-5940

Tokyo Liaison Office
Fukoku Seimei Building, 23rd floor (Room 2311)
2-2-2 Uchisaiwaicho, Chiyoda-ku,
Tokyo 100-0011, Japan
Tel: +81-(0)3-3580-1981; Fax: +81-(0)3-3580-1980

International

RIKEN Beijing Representative Office
#1121 B Beijing Fortune Building, No.5, Dong San Huan Bei Lu, Chao Yang District, Beijing
100004, China
Tel: +86-10-6590-8077; Fax: +86-10-6590-8270

RIKEN Singapore Representative Office
11 Biopolis Way, #07-01/02 Helios 138667, Singapore
Tel: +65-6478-9940; Fax: +65-6478-9943

RIKEN BNL Research Center
Building 510A, Brookhaven National Laboratory,
Upton, New York 11973, USA
Tel: +1-631-344-8095; Fax: +1-631-344-8260

RIKEN Facility Office at RAL
UG17 R3, Rutherford Appleton Laboratory,
Harwell Science and Innovation Campus,
Didcot, Oxfordshire
OX11 0QX, UK
Tel: +44-1235-44-6802; Fax: +44-1235-44-6881

RIKEN–MIT Center for Neural Circuit Genetics
MIT 46-2303N, 77 Massachusetts Avenue, Cambridge,
Massachusetts 02139, USA
Tel: +1-617-324-0305;
Fax: +1-617-324-0976, +1-617-452-2588

RIKEN–HYU Collaboration Research Center
Fusion Technology Center 5F, Hanyang University,
17 Haengdang-dong, Seongdong-gu,
Seoul 133-791, South Korea
Tel: +82-(0)2-2220-2728; Fax: +82-(0)2-2220-2729

RIKEN-KRIBB Collaboration Research Center for Chemical Biology
685-1 Yangcheonri, Ochang, South Korea

RIKEN-USM Joint Laboratory for Bioprobe Discovery
11800 Universiti Sains Malaysia, Pulau
Pinang, Malaysia

RIKEN-XJTU Joint Research Center
28 West Xianning Road, Xi'an, China

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