RIKEN

ANNUAL REPORT
2010–2011

Science Serving Society

Message from the President

The peace and calm of fiscal year 2010 was shattered on March 11, 2011, a few weeks before the end of the year, by a natural calamity of historic significance. A massive earthquake struck the Pacific coast of eastern Japan, followed by the giant tsunami and the subsequent crippling of the Fukushima Daiichi Nuclear Power Plant. This disaster has had a deep impact on science and technology research.

The calamity of March 11 is a painful reminder that though we benefit from the bounties of the natural world, we must never forget that nature can also be harsh and brutal. It was a devastating experience, and we will need to work hard to bring about a rebirth of the Tohoku region and indeed all of Japan. In this respect, I would like to mention that some RIKEN personnel, both Japanese and from abroad, were quick to volunteer to help the victims in the affected areas, cooking and distributing meals and clearing the debris. Also, RIKEN radiation experts went to areas close to the Fukushima Daiichi Nuclear Power Plant to assist in checking residents for exposure to excessive radiation.

This experience has reinforced our conviction that the great mission of science and technology is to promote the survival of the human race, the preservation and prosperity of nations, and our achievement of a fulfilling life. For Japan, which is sorely lacking in natural resources, prowess in science and technology is vital to our survival as a viable nation with a strong global presence.

More than ever, RIKEN must ask what it can do, as a core research institution in Japan, to contribute to Japan's global presence and to make scientific contributions with global impact. For this, we must attract excellent researchers from around the world, and also encourage our own researchers to go overseas, to help build a global system for the cross-migration of extremely talented scientists and technologists.

This devastating natural calamity has brought to the fore a number of urgent global issues. To solve these issues, we must bring together a wide range of scientific and technological knowledge. Now is the time to undertake the urgent task of reforming the entire structure of research in science and technology. I believe the national policy of Japan should involve not just science and technology (ST), not even just science, technology and innovation (STI), but additionally 'rebirth' and 'reform' for an all-encompassing policy of 'STIR'.

The acronym STIR implies 'mixing' and 'mingling'. It is my strong belief that we need to promote a process of 'mingling', not only of different scientific fields but between the natural sciences and society, and between Japan and the rest of the world. Only this kind of meeting and synthesis of ideas can enable a rebirth of Japan as a new nation with global influence.

In this spirit of mixing, Yasunori Yamazaki of the RIKEN Advanced Science Institute achieved a major scientific breakthrough this year, producing antihydrogen in work undertaken as part of an international collaborative group with CERN. Likewise, a comprehensive collaborative agreement with the Max Planck Institute signed this year promises to lead to new science and technology fields that are cross-boundary and interdisciplinary. As Japan's flagship research institution, RIKEN is committed to playing a major role in promoting the rebirth of society through these kinds of collaborations as well as through our own original research.

The scientific achievements described in this year's Annual Report have been selected as illustrations of our determination to carry out our mission and further establish RIKEN's role as a global leader for scientific research.

NOYORI Ryoji (DEng)
President, RIKEN

Introduction to the RIKEN Annual Report 2010–2011

RIKEN is a core research organization in Japan and an internationally acknowledged leader in a wide range of scientific disciplines. An independent administrative institution funded substantially by the Japanese government, RIKEN's occupies an important position in Japanese society as shown by its response to the recent Tohoku-Kanto earthquake, where it was able to place its knowledge and expertise at the service of the nation. More than ever, RIKEN is determined to maintain a commitment to fundamental research in the natural sciences, and drive national scientific development by promoting international collaboration and raising the profile of Japanese science at home and abroad.

RIKEN is proactive in seeking to promote an appreciation for science and technology in the public sphere as the foundation for our modern economy and way of life. The basis for this lies in RIKEN's support for curiosity-driven research that leads to the scientific discoveries that will shape our future—a role that has grown out of its unique history and research culture, and for which it is renowned internationally.

The RIKEN Annual Report is much more than a simple statement of the financial and academic performance of RIKEN over the past financial year. It also seeks to provide a window into its centers and institutes, their latest research achievements and future directions. This year's Annual Report is divided into four sections: Introduction, Inside RIKEN, Opportunities for International Scientists, and Performance and Organization. The Introduction (starting page 4) features a roundup of news stories from RIKEN over the year, a brief history of the development of RIKEN and a summary of RIKEN's presence in Japan. Inside RIKEN (starting page 9) presents profiles of the five main RIKEN institutes at Wako, Tsukuba, Yokohama, Kobe and Harima and touches on the diverse range of research that is carried out there across the entire range of the natural sciences from astrophysics and quantum science, to cell biology and neuroscience. This section outlines the key roles that each of the centers and institutes play in the mission of RIKEN and showcases some examples of their research successes of the past year. The third section of the Annual Report commencing on page 41 outlines programs targeted at attracting international researchers to join the RIKEN team, including the Initiative Research Unit Program, the Foreign Postdoctoral Researcher Program, the International Program Associate and visiting scholar programs.

The final section of the Annual Report (starting page 47) summarizes information relating to the organization and performance criteria for the 2010–2011 fiscal year. The section commences with a description of the governance of RIKEN and details of the Advisory Council. Following this is a statistical account of RIKEN's financial and research performance over the period. Despite recent difficulties, RIKEN has maintained its commitment to supporting and developing its creative research culture and championing the need for expanded research funding and facilities. As the figures show, RIKEN has remained steadfast in pursuing its key performance criteria—research publications, patent applications, commercialization, funding sources and workforce diversity—and continued with its proactive approach of recruiting talented non-Japanese researchers through its international support programs to make it easier than ever before for young and highly recognized researchers from abroad to join RIKEN and contribute to research at the forefront of science.

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Annual news roundup

Making a mark

The 2010–2011 fiscal year proved to be yet another of scientific excellence at RIKEN, whose researchers have extended their influence across the world to make major contributions to international research. Whether reaching beyond the limit of the known isotopes, trapping antimatter or probing the frontiers of the human mind, RIKEN researchers continue to open new worlds in science.

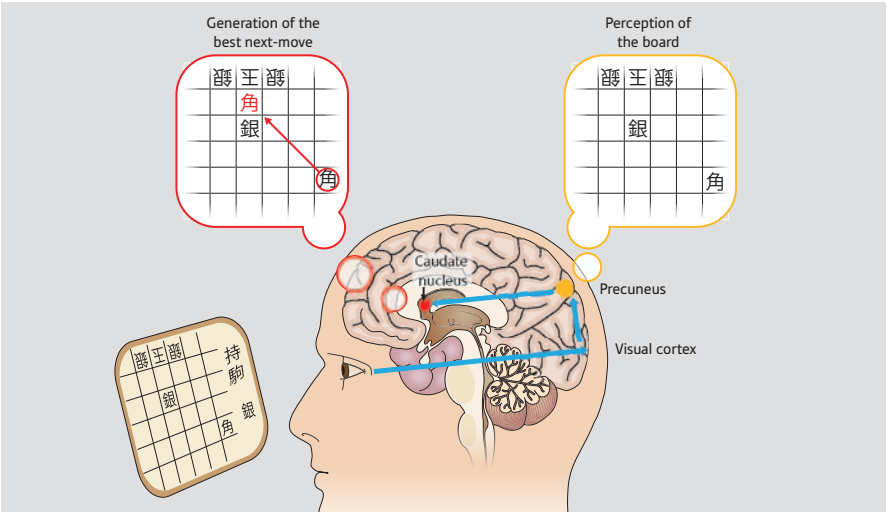
RIKEN RESEARCHERS IDENTIFY THE ORIGINS OF EXPERT INTUITION

In January 2011, scientists at the RIKEN Brain Science Institute (BSI) achieved an important step forward in uncovering the neural mechanisms underpinning cognitive expertise in board game play. Writing in the renowned journal *Science*, a team led by Keiji Tanaka described a series of studies that compared the way in which professional and amateur players of *shogi*, a Japanese board game akin to chess, analyze the state of play in a game to determine their next move. Although the psychological study of board game strategies has been ongoing for more than a century, until recently relatively little was known about the fundamental underlying neural mechanisms that govern behavior in these situations.

The BSI team used functional magnetic resonance imaging—a non-invasive technique that pinpoints which areas of the brain are active at any given moment—to analyze the response at the neural level of professional *shogi* players to a number of different game patterns. They then compared these with the reactions of high- and low-ranked amateur players to the same problems. In the experiment, players were asked to nominate their next best-move responses to a range of different board patterns after being shown the problem for either one or eight seconds with the expectation that the response to the one-second, short-term problem would be expected to rely solely on intuition, whereas the response to the eight-second, longer-term scenario would be the product of conscious analysis.

The researchers discovered that when faced with generating next-move options in response to short-term problems, the brains of professional *shogi* players displayed activity in the caudate nucleus of the basal ganglia, a more primitive region of the brain. In the case of long-term problems, activity switched to the precuneus of the parietal lobe in the cerebral cortex, a region of the brain responsible for the integration of sensory information. By contrast, the response of amateur players to both short- and long-term problems arose from the cerebral cortex alone. The experiments provide solid evidence for the first time of the difference between the brains of professionals and amateurs and strongly suggest that the brain of an expert *shogi* player is able to perceive board patterns rapidly and generate next-moves instantaneously without recourse to conscious thought. The strong correlation discovered between the precuneus and caudate nucleus of the basal ganglia in the brains of the expert players suggests that the precuneus–caudate circuit has been optimized for rapid response to gameplay situations.

The BSI work is a crucial first step in understanding the elusive origins of expert intuition and establishing a vital link between brain science and cognitive psychology, opening the door to the design of new types of expert systems.



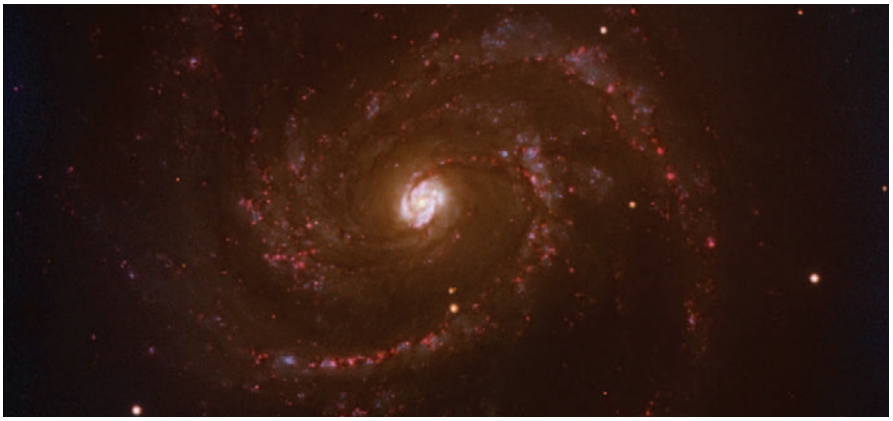
After seeing the state of play, professional *shogi* players respond intuitively to a game situation by recognizing the pattern in the precuneus area of the brain, which passes to the caudate nucleus for a response.

Wan, X. *et al.* The neural basis of intuitive best next-move generation in board game experts. *Science* 331, 341–346 (2011).

STELLAR PHYSICS BROUGHT DOWN TO EARTH

As part of RIKEN's mission to push back the frontiers of basic science, scientists from the RIKEN Nishina Center for Accelerator-Based Science (RNC) led by Toshiyuki Kubo have used the next-generation heavy ion superconducting ring cyclotron at the Radioactive Isotope Beam Factory (RIBF) to create a slew of new, heavy radioactive isotopes—unstable variants of chemical elements containing different numbers of neutrons than the stable types. The newly discovered isotopes cover a region of the nuclear chart that has never before been explored.

In a flurry of scientific productivity, the researchers took only four days to create no fewer than 45 previously unknown radioisotopes using the RIBF, which accelerates atoms of uranium-238 to 70% of the speed of light to be bombarded against targets made of the metals beryllium and lead. These collisions produce an array of exotic, often short-lived radioisotopes that were detected using an extremely sensitive radioactive isotope beam separator called BigRIPS. The group of researchers at the center of these recent



The high neutron flux in the heart of supernovae is needed for the process that underlies the synthesis of half the elements heavier than iron. Research on unstable isotopes using the RIBF provides insight into such processes.

discoveries has been working on the design and construction of the BigRIPS beam separator for more than 10 years, and its use has finally allowed the researchers to distinguish between individual isotopes.

The researchers' work, which was published in the *Journal of the Physical Society of Japan*, led to the creation of radioisotopes of elements ranging from manganese to barium. However, the creation of palladium-128 garnered special attention due to the fact that its nucleus contains 82 neutrons, one of the so-called 'magic numbers' of neutrons that confers the isotope with unusually high stability.

This work is just one of many important discoveries made at the RNC—named after Yoshio Nishina, a pioneering figure of pre- and postwar physics in Japan—since its inauguration in 2006. The RIBF, construction of which was commenced in 1997, is at the heart of the RNC, providing the highest-intensity radioactive isotope beams in the world. In past years, this has allowed RIKEN scientists to discover other important isotopes such as palladium-125 and palladium-126. Refinement of the cyclotron setup is continually delivering higher beam intensities, with the ultimate target to deliver intensities over 1,000 times higher than current levels. It is anticipated that the ongoing development of the facility will stimulate the formation of even more international collaborations with physicists wishing to study the conditions of the very early Universe and the state of matter in the heart of supernovae.

Ohnishi, T. *et al.* Identification of 45 new neutron-rich isotopes produced by in-flight fission of a ^{238}U beam at 345 MeV/nucleon. *J. Phys. Soc. Jpn* **79**, 073201 (2010).

GOING TO THE HEART OF THE ANTIMATTER

RIKEN scientists are at the forefront of international efforts to expand our understanding of antimatter. In a study published in 2010 in *Physical Review Letters*, researchers from RIKEN reported the first experimental setup and technique for measuring important fundamental quantities, known as ground-state hyperfine transitions, of antihydrogen.

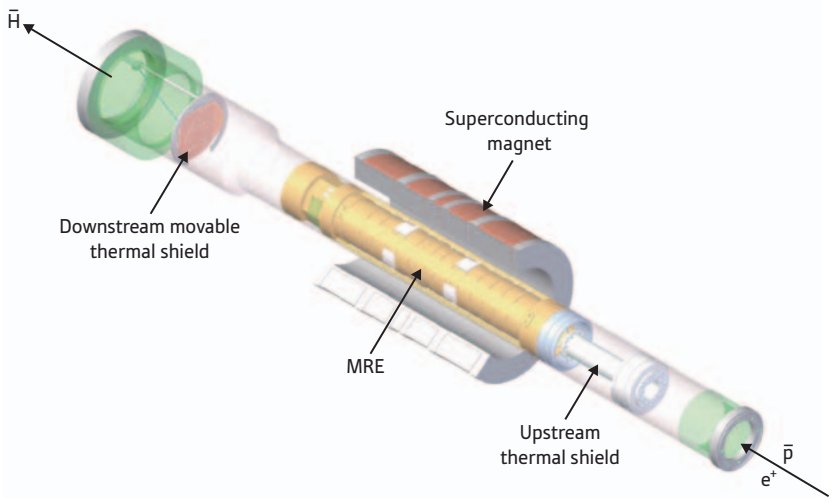
Antihydrogen, the antiparticle equivalent of hydrogen, is the simplest of all 'antiatoms', and was first produced in large quantities in 2002 and finally isolated only in 2010 at the European Organization for Nuclear Research (CERN) in Switzerland by a team including scientists from RIKEN. Antiatoms such as antihydrogen are of interest to scientists as they allow stringent testing of a phenomenon known as CPT symmetry, a fundamental symmetry in physics that is expected to explain why the Universe is composed almost entirely of matter rather than antimatter.

The new technique, developed by an international team led by RIKEN researchers, uses symmetrical magnetic fields to funnel antiprotons and positrons, the alter-egos of protons and electrons from which normal hydrogen is composed, into a 'cusp' trap to assemble atoms of antihydrogen. A key strength of the new technique is the high efficiency with which the constituent antiparticles are converted into atoms of antihydrogen—some 7% of antiprotons introduced into the experimental setup were successfully incorporated.

The new setup is an important precursor to developing the capacity to generate antihydrogen as a beam. The development of such a system would represent a significant improvement on current methods, which require the antihydrogen to be trapped and isolated—a much more challenging task. It would also allow the extraction of antihydrogen atoms as a higher-density source of the antiparticle in a magnetic-field-free environment—a key requirement for analysis by high-precision microwave spectroscopy.

With these achievements under their belts, RIKEN researchers are looking to the future and the full development of an antihydrogen beam which will, it is hoped, bring scientists one step closer to solving one of the most fundamental puzzles in science: the scarcity of antimatter in the Universe.

Enomoto, Y. *et al.* Synthesis of cold antihydrogen in a cusp trap. *Phys. Rev. Lett.* **105**, 243401 (2010).



The central section of the 'cusp' trap for capturing antiprotons.

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

1987 RIKEN's ring cyclotron completed

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

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

Brain Science Institute established in Wako

RIKEN BNL Research Center established at Brookhaven National Laboratory, USA

1998 Genomic Sciences Center established in Yokohama

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

Center for Developmental Biology established in Kobe

2001 BioResource Center established in Tsukuba

Research Center for Allergy and Immunology established in Yokohama

2002 Discovery Research Institute established in Wako

Kobe Institute established

PRIVATE RESEARCH FOUNDATION AND CORPORATION PERIOD (1917–1958)

PUBLIC CORPORATION PERIOD (1958–2003)

1913

The birth of the RIKEN Spirit

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

1997

Japanese photon science enters a new age

With the construction of the SPring-8 third-generation synchrotron radiation facility in Harima in 1997, RIKEN was instrumental in bringing Japan to the forefront in photon science—a testament to the successful partnership between RIKEN and the Japan Atomic Energy Research Institute in its development. The RIKEN Harima Institute established on the site of the SPring-8 complex in 1997 continues to advance the field of accelerator science and develop new uses for this world-class research facility.

2003 RIKEN reorganized as an Independent Administrative Institution

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

2007 Molecular Imaging Research Program established in Kobe

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

INDEPENDENT ADMINISTRATIVE INSTITUTION PERIOD (2003–)

2004 Discovery of element 113 by RIKEN researchers

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

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

2011 SACLA X-ray Free-Electron Laser (XFEL) facility completed in Harima

Superconducting Ring Cyclotron at the RIBF

2004

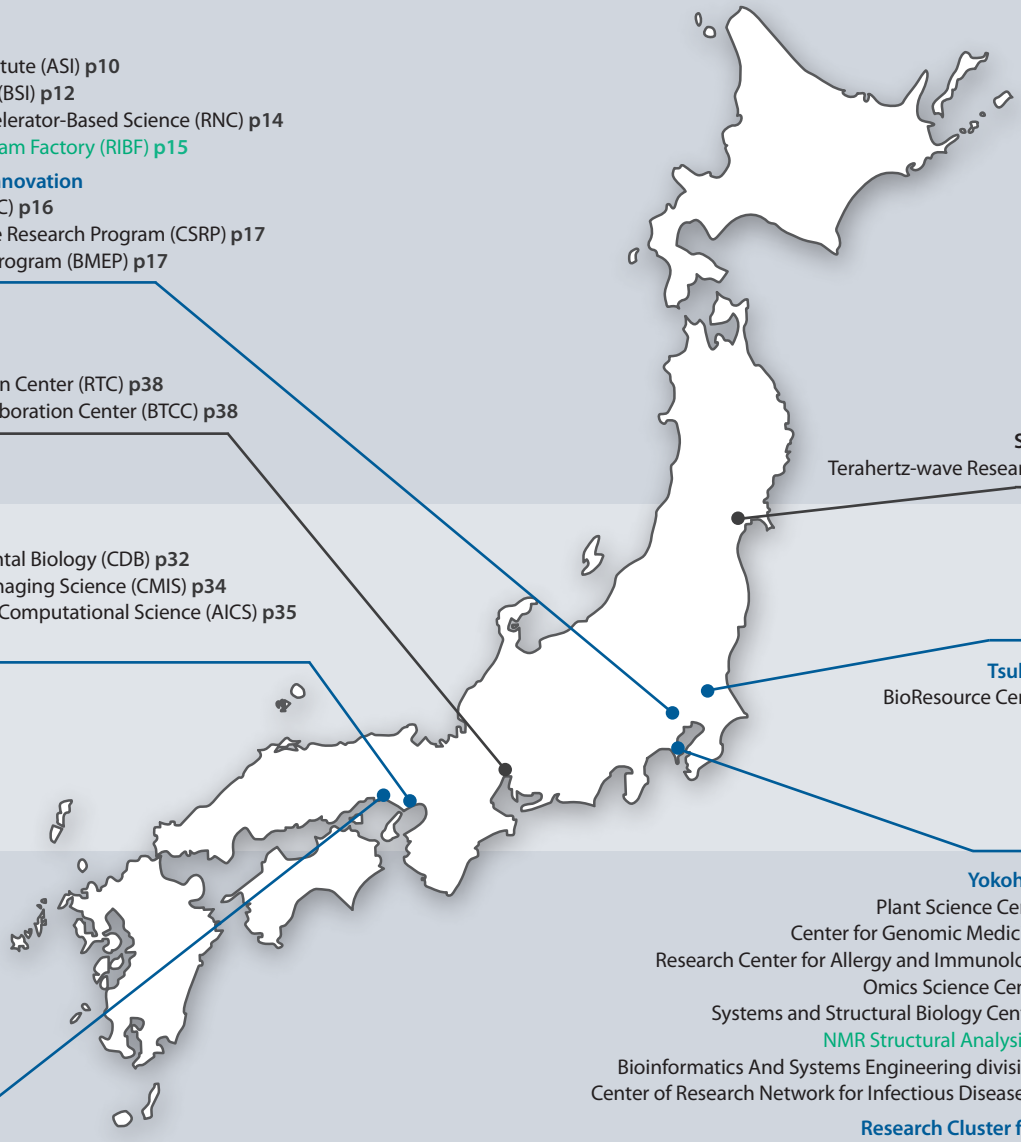
The discovery of element 113

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

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. RIKEN now supports five major institutes and two research facility sites across Japan. It also maintains two major research facilities: the K computer under construction on Kobe Port Island and the SPring-8 synchrotron radiation and SACLA X-ray Free Electron Laser (XFEL) facilities in Harima.



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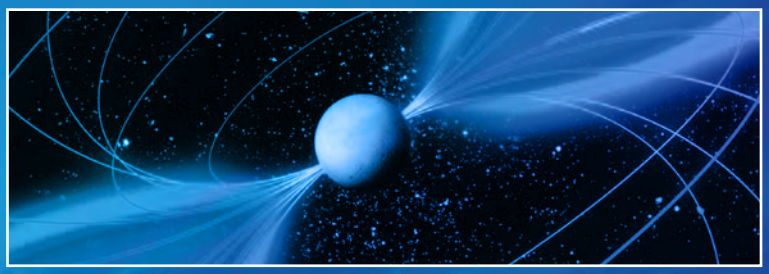
INSIDE RIKEN



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.

Kohei Tamao

WAKO INSTITUTE

RIKEN Advanced Science Institute

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

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

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

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

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

The institute's impressive list of research achievements in 2010 is a testament to the effectiveness of the ASI's approach to research. These achievements includes the top physics breakthrough of the year according to *Physics World*. "Yasunori Yamazaki from the ASI's Atomic Physics Laboratory and his colleagues participated in an international research project at CERN that successfully trapped and manipulated antihydrogen atoms," says Tamao. The achievement marks a milestone

in fundamental physics (see *Antimatter atoms ready for their close-up*).

Also in physics, a collaborative team involving ASI researchers demonstrated for the first time the generation of intense, fully coherent light pulses at extreme ultraviolet wavelengths using the SPring-8 compact self-amplified spontaneous emission source (SCSS)—the X-ray Free Electron Laser prototype—at the RIKEN Harima Institute, paving the way for frontier research in the soft X-ray and X-ray regions (*Opt. Express* **19**, 317–324, 2011). In biology, Tsutomu Tsuchida and Shogo Matsumoto of the ASI and colleagues discovered a symbiotic bacterium that modifies the body color of aphids, suggesting new perspectives for understanding biological ecology and environmental adaptation (*Science* **330**, 1102–1104, 2010). In chemistry, Mikiko Sodeoka and colleagues also succeeded in a world first with the total synthesis of chaetocin in work that is expected to lead to the development of new anticancer drugs (*J. Am. Chem. Soc.* **132**, 4078–4079, 2010).

In tandem with its strong internal promotion of innovative research, the ASI is also active in securing closer ties with some of the world's most prestigious research institutes. In early 2011, the ASI established a joint research center with the Max Planck Institute in Germany. "The RIKEN–Max Planck Joint Research Center will develop the already strong research collaboration in chemical biology between the ASI and the Max Planck Institute," says Tamao.

The coming year also marks a number of other project starts at the ASI, including a new environmental initiative as part of the 'Green-forefront Materials' department. "This year we will launch a new team within that department to develop thin-film organic photovoltaic devices for next-generation solar-energy conversion," says Tamao. "That's the great thing about the ASI, we can bring together the best researchers to develop new science."

Upmost in the minds of many researchers, of course, are the calamitous events of March 2011 in Northern Japan. "The ASI will continue to strive to steadily pursue basic research in all disciplines of the natural sciences and technology under any conditions, including the extraordinary situation following the disasters in Japan this year. The ASI's unique systematic research structure must be maintained and even strengthened in order to assist in implementing national strategies and policies."

Antimatter atoms ready for their close-up

Controlling antihydrogen atoms using two different methods brings physicists closer to answering quantum and cosmic questions

Two international teams of physicists, including RIKEN researchers, have trapped and manipulated antihydrogen atoms in milestone experiments that should help to reveal why antimatter is so rare in our Universe.

The simplest and most abundant atom in the Universe—hydrogen—consists of a positive proton and an electron. Its opposite number, antihydrogen, contains a negative antiproton and a positron, and teaming the antiparticles without allowing them to touch any ordinary matter is a ticklish business. In parallel research efforts, known as ALPHA and ASACUSA, the international teams of physicists have shown how to handle antihydrogen atoms in a way that will soon allow their properties to be investigated precisely and compared with normal hydrogen. Physicists are keen to make this comparison because one of the foundations of modern quantum physics—the charge, parity and time reversal symmetry theorem—states that hydrogen and antihydrogen should have identical energy levels, producing matching spectra when probed with light.

"The challenge is the temperature of antihydrogen atoms," says Yasunori Yamazaki of the RIKEN Advanced Science Institute, who is involved with both the ALPHA and ASACUSA experiments. Fast-moving antiprotons as hot as 100,000 kelvin must be chilled to less than 0.5 kelvin to form trappable antihydrogen.

In recent experiments, the ALPHA researchers collided about 30,000 antiprotons with electrons to cool them to roughly 200 kelvin in a cloud about 1.6 millimeters across. They cooled a separate pool of positrons by allowing the hotter particles to 'evaporate' away from the rest, leaving a 1.8 millimeter-diameter cloud of about two million particles at roughly 40 kelvin. The researchers slowly coaxed the antiprotons towards the positrons by changing the electric field, and allowed them to mix for just a second. They then removed all unreacted antiparticles from the trap, and after about 0.2 seconds opened the magnetic bottle to look for trapped antihydrogen atoms. As the trapped antihydrogen atoms were released, they drifted towards the sides of the trap, where they annihilated, emitting energetic 'pions', which were registered by silicon detectors around the bottle. Overall, they found 38 trapped antihydrogen atoms from 335 experimental runs[1].

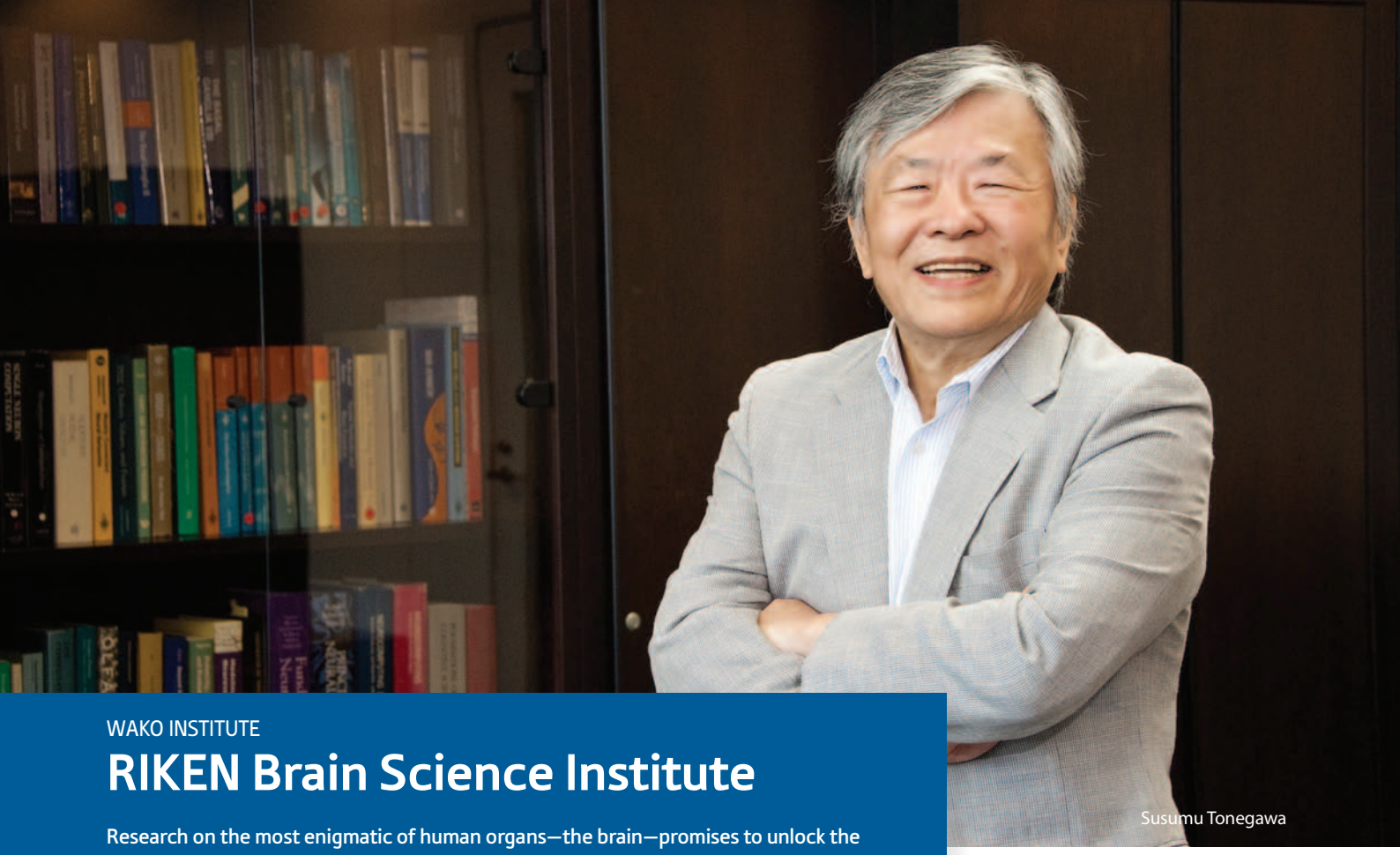
Yamazaki thinks that antihydrogen could be trapped for much longer, and the ALPHA team is now making preparations for laser spectroscopy measurements to confirm this possibility. The strong magnetic field gradient of the magnetic bottle, however, means that high-resolution spectroscopy is not straightforward.

The ASACUSA experiment, on the other hand, collects antiprotons and positrons in a 'cusp trap', where the use of symmetrical magnetic and electric fields allows large numbers of antiprotons and positrons to be trapped stably. Recent experiments have shown that the cusp trap can successfully synthesize antihydrogen atoms[2].

This approach has unique advantages, says Yamazaki. "First of all, we can extract antihydrogen atoms as an intensified spin-polarized beam in a magnetic-field free region, which enables high-resolution spectroscopy of ground state hyperfine transitions. Secondly, the temperature of the antihydrogen atoms can be much higher—say 10 kelvin—which makes it orders of magnitude more efficient to synthesize a usable number of antihydrogen atoms," explains Yamazaki. "We think we can confirm the beam next year, and if everything goes well, we can also get some spectroscopic results for the first time. I feel that these two achievements are really big milestones towards realizing low-energy antimatter physics for the first time."

[1]Andresen, G. B. *et al.* Trapped antihydrogen. *Nature* **468**, 673–676 (2010).

[2]Enomoto, Y. *et al.* Synthesis of cold antihydrogen in a cusp trap. *Phys. Rev. Lett.* **105**, 243401 (2010).



Susumu Tonegawa

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.

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

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

In the past year, researchers from the BSI reported exciting findings across the spectrum of brain science. In a recent study, Keiji Tanaka and his colleagues investigated patterns of brain activity in the brain of experts of a challenging intellectual game called *shogi*. Their findings show that experts process advanced problems in a different part of the brain compared with non-experts and that mastering a skill involves changes in the location of brain function (see *Revealing how experts' minds tick*).

The BSI's Hitoshi Okamoto and colleagues recently reported a study on the brain regions governing fear behavior in zebrafish—a model organism for brain research. By expressing fluorescent proteins in the zebrafish brain as genetic tracers, they revealed the existence of a specific pathway connecting the habenula to a structure that is likely to correspond to regions in the mammalian brain implicated in the modulation of fear behavior. In the future, these findings may contribute to the treatment of fear-related disorders, such as anxiety and post-traumatic stress disorder (*Nature Neurosci.* **13**, 1171–1180, 2010).

In developmental neurobiology, a team led by Hiroyuki Kamiguchi reported the discovery of a fundamental mechanism underlying neuron development. Newborn neurons extend axons toward distant targets guided by the repulsion and attraction of a dynamic structure at the growing axon tip called the growth cone. The team showed that the growth cone turns in response to repulsive cues by a process called endocytosis, whereby portions of the cone's membrane are removed and internalized resulting in steering of the growth cone away from the cue (*Neuron* **66**, 370–377, 2010).

These discoveries and others by BSI laboratories represent groundbreaking achievements today, yet the BSI realizes that fostering the next generation of young researchers is essential for the sustainable development of the neuroscience community. In 2010, the BSI established the Brain Science Training Program to provide basic training for a select group of graduate students from Japanese universities throughout the year. The program is developed in close collaboration with the BSI's academic partners and takes full advantage of the diversity of expertise within the institute.

The BSI also organizes the BSI Seminar Series, at which young researchers can meet world-class scientists from across the globe. In addition, the BSI Summer Program for graduate students offers the choice of a two-month laboratory internship in a BSI laboratory, or an intensive two-week lecture course featuring distinguished international faculty, providing a

unique opportunity for young researchers to visit Japan to advance their scientific knowledge. Applications are received from around the world and 85% of the roughly 50 students selected for the program come from overseas universities.

Some Summer Program participants eventually come back to the BSI as investigators or researchers. In fact, 20% of the institute's 500 researchers and technical staff are from overseas, representing over 30 countries. However, the internationalization of the institute extends beyond its on-campus researchers. The BSI conducts research with major academic institutions overseas like the Massachusetts Institute of Technology (MIT), where the BSI supports a joint research center with the MIT's Picower Institute for Learning and Memory—the RIKEN–MIT Center for Neural Circuit Genetics.

The partnerships forged by the BSI also extend to industrial collaborations. In addition to a number of joint research projects with private corporations, the BSI has two major collaborative centers—the RIKEN BSI–Toyota Collaboration Center and the RIKEN BSI–Olympus Collaboration Center. Through such partnerships with industry, the BSI strives to find ways to benefit society by applying basic knowledge gained from research to the development of useful products for business ventures.

In the continuing effort to globalize, the BSI is extending growth and innovation beyond research to its administration. A significant recent development is the hiring of Charles Yokoyama, former senior editor of the journal *Neuron*, as the BSI's director of research administration, to lead efforts in improving research manuscript performance and to coordinate strategy in international interactions. His work has already made a substantial impact on the quality of research manuscripts from the BSI.

As expectations for brain science grow, and the responsibility of researchers to make fundamental discoveries for the benefit of society increases, the role played by the BSI in basic and translational brain research is taking on a greater level of significance. One key area of basic research being developed at the BSI is the elucidation of neural circuit functions. In 2011, the Neural Circuit Genetics Research Building was established in the campus and serves as a beacon for the recruitment of talented young scientists from all over the world to energize the important mission of the BSI. "I've been at the reins of the BSI for two years now," says Tonegawa, "so I know how important it is for the institute to continuously evolve."

Revealing how experts' minds tick

Neural activity representing intuitive responses in the brains of professional board game players shows what sets experts apart

Primates, particularly humans, are set apart from other vertebrates by more than a huge expansion of the cerebral cortex, the region of the brain used for thinking. The connection and coordination of the cerebral cortex with other, older parts of the brain also play a significant role, according to findings published recently in *Science* by a research team from the RIKEN Brain Science Institute (BSI) in Wako.

The researchers, led by Keiji Tanaka, found that professional players of the Japanese chess-like game of *shogi* can use part of brain associated with intuitive or habitual behaviors to establish a best next-move in a way that distinguishes them from amateurs. One result of experience and training seems to be the ability to shunt some immediate neural tasks from the cerebral cortex to the more intuitive basal ganglia, leaving the cortex free for planning higher-level strategy.

"Our findings may be regarded as showing that in amateur players problem-solving occurs mostly in the newly developed brain structure, but in professionals an important part of the process goes to the old brain structure," Tanaka says. "This shift makes the process quick and unconscious."

Investigating mechanisms of higher brain functions of decision making has been one of the prime interests of Tanaka's laboratory at the BSI. An important question in this field, which has long been a subject of inquiry, is how experts differ from the rest of us.

The psychological study of board game players has led researchers to propose that expert chess players perceive patterns more quickly than amateurs by matching them to a series of stereotyped arrangements known as 'chunks'. The theory is that these chunks are associated with best next-moves in the long-term memory of expert chess players, so they can use them as a rapidly accessed starting point for responding to the problem.

To test this theory, Tanaka and his colleagues worked with groups of professional and high- and low-rank amateur players of *shogi*. They studied short- and longer-term responses of players when asked to plot the best next-move in various *shogi* problems, akin to chess problems. *Shogi* problems can be more complex than those of chess because captured *shogi* pieces are allowed to re-enter play on the side of the player who has taken them.

Members of Tanaka's team with significant expertise in functional magnetic resonance imaging (fMRI) used this non-invasive technique to pinpoint which parts of the brain are active at a particular time. They initially presented *shogi* players with board game patterns of different types as well as other completely different stimuli such as scenes and faces. The board game patterns, but not the other scenes, stimulated activity in the posterior precuneus region of the cerebral cortex of all *shogi* players. Previous fMRI studies have shown that the precuneus is generally associated with tasks involving visuo-spatial imagery, the relationship of shapes to one another. In this study, activity was particularly strong in professional players presented with *shogi* opening and endgame patterns. The researchers suggest this is associated with pattern recognition specific to their area of expertise.

The players were also asked to nominate the best next-move in a series of *shogi* problems given one or eight seconds to study the presented pattern. In the one-second case, professional players, and not the amateurs, displayed activity in the caudate nucleus of the older, more primitive part of the brain, the basal ganglia. In the eight-second case, the neural activity was confined to the cerebral cortex. The researchers propose, therefore, that development of an intuitive response is a result of the training and experience that marks experts.

"To further elucidate processes of intuitive problem-solving," says Tanaka, "we need to establish primate models, in which a wider range of experimental methods can be applied."

Wan, X. *et al.* The neural basis of intuitive best next-move generation in board game experts. *Science* **331**, 341–346 (2011).

WAKO INSTITUTE

RIKEN Nishina Center for Accelerator-Based Science

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

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

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

In 2006, the RNC's research facilities were given a huge boost with the introduction of the Radioactive Isotope Beam Factory (RIBF), a next-generation heavy-ion research facility, which researchers are using to shed some light on the ultimate picture of nuclei and thus propel forward our understanding of how heavy elements were first formed in the Universe. Although other facilities with comparable capabilities are under construction

Hideto En'yo

at other leading nuclear physics laboratories around the world, such facilities take many years to bring online. "The RIBF will probably maintain its unrivalled position in the world for another 10 years," says En'yo.

Results published in fiscal 2010 by the RNC reflect the significant and central role of the RIBF in the center's research. Using the RIBF and a new, highly sensitive projectile fragment separator called BigRIPS, Hiroyoshi Sakurai and Shunji Nishimura recently led a research team in the first-ever measurement of the half-lives of 18 rare isotopes. The data provide a long-awaited test of theoretical predictions and will help nuclear physicists understand the 'r-process'—a fundamental source of many of the atomic elements heavier than iron (*Phys. Rev. Lett.* **106**, 052502, 2011).

A team of researchers led by Pieter Doornenbal from the RNC also used the capabilities of BigRIPS to produce three exotic isotopes of sodium—^{31}Na, ^{32}Na and ^{33}Na, which they found to be unexpectedly deformed. "This finding opens the possibility of observing such deformation in neighboring nuclei that are expected to be created for the first time by the RIBF, and gives us greater insight into the formational mechanisms of a group of nuclei called the island of inversion, where the order of nuclear orbitals is inverted," says Doornenbal (*Phys. Rev. C* **81**, 041305, 2010).

In other research, the RNC's Toshiyuki Kubo has been leading a research team in a search for new and rare isotopes using the unique capabilities of the RIBF. In 2010, the group reported the discovery of 45 new isotopes, providing

a basis for an enhanced understanding of the nuclear process that produces roughly half the elements heavier than iron (see *Pushing the boundaries of the isotope frontier*).

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

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

Radioactive Isotope Beam Factory

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

Pushing the boundaries of the isotope frontier

The discovery of 45 new neutron-rich isotopes using the Radioactive Isotope Beam Factory provides clues to the stellar formation of heavy elements

All of the elements we are familiar with have their origins in the interior of stars. However, scientists have yet to fully understand the stellar processes that produce many of the heavier elements in the periodic table. A team of scientists led by Toshiyuki Kubo at the RIKEN Nishina Center for Accelerator-Based Science have now discovered 45 new isotopes that could help establish an understanding of the nuclear process that produces roughly half the elements heavier than iron. The discoveries are some of the first results from the Radioactive Isotope Beam Factory (RIBF), RIKEN's next-generation heavy-ion accelerator.

The RIBF was designed to explore nuclei beyond the limits of the known isotopes, near the so-called neutron 'drip-line' where nuclei can be produced only by collisions in particle accelerators. These nuclei contain so many neutrons that they survive for only fractions of a second before decaying to more stable forms.

Neutron-rich isotope research is important for understanding how stars produce heavy elements. The merging of two high-energy nuclei, or fusion, can form elements up to iron. However, scientists believe that roughly half of the elements heavier than iron are produced by the 'r-process', by which a nucleus is bombarded and bloated with neutrons so rapidly that it has no time to stabilize by beta decay, instead decaying through a series of unstable intermediate nuclei. According to theoretical models, many of the rare isotopes discovered using the RIBF act as the intermediate nuclei in the r-process.

"If we understand the structure of the nuclei of these new neutron-rich isotopes, we can better understand the path and pace of the r-process and how the process is constrained by temperature and density," says Mike Famiano, a member of Kubo's team.

The RIBF produces rare isotopes by accelerating ionized uranium-238—an element heavy enough to break into other large nuclei—to close to the speed of light and then smashing these ions into a target of beryllium or lead. The collision causes the uranium nucleus to undergo fission and split into smaller nuclear 'fragments' that are collected and analyzed in the fractions of a second before they decay.

It was in such fragments that Kubo and colleagues discovered the 45 new isotopes, which span the periodic table from manganese to barium. To produce fragments over this wide range, Kubo's team designed a means of identifying the nuclear fragments quickly and accurately, and the RIBF accelerator group designed a cyclotron capable of accelerating uranium.

The results not only provide insights into the stellar production of heavy elements, but also enable Kubo's team to test the limits of theoretical nuclear models. Kubo says they will next focus on the new isotopes palladium-128 and nickel-79 because they are similar to known nuclei with a 'magic number' of neutrons or protons, which are extraordinarily stable. Near the neutron drip-line, however, nuclei may have different magic numbers, a possibility that the new isotopes will allow nuclear physicists to test.

As the first next-generation accelerator for studying rare isotopes, the RIBF is in a prime position to keep opening new doors in nuclear physics research. Similar facilities are under construction in Germany and the US, and Kubo points out that the teams working at the three new-generation facilities are already collaborating with each other.

"The discovery of new, rare isotopes is the first validation of the extended capability of these new-generation facilities," explains Kubo. The aim now is to increase the intensity of the uranium beam at RIBF to 1,000 times higher than present. "We expect to discover many new isotopes and expand the frontier of nuclear physics to a large extent."

Ohnishi, T. *et al.* Identification of 45 new neutron-rich isotopes produced by in-flight fission of a ^{238}U beam at 345 MeV/nucleon. *J. Phys. Soc. Jpn* **79**, 073201 (2010).

Research Cluster for Innovation

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

RIKEN Innovation Center

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

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

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

The RInC has recently established a new program that will propel research to another level. As part of the Social Platform Technology Development program, RIKEN proposes ideas to private companies that could be developed into next-generation core technologies, and develops new collaboration centers to find useful real-world applications for the research.

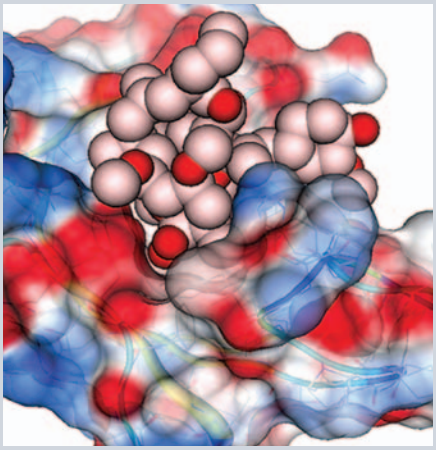
"One of the most important things is to increase the number of researchers who can work with industry. Earning trust from the scientific community and creating jobs that contribute to industry can be achieved simultaneously," says Yoshiharu Doi, director of the Research Cluster for Innovation.

RIKEN Program for Drug Discovery and Medical Technology Platforms

In Japan, life sciences are producing high-quality results from basic research; however, in terms of translating basic research results from universities and research institutions into drug discovery and medical technology, the process is relatively inefficient and time-consuming. In the West, this bridging role is carried out by bioventure companies, but such companies remain underdeveloped in Japan, which has hampered drug development.

The RIKEN Program for Drug Discovery and Medical Technology Platforms was launched in April 2010 in order to make the most out of the medical technology and drug discovery platforms that had been cultivated at RIKEN, and to fulfill this bridging role. In less than a year since then, nine drug discovery units, organized into four centers, have been established within RIKEN under the program, comprising 22 drug discovery projects selected from RIKEN, universities and research institutes. The projects focus on the development of drugs to treat illnesses that pharmaceutical companies find difficult to approach, as well as rare (orphan) diseases. Examples of these projects include cancer treatment drugs based on the use of natural killer T cells, drugs for Alzheimer's treatment that target tau proteins, 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.

Management plays an important role in competing in innovation on a global level. When this program was founded in 2010, particular emphasis was placed on the establishment of a sound management system. For each separate theme, members of each center's drug development units form teams that go beyond the regular organizational bounds, supported by a manager who is well-versed in portfolios, clinical development, regulations and business development.



As RIKEN does not have its own hospital facilities, an exit for the program has been established via alliances with companies and medical institutions. "In fiscal 2010, many such cooperative relationships were established," says the program's director, Toshio Goto, "including putting into motion comprehensive tie-ups with leading pharmaceutical companies and arranging collaborative research with bioventures and mid-level companies."

Computational Science Research Program

Japan's new 10 petaflops supercomputer—to be known as the 'K computer'—under development on Kobe Port Island and due to be opened for use in 2012 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 like this new facility are becoming increasingly important for research, providing a research tool for a wide range of fields, making a significant contribution to the design and development of a variety of products, and forming an indispensable part of the continuing advancement of science and technology.

Since 2006, the Computational Science Research Program (CSRP) has been responsible for the development and distribution of software to make maximum use of the supercomputer, as well as the construction of a world-class supercomputing research and education base at the new facility.

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

Program Director Koji Kaya plans to distribute the software to industry in the hope that they will be used in real-world applications, such as in genetic medicine and protein analysis for drug design. "People didn't think computers 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 quite accurately," says Kaya.

RIKEN Biomass Engineering Program

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

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

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

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

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

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

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

TSUKUBA INSTITUTE

RIKEN BioResource Center

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

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

Yuichi Obata

As of January 2011, the BRC held the largest number of cell lines in the world, and has the second-largest number of new microorganism registrations. It is also the second-largest public repository of mouse strains, and one of the world's top-three centers for the model plant *Arabidopsis thaliana* and genetic resources.

"Prior to the establishment of the BRC, Japanese researchers were forced to rely upon long-established bioresource centers in Europe and the US. Now, however, after just 10 years, the BRC has earned a strong reputation, both domestically and internationally,

In 2010, the BRC hosted the second conference of the Asian Network of Research Resource Centers (ANRRC), a network of institutions dealing with bioresources in Asia. The participating countries agreed to the charter that ensures the freedom of academic use for bioresources, and also freedom of publication of research results using the resources. The charter for the ANRRC also ensures compliance with the Convention on Biological Diversity.

as one of the world's top bioresource repositories," says Obata. In fiscal 2010, the combined domestic and international distributions of bioresource materials included 2,836 mouse strains, 1,962 experimental plant, 4,628 cell lines, 1,307 genetic materials and 3,234 microorganisms.

In the past year, researchers from the BRC made a number of important discoveries in the development of bioresources. Chief among these was research showing a dramatic, tenfold improvement in the success rate of cloning by a procedure known as somatic cell nuclear transfer, which involves replacing the nucleus of an egg cell with that from a mature cell. More than 10 years after the birth of the first cloned sheep, 'Dolly', the efficiency for cloning of mammal cells is still only a few percent, which is an impediment to practical application of the technology. It is expected that the BRC's recent results will be a stepping stone to greater practical applications (see *X marks the spot*).

January 2011 marked the tenth anniversary of the BRC, and in commemoration of the milestone the center will hold an open symposium in July 2011 on the exploration of life sciences using bioresources, including health, food and the environment.

"Over the next 10 years, I think there will be steady progress in analyzing the characteristics and functions of the many new bioresources being developed on the basis of genomics research," says Obata. "We are preparing ourselves to deal with newly developed bioresources within an international framework, including ways to handle bioresource-related information, and how to offer and disseminate the bioresources themselves."

RIKEN BioResource Center

The RIKEN BioResource Center (BRC) in Tsukuba, established in 2001, has quickly developed into one of the world's most important repositories and distribution centers of biological materials for life science research, emphasizing resources that are unique to Japan. The center's distinguished position derives from its capacity to handle a wide range of living strains of experimental animals and plants, cell lines of human and animal origin, genetic material and microorganisms. The center is particularly famous for its lines of human induced pluripotent stem cells.

X marks the spot

Cloning efficiency is undermined by widespread disruption of genomic regulation resulting largely from defective expression of a single gene

The success rate of producing mice using SCNT cloning improves considerably after disrupting the *Xist* gene on the activated X chromosome of the donor nucleus.

Despite the name, not all clones are created equal. This is especially true for the products of somatic cell nuclear transfer (SCNT), which entails the transplantation of the nucleus from a mature somatic cell, or non-reproductive cell, into an oocyte, or immature female ovum, whose nucleus has been removed. The result is a genomically reprogrammed cell that has been 'tricked' into acting like a fertilized egg, and subsequently develops into a clone of the nucleus-donor organism. However, the success rate for this procedure is remarkably low and many of the resulting clones exhibit a spectrum of developmental problems.

"We wanted to know if there were any clone-specific gene expression patterns in these embryos that might be related to their phenotypic abnormalities," says Atsuo Ogura of the RIKEN BioResource Center in Tsukuba. To solve this mystery, Ogura and colleagues performed an extensive analysis of gene expression activity, comparing the profiles of SCNT-derived mouse embryos versus healthy embryos obtained from *in vitro* fertilization (IVF).

They observed a striking pattern of clone-specific reduced expression of genes situated on the X sex chromosome. This suggested that there may be a malfunction in the activity of the *Xist* locus, which ensures that gene expression levels in female cells mirror those of their single X chromosome-bearing male counterparts. "In female somatic cells, one of the X chromosomes is inactivated by RNA transcripts from the *Xist* gene on the same X chromosome," explains Ogura. "Both male and female embryos have an X chromosome inherited from the mother (oocyte). This oocyte-derived X chromosome is always active, while the sperm-derived X chromosome in females is inactive."

This memory appeared to be lost or disrupted in SCNT embryos, with many embryos showing evidence of widespread gene inactivation on both X chromosomes as early as the four-cell stage. However, the researchers found that this effect could be mitigated considerably by deriving SCNT embryos from donor nuclei in which the active X chromosome contains a defective copy of *Xist*. Strikingly, this also helped to normalize the expression of many non-X-linked genes that were abnormally regulated in SCNT but not IVF embryos, indicating that the effects of this X chromosome inactivation were more far-reaching than expected.

This strategy yielded an eight- to ninefold improvement in their SCNT success rate in mice. Ogura and colleagues now hope to confirm that the same mechanism is specifically impeding cloning in other animal species as a prelude to the development of methods that might broadly bolster the efficacy of SCNT for both research and therapeutic applications.

Inoue, K. *et al.* Impeding *Xist* expression from the active X chromosome improves mouse somatic cell nuclear transfer. *Science* **330**, 496–499 (2010).

YOKOHAMA INSTITUTE

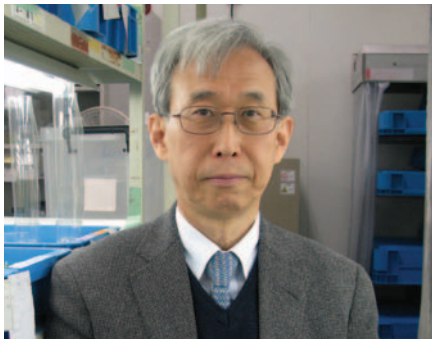
RIKEN Plant Science Center

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

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

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

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



Kazuo Shinozaki

Since 2005, the PSC has been working on the second, 15-year phase that aims to quantitatively and qualitatively improve plant production based on functional genomics in model plants with known genomic sequences, such as *Arabidopsis* and rice. Research on metabolic systems is a particular focus of the research. In collaboration with various universities and international organizations, as well as various companies, the PSC is using its research findings on model plants to improve the production of crops and trees and thus hopefully ensure a reliable supply of food and energy from plants.

If the research findings of 2010 are anything to go by, the PSC is well on its way to achieving its goals. In the year, Ken Shirasu and colleagues from the PSC published research that explains the remarkable prevalence of one of the scourges of the developing world, the root parasite *Striga hermonthica*. The researchers showed that the parasite has the ability to steal genes from the host plant (see *Gene theft by a parasitic plant*).

In other work on the *Striga* root parasite, Yuichiro Tsuchiya from Yuji Kamiya's group at the PSC with colleagues from the University of Toronto in Canada set out to clarify some of the fundamental characteristics of strigolactone—a plant hormone released by host plants that triggers the germination of parasites such as *Striga* and *Orobanche*. Through chemical genetic screening using the model plant *Arabidopsis thaliana*, the researchers showed that strigolactone, rather than simply acting as a seemingly self-destructive promoter of parasitic invasions, is in fact involved in the light-adaptive growth mechanism of plants. This might suggest that parasites evolved

sensitivity to strigolactone to gain advantage in light-limited growth conditions. Importantly though, the genes identified through the genetic screens may help in breeding varieties of plants that emit low levels of strigolactones and are thereby less susceptible to parasitization (*Nature Chem. Biol.* **6**, 741–749, 2010).

Researchers at the PSC have been investigating a variety of new methods for characterizing plant systems. One of these methods is called 'metabolomics'—a comprehensive chemical analysis to determine the products of metabolism in a plant system. Metabolomics can help unravel the complex metabolic pathways in such systems, which involve a constant flux of many enzymes and the chemical constituents of cells. A research team led by Kazuki Saito in 2010 published research on the use of metabolomics to help differentiate genetically modified (GM) tomatoes from unmodified varieties. "Our aim was not to show that the GM tomatoes are safe, but rather to examine the chemical diversity of GM tomatoes compared with natural variants, and to possibly narrow down the list of potentially problematic metabolites," explains Saito. The researchers found that the ripening GM tomatoes had a reproducible metabolic signature, and that over 92% of their metabolites showed an acceptable range of variation similar to that of the traditional varieties (*PLoS ONE* **6**, e16989, 2011).

Since relying on plant science alone is not enough to achieve all of the PSC's goals, collaboration with other fields and organizations is necessary. This is where the PSC makes use of its strong connections with the Japanese government's Ministry of Agriculture, Forestry and Fisheries and overseas organizations such as the Nanjing Forestry University and the Vietnam Forestry Science Institute, which allow it to expand its scope of research.

The PSC's strong international presence is confirmed by the fact that over half of the 1,300 attendees at the International Conference on Arabidopsis Research, hosted by the PSC in June 2010 in Yokohama, were from overseas. Held under the slogan of '2010 and Beyond', the conference presented a summary of the past 10 years' research results and how the PSC aims to move forward.

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 centers," he says.

Gene theft by a parasitic plant

Plant genome evolution requires reassessment with the discovery that parasitic plants can 'steal' nuclear genes from their hosts

The exchange of genes between non-mating species—a process known as horizontal gene transfer (HGT)—is common in bacteria but seemed confined to mitochondrial genes in plants. HGT between plants and microbes has also been documented.

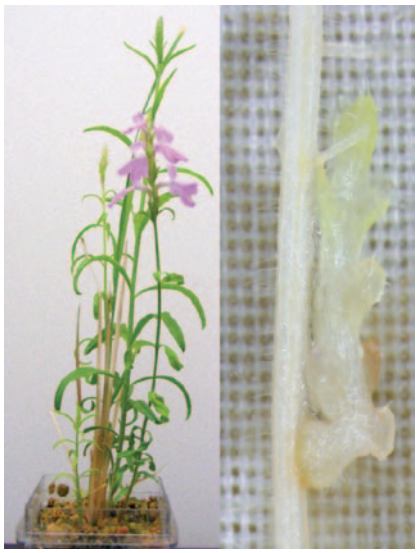
A team of researchers led by Ken Shirasu of the RIKEN Plant Science Center, Yokohama, has published evidence for nuclear gene transfer between host and parasite plant species. Mitochondrial genes are those of cellular organ-like structures, whereas nuclear genes belong to the cell's nucleus and are therefore part of the plant's main genome.

The findings mean that, in principle, parasitic plants could adapt rapidly by acquiring useful genes from their hosts rather than having to evolve new functions *de novo*—just as today's plant breeders genetically modify crop plants by introducing into them genes for desirable traits, such as disease resistance, from other species.

As a model system, the researchers focused on the flowering plant known as purple witchweed (*Striga hermonthica*); it is a root parasite of sorghum (*Sorghum bicolor*), rice (*Oryza sativa*) and other cereals. The species is a major agricultural menace responsible for devastating crop infestations in subtropical Africa.

Sorghum and rice are members of the grass family. Like all other witchweed hosts, they are monocots, meaning that their seedlings have just one embryonic leaf, or cotyledon. In contrast, the seedlings of witchweed have two cotyledons, making it a dicot. "We reasoned that the discovery of monocot-specific genes in witchweed would provide compelling evidence for the existence of nuclear HGT between host and parasite plant species," says Shirasu.

By screening 17,000 witchweed genes, the researchers identified one gene, *ShContig9483*, similar to genes in sorghum and rice, but not present in parasitic or non-parasitic relatives (eudicots) of witchweed.



A photograph of flowering purple witchweed, *Striga hermonthica*, parasitizing rice (left), and a magnified photo of an *S. hermonthica* seedling invading a rice root (right).

An evolutionary 'gene tree' built by the researchers, using DNA sequences of *ShContig9483* and related protein-coding genes, revealed that the position of *ShContig9483* in the tree is not consonant with witchweed evolutionary relationships.

"Our analyses indicate that *S. hermonthica* most likely acquired *ShContig9483* from sorghum or a related grass species, and that the transfer event was relatively recent," Shirasu notes. "Although we do not, as yet, know the function of the protein encoded by *ShContig9483*, ours is the first clear evidence of nuclear HGT between host and parasite plant species," he adds.

The researchers believe that other similar cases of nuclear HGT await discovery and that HGT may be a powerful force in plant genome evolution, facilitating rapid adaption through the acquisition of new genes.

Yoshida, S., Maruyama, S., Nozaki, H. & Shirasu, K. Horizontal gene transfer by the parasitic plant *Striga hermonthica*. *Science* **328**, 1128 (2010).

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.

The biological sciences are in the midst of a profound paradigm shift. Thanks to rapid technological progress over the past few years, a vast amount of biological data are being churned out every day, and powerful but affordable sequencers are now able to sequence a human genome within just a few weeks. "Biology has become mathematics," says Naoyuki Kamatani, director of the RIKEN Center for Genomic Medicine (CGM). "But mathematics for biology is different from that for physics and chemistry because biological phenomena are uncertain."

These uncertainties mean that the outcome for each individual person cannot be predicted accurately. Researchers continue to search for the right analytical and statistical approaches to fully utilize genetics for personalized medicine—a fledgling concept to develop optimal treatment for each patient based on his or her specific genetic makeup. This is an area in which the CGM leads the world. Its predecessor, the SNP Research Center, which was renamed in 2008, revolutionized biological research with the development of the genome-wide association study (GWAS) method in 2002. This approach allows researchers to seek genes linked to diseases

Naoyuki Kamatani

or drug responses by examining more than 10,000 markers of the genome in thousands of people. The method is now so widespread that the majority of papers in the world's top genetics journals involve a GWAS.

In addition to the GWAS method and its battery of next-generation sequencers, the CGM has cultivated its renowned strength in determining genotypes with high precision using enormous amounts of genomic and clinical data, and in analyzing these data using powerful mathematics. It is anticipated that such studies will go a long way to constructing a comprehensive genetic variant database on which personalized medicine can be developed. "We would like to offer medicine tailored to individuals," says Kamatani. "Each person is different, so it is impossible to develop treatments that suit everyone 100%."

The 12 research teams that comprise the CGM are engaged in research themes ranging from genotyping development, statistical analysis and biomarker development, to pharmacogenomics and the analysis of disease. Although focused on the genome, Kamatani points out that an integrative approach is essential. "The important thing is to find laws that integrate different parts, from the genome, RNA, proteins and cells, to organs and humans."

The center's major achievements in 2010 well illustrate its cutting-edge position in the field, filling some of the gaps in global genetic research. One such problem was the heavy focus of GWAS studies on Caucasian ethnic populations in examining the link between genetic variations and common diseases. In the first study of the Japanese genome, the team of Tatsuhiko Tsunoda has not only carefully compared three different approaches for accurately determining such variations,

but also noted explicitly the error rate, which is difficult but highly important to address (see *Embracing our differences*).

In collaboration with Takashi Kadowaki of the University of Tokyo, Shiro Maeda discovered that a specific genetic variant puts individuals of Asian ancestry at risk of developing type 2 diabetes but not their European counterparts (*Nature Gen.* **42**, 864–868, 2010). "Although this population-specific effect needs to be validated further, the present study is the first to show the existence of a disease-susceptibility locus for diabetes in a population-specific manner with genome-wide significant levels of association," Maeda says.

In other GWAS studies, Hidewaki Nakagawa and collaborators identified five new susceptibility loci for prostate cancer in the Japanese population (*Nature Gen.* **42**, 751–754, 2010). Interestingly, although many of the cancer-associated genetic variations that had been previously identified in European populations also exhibited significant linkage among Japanese subjects, more than one third did not. Elsewhere, CGM researchers have identified susceptibility genes linked to various diseases, including a kidney disorder associated with diabetes, osteoarthritis, rheumatoid arthritis and serious skin disorders resulting from treatment with carbamazepine, a mood-stabilizing drug.

The CGM's strong research competitiveness has made it possible for Japan to make an early contribution to the International Cancer Genome Consortium. RIKEN and other Japanese research institutes and universities have generated datasets for virus-associated hepatocellular carcinoma. Under the Global Alliance for Pharmacogenomics—an alliance between the CGM and the National Institutes of Health in the US—researchers are working on 19 projects to identify genetic variants that could contribute to individual responses to medicines, including rare and serious side effects. Among other international efforts, the CGM has invited researchers from Asian and African countries to undertake GWAS studies on diseases that are widespread in their countries, such as AIDS, tuberculosis and malaria.

Looking forward, Kamatani is planning to reinforce international pharmacogenomics efforts. "Many people think that the important thing in drug development is to make compounds. But the real challenge begins after a drug is made. It is difficult to prove safety and efficacy after the drug is being dosed in a patient," he says.

Embracing our differences

The first Japanese human genome sequence suggests that genetics researchers may be overlooking rare but potentially important variations

The assembly of the first human genome sequence in 2003, although a momentous occasion in scientific history, was only a first step toward understanding the extent and biological importance of human genetic variation. This 'reference genome'—known as NCBI36—was not derived from a single individual, but is instead a patchwork constructed from several anonymous donors. Researchers have since taken advantage of increasingly powerful and affordable gene sequencing technology to construct full genomes from several individuals of European, African and Asian ancestry. However, such analyses still face major obstacles, even with the benefit of high-throughput 'next-generation' sequencers.

"Sequencing errors are still problematic because they are relatively frequent," explains Tatsuhiko Tsunoda of the RIKEN Center for Genomic Medicine in Yokohama. "Sophisticated methodologies are necessary for detecting genetic variations."

In partnership with RIKEN colleague Akihiro Fujimoto, Tsunoda developed more sophisticated methods for sequence data analysis. As a test of their approach, they assembled the first complete genome sequence from an individual of Japanese ancestry. The study has revealed a surprising number of potentially medically relevant sequence and structural variations, both large and small, which have not been identified in previously assembled human sequences. In fact, their analysis of individual NA18943 revealed a striking amount of variability relative to NCBI36. "We found a roughly 0.1% difference between our assembled DNA sequences compared to the reference genome, with approximately three million base-pairs of novel sequences, as well as 3.13 million single-nucleotide variations (SNVs)," says Tsunoda.

Novel SNVs are a challenge to identify, as it is often difficult to be certain whether a putative base change represents a true difference from the reference sequence or is merely the result of an error in the sequencing process. To maximize their accuracy, the researchers carefully compared three different approaches, developing a method that ultimately allowed them to achieve a low rate of false-positive SNV identification.

Notably, a large percentage of the novel SNVs detected in this study represented variations to genes that either disrupt protein production (nonsense mutations) or markedly alter the encoded protein sequence (nonsynonymous SNVs). The researchers hypothesize that such variations are likely to be rare within populations because of their potential contribution to human disease, since they would be strongly selected against over the course of evolution.

Tsunoda and colleagues observed a similar pattern when they compared NA18943 to six other previously characterized individual genomes. Of the nonsense SNVs identified within this collected dataset, 63% were 'singletons', or variants that occurred only once across all seven genome sequences. Further, the total collection of nonsynonymous SNVs contained significantly more singletons than were found among the set of non-protein-altering, synonymous SNVs.

Their analysis also revealed numerous regions where the NA18943 genome had been subject to insertions or deletions, more than 350 of which were predicted to markedly alter or disrupt the coding sequence of a gene. Notably, a significant percentage of these were detected within genes involved in olfactory or chemical stimulus perceptions, both of which are known to vary extensively between individuals.

The findings collectively confirm that the genome of any given individual is likely to exhibit large numbers of rare, but functionally meaningful, variations relative to the general population or even individuals who are closely related from an evolutionary perspective. "We will have to sequence many more individuals within our population as well as across other populations around the world in order to obtain a clearer, more complete picture of the human genome, particularly for personalized medicine," says Tsunoda.

Fujimoto, A. *et al.* Whole-genome sequencing and comprehensive variant analysis of a Japanese individual using massively parallel sequencing. *Nature Genet.* **42**, 931–936 (2010).

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 soon become a reality thanks to research conducted by RIKEN's Research Center for Allergy and Immunology (RCAI), which has developed a hay fever vaccine it hopes will improve people's quality of life. Research to develop this vaccine is currently being carried out in collaboration with Torii Pharmaceutical Company.

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

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

Masaru Taniguchi

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

Some of the findings published by the RCAI in 2010 show much promise in alleviating the suffering of people afflicted with serious illnesses. Taniguchi himself led a team that conducted a clinical trial in collaboration with researchers at Chiba University Hospital in Japan, in which advanced lung cancer patients received injections of immune cells impregnated with α-galactosylceramide to activate natural killer T (NKT) cells. NKT cells release a torrent of molecules that trigger both the protective and innate immune systems necessary to eliminate pathogens or even thwart tumor growth. In comparison to untreated counterparts, a striking seven-fold improvement in the median survival time was observed in 60% of treated cancer patients. "The effects are superior to other molecular-targeted cancer drugs," says Taniguchi (see *Creating a life-saving killer*).

In other research, Hiroshi Ohno and Shinji Fukuda from the RCAI led a collaborative research team in investigating the role of gut bacteria in protecting the body from food poisoning using a 'multi-omics' approach that involved a systematic analysis of metabolites

in the complex ecosystem of the gut. Their research on several different strains of bifidobacteria—one of the families of natural bacteria that reside in the human gut—helped connect some important dots in our understanding of the protective benefits conferred by gut flora. They found that mice with higher levels of certain bifidobacteria were particularly resistance to poisoning with a virulent strain of *Escherichia coli* known as O157. Common to all of these protective bifidobacteria are high rates of acetate production as a byproduct of carbohydrate digestion. Acetate in turn has been shown to be effective in mitigating the effects of the Shiga toxin produced by *E. coli* O157. The results therefore suggest that acetate-producing bacteria help prevent poisoning by actively preserving the integrity of the intestinal wall and keeping Shiga toxin out of the bloodstream (*Nature* **469**, 543–547, 2011).

Looking to the future, a great deal of emphasis is being placed on nurturing young researchers based on RIKEN's belief that new areas of study must be continuously developed. It is a belief strongly held by Taniguchi. "The only way to have fresh areas of study is by developing young blood."

In this endeavor, the RCAI has developed the role of Young Chief Investigator, a new program that will provide a career path for researchers aged 40 or younger. Those chosen for the program run independent research laboratories on multidisciplinary research that bridges immunology with other research fields, while being mentored by specialists outside the RCAI in related fields.

The RCAI understands the importance of developing young immunology researchers and postgraduate students with an international mindset, which is why it conducts its annual International Summer Program. The program was a particular success in 2010, being held in conjunction with the International Congress of Immunology, which had Japan as its venue for the first time in 27 years.

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

"I am looking forward to the day when these young talented researchers become the leaders in the field of immunology," says Taniguchi.

Creating a life-saving killer

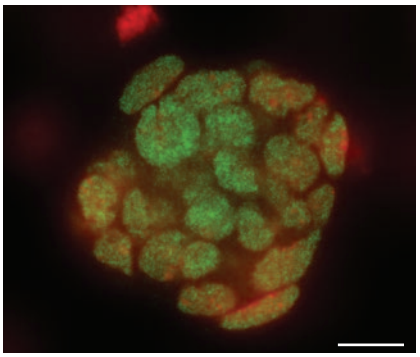
Cancer may be kept in check by a method for generating patient-specific immune cells with antitumor activity

Upon receiving the appropriate activating signal, natural killer T (NKT) cells live up to their name, releasing a torrent of molecules that trigger the protective immune response necessary to eliminate pathogens and thwart tumor growth.

These cells represent a promising clinical tool, as demonstrated in a recent clinical trial in collaboration with researchers at Chiba University Hospital in Japan, in which lung cancer patients received NKT-stimulating injections of dendritic cells that had been pretreated with α-galactosylceramide[1]. Some 60% of treated patients exhibited a striking seven-fold improvement in their median survival time relative to their untreated counterparts. "The effects are superior to other molecular-targeted cancer drugs," says Masaru Taniguchi of the RIKEN Research Center for Allergy and Immunology (RCAI), Yokohama, whose team participated in this study. "However, this therapy is not applicable to two-thirds of patients because of their limited number of NKT cells."

To solve this problem, Taniguchi teamed up with RCAI colleague Haruhiko Koseki to develop a method for generating transplantable NKTs[2]. They derived these from induced pluripotent stem cells (iPSCs), embryonic-like cells that are typically generated via virus-mediated delivery of 'reprogramming genes' into skin cells. However, NKT maturation involves a complex genomic rearrangement event, making them difficult to derive from conventional iPSCs. Taniguchi and Koseki devised a novel approach for generating mouse iPSCs from existing NKTs, which have already undergone this rearrangement. They used these iPSCs to generate large numbers of new NKTs *in vitro*.

Their method efficiently produced mature NKTs, which rapidly established a stable population within the liver upon transplantation into mice. To the researchers' pleasant surprise, these new NKTs displayed typical activation behavior in response to α-galactosylceramide-treated dendritic cells and proved capable of coordinating an effective immune response. "In general, cells generated from *in vitro* culture die quickly *in vivo* or are killed by host immune cells…however, this was not the case here," says Taniguchi. "We detected iPSC-derived NKT cells with adjuvant activity and tumor-eradicating effects two weeks after cell transfer."



A cluster of undifferentiated iPSCs derived from reprogrammed NKTs with high expression levels of the Oct3/4 pluripotency factors (green fluorescence) (DAPI, red; scale bar, 10 μm).

Taniguchi, Koseki and colleagues are now keen to begin working with human NKT cells. This transition will involve many new challenges, but the researchers see great clinical potential in their approach—particularly in the US, where the Food and Drug Administration has approved development of cell-based therapies.

"NKT cell-targeted adjuvant cell therapy is applicable to any type of cancer patient, because it can overcome their immunodeficient status and enhances the antitumor responses that are weak in a cancer patient," says Taniguchi. "NKT cell-targeted therapy is also quite effective in head and neck cancer patients, irrespective of the histological type of the tumor."

[1]Motohashi, S. *et al.* A phase I-II study of alpha-galactosylceramide-pulsed IL-2/GM-CSF-cultured peripheral blood mononuclear cells in patients with advanced and recurrent non-small cell lung cancer. *J. Immunol.* **182**, 2492–2501 (2009).

[2]Watarai, H. *et al.* Murine induced pluripotent stem cells can be derived from and differentiate into natural killer T cells. *J. Clin. Invest.* **120**, 2610–2618 (2010).

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 Spanish Flu of 1918 claimed the lives of at least 50 million people worldwide. It is not surprising then that influenza A (H1N1) caused panic in 2009 as it spread around the world at an alarming speed. One of the main institutions that the Japanese government turned to at the time of the epidemic to develop an H1N1 detection technique was the RIKEN Omics Science Center (OSC). The result: the OSC was able to reduce the analysis time for H1N1 to just half an hour using its smart amplification (SmartAmp) technology, allowing genetic diagnosis to be carried out immediately after initial consultation—an outstanding result that was aired in a documentary on Japanese television.

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

The core of research carried out at the OSC is focused on the comprehensive 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.

Yoshihide Hayashizaki

The strength of the international network established at the OSC is illustrated by one particular research finding produced by the center last year. Piero Carninci from the OSC, working with an international team of collaborators, extended a technique called 'cap-analysis of gene expression' (CAGE), an invaluable tool for genetic profiling that allows libraries of partial sequences to be compiled from a large percentage of cellular RNA. This is important because knowledge of a cell's RNA content gives a complete snapshot of its gene expression activity, providing information about how a cell functions and how it is disrupted by disease and environmental changes.

Carninci's group was able to overcome the need for the large quantities of genetic material normally required for CAGE by developing two variants of the method, bringing analyses within reach. The first—nanoGAGE—can be applied to just 10 nanograms of RNA, representing a 5,000-fold reduction of the amount of material needed for analysis. The second variant—CAGEscan—can yield sequence data from both ends of the RNA molecule. It is hoped that these techniques will open up a range of genetics and cell biology studies that have previously been impossible. "These technologies could also be used on biopsies or samples, or to look for diagnostic markers in the blood," Carninci says (*Nature Methods* **7**, 528–534, 2010).

The high profile of research conducted by the OSC over the years was highlighted in 2010 when the journal *Science* recognized

work by Hayashizaki on non-coding RNA as having contributed to one of the journal's 10 Insights of the Decade (*Science* **330**, 1614, 2010). That research rewrote the text books on cellular and genetic biology by showing that non-coding RNA, rather than playing the role of mere messengers, in fact appears in a multitude of forms with a surprising complexity of roles in cellular processes and gene regulation (*Science* **309**, 1559–1563, 2005).

One of the OSC's greatest achievements for fiscal 2010 was the initiation of FANTOM5, the fifth phase of the Functional Annotation of Mammalian Genome (FANTOM) project—an international research consortium founded in 2000 to assign functional annotations to the full-length complementary DNA collected during the Mouse Encyclopedia Project at RIKEN. The aim of the FANTOM5 project—the biggest consortium in the world in life sciences—is to comprehensively elucidate the control mechanisms that regulate the behavior of various cells and clarify the differences in gene networks among different types of cells. In February 2011, RIKEN hosted an international symposium for FANTOM5 that was attended by 180 researchers from 51 institutions in 19 countries. The strong connections forged with researchers from around the world through such events is one of the key factors that allows the OSC to convert basic research results into actual applications for medical use.

Research conducted under the FANTOM4 consortium, including Hayashizaki and OSC Project Director Harukazu Suzuki, also made waves in 2010. In an exhaustive screening process, the researchers produced the first atlas of transcription factor interactions—a process that controls the activation of genes (see *Mapping the power of networking*).

In the coming years, Hayashizaki sees the role of the OSC as maintaining and building upon the favorable outcome of the recent FANTOM5 symposium. In addition to strengthening international collaboration, the gathering provided an opportunity for young researchers to talk to famous researchers. These future leaders will be assisted by the Life Science Accelerator—a multi-purpose, large-scale analysis system that is currently being developed by the OSC to carry out rapid analysis of molecular networks. "We would like to build upon the basic research carried out on intracellular gene networks and utilize the knowledge that we have obtained to work closely with companies and hence act as a foundation for life sciences in Japan," says Hayashizaki.

Mapping the power of networking

An atlas of protein–protein interactions reveals the collaborative efforts underlying gene regulation in mice and humans

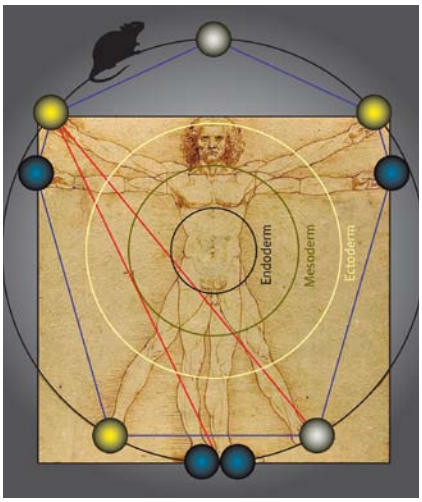
Transcription factor (TF) proteins act as switches that turn genes on and off, and the timing and localization of their activity ensures that genes are activated only when and where they are needed—an essential consideration in processes like embryonic development.

However, the TF–gene relationship is seldom simple. "In many cases, TFs work as complexes in which two or more proteins physically interact," explains Harukazu Suzuki, project director at the RIKEN Omics Science Center, Yokohama, and scientific organizer of the international FANTOM4 Consortium. "Depending on the combination, expression of different sets of genes is regulated; thus, these protein–protein interactions are essential information for analysis of transcriptional network regulation."

Both research organizations have made it their business to untangle these networks, and recent work from Suzuki and collaborators provides a useful foundation for mapping functional TF associations.

The research team generated protein-producing clones for a majority of the known transcription factors from humans and mice and used these to perform 'two-hybrid' experiments that reveal physical interactions between pairs of proteins in both species. An exhaustive screen of both pools of clones enabled the assembly of an 'atlas' of 762 and 877 likely TF–TF interactions in humans and mice, respectively, with subsequent experiments suggesting that these data potentially represent approximately one-quarter of all such interactions.

They then determined where each TF is produced in an effort to classify individual factors as tissue-localized 'specifiers' or broadly expressed 'facilitators'. Further analysis enabled them to identify clusters of interactions associated with different subsets of tissues, revealing a fraction of TF–TF associations that help coordinate the development of embryonic tissue into the diverse range of cell types seen in mature organisms.

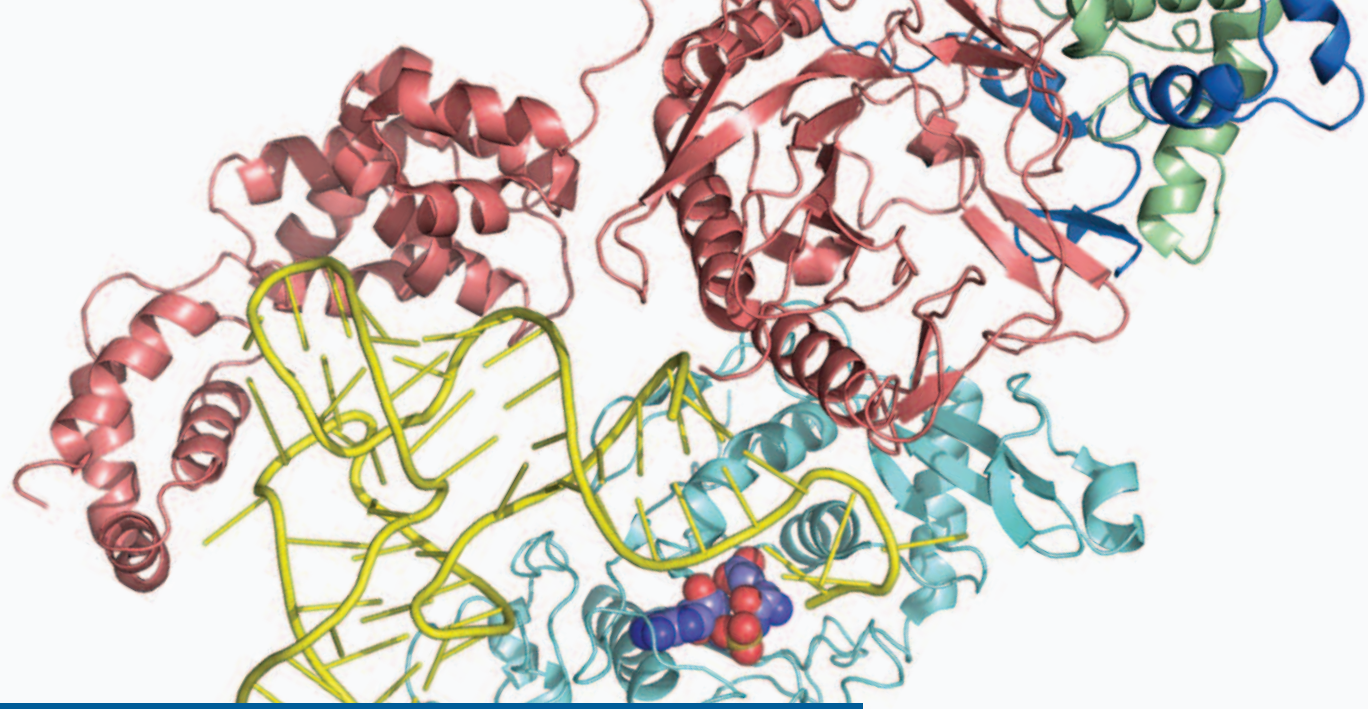


An atlas of TF–TF interaction networks in humans and mice may offer powerful new insights into the principles of gene regulation and reveal new strategies for treating disease.

"We identified a small protein–protein interaction sub-network consisting of only 15 TFs, which plays a crucial role in the regulation of cell fate," says Suzuki. Strikingly, this network contained mostly promiscuously expressed 'facilitators', suggesting that the localization of multi-factor interactions is as important as the restricted expression of individual factors in governing tissue-specific gene expression.

Suzuki and colleagues hope to expand this 'first draft' atlas soon, and to explore the clinical implications of disruptions within these interaction networks. "We would like to expand the information to include diseased tissues and cells, and especially cancer," he says. "By comparing these TF interaction networks to normal ones, we may be able to identify TFs involved in these diseases…and the associated interactions may offer novel targets for therapy."

Ravasi, T. *et al.* An atlas of combinatorial transcriptional regulation in mouse and man. *Cell* **140**, 744–752 (2010).



YOKOHAMA INSTITUTE

RIKEN Systems and Structural Biology Center

Research spanning different scientific fields at the RIKEN Systems and Structural Biology Center (SSBC) takes life sciences into another 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 life sciences and material science, expanding the logical design of biomolecular mechanisms and increasing predictability in life sciences. "Our center's mission involves focusing on life phenomena that cover a wide range of scientific fields," says Shigeyuki Yokoyama, director of the SSBC.

Initially known as the Genomic Sciences Center, which was established in 1998, the SSBC has elucidated the structures of many important analysis-defying proteins. The period between 2002 and 2007 was a particularly productive time for the center, when it determined 2,700 protein structures and functions through the National Project on Protein Structural and Functional Analyses.

Building on that experience, the center carries out analyses on even more challenging proteins to elucidate the mechanisms of interactions in biomolecular systems at a tertiary structural level. Reconstruction of the functions *in vitro* as biological systems on the basis of these results is anticipated to provide a deeper understanding of life.

Shigeyuki Yokoyama

The center also uses the results to find treatments for various diseases. "We work on illnesses such as cancer that affect a large number of people in society. This not only improves people's health but ends up having a positive effect on the economy," says Yokoyama. Starting in 2010, the SSBC is now involved 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.

The medical industry in fact stands to be one of the beneficiaries of research results recently garnered by researchers at the SSBC. In 2010, a team led by the SSBC's Ichiro Hirao successfully synthesized an unnatural fluorescent base-pair system that can be incorporated directly into DNA and RNA molecules in the form of tags or small, light-emitting molecules. As this addition only creates a minimal disruption to the delicate biochemical functions of the cells, there is much expectation that it could be used for advanced medical techniques such as DNA-based diagnostic testing (*J. Am. Chem. Soc.* **132**, 4988–4989, 2010).

Hirao also led a team that designed an artificial base pair of a fluorophone and quencher. The fluorescence of this base pair can be switched on and off depending on the DNA activity. Hirao's goal is to apply this system to *in vivo* cell experiments. "If it is possible, we will see the on-off switching of a specific gene expression," he says (*J. Am. Chem. Soc.* **132**, 15418–15426, 2010).

In 2010, Yokoyama himself was involved in the first crystal structure analysis of a large bacterial RNA polymerase–transcription factor

complex. The success of the research team in the difficult step of crystallizing the complex for analysis itself represents a major breakthrough (see *Caught in the act*).

Yokoyama and a colleague Takuhiro Ito also recently published results that help shed light on one of the mysteries of protein synthesis. In certain types of single-celled organisms such as bacteria, the process by which amino acids are transferred to the protein-synthesizing machinery in the cell sometimes involves the formation of an intermediate complex that cannot be produced directly by the organism. An example is the complex called Gln-tRNA^{Gln}, which is formed by a two-step process that starts with the action of a particular enzyme. What is perplexing is that the second step involves the enzyme making a 'wrong move' that risks producing harmful byproducts. Through high-resolution structural analyses of various hybrids of the enzymes and amino acids involved, Yokoyama and Ito showed that two enzymes actually work in concert, acting consecutively and seamlessly in a manner that ensures the formation of the correct complex with high likelihood (*Nature* **467**, 612–616, 2010).

Beyond its own research, the SSBC maintains close ties with researchers throughout Japan, and researchers at other universities and institutions benefit from the SSBC's policy to provide its equipment for external use. The nuclear magnetic resonance (NMR) facility consists of 35 NMR instruments for the structural and functional analysis of proteins, a valuable resource for researchers including young scientists who do not have the budget to purchase their own machines.

With the center now well established and the research flowing, Yokoyama is setting new goals for the SSBC. "It is my earnest desire to create a paradigm shift in how life sciences are carried out. The more I discover about nature, the more I feel there is a need to understand and not look down upon it. My mission is to verify the nature of life sciences," he says.

NMR Structural Analysis Pipeline

The nuclear magnetic resonance (NMR) facility at the RIKEN Yokohama Institute is the world's largest, equiped with 35 high-performance NMR machines for the structural and functional analysis of proteins.

The NMR Structural Analysis Pipeline constitutes a cascade of processes, from judgment of sample behavior, to the preparation of stable isotope-labeled samples, NMR measurements and finally systematic structural determination. The facility aims to bridge the life sciences and materials science through cutting-edge technology.

Caught in the act

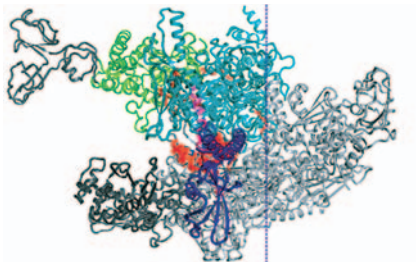
An analysis of the interactions of a gene-reading enzyme with an inhibitor protein provides surprising insights

Within the cells, the RNA polymerase (RNAP) protein complex clutches DNA like a crab claw, scanning across gene-coding regions and transcribing these sequences into the messenger RNA molecules that will ultimately provide the blueprint for protein production.

This process can be impaired or assisted through interactions with proteins known as transcription factors, but understanding how these factors influence RNAP function can pose a serious challenge for structural biologists. "It is very difficult to crystallize RNAP, which is an unusually large enzyme," says Shigeyuki Yokoyama, director of the RIKEN Systems and Structural Biology Center in Yokohama. "In particular, no crystal structures of bacterial RNAP-transcription factor complexes have ever been reported." Recently, however, Yokoyama and colleagues successfully obtained a crystal structure that captures RNAP in the midst of transcription while bound to Gre factor homologue 1 (Gfh1), a transcription factor from the bacterium *Thermus thermophilus*.

RNAP consists of several discrete modules connected by flexible linker regions (see image), with most of the enzymatic machinery residing in the 'shelf' and 'core' modules that serve as the main body of the RNAP 'claw'. In their structure, the researchers uncovered a never-before-seen arrangement of the RNAP modules, where some sort of 'ratcheting' action has created notable displacement between the shelf and core relative to its normal structure.

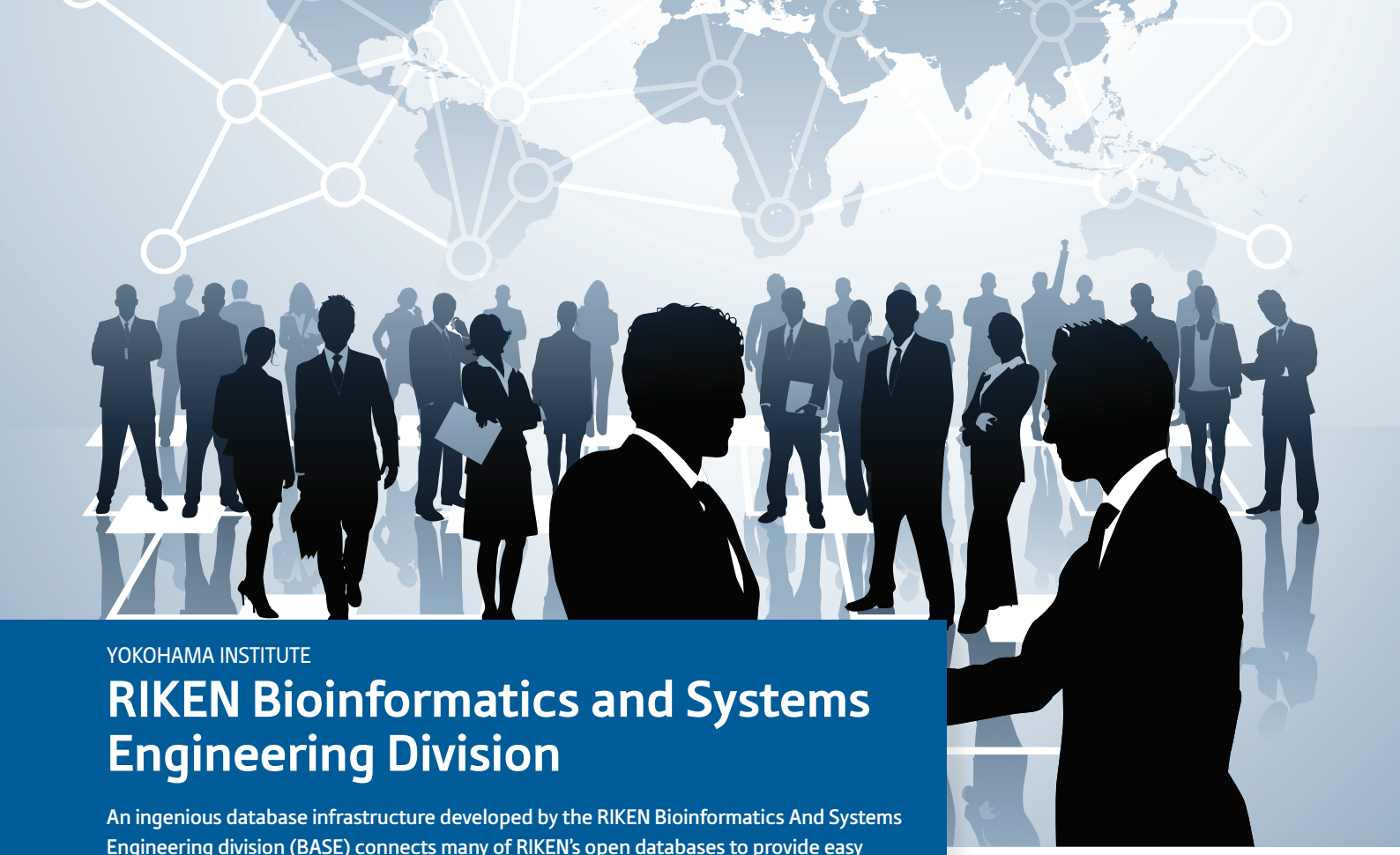
In fact, the binding of Gfh1 appears to lock RNAP into this configuration. This transcription factor—a known inhibitor—inserts itself into a channel on the complex that normally accepts nucleotides for addition onto newly synthesized RNA molecules. However, such insertion would be impossible with the normal RNAP complex, where the channel is too narrow. This suggests that RNAP executes this unexpected ratcheting motion as part of its normal behavior, which in turn leaves it vulnerable to Gfh1 inhibition. "This conformational change was most surprising," says Yokoyama. "It was simply impossible to predict this before the structure of RNAP-Gfh1 was solved."



Crystal structure of RNAP

In subsequent biochemical experiments, he and his colleagues managed to essentially catch RNAP in the act of ratcheting, providing further evidence that this behavior occurs spontaneously in nature and is likely to contribute directly to the enzyme's transcriptional activity. "We hypothesize that RNAP uses this ratcheted state to slide along DNA chains as an intermediate step in the course of normal transcription," says Yokoyama. "This state may also be used an intermediate for transcriptional termination, in which the RNA dissociates from the RNAP." He adds that validating these and other hypotheses will be top priorities for future experimental efforts.

Tagami, S. *et al.* Crystal structure of bacterial RNA polymerase bound with a transcription inhibitor protein. *Nature* **468**, 978–982 (2010).



YOKOHAMA INSTITUTE

RIKEN Bioinformatics and Systems Engineering Division

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

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

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

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

In order to achieve this, BASE has constructed a new type of technical database infrastructure called SciNetS, a scalable system based on structured content known as the semantic web. SciNetS can host thousands of different databases simultaneously in its cloud system, which allows every user to access all data using a common interface.

Tetsuro Toyoda

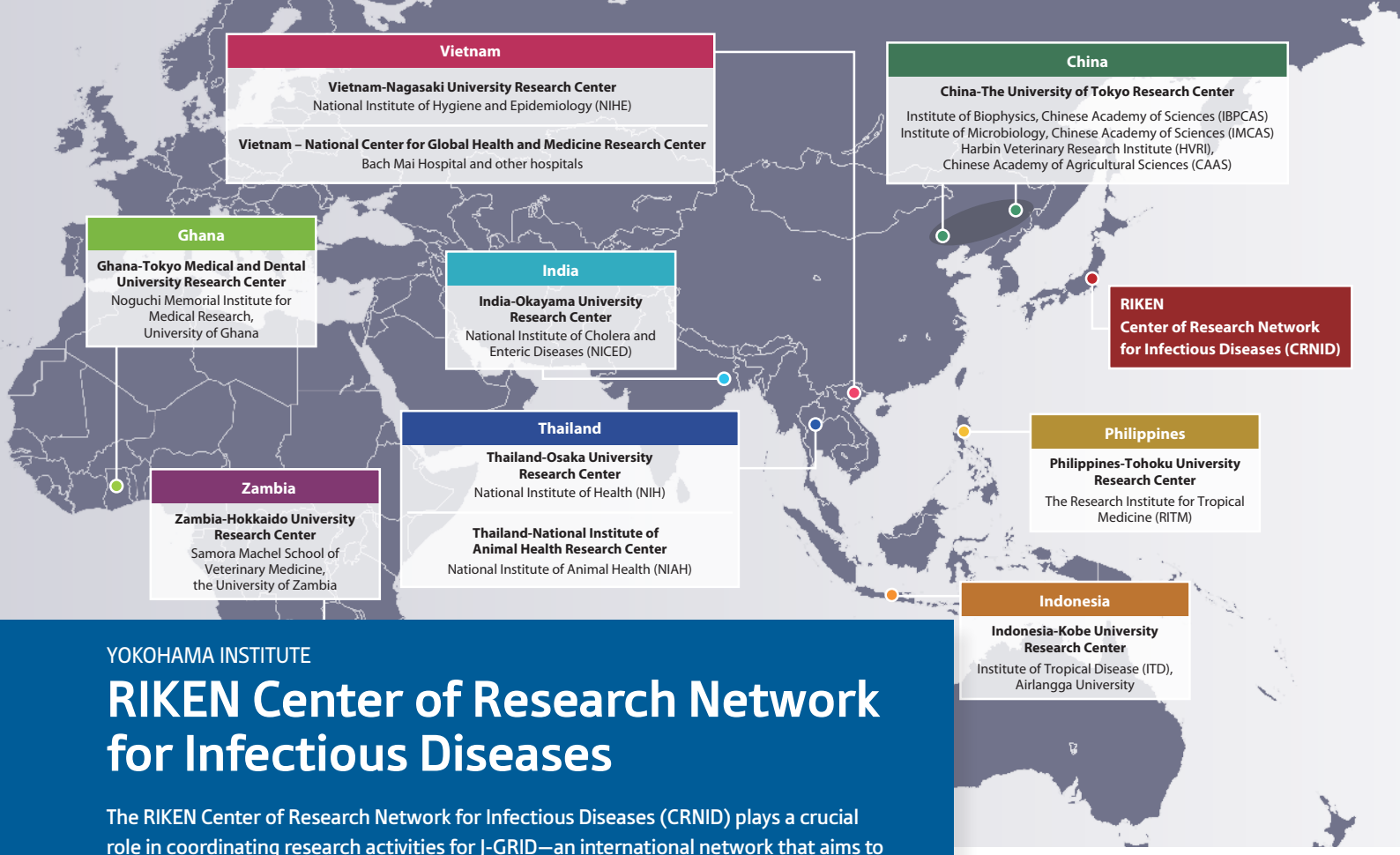
"SciNetS allows data from each of RIKEN's separate centers to be used more easily and permanently, by both in-house and external researchers, and ensures that data will not be lost from the 400 database projects stored within SciNetS, even after the laboratory that originally generated the database is 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 easily available to all in-house scientists.

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

SciNetS plays a central role on both domestic and international levels. Internationally, it acts as Japan's hub node by connecting with international databases, while on a domestic level it supplements the Integrated Database Project funded by the Japanese government—a project that has as its core institution the Database Center for Life Sciences.

BASE's activities, however, do not stop there. "In 2010, when we held the International Rational Genome Design Contest, or GenoCon, we were able to offer information and tools from our databases via a safe web browser link. This allowed us to make use of our database infrastructure safely, as well as reach out to high school students, which encompasses a wider audience than we normally have. In this way we were able to provide educational benefits too," says Toyoda.



YOKOHAMA INSTITUTE

RIKEN Center of Research Network for Infectious Diseases

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

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

Since 2005, J-GRID has expanded to include 12 research centers in 8 countries (6 in Asia and 2 in Africa). The research centers were each established on a bilateral basis between a Japanese university/institution and a counterpart in the host country.

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

Recent research by J-GRID includes a number of outstanding results generated using

conventional microbiological approaches. One remarkable case is the surveillance of cholera and enteric diseases conducted at the collaboration center in India. "That study represents the first unbiased, large-scale surveillance study accurately depicting what is going on in developing countries, I was very impressed," says Nagai. The CRNID has placed particular emphasis on diagnostic technology innovation. The Thai collaboration center recently showed that the loop-mediated isothermal amplification (LAMP) technology for the detection of nucleic acids developed by a Japanese company is extremely useful for the diagnosis of cholera and *Streptococcus suis* infection in the field and peripheral labs. Importantly, the method is inexpensive as well as rapid, specific and sensitive. The CRNID has also been involved in the development of an extreme opposite technology in an economic sense—robotics-assisted pathogen identification (RAPID). This technique is based on a metagenomic approach using high-throughput, next-generation sequencers and a strong database, and is thus suitable for a central laboratory. The feasibility of using RAPID in the case of an etiologically unknown disease outbreak to narrow down the causative candidate has been demonstrated in several model cases and is now set up at Osaka University. It will be shared with all members of J-GRID.

The CRNID's role continues to expand. "But the major role remains the encouragement of the respective research centers to produce remarkable research outcomes and disseminate them to the public," says Nagai. Publicizing J-GRID is also an important role, and the CRNID organizes annual meetings of J-GRID and maintains a project website and publishes e-mail newsletters, booklets and leaflets. Strengthening the interaction of J-GRID with national and international networks having similar missions is similarly an important task. "I think all efforts should converge on making J-GRID sustainable for many years to come."

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 an eye to developing a deeper understanding of the formation of multicellular bodies, as well as possible future applications in regenerative medicine.

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

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

Masatoshi Takeichi

At the time when the CDB came into existence, the city of Kobe was deemed an ideal location because of the recently created Kobe Medical Industry Development Project—a cluster of 11 core research facilities as well as over 200 private companies. Takeichi believes that due to the collaboration that exists between public, academic and corporate research organizations, the complex sets up an environment that is conducive to producing excellent research results.

The year 2010 was yet another in which the CDB notched up many significant achievements. As one example, scientists led by the CDB's Yoshiki Sasai made an important breakthrough in the study of human embryonic stem cells (hESCs), which have proved difficult to maintain in culture. The group identified the molecular mechanism behind these cells' tendency to commit a kind of programmed suicide known as apoptosis when separated from their colonies, a process that they had previously shown could be stopped by treatment with a chemical inhibitor known as ROCK. In their recent findings, the Sasai group showed that apoptosis is heralded by changes in cell morphology they dubbed the 'dance of death', and that the apoptosis-blocking effect could be traced to ROCK's interaction with a molecular circuit known as the Rho signaling pathway (*Cell Stem Cell* **7**, 225–239, 2010).

Other CDB research, led by Hitoshi Niwa, has unveiled a unique feature of genetic regulation in mammalian embryonic stem cells, showing how this early embryonic cell population keeps levels of certain gene

products in check. The lab looked at the process of X inactivation, in which one of the two X chromosomes in female mammals is epigenetically silenced, and found that this occurs in a random fashion, affecting either the paternal or maternal chromosome with equal frequency (*Development* **138**, 197–202, 2011). And in more biomechanical work, a team led by Shigenobu Yonemura confirmed the role of a molecule called α-catenin in linking cell adhesion to the cytoskeleton, a function that had long been suspected but which had come under doubt in recent years (see *A matter of give and take*).

One of the reasons for the CDB's success is that it not only conducts purely academic research on development, regeneration and stem cells, but also tries to develop ways to find practical applications of the findings. This is supported by an organizational structure that aggressively strives to recruit talented researchers. The addition of three new researchers in fiscal 2010 has brought fresh ideas and energy to the center and contributed to the exploration of research in the fields of development, organogenesis, regeneration and stem-cell biology.

As a measure of the top-level research conducted by CDB researchers, two of them were selected last year by the Japanese government to receive prestigious Commendations for Science and Technology. One of the researchers, Teruhiko Wakayama from the Laboratory for Genomic Reprogramming, was recognized for his work on animal cloning technology dating back to 1997 when he was a member of the first-ever team to clone a mouse. The other researcher, Jun-ichi Nakayama from the Laboratory for Chromatin Dynamics, was awarded the Young Scientist's Prize for his research on how dynamic structural changes to chromatin—structural complexes consisting of proteins and DNA—regulate gene expression.

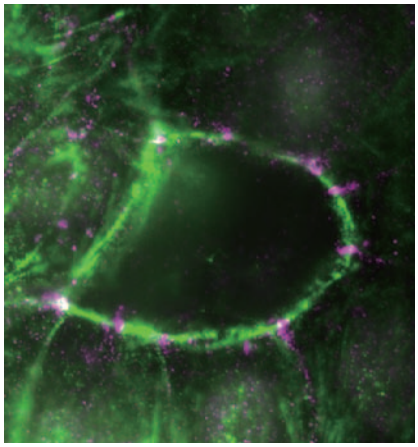
Researchers at the CDB are fortunate that, unlike many universities, the center has the liberty to choose how it achieves its goals for developmental biology. The center takes a balanced approach between trying to understand the mechanism of animal development, which will contribute to understanding why humans exist, and applying findings to useful medical applications. "Technological advances such as next-generation sequencers allow us to study genetic conditions in more detail than was previously possible, which will lead to more in-depth research on complex mechanisms in the future," says Takeichi.

A matter of give and take

Sheets of cells stick together by monitoring and responding to the pull of their neighbors

Many surfaces within the body are lined with tightly interconnected sheets of epithelial cells, with individual cells tethered to one another via complexes known as adherens junctions.

These sheets undergo considerable reorganization during embryonic development and wound healing; accordingly, adherens junctions are not merely 'cellular staples', but appear to provide an important mechanism for monitoring adjacent cells. "I imagine that cells confirm whether their neighbors are alive and have the same adhesion molecules by 'pulling' adjacent cells through adherens junctions," explains Shigenobu Yonemura of the RIKEN Center for Developmental Biology in Kobe. "Dead cells cannot pull back, and thus would not be recognized as members of the epithelial cell sheet."



A cell 15 minutes after wounding, showing the formation of a 'purse string'-like rearrangement punctuated by force-detecting adherens junctions (magenta).

Yonemura's team has uncovered evidence that adherens junctions counter tensions generated through intercellular interactions via their associations with cytoskeletal actin filaments, spotlighting a potentially important association between adherens junction component α-catenin and the actin-binding protein vinculin. By further exploring the relationship between these two proteins, his team has now achieved a breakthrough in understanding adherens junction-mediated force detection.

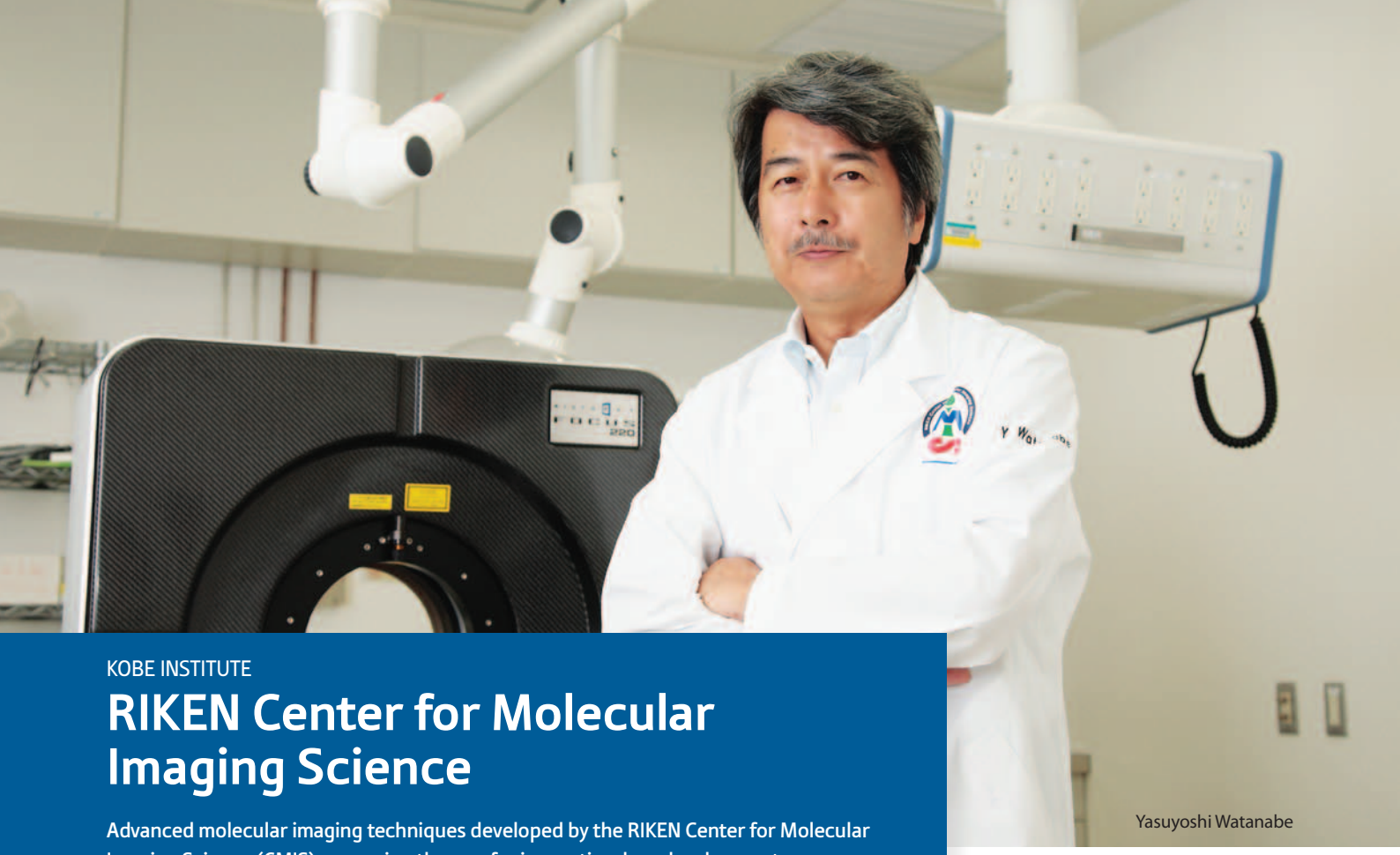
The researchers identified a vinculin-binding region in the middle of α-catenin, and also identified a second segment of the protein that actively inhibits this interaction. At one end, α-catenin also contains an actin-binding region, and Yonemura and colleagues found that this association appears to be essential for relieving this self-inhibition, suggesting that the α-catenin–vinculin interaction is force-dependent.

Subsequent experiments enabled the team to construct a model in which α-catenin is normally collapsed like an accordion, with the inhibitory domain masking the vinculin binding site. However, increased tension extends the protein and exposes this site, enabling further interactions with the cytoskeleton that effectively counter the force pulling against a given adherens junction. The result is essentially a 'tug of war' between cells, with the integrity of the epithelium hanging in the balance.

If accurate, this model offers a simple explanation for how epithelial cells can react rapidly to rearrangements in their local environment. "The central part of the mechanism involves the protein structure of α-catenin—no enzymatic reaction is required," says Yonemura. "Because of this, sensing and response take place at the same time and place."

His team is now designing experiments to confirm this α-catenin rearrangement in response to applied force, but Yonemura believes they may have potentially uncovered a broadly relevant model for cellular communication. "Because the mechanism is so simple, I think that it could be fundamental and used among a wide variety of cells," he says.

Yonemura, S., Wada, Y., Watanabe, T., Nagafuchi, A. & Shibata, M. α-Catenin as a tension transducer that induces adherens junction development. *Nature Cell Biol.* **12**, 533–542 (2010).



Yasuyoshi Watanabe

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.

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

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

Molecular imaging can also be used to diagnose illnesses such as dementia, cancer, diabetes and even fatigue. CMIS researchers are seeking to comprehend the onset of such symptoms in our body by imaging disease-related biomarker molecules, and pursuing technological innovation for predictive and preemptive medicine.

RIKEN researchers have for many years been at the forefront of molecular imaging research, and their efforts accelerated in 2005 with the launch of the national Molecular Imaging Research Program. The base for the program in Kobe was reorganized as the CMIS in 2008. Since April 2010, the CMIS has been playing a central role in the government's new initiative, the Japan Advanced Molecular Imaging Program (J-AMP).

In 2010, the CMIS took a place on the board of the third World Molecular Imaging Congress in Kyoto. In terms of research, the CMIS has continued to unveil impressive achievements in drug discovery, diagnostics and therapeutic biomarkers. For example, thanks to a site-selective reaction developed by a team led by Hiroshi Mizuma and Hirotaka Onoe from the CMIS, molecular imaging of the brain in living conscious animals is now possible with minimal impact on their physiological condition (*J. Nucl. Med.* **51**, 1068–1075, 2010). In a separate study led by the CMIS's Tadayuki Takashima, CMIS researchers teamed up with colleagues from the University of Tokyo to develop a PET probe to observe in living mice the functions of multidrug resistance-associated protein 2—one of the most important proteins associated with hepatobiliary transport (*J. Pharmacol. Exp. Ther.* **335**, 314–323, 2010).

Watanabe sees a challenging but rewarding future for the CMIS, which he believes is well positioned to become the global leader in molecular imaging. More extensive collaboration with the corporate sector will be an important driver of the CMIS's growth, and already the center has seen a rise in the number of joint projects with the healthcare sector to 45 in 2010 from 30 the previous year. "We want to create a center where we can test molecules or compounds in humans quickly and safely," Watanabe says. "Clinical institutions cannot afford such tasks. This has become another role of a basic research center like the CMIS."

FEATURED FACILITY

K computer

Japan's new supercomputer in Kobe, nicknamed simply 'K', will provide an unprecedented 10 petaflops of computing power on completion in 2012. A strategic facility of national importance established with government support and with RIKEN as the operating partner, the K computer will not only accelerate research—in its very development RIKEN has shown the world the future of computational science.

Under construction since 2006, the K computer—its name derived from the Japanese *kei* for the number '10 peta'—will be a state-of-the-art supercomputer ranking among the top facilities in the world when it is commissioned for operation toward the end of 2012. The K computer has been designated as a key technology of national importance that will be used for major national projects such as the integrated simulation of living matter and integrated nanoscience simulation. What really sets the K computer apart from its predecessors, however, is that when the doors open, the facility will be ready for research.

"In 2002, Japan's Earth Simulator was the fastest supercomputer in the world," says Kimihiko Hirao, director of the newly established RIKEN Advanced Institute for Computational Science (AICS). "In September 2010, we installed the first eight of the K computer's 800 supercomputer racks, and we have already doubled that performance. The field of supercomputing advances rapidly, so speed isn't everything—we need to improve the supercomputer's overall specifications."

Collaboration between the developers of a supercomputer and its users has previously come after a supercomputer has been opened for operation, leading to years of additional development before real research can begin. In July 2010, RIKEN established the AICS at the site of the supercomputer facility well ahead of the planned commissioning date in order to bring leading researchers and developers together to complete the implementation and uncover research themes. This marks a distinct divergence from the industry norm, and the benefits for research will be profound.

"Supercomputers are now needed for all fields of science and engineering—it's a fundamental technology and science cannot evolve without it. Previously it might have been okay for researchers and developers in computer science to work separately from the researchers who conduct simulations using the facility. Supercomputers like the K computer, however, are huge and sophisticated massively parallel machines, and it is a challenge to bring out their brilliant potential," says Hirao.

RIKEN's breadth and depth of research has allowed it to bring together scientists from a range of disciplines to work toward solutions that will support enhanced cross-disciplinary collaboration using the K computer. Through the AICS, RIKEN is promoting such collaborations in a bid to elevate the field of computational science to the next level and create a world-class computational science hub that Japan can be proud of. "Supercomputers have been considered difficult to apply for medicine and life science research, but these are the fields in which collaborations using supercomputers hold the most promise, " says Hirao.

Already, eight research projects using the supercomputer have been initiated, and in March 2011, the first international conference was held at the AICS to help promote the K computer to the world and stimulate collaboration. "Looking to the future, it will be important for all sides of research to work together. With the K computer and the AICS, we want to catch the future ahead of others."

Tetsuya Ishikawa

HARIMA INSTITUTE

RIKEN SPring-8 Center

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

With the completion of the 8 GeV super photon ring (SPring-8) in 1997, 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 more than 14 years old, however, SPring-8 remains the largest third-generation synchrotron in the world, and thanks to continued joint development by the Japan Synchrotron Radiation Research Institute (JASRI) and RIKEN, continues to maintain its world-leading status.

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

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

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

In March 2011, a major addition was made to the SPring-8 facility. Coherent light, in which all of the light waves are in-phase, has been around for a long time in the form of lasers. It can be used to probe surface structures because the light has a wavefront that can be reflected and analyzed. However, such light sources have not been available at the X-ray wavelengths needed for resolving atoms and molecules. RIKEN began developing the X-ray Free Electron Laser (XFEL) concept over a decade ago, and in March of this year the new light source, called the SPring-8 Angstrom Compact Free Electron Laser (SACLA), finally went into operation. "An XFEL requires a long linear undulator. We realized that by using the in-vacuum type undulator developed at SPring-8, we could construct an XFEL a quarter of the length of similar facilities proposed in Europe or the US."

The SACLA XFEL—the second of its kind in the world following LCLS in the US—promises to open entirely new areas of research. "When light is not coherent, molecules need to be crystallized in order to determine their structure," says Ishikawa. Many molecules such as protein complexes, however, are very difficult to crystallize. The XFEL is expected to allow such targets to be characterized without crystallization, and this could lead to a revolution in structural biology research and

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

The range of science that can be conducted using SPring-8 can be gleaned from findings published by RSC researchers in 2010. Exemplifying the continuing work by the RSC to improve the light sources at SPring-8, Ishikawa and RSC colleague Tadashi Togashi led a team of researchers in demonstrating a method to suppress random fluctuations in the free-electron laser (FEL) output spectrum. By seeding the FEL with high-order harmonic laser light, they obtained a 650-fold increase in radiation intensity with a narrow spectral profile and a dramatic reduction in uncontrolled spectral spikes (*Opt. Express* **19**, 317–324, 2011).

In chemistry, Takashi Tokushima from the RSC and colleagues from RIKEN and Hiroshima University used SPring-8 to measure the solvation effects of acetic acid molecules in acetonitrile with atomic precision. Their approach could be used to unlock the secrets of many solvent-based reactions, providing crucial information for understanding essential reactions such as enzyme-based catalysis (*Phys. Chem. Chem. Phys* **12**, 9165 –9168, 2010).

In structural biology, the RSC's Saori Maki-Yonekura and Koji Yonekura, in collaboration with Keiichi Namba from Osaka University, developed a cryogenic electron microscopy method that they used to elucidate the mechanism by which motile bacteria change swimming patterns (see *Unraveling how bacteria motor along*).

In materials physics, Munetaka Taguchi and colleagues from the RSC and other institutions published results that solve the mystery of an unusual semiconducting phase of the titanium oxide Ti_4O_7. Using a combination of laser, soft X-ray and hard X-ray photoemission spectroscopy, they resolved the electronic properties of this enigmatic phase for the first time (*Phys. Rev. Lett.* **104**, 106401, 2010).

The fields of science making use of SPring-8 are ever-expanding, and with the new capabilities offered by the XFEL, 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."

Unraveling how bacteria motor along

Motile bacteria switch between swimming patterns through conformational changes of a constituent protein of the propeller-like flagellum

Analysis of the protein structure of the 'motor' of motile bacteria at high resolution by Saori Maki-Yonekura and Koji Yonekura of the RIKEN SPring-8 Center, Harima, and Keiichi Namba of Osaka University has revealed the mechanism for transitioning between different movements.

The flagellum has a rotary motor embedded in the cell membrane and a propeller-like filament connected to the motor by a universal joint. "It's a tiny machine, but amazingly well designed for its function," says Yonekura.

When moving along chemical or temperature gradients, bacteria alternate between 'running' and 'tumbling'. Switching between these swimming patterns involves a reversal in motor rotation every few seconds.

In most species of bacteria, the flagellar filament— composed solely of the protein flagellin—is formed of 11 'protofilaments', the flagellin subunits of which are arranged to form nearly longitudinal helical arrays. Motor reversal switches the structure between left-handed and right-handed helical shapes, involving different combinations of 'L' and 'R' type protofilaments.

Biologists usually study protein structure using X-ray crystallography. But flagellin forms filaments that prevent crystallization. Cryo-electron microscopy (cryo-EM) can be used, but the resolution is usually not high enough to see atomic details, because electron irradiation severely damages biological samples. "We developed techniques to analyze the structure at high resolution using cryo-EM," explains Yonekura.

The researchers previously derived the structure of the R-type flagellar filament of *Salmonella enterica*. Their latest analysis has revealed the structure of the L-type filament using cryo-EM.

In the running mode of swimming, the flagellar motor rotates counter clockwise as viewed from outside the cell, and several flagellar filaments in the left-handed helical shape form a bundle that propels the bacterium forwards from behind. On motor reversal, twisting causes these filaments to transform into a right-handed shape and to disengage from the bundle, causing the cells to tumble and change direction.

By comparing the structures of the L- and R-type filaments, the researchers found flexible changes in the conformation of flagellin within the filament. "The flagellar filament must be flexible enough for morphological transitions needed to change swimming direction, but strong enough to withstand high-speed rotation of the motor," explains Yonekura. The researchers hope that their research will help in the development of new drugs against pathogenic bacteria, and eventually lead to an artificial nano-screw.

Maki-Yonekura, S., Yonekura, K. & Namba, K. Conformational change of flagellin for polymorphic supercoiling of the flagellar filament. *Nature Struct. Mol. Biol.* **17**, 417–422 (2010).

SPring-8 and SACLA XFEL

The SPring-8 synchrotron radiation facility in Harima is the largest third-generation synchrotron in the world and one of the most advanced of its class. The facility is used by researchers from around the world to conduct advanced research in fields from materials science to life science and industrial applications. The new SACLA facility and its X-ray Free Electron Laser (XFEL), which opened for research in March 2011, is also the most advanced of its kind, producing a coherent X-ray beam a billion times brighter than that available from SPring-8, opening up a range of new possibilities for science.

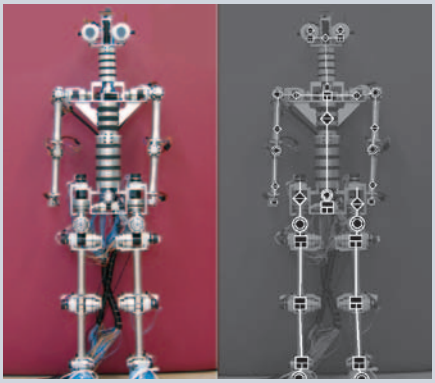
RIKEN Nagoya and Sendai Facilities

The RIKEN collaboration centers at RIKEN's Nagoya Facility bring together RIKEN researchers and scientists from industry to work together on medium- and long-term projects for integrated and applied research. At RIKEN's Sendai Facility, researchers conduct applied research in the field of terahertz wave technology.

RIKEN Nagoya Facility

RIKEN–TRI Collaboration Center for Human-Interactive Robot Research

The RIKEN-TRI Collaboration Center for Human-Interactive Robot Research (RTC) was established at RIKEN's Nagoya Facility in 2007 as a joint collaboration project between RIKEN and Tokai Rubber Industries (TRI). The center's mandate from the very beginning was to develop a human interactive robot that can be employed at care facilities to help reduce the physical burden of care-givers. A nursing-care assistant robot was successfully developed in 2009 through the integration of RIKEN's control, sensor and information processing abilities and TRI's material and structural design technologies. The Robot for Interactive Body Assistance, or RIBA, has strong human-like arms and novel tactile guidance methods based on high-accuracy tactile sensors, allowing it to lift a person weighing over 60 kilograms from a bed or wheelchair. Key features of RIBA include a soft body shell and visual and auditory sensors for tracking subjects.



RIKEN BSI–Toyota Collaboration Center

The RIKEN BSI–Toyota Collaboration Center (BTCC) came into being in 2007 as a result of a series of talks between the RIKEN Brain Science Institute (BSI) and the Toyota Motor Company, who together decided to take advantage of the possibilities opened up by the integration of brain science and engineering. The three domains of research within the BTCC—neuro-driving, neuro-robotics and health protection—are carried out by eight research units that include adjunct researchers from Toyota to ensure the smooth transfer of technology. The collaborative research includes studies of rhythm-based brain computation and non-invasive brain–machine interfaces. In 2009, the BTCC successfully developed a wheelchair that can be maneuvered by the user's brain waves. The research units are located at both the Nagoya Facility and the Wako campus.

RIKEN Sendai Facility

Terahertz-wave Research Group

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

Research under the THz program extends from the technology for generating and detecting THz waves, to the possible uses of the technology and the responses of different compounds and media to THz signals. Researchers from the program recently reported the development of an organic nonlinear optical crystal that offers sensitive detection of THz waves at room temperature, while other research has clarified some of the mechanisms responsible for producing the characteristic 'fingerprint' THz absorption signature for a biodegradable polymer in work that will help in establishing signatures for real-world applications. The Terahertz Quantum Device Team under the leadership of Hideki Hirayama is developing THz quantum cascade lasers (THz-QCLs) and THz photodetectors in order to establish new application fields for THz light. The team recently developed a THz-QCL with high operating temperature and reduced threshold current.

RIKEN in the USA

RIKEN maintains close cooperative research ties with leading institutes around the world. In the USA, RIKEN operates joint research centers with Brookhaven National Laboratory in New York and the Massachusetts Institute of Technology in Cambridge.

RIKEN BNL Research Center

The RIKEN BNL Center, run in collaboration with the Brookhaven National Laboratory (BNL) in New York, is one of RIKEN's key research projects outside Japan. Established in 1997, the program focuses on the study of strong interactions using the 2.4 mile Relativistic Heavy Ion Collider (RHIC) at the BNL, the world's first heavy-ion collider. Major research activities undertaken at the RIKEN BNL Center include projects in the fields of spin physics, quark gluon plasma, lattice quantum chromodynamics and upgrades of facilities on the ongoing Pioneering High Energy Nuclear Interaction Experiment (PHENIX), one of the two main detectors at the RHIC. A particular area of research interest is the investigation of the spin structure of the proton with the aim of measuring the contributions made by particles known as gluons to proton spin using the RHIC polarized proton–proton collider. Researchers at the BNL also study quark gluon plasma, a hot and high energy density environment that is believed to have existed in the immediate aftermath of the Big Bang and which can be generated by colliding the nuclei of gold atoms in the RHIC.

The RIKEN BNL Center is headed by emeritus director Tsung-Dao Lee and run by its director Nicholas Samios. Approximately 60 scientists work at the center at any one time, divided into theoretical and experimental groups. In addition to carrying out cutting-edge research in high-energy physics, the RIKEN BNL Center also stresses the development of the next generation of young physicists. As part of this, the center maintains an active and structured workshop program on strong interaction physics consisting of around 10 workshops a year, the results of which are published regularly online as proceedings notes.

The Relativistic Heavy Ion Collider at the BNL

RIKEN–MIT Center for Neural Circuit Genetics

RIKEN has maintained a close partnership with the Massachusetts Institute of Technology (MIT) for over 10 years, ever since the establishment of the RIKEN–MIT Neuroscience Research Center in 1998. The RIKEN–MIT Center for Neural Circuit Genetics (CNCG), established in 2008, is a joint initiative between the RIKEN Brain Science Institute (BSI) at the RIKEN Wako campus in Japan and the MIT's Picower Institute for Learning and Memory. Headquartered in Cambridge, Massachusetts, the center is headed by Susumu Tonegawa, the 1987 Nobel Laureate in Physiology or Medicine and also director of the BSI. The focus of research carried out at the CNCG covers investigation of the molecular, cellular and brain system mechanisms that underpin learning and memory as well as other cognitive functions. This is achieved by combining analytical methods with genetic techniques such as transgenics, knockouts and virus vector-mediated genetic manipulations. In carrying out this work, CNGC scientists adopt a highly interdisciplinary approach that brings together molecular and cellular biology as well as immunohistology, electrophysiology and microscopy.

The CNCG is a long-term and robust collaborative research initiative that builds on the expertise of the two organizations and actively encourages scientific exchange of research staff between RIKEN and MIT. Recent notable research successes from the joint center include a breakthrough in our understanding of the mechanism by which mammals store and consolidate spacial information obtained during the exploration of new environments, and the mechanism by which the brain regulates restructuring of neuronal connections during the processes of learning and memory-building. Another important development is the identification of certain genes such as calcinearine and PAK kinase, whose reduced activities increase susceptibility to schizophrenia and Fragile X mental retardation.

RIKEN in Europe and Asia

RIKEN operates joint research centers with the Rutherford Appleton Laboratory in the UK and the Max Planck Society in Germany, and is active in forging new and closer relationships with research institutions throughout Asia.

RIKEN Facility Office at RAL

In Europe, RIKEN maintains a strong research presence at the Rutherford Appleton Laboratory (RAL) located in Oxfordshire, UK, where it operates the RIKEN–RAL Muon Facility—the strongest pulsed source of muons in the world and a hub for international muon research. Muons are unstable sub-atomic particles about 200 times heavier than an electron. In addition to their intrinsic scientific interest, muon research has a range of potential applications including high-temperature superconductor research and clean power generation by nuclear fusion.

RIKEN's involvement in muon research at RAL dates back to 1990 when the original agreement to set up the center was signed. The agreement was renewed for a further 10 years in 2000 and a new agreement further extending RIKEN's presence at RAL was signed by RIKEN President Ryoji Noyori in 2010. Under this agreement, which guarantees RIKEN's presence at RAL until 2018, RIKEN will assume responsibility for construction, operation, maintenance and administration of the muon facility with RAL continuing to provide the high-intensity proton beam key to the generation of the muon beam at the heart of the center. The RIKEN team at the RIKEN–RAL Muon Facility is coordinated by the RIKEN Facility Office at RAL and brings together RIKEN scientists based at RAL and colleagues from the RIKEN Nishina Center for Accelerator-Based Science in Wako, Japan. Muon research carries a particular significance for RIKEN as Yoshio Nishina, the founding father of modern Japanese nuclear physics and a leading pre-war chief scientist at RIKEN, was one of the first people to detect the presence of muons in cosmic rays in 1937. His observations followed earlier landmark theoretical work in the field by another high-ranking RIKEN scientist, Hideki Yukawa, who subsequently became the first-ever Japanese Nobel Laureate, receiving the physics prize in 1949.

RIKEN–RAL Muon Facility

The RIKEN–RAL Muon Facility is based at the ISIS pulsed neutron and muon source of the Rutherford Appleton Laboratory (RAL). Key projects carried out at the center include the study of condensed matter and molecular physics by muon spin relaxation methods, ultralow-energy muon beam development for the examination of surfaces, the measurement of muonic X-rays and muon-catalyzed fusion. The latest agreement to extend collaboration between RIKEN and RAL sets out a renewed path in advanced muon science.

RIKEN in Asia

RIKEN has developed research ties with many countries in Asia. In Korea, RIKEN maintains a joint research program with Hanyang University in Seoul (the RIKEN–HYU Collaboration Research Center) to support 'fusion' research by the Asian Research Network. The RIKEN Advanced Science Institute is also collaborating with the Korea Research Institute of Bioscience & Biotechnology on research in chemical biology, and RIKEN has recently entered into a collaboration agreement with Seoul National University. In China, RIKEN maintains a presence in the country through the RIKEN Beijing Representative Office, which has been instrumental in strengthening research ties. RIKEN has also signed a cooperation agreement with Xi'an Jiaotong University in a first step toward establishing a joint laboratory, and has in place joint graduate school agreements with a total of 14 Chinese institutions, including Fudan University and Jilin University. In Southeast Asia, RIKEN's Singapore Representative Office serves as a base for broadening RIKEN's cooperation with institutions in the region. Agreements have been signed with the Thailand National Science and Technology Development Agency, Universiti Sains Malaysia and Padjadjaran University in Indonesia.

RIKEN–Max Planck Joint Research Center

RIKEN and the Max Planck Society in Germany have been cooperating in a diverse range of research fields including physics, chemistry and biology for more than a quarter of a century. In 2011, the RIKEN–Max Planck Joint Research Center was established to conduct collaborative research on systems chemical biology—a field that seeks to achieve a systematic understanding of biological systems from a chemistry perspective. The joint research center 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, directed by Herbert Waldmann, of the Max Planck Institute for Molecular Physiology, to create one of the world's leading banks of natural and synthetic compounds. The joint initiative also calls for strengthening of the collaboration on disease glycomics and oligosaccharide synthesis between the RIKEN ASI's Systems Glycobiology Research Group, directed by Naoyuki Taniguchi, and the Max Planck Institute of Colloids and Interfaces, directed by Peter Seeberger.

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.

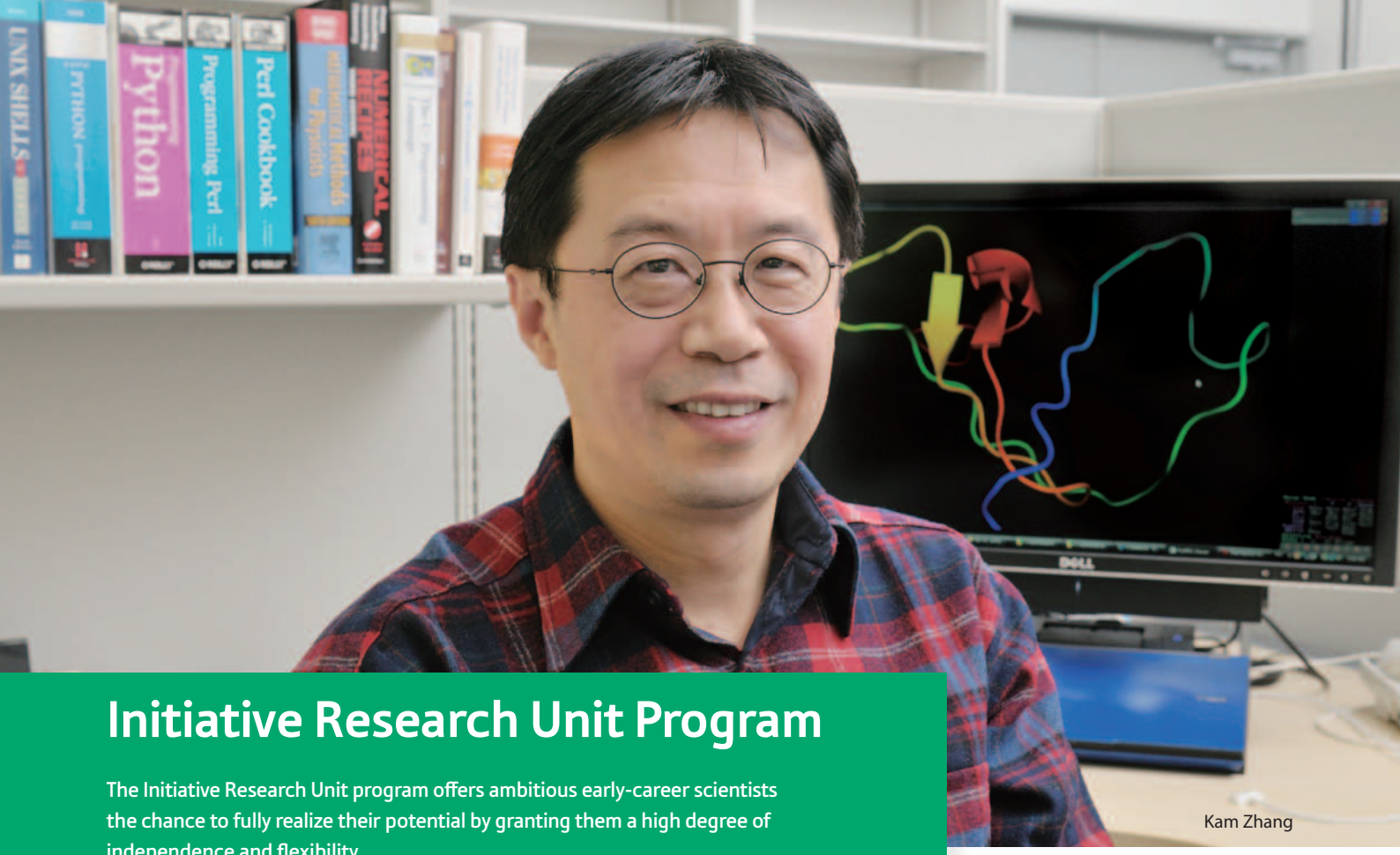
Life at RIKEN

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

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

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

Life at RIKEN
a resource for prospective RIKEN researchers
www.lifeatriken.com



Kam Zhang

Initiative Research Unit Program

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

RIKEN makes it a point to provide as much support as possible to the non-Japanese researchers working at its facilities. This also holds true in the case of the Initiative Research Unit (IRU) program. The IRU program was established to give ambitious early-career scientists in their 30s and 40s the independence and flexibility they need to realize their potential. This program has been offered since 2001, and as of April 2011 there are six IRU leaders at RIKEN.

Initiative research scientist Kam Zhang, who comes from the US, was drawn to the IRU program for clear-cut reasons. "I was attracted by RIKEN's world-renowned reputation and the cutting-edge science that it carries out," Zhang says.

The focus of research in Zhang's laboratory is to understand and modulate protein functions through computational studies of protein structures. Proteins have intricately folded three-dimensional structures, and it is these structures that are responsible for a protein's complex biological functionality. Correctly folded native structures are critical for the proper functioning of a protein in a cell, and even small deviations from this native structure can lead to malfunction of the protein and in some cases disease. Zhang's team is developing methods for protein structure prediction and applying design principles to create proteins with novel architectures, new biological functions and effective therapeutics. The team is also using a scaffold-based drug design method to discover new inhibitors for various drug targets.

Research is facilitated by the fact that IRUs are encouraged to make full use of RIKEN's comprehensive array of research equipment and facilities, which Zhang describes as "world-class."

Applications come in from around the globe for the program. In order to be eligible, applicants must hold a doctoral degree in physics, engineering, chemistry, medicine or the life sciences, and possess the ability to propose and implement an ambitious research plan. Unit leaders are expected to select their own research staff comprising three researchers or technical staff, and then lead the research effort of the unit. In this respect, Zhang's task has been made easier by those around him. "My colleagues and administrative staff are all extremely supportive," he says.

Researchers who fulfill the criteria are offered a one-year contract, which is renewable for up to five years. Initiative Research Units are provided with an annual grant of about 50 million yen, which covers a yearly salary of 10 million yen as well as research and personnel expenses.

After three years and six months, a committee will carry out a mid-term evaluation of the unit. For those newly employed as IRU researchers after the system was reviewed in FY2009, if deemed exceptionally good, the unit leader will be recommended for a limited-term or permanent principal investigator position to continue research upon completion of the five-year term.

Having been in the IRU for over two years, this is how Zhang evaluates his time there: "There are so many world-class scientists who are experts in very diverse fields at RIKEN that we can interact with. It has been a joy to work here."

Further information
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Karin Sörgjerd

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.

Every now and then we all need a helping hand to make it in the world. For postdoctoral researchers, this time comes once they have completed their research, 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 such a stepping stone, providing 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.

Karin Sörgjerd is one of the 54 FPRs currently enrolled in the program. After completing her PhD in protein chemistry at Linköping University in Sweden, Sörgjerd started as an FPR in April 2009 to conduct research under the direction of Mizuo Maeda in the RIKEN Advanced Science Institute Bioengineering Laboratory. There she is involved in the investigation of protein-misfolding diseases such as Alzheimer's and Parkinson's. "The laboratory that I work in includes researchers with a diversity of expertise, ranging from polymer chemistry to molecular biology, which makes our research environment exciting to be in," Sörgjerd says.

RIKEN hopes that the introduction of promising young researchers such as Sörgjerd will create an invigorating research climate that transcends differences of nationality.

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.

RIKEN realizes that moving to Japan to conduct research is not always a smooth transition. Foreign researchers 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.

Before moving to Japan, Sörgjerd was worried about having to overcome possible language barriers and cultural clashes—but she realized later that she need not have. "As a new member of the Bioengineering Laboratory, I was made to feel welcome from the first day. Any of the fears that I may have had were unfounded because of the friendliness of the Japanese people as well as the organizational environment at RIKEN," Sörgjerd says.

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. "Moving from Sweden to Japan was a big adventure that changed my life dramatically," says Sörgjerd. "Thanks to the FPR program and to my laboratory colleagues, it has turned out to be an extremely positive experience. I consider myself to be a very privileged and lucky person."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.

Further information
Web: www.riken.jp/fpr/
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Ju-Hyung Kim

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.

"Science knows no country," said the famous French biologist, Louis Pasteur, and these words are behind the philosophy of the programs offered by RIKEN to non-Japanese researchers.

Launched in 2006, one of these programs offers doctoral students the opportunity to further their doctoral studies as an International Program Associate under the supervision of a senior RIKEN scientist. RIKEN invites non-Japanese doctoral candidates enrolled in PhD programs at universities that are participating in RIKEN's Joint Graduate School Program to carry out research at RIKEN as International Program Associates (IPAs). So far, 67 IPAs have been accepted and the aim is to increase the number to 100 in the near future. In October 2010, current IPAs hailed from universities located on three continents, including Peking University and Shanghai Jiao Tong University in China, Pohang University of Science and Technology in Korea, the Indian Institute of Technology Bombay in India, and Karolinska Institutet in Sweden.

For researchers like Ju-Hyung Kim from South Korea, enrolling in the program was an easy decision. "I studied at RIKEN for two months as an intern on the Winter Institute Program (Research Exchange Activities for Korean Graduate Students in Science and Technology) for my master's degree, during which time I was able to observe many beneficial aspects for researchers working at RIKEN—this turned out to be an experience that was very helpful in making up my mind to join RIKEN again for my PhD studies," Kim says.

While carrying out his PhD studies at the University of Tokyo, Kim is supervised by Yousoo Kim at RIKEN's Surface and Interface Science Laboratory. The research he has conducted at RIKEN to date aims to unveil the fundamental properties of various organic molecules on metal surfaces using scanning tunneling microscopy/spectroscopy (STM/STS) and density functional theory (DFT) calculations. IPAs such as Kim are welcomed at RIKEN as a source of new ideas and perspectives in research fields that include physics, chemistry, biology, medical science and engineering. In order to qualify as an IPA, applicants must be non-Japanese nationals, hold a master's degree, and must be enrolled as a doctoral candidate at a university that has signed or is willing to sign an agreement with RIKEN for the Joint Graduate School Program.

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 of joining the program go far beyond monetary value. Created as part of RIKEN's mission to foster the development of scientists for the future, this program is based on a respect for different countries' cultures and the desire to foster international cooperation and mutual understanding among individuals. Kim's experience as an IPA is a testament to what can be achieved through the program: "The atmosphere at RIKEN is such that researchers from various fields can freely carry out discussions, and I have sometimes seen this lead to interesting collaborations with other research groups from completely different backgrounds."

Further information
Web: www.riken.jp/ipa/
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Visiting scholar programs

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

BSI SUMMER PROGRAM

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

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

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

The 2010 summer program was held under the theme of 'network interactions', exploring the integration of sensory and internal information that leads to cognition and emotion. Due to the recent disaster in Northern Japan, the 2011 BSI Summer Program has been cancelled. However, RIKEN is looking forward to seeing motivated students once again at the 2012 Summer Program.

NISHINA SCHOOL

The Nishina School, initiated as part of an agreement between RIKEN and China's Peking University in 2008, offers undergraduate students and selected doctoral students from Peking University a unique opportunity to acquire hands-on experience in theoretical and experimental nuclear physics at the RIKEN Nishina Center for Accelerator-Based Science in Wako. The third Nishina school was held on 5–15 October 2010, and included lectures and practical training for eight exceptional participants.

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

RCAI INTERNATIONAL SUMMER PROGRAM

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

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

CHEIRON SCHOOL

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

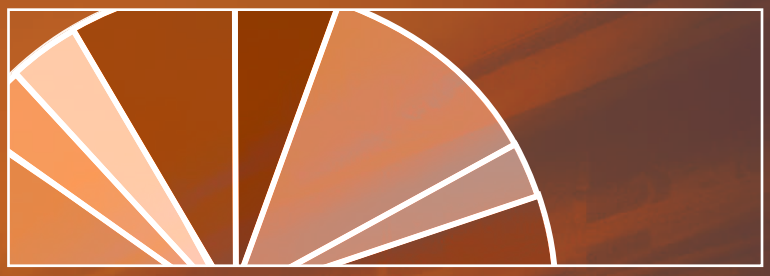
The school is cosponsored by RIKEN, the Japan Synchrotron Radiation Research Institute (JASRI), the High Energy Accelerator Research Organization (KEK) and AOFSRR. The curriculum includes lectures and practical demonstrations on synchrotron radiation science and technology, covering a wide-range of topics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

OTHER PROGRAMS

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

Further information
Visit the host center's website or contact the global relations office.
E-mail: gro-pr@riken.jp

PERFORMANCE AND ORGANIZATION



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

Governance and Advisory Council

In pursuit of excellence

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

Organizational governance

RIKEN's highest policy-making body is the Board of Executive Directors, composed of the president and executive directors. The administration of affairs at the institute level is the domain of institute directors, who each oversee and manage the operations of an entire RIKEN campus. Within each RIKEN campus, individual research centers and institutes are managed by a director who exercises strong leadership in the strategic management of the research center or institute. In making decisions on the direction of research and administration, RIKEN strives to strike a balance between top-down and bottom-up approaches by seeking the advice and cooperation of committees and councils established with the aim of achieving optimal scientific governance.

The **Committee for Research Strategy** is a board composed of distinguished scientists from both within and outside RIKEN. The board examines a wide range of research activities in RIKEN and discuss plans for research promotion strategies.

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

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

Advisory Councils

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

The **RIKEN Advisory Council** is composed of world-famous scientists, both Japanese and international, as well as individuals with experience in managing research institutes. The RAC meeting, held twice as part of every five-year plan, provides recommendations

on both general research activities and the overall management of RIKEN, and provides guidance on future research strategies and improvements to management structures. There have been seven RAC meetings since 1993, and the eighth will be held in October 2011, to be chaired by Rita R. Colwell of the University of Maryland (USA) along with vice-chairs Howard Alper (University of Ottawa, Canada), Colin Blakemore (University of Oxford, UK) and Hiroo Imura (Foundation for Biomedical Research and Innovation, Japan).

The progress of recommendations under the report of the seventh RAC, 'Laying the Foundation for Creative Advancement', will be evaluated as part of the eighth RAC meeting. The forthcoming meeting will also assess the quality and excellence of RIKEN's research, and make recommendations for the development of the next five-year plan.

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

Members of the 2011 RIKEN Advisory Council

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Karin Markides
Chemistry
President, Chalmers University of Technology, Sweden

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

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

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

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

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

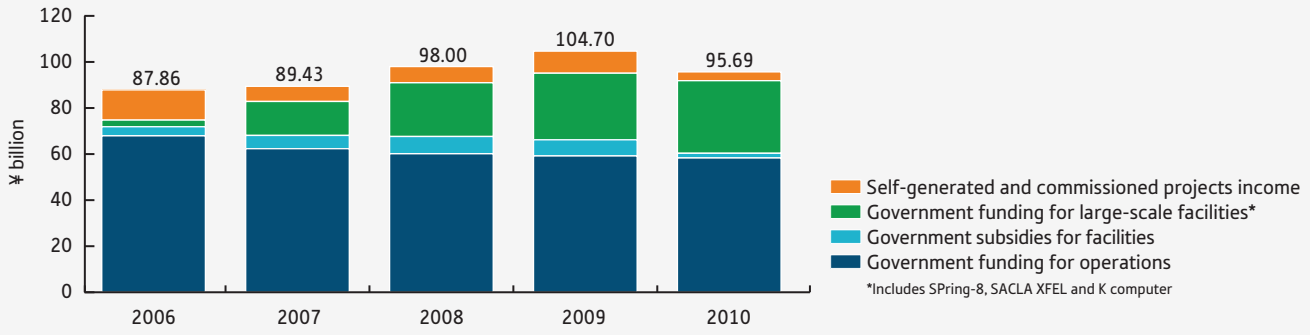
(as of May 2011)

Budget profile

Income

As an independent administrative institution, RIKEN draws the majority of its funding from the Japanese government. Ever conscious of the importance of diversifying its funding streams, however, RIKEN continues to work hard to obtain funding from other sources.

The single biggest source of income for RIKEN comes in the form of direct grants from government, providing funding for general operations and facility maintenance. Over the past four years, government subsidies for the operation and construction of large-scale facilities, such as the SPring-8 synchrotron radiation and SACLA X-ray Free Electron Laser (XFEL) facilities in Harima and the K computer in Kobe, have accounted for a sizable portion of overall income.

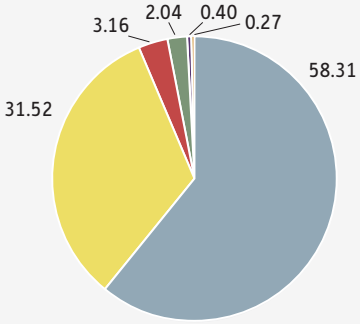


Additional revenue streams

In addition to direct financing from central government, RIKEN also obtains funding from a variety of other governmental bodies, such as the Ministry of Education, Culture, Sports, Science and Technology (MEXT), the Japan Science and Technology Agency (JST), the Ministry of Health, Labour and Welfare (MHLW) and the Ministry of the Environment (MOE), as well as other public and private organizations.

Category		FY2008	FY2009	FY2010
				¥ million
Competitive funds	Grants-in-Aid for Scientific Research	3,728	3,790	4,015
	Grants-in-Aid for Scientific Research (MHLW, MOE)	82	229	109
	Special Coordination Funds for the Promotion of Science and Technology	37	65	210
	Projects funded by organizations that fund science and technology	1,711	2,535	2,325
	Basic Research Programs (JST)	2,925	6,193	2,257
	Other publicly supported projects	393	484	556
	Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST)		565	1,777
Sub-total		8,876	13,861	11,249
Non-competitive funds	Government-commissioned research	3,682	2,685	2,178
	Government-related commissioned research	238	246	254
	Government grants	19	539	3,714
	Contributions	167	152	65
Sub-total		4,106	3,622	6,211
International grants and domestic foundation grants		375	273	330
Private commissioned research		1,178	968	1,047
Total		14,534	18,725	18,838

2010

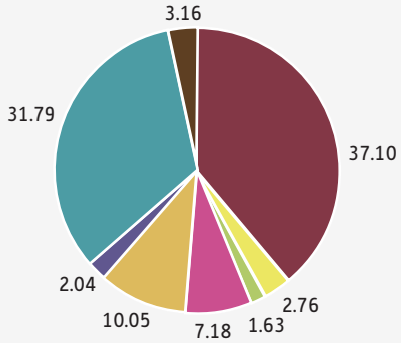


Total: ¥95.69 billion

Income by source

As in previous years, funding for general operations accounts for the largest share of overall income, in fiscal 2010, followed by government subsidies for the operation and construction of RIKEN's major facilities—SPring-8, the SACLA XFEL and the K computer.

- Funding for operations
- Subsidies for large-scale facilities
- Commissioned projects income
- Subsidies for facilities
- Operational & non-operational income
- Income from shared use of large-scale facilities

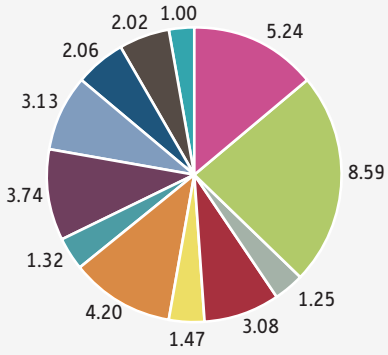


Total: ¥95.69 billion

Expenditure by category

RIKEN devotes the great majority of its income to funding its primary research activities at the RIKEN research centers and institutes, and in operating and developing its large-scale facilities. It also invests considerable sums in the management of its research infrastructure. Management costs account for about 10% of total expenditure.

- Centers and facilities
- Yokohama Institute shared research funds
- Innovation promotion
- Research infrastructure management
- Management costs
- Facilities
- Operation & construction of large-scale facilities
- Commissioned projects



Total: ¥37.10 billion

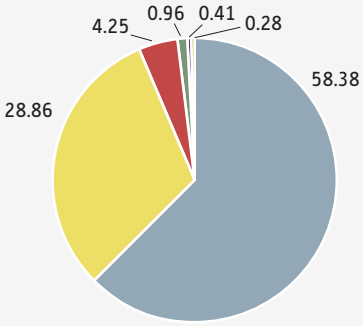
Expenditure by research center

Among RIKEN's research centers, RIKEN allocates over a quarter of the available funding to the Brain Science Institute, with other centers such as the Advanced Science Institute, the Center for Developmental Biology and the Nishina Center for Accelerator-based Science also claiming sizable portions.

- Advanced Science Institute
- Brain Science Institute
- Plant Science Center
- Research Center for Allergy and Immunology
- Center for Genomic Medicine
- Center for Developmental Biology
- Center for Molecular Imaging Science
- Nishina Center for Accelerator-Based Science
- BioResource Center
- SPring-8 Center
- Life science platforms*
- Research programs for green innovation

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

2011

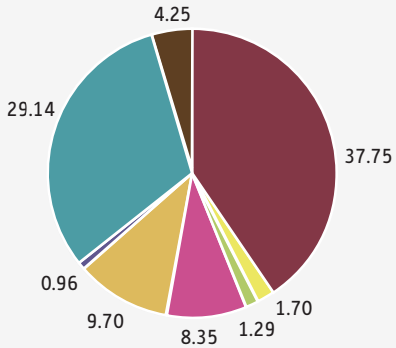


Total: ¥93.14 billion

Income by source

Looking forward to fiscal 2011, with the completion of the SACLA XFEL facility in Harima and the building to house the K computer in Kobe, there will be a drop in government subsidies for large-scale facilities.

- Funding for operations
- Subsidies for large-scale facilities
- Commissioned projects income
- Subsidies for facilities
- Operational & non-operational income
- Income from shared use of large-scale facilities

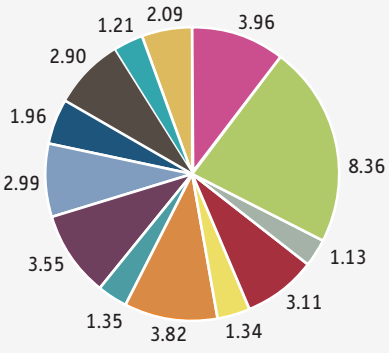


Total: ¥93.14 billion

Expenditure by category

The expenditure figures for fiscal 2011 remain largely similar to the 2010 figures despite the tight economic climate over the past few years. Expenditure on the operation and construction of large-scale facilities sees a modest drop in the coming year, while expenditure on research infrastructure management will expand in 2011 to enhance scientific governance.

- Centers and facilities
- Yokohama Institute shared research funds
- Innovation promotion
- Research infrastructure management
- Management costs
- Facilities
- Operation & construction of large-scale facilities
- Commissioned projects



Total: ¥37.75 billion

Expenditure by research center

Most of RIKEN's operational research divisions are expected to maintain similar expenditure levels into 2011. A new addition in the coming year is the Quantitative Biology Center (QBiC)—an entirely new center established on the basis of research by the Advanced Computational Sciences Department of the Advanced Science Institute.

- Advanced Science Institute
- Brain Science Institute
- Plant Science Center
- Research Center for Allergy and Immunology
- Center for Genomic Medicine
- Center for Developmental Biology
- Center for Molecular Imaging Science
- Nishina Center for Accelerator-Based Science
- BioResource Center
- SPring-8 Center
- Life science platforms*
- Research programs for green innovation
- Quantitative Biology Center

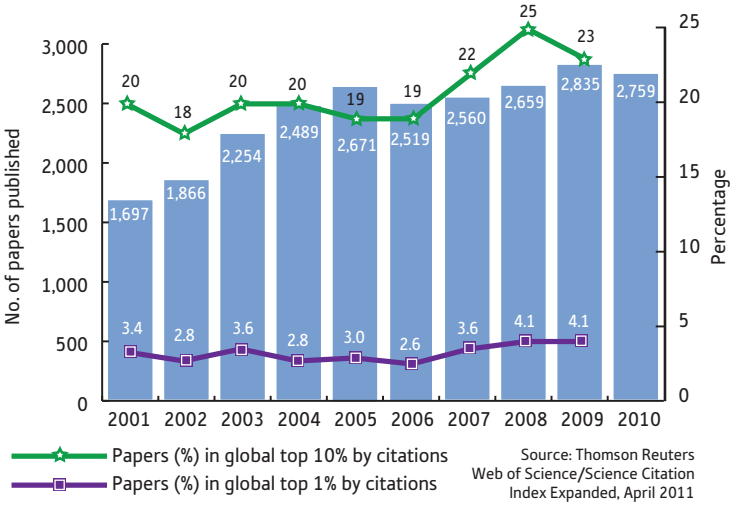
*The life science platforms include the Omics Science Center, the Systems and Structural Biology Center, and the Bioinformatics And Systems Engineering division (BASE).

Research output

World-class research

Innovative, high-quality research is the lifeblood of RIKEN, and the organization has seen a steady rise in research publications over the past decade. Testifying to the exceptional quality of research carried out at RIKEN, the citation rates for articles published by RIKEN researchers exceed the international standard—the proportion of RIKEN papers rated in the top 10% of all articles published globally based on citations* remains above 20%, and the proportion of papers in the top 1% of most highly cited articles is steady at more than 4%.

*Citation data for papers published globally in 2009



Source: Thomson Reuters Web of Science/Science Citation Index Expanded, April 2011

RIKEN RESEARCH

Showcasing the best of RIKEN

Bringing the best of research from RIKEN to the international community and raising awareness of RIKEN as a global brand are at the heart of RIKEN's science communication strategy. Two key tools for the realization of these aims are the bilingual *RIKEN RESEARCH* website—published in English and Japanese—and the associated English-language monthly magazine, which is distributed both in printed form and as a free download. Together these present the very best of the research published by RIKEN every year in an accessible, easy-to-read format. The publication also provides regular insights into the people, facilities and programs that make up daily life at RIKEN. In fiscal 2010, the website was visited by readers from 181 countries and registered 26% more visits than the previous year, whilst the number of people registering for the e-mail alert service rose by 40%. Over the same period, issues of the *RIKEN RESEARCH* monthly print magazine featuring research highlights covering 120 carefully selected papers published by RIKEN scientists were distributed to top-flight researchers and institutions around the world.

www.rikenresearch.riken.jp

RIKEN 'Baton Zone'

Bringing RIKEN and industry together

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

Integrated Collaborative Research Program with Industry

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

Industry–RIKEN Collaboration Centers

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

Technology transfer

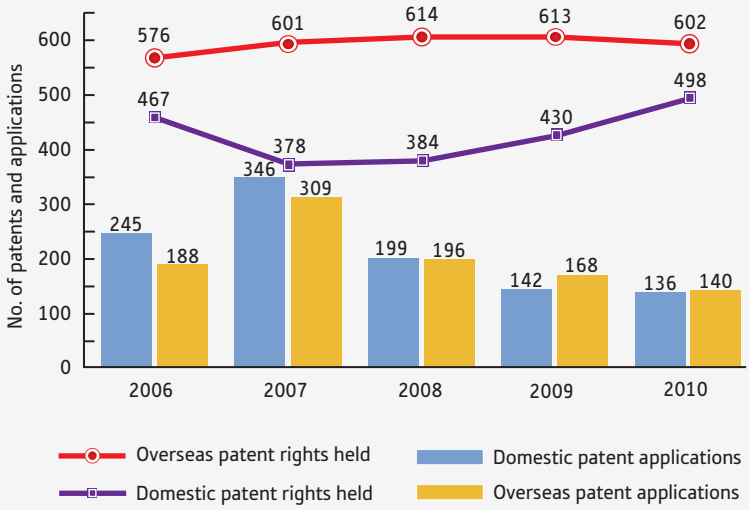
Patent activity in 2010

In addition to creating intellectual output in the form of published research papers, RIKEN actively seeks to exploit its discoveries and inventions of commercial value, and secure legal protection for its research achievements by registering many patents each year. The RIKEN technology transfer portfolio is managed by the Technology Transfer Office (TTO), which functions as a conduit between RIKEN and the private sector. The TTO is responsible for licensing of intellectual property, collaboration with industry and the acquisition of external and competitive funding. It also supports RIKEN scientists in developing practical applications for their research.

Patent applications and registrations

Patents are managed by the patent liaison staff who make strategic applications for patents, and practical implementation coordinators who assemble terms for each application, investigate the possibility of implementation from the application stage, and carry out discussions with inventors. In order to turn research results into practical outcomes more effectively, the patent liaison staff and practical implementation coordinators collect additional data to be incorporated into the patent at the time of submission and thereby strengthen the contents of the filling.

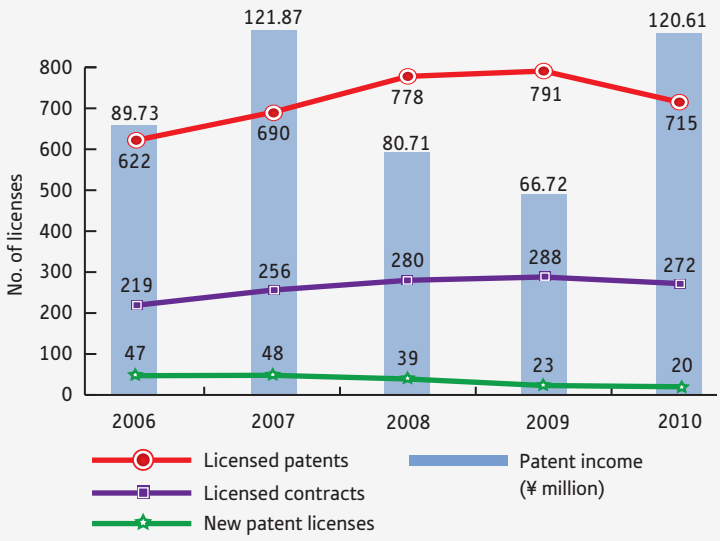
In fiscal 2010, 276 patent applications were filed, almost half of which were overseas. At the end of this fiscal year, RIKEN held the rights to a total of 1,100 patents, representing an increase on the previous year. Of the total, approximately 55% related to patents of overseas origin.



Patent licenses and contracts

Information on RIKEN's patents are publicly available on RIKEN's website. The practical implementation coordinator also approaches companies directly to support technology transfer through activities such as explaining research results.

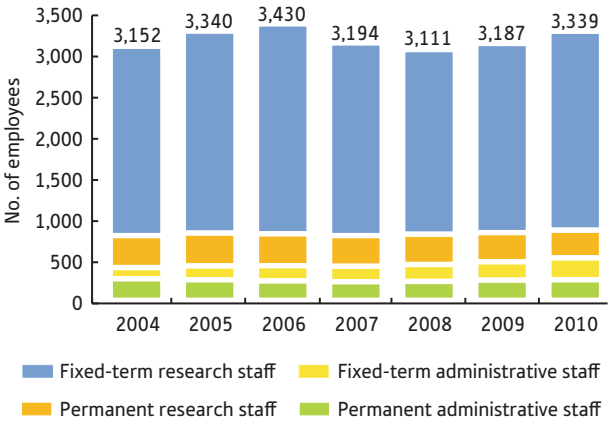
The number of patents licensed by RIKEN in 2010 was 715, and the number of licensing contracts entered into by the organization was 272. Since 2006, the current total number of patent licenses issued by RIKEN has grown by 15%, whereas the number of contracts issued has grown by 24%.



Personnel

Excellence and diversity

RIKEN personnel are employed under a two-track system in which some staff, normally those involved in curiosity-driven research in laboratories headed by chief scientists, are recruited to tenured positions with mandatory retirement at age 60, and others are employed on fixed-length contracts associated with projects of predetermined and finite duration at a given RIKEN research center. The total number of staff employed at RIKEN rose in 2010 compared with the previous twelve months, with the majority of the increase in fixed-term staff.



as of March 31, 2011

International research staff at RIKEN

RIKEN strives to create a research environment that fosters the very best international research by bringing together the brightest and best people, regardless of nationality or gender. In 2010, RIKEN hosted researchers from 53 countries and regions around the world, with the majority from China, Korea and the USA. The number of non-Japanese research staff increased substantially in 2010 compared with the previous year, now accounting for 14% of all researchers at RIKEN.

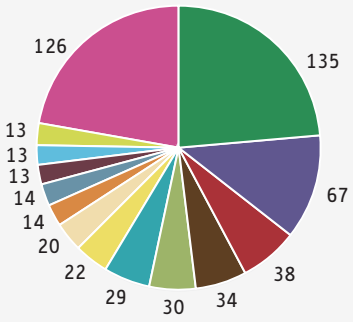
Region

Employed research staff, visiting researchers and students

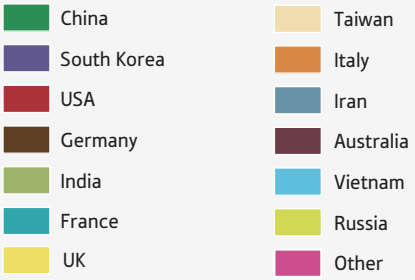
as of October 1, 2010

Country and territory

Employed research staff, visiting researchers and students



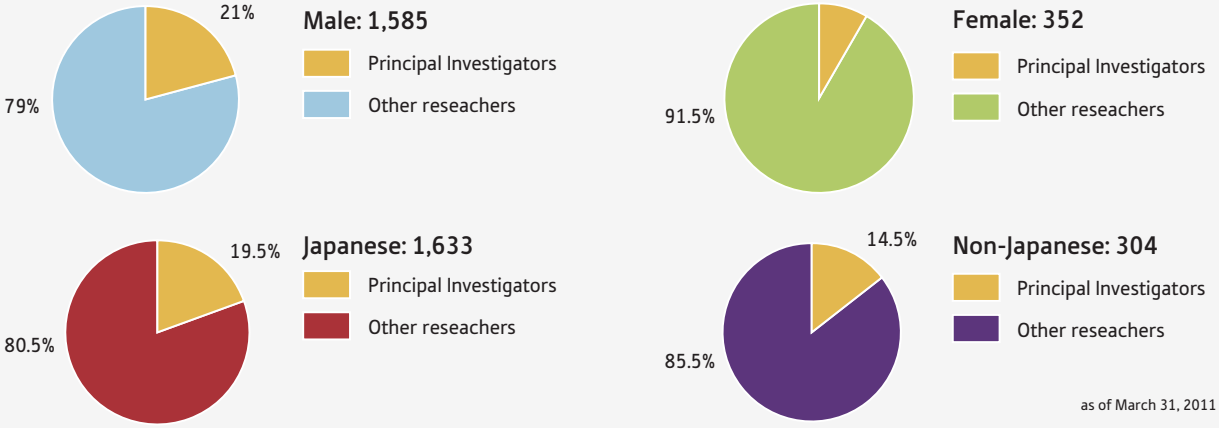
Total: 568



as of October 1, 2010

Diversity at RIKEN

Research staff employed by RIKEN



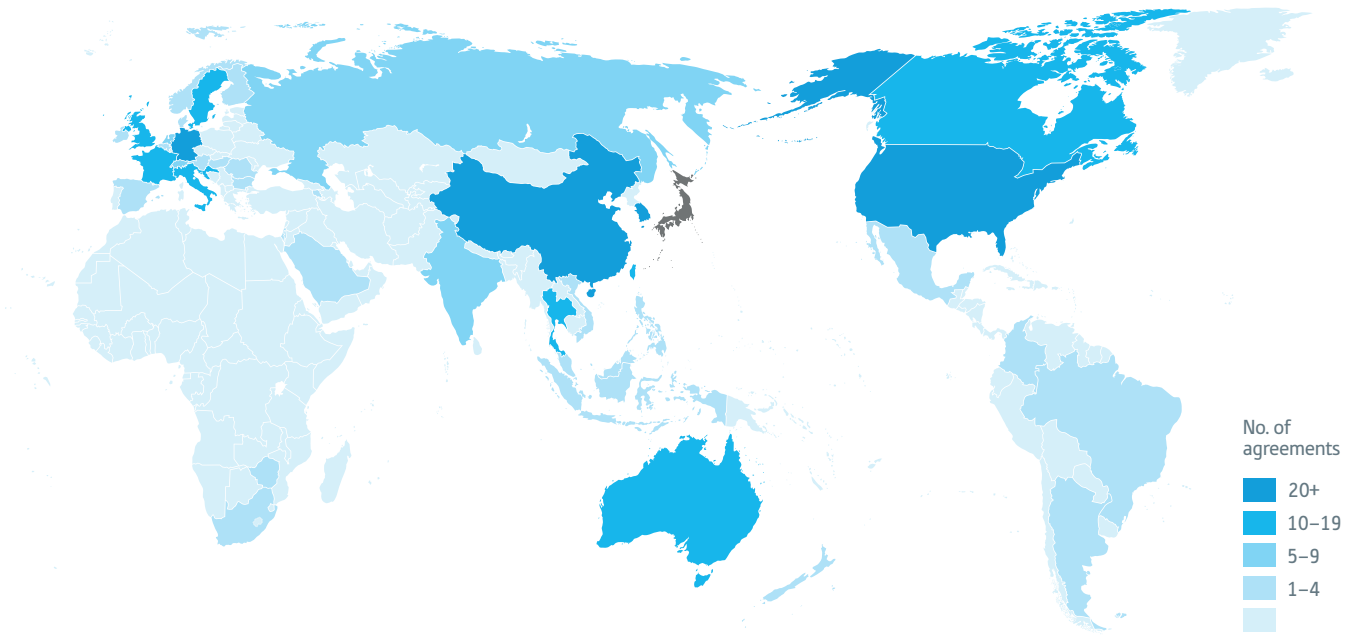
as of March 31, 2011

International collaboration

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 below outlines the distribution of these reciprocal research arrangements.

Region	No. of countries in each region	No. of collaboration agreements
Africa	2	4
Asia	10	135
Europe	19	130
Middle East	2	4
North America	2	54
Oceania	2	16
South America	4	8
Total	**41**	**351**

as of March 31, 2011



RIKEN directory

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RIKEN Research Center for Allergy and Immunology
RIKEN Omics Science Center
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RIKEN Quantitative Biology Center
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