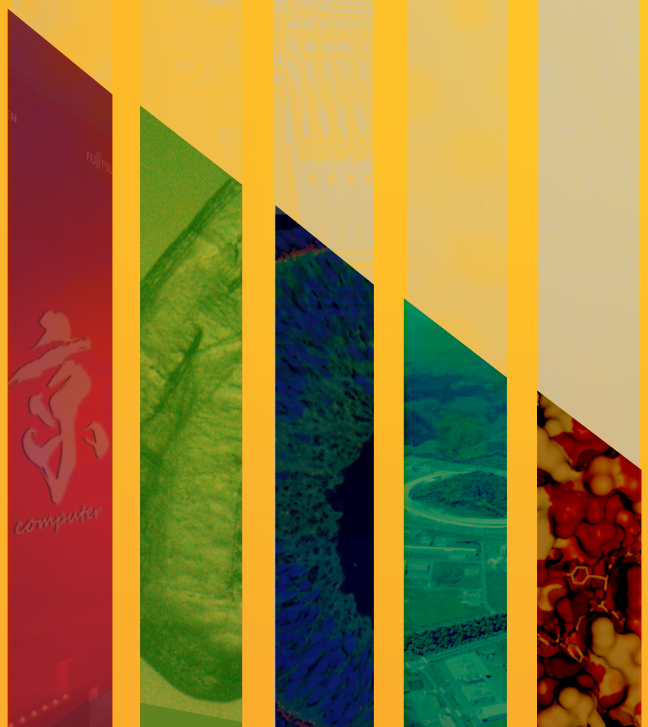
RIKEN

Science Serving Society

# ANNUAL REPORT 2012–2013



# ANNUAL REPORT 2012–2013

## Message from the President

This year marked the final year of our current five-year term, and hence it has been a year for pulling things together. Thanks to the efforts made during the past five years to strengthen our research infrastructure, in September 2012 we opened for public use the K computer, which had earned the honor of being rated as the world's fastest supercomputer. Another major achievement was the full start-up of the SACLA X-ray Free Electron Laser in March 2012. We have high expectations that these new facilities will contribute to the creation of a sustainable society by allowing research in areas such as new material development, the elucidation of biological processes, drug development, and earthquake and tsunami prediction. They also will contribute to the advancement of human society, and lead to research outcomes that will help invigorate industry. Simultaneously, we have engaged in preparations for our upcoming five-year term. We will carry out a major reorganization in April 2013, and with it embark on a bold new path.

In 2012 we took a major step onto the world stage by hosting, together with the National Institute of Advanced Industrial Science and Technology, the first Global Summit of Research Institute Leaders. We brought together the heads of nearly 20 institutes from around the world to hold vigorous discussions on the role of science and technology in promoting a sustainable society, as well as the issues of brain circulation and brain drain, which are important for the development of human resources. I believe that one critical role of RIKEN is to carry out research that will be helpful in solving the issues that confront all of us, in partnership with the global scientific community. Today's rapid globalization has given us renewed awareness of the importance of cooperation extending beyond the limits of research fields, institutes, regions, and nations in order to resolve our problems. For science and technology, this is particularly true. At RIKEN, we will endeavor to carry out world-leading research in close collaboration with our partners in Japan and throughout the world.

This Annual Report offers a view of RIKEN's endeavors to help build a future of hope for humanity. Our objective is not only to push back the frontiers of science, but also to become an essential contributor to society. We will always keep an eye on where we are and never cease our 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

# Introduction to the RIKEN Annual Report 2012–2013

RIKEN is a core international research hub in Japan renowned for high-quality research in a diverse range of scientific disciplines. Established in Tokyo in 1917 as the RIKEN Foundation, today we are an independent administrative institution funded substantially by the Japanese government, and for more than 90 years we have played a defining role in the scientific progress of Japanese society. This was illustrated by our response to the 2011 Great East Japan Earthquake, when we extended our knowledge and expertise to the service of the nation. Such challenges have renewed RIKEN's long-held commitment to fundamental research in the natural sciences, the advancement of national scientific innovation and development through continued international collaboration, and the elevation of Japan's scientific profile on the world stage.

In society at large, we endeavor to cultivate a heightened awareness of and appreciation for science and technology as the foundation of today's economy and standard of living. The future of scientific research will continue to be shaped by RIKEN's ongoing promotion of curiosity-driven research, which—along with our distinguished history and unique research culture—will continue to lead to new scientific discoveries.

The RIKEN Annual Report goes beyond a simple assessment of the financial and academic performance of RIKEN over the past financial year and shines a spotlight on our centers and institutes, our latest research achievements and our future directions.

The year 2013 concludes RIKEN's second five-year term since we commenced operating as an independent administrative institution in 2003. Our second five-year term set for us three strategic challenges—to make great strides in scientific and technological development, to deliver science and technology that benefits society, and to establish RIKEN as a globally recognized research institute—and our Annual Report for the fiscal period 2012–2013 shows we are well on track to meet these goals.

In the year 2012, RIKEN's award-winning K computer (p. 4)—one of the most powerful supercomputers in the world—was opened for public use to members of academia and industry, enabling our collaboration with users of the K computer to translate the facility's outstanding simulation accuracy and computational speed into top-class advancements in research and technology. Also in 2012, a team of RIKEN researchers obtained data unambiguously identifying the elusive element 113, adding a new element to the periodic table and leading researchers in the team to claim naming rights for the element (p. 4). In recent years, we have also seen other landmark achievements by RIKEN researchers, such as the creation of optic cup tissue from human embryonic stem cells and the opening of the SPring-8 Angstrom Compact Free Electron Laser (SACLA) facility, which emits an x-ray laser a billion times brighter than the SPring-8's previous technology.

Our report showcases RIKEN's five main institutes at Wako, Tsukuba, Yokohama, Kobe and Harima and highlights the latest research these institutes conduct across the entire range of the natural sciences, from astrophysics and quantum science to cell biology and neuroscience (from p. 7). These profiles outline the key roles that each of the centers and institutes play in our mission and demonstrate some examples of the centers' research successes of the past year.

In order for us to make great advances in science and technology as a world-class institute, it is essential that we attract top talent from around the world. We place great importance on nurturing young researchers, and so we offer various research programs for international researchers, including the Initiative Research Unit Program, the Foreign Postdoctoral Researcher Program, the International Program Associate and programs for visiting scholars (from p. 41).

The progress we have made since our foundation in 1917 to the end of our second five-year term in 2013 is clearly presented in our History of RIKEN timeline (pp. 48–49) and our 5-year timeline (pp. 50–51). Covering the first 90 years of RIKEN and the most recent 5 years respectively, these engaging timelines track the rise of RIKEN from a fledgling private research foundation to the cutting-edge and internationally renowned institute it is today.

As the figures show (from p. 54), we have devoted our efforts at RIKEN to pursuing key performance criteria—research publications, patent applications, commercialization, funding sources and workforce diversity—as well as to maintaining an international makeup through our recruitment of talented non-Japanese researchers via international support programs and by providing great opportunities for young and distinguished researchers from overseas to play a key part in our mission. The figures provide a tantalizing introduction to RIKEN and how we continue to contribute to research at the frontline of science.

# Table of contents

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Annual news roundup

# Building on success

The 2012–2013 fiscal year saw many long-awaited achievements for RIKEN—the start of practical operation of the state-of-the-art K computer, the first self-organized development of human retinal cells from stem cells, the authoritative identification of element 113, and participation in the First Global Summit of Research Institute Leaders in Kyoto.

## The K computer comes online

In September 2012, Japan's new national supercomputer, the K computer in Kobe, was made available for the first time for use by academia and industry, marking the project's last and most important milestone and ushering in a new era of supercomputer-based research in Japan.

Developed by RIKEN and Fujitsu since 2006 with funding from the Japanese government's High Performance Computing Infrastructure (HPCI) initiative, the K computer has been anticipated to be the forerunner to a new generation of supercomputers. Providing computational power of up to 10 petaflops ($10^{16}$ operations per second), the K computer secured first place in the June and November 2011 global TOP500 supercomputer rankings. The supercomputer was also awarded top accolades in the High Performance Computing Challenge and the Gordon Bell Prize —awards highlighting the facility's world-class performance in real-world applications.

The K computer brings together leading technologies such as ultrafast energy-efficient processors and massive interconnectivity to provide researchers with unprecedented computing power, opening up opportunities for simulations at scales and complexities never before attempted.


**RIKEN's award-winning K computer**

The facility is expected to 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 search for the origin of matter and the Universe, with support from and coordination by the RIKEN Advanced Institute for Computational Science.

Access to the K computer by researchers and industry is managed by the Research Organization for Information Science and Technology (RIST), which is a Registered Institution for Facilities Use Promotion, a non-profit organization for the promotion of the development and utilization of computational science and technology. The first successful proposals for use of the K computer were announced by the RIST in September and cover 62 projects, including 29 general use projects, 8 young researcher projects and 25 industry-related projects, as well as 31 projects fulfilling the various HPCI strategic programs.

RIKEN will work together with users to translate the supercomputing power of the K computer into world-class advancements in research and technology. The exceptional simulation capabilities of the supercomputer are expected to drive breakthroughs in fields such as next-generation semiconductor materials for faster, lower-powered electronic devices, dye-sensitized solar cells for more efficient solar energy conversion, climate modeling and earthquake and tsunami prediction, and to dramatically improve the speed and efficiency of drug discovery.

## Patience leads to success in the search for element 113

In August 2012 after more than nine years of painstaking effort, a research team led by Kosuke Morita at the Superheavy Element Laboratory of the RIKEN Nishina Center for Accelerator-Based Science finally captured evidence that for the first time unequivocally identifies element 113.

Currently known by its provisional name, ununtrium, element 113 is a member of the superheavy group of elements—highly unstable elements with more than 92 protons that can only be created in nuclear reactors or particle accelerators and typically exist for just milliseconds.

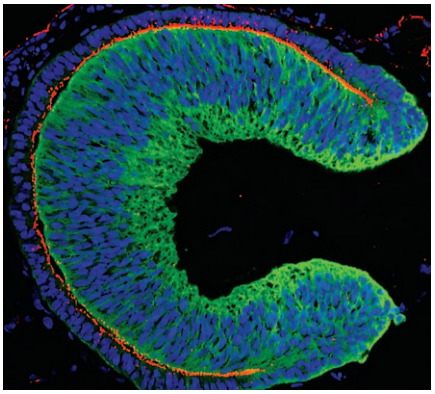
Researchers from the USA, Russia and Germany have already identified all of the synthetic superheavy elements between element 93 and 116 with the exception of 113 and 115. Morita and his colleagues first caught a glimpse of the elusive element 113 in 2004 and 2005, but confirming its identity required years of effort to observe a rare alternative radioactive decay route consisting of a specific chain of 6 alpha decays.

"I would like to thank all the researchers and staff involved in this momentous result, who persevered with the belief that one day, 113 would be ours," said Morita following the announcement of the groundbreaking observations.

# The first human self-organized eye tissue grown in the lab

The Laboratory for Organogenesis and Neurogenesis at the RIKEN Center for Development Biology, headed by Group Director Yoshiki Sasai, has made major research achievements in the area of guided differentiation of embryonic stem cells (ESCs), including the controlled development of various neuronal cell types and the self-organization of complex tissue-like structures involving multiple cell types. The laboratory's latest breakthrough by Tokushige Nakano and colleagues was the development of a culture system that induces human ESCs to form the complex, self-organized retinal tissue of the optic cup.

Since the first derivation of human ESCs in 1998, there has been intensive research on how these remarkable building blocks of biological development can be induced to form the vast array of specialized cells and complex tissue that comprise the human body. Steering the process of stem cell differentiation involves the subtle doctoring of culture tissue with specific combinations of growth factors, and to date most of the achievements in this field have been in the successful differentiation of single classes of specialized cells. Finding the right combination of growth factors and other parameters that prompt the differentiation of ESCs into complex tissues consisting of the correct mix of cell types is significantly more challenging.





**An embryonic eye derived from human embryonic stem cells**

In 2011, Sasai's team demonstrated that mouse ESCs can be induced to form self-organized optic cup tissue using a similar approach to one they used previously to form cerebral cortex tissue. In the lab's latest work reported in June 2012, Nakano and his team successfully adapted the method for use with human ESCs.

The researchers found that the retinal precursor cells formed from an initial population of 9,000 human ESCs and began to self-organize into a recognizable optic cup in about two weeks. Further complex differentiation occurred after isolation of the neural retina from the optic cup structure, including the formation of ganglion cells, photoreceptors and other cells by day 40, and the eventual development into a laminar retinal structure after 126 days.

Nakano's team also developed a novel cryopreservation technique to overcome the considerable difficulties presented by the 100-day development time.

"We are hopeful that these findings may help to lay a foundation for regenerative medicine in which intact organ tissues, not just groups of cells, can be developed for use in cell transplantation," said Sasai on the announcement of his laboratory's latest breakthrough.

# First Global Summit of Research Institute Leaders

Since 2004, the Science and Technology in Society (STS) forum has been held annually in Kyoto, Japan, to promote informal discussions among researchers, policy makers and business leaders from around the world on the problems and challenges facing the application of science and technology in society. To encourage discussions among leaders, the first annual Global Summit of Research Institute Leaders was held in October 2012 in conjuction with the forum, with the attendance of STS forum chair, Koji Omi. Representing RIKEN was President Ryoji Noyori, who co-chaired the summit alongside Alain Fuchs, the president of the National Centre for Scientific Research (CNRS) in France.

The summit hosted participants from 12 countries and 16 research organizations, with presentations and discussions addressing issues such as the circulation of skilled labor, balancing basic and applied research, quantifying return on investment in research and development, integrating researchers from different cultures within a team, and collaboration between research centers and universities to nurture the next generations of researchers. The summit concluded with the issuing of a joint statement calling for enhanced international collaboration transcending national and regional boundaries to address global concerns such as changing demographics, diminishing natural resources and the spread of contagious diseases.

## 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. RIKEN also maintains five major research facilities. Among them are the K computer on Kobe Port Island and the SPring-8 Synchrotron Radiation and SACLA X-ray Free Electron Laser (XFEL) in Harima. In 2012, these world-class high-performance facilities became available for shared use.

### RIKEN Headquarters

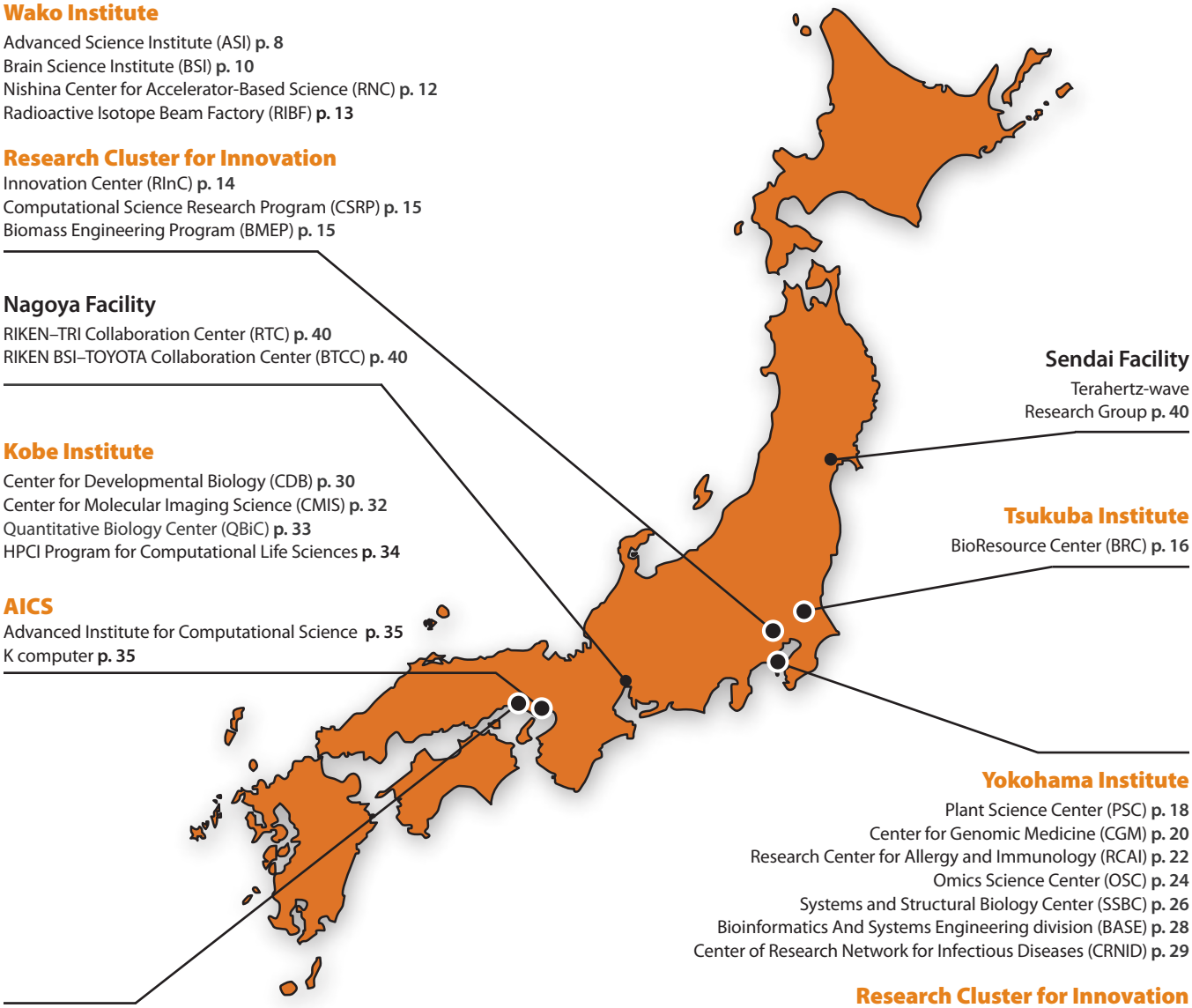
### Wako Institute
Advanced Science Institute (ASI) **p. 8**
Brain Science Institute (BSI) **p. 10**
Nishina Center for Accelerator-Based Science (RNC) **p. 12**
Radioactive Isotope Beam Factory (RIBF) **p. 13**

### Research Cluster for Innovation
Innovation Center (RInC) **p. 14**
Computational Science Research Program (CSRP) **p. 15**
Biomass Engineering Program (BMEP) **p. 15**

### Nagoya Facility
RIKEN–TRI Collaboration Center (RTC) **p. 40**
RIKEN BSI–TOYOTA Collaboration Center (BTCC) **p. 40**

### Kobe Institute
Center for Developmental Biology (CDB) **p. 30**
Center for Molecular Imaging Science (CMIS) **p. 32**
Quantitative Biology Center (QBiC) **p. 33**
HPCI Program for Computational Life Sciences **p. 34**

### AICS
Advanced Institute for Computational Science **p. 35**
K computer **p. 35**



### Sendai Facility
Terahertz-wave
Research Group **p. 40**

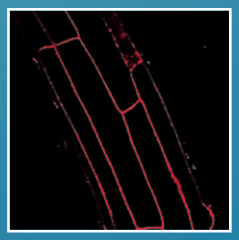
### Tsukuba Institute
BioResource Center (BRC) **p. 16**

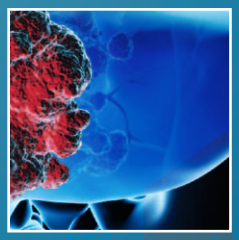
### Yokohama Institute
Plant Science Center (PSC) **p. 18**
Center for Genomic Medicine (CGM) **p. 20**
Research Center for Allergy and Immunology (RCAI) **p. 22**
Omics Science Center (OSC) **p. 24**
Systems and Structural Biology Center (SSBC) **p. 26**
Bioinformatics And Systems Engineering division (BASE) **p. 28**
Center of Research Network for Infectious Diseases (CRNID) **p. 29**

### Research Cluster for Innovation
Program for Drug Discovery and Medical Technology Platforms **p. 14**

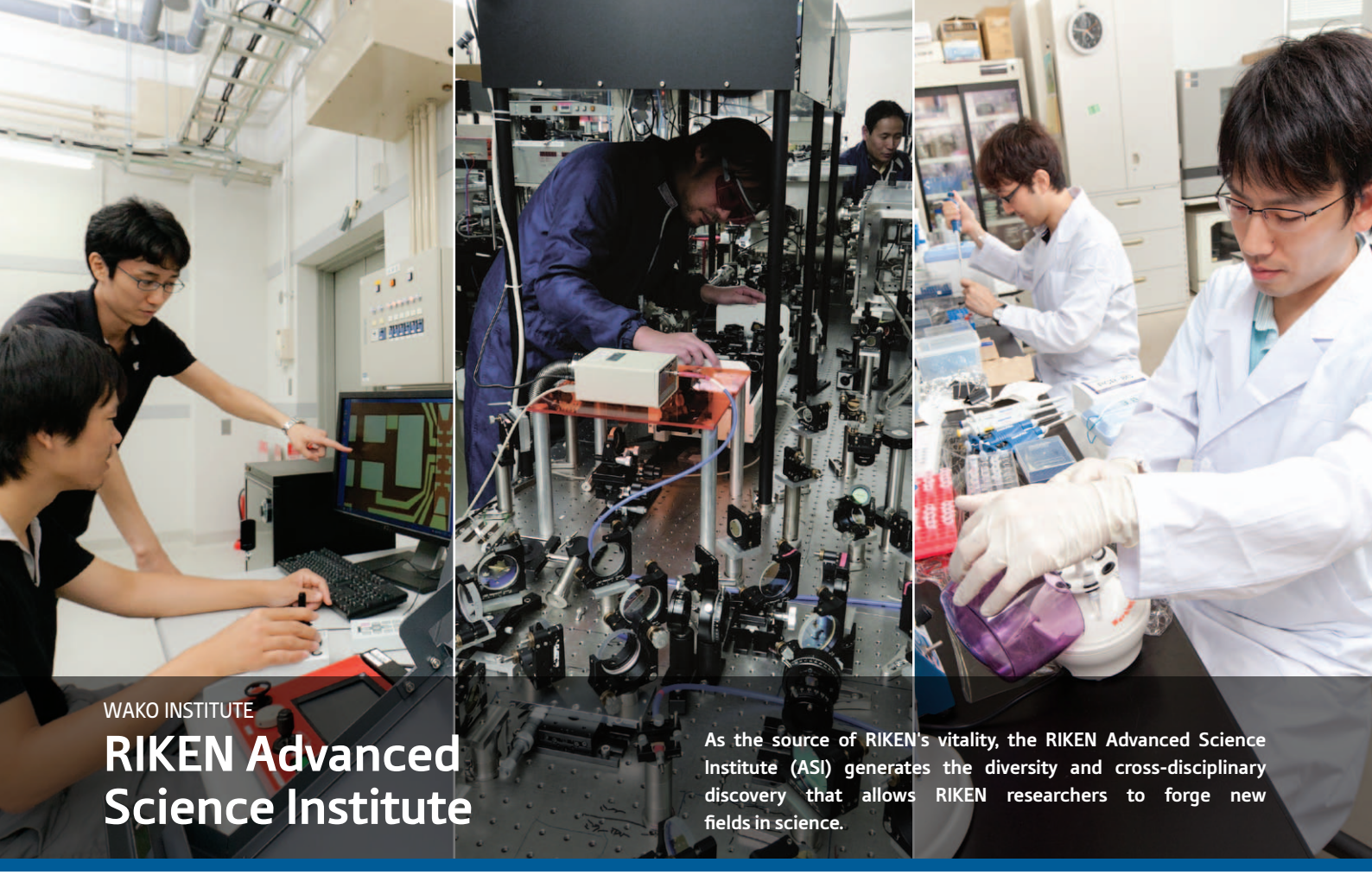
### Harima Institute
SPring-8 Center (RSC) **p. 36**
SPring-8 Synchrotron Radiation Facility **p. 36**
SACLA X-ray Free Electron Laser (XFEL) Facility **p. 36**

# 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 source of RIKEN's vitality, 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. 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. 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.

ASI has a systematic three-layered research structure for cultivating new fields in science. First, 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. 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, ASI is active in pursuing new research that spans multiple fields. For example, in the Extreme Photonics Department, researchers are working on challenging projects at the boundary of multiple disciplines such as physics, chemistry, engineering and biology. This is one of 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.

Kohei Tamao

Tamao believes that this innovative approach to research has given 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 2012 is testament to the effectiveness of ASI's approach to research.

Keisuke Isobe and colleagues at ASI overcame the resolution and imaging-depth limitations of nonlinear optical microscopy by using spatial overlap modulation. The technique makes it possible to resolve mouse brain structures at depths of 240 micrometers, where traditional nonlinear microscopy begins to fail. This type of visualization can be used to track signal transmission down axons in the brain, and can be readily implemented into existing nonlinear microscopes (see *Optical microscopes delve deeper* on right).

The inability of DNA to dissolve in organic solvents has hindered its wider application in experiments. Hiroshi Abe, Yoshihiro Ito and their colleagues have successfully demonstrated that DNA, with the addition of a long polyethylene glycol (PEG) chain, dissolves in most organic solvents. The retention of DNA's structure in organic solvents also preserves its ability to function as a catalyst. With this discovery, DNA is proving to be a useful tool in nanobiotechnology (*Angewandte Chemie International Edition* **51**, 6475–6479, 2012).

In response to thermal stress, the Hsp70 molecular chaperone is transported into the nucleus. Until recently, the physiological significance of this phenomenon was unknown. A team led by Naoko Imamoto identified a protein named "Hikeshi", a transport carrier for stress-induced nuclear import of Hsp70, which is key to the survival of cells after stress. This helped to reveal the molecular mechanisms by which cells recover from stress-induced damage (*Cell* **149**, 578–589, 2012).

Conventional electronics is approaching quantum scaling limits, motivating researchers to develop alternative technologies. At ASI, Yoshihiro Iwasa's team has created the world's first transistor that drives a phase transition at room temperature using a potential of only 1 V. The switching mechanism provides a novel building block for ultra-low-power devices, non-volatile memory and optical switches based on a new device concept (*Nature* **487**, 459–462, 2012).

ASI has also seen the development of new materials. "In the Correlated Electron Research Group, many new materials related to dissipationless electronics, cross-correlation functions, and Mottronics are being produced to advance low-power electronics," says Tamao. "That's the great thing about ASI, we can bring together the best researchers to develop new science."

# Optical microscopes delve deeper

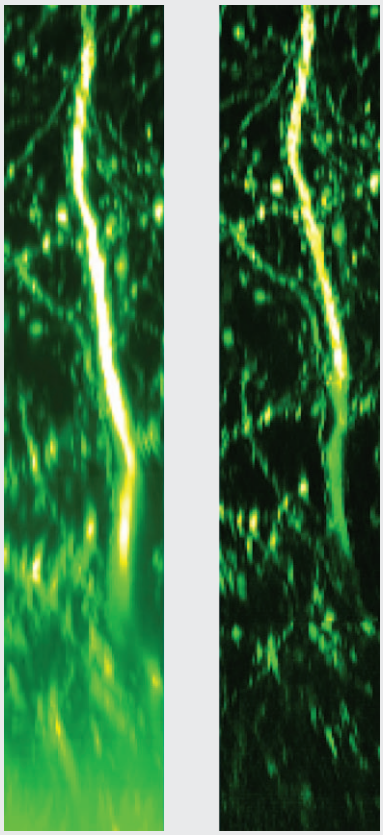
## Advances in nonlinear microscopy allow researchers to take detailed images deep below the surface of samples

Optical microscopes, also known as light microscopes, provide detailed images of sample surfaces, but their use in looking below the surface is limited. A workaround is to look for signals given off by a sample of interest when it interacts simultaneously with two particles of light (or photons), using a technique called nonlinear spectroscopy. Now, Keisuke Isobe and colleagues at ASI have shown how nonlinear techniques can be used to peer even more deeply into a sample[1].

The most common type of optical microscope is a linear instrument. This means that the atoms of a sample of interest interact with only one photon at a time. As common and productive as it is, however, this linear approach has limitations that are surpassed by nonlinear microscopy. For example, a small volume of the sample can be isolated under a nonlinear microscope by illuminating it with two intersecting, non-parallel light rays. Background noise can be easily filtered out. The resulting high signal-to-noise ratio allows the operator to take detailed images, including from below the sample surface. However, when depths become particularly large, noise increases to the point that even nonlinear images begin to lack clarity.

Isobe and colleagues demonstrated a technique that can decrease background noise by a factor of 100 and can increase imaging depths by a factor of two over traditional nonlinear approaches. These traditional approaches maximize the volume of overlap of two different pulses of light at some point of interest inside the sample. Instead, the Japan-based team used beam-pointing optics to periodically modulate this spatial overlap. The signal produced in the center of the volume of interest was modulated at twice the overlap modulation frequency. Isobe says that the signals produced away from the center were modulated at lower frequencies.

By filtering out these lower-frequency signals, the researchers succeeded in greatly reducing background noise. When Isobe and colleagues applied this technique to the imaging of mouse brains, spatial overlap modulation allowed them to resolve structures at depths of 240 micrometers, where traditional nonlinear microscopy began to fail (Fig. 1). The overlap modulation also significantly increased resolution.



From Ref. 1 © 2012 The Optical Society

**Figure 1: Nonlinear optical microscopy images of mouse brain tissues. The top image is the result of a traditional imaging approach, while the bottom image uses spatial overlap modulation. The images measure 32 micrometers across and 300 micrometers deep.**

Isobe says this kind of visualization can be used to track signal transmission down axons in the brain, and can be readily implemented into existing nonlinear microscopes. "We also plan to investigate its use for medical interventions," he says, "like laser surgery."

1. Isobe, K., Kawano, H., Takeda, T., Suda, A., Kumagai, A., Mizuno, H., Miyawaki, A. & Midorikawa, K. Background-free deep imaging by spatial overlap modulation nonlinear optical microscopy. *Biomedical Optics Express* **3**, 1594–1608 (2012).

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

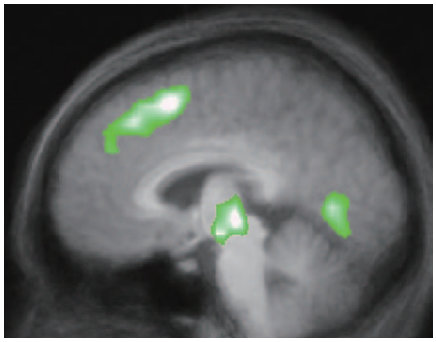
The human brain, beyond controlling mere physiological functions such as our heartbeat and breathing, provides the remarkable functions that make humans 'human'—our sensations and the ability to make decisions, have abstract thought, store memories and use language. "Our mission at BSI is to understand how the brain, a remarkable organic machine that was built over the course of human and pre-human evolution, works in health and goes awry in disease," says Susumu Tonegawa, director of the RIKEN Brain Science Institute (BSI).

Since its founding in 1997, 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 BSI have made several notable findings across the spectrum of brain science research. In a recent study, Tomomi Shimogori and her team published a detailed comparison of genes in the marmoset—a small primate—and the mouse brain. The findings indicated that existing cortical areas are genetically conserved between the species: most genes showed the same broad expression patterns in the mouse and the marmoset brain. However, the expression of some genes was very different in particular brain areas, especially in regions thought to be involved in higher cognitive functions. This work by Shimogori's team offers clues into the evolution and expansion of primate-specific brain regions (*The Journal of Neuroscience* **32**, 5039–5053, 2012).

Motomasa Tanaka and his team discovered that prions, notorious for detrimental brain diseases, can be beneficial to yeast under stress. The team found that Mod5-containing yeast was able to grow in the presence of lethal antifungal drugs. This finding revises the view of prions as being disease-causing and opens up the possibility of a similar biological role—that of conferring a fitness advantage in response to environment stress—in human cells and the brain (*Science* **336**, 355–359, 2012).

BSI has also been active in the area of social cognition research. Hiroyuki Nakahara and colleagues examined how humans predict the behavior of others around them. Participants' brains were scanned (above) while they were making a simple decision and while they predicted decisions made by other people around them related to the same task. Using functional imaging and mathematical modeling the authors showed that humans use a part of the brain called the prefrontal cortex to process information about other people and adjust their own behavior accordingly (*Neuron* **74**, 1125–1137, 2012).



**Prefrontal cortical areas, important parts of the brain circuit used in predictive tasks, are activated (green) when simulating others' decisions.**

Tadaharu Tsumoto's group addressed the question of how neural circuits underlying vision can adapt to long-lasting changes in incoming electrical activity, a process called plasticity. The authors showed that plasticity occurs in the GABAergic interneuron whose role is to suppress excess brain activity. These findings suggest that plasticity has an essential role in shaping vision (*The Journal of Neuroscience* **32**, 13189–13199, 2012).

The institute recognizes that brain science is an increasingly collaborative discipline. BSI has two major cooperative centers—the RIKEN BSI-TOYOTA Collaboration Center and the RIKEN BSI-OLYMPUS Collaboration Center. It is also a key collaborator with major academic institutions overseas. BSI conducts research with the Massachusetts Institute of Technology (MIT), where BSI supports a joint research center with the MIT's Picower Institute for Learning and Memory—the RIKEN-MIT Center for Neural Circuit Genetics.

Susumu Tonegawa and colleagues were able to activate population cells in the brain circuits of mice by artificially using light, causing the mice to recall information of a specific memory type. This will enable scientists to directly identify and manipulate memory cells (see *Old cells learn new tricks,* p. 11).

These discoveries and others by BSI laboratories represent groundbreaking achievements today, yet BSI realizes that fostering the next generation of young researchers is essential for the development of neuroscience.

As part of this mission, the Brain Science Training Program provides basic training for a select group of graduate students from Japanese universities. 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 probed the collective interaction of neurons under the theme, "The Collective Brain."

As expectations for brain science grow, the role played by BSI in basic and translational brain research is taking on a greater level of significance. One key area of basic research being developed at BSI is the elucidation of neural circuit functions. BSI's Neural Circuit Genetics Research Building serves as a beacon for recruiting young scientists around the world to energize the important mission of BSI. Accordingly, Tonegawa is anticipating a bright future.

"Among the various fields of science," he says, "only brain science has a scope broad enough to cover the full range of human activities. BSI builds on this fact by striving toward a new and comprehensive vision of science, one whose reach goes beyond the bounds of convention to provide a clearer understanding of what it is to be human."

# Old cells learn new tricks

## As certain neurons within the hippocampus of the brain mature, their contributions to memory and perception change

A key collaborator with major international academic institutions, BSI conducts research with the Massachusetts Institute of Technology (MIT), where BSI supports a joint research center with the MIT's Picower Institute for Learning and Memory—the RIKEN–MIT Center for Neural Circuit Genetics.

In 2012, this center, which is led by BSI's Director, Susumu Tonegawa, made a landmark discovery on the mechanism for memory.

Neuroscientists have generally believed that distinct segments of the hippocampus are responsible for pattern separation—recalling past actions to identify differences between highly similar yet distinct events—and pattern completion—using isolated pieces of information to reconstruct stored memories. "These two functions have been thought to be opposing and competing processes," explains Toshiaki Nakashiba, a researcher with Susumu Tonegawa's team.

Tonegawa, Nakashiba and colleagues, however, have demonstrated that both processes are managed within the dentate gyrus, with specific contributions from two distinct subsets of granule cell neurons (GCs)[1].

The dentate gyrus is one of the only parts of the brain that replenishes neurons in adult life (Fig. 1). At first, newly generated 'young GCs' are highly active, but gradually they settle down and become virtually indistinguishable from GCs formed before birth. The researchers developed genetically modified mice in which they could broadly inactivate, and re-activate, synaptic transmission from 'old GCs' while retaining intact transmission from young GCs. Thus, the strain serves as a good model for studying the distinct roles of these dentate gyrus cells in neural circuits and mental processes.

The group designed a series of experiments that allowed them to characterize the relative contributions of these different generations of adult-born GCs to memory function. Their findings suggested a primary role for young GCs in pattern separation and also provided compelling evidence that older GCs play a key role in pattern completion; therefore, changes in cellular demographics could have serious consequences as the balance between pattern separation and completion abilities could be altered as a result of the loss of old neurons.

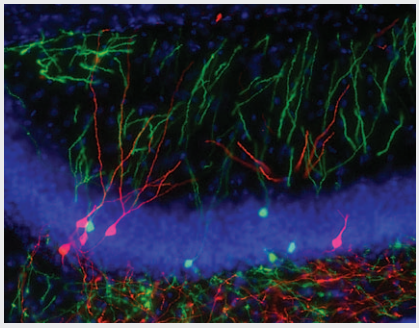
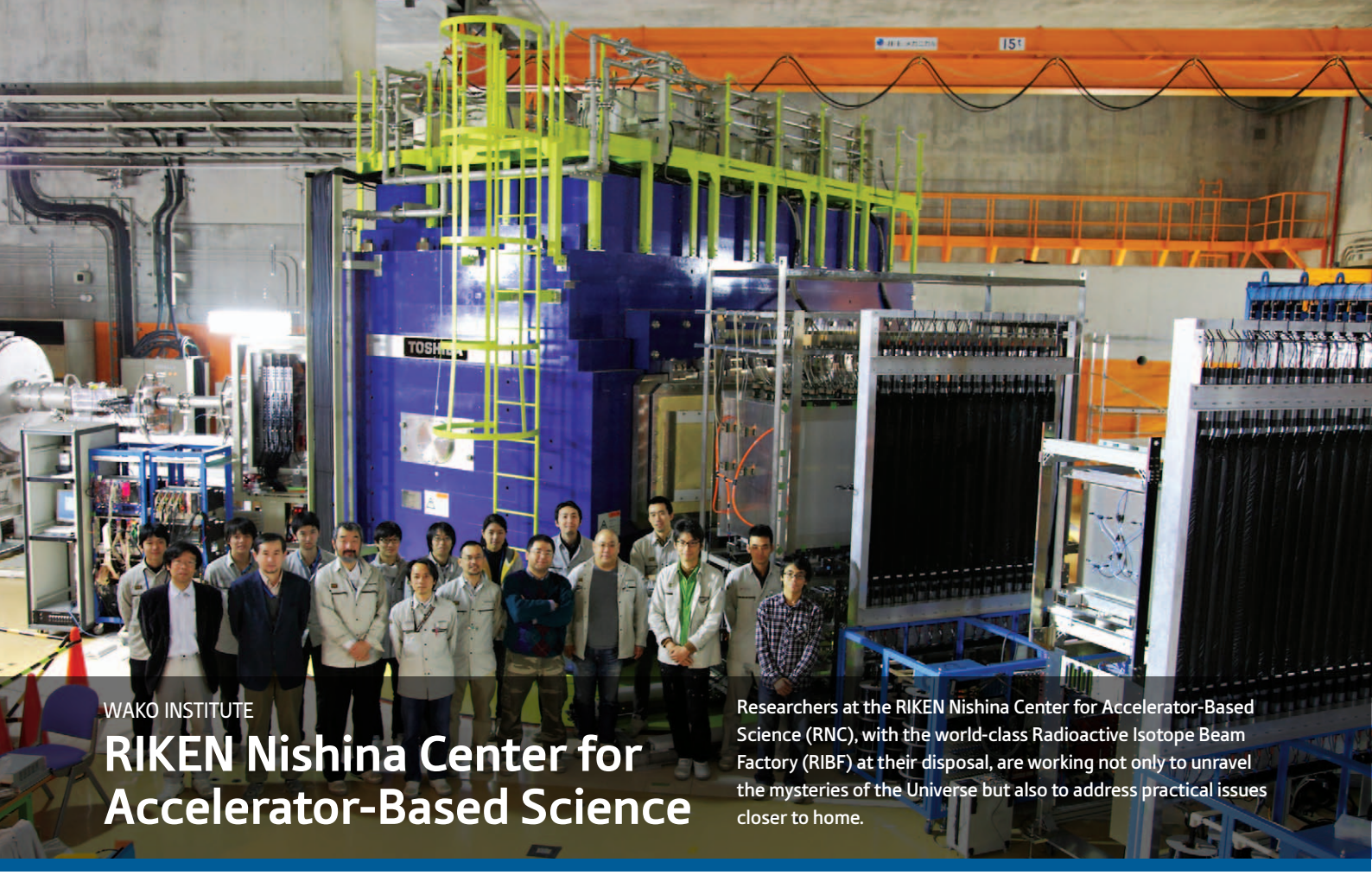


**Figure 1: Granule cells within the dentate gyrus play distinct roles in memory formation and recall as they age (green, old granule cells; red, young granule cells).**



The research suggests that newly formed young GCs may be best-equipped to achieve the recognition of novel elements required for pattern separation, whereas older, more thoroughly integrated GCs are more likely to act as established sources of information for region CA3 that facilitate memory recall through pattern completion. Nakashiba anticipates that the results of these studies could ultimately have important implications for understanding the neurological roots of cognitive deficits associated with disease, brain damage or old age.

1. Nakashiba, T., Cushman, J.D., Pelkey, K.A., Renaudineau, S., Buhl, D.L., McHugh, T.J., Barrera, V.R., Chittajallu, R., Iwamoto, K.S., McBain, C.J., *et al.* Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. *Cell* **149**, 188–201 (2012).



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.

In 2006, 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 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.

"In 2012, in addition to putting all necessary experimental equipment in place, the center has also installed the world's top-performance accelerator. Having set up our facilities in perfect order, RNC expects the coming 5 years to be a time to reap the harvest," says the center's director, Hideto En'yo.

In 2012, a team of scientists from Japan and China, led by RNC researcher Kosuke Morita, achieved the most unambiguous data to date on the elusive 113th atomic element. A chain of six consecutive alpha decays, produced in experiments at the RIBF, conclusively identifies the element through connections to well-known daughter nuclides. With their groundbreaking discovery, Morita and colleagues set the stage for Japan to claim naming rights for the element. To further challenge themselves, the team is venturing into the uncharted territory of element 119 and beyond (see *Search for element 113 concluded at last,* p. 13).

"We are very happy that we have discovered the 113th atomic element," says En'yo. "This is certainly a wonderful achievement for RNC. Hopefully we can fulfill Yoshio Nishina's dream of naming the element 'Japonium'—an honor to our country."

Yuichi Ichikawa, Hideki Ueno and colleagues developed a novel method for controlling spin in a system of rare isotopes. The degree of freedom of spin in quantum systems serves as an unparalleled laboratory where intriguing quantum physical properties can be observed, and the ability to control spin is a powerful tool in physics research. The discovery is not only beneficial to research on the nuclear structure of species situated outside the traditional region of the nuclear chart, but also to applications in material research where spin-controlled radioactive nuclei implanted in a sample serve as probes into the structure and dynamics of condensed matter (*Nature Physics* **8,** 918–922, 2012).

Hideto En'yo

In 2013, the RIBF Research Division continues to play a pivotal role in two exciting 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 supernova explosions. The EURICA project utilizes 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 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 can 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 commenced in June 2012 and will run through to June 2013.

Another landmark project for the RIBF Research Division is the large-acceptance multiparticle spectrometer, the Superconducting Analyzer for Multi-particles from Radio Isotope Beams (SAMURAI). The SAMURAI comprises a sizable 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 halos or skin structure, which appears uniquely in extremely neutron-rich or -deficient systems. This instrument is also 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.

It is En'yo's hope that RNC will continue to act as a core facility for researchers all over the world. And research at 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 RNC.

"One of our featured methods for applied research is to use a heavy-ion beam to develop new strains of plants. I feel that in the future we will be able to produce research results that lead to ways to solve food shortages and energy issues."

# Search for element 113 concluded at last

## After many years of painstaking work, RIKEN researchers prove third time's a charm

The most unambiguous data to date on the elusive atomic element 113 has been obtained by researchers at RNC. A chain of six consecutive alpha decays, produced in experiments at RIBF, conclusively identifies the element through connections to well-known daughter nuclides. The groundbreaking result[1] sets the stage for the leading researchers to claim naming rights for the element.

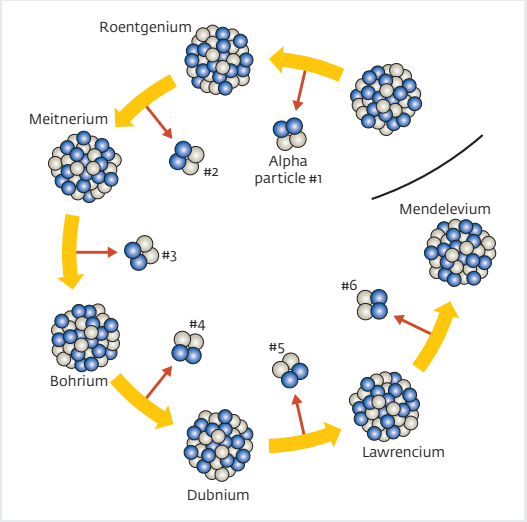





**Figure 1: Element 113 was identified by the alpha particles that are created when a heavy nucleus decays to a lighter one. Six alpha particles were measured at times corresponding to the half-life of the six decays matching element 113 decaying sequentially to mendelevium.**

The search for superheavy elements is a difficult and painstaking process. Such elements do not occur in nature and must be produced through experiments involving nuclear reactors or particle accelerators, via processes of nuclear fusion or neutron absorption.

For many years Morita's team has conducted experiments at the RIKEN Linear Accelerator Facility in Wako, near Tokyo, in search of the element, using a custom-built gas-filled recoil ion separator (GARIS) coupled to a position-sensitive semiconductor detector to identify reaction products. On 12 August 2012 those experiments bore fruit: zinc ions travelling at 10% the speed of light collided with a thin bismuth layer to produce a very heavy ion followed by a chain of six consecutive alpha decays identified as products of an isotope of element 113.

While the team detected element 113 in experiments conducted in 2004 and 2005, earlier results identified only four decay events followed by the spontaneous fission of dubnium-262 (element 105). In addition to spontaneous fission, the isotope dubnium-262 is known to also decay via alpha decay, but this was not observed, and naming rights were not granted since the final products were not well-known nuclides at the time. The decay chain detected in the latest experiments, however, takes the alternative alpha decay route (Fig. 1), with data indicating that dubnium decayed into lawrencium-258 (element 103) and finally into mendelevium-254 (element 101). The decay of dubnium-262 to lawrencium-258 is well known and provides unambiguous proof that element 113 is the origin of the chain.

Combined with their earlier experimental results, the team's groundbreaking discovery of the six-step alpha decay chain promises to clinch their claim to naming rights for element 113.

"For over 9 years, we have been searching for data conclusively identifying element 113, and now that at last we have it, it feels like a great weight has been lifted from our shoulders," says Morita. "I would like to thank all the researchers and staff involved in this momentous result, who persevered with the belief that one day, 113 would be ours. For our next challenge, we look to the uncharted territory of element 119 and beyond."

1. Morita, K., Morimoto, K., Kaji, D., Haba, H., Ozeki, K., Kudou, Y., Sumita, T., Wakabayashi, Y., Yoneda, A., Tanaka, K., *et al.* New result in the production and decay of an isotope, $^{278}$113, of the 113th element. *Journal of the Physical Society of Japan* **81,** 103201 (2012).

# 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 always one of them. Based on RIKEN's 'baton zone' model (see p. 55) for efficient technology transfer, the RIKEN Innovation Center (RInC) was created in 2010 to link researchers at RIKEN with counterparts in private companies to promote more effective technology transfer.

RInC supports this collaboration by providing a location and framework for these researchers to advance their research rapidly. RInC's motto for meeting the needs of industry is 'from challenge to achievement.'

Collaborations with private companies are initiated when potential partners 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 establishes a project team in which the private company takes 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.

The Sugiyama Laboratory opened on 1 April 2012 as a sponsored laboratory at RInC with funding from 27 companies. The laboratory aims to develop an integrated drug discovery support system using leading-edge modeling and simulation methods, as well as the prediction of drug interactions.

"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, 10 drug discovery units, organized into 5 centers, have been established within RIKEN under the program, comprising 30 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.

RIKEN filed several patent applications in FY2012 and is actively carrying forward negotiations with R&D companies to seek a possible alliance in drug development. While some projects were finalized in 2012, around 10 new projects—encompassing areas such as nucleic acid medicine and antimetastatic drugs—have been launched.

"In FY2011, relatively late-stage projects were carried out," says Program Director Toshio Goto. "In our Alzheimer's 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."

Good management is critical for competing with 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 outlet for the program has been established via alliances with companies and medical institutions.

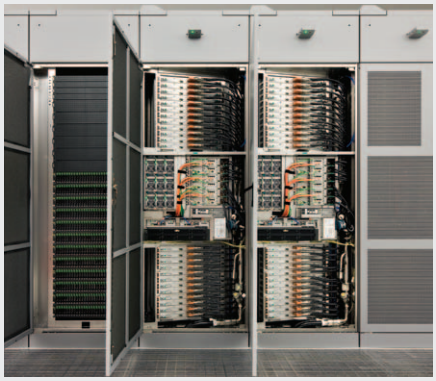
## RIKEN Computational Science Research Program

Japan's award-winning 10 petaflop supercomputer—the K computer—is part of the Japanese government's strategic policy of maintaining and improving Japan's international competitiveness in science and technology.

As the operating partner, RIKEN has been working closely with academia and industry to develop this key piece of national technology. Supercomputers 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 advancing science and technology. Since 2006, the RIKEN Computational Science Research Program (CSRP) has been responsible for the development and distribution of software to maximze 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 genomics and the molecular and cellular levels 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.

Of the 31 software program systems developed at the CSRP, two-thirds are approaching the final goal of petaflops computation. "Collaboration in multi-scale simulations are underway in order to overcome the hurdle of hierarchy," says Program Director Koji Kaya. "One of the distinctive results of this challenge is seen in the collaboration of quantum mechanics, molecular dynamics and coarse-grained model simulations for the dynamical motion of membrane proteins."



Kaya plans to distribute the software to industry in the hope that they will be used in real-world applications. "Before the era of the K computer, people didn't believe that computation could make precise predictions for use in drug development, but with large-scale computers like the K computer, we will be able to simulate drugs with high accuracy," says Kaya.

## RIKEN Biomass Engineering Program

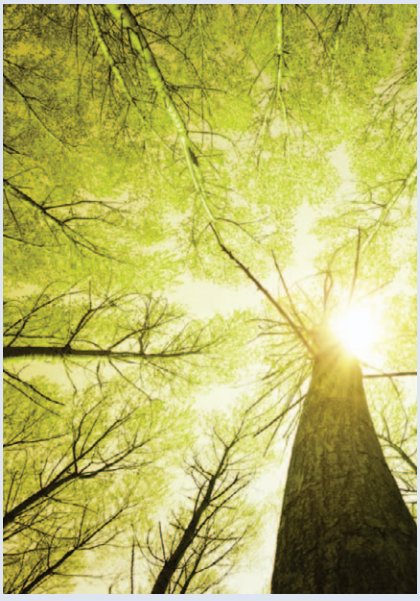
The RIKEN Biomass Engineering Program (BMEP) was established in April 2010 to lead the way in green biotechnology by establishing bioprocesses that produce biomaterials and bioplastics from plant biomass.

"The BMEP is an interdisciplinary R&D program that links together plant science, microbial science, enzyme research and bioresource research to create non-foodstuff biomass," says Kazuo Shinozaki, the program's director.

"One of our most important goals is to establish an innovative technological infrastructure that will dramatically streamline biomass processes. This is to be achieved through basic research geared toward consistent problem-solving in areas ranging from the functional improvement of plants to useful biomass applications."

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 bioplastics and other biomaterials, 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 six research teams working in the areas of cellulose production, synthetic genomics, enzymes, cell factories, 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 2012, BMEP researchers found that a certain sugar alcohol acts as an efficient nucleation agent for biosynthesized polyhydroxyalkanoates (PHAs), and is an important additive to the advanced processing technology for PHAs currently being developed in collaboration with a chemical company. BMEP researchers also revealed that wood formation is regulated by NAC transcription factors and wood characters can be engineered by controlling these NACs, leading to high levels of woody biomass.

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, biotechnology and innovation 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 in Japan for researchers through the collection, preservation and distribution of bioresources. Through these activities, BRC supports studies in a range of fields, from basic research to the treatment of disease, drug discovery, food production and even environmental conservation. BRC is guided in this mission by its founding principles of 'Trust', 'Sustainability', and 'Leadership'.

A key characteristic of 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.

The variety of bioresources required for research and development has been increasing dramatically, having already exceeded the capacity of a single biological center like BRC or even all centers in an entire country.

**Yuichi Obata**

The International Mouse Phenotyping Consortium (IMPC) is an international collaborative initiative that was established by 16 institutions from 9 countries in September 2011. The IMPC is undertaking a standardized systematic genome-wide phenotyping project of knock-out mice that aims to generate 20,000 strains of mice in 10 years. BRC is a steering committee member of the IMPC and is participating in the consortium as a production and phenotyping center. To disseminate this global effort to Japanese scientists, BRC held the IMPC International Symposium in Tokyo in September 2012.

Along with other centers, 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 some damage to its facilities. The disaster underlined to BRC the importance of maintaining bioresources and emergency planning. After the earthquake, BRC acquired governmental funding to build self-sufficient water supplies, as well as enlarging the center's fuel capacity for emergency electricity and setting up liquid nitrogen generation machines. These lifelines commenced operation in 2012.

Kyoto University Professor Shinya Yamanaka won the Nobel Prize for Physiology or Medicine in 2012 for his revolutionary discovery that mature, specialized cells in the body can be converted into induced pluripotent stem (iPS) cells. During his research, Yamanaka deposited his iPS cells and a mouse strain that was used to create iPS cells at the BRC facility, and the center has been distributing these valuable bioresources to scientists around the world.

In efforts to support world-leading research on regenerative medicine involving stem cell resources, such as iPS cells, 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, BRC is promoting research not only in regenerative medicine but also in drug discovery by facilitating a better understanding of disease mechanisms, thereby 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, BRC is moving forward with renewed passion to promote the research and development of life sciences and to create novel value by facilitating the use of 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 are considering 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 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.

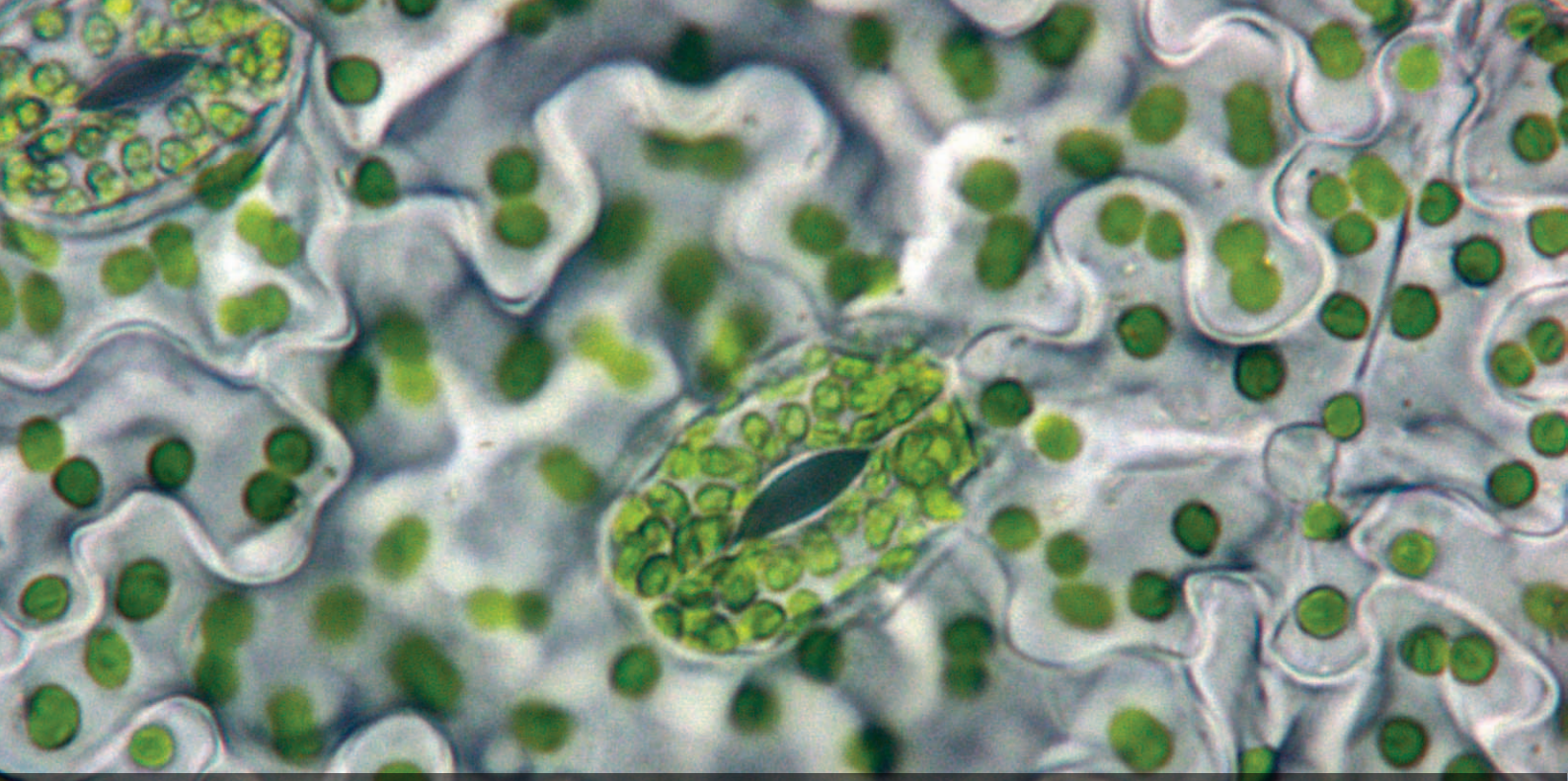
Ogura and his team previously determined that *Xist* is inappropriately activated in SCNT embryos[2], impairing expression of essential genes, and have now set about correcting this defect. Irreversibly inactivating this gene is not an option, so the researchers injected molecules called 'short interfering 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%—a ten-fold improvement over 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* **108**, 20621–20626 (2011).

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 PSC has established an international reputation as one of the world's leading research centers in plant science.

"Our overall aim is to elucidate important plant functions in order to contribute to 'green innovation' related to food, energy and environmental issues through genomic and metabolic analysis," says PSC Director Kazuo Shinozaki. "The significance of our research has been partly shown by the high citation rate of published manuscripts and the various invited talks given by PSC principal investigators at international conferences. I was also lucky enough to be selected as one of the 'Hottest Researchers' by Thomson Reuters in April 2012."

Kazuo Shinozaki

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, 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.

Since 2005, 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. Investigation of metabolic systems is a particular focus of the research. In collaboration with various universities and international organizations, as well as various companies, PSC is using its research findings on model plants to improve the production of crops and trees and thus help ensure a reliable supply of food and energy from plants.

In 2012, Miki Fujita, Kazuo Shinozaki and colleagues at PSC discovered that the gene *resistant to methyl viologen 1* (*RMV1*) is involved in the transport of paraquat and polyamines in *Arabidopsis* plants. The identification of such transporters may facilitate developments in fields as diverse as cancer treatments—reduced polyamine uptake is linked to the efficacy of certain anticancer drugs—and genetically modified crops. The team demonstrated that most paraquat-tolerant varieties of *Arabidopsis* remained susceptible to other oxidative stress inducers, implying tolerance was due to reduced uptake rather than limitation of paraquat's oxidative effects. Fujita is now aiming to identify other polyamine transporters and investigate their biological significance

in terms of plant growth and stress responses (see *Lessons from herbicide tolerance* on right).

A research team led by Kazuki Saito and Fumio Matsuda has begun to decipher how genetic variations affect metabolite production in rice. While many metabolites appeared to be primarily modulated by non-genetic factors, the team found clear evidence for heritable factors that affect production, in addition to identifying a cluster of loci on chromosome 3 that coordinates production of a number of different amino and fatty acids. This new information will be invaluable for future efforts towards crop enhancement (*The Plant Journal* **70**, 624–636, 2012).

While movement of the plant hormone abscisic acid (ABA) within plants has been documented, the molecular mechanisms that regulate ABA transport are not fully understood. By using a modified yeast two-hybrid system, Mitsunori Seo's research unit has identified four members of the NRT1/PTR family as candidates for ABA importers. The results can be applied to identify transporters of other hormones, such as gibberellins and jasmonates, to develop new strategies to increase crop yields (*Proceedings of the National Academy of Sciences USA* **109**, 9653–9658, 2012).

PSC researchers Yoshiteru Noutoshi, Ken Shirasu and colleagues successfully uncovered five novel immune-priming compounds in *Arabidopsis* plants through a new high-throughput screening technique they developed. Further investigation revealed that the five compounds inhibit two enzymes that inactivate the defense hormone salicylic acid (SA), which protect plants from pathogens by activating the plant immune system. Their discovery establishes this new technique as a powerful asset in the battle to protect crops from damaging pathogens, particularly *Pseudomonas* bacteria (*The Plant Cell* **24**, 3795–3804, 2012).

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

# Lessons from herbicide tolerance

## Discovery of an uptake mechanism for key cellular components in Arabidopsis plants gives insights into potential cancer treatments and GM crops

Polyamines are widespread and important organic compounds involved in multiple cellular processes in living organisms. Their levels are highly regulated through a combination of processes including synthesis, breakdown and transport. However, the mechanisms of polyamine transport are still largely unknown.

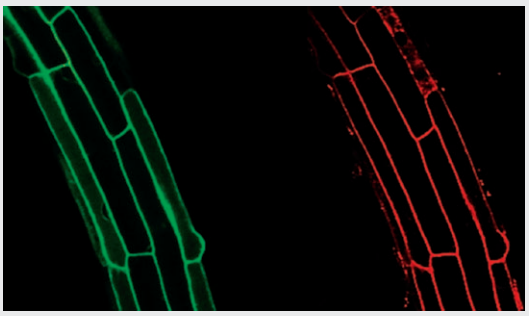




**Figure 1: Fluorescent labeling reveals expression of the *RMV1* gene, localized to cell membranes of *Arabidopsis* root cells. The left panel shows the GFP-labeling, the right panel is under a red filter showing plasma membrane stained with 'FM 4-64'.**

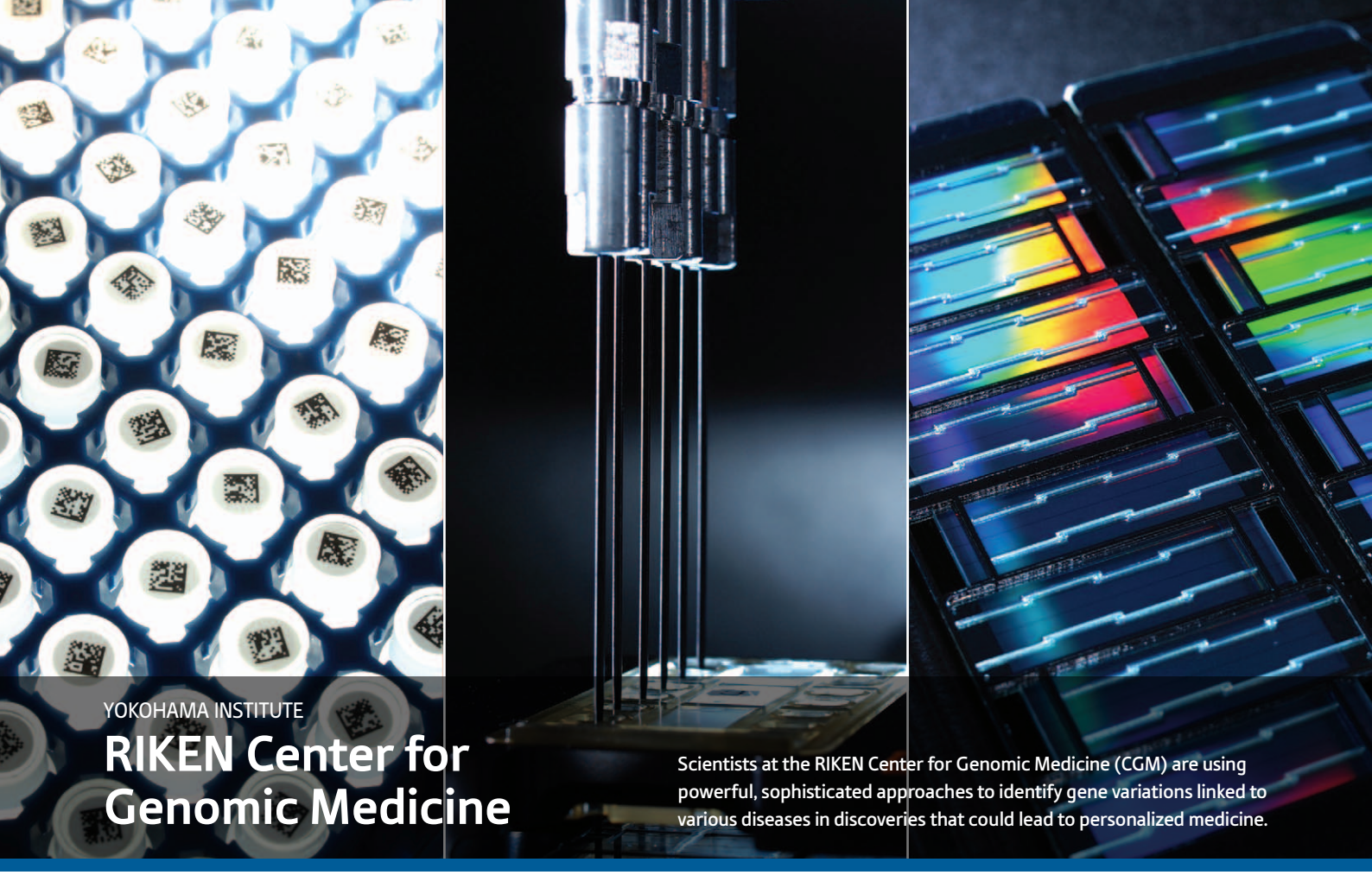
Since the widely used herbicide paraquat (methyl viologen) follows the same transport pathways as polyamines, Miki Fujita and colleagues at PSC analyzed natural variability in paraquat susceptibility in the model plant *Arabidopsis thaliana*. They found that the gene *resistant to methyl viologen 1 (RMV1)* is involved in the transport of both paraquat and polyamines in *Arabidopsis*[1].

Paraquat's herbicidal activity results from causing oxidative stress in plant tissues. However, Fujita and colleagues found that most paraquat-tolerant varieties of *Arabidopsis* remained susceptible to other oxidative stress inducers, implying tolerance was due to reduced uptake rather than limitation of paraquat's oxidative effects. By crossing different paraquat-resistant varieties, they showed that paraquat-tolerance was linked to a single locus, while cloning and complementation techniques revealed its genomic location. Using transgenic plants in which they had placed the fluorescent jellyfish protein, green fluorescent protein (GFP), under the same genetic control as *RMV1*, the researchers revealed that its expression is localized to the cell membrane (Fig. 1), indicating a likely role in uptake or transport of molecules into cells.

Fujita and colleagues then verified that *RMV1* mediates paraquat uptake by studying *Arabidopsis* plants in which *RMV1* is inactivated by mutation: these plants showed higher paraquat tolerance, indicating reduced paraquat uptake or transport. These mutants also showed increased tolerance to certain polyamines, indicating that the same locus is involved in polyamine transport. However this effect was relatively slight, suggesting to Fujita and her team that other polyamine transporter genes might exist in the *Arabidopsis* genome.

Fujita is now aiming to identify other polyamine transporters and investigate their biological significance in terms of plant growth and stress responses. The identification of such transporters may facilitate developments in fields as diverse as cancer treatments—reduced polyamine uptake is linked to the efficacy of certain anticancer drugs—and GM crops. "It is really urgent to create the next generation of herbicide-resistant crops," Fujita says. Some hurdles remain, however: paraquat is banned in many countries due to its toxicity, but these findings are a step towards creating more environmentally friendly herbicide-resistant crops.

1. Fujita, M., Fujita, Y., Iuchi, S., Yamada, K., Kobayashi, Y., Urano, K., Kobayashi, M., Yamaguchi-Shinozaki, K. & Shinozaki, K. Natural variation in a polyamine transporter determines paraquat tolerance in *Arabidopsis*. *Proceedings of the National Academy of Sciences USA* **109**, 6343–6347 (2012).



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 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, CGM is now generating a large amount of SNP-genotyping data for the genome-wide association study (GWAS) of common diseases with the BioBank Japan Project.

The GWAS method itself has its roots in the SNP Research Center (renamed 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 genome markers in thousands of people. Today the methodology is widely applied in international genetics research.

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, 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 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 in 2012 well illustrate its cutting-edge position in the field.

Michiaki Kubo

Toshihiro Tanaka and his team conducted a meta-analysis in individuals of European ancestry, including 6,707 with and 52,426 without atrial fibrillation. The study identified six new susceptibility loci for atrial fibrillation, other than three which were already known. The identified loci implicate candidate genes that encode transcription factors related to cardiopulmonary development, cardiac-expressed ion channels and cell signaling molecules (*Nature Genetics* **44**, 670–675, 2012).

Hidewaki Nakagawa and his colleagues sequenced and analyzed the whole genomes of 27 hepatocellular carcinomas (HCC). They discovered that multiple chromatin regulators were mutated in some 60% of tumors. The team also learned that the integration of the hepatitis B virus genome in the *TERT* locus was frequently observed in a high clonal proportion. From these findings, it is expected that new cancer drugs targeting mutations in chromatin regulators in HCCs will be developed (see *Pinpointing a driver of liver cancer* on right).

Shiro Ikegawa and colleagues identified *PAPSS2* as the disease gene for an autosomal recessive brachyolmia. *PAPSS2* mutations have produced a skeletal dysplasia family, with a gradation of phenotypes ranging from brachyolmia to spondylo-epi-metaphyseal dysplasia. The group expects the finding will lead to further understanding of the disease and advances in therapeutic treatments (*Journal of Medical Genetics* **49**, 533–538, 2012).

Yukinori Okada conducted a meta-analysis of genome-wide association studies for kidney function-related traits, including 71,149 East Asian individuals and 110,347 European individuals. As a result, they identified 17 loci newly associated with kidney function-related traits and the risk of chronic kidney disease (CKD). These findings provide new insight into the genetics of kidney function (*Nature Genetics* **44**, 904–909, 2012).

Lung adenocarcinoma is the most common histological type of lung cancer, and its incidence is increasing worldwide. To identify genetic factors influencing risk of lung adenocarcinoma, CGM and the National Cancer Center (NCC) conducted a genome-wide association study, and identified two new susceptibility loci. These data provide further evidence supporting a role for genetic susceptibility in the development of lung adenocarcinoma (*Nature Genetics* **44**, 900–903, 2012).

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

"Advances in the knowledge of human genetic variation relating to health and diseases are key to the realization of personalized medicine. Our goal is to facilitate the translation of research discoveries into clinical drug therapies that may one day be finely tuned to meet the needs of individual patients."

# Pinpointing a driver of liver cancer

## Identification of mutations common to half of all liver cancers provides leads for new therapeutics

Liver cancer is the sixth most common cancer worldwide and the third leading cause of cancer-associated deaths. Yet even for such a frequent and deadly disease, the pathogenesis of this cancer remains obscure. Now, a team of scientists in Japan has shown that genes involved in regulating how tightly DNA is wound into chromosomes are commonly mutated in liver tumors[1] (Fig. 1). The finding points to potential new and much-needed therapeutic strategies.

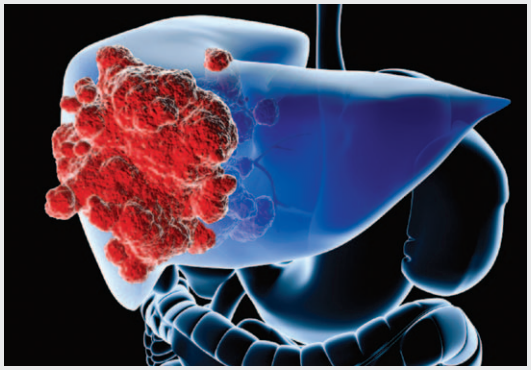


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**Figure 1: Some 50% of liver cancer tumors carry mutations in a gene that encodes chromatin regulators.**

"Several types of drugs under development target chromatin regulators, and these drugs may be effective in liver cancer," says Hidewaki Nakagawa, a cancer geneticist at CGM, who led the work.

Nakagawa and his colleagues decoded the entire genomes of liver tumors from 27 different patients—25 of whom carried hepatitis viruses, the most common cause of liver cancer, and two without associated infections. They also sequenced the DNA of matched healthy white blood cells for comparison.

No two cancers were alike, even when the researchers analyzed the whole genomes of pairs of liver cancers that arose independently in the same individual—not from metastasis. "Their genomic alterations were completely different and independent, indicating heterogeneity of liver cancers in the same patient," Nakagawa says.

Some striking patterns emerged. Across all 27 cancer genomes, the researchers discovered more than 2,000 protein-altering mutations, with frequent alterations occurring in 15 different genes—many of which affect chromatin, the mass of DNA and proteins that condense to form chromosomes and affect gene expression. Notably, 14 of the 27 tumors had mutations in at least one chromatin regulatory gene. In cell culture, liver tumors lacking these genes displayed a marked increase in cell proliferative capacity. "Genetic alterations in chromatin regulators can regulate and produce epigenetic alterations in cancer," Nakagawa explains.

The findings are consistent with those reported last year by an independent group that showed that *ARID2*, a chromatin remodeling gene also implicated by Nakagawa and his team, was mutated in six of the 33 liver cancers considered[2].

In addition to chronicling the mutational profile, Nakagawa and his colleagues determined where hepatitis B-associated tumors had the viruses inserted into their genomes. Consistent with independent findings reported in the same issue of *Nature Genetics*[3], in four of the 11 relevant cancers they found viral integration within or near the *TERT* gene, which is involved in maintaining the caps on the end of chromosomes. Targeting the *TERT* locus, therefore, offers another therapeutic drug lead for this nasty cancer.


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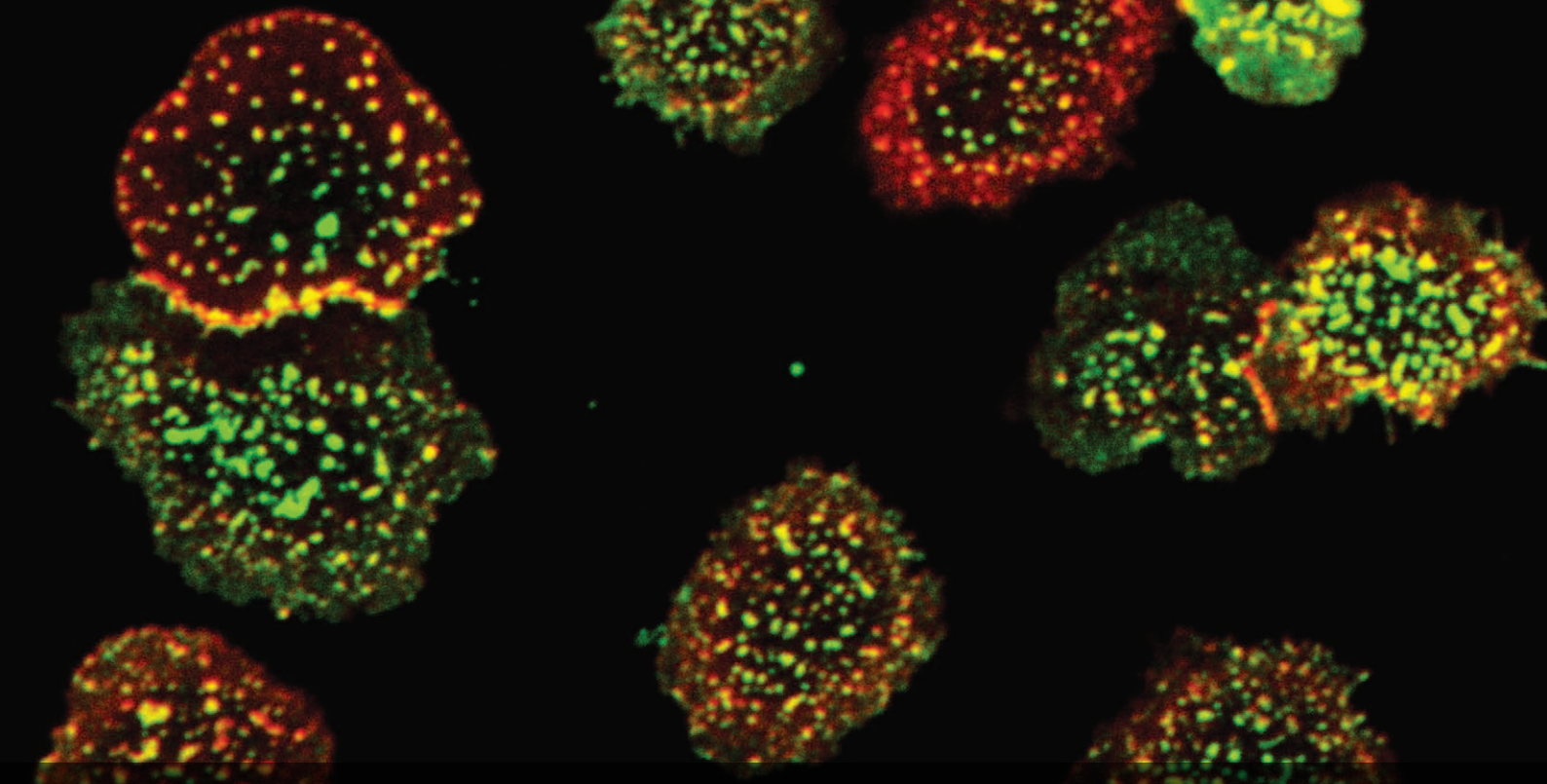

YOKOHAMA INSTITUTE

# 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 is developing a hay fever vaccine that 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.

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.

To understand the process of disease development and to identify critical events which discriminate between healthy and diseased status, RCAI established an interdisciplinary biomedical research platform and international consortium of research groups that share a common interest in human immunology. One such project is the Medical Immunology World Initiative (MIWI), which RCAI launched as a new human immunology platform. The goal of MIWI is to use integrative immunological approaches such as humanized mice to obtain fundamental knowledge about the human immune system and the underlying mechanisms of disease development and to discover new principles for diagnosis and treatment.

Masaru Taniguchi

Results published in 2012 highlight RCAI's key advancements in immunology research. A group led by Sidonia Fagarasan showed that programmed cell death protein 1 (PD-1) regulates gut microbiota through the selection of immunoglobulin A (IgA)-secreting plasma cell repertoires with appropriate bacteria-binding capacity. They found that the gut bacterial communities of PD-1-deficient mice were skewed, resulting in generalized activation of B and T cells. Their findings identify a key role for PD-1 in the maintenance of the gut's mucosal barrier through its regulation of antibody diversification and prevention of autoimmunity (*Science* **336**, 485–489, 2012).

Collaborative research by Hiroshi Ohno, Tsuneyasu Kaisho and Ifor Williams revealed that the transcription factor Spi-B is necessary for the differentiation of intestinal microfold cells (M cells)—intestinal epithelial cells that initiate mucosal immune responses—in mice. They also demonstrated that Spi-B was induced early during M-cell differentiation, suggesting that Spi-B may act as a master regulator (see *A blueprint for the gut's antimicrobial defenses*, p. 23).

Takashi Saito and colleagues made further discoveries relating to PD-1: using single-cell imaging they elucidated a mechanism whereby PD-1 generates T cell receptor (TCR)-PD-1 microclusters which act on TCR downstream signaling molecules to suppress the activation of T cells and block the TCR-induced activation signal. They also showed that this PD-1-mediated inhibitory mechanism operates in activated T cells established both *in vitro* and *in vivo*, and that the efficient attenuation of TCR-activation signal by PD-1 requires not only PD-1 clustering but also its colocalization at TCR microclusters (*The Journal of Experimental Medicine* **209**, 1201–1217, 2012).

A group led by Toshitada Takemori demonstrated that B cell memory is generated along two fundamentally distinct cellular differentiation pathways. This RCAI research offers insight into how the immune system is able to respond with specificity to pathogens and to mount rapid responses to their antigenic variants (*The Journal of Experimental Medicine* **209**, 2079–2097, 2012).

RCAI understands the importance of training young immunology researchers and postgraduate students with an international mindset. As part of this endeavor, RCAI conducts its annual International Summer Program, as well as the center's new Young Chief Investigator program which provides a career path for researchers aged 40 or younger. Those chosen for the program run independent research laboratories focusing on multidisciplinary research that bridges immunology with other research fields, while being mentored by specialists external to RCAI.

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

Looking to the future, much emphasis is being placed on research into integrative medical immunology. For this purpose, RCAI is committed to nurturing young researchers to lead this pioneering area. "The research conducted during RCAI's first 11 years has opened the door to new directions in human immunology, and the current endeavors of RCAI investigators continue to spearhead global immunology research, connect scientists around the world and improve human well-being," says RCAI Director Masaru Taniguchi.

# A blueprint for the gut's antimicrobial defenses

## The identification of a developmental 'master switch' helps scientists explore the function of intestinal cells that help prevent infection

Every bite of food or drink of water is an invitation for potentially harmful bacteria and viruses to set up shop in the body. In order to protect against such invaders, the mucous membrane that lines the intestine contains clusters of specialized microfold cells (M cells), which can absorb foreign proteins and particles from the digestive tract and deliver them to the immune system.

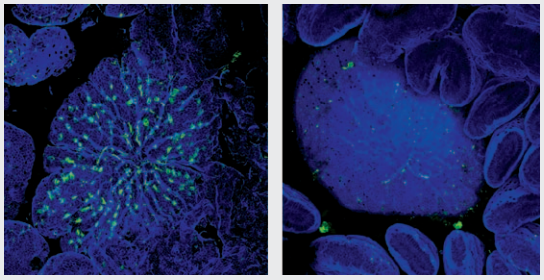

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**Figure 1: Fluorescent labeling of GP2, a protein expressed in M cells (left) reveals that this cell population is virtually absent in mice lacking the gene encoding Spi-B (right).**

New work from Hiroshi Ohno's group at RCAI, in collaboration with Ifor Williams and colleagues at Emory University in Atlanta, Georgia, has revealed valuable insights into how these M cells develop[1]. Previous research from Williams' group showed that a signaling protein called RANKL switches on M cell development[2] but virtually nothing was known about the subsequent steps in this process. To find out, Ohno and Williams looked for genes that get switched on when intestinal cells undergo differentiation in response to RANKL exposure.

They discovered that treatment with RANKL causes immature intestinal epithelial cells to sharply increase the production of Spi-B, a protein that regulates the expression of other developmental genes. To test the specific contribution of this protein to M cell maturation, the researchers collaborated with Tsuneyasu Kaisho's group at Osaka University, which had engineered a genetically modified mouse strain lacking the gene encoding Spi-B. The resulting animals were devoid of mature M cells (Fig. 1). On the other hand, intestinal development as a whole was unaffected by the absence of Spi-B, demonstrating that this protein's impact is limited to this specific class of cells within the gut.

M cells normally localize to immune structures known as Peyer's patches (PPs). Bacteria such as *Salmonella enterica* Typhimurium (*S.* Typhimurium) will normally accumulate within these PPs shortly after inoculation. This uptake was considerably reduced in Spi-B-deficient mice, indicating the absence of a functional M cell population. The mice showed a considerably weakened immune response following oral administration of *S.* Typhimurium bacteria relative to wild-type animals, demonstrating the importance of M cell-mediated microbial uptake.

The identification of this critical 'master switch' for M cell development opens exciting new avenues of research into these mysterious cells. Ohno is eager to investigate the details of how the cells perform their critical immunity-training function. "These questions could not be answered previously because of the lack of M cell-deficient mice," he says. "But now, 'knockout' mice that specifically lack Spi-B in their mucosal epithelium will provide the ideal tool for such studies."


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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 RIKEN 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 OSC are clearly carried out with medical research being the ultimate goal," says OSC Director Yoshihide Hayashizaki. Through joint efforts with industry, OSC aims to develop practical applications of their basic research to clinical medicine.

As part of its mission to conduct research leading to regenerative medicine, OSC plays a vital role in FANTOM5, the fifth phase of the Functional Annotation of the Mammalian Genome (FANTOM) project. An international research consortium founded in 2000 by Hayashizaki and his colleagues, FANTOM assigns functional annotations to the full-length

Yoshihide Hayashizaki

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 FANTOM5 will be applied in cell conversion technology, bringing us one step closer to the realization of regenerative medicine.

In February and October 2011, RIKEN hosted an international symposium for FANTOM5. The strong connection forged with researchers from around the world through such events is one of the key factors that allows 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 primary technologies in the field of RNA research, as well as to studies conducted by the Karolinska Institutet, he was appointed Honorary Doctor of Medicine in 2012 at the Karolinska Institutet in Sweden. The honorary doctorate is awarded to researchers who have made an important contribution to research at the institution.

OSC continues to make strong contributions to transcriptional analysis techniques. Building on previous research by OSC, Takahiro Suzuki and his team developed a method to identify transcription factors, which, with the genes they regulate, form transcriptional regulatory networks that underpin cellular functions. They then demonstrated that human cells could be reprogrammed—converted from one cell type to another—through the introduction of key transcription factors identified by the new method. In line with OSC's goals for clinical application of its work, this method has potential uses in regenerative medicine and drug discovery, as such direct cell reprogramming

to avoid problems associated with embryonic and induced pluripotent stem cells (*PLoS ONE* **7**, e33474, 2012).

RIKEN's original cap analysis of gene expression (CAGE) protocol was employed as one of the standard technologies in the international Encyclopedia of DNA Elements (ENCODE) Project, organized with the goal of describing all functional elements encoded in the human genome. Piero Carninci and colleagues used CAGE to identify transcription starting sites in the genome by studying RNA isolated from a number of subcellular compartments in 15 different cell lines. This work has made great contributions to the mapping of RNA-transcribed regions, the elucidation of the biochemical functions of the genome, and the current understanding of the organization and regulation of genes (*Nature* **489**, 57–74, 2012; *Nature* **489**, 101–108, 2012). In other research, the CAGE protocol was further improved by Masayoshi Itoh and colleagues, who developed an automated system that drastically reduces the time and cost required by CAGE (see *Building a faster snapshot of cell function* on right).

OSC has also made exciting discoveries relating to non-coding RNA. In a collaborative research study based on work from the FANTOM project, Carninci and colleagues discovered a class of non-coding antisense RNAs. Antisense RNAs have traditionally been thought to repress the expression of the coding RNA, but by studying *Uchl1*—a mouse gene involved in brain function and neurodegenerative diseases—the group determined that this class of non-coding antisense RNAs actually enhances protein synthesis of their coding genes (*Nature* **491**, 454–457, 2012).

Mitsuoki Kawano and colleagues found novel small non-coding RNAs in sperm that are transferred to the nucleus of the ovum at fertilization and are stably maintained in the early stages of embryo development. This is the first report of functional RNA in sperm, and suggests a potentially important role for RNA in delivering genetic information to the next generation (*PLoS ONE* **7**, e44542, 2012).

With OSC firmly established as a leader in the field, Director Hayashizaki looks ahead to future collaborations. "I've been project leader of genome research at RIKEN for 18 years. In that time, we have developed novel technologies and methods for transcriptome analysis. Now it's time to expand the application of our work into the medical field by further strengthening ties within RIKEN and Japan, as well as with research institutes around the world."

# Building a faster snapshot of cell function

**Automation of a protocol for rapidly analyzing gene expression on a large scale will yield faster results at less cost**

To generate an overall view of cell function, molecular biologists build simultaneous expression, or activity, profiles of thousands of genes. Gene expression begins with a process called transcription, during which the DNA sequence encoding a gene is copied into RNA. The information contained in the transcript is then translated into a chain of amino acids that folds up to form a functional protein molecule.




**Figure 1: The automated CAGE cDNA preparation system for rapid genome-wide gene expression analysis.**

Building on a technique called cap analysis of gene expression (CAGE) to identify and analyze transcription start sites and their expression levels, a research team in Japan, led by Masayoshi Itoh of OSC, has developed a large-scale technique for analyzing gene expression that increases productivity eight-fold compared to previous methods[1].

The original CAGE protocol involves 17 steps including a process that 'traps' the ends of the original transcripts, numerous extractions using organic solvents, and centrifugation to create complementary DNA (cDNA) libraries[2]. Itoh and his colleagues simplified and eliminated the PCR amplification step to reflect the original expression profile[3]. The prepared libraries consisted of millions of DNA molecules, each corresponding to the transcription start site. The researchers then determined the sequence of these cDNA molecules, and the amount of each one, using a single molecule sequencer called the HeliScope Genetic Analysis System.

Since each step in the original protocol was performed manually, the technique was labor intensive and it took approximately six weeks to prepare 96 cDNA libraries. Itoh and colleagues currently have two of the new systems in place, allowing them to generate 192 cDNA libraries every eight days. The automation cuts sequencing costs because it involves less manual work, and the system can be used with the three most common DNA sequencing platforms.

Itoh and his colleagues achieved this improvement by adapting CAGE so that all the steps are completed by an automated system consisting of a robotic manipulator arm equipped with an 8-channel liquid-handling device (Fig. 1). They simplified the protocol further by using magnetic beads to purify the cDNA. The automated method is significantly faster than the original protocol and reliably produces highly accurate sequences. Since constant supervision is not required, two or more systems can be easily operated simultaneously.

"We are currently developing the automation system for the next generation Illumina HiSeq2000 sequencing platform," says Itoh. "This involves improving the steps that produce and trap the transcription start site cDNAs, and we aim to establish the new library preparation system in the first half of 2012."

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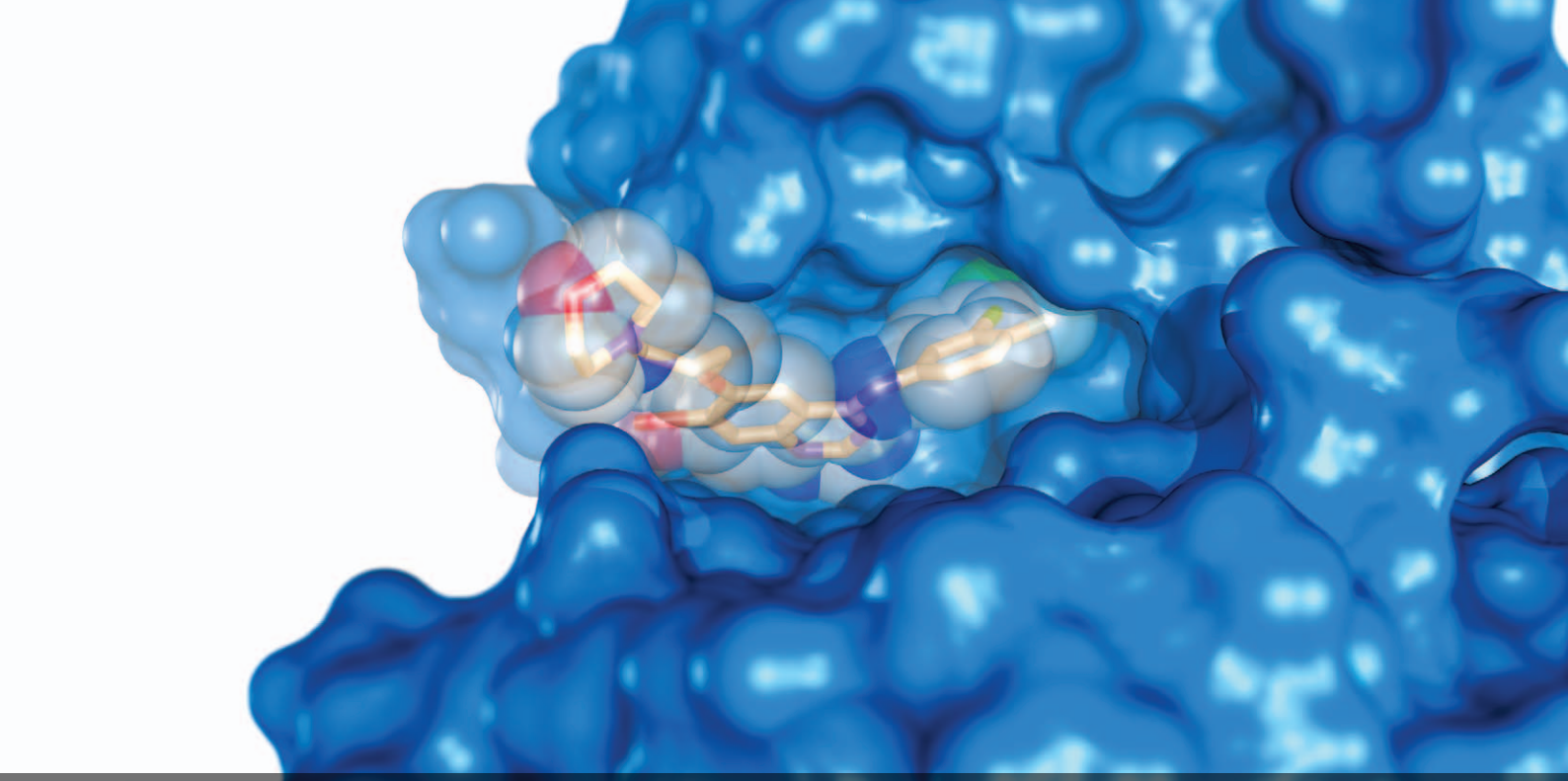

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# RIKEN Systems and Structural Biology Center

**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 materials science, expanding the rational design of biomolecular mechanisms and increasing predictability in the life sciences.

Biomolecular systems are made up of a very large number of molecules. SSBC has had great success in preparing large numbers of component elements of such biomolecules and determining the interactions among them through their mechanisms at the three-dimensional level. The center has also worked to reproduce the functions of higher-order systems *in vitro*, and to engineer systems based on these findings.

Initially established in 1998 as the Genomic Sciences Center, SSBC has successfully built a research infrastructure to elucidate the structure and function of complex targets through the Protein 3000 project and the Targeted Proteins Research Program encompassing areas such as high molecular-weight nucleosomes, polymerases and ribosomes vital to genetic systems and membrane proteins vital to cellular systems. We have also realized many important findings by leveraging this infrastructure in efforts to extend the genetic code.

In 2012, Seiko Yoshikawa and colleagues established the structural basis for the altered drug sensitivities of non-small-cell lung cancer (NSCLC)-associated mutants of human epidermal growth factor receptor (EGFR). EGFR has an essential role in multiple signaling pathways, including cell proliferation and migration. The research team has also succeeded in identifying the exact amino acid residues that affect levels of resistance to tyrosine kinase (TK) inhibitors (see *Finding cancer's escape route*, p. 27).

The previously unknown structural basis of the leukocyte cell-surface antigen CD38 tetramerization on the cell surface was elucidated by Miki Hara-Yokoyama and colleagues using site-specific crosslinking in combination with x-ray crystallography. CD38 is a major nucleotide-metabolizing enzyme involved in calcium mobilization in mammals. *N*-linked glycosylation of CD38 has been revealed to play a role in preventing aggregation of the tetramer (*Structure* **20**, 1585–1595, 2012).

Shigeyuki Yokoyama

SSBC researchers Shinjiro Hino and colleagues proposed a novel mechanism where lysine-specific demethylase 1 (LSD1) regulates cellular energy balance through coupling with cellular flavin adenosine dinucleotide (FAD) biosynthesis. The team demonstrated that the loss of LSD1 function induces a number of regulators of energy expenditure and mitochondrial metabolism, resulting in the activation of mitochondrial respiration (*Nature Communications* **3**, 758, 2012).

Rie Yamashige and colleagues have uncovered a highly specific unnatural base pair

system between 7-(2-thienyl)imidazo[4,5-b] pyridine (Ds) and 2-nitro-4-propynylpyrrole (Px). Their studies of the Ds–Px pair in the polymerase chain reaction (PCR) have confirmed the utility of a third base pair as a replicative component with high efficiency and fidelity, besides the natural A–T and G–C base pairs. The development of unnatural base pairs for specific PCR amplification is a seminal milestone toward the next generation of biotechnology (*Nucleic Acids Research* **40**, 2793–2806, 2012).

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 SSBC Director Shigeyuki Yokoyama.

Since 2010, 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. One significant achievement was the structural analysis of a leukemia-related protein and the identification of an inhibitor candidate as part of research being conducted by the RIKEN Research Center for Allergy and Immunology.

Beyond its own research, SSBC maintains close ties with researchers throughout Japan, and non-RIKEN researchers benefit from SSBC's policy to provide its equipment for external use. The nuclear magnetic resonance (NMR) facility operates 24 NMR instruments which provide 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 SSBC. "It is my earnest desire to create a paradigm shift in how life science research is carried out. We plan to create a platform for developing 'agent molecules', which can control cell and cellular activities.

Moreover, we plan to apply genetic code expansion to develop an advanced system for producing modified proteins. We aim to further contribute to 'life innovation', such as drug development and medical care based on structural-biology technology to understand multi-level mechanisms of molecular networks in cells relating to DNA, RNA and proteins."

# Finding cancer's escape route

**By determining the structural effects of tumor-causing mutations, scientists obtain valuable information for drug discovery**

For many patients with non-small-cell lung carcinoma (NSCLC), tumorigenesis is fueled by mutations that hyperactivate the epidermal growth factor receptor (EGFR) signaling protein. These individuals may benefit from treatment with drugs such as gefitinib, a chemical inhibitor of EGFR, although additional mutations in EGFR can render the cancer drug-resistant.

Accordingly, scientists are struggling to overcome NSCLC recurrence. "The mutations related to drug sensitivity and those that cause drug resistance cannot be understood without the structures of these EGFR variants," explains SSBC Director Shigeyuki Yokoyama. By teaming up with Tadashi Yamamoto's group at the University of Tokyo, Yokoyama and colleagues have now made major headway in clarifying the roots of resistance and how they might be exploited with future drugs[1].

The researchers performed structural and biochemical analysis of an EGFR variant containing the gefitinib sensitivity-inducing G719S mutation, either alone or with the additional resistance mutation T790M (Fig. 1). Remarkably, they determined that although G719S binds strongly to gefitinib, G719S/T790M binds the drug even more tightly. "This appears to be contradictory to the drug resistance phenotype," says Yokoyama.

Further investigation offered potential explanations for this paradox. First, the T790M mutation appears to stabilize a network of amino acids that maintain EGFR in a continuously active state. Additionally, EGFR must bind molecules of adenosine triphosphate (ATP) to perform its signaling activities, and the researchers determined that G719S/T790M has a markedly increased capacity for ATP binding relative to G719S. This enhancement of ATP binding caused by the T790M mutation, could therefore render EGFR resistant to gefitinib in spite of its strong affinity for the drug.

Yokoyama and Yamamoto also identified the mechanistic basis for the strong drug response observed for both G719S and another common gefitinib-sensitive EGFR variant, L858R. In both cases, they identified specific rearrangements that essentially widened the protein's ATP-binding site, creating sufficient space for gefitinib to bind and interfere with signaling.

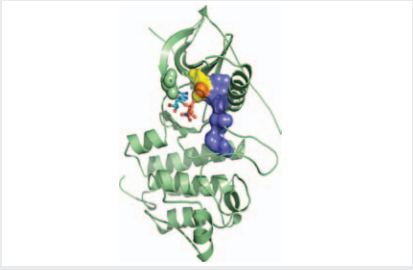

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**Figure 1: Structure of the gefitinib-resistant EGFR double mutant bound to a chemical analogue of ATP (represented by the stick diagram), where green spheres represent the G719S mutation and yellow spheres represent the T790M mutation. These mutations keep the receptor active by stabilizing a network of amino acids known as the 'hydrophobic spine' domain (blue spheres).**

Collectively, these structural findings could prove invaluable for uncovering new vulnerabilities in drug-resistant cancers. Yokoyama and colleagues recently used computer simulations to identify vulnerabilities in the G719S/T790M double-mutant[2]. These new data should enable even more accurate drug design against EGFR as well as other cancer-linked signaling proteins in the future. "We are planning to increase inhibitor specificity based on structure determination of the complexes between drug-resistant EGFR mutants and various compounds," says Yokoyama. "This structure-based drug discovery should yield more powerful and useful anti-cancer drugs."

1. Yoshikawa, S., Kukimoto-Niino, M., Parker, L., Handa, N., Terada, T., Fujimoto, T., Terazawa, Y., Wakiyama, M., Sato, M., Sano, S. *et al.* Structural basis for the altered drug sensitivities of non-small cell lung cancer-associated mutants of human epidermal growth factor receptor. *Oncogene* **32,** 27–38 (2012).
2. Sato, T., Watanabe, H., Tsuganezawa, K., Yuki, H., Mikuni, J., Yoshikawa, S., Kukimoto-Niino, M., Fujimoto, T., Terazawa, Y., Wakiyama, M. *et al.* Identification of novel drug-resistant EGFR mutant inhibitors by in silico screening using comprehensive assessments of protein structures. *Bioorganic and Medicinal Chemistry* **20,** 3756–3767 (2012).

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YOKOHAMA INSTITUTE

# RIKEN Bioinformatics And Systems Engineering Division

**An ingenious knowledge-integration infrastructure developed by the RIKEN Bioinformatics And Systems Engineering division (BASE) systematically integrates RIKEN's open databases into an encyclopedia of resources that provide researchers at RIKEN and around the world with comprehensive access to data.**

The mission of RIKEN, expressed in the words of President Ryoji Noyori, is to promote "the integration of individual wisdom into 'RIKEN Wisdom', and its further integration into social wisdom." In order to achieve this purpose, RIKEN Bioinformatics And Systems Engineering divison (BASE) has been established and strongly promotes knowledge integration as the encyclopedia of RIKEN Wisdom.

"The research resource databases produced by each RIKEN center's activities are so complex that we had to systematically reorganize all data as an encyclopedia based on the framework of Semantic Web and standard ontology," says Tetsuro Toyoda, director of BASE.

Established in 2008, BASE analyzes the vast amounts of life science data generated at 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.

Tetsuro Toyoda

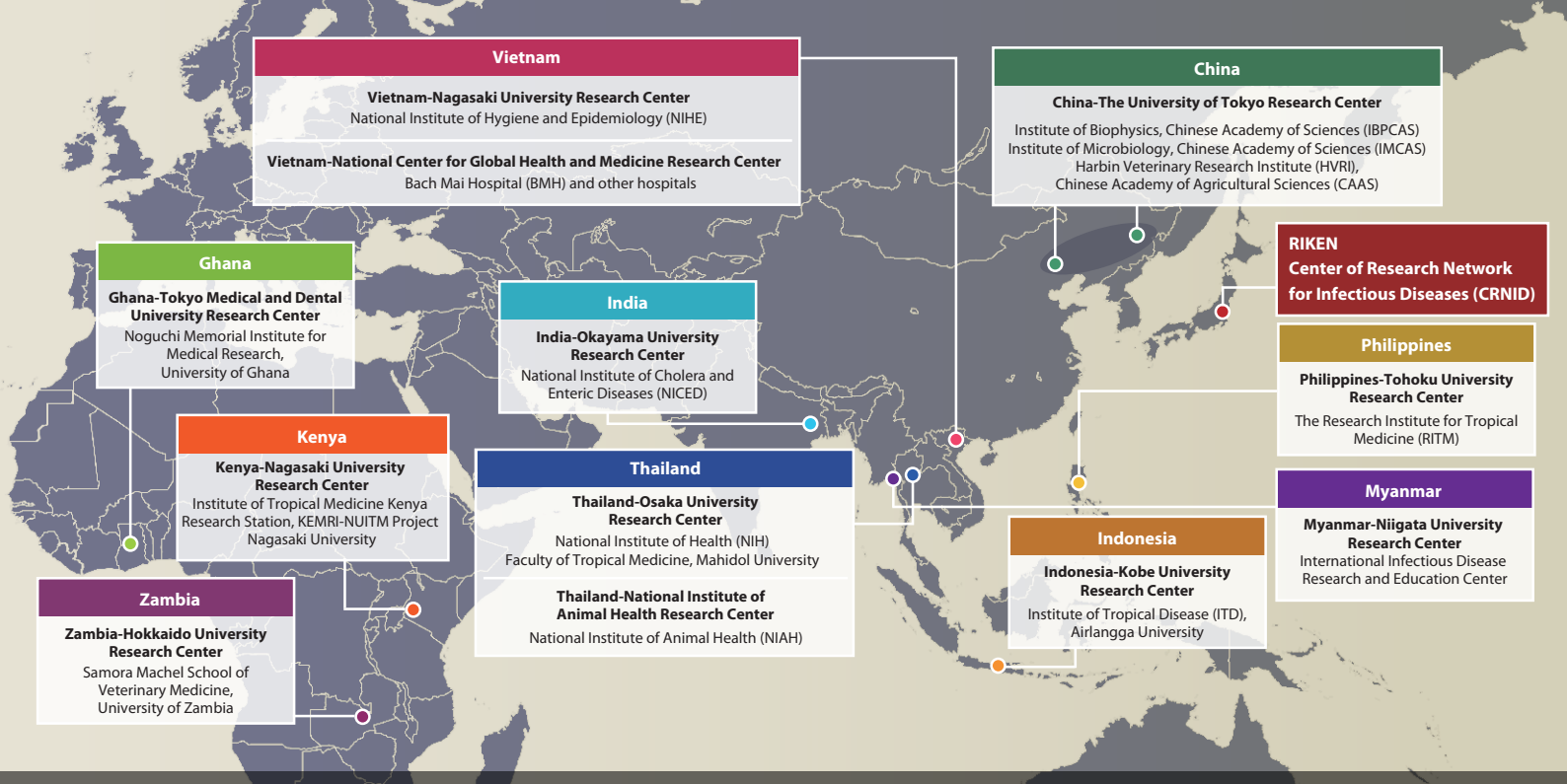
"SciNetS aims to allow data from each of RIKEN's separate centers to be used more easily and permanently, by both in-house and external researchers, and to ensure that data will not be lost from the 400 database projects stored within SciNetS, even after the laboratory that originally generated the database is closed," says Toyoda.

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 can be made available to all in-house scientists.

The SciNetS infrastructure is designed such that when a set of data is selected, life sciences data from 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. Globally, it acts as a hub for Japan's 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 (JST) by promoting the National Bioscience Database Center (NBDC) project.

In 2012, BASE researchers developed key improvements to a technique for the full-length reconstruction of RNA transcripts. Usual problems with this technique include noise and bias which interfere with correct reconstruction. BASE's new method, however, is robust against these complications, enabling accurate transcript reconstruction using any kind of equipment (*Bioinformatics* **28**, 929–937, 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 Network on Infectious Diseases (J-GRID).

"Infectious diseases heed no national borders," says Yoshiyuki Nagai, director of 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 appointed two associate members, Kenya and Myanmar, in 2011. These research collaboration centers were each established on a bilateral basis between a Japanese university or 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.

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 2 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.

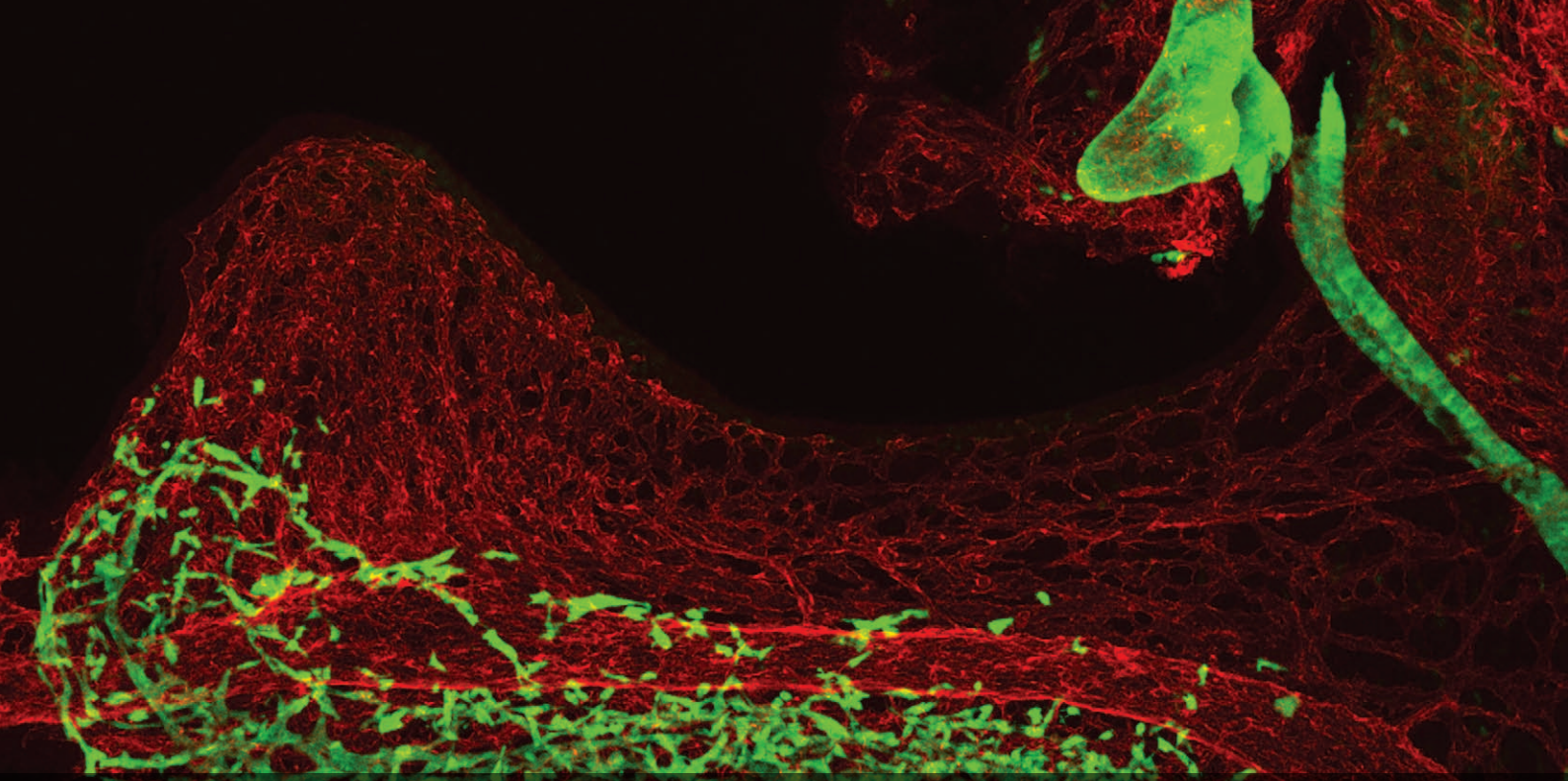
Nagai cited the study conducted by Anusak Kerdsin and colleagues (*Lancet* **378**, 960, 2011), which reported two cases of *Streptococcus suis* infections with previously unreported serotypes in Thailand. In addition, Kazunori Oishi, the principal investigator of this research, was awarded a commendation 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.

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. CRNID plays a key role in publicizing J-GRID by developing and improving the project website, publishing email newsletters, booklets and leaflets, and organizing public seminars.

CRNID is also making efforts to strengthen the interaction of J-GRID with national and international networks sharing similar missions.

"The mid-term evaluation by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) in Japan in FY2012 commended J-GRID as an ideal model led by Japan, a world-leader in science and technology, and highly recommended that the program be continued even after 2015," 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.

"The study of developmental biology lies at the foundation of the many-varied research interests at our center," says CDB Director Masatoshi Takeichi.

"While much of what we do is primarily aimed at a fundamental understanding of biological processes and mechanisms, we also have labs now working on translating such findings into clinical applications."

At the time when 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 depth of the CDB research community was highlighted by the diversity of major findings published in 2012. A time-lapse imaging technique developed by Kazuo Yamagata and colleagues uncovers problems with the success rate of cells cloned by the somatic cell nuclear transfer (SCNT) technique. Preliminary evidence presented by the research team suggests links between abnormalities associated with SCNT and embryonic viability, which is potentially related to fertility problems in women (see *Clones off to a bad start*, p. 31).

Fumio Matsuzaki reported on neural stem cells—called neuroblasts—in *Drosophila* and revealed how molecular factor Tre1 regulates the way neuroblasts align with respect to the epithelium in the developing brain. As this mechanism may be widely conserved in the orientation of asymmetric divisions or the polarity of cells relative to adjacent tissues, it may be important for directional tissue growth and the establishment of stem cell environments (*Developmental Cell* **22**, 79–91, 2012).

Masatoshi Takeichi

A team led by Carina Hanashima showed how the receptor protein Robo1 helps determine the positioning of certain neurons in the neocortex, the highly stratified and

critically important surface layer of the mammalian brain. The means by which its layered organization is established has remained unclear, and this study provides new insights into the molecular control systems behind the locations of cortical neurons within their tissue environment (*Cerebral Cortex* doi: 10.1093/cercor/bhs141, 2012).

Hideki Enomoto and colleagues made a startling discovery in their ongoing work on the enteric nervous system when they observed how some enteric neural crest cells take a shortcut across the mesentery on their way to the large intestine. This has important implications for the study of Hirschsprung's disease, a pediatric condition in which the lower gut is incompletely innervated and which affects around 1 in 5,000 children born in Japan (*Nature Neuroscience* **15**, 1211–1218, 2012).

In a separate study, Hideki Enomoto's team also showed how mutations in the gene *Phox2b* are linked to a range of diseases of the autonomic nervous system, including Hirschsprung's disease, that are caused by defects in the development of neural crests—transient cells that migrate to various locations and differentiate into a range of cell types (*Journal of Clinical Investigation* **122**, 3145–3158, 2012).

Yoshiki Sasai's research group showed that cultured human embryonic stem cells (ESCs) can be induced to self assemble into complex structures that closely mirror natural tissues—specifically the embryonic optic cup and neural retina—recapitulating work previously completed in mouse ESCs. This is the first report to reveal autonomous self-organizing behavior in human ESCs (*Cell Stem Cell* **10**, 771–785, 2012).

Researchers at 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.

"These are exciting times for developmental biology and an ever-expanding number of related fields," says Takeichi. "Technological advances allow us to study genetic conditions in more detail than ever before. Through our work, we look forward to helping drive a new generation of research insights that will produce both scientific knowledge and benefits to humankind."

# Clones off to a bad start

## Time-lapse imaging of embryos reveals complications that undermine cloning efficiency and potentially contribute to human fertility issues

In 1996, the technique known as somatic cell nuclear transfer (SCNT) transformed the idea of cloning from science fiction into reality. SCNT entails removing the nucleus from an adult somatic cell of the animal being cloned (Fig. 1), and then transplanting it into an oocyte from which the nucleus has been extracted. However, the success rate remains low, and the inability to directly link SCNT-associated abnormalities with embryonic viability has made it difficult to understand why. Now, an imaging technique devised by Kazuo Yamagata of CDB and colleagues has revealed a key checkpoint in this process[1].

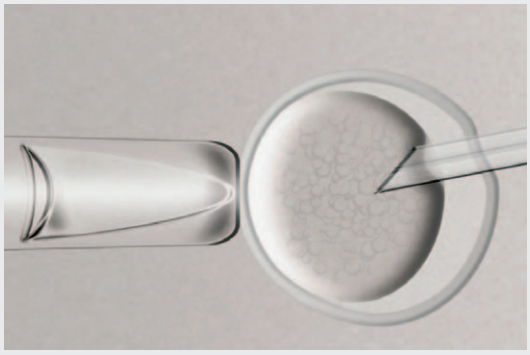


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**Figure 1: The removal of a nucleus from an oocyte as a prelude to SCNT.**

Like all good spies, biologists snooping into the inner workings of embryonic development avoid interfering with the target of their surveillance. Unfortunately, standard imaging techniques are traumatic: cells are forced to overexpress fluorescent proteins before being bombarded with powerful lasers to illuminate the proteins. "This can cause what is known as 'phototoxicity', which reduces the viability of the cell," explains Yamagata.

His team therefore adapted a technique that they first developed in 2009[2]. They injected mouse oocytes with fixed amounts of RNA molecules encoding a nuclear protein and a cytoplasmic protein, each carrying a different fluorescent label. Using a specially designed microscope, the researchers collected time-lapse imaging data as the embryos developed over the next four days. Importantly, once the injected RNA was expended, the embryos continued to develop normally, revealing which changes proved most damaging to overall viability.

This imaging approach revealed that the SCNT embryos were highly prone to disruptions in how their genetic material was partitioned during cell division, a characteristic termed 'abnormal chromosomal segregation' (ACS). Some embryos exhibiting ACS developed normally and yielded apparently healthy mouse pups. However, when ACS emerged during the first three cell divisions, subsequent development was irreparably sabotaged, suggesting the existence of a critical window in which normal cell division is essential. "I think our [work] is the first to [show] a direct link between chromosome segregation errors and SCNT failure," says Yamagata.

Scientists have hypothesized that epigenetic abnormalities—disruptions in chemical modifications associated with chromosomal DNA—undermine SCNT success, and Yamagata's team has found preliminary evidence potentially connecting these abnormalities. "Our data clearly suggest that some linkage between epigenetic status and genetic stability may exist," he says. Understanding this connection and other contributors to early-stage ACS should benefit humans as well as mice. "It is well documented that infertility and early pregnancy loss are caused by chromosome instability," explains Yamagata.

1. Mizutani, E., Yamagata, K., Ono, T., Akagi, S., Geshi, M. & Wakayama, T. Abnormal chromosome segregation at early cleavage is a major cause of the full-term developmental failure of mouse clones. *Developmental Biology* **364**, 56–65 (2012).
2. Yamagata, K., Suetsugu, R. & Wakayama, T. Long-term, six-dimensional live-cell imaging for the mouse preimplantation embryo that does not affect full-term development. *Journal of Reproductive Development* **55**, 343–350 (2009).

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 development of molecular and genomic studies has opened a new realm of scientific research on humans, but the difficulty of 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 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 to do 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.

CMIS aims 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 CMIS in 2008. Since April 2010 and continuing in 2013 CMIS has been playing a central role in the government's new initiative, the Japan Advanced Molecular Imaging Program (J-AMP). In 2012, CMIS hosted the J-AMP symposium in Kobe.

CMIS strongly promotes the translation of its research achievements into clinical applications. Ketoprofen methyl ester, which CMIS has shown to be a useful imaging biomarker for brain inflammation in rats, is now being clinically tested for the diagnosis of dementia in humans. PET imaging of refractory breast cancer is another successful example. Breast cancer patients with mutations in HER2, a common oncogene, can be cured by targeted therapy using the antibody drug, Trastuzumab, but an invasive needle biopsy is required to confirm correct diagnosis in advance. CMIS has confirmed for the first time in the world, in collaboration with the National Cancer Center in Tokyo, that PET imaging using a radiolabeled antibody drug can detect HER2-positive tumors in patients. This means that noninvasive diagnostic imaging has the potential to be a powerful tool for personalized medicine (*Journal of Clinical Oncology* **30**, 2012, suppl; abstr 10519).

CMIS is also continuing to uncover the linkages between molecular dynamics in living animals and specific biological phenomena. For example, a new approach using PET imaging in conscious marmosets identifies the close relationship between serotonin and specific brain regions that are involved in the regulation of social behavior. The study leads to a better understanding of complex social disabilities such as depression, anxiety disorders and autism (*Cerebral Cortex* doi: 10.1093/cercor/bhs196, 2012). "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 CMIS."


KOBE INSTITUTE

# RIKEN Quantitative Biology Center

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

Led by director Toshio Yanagida, the RIKEN Quantitative Biology Center (QBiC) brings together researchers from different fields for the quantitative study of the cell. Established in early 2011, QBiC aims to advance research in whole-cell modeling by studying molecular and cellular properties and interations to reveal the principles that generate complex biological systems. The center aims to replicate the dynamics of the cell through innovative technologies developed by the center's three core research groups: Cell Dynamics, Computational Biology, and Cell Design.

"Even within a very short time frame, we are already showing our ability to develop new technologies for the study of cell dynamics. I think it is a testament to not only the passion of our members, but also the key relationships between our core research groups at our institute. Not only do we need bright, motivated people to succeed, we also need these people to interact and engage with one another. Although it is still early, I think we are on the right track," says Yanagida.

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 molecular behavior.

This core is generating a number of groundbreaking technologies including those in single-molecule imaging, such as 3D and multicolor imaging, and single-cell molecular detection, such as nanospray mass spectroscopy.

The Computational Biology Research Core uses the data produced by the Cell Dynamics Core to mathematically analyze complex biological systems in detail. Through the development of unique modeling technologies that can predict cellular systems, this core will simulate the behaviors of molecules, intracellular particles and cells, as these underpin complex biological processes.

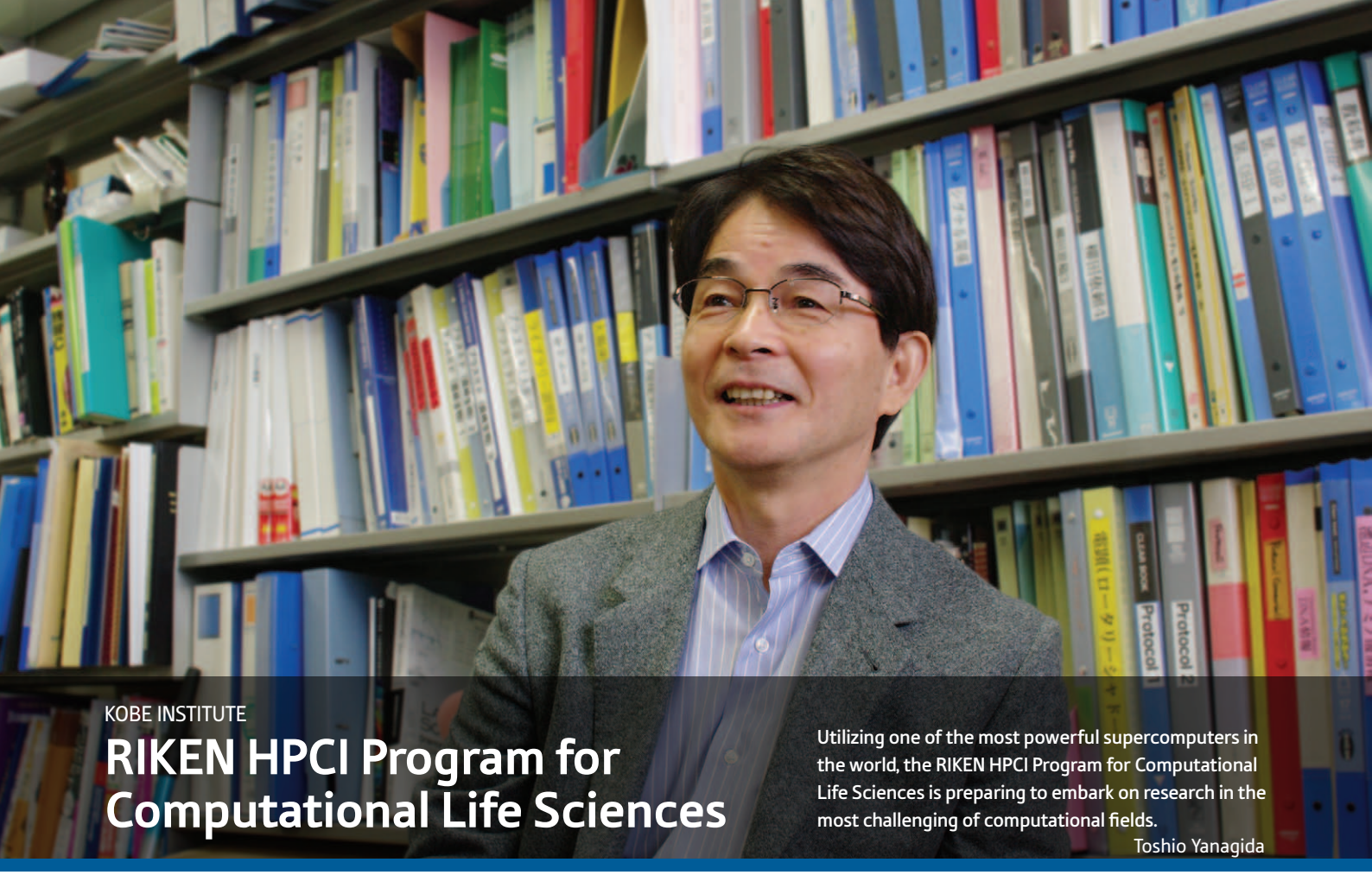
As an emerging area of biology that fuses science with engineering, synthetic biology focuses on the creation of new biological systems and devices which provide models to explore cellular responses and functions. With laboratories specializing in synthetic biology, cell-free protein synthesis and integrated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

Despite its relative youth, QBiC is already seeing success in a range of fields. For example, Tomonobu Watanabe's group reported on a bioprobe that can detect the strain experienced by a molecule of interest, offering a new metric for evaluating how the cellular environment affects molecular function (*Chemical Communications* **48**, 7871–7873, 2012).

In other research, Toshio Yanagida and his team propose that motor proteins at the nanoscopic level work with a high degree of randomness enabling them to function at high efficiency (*Nature Communications* **3**, 956, 2012). Such insight may lead to new paradigms for the design of miniature machines.

In November 2012, QBiC held its inaugural symposium, "Toward whole-cell modeling." The event attracted over 300 people including 14 speakers from QBiC and 12 speakers from universities and research institutes in Japan and overseas.

While the presentations diverged in methods and techniques, they all focused on understanding the operating principles of cellular dynamics. The symposium also provided a venue for QBiC to comprehensively share its research directly with an international audience.



KOBE INSTITUTE

# RIKEN HPCI Program for Computational Life Sciences

**Utilizing one of the most powerful supercomputers 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

Japan is home to one of the most powerful supercomputers in the world: the K computer. In June 2011, the K computer was ranked as the world's fastest supercomputer with a rating of more than 8 petaflops, and in November 2011 it became the first computer in the world to exceed 10 petaflops. There is unprecedented pressure on the supercomputer program to both deliver tangible results and tackle ever-larger 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 K computer. 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 life sciences.

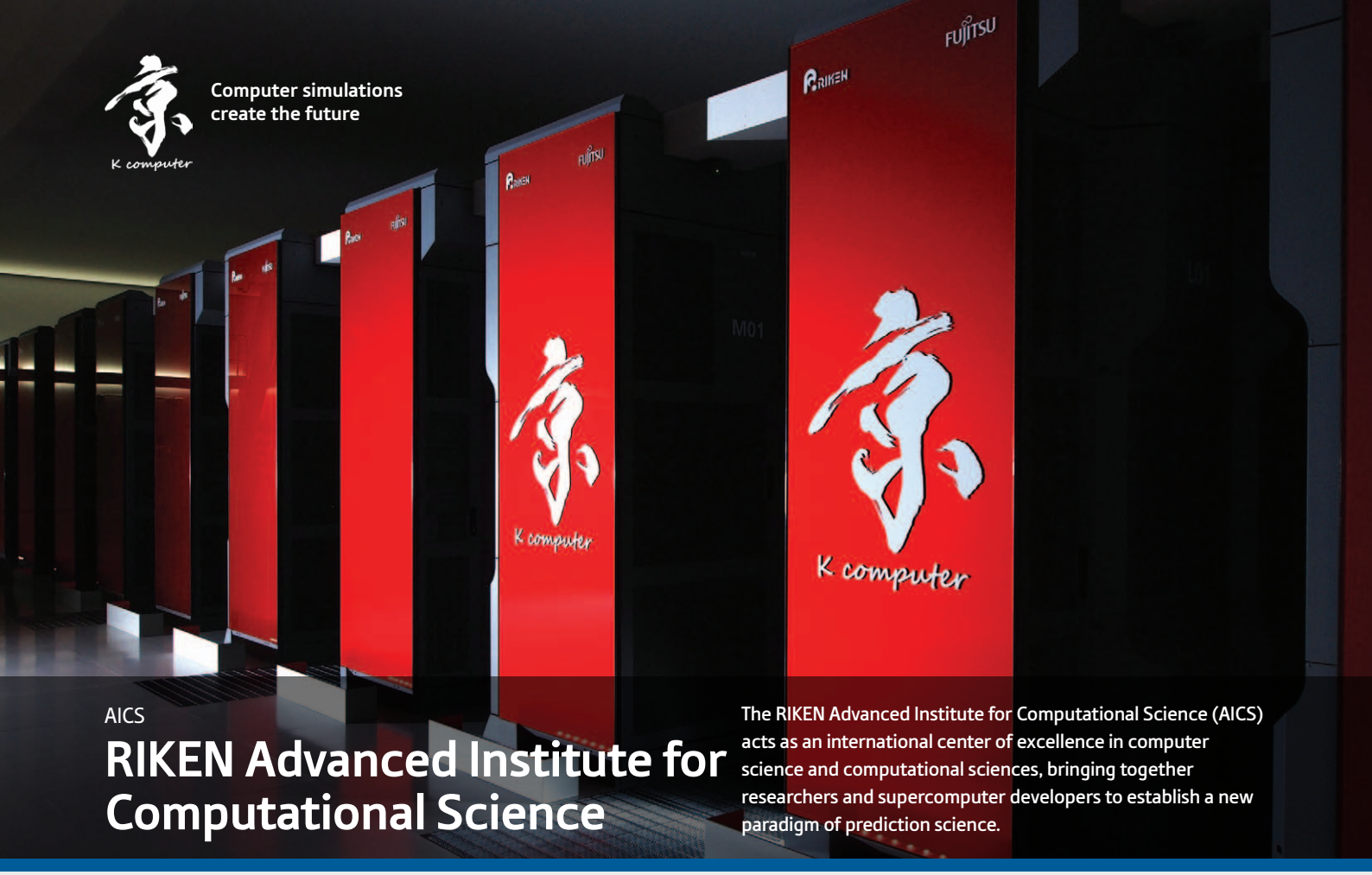
The use of computational approaches in biology and the life sciences is a recent and largely uncharted realm of research. Biological systems do not lend themselves well to computational simulation. The massive number of possible variables, heterogeneity and complexity of life systems have meant that 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 tremendous 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 this 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 started with the aim of having a series of well-structured research programs.

Research focuses 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. For example, Yuji Sugita's study focuses on simulations of biomolecules in cellular environments (*Journal of the American Chemical Society* **134**, 4842–4849, 2012). "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, computer simulation has the potential to contribute significantly to biology and medicine."




AICS

# RIKEN 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 the 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 supercomputer, the K computer, is set to provide an unprecedented level of computing power to researchers. In 2011 the facility topped the global supercomputer rankings with a benchmark performance of over 10 petaflops, or $10^{16}$ operations per second, making it 250 times faster than the first-generation Earth Simulator. In 2013, the K computer continues to be one of the most powerful supercomputers in the world.

Full operation of the supercomputer commenced in September 2012, and RIKEN has been entrusted with the management and ongoing development of this shared resource of strategic national importance. 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 AICS Director Kimihiko Hirao. "We have already astonished the world by introducing the award-winning supercomputer; 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 computer scientists and engineers responsible for the development of the supercomputer itself.

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. "AICS is committed to producing exciting results in computer science that will bring intellectual contributions to humankind," says Hirao. "Computer simulations create our future."

HARIMA INSTITUTE

# RIKEN SPring-8 Center

**Located on the same site as the world-class SPring-8 synchrotron radiation facility and the SACLA XFEL 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 16 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 RSC. "Our mission at RIKEN has been to keep SPring-8 in the top position. That position was reinforced in 2005 when RIKEN founded 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 added 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 1-kilometer beamline. RIKEN initiated these developments," says Ishikawa. In 2012, Ishikawa received the Medal of Honor with Purple Ribbon from the Japanese government for his contribution to the development of x-ray engineering at the SPring-8 facility. This technology is adopted as the standard not only at SPring-8 but at other facilities worldwide.

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," explains Ishikawa. "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."

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. 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," says Ishikawa.

In June 2011, the SACLA successfully achieved first light, and in autumn 2011 the SACLA team succeeded in producing an x-ray laser with a target value wavelength of 0.6 ångströms. User operation commenced in March 2012 and 52 proposals were accepted as the first experiments to begin using SACLA (see *Powerful x-rays for less,* p. 37).

The SACLA XFEL—the second of its kind in the world following the Linac Coherent Light Source (LCLS) in the United States—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 is able to produce ultrashort pulses of light that could be used to analyze ultrafast processes and chemical reactions we know very little about, like 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."

In a notable achievement from SPring-8, Yoshitsugu Shiro and colleagues solved the crystal structure of quinol-dependent nitric oxide reductase (qNOR) from the bacterium *Geobacillus stearothermophilus* to a resolution of 2.5 ångströms, providing insights into the microbial denitrification process (*Nature Structural & Molecular Biology* **19**, 238–245, 2012).

Also at SPring-8, Masaki Takata and colleagues have successfully demonstrated how the thermoelectric properties of clathrates are enhanced by their unusual atomic structure, revealing a potential route to more efficient energy usage. The team hopes to extend their method to other electronic functions such as superconductivity and ferroelectricity (*Physical Review B* **85**, 144305, 2012).

The SACLA team has produced reflective optics with nanometer accuracy, focusing a 10 keV XFEL to an area of 0.95 x 1.20 square micrometers, to preserve a coherent wavefront. The near 100% efficiency allows a 40,000-fold increase in the fluence. This discovery can be applied to the generation of a highly powerful nanobeam for the advancement of microscopic research and development of nonlinear optical sciences under extreme conditions (*Nature Photonics* **7**, 43–47, 2012).

The fields of science utilizing SPring-8 are ever-expanding, and with SACLA, 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."

# Powerful x-rays for less

## Design improvements enable construction of compact x-ray lasers at ultrashort wavelengths, which can measure individual atoms

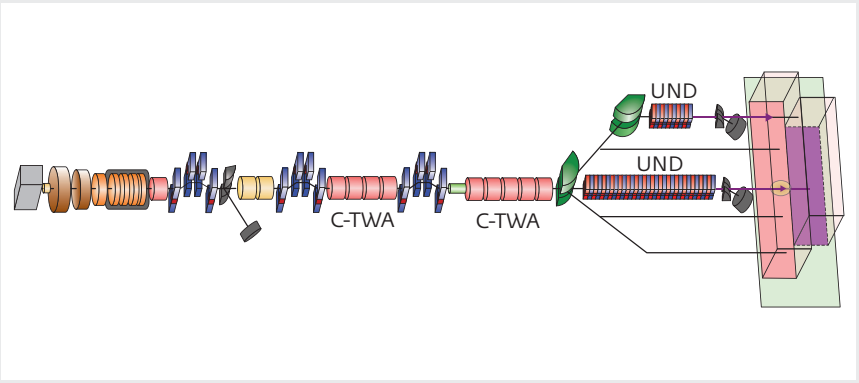





**Figure 1: A conceptual diagram of SACLA. The laser consists of various electron acceleration stages (C-TWA) and focusing elements. Key to achieving short wavelength operation is, however, the design of the undulator (UND).**

Studying small objects typically requires big machines. For example, the study of single atoms with a laser requires x-ray radiation of such high energy that it is only produced by accelerating electrons in large facilities. Researchers at RSC have developed a more affordable electron laser design, SACLA, which is not only compact and therefore economic to build but also delivers x-rays with unprecedented short wavelengths[1].

User operation of SACLA began in March 2012. Makina Yabashi from the research team describes typical research as nonlinear interactions of light and matter, biological imaging and ultrafast phase-transition in materials.

Construction of a high-energy laser is based on the concept that electrons accelerated by going very fast around a curve also emit radiation. The energy of this radiation, and therefore its wavelength, depends on the acceleration. The tighter the curved path, the shorter the wavelength of the light emitted. This is the operating principle of free electron lasers (Fig. 1).

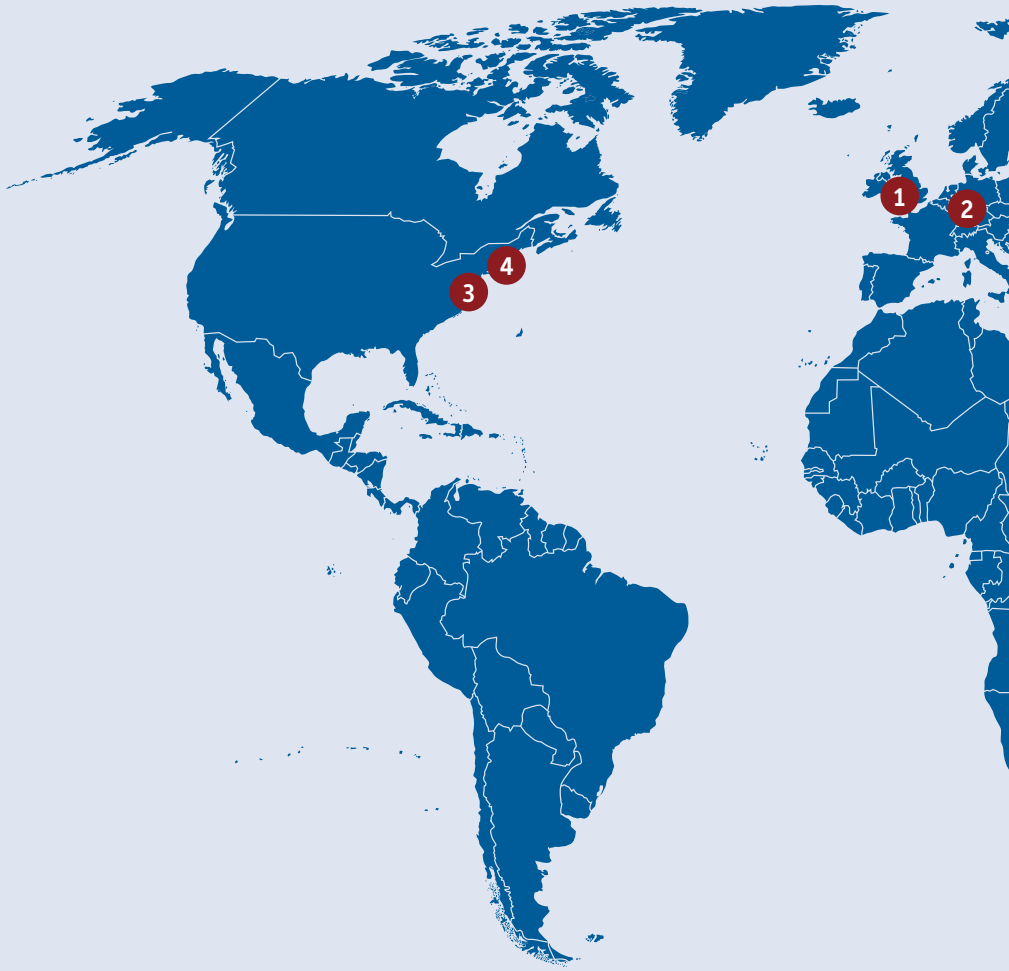
At SPring-8 the aim was to push free electron lasers to new limits by producing ever shorter wavelengths. This means sending electrons on a very tight twisting path in a section of the laser known as the undulator. Normally, the period of the curved electron beam is about several centimeters. The SACLA team has realized a period of only 1.8 centimeters by directly placing the magnets that deflect the electron beams into the vacuum chamber of the beam. This has enabled a reduction of laser wavelength down to 0.6 ångströms, which is about the radius of a hydrogen atom.

One benefit of SACLA is that, in comparison to other free-electron lasers, the device is smaller. "Our x-ray free electron laser facility has been designed to achieve a much more compact scale compared to those in the US and Europe," explains Yabashi. "The major reduction in construction and operating costs enables many research institutes or universities to build such a machine, and to utilize powerful laser light in a broad range of applications from biology, chemistry to physics," he says.

The team plans to increase the energy density of the laser beam, which would, for example, make biological imaging easier. Already there is strong interest from scientists to use the laser and other institutions are planning similar machines. In the meantime, SACLA is open for business.

1. Ishikawa, T., Aoyagi, H., Asaka, T., Asano, Y., Azumi, N., Bizen, T., Ego, H., Fukami, K., Fukui, T., Furukawa, Y., *et al.* A compact X-ray free-electron laser emitting in the sub-ångström region. *Nature Photonics* **6**, 540–544 (2012).

# RIKEN—A global presence




## RIKEN-RAL Muon Facility 1

Rutherford Appleton Laboratory (RAL)
Oxfordshire, UK

nectar.nd.rl.ac.uk/en.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 in the 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 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 and ubiquitous intelligence systems. 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 biologically 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 with a focus on tropical diseases.

## RIKEN Beijing Representative Office 6

Beijing, China

www.riken.org.cn

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 the international mobility of Chinese researchers—attracting them from overseas then 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. It 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

RIKEN-HYU is a joint research program carried out in collaboration with Hanyang University in Seoul, South 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 South Korea, RIKEN conducts collaborative research with a number of institutions including Seoul National University, Hanyang University, and the Pohang University of Science and Technology. 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 marked the commencement of joint research in topics at the interface of chemistry and the life sciences.

In China, RIKEN maintains a presence through its Beijing Representative Office, which was 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 research network throughout the country, which already includes joint graduate school agreements with 15 Chinese institutions of higher education, such as 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. The establishment of the center comes on the back of previous research initiatives in a diverse array of fields including ubiquitous intelligence systems.

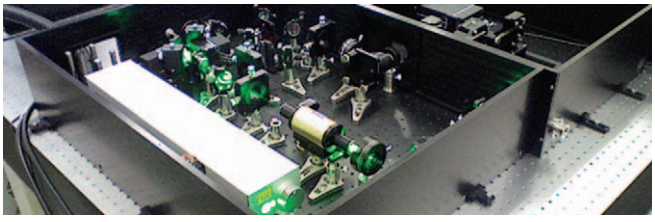
In May 2012, events were held at RIKEN in Wako and Tokyo to celebrate 30 years of friendship between RIKEN and the Chinese Academy of Sciences. A joint workshop was also held at Tsinghua University in October 2012 to mark the beginning of a new relationship between RIKEN and Tsinghua University.

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, 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 Universiti Sains Malaysia (USM) in September 2011 marked the culmination of existing research collaborations between RIKEN and USM. The joint laboratory aims to isolate and investigate novel biologically active compounds from tropical plants found in Southeast Asia. The collaboration between RIKEN and USM was expanded in 2012 to include muon science research. RIKEN's research portfolio in Southeast Asia also includes joint research agreements with the Universiti Malaya of Malaysia, the Thailand National Science and Technology Development Agency, and Indonesia's Padjadjaran University.

RIKEN is also in the initial stages of discussing new research collaborations with renowned Indian organizations including the Jawaharlal Nehru Center for Advanced Scientific Research, the Indian Institute of Science and the National Center for Biological Sciences in Bangalore. In October 2012, a new joint graduate school program agreement was finalized with the Indian Association for the Cultivation of Science in Kolkata.

## 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 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

Established jointly by RIKEN and Tokai Rubber Industries, the RIKEN-TRI Collaboration Center for Human-Interactive Robot Research (RTC) aims to develop a human interactive robot for use in care facilities and hospitals. To date, RTC has developed three types of robots: the Robot for Interactive Body Assistance (RIBA), the RIBA-II and the RIBA-IIx in 2009, 2011 and 2012, respectively. The center also places strong emphasis on developing fundamental element technologies such as rubber-based soft tactile sensors and soft actuators for human–robot interaction.

The RIKEN BSI–TOYOTA Collaboration Center (BTCC), established in 2007, aims to improve the neuro-rehabilitation of stroke patients with the utilization of robot technology. BTCC is composed of three research domains: neuro-driving, neuro-robotics and health protection. In 2012 BTCC proposed a method for assessing the impairment level of stroke patients by analyzing human behavior and combining the method with robot technology developed by BTCC. This method will be a key factor in creating novel rehabilitation systems for stroke patients.

# 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

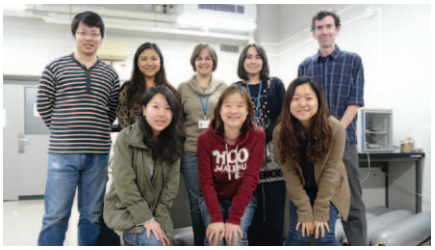
# Life at RIKEN

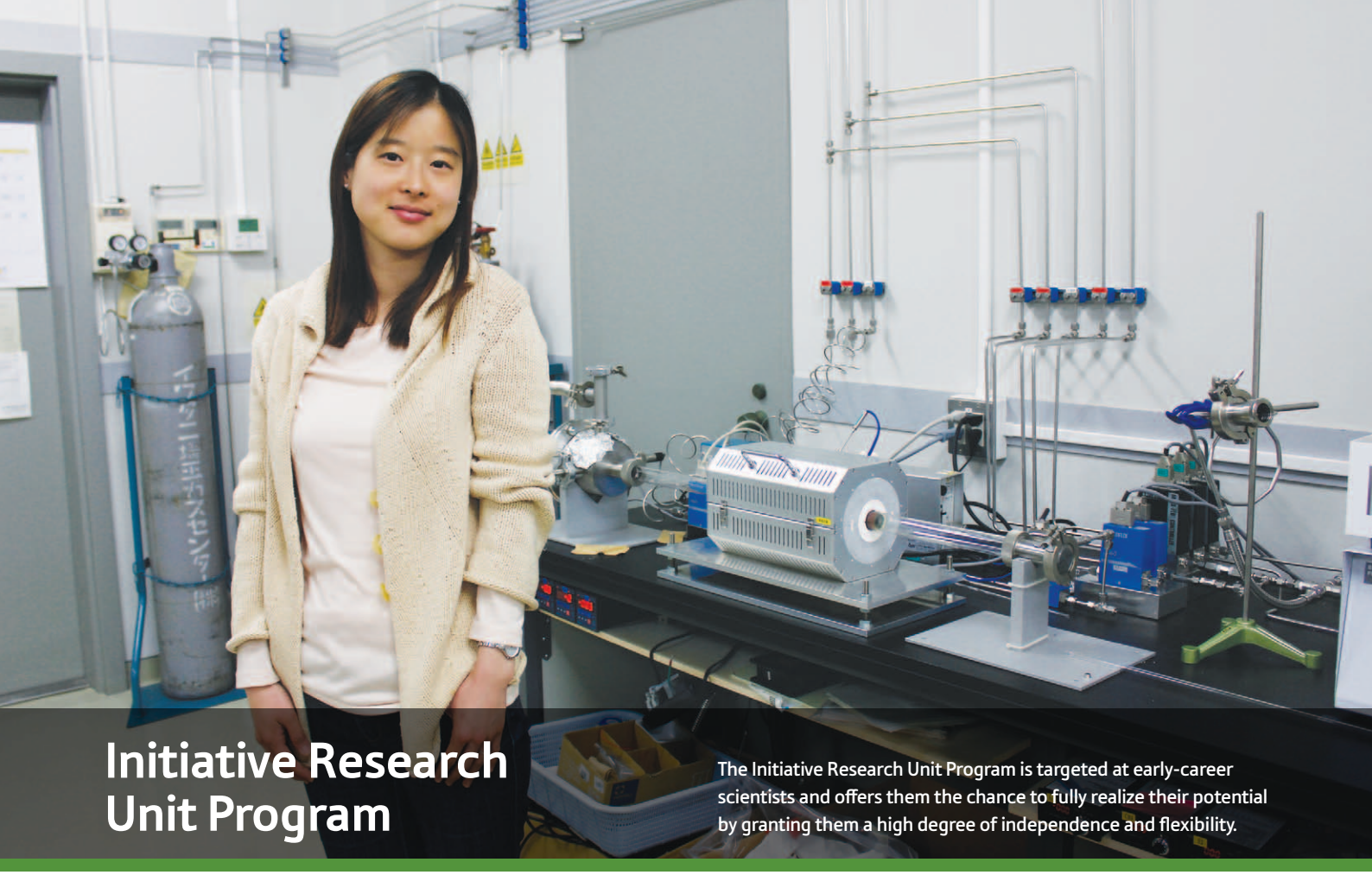
RIKEN's success as a research organization comes from the quality of our people. From the beginning, we have always strived to recruit the best and the brightest scientists into our ranks, and in recent years we have begun to focus on attracting the cream of international research talent, both younger and senior. With the conviction that science knows no borders, we are actively pursuing ever greater internationalization and we are currently home to over 600 scientists from more than 50 different countries on all 5 continents.

RIKEN offers its staff a supportive, diverse and inclusive place to work. Our services make it easier for foreign researchers to adapt to working and living in Japan. Our staff are dedicated to ensuring that information is available in English—the international language of science—and our help desks are located at different campuses where newcomers and their families can access useful information on support services, immigration issues, healthcare and education systems, as well as Japanese customs and culture. At RIKEN we offer on-campus housing at some campuses, while at others we provide assistance in finding housing off campus. We also arrange Japanese language programs to help researchers make the most of their time in Japan.

RIKEN has a Mutual Benefit Society for employees, in which all full-time personnel are automatically enrolled, that funds a diverse range of sports and culture clubs at RIKEN, sponsors numerous events and activities, and otherwise provides a framework for all RIKEN employees to interact, learn about Japan and forge new friendships.

We encourage our staff to maintain a healthy work–life balance, and we are committed to ensuring that all of our people at RIKEN enjoy the best possible working environment.





# 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 February 2013 there were seven 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 lithium (Li) batteries for clean energy storage in advanced electrical vehicles. In particular, Byon's research focuses on lithium-oxygen ($Li\text{-}O_2$) batteries. "The most critical challenge for us is to understand the 'true' reaction inside the $Li\text{-}O_2$ battery. We have developed a real-time monitoring x-ray diffraction (XRD) $Li\text{-}O_2$ battery and we were able to evaluate its $Li\text{-}O_2$ electrochemical reaction efficiency. Based on these real-time operating tools, we can endeavor to demonstrate the chemical reaction in $Li\text{-}O_2$ batteries and aim to find a way to improve battery performance."

Researchers on the IRU Program are able to make full use of RIKEN's comprehensive array of research equipment and facilities, including the SPring-8 synchrotron radiation facility and its X-ray Free Electron Laser (SACLA), a point which Byon cites as a major attraction to working at RIKEN.

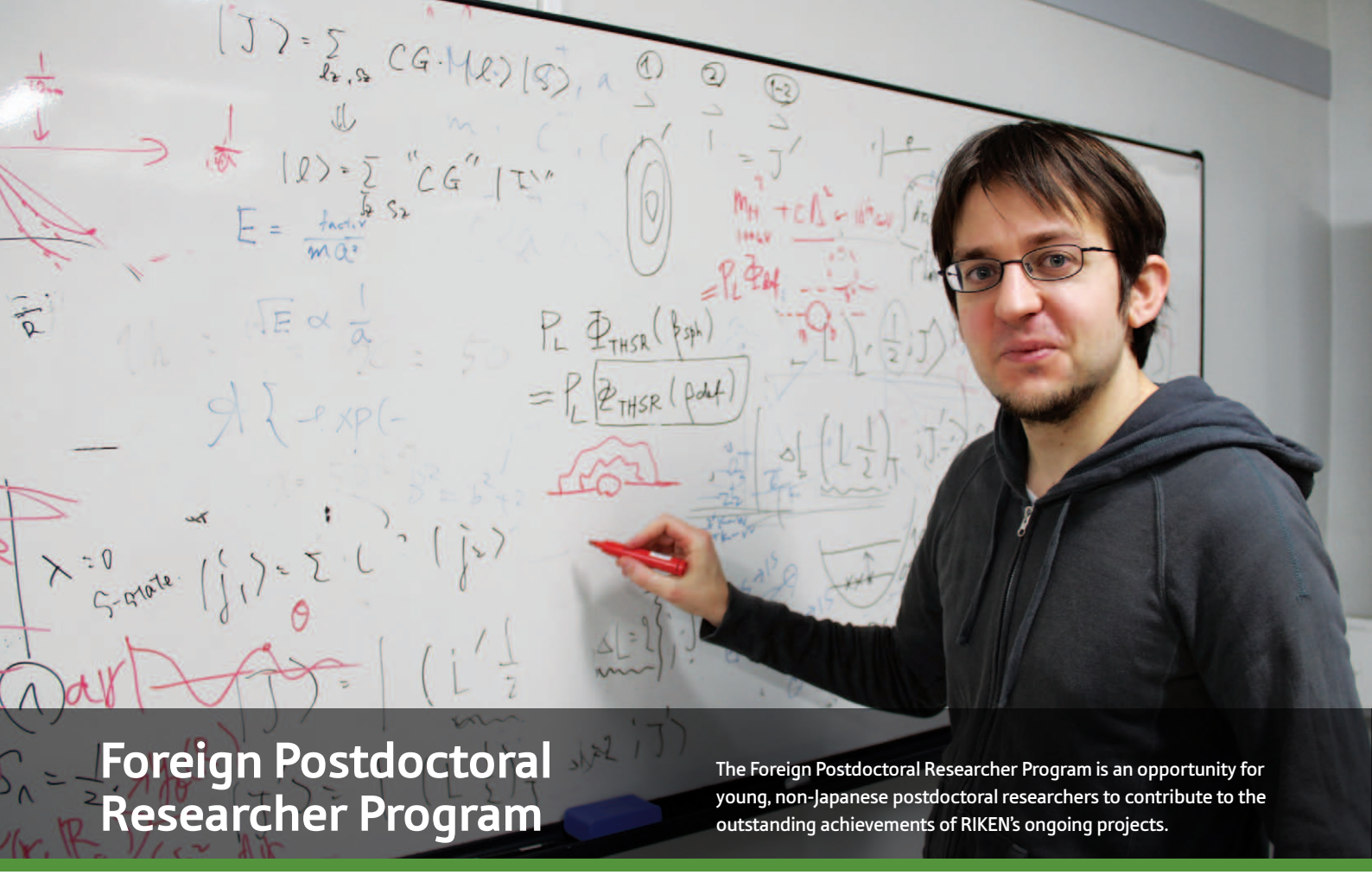
Eligible applicants must hold a doctoral degree in physics, engineering, chemistry, medicine or the life sciences, and be able to propose and implement an ambitious research plan. Unit leaders select their own research staff, comprising three researchers or technical staff, and lead the research effort 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 convinced 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 need assistance to advance their scientific career. For postdoctoral researchers, this need 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.

Philipp Gubler joined RIKEN via the FPR Program upon completing his PhD studies at the Tokyo Institute of Technology in March 2012. Originally from Switzerland, Gubler is a theoretical physicist with an interest in the strong interaction which governs the properties of nuclei at the center of atoms. As part of the Strange Nuclear Physics Laboratory led by Associate Chief Scientist Emiko Hiyama, Gubler's research explores the outcome of matter when it is heated to extremely high temperatures. "While the study of this subject is technically very challenging, I look forward to making real progress during my time here at RIKEN," says Gubler.

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.

"The research environment provided here at RIKEN is really attractive, and the FPR position gives me a lot of freedom to pursue my scientific goals," says Gubler. "I also find it very helpful to have a generous grant allowing me to attend several international conferences."

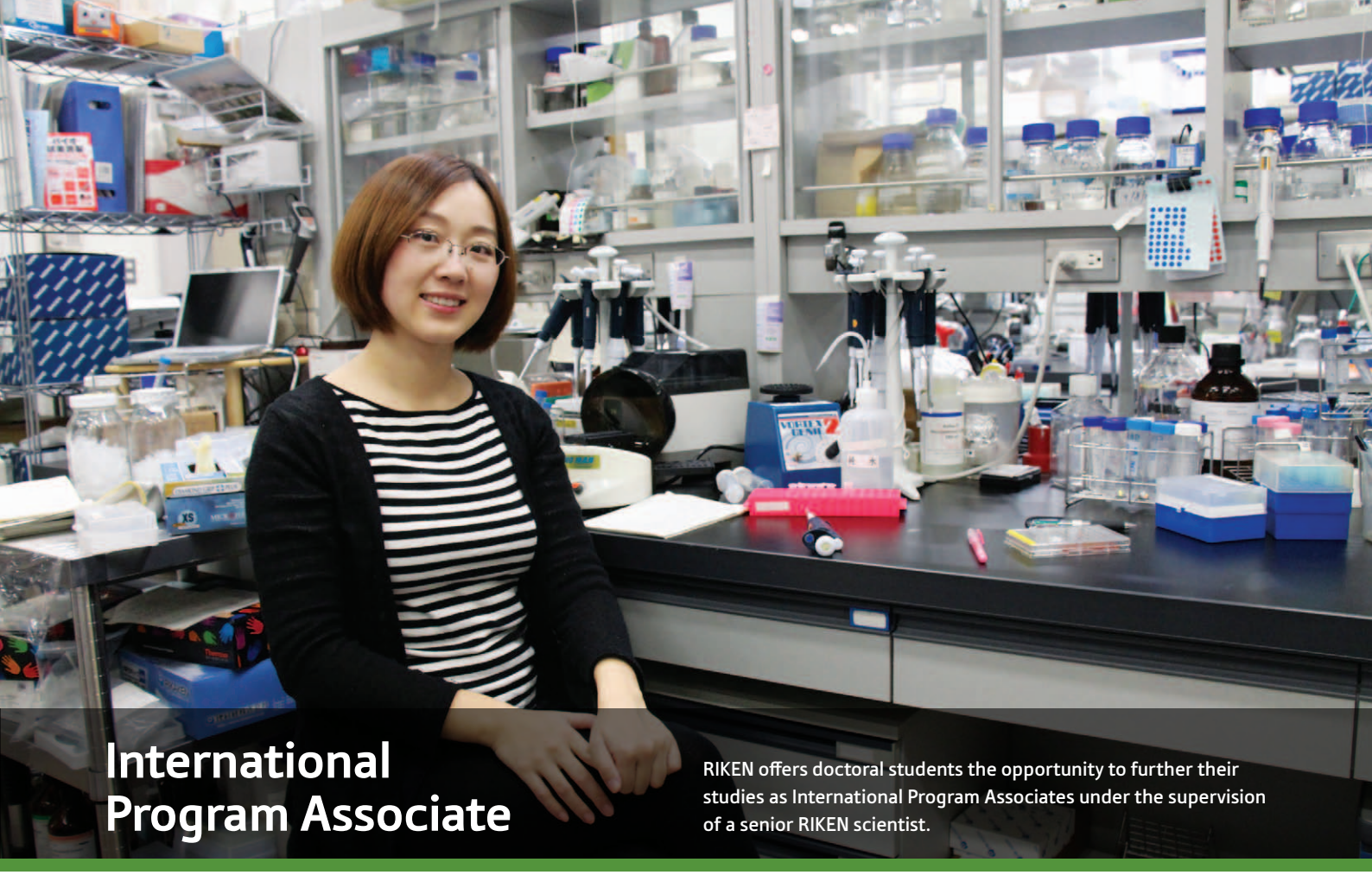
RIKEN realizes that moving from one's home country to Japan to conduct research is not always an easy transition. Foreign researchers at RIKEN are encouraged to join various sports and recreational clubs so that they can achieve a better work–life balance and develop relationships with their Japanese 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.

"RIKEN is a very international place and working here without much knowledge of Japanese is definitely possible. I am really grateful for all the assistance I have received so far from RIKEN staff since I started with the FPR Program. They are very supportive and can help out with various matters, be it with grant applications, academic issues or life in Japan," remarks Gubler.

The FPR 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/careers/programs/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, 105 IPAs have been accepted and the aim is to increase the number to 100 annually in the near future. In March 2012, IPAs hailed from 48 universities located on 4 continents, including Peking University and Shanghai Jiao Tong University in China, Pohang University of Science and Technology in South 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 nanomaterials, 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/careers/programs/ipa/
E-mail: ipa-info@riken.jp

# Programs for visiting scholars

**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 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 BSI as laboratory heads and researchers. In 2012 the application process was very competitive and at an all-time high: the program received 200 applications for the 30 spaces available in the lecture course, and 86 applicants applied for the 15 advertised internship positions.

### 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 (RNC) in Wako. The fifth Nishina School was held from 2 to 12 October 2012, and included lectures and practical training for nine exceptional participants. In 2012, the first Nishina School from Seoul National University (SNU) was held from 6 to 10 August, initiated as part of an agreement between RIKEN and SNU in 2010. Through the Nishina School, RIKEN is fostering an interest in physics research among undergraduate students and strengthening research and educational ties with China and South Korea.

### 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 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 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 facility. The Cheiron School's main aim is to provide useful and basic knowledge as well as perspectives of synchrotron radiation science and technology for graduate students, postdoctoral fellows, young scientists and engineers who wish to pursue their career in fields utilizing synchrotron radiation at facilities in the Asia-Oceania region.

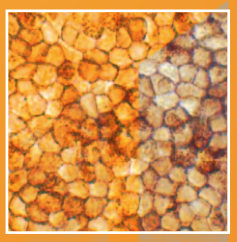
The school is co-sponsored by RIKEN, the Japan Synchrotron Radiation Research Institute (JASRI), the High Energy Accelerator Research Organization (KEK) and AOFSRR. The curriculum includes lectures and hands-on experience of synchrotron science and technology, covering a wide range of topics from accelerator 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 for researchers, and an agreement between RIKEN and the German National Academic Foundation (RIKEN–SDV) to accept graduate students. RIKEN is accepting postdoctoral researchers and graduate students through the Japan Society for the Promotion of Science (JSPS). RIKEN also maintains programs to accept undergraduate and graduate students from the Massachusetts Institute of Technology (MIT) in the United States and with South Korean universities through the JISTEC Winter Institute.

**Further information**
Visit the host center's website or contact the Global Relations Office.
E-mail: 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

## 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. 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

**1986** Frontier Research program established

**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

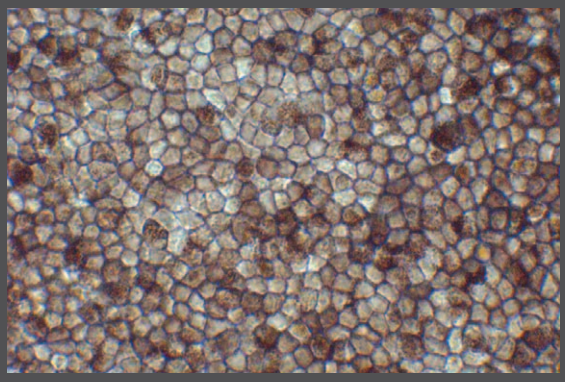
**The birth of the RIKEN Spirit**

The idea of establishing a national research institute for the study of pure science in Japan can be traced back to a 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. The institute that was established then went on to become RIKEN as we know it today.

# 2000

**The start of a decade of achievement in developmental biology**

The Center for Developmental Biology (CDB) at the RIKEN Kobe Institute has contributed many notable breakthroughs to the field of developmental biology since its establishment in the year 2000. CDB's efforts have focused on the translation of basic research—in areas such as pluripotent stem cells—into clinical applications. CDB researchers have also made significant methodological contributions, including a suspension-based culture system for the growth of embryonic stem cells. Retinal diseases offer an excellent example of the potential for CDB-led research in clinical applications. A team led by Masayo Takahashi has successfully induced the differentiation of retinal pigment epithelial cells from stem cells in qualities sufficient for use in transplantation—with the aim of improving or restoring vision in patients.



Retinal pigment epithelial cells

**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

**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**
- Initial observation of element 113 by RIKEN

**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**
- Confirmation of element 113 by RIKEN
- RIKEN–XJTU Joint Research Center established

RILAC ion accelerator at the RIBF

# 2004

**Initial observation 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, which goes by the provisional name of ununtrium. The new element lasted just a fraction of a millisecond. In 2012, Morita and colleagues created a third atom of element 113, adding a new element to the periodic table.

# Five years at a glance

RIKEN is a world-class research hub in Japan renowned for quality research in a diverse range of scientific disciplines. In this age of knowledge accumulation and sharing, RIKEN endeavors to establish collaborations with top international research institutes to provide new opportunities for staff and students.

In recent years, RIKEN has seen research breakthroughs using stem cells and iPS cells, an award-winning supercomputer, and one of the brightest x-ray beams in the world. RIKEN researchers have created element 113, qualifying RIKEN researchers to claim naming rights for the element. Several top international scientists were inaugurated as RIKEN Honorary Fellows, which further strengthens RIKEN's presence in the global research scene.

RIKEN is also credited for organizing important events that brought leaders and young researchers from all over the world to Japan. Over the past five years, RIKEN has gone from strength-to-strength, and will continue to expand the frontier of scientific research in the years to come.

## 2008

### RIKEN BRAIN SCIENCE INSTITUTE (BSI) AND TOYOTA JOIN FORCES FOR SMARTER MACHINES

The RIKEN BSI–Toyota Collaboration Center was established to promote the integration of neuroscience research and industrial technology. In particular, the center is investigating the causes of accidents, improving affinity between machines and humans, and clarifying the relationship between brain function and both physical and mental health.

### EXTENDING SUPPORT FOR SICHUAN EARTHQUAKE VICTIMS

To show support for Chinese graduate students who were affected by the devastating Sichuan earthquake, RIKEN offered five short-term research positions to graduate students from the Chinese Academy of Sciences, and three each to graduate students from Sichuan University and Southwest Jiaotong University.

### RIKEN AND PEKING UNIVERSITY OPEN UP NEW OPPORTUNITIES FOR STUDENTS

RIKEN and Peking University signed an agreement allowing Peking University students to conduct research at RIKEN's world-class facilities. At the same time, a special basic course was set up for nuclear physics students at the Nishina School.

### CRYSTALLIZATION PROCESS OBSERVED IN REAL TIME

A team of researchers at the SPring-8 Center observed in real-time the phase change of a material used in super-fast optical recording. The achievement was anticipated to further speed up the development of high-speed optical recording media.

### CONTRIBUTIONS TO STEM CELL RESEARCH

The RIKEN BioResources Center forged an agreement with Kyoto University to distribute induced pluripotent stem cells (iPS cells) developed by Professor Shinya Yamanaka. Yamanaka's research was also facilitated by resources created at RIKEN.

## 2009

### DISTRIBUTING HUMAN iPS AND ES CELLS FOR FREE

In collaboration with Kyoto University, BRC started a service to provide human induced pluripotent stem (iPS) cells and human embryonic stem (ES) cells to nonprofit research organizations for teaching and research purposes.

### FASTEST DETECTION OF H1N1 EVER

In response to the government's urgent need for rapid detection of the novel influenza A (H1N1) virus and diagnosis of H1N1 infections, the RIKEN Omics Science Center developed a detection technique that reduced the single nucleotide polymorphism (SNP) analysis time to just half an hour.

### FIRST NOYORI SUMMER SCHOOL HELD

The Noyori Summer School, which offers opportunities for young researchers from different countries and fields to meet and interact, was held for the first time. Approximately 60 PhD students attended the 2-day event at the RIKEN Harima Institute.

### INTERNATIONAL JOINT GRADUATE SCHOOL PROGRAM LAUNCHED

RIKEN signed a renewable five-year agreement with the Indian Institute of Technology Bombay (IITB) to launch the International Joint Graduate School Program for PhD students in science and technology. The program was designed to offer a top-class research environment for young IITB graduate students.

### NEW TOOLS TO UNRAVEL NUCLEAR STRUCTURES

The Radioisotope Beam Factory at the RIKEN Nishina Center for Accelerator-Based Science was built to generate the world's highest-energy radioisotope beams for use in nuclear experiments. The new facility has greatly expanded the landscape of nuclear science.

# 2010

### ONE STEP CLOSER TO SOLVING ANTIMATTER PUZZLE

RIKEN researchers reported the first experimental setup and technique for measuring ground-state hyperfine transitions of antihydrogen. The new setup was an important precursor to developing the capacity to generate an antihydrogen beam.

### CHERRY BLOSSOM ALL YEAR ROUND

RIKEN scientists successfully created a new breed of cherry blossom tree that blooms throughout the year. The team's use of heavy ion beams to generate new breeds of plants by mutagenesis, an approach to horticulture unique to Japan, drew great attention worldwide.

### NOBEL LAUREATES SAY NO TO BUDGET CUTS

On 26 November, eight Nobel laureates, including Ryoji Noyori, president of RIKEN, and Susumu Tonegawa, director of the RIKEN Brain Science Institute, delivered a message rejecting proposed cuts to basic science budgets to Yukio Hatoyama, the Japanese prime minister.

### 20 YEARS OF COLLABORATIVE MUON RESEARCH CELEBRATED

After two decades of successful collaboration, a new agreement for research in advanced muon science between Japan and the UK was formalized by the president of RIKEN, Ryoji Noyori, and the chair of the Science and Technology Facilities Council, Keith Mason.

### JOINT SCIENTIFIC WORKSHOP MARKS NEW AGREEMENT

To commemorate the new collaboration agreement between RIKEN and McGill University in Canada, the two partners held a joint scientific workshop in Mont Tremblant, Quebec, Canada, with the aim of strengthening their collaborative relationship through greater communication between their respective research communities.

# 2011

### EXTENDING SUPPORT IN AFTERMATH OF MASSIVE QUAKE

Following the March 2011 earthquake, support activities for staff and students were launched together with up-to-date information provided on the "Life at RIKEN" website. The use of the accelerator at the Wako campus and the RIKEN Integrated Cluster of Clusters supercomputer was limited to save energy.

### SUPERCOMPUTER AWARDED HIGHEST HONOR

RIKEN's supercomputer—known as the K computer—took first place consecutively on the 37th and 38th TOP500 list announced at the International Supercomputing Conference. It was the first time since June 2004 that a Japanese supercomputer achieved world number-one status.

### POWERFUL NEW X-RAY LASER CREATED

An x-ray laser beam with a wavelength of 1.2 ångströms was successfully created using the SPring-8 Angstrom Compact Free Electron Laser (SACLA). The new facility enables researchers to observe and manipulate objects on an unrivalled scale.

### DISTINGUISHED PROFESSORS APPOINTED AS RIKEN HONORARY FELLOWS

Nobel laureates Yuan T. Lee, based at the University of California, Berkeley, Elias James Corey, from Harvard University, and David Baltimore, of the California Institute of Technology (Caltech), were inaugurated as RIKEN Honorary Fellows.

### RIKEN STRENGTHENS TIES WITH CHINA

RIKEN opened the RIKEN Beijing Representative Office, and signed an agreement with the Department of International Cooperation of the Chinese Ministry of Science and Technology to work together to promote research cooperation.

# 2012

### SUPERCOMPUTER AND POWERFUL X-RAY BEAM OPENED TO SCIENTISTS

The K computer, a key technology of national importance funded by the Japanese government (with RIKEN serving as the operating partner), and SACLA, which produces an x-ray laser beam a billion times brighter than the SPring-8's previous technology, opened for shared use.

### ELUSIVE ELEMENT 113 REVEALED

Kosuke Morita and colleagues recorded the most unambiguous data to date on the atomic element 113. Their groundbreaking achievement set the stage for RIKEN researchers to claim the naming rights for an atomic element.

### FIRST GLOBAL SUMMIT FOR RESEARCH INSTITUTE LEADERS

Leaders from 16 research institutes in 12 countries gathered in Kyoto for the First Global Summit of Research Institute Leaders. At the close of the summit, the participants agreed to a joint statement that called for enhanced international collaborations addressing global concerns.

### 30 YEARS OF FRIENDSHIP BETWEEN TWO TOP INSTITUTES

RIKEN and the Chinese Academy of Sciences celebrated 30 years of friendship and cooperation. A commemorative event held in Tokyo drew more than 200 attendees, including both organizations' presidents, Ryoji Noyori and Bai Chunli, and featured lectures given by outstanding scientists from the two institutes.

### BREWING YEAST CREATED WITH RIKEN ION BEAM TECHNOLOGY

In an exciting collaboration between RIKEN researchers and the Saitama Industrial Technology Center and the Saitama Sake and Shochu Makers Association, heavy ion beams were used to produce a new brewing yeast. The new yeast was then used in the production of three commercial sake brands in Saitama prefecture.

## Governance and Advisory Councils

# 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 amid 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.

**RIKEN Advisory Council in 2011**

## 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 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 7th and 8th RIKEN Advisory Councils

Since its establishment in 1917, RIKEN has achieved important breakthroughs in many scientific fields. As we entered the 1990s, however, we began to realize that in order to maintain our mission in the twenty-first century—a time of rapid advances in science and technology—we would require objective guidance on our research activities, research management, and organizational administration from an international perspective. To fulfill this need, the RIKEN Advisory Council (RAC) was created and in June 1993 held its inaugural meeting. In this single step, RIKEN became the first Japanese institution to adopt an international external evaluation system. Since the RAC's inception, other organizations in Japan have followed suit and adopted the same approach. Eight RAC meetings have been held so far, most recently in 2011. With pioneering activities such as these, RIKEN leads the way in enhancing Japan's scientific research structure in line with a global standard.

**Howard Alper***
*Chemistry*
University of Ottawa, Canada
Science, Technology and Innovation Council, Canada

**Yuichiro Anzai**
*Informatics/cognitive science*
Faculty of Science and Technology, Keio University, Japan

**Teruhiko Beppu***
*Applied microbiology*
Nihon University, Japan

**Colin Blakemore***
*Neuroscience*
University of Oxford, UK

**Allan Bradley**
*Genetics*
Wellcome Trust Sanger Institute, UK

**Rita R. Colwell***
*Oceanography*
University of Maryland, USA

**Max D. Cooper**
*Medicine*
Emory University, USA

**Hidetoshi Fukuyama***
*Basic solid state science*
Tokyo University of Science, Japan

**Sydney Gales**
*Nuclear physics*
Grand Accélérateur National d'Ions Lourds, France

**Mitiko Go***
*Bioinformatics*
Research Organization of Information Systems, Japan

**Sten Grillner**
*Neuroscience*
Karolinska Institutet, Sweden

**Wilhelm Gruissem**
*Plant biotechnology*
Institute of Plant Sciences, Switzerland

**Jean-Louis Guenét***
*Veterinary medicine, mouse genetics*
Institut Pasteur, France

**Zach W. Hall***
*Neuroscience*
University of California, San Francisco, USA

**Jerome Hastings***
*Applied physics*
SLAC National Accelerator Laboratory, USA

**Stephen F. Heinemann**
*Molecular neurobiology*
Salk Institute, USA

**Toshiaki Ikoma**
*Electronics*
Canon Inc., Japan

**Hiroo Imura***
*Medicine, endocrinology*
Foundation for Biomedical Research and Innovation, Japan

**Biao Jiang***
*Chemistry*
Chinese Academy of Sciences, China

**Paul Kienle***
*Physics*
Munich University of Technology, Germany

**Bengt Långström***
*Biochemistry*
Uppsala University, Sweden

**Mark Lathrop***
*Gene science*
Center National de Génotypage, France

**Yuan Tseh Lee**
*Chemistry*
Academia Sinica, Taiwan

**Karin Markides***
*Chemistry*
Chalmers University of Technology, Sweden

**Rainer E. Metternich***
*Drug discovery/medical chemistry*
caprotec bioanalytics GmbH, Germany

**Takehiko Sasazuki**
*Medicine, immunology*
National Center for Global Health and Medicine, Japan

**Austin Smith**
*Stem cell biology*
University of Cambridge, UK

**Raymond Stevens**
*Structural biology*
The Scripps Research Institute, USA

**Sukekatsu Ushioda**
*Surface properties*
National Institute for Materials Science, Japan

**Hans L. R. Wigzell**
*Medicine, immunology*
Karolinska Institutet, Sweden

**Chi-Huey Wong**
*Chemical biology*
Academia Sinica, Taiwan

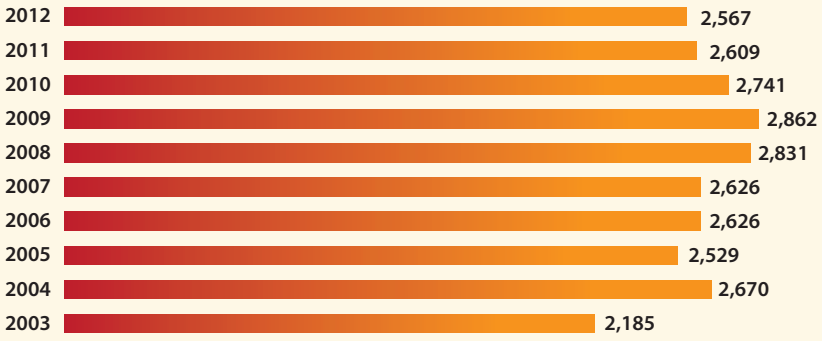
*Members who have served on both the 7th and 8th RIKEN Advisory Councils

# Research output

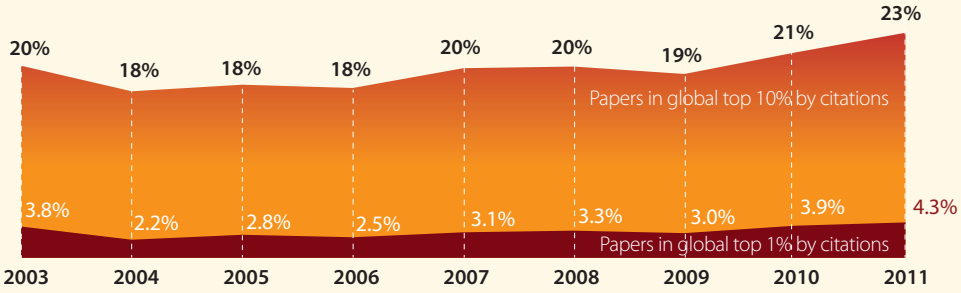
## World-class research

Cutting-edge, first-class research is at the heart of RIKEN's activities. The institution 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 around 20%, and the proportion of papers in the top 1% of most highly cited articles is steady at more than 3% since 2007.

**Papers published 2003–2012**




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




Source: Thomson Reuters Web of Science/Science Citation Index Expanded, May 2013
Essential Science Indicators has been updated as of May 1, 2013 to cover a 10-year-plus-two-month period (January 2003–February 2013).

## Communicating outstanding research

www.riken.jp/en/

Bringing the best of research from RIKEN to the international community and raising awareness of RIKEN as an international leader in scientific research are at the core of RIKEN's science communication strategy.

RIKEN is active on many fronts to achieve these aims, making use of a variety of channels to communicate with its different audiences within and outside Japan.

RIKEN's website is its face on the Internet and its main channel to reach a broad range of audiences including the general public, the international scientific community and the local RIKEN community. It has been designed to cater to the needs of these different groups, providing the latest news updates, research highlights and general information about working at RIKEN and living in Japan.

To communicate with an even broader audience, RIKEN is also present on social media, regularly posting on Twitter and YouTube in both English and Japanese.

Frequent press releases are issued to the Japanese and international media, ensuring that important research achievements are readily communicated to the public in a rapid and timely manner.

In addition, reports on outstanding research are published regularly, both online and in print format, in the magazine *RIKEN Research*, whose aim is to showcase the very best of research from RIKEN to the international scientific community.

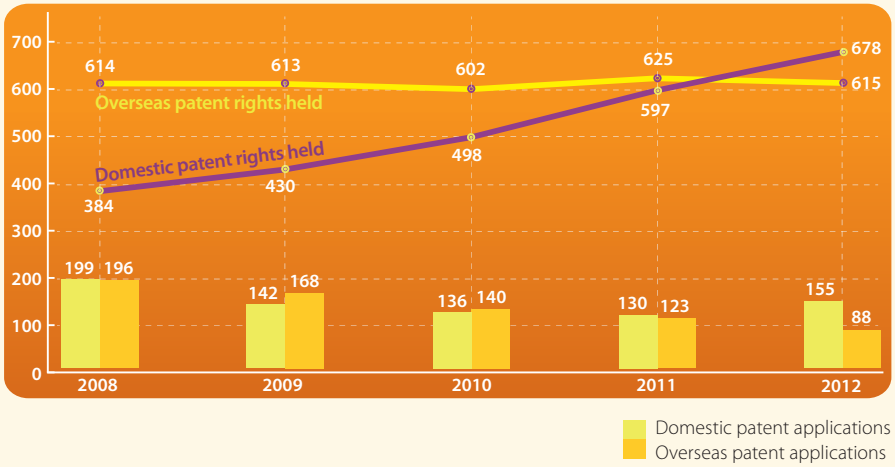
# Technology transfer

## Patent activity in 2012

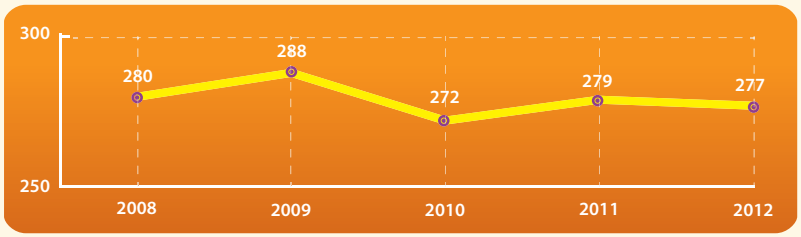
RIKEN not only disseminates its research results each year in top-tier science journals, it also actively harnesses those discoveries and inventions with commercial potential and secures legal protection for its research achievements by registering many patents every year. The Technology Transfer Office (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.

**680**
RIKEN patents are licensed in 2012

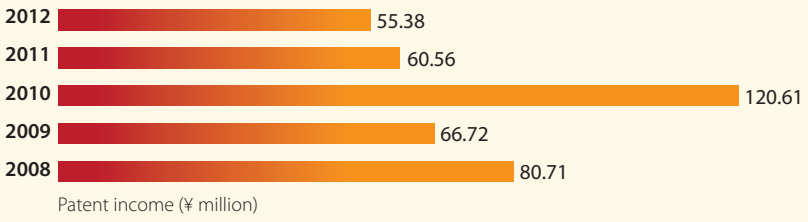
### Patent applications and registrations




### Contracts in place at the end of the fiscal year




### Patent income




## 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 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 2013, there were 11 active collaborative teams.

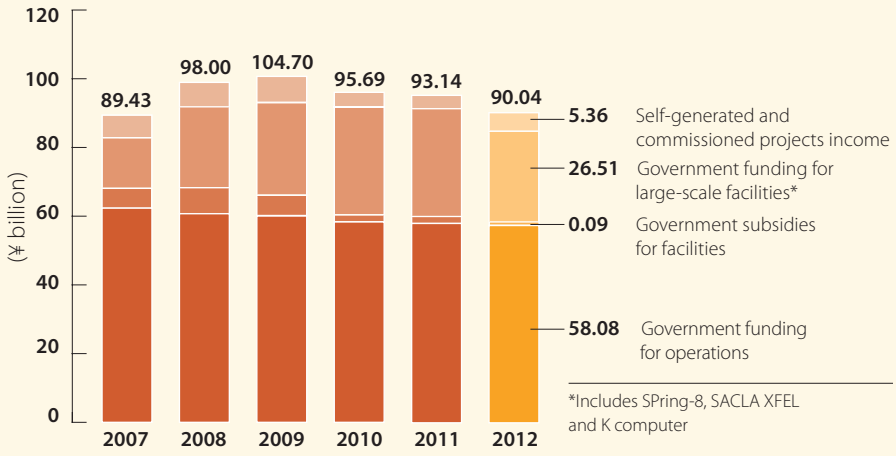
Industry–RIKEN Collaboration Centers
Based on proposals made by private companies, collaboration centers are set up in RIKEN institutes and centers to provide a research environment where a comprehensive relationship between the two parties accelerates the realization of medium- to long-term projects. As of March 2013, there were five 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 the total income of the past several years.




RIKEN's total income for 2012 was

**¥90.04 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.

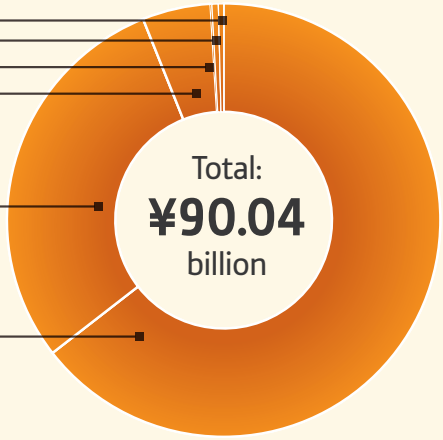
| Category | | FY2010 | FY2011 | FY2012 |
|---|---|---|---|---|
| | | | | ¥ million |
| Competitive funds | Grants-in-Aid for Scientific Research | 4,015 | 4,129 | 4,080 |
| | Grants-in-Aid for Scientific Research (MHLW, MOE) | 109 | 85 | 449 |
| | Special Coordination Funds for the Promotion of Science and Technology | 210 | 0 | 0 |
| | Projects funded by organizations that fund science and technology | 2,325 | 2,343 | 2,425 |
| | Basic Research Programs | 2,257 | 1,376 | 1,456 |
| | Other publicly supported projects | 556 | 552 | 384 |
| | Leading-edge Research Promotion Fund | 1,777 | 1,840 | 1,589 |
| **Sub-total** | | **11,249** | **10,325** | **10,382** |
| Non-competitive funds | Government-commissioned research | 2,178 | 1,787 | 2,417 |
| | Government-related commissioned research | 254 | 492 | 522 |
| | Government grants | 3,714 | 2,420 | 1,763 |
| | Contributions | 65 | 52 | 88 |
| **Sub-total** | | **6,211** | **4,751** | **4,790** |
| International grants and domestic foundation grants | | 330 | 231 | 309 |
| Private commissioned research | | 1,047 | 1,562 | 1,413 |
| **Total** | | **18,838** | **16,870** | **16,895** |

(as of March 2013)

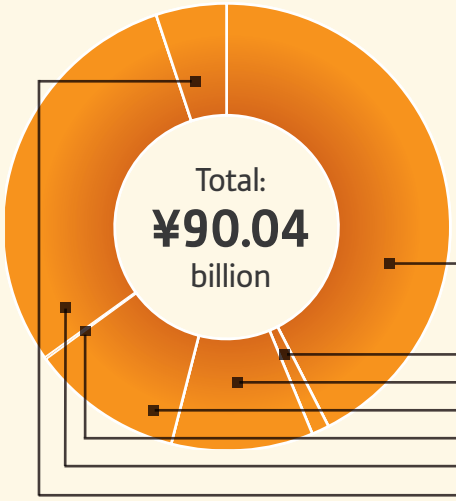
# Income

## Income by source 2012

| | |
|---|---|
| Income from shared use of large-scale facilities | 0.35 |
| Operational and non-operational income | 0.43 |
| Subsidies for facilities | 0.09 |
| Commissioned projects income | 4.59 |
| Subsidies for large-scale facilities | 26.51 |
| Funding for operations | 58.08 |




# Expenditure




## Expenditure by category 2012

| | |
|---|---|
| 38.24 | Centers and facilities |
| 1.14 | Innovation promotion |
| 9.22 | Research infrastructure management |
| 9.90 | Management costs |
| 0.09 | Facilities |
| 26.85 | Operation and construction of large-scale facilities |
| 4.59 | Commissioned projects |

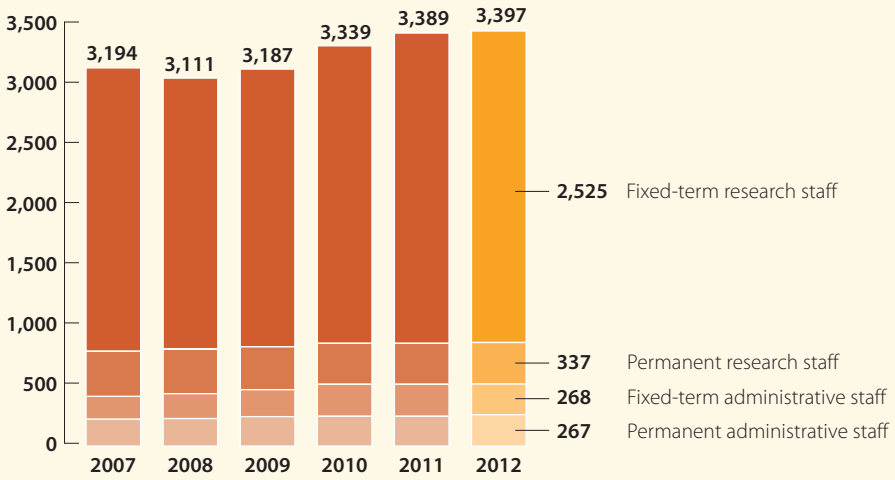
| Expenditure by research center | FY2012 (¥ billion) |
|---|---|
| Advanced Science Institute | 3.58 |
| Brain Science Institute | 8.16 |
| Plant Science Center | 1.13 |
| Research Center for Allergy and Immunology | 3.10 |
| Center for Genomic Medicine | 1.18 |
| Center for Developmental Biology | 3.86 |
| Center for Molecular Imaging Science | 1.19 |
| Nishina Center for Accelerator-Based Science | 3.44 |
| BioResource Center | 2.92 |
| SPring-8 Center | 1.90 |
| Life science platforms* | 2.78 |
| Yokohama Institute shared research funds | 1.69 |
| Research programs for green innovation | 1.21 |
| Quantitative Biology Center | 2.10 |
| **Total** | **38.24** |

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

# Personnel

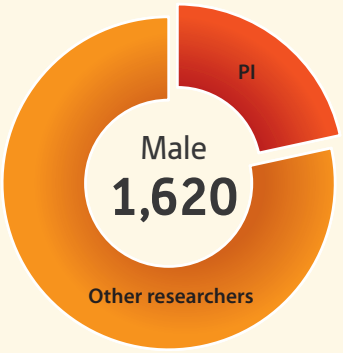
## Research and administrative employees

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.

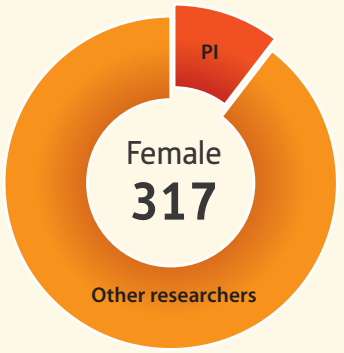



In 2012 RIKEN employed
**3,397**
research and administrative staff

## Diversity of RIKEN scientists

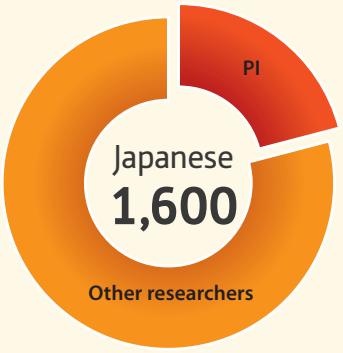



**350** Principal Investigators
**1,270** Other researchers

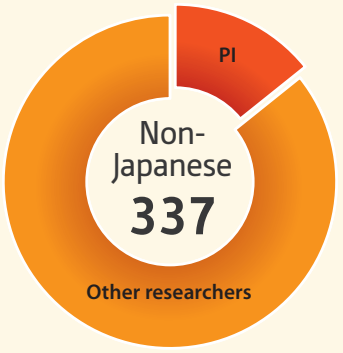



**33** Principal Investigators
**284** Other researchers

**1,937**
scientists work for RIKEN



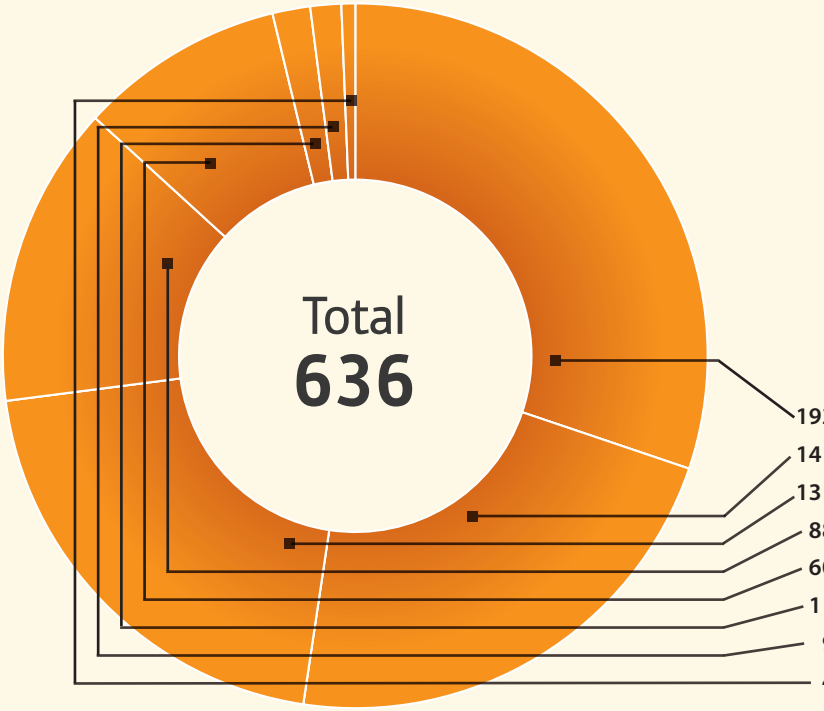

**335** Principal Investigators
**1,265** Other researchers




**48** Principal Investigators
**289** Other researchers

(as of March 2013)

## International staff, visiting scientists and students at RIKEN




**Region**

192 Europe
141 China
131 Asia-Pacific (excl. China and Korea)
88 South Korea
60 USA and Canada
11 Oceania
9 South America
4 Africa

### Europe
Armenia, Belarus, Belgium, Bulgaria, Croatia, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Moldova, Netherlands, Poland, Romania, Russia, Slovakia, Spain, Sweden, Switzerland, Turkey, Ukraine, UK.

### Asia
Bangladesh, China, Hong Kong, India, Indonesia, Israel, Iran, South Korea, Malaysia, Mongolia, Nepal, North Korea, Pakistan, Philippines, Singapore, Syria, Taiwan, Thailand, Vietnam.

### North America
Canada, USA.

### South America
Chile, Colombia, Brazil, Mexico, Peru.

### Oceania
Australia.

### Africa
Egypt, Kenya, Sudan.

**Total: 56 countries**

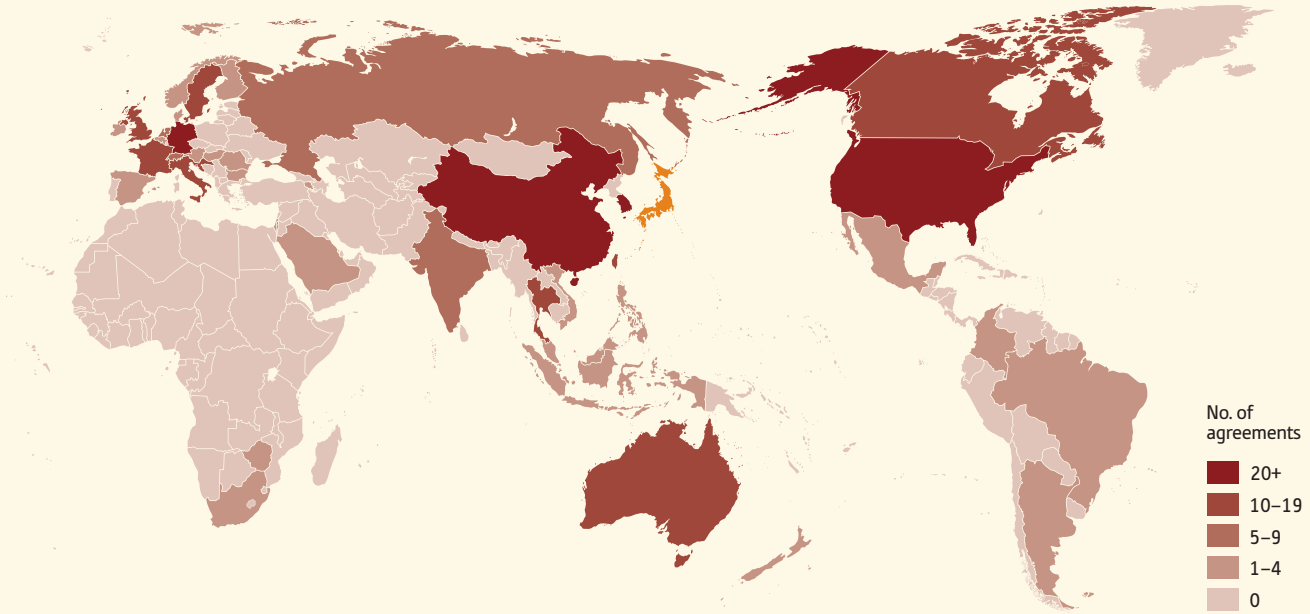
In 2012 RIKEN had **386** non-Japanese researchers and technical staff

and invited **250** visiting researchers and students

| Top 7 overseas countries and regions represented at RIKEN | | |
|---|---|---|
| 1 | China | 141 |
| 2 | South Korea | 88 |
| 3 | USA | 45 |
| 4 | India | 39 |
| 5 | France | 33 |
| 6 | Germany | 29 |
| 7 | UK | 27 |

(as of October 2012)

# International collaboration




| Region | No. of partner countries in each region | No. of collaboration agreements |
|---|---|---|
| North America | 2 | 69 |
| South America | 4 | 12 |
| Oceania | 2 | 21 |
| Asia | 11 | 161 |
| Middle East | 2 | 3 |
| Europe | 21 | 165 |
| Africa | 4 | 7 |
| **Total** | **46** | **438** |

(as of March 2013)

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) |
| | Universiti Sains Malaysia (USM) |
| 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 (BPPT) |
| India | Department of Science and Technology (DST) |

| NORTH AMERICA | |
|---|---|
| Canada | National Research Council Canada (NRC) |
| | McGill University |
| **SOUTH AMERICA** | |
| Brazil | Amazonas State University (UEA) |
| **OCEANIA** | |
| Australia | Australian Commonwealth Scientific and Industrial Research Organisation (CSIRO) |
| **MIDDLE EAST** | |
| Israel | Weizmann Institute of Science |
| **EUROPE** | |
| Sweden | Karolinska Institutet (KI) |
| UK | 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 2013)

# RIKEN directory

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