RIKEN ANNUAL REPORT 2009–2010

Science Serving Society

RIKEN

Message from the president

From Individual Knowledge to RIKEN Knowledge and to Societal Knowledge

Basic science is a source of human knowledge and has permanent cultural value. Technology realized through the utilization of scientific knowledge is the foundation of civilized society. And, the creation of innovations based on science-based technology is indeed the source of international competence which affects the very existence of nations. It is also a pillar of international contribution towards the continued existence of humankind. In particular, for Japan with sparse natural resources superior science is needed, if it is to reach its professed goal to be a nation distinguished for its science-based technology.

Yukichi Fukuzawa, who made exceptional contributions to Japan's modernization, asked his talented disciples the question, "What is the knowledge required by our time?" to guide them to follow his ideals. Looking back over the history of science, we realize that the essence of science to seek the truth has not changed. But, the role of science in society has changed greatly since the time of Galileo and Newton, and even as recently as the time of Einstein. Science and society are now destined to be intertwined.

We are now living in the interval between millennia rather than between centuries. We must realize that our time is entirely different from the preceding millennium. In our global society in which diverse cultures move in every direction, the key to survival is to learn how we can adapt to the rapidly changing world. We must try to create new social values by undergoing a fundamental re-setting of our mindset. In this regard we would like to play a role of becoming a source of innovations by unifying individual capabilities and basic scientific knowledge.

Scientific research is initiated by individual ideas. But, what individuals can accomplish is very limited. At RIKEN, we endeavor to contribute to society by channeling knowledge created by individuals (individual knowledge) to the knowledge of the entirety of RIKEN (RIKEN knowledge) and finally to the knowledge commonly shared by society at large (societal knowledge). Furthermore, we will strengthen our collaboration with the industrial sector, and we have started the RIKEN Research Cluster for Innovation from April 2010 to promote cross-disciplinary research.

We will continue to promote genuine and systematic research activities and at the same time we will engage in the development of strategic key technologies of national importance. International collaboration is also our important mission.

We will work most vigorously to open up the frontier of knowledge and to return the fruits of our endeavor to society. I hope very much that you will become familiarized with our most recent research activities from this Annual Report and that you will strongly support our activities.

NOYORI Ryoji (DEng)
President, RIKEN

Introduction to the RIKEN Annual Report 2009–2010

RIKEN is Japan's flagship research organization and a world leader in a wide range of research fields. An independent administrative institution funded substantially by the Japanese government, RIKEN's role in advancing Japanese science continues to expand, and its influence—both nationally and internationally—has held strong despite considerable challenges posed by the recent global financial crisis. By maintaining a commitment to fundamental research in the natural sciences, promoting international collaboration through its many visiting research programs, and communicating its achievements to the public and the scientific community at home and abroad, RIKEN is actively fostering an appreciation for science and technology as the foundation for our modern economy and way of life.

The RIKEN Annual Report offers a snapshot of RIKEN's financial and academic performance for the past financial year, while also providing a unique glimpse into the research achievements and organizational culture for which RIKEN is admired.

The annual report for fiscal 2009–2010 is divided into four sections: the Year in Review, the Year in Research, the History of RIKEN, and the Year in Figures.

In the first of these sections you will find a roundup of some of RIKEN's public activities through the year (see page 6), and an in-depth interview with the RIKEN president, Nobel laureate Ryoji Noyori, and the chair of the RIKEN Advisory Council, Zach Hall, on the future directions of RIKEN and its role as a publicly funded research organization (see page 8). For those unfamiliar with RIKEN, the annual report includes sections on the organization's international research programs and its campuses and facilities, major new projects and governance structure (see page 10).

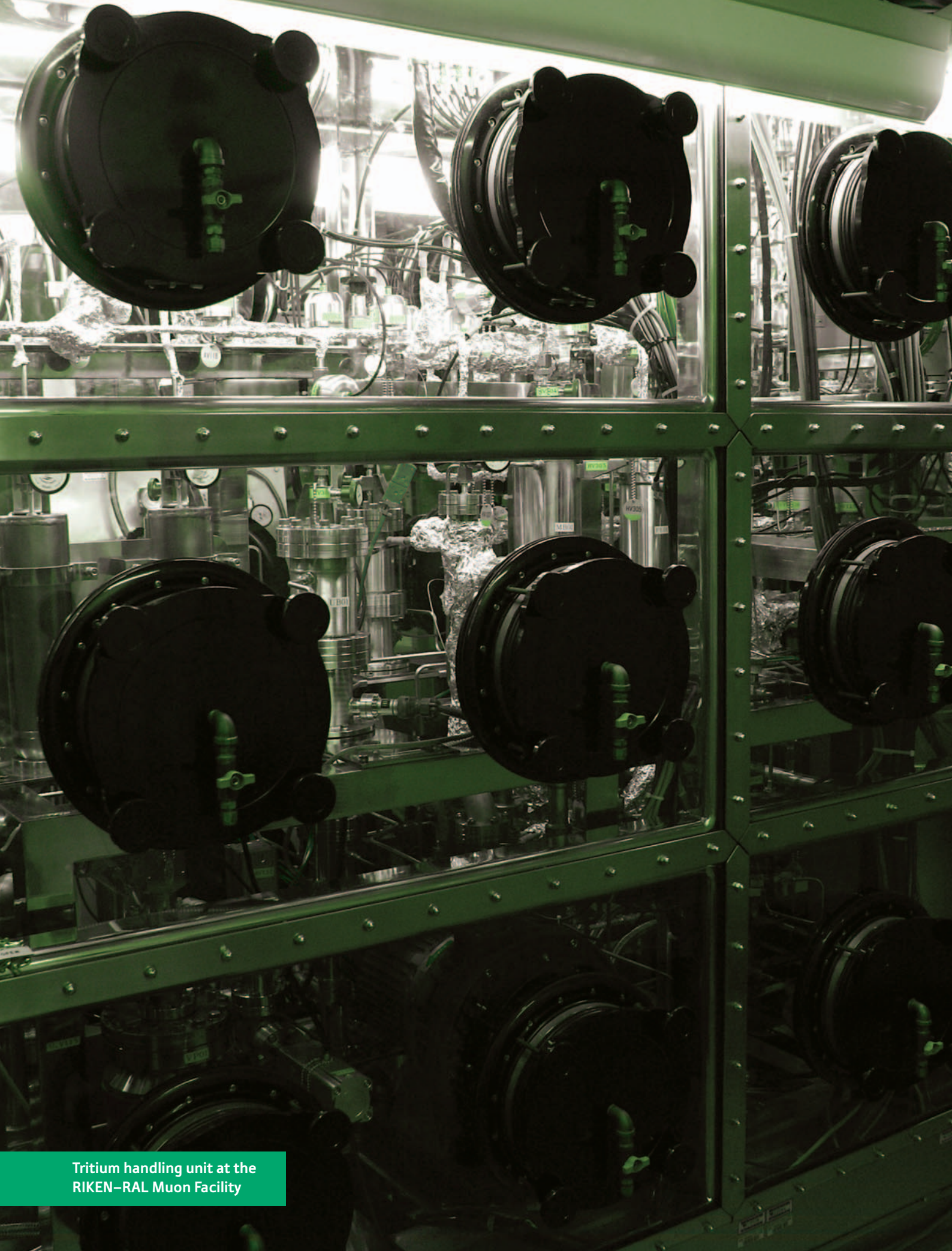
The most important performance criterion for any research organization is research output, in terms of both novelty and relevance to society. More than 15 institutes and research centers come under the RIKEN umbrella, representing a fertile ground for scientific discovery across the natural sciences, from astrophysics and quantum science, to cell biology and neuroscience. Section two of the annual report, beginning on page 20, seeks to illustrate RIKEN's achievements in research over the past year, presenting a collection of research highlights and research summaries outlining some of RIKEN's most groundbreaking discoveries for the period.

Section three of the report provides an insight into the history that has made RIKEN what it is today with articles recounting its formative years and its rise to the challenge of upheaval in postwar Japan (see page 46).

Closing out the annual report are RIKEN's latest performance results for the 2009–2010 fiscal year (see page 50). In a challenging period that saw a shrinking of many economies around the world, RIKEN remained steadfast in its commitment to supporting its creative research culture and championing the need for expanded research funding and facilities. As the performance figures show, RIKEN has maintained its leading status in all its key performance criteria—research publications, patent applications, commercialization, funding sources and workforce diversity. Furthermore, it has extended its international support programs to make it easier than ever before for both young and highly recognized researchers from abroad to join RIKEN and contribute to research at the forefront of science.

We hope that you enjoy reading this year's RIKEN Annual Report and that in doing so you will come to know better the research, people and history of Japan's flagship scientific research organization.

RIKEN Annual Report 2009–2010



Tritium handling unit at the RIKEN–RAL Muon Facility

THE YEAR IN REVIEW

The 2009–2010 financial year saw the fruition of much of RIKEN's restructuring and developmental activities in recent years. With an eye to internationalization and greater collaboration with the world's leading research institutes, RIKEN's position as Japan's pre-eminent research organization has been fortified through its commitment to strategic restructuring and expansion of its facilities and international profile.

Annual news roundup

A year of outreach

In pursuing scientific excellence, RIKEN extends its influence across the world to make real and long-lasting contributions to society at both the local and international level, and RIKEN's high-profile activities in 2009–2010 continued to support these endeavors.

New robot to reduce burden on care facilities

In 2009, collaborating researchers from RIKEN and Tokai Rubber Industries (TRI) released a new robot designed to assist personnel and patients in care facilities. The Robot for Interactive Body Assistance (RIBA), which makes use of the latest in sensor, control, information processing, mechanical and materials technologies, was developed by the RIKEN–TRI Collaborative Center for Human-Interactive Robot Research (RTC) in Nagoya to address the challenges of an aging population. RIBA is the first of its kind in the world and is capable of safely lifting and moving a human patient of up to 61 kg from a bed to a wheelchair and back.

The task of lifting and moving a patient, carried out several times a day, is one of the most exhausting activities for care-givers. In assisting in this task, RIBA brings together cutting-edge sensor and information-processing technology developed at RIKEN with materials technology developed at TRI to overcome the safety and performance limitations of its predecessor—an earlier model named RI-MAN. Using human-like arms equipped with high-precision tactile sensors and a body encased in soft urethane foam, RIBA's design guarantees patient safety and comfort.

As one part of a larger strategy to pursue advances in robot technology for care-giving support, the successful development of RIBA marks a critical step towards tackling the problems of an aging society. The RTC envisions bringing robots like RIBA to market in the near future.

The Robot for Interactive Body Assistance (RIBA) developed at the RIKEN–TRI Collaborative Center for Human-Interactive Robot Research will soon be providing invaluable assistance to care-givers.

RIKEN strengthening ties with China

On October 24, RIKEN Executive Director Kenji Takeda visited Zhejiang University in China to sign an important collaborative agreement between the two institutions. The agreement sets down plans to establish a platform for identifying candidate compounds for drug discovery research using structural biology and imaging techniques. It also calls on the institutions to exchange research personnel, and will involve a future transfer of RIKEN nuclear magnetic resonance imaging facilities to Zhejiang University and the establishment of a laboratory for joint research.

The day before the signing of this agreement, on October 23, a two-day joint symposium for young researchers was held at Shanghai Jiao Tong University on the topic of nano materials and technology. The symposium provided a venue for young researchers from RIKEN and the university to present and actively discuss their research. Shigenori Fujikawa, who acted as symposium coordinator on behalf of RIKEN, reported that the event "changed everyone's perception of China. We were amazed by the transformation China has undergone."

Indeed, RIKEN has been working for some time toward strengthening its collaborative ties with Chinese research institutions. In 2006, RIKEN sent a representative to begin preparations for opening a RIKEN office in Beijing, and every year since then RIKEN President Ryoji Noyori has given special lectures at Peking University and other major Chinese universities. In addition to the collaborative agreements already in place, a number of Chinese graduate students and researchers have come to work at RIKEN and to attend workshops.

These endeavors coincide with the Japanese government's initiatives toward the creation of an East Asian Community, and there is a general consensus on both sides that Japan and China must cooperate and strengthen their relationship. In China, the promotion of major research projects with Japan is clearly seen by the government as symbolic of the cooperative ties between the two countries. The Chinese government likewise hopes for more personnel exchanges including top-level scientists, and is eager to establish collaborative research laboratories. RIKEN is actively working now to draft concrete measures with the aim of realizing these objectives.

Symposium on emerging and reemerging infectious diseases held in Tokyo

On October 9, the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) and the RIKEN Center of Research Network for Infectious Diseases (CRNID) held a one-day symposium entitled 'Building an Africa–Asia Knowledge Network on Infectious Diseases' at the Marunouchi Building in Tokyo. The symposium capped off

five years of research under the Program of Founding Research Centers for Emerging and Reemerging Infectious Diseases initiated by the MEXT in 2005, and featured talks by leading Japanese and international scientists.

The pressing need for research in the area of emerging and reemerging infectious diseases has been reiterated in recent years with the worldwide spread of the 2009 pandemic influenza and the severe acute respiratory syndrome (SARS). "While infectious diseases heed no national borders," RIKEN CRNID Director Yoshiyuki Nagai pointed out in his introduction, "there are borders in research on infectious diseases." The CRNID, which coordinates a network of 12 research centers across eight countries in Africa and Asia, was created to bridge these borders. Through partnerships fostered by the network, Japanese universities and research institutes work with universities in target countries toward advances in on-site diagnosis and treatment.

The issue of Asian countries becoming 'hot spots' for disease emergence was emphasized in a presentation by Paul Brey, director of the Institut Pasteur in Laos, who noted that factors such as animal reservoirs and the consumption of wild animals accelerate the spread of infection. Brey drew attention to the need for the "networking of networks" in research, a sentiment echoed in presentations on the situations in Vietnam, India, Indonesia and the Philippines. Naoto Keicho, director of the Department of Respiratory Diseases at the International Medical Center of the Japan Research Institute, drew attention to the importance of international cooperation in his studies on tuberculosis in Vietnam. "We cannot focus only on Vietnam," he said, "we have to think about all of Asia."

In the second half of the symposium, Yoshihiro Kawaoka, director of the International Research Center for Infectious Diseases, emphasized the difference between the 2009 pandemic influenza and the seasonal flu, stressing the danger that the 2009 pandemic flu could mutate into a more virulent strain. Koichiro Kudo, director of the Disease Control and Protection Center, reported on his experience visiting Mexico in August to investigate actual cases and on-site treatment methods. These presentations set the stage for a panel discussion focusing on global and domestic responses to the pandemic, including a debate on the effectiveness of vaccines and other preventive measures.

In closing remarks, Nagai highlighted the need for emerging and reemerging infectious diseases to be granted a higher priority in government policy, and looked ahead to the next phase of research in the project of founding research centers.

First Noyori Summer School held at RIKEN Harima Institute

With its increasingly international profile, RIKEN faces a growing need to offer opportunities for young researchers from different countries and fields to meet and interact. The Noyori Summer School, held for the first time in 2009, was created with the aim of answering this need through the support of cross-disciplinary, international interaction.

Roughly 100 PhD students in the International Program Associate, Asia Program Associate and Junior Research Associate programs, conducting their research at RIKEN, gathered at the RIKEN Harima Institute on September 4–5 for a program that included presentations, tours and question and answer sessions.

On the second day, RIKEN President Ryoji Noyori gave a keynote lecture entitled 'To my young colleagues'. In the lecture, Noyori drew an analogy between scientific research and stacking stones on a foundation to create a large, majestic structure. He emphasized that Nobel prizes are awarded, however, to the person who puts a stone in a new and different place. "You are the scientists of tomorrow," he said. "Do you have the courage to place a stone outside the grand and beautiful structure that looms above you?"

In a discussion period entitled 'Hear from Dr Noyori', attendees asked RIKEN's president about success in research, the choices in a scientific career, and the contribution of science to society. "Continuity is at the core of tradition," Noyori explained in response to one question, "but there cannot be new science if we simply believe everything our teachers and textbooks tell us. For you young people, your task is to challenge the accepted theories of today."

While emphasizing creativity and originality, Noyori also highlighted the need to build strong relationships. "It is important that you broaden your perspective while you are still young," he said. "I also urge you to make many friends. Friendships are to be treasured for a lifetime."

One of the attendees, Caroline Rabot from France, said, "The Noyori Summer School was a great chance to meet with colleagues from different research fields and nationalities. It was very exciting to discuss about their research, to build a network and to hear from outstanding scientists such as Dr Noyori and Dr Ishikawa, director of the RIKEN SPring-8 Center." Another attendee, Nuttapol Tanadchangsaeng from Thailand, agreed. "I felt two days seemed so short. Although everyone came from different fields of research, it was a great opportunity at the Noyori Summer School to exchange our knowledge."

Brains interact at the 2009 RIKEN BSI Summer Program

Now in its 12th year, the summer program at the RIKEN Brain Science Institute (BSI) again this year offered its participants a unique introduction to the field of brain science, with a high-profile lecture series and hands-on laboratory internships. Under the theme of 'Interacting Brains', this year's lecture program focused on how brains of diverse animals are specialized for interaction.

The internship program ran from 1 July to 26 August, and included an 11-day lecture course. While some participants attended only the lectures, others in the internship program had the option of enrolling in both the lecture and laboratory components of the program.

Stella Barth, an undergraduate neurobiology major at Harvard University, expressed enthusiasm about her experience. "The researchers here were very welcoming and supportive," Barth said of Kazuo Okanoya's Laboratory for Biolinguistics. "As an undergraduate, I was also granted more independence than I've ever had before."

For undergraduate interns, the program offers a unique introduction to laboratory research. Barth, whose research focus is on the biology of birdsong, described her excitement at being invited to participate in brain surgery on a Bengalese finch. "I've never had that chance before," she said. Ai-hong Song, another participant in this year's summer program, remarked on the institutional connection she had established through the internship component of the program. Song's research in the BSI program followed on her recent findings on cytoplasmic transport in neurons.

"For me, this is just the beginning," she said. "The program has provided a great chance to initiate collaborative research between Atsushi Miyawaki's Laboratory for Cell Function Dynamics, where I did my internship here, and my home institution, the Institute of Neuroscience in Shanghai," she explained.

Special interview

Gaining strength from change

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

RIKEN has undergone a great amount of change since the previous RAC meeting in 2006—some in response to scientific developments, and some specifically prompted by recommendations from the RAC.

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

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

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

RIKEN takes the RAC's recommendations seriously, and sees many advantages in receiving this advice.

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

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

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

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

The RAC presents many recommendations, but a few are particularly urgent or salient.

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

Noyori: Scientists are used to having their work evaluated in many ways, but management, in Japan at least, is never subjected to these same kinds of assessments. We are very proud that our organization will be able to pioneer

RAC Chair Zach Hall (left) with RIKEN President Ryoji Noyori (right)

that reform. The operation of RIKEN, Japan's flagship institute, is open to the world and totally transparent.

RIKEN, with its strengths in the physical and life sciences and its significant large-scale infrastructure facilities, is in a unique position to address the critical challenges of food, environment, energy and health.

Noyori: We have many strong individual research programs, so the key will be finding ways of integrating and building linkages between them. But, we will still need to work together with many external stakeholders. Building such networks is very important and already underway. We have many excellent scientists, but individual efforts will not be enough to address the many serious challenges the world now faces. RIKEN must fulfill our responsibility to future generations.

The global economic crisis has struck particularly hard in Japan, imposing inevitable constraints on RIKEN's new directives and ambitions.

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

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

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

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

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

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

Adapting and evolving to rapid change is challenging, but there is significant value in transformation.

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

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

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

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

International programs

Research starts at RIKEN

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.

The success of RIKEN is based on its people, and it is only by investing in the best people that RIKEN will continue to grow and develop in the future. As well as recruiting top scientists from Japan, RIKEN is actively pursuing greater internationalization and setting its sights on attracting the cream of scientific talent, both young and established, from around the world. These efforts take many forms, from forging closer links with Japanese and international universities, research institutions and corporations, to introducing dedicated programs aimed at assisting foreign researchers become established as part of RIKEN's many research teams. RIKEN aims to help all its researchers realize their full scientific potential and lay the groundwork for long-term careers in research.

RIKEN strives to provide the best and most exciting opportunities for young scientists, both Japanese and international, in the crucially important early stages of their careers. One manifestation of this support comes in the form of RIKEN-funded programs for those wishing to join RIKEN in the fields of physics, chemistry, biology, medical science or engineering for short or long terms; and while RIKEN may not be able to help with all the difficulties foreign researchers will face in their daily life in Japan, it can at least guarantee a scientific experience that is second to none.

Life at RIKEN
a resource for prospective RIKEN researchers

Launched in 2009 with the aim of attracting international scientists, **www.lifeatriken.com** features a comprehensive overview of RIKEN and the many opportunities it offers. With detailed information on RIKEN's facilities, research opportunities and benefit and support systems, **www.lifeatriken.com** will enable both students and senior researchers to make the most of their time in Japan. It also highlights the major achievements and key figures that have shaped RIKEN's century-long history.

A summary of the programs available for non-Japanese researchers can be found at: **www.lifeatriken.com/join-riken.html**

Further details of the programs are available at: **www.riken.jp/engn/r-world/research/research**

Please contact the RIKEN Global Relations Office with all other enquiries (email: **gro-pr@riken.jp**).

International Program Associate

For doctoral candidates

RIKEN offers doctoral students the opportunity to complete their doctoral studies as a RIKEN International Program Associate (IPA) under the supervision of a senior RIKEN scientist. IPAs serve as a source of new ideas and perspectives in research on physics, chemistry, biology, medicine and engineering, and are granted the opportunity to take full advantage of the RIKEN research environment through collaboration and use of shared equipment and facilities.

IPA applicants should be non-Japanese nationals who are, or are soon to be, holders of a master's degree and who have enrolled as a doctoral candidate at a university that has signed (or shows a willingness to sign) an agreement with RIKEN for the Joint Graduate School Program. Funding for the IPA position extends for a maximum of three years (four years in the case of a PhD in medicine) and covers daily living expenses, housing costs and one return trip between RIKEN and the researcher's home country.

The RIKEN researchers in charge of supervising successful applicants must also hold concurrent positions as visiting faculty at a collaborating Japanese or overseas university. RIKEN has thus far accepted about 50 IPAs and aims to increase the number of IPAs to 100 in the near future.

www.riken.jp/engn/r-world/riken/organ/ipa.html

Foreign Postdoctoral Researcher Program

For postdoctoral researchers

The Foreign Postdoctoral Researcher (FPR) program is an opportunity for young, non-Japanese postdoctoral researchers to contribute to the outstanding achievements of RIKEN's ongoing projects. Working under the direction of a laboratory head, successful applicants have the chance to bring their creative and original ideas to life. Experiences at RIKEN provide the foothold young researchers need to build a successful career in science.

The FPR program is among a set of initiatives at RIKEN aimed at creating a stimulating, borderless research environment that will position RIKEN at the forefront of global science and technology.

FPR applicants should be in possession of a doctoral degree by the starting date, and will usually have less than five years' postdoctoral research experience. The contract is initially for one year, and may be renewed for up to three years. In addition to generous remuneration, an annual research budget of one million yen will also be provided. There are currently close to 35 FPRs, and RIKEN will accept and maintain up to 50 FPRs by 2011.

www.riken.jp/fpr

Initiative Research Unit Program

For leaders in their fields

Successful world-class researchers often reach full stride only in their 30s and 40s. The Initiative Research Unit (IRU) program offers ambitious young scientists the chance to fully realize their potential by granting them a high degree of independence and flexibility. The IRU program currently consists of eight research units, led by both Japanese and international mid-career scientists.

IRU applicants should hold a doctoral degree in a field of the natural sciences, and have a proven track record of experience and achievement, including the ability to design and implement an ambitious research plan and manage a small research unit. The full-time position initially carries a one-year contract, but is renewable for up to five years. Each unit is provided an annual grant of about 50 million yen, which covers the leader's annual salary of around 10 million yen as well as research and personnel expenses. Each unit also receives a start-up subsidy in the first year of up to 10 million yen for establishing a laboratory. The leader will have access to RIKEN's common equipment and facilities as well as the freedom to select research and technical staff and apply for competitive grants.

www.riken.jp/r-world/research/research/iru/IRU.pdf

www.riken.jp/engn/r-world/research/research/basic/kokusai2010/index.html

Major projects

New facilities keep RIKEN at the forefront of research

In addition to the many individual laboratories and centers that make up its research resource portfolio, RIKEN is actively pursuing a number of large-scale, long-term projects that will deliver major research infrastructure improvements and establish world-class resources for the benefit of domestic and international researchers. The X-ray Free-Electron Laser (XFEL) facility at the RIKEN Harima Institute and the RIKEN Next-Generation Supercomputer Research and Development Center are just two of these initiatives.

X-ray Free Electron Laser (XFEL) facility at the RIKEN Harima Institute

The brightest in the East

The twin discoveries of X-rays and lasers have had an enormous impact on society, making possible new discoveries in science, opening the door to new industries and providing indispensable tools for medicine.

The X-ray Free Electron Laser (XFEL) facility at the RIKEN Harima Institute marries these two disciplines, extending laser technology into the X-ray region of the electromagnetic spectrum to form what will be, when completed in 2011, the brightest light in the eastern hemisphere. Using beams of electrons travelling at close to the speed of light, the XFEL facility will produce a completely new kind of light with radiation beams a billion times brighter and pulse lengths a thousand times shorter than those available from conventional X-ray sources. The facility will allow scientists to observe natural phenomena that are either too fast or too small to be seen clearly using current methods. Projects in the pipeline include observation of the vibration of individual atoms in chemical reactions and real-time monitoring of proteins, viruses and the development of nanomaterials. The RIKEN Harima Institute has already received many proposals from around the world from teams keen to get their hands on this pioneering laser. “With the addition of the XFEL facility, the RIKEN Harima Institute will soon become a world-class hub of excellence for photon science,” says Tetsuya Ishikawa, XFEL project manager.

RIKEN Next-Generation Supercomputer Research and Development Center, Kobe

Fast forward to ten petaflops computing

Computational methods have established themselves as tools for scientific research that are every bit as important as more traditional theoretical and experimental approaches. The Next-Generation Supercomputer project was commenced in 2006 by the Japanese government with RIKEN as the operating partner as part of the national long-term commitment to advancing the state of the art in computational science. The project, scheduled for completion in 2012, aims to offer ten petaflops performance—equivalent to 10^{16} operations per second—and seeks to establish a platform not only for basic academic research but also for commercial applications that will strengthen Japan's competitiveness in a wide variety of topics of direct benefit to society. Current areas for investigation include materials science, nanotechnology and the life sciences, such as the 'Next-Generation Integrated Simulation of Living Matter' project that aims to model everything from molecules to organs in the human body.

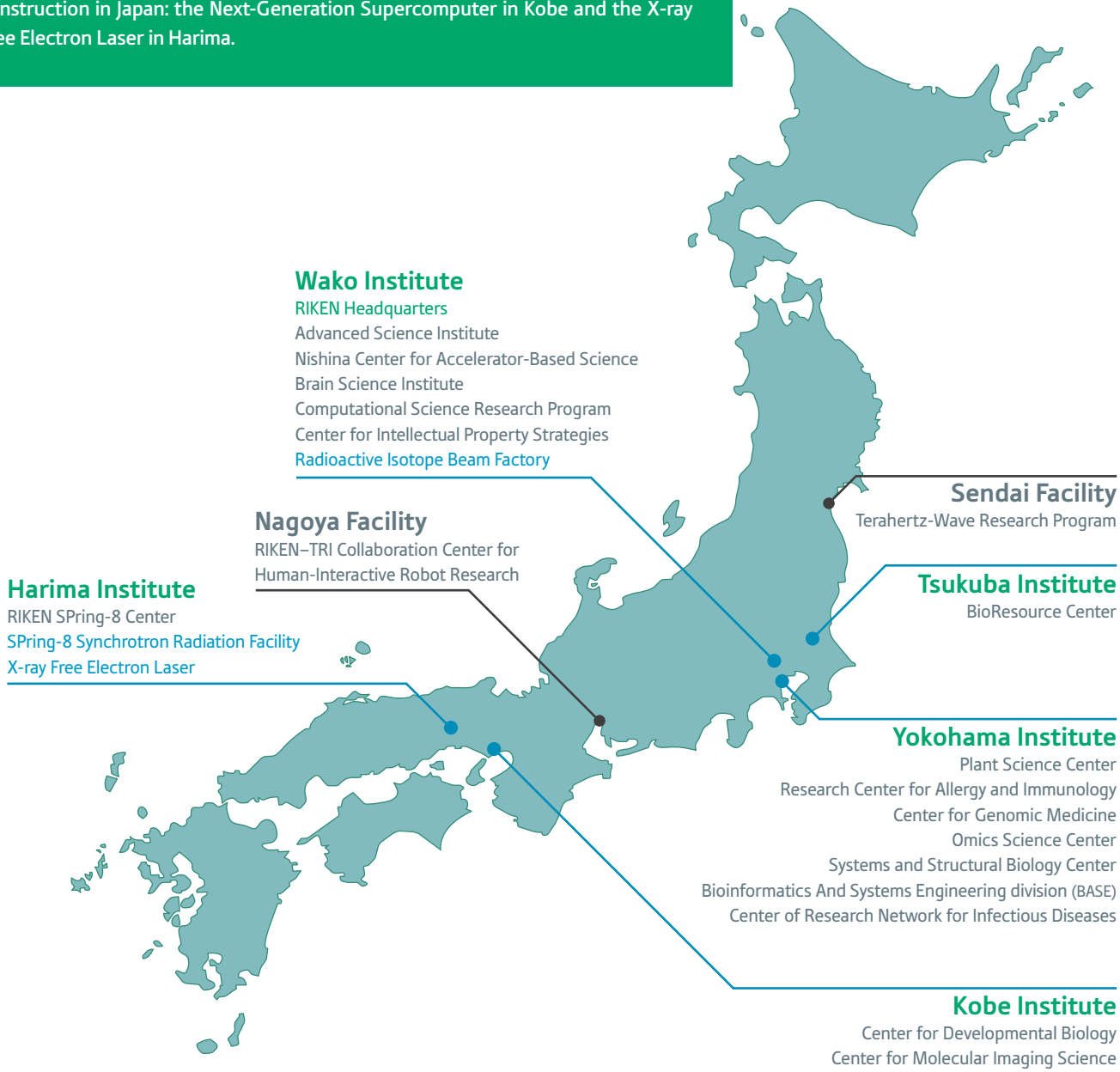
Originally conceived as a vector–scalar hybrid, the project was reconstituted in 2009 with an all-scalar processing architecture and was expanded under the umbrella of the High Performance Computing Infrastructure initiative to offer services that meet the needs of a diverse user base.

A key goal is the development of distinctive software applications and platforms that can be introduced immediately after the facility becomes operational. "We need to be well-positioned to generate research outcomes soon after the project is completed," comments Project Leader Tadashi Watanabe. "We intend to use every second of machine operation time," he adds.

Research institutes, centers and facilities

From Japan to the world

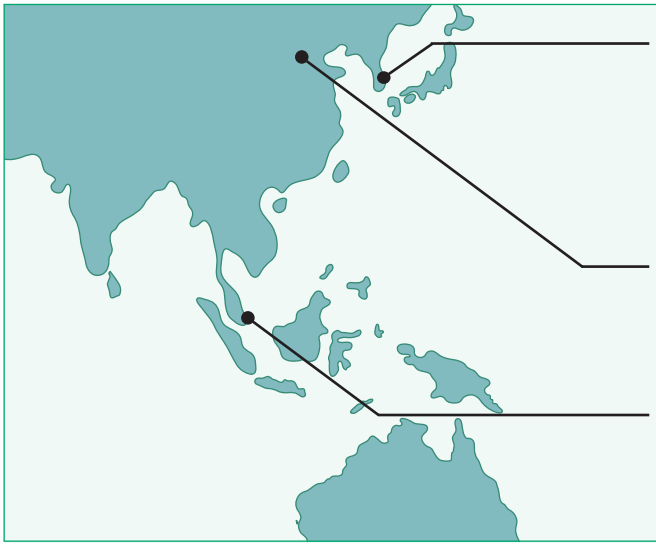
Since relocating its original campus from central Tokyo to Wako on the city's outskirts in 1967, RIKEN has rapidly expanded its domestic and international network of centers and facilities. RIKEN now supports five major institutes and two research facility sites in Japan, and six collaborative research centers around the world. And RIKEN continues to grow, with two major new research facilities now under construction in Japan: the Next-Generation Supercomputer in Kobe and the X-ray Free Electron Laser in Harima.



Japan

Global presence

RIKEN in Asia



RIKEN–HYU Collaboration Research Center Flucto-Order Functions Research Team
Fusion Tech Center
Hanyang University (HYU)
Seoul, Korea
arn.local.frs.riken.jp/research-e.html

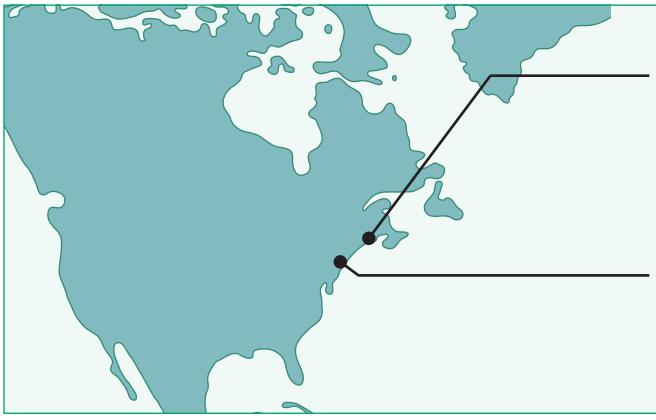
RIKEN China Office
Beijing, China
china.riken.jp

RIKEN Singapore Representative Office
Biopolis, Singapore
www.riken.sg

RIKEN in Europe

RIKEN Facility Office at RAL
RIKEN–RAL Muon Facility
Rutherford Appleton Laboratory (RAL)
Oxfordshire, UK
riken.nd.rl.ac.uk/ral.html

RIKEN in the USA



RIKEN–MIT Center for Neural Circuit Genetics
Massachusetts Institute of Technology (MIT)
Cambridge, Massachusetts, USA
web.mit.edu/picower/about/rikenmit.html

RIKEN BNL Research Center
Brookhaven National Laboratory (BNL)
Upton, New York, USA
www.bnl.gov/riken

RIKEN in Japan

Wako Institute

The Wako campus, the site of the Wako Institute and the RIKEN Headquarters, is located about 30 minutes by train from central Tokyo and serves as RIKEN's center of global operations as well as hosting some of RIKEN's most prestigious research centers and facilities. The **RIKEN Nishina Center for Accelerator-Based Science** (RNC) at the Wako Institute is home to several large-scale projects investigating various fundamental aspects of nuclear physics. At the heart of the RNC is the **Radioactive Isotope Beam Factory** (RIBF), a set of five heavy-ion particle accelerators with which RIKEN physicists study nuclei under extreme conditions and produce novel radioactive isotopes.

The **RIKEN Advanced Science Institute** (ASI) at Wako is where scientists pursue explorative research to establish new fields in all areas of the natural sciences with a strong emphasis on interdisciplinary research. The institute retains a flexible structure that is capable of adapting to new concepts and trends in science.

Working closely with the RIKEN administration at Wako is the **Center for Intellectual Property Strategies** (CIPS), which is charged with managing technology transfer and interactions between RIKEN and industry. The CIPS oversees the portfolio of 25 RIKEN venture capital companies and coordinates supporting research in areas as diverse as nano-functional materials and computational cell biomechanics.

The **RIKEN Brain Science Institute** (BSI), also at Wako, was established in 1997 and continues to attract promising scientists, domestically and internationally, to conduct research into how genes, proteins, cells and neural circuits work to regulate emotions, intelligence and behaviors. The RIKEN BSI enjoys a distinguished international reputation as an innovative, interdisciplinary and collaborative center for brain science research.

The **Computational Science Research Program** (CSRP) is also located centrally at the main RIKEN campus, where researchers work toward creating new and better prediction-based methodologies for real-world applications in science and provide computational support for research at RIKEN. The CSRP develops software for the simulation of natural phenomena, and will make use of the Next-Generation Supercomputer to conduct petaflops-scale simulations of biological processes such as blood-flow, drug metabolism, the dynamics of the brain and neural systems, genomic data assimilation and systems biology.

Yokohama Institute

RIKEN's Yokohama Institute was inaugurated in 2000 as a center for biology, genetics and immunology research. The **RIKEN Systems and Structural Biology Center** (SSBC), one of seven major centers at the Yokohama campus, is at the forefront of efforts to understand the underlying mechanisms of essential cellular processes. Using tools to modulate and re-engineer these pathways, the RIKEN SSBC develops treatments for human disease and generates useful new biomaterials and chemical products.

The **RIKEN Omics Science Center** (OSC) conducts research toward mapping the complex networks of interactions between nucleic acids and proteins that guide an organism's development and survival. The RIKEN OSC is spearheading the ambitious 'Life Science Accelerator' project, an innovative experimental and analytical framework that promises to greatly expedite the identification and integration of these networks.

The **RIKEN Plant Science Center** (PSC) is working to achieve breakthroughs in plant research including food and energy production, environmental remediation and drug discovery through investigation of biological mechanisms for plant growth and productivity. Research at the RIKEN PSC will contribute to protecting crops from environmental challenges such as climate shift, insects and infection. The development of plant strains optimized for the production of useful plant-based compounds and materials is also a target of research at the RIKEN PSC.

At the **RIKEN Center for Genomic Medicine** (CGM), researchers analyze the genomes of thousands of patients in search of tiny variations that could link genes to diseases. Research at the RIKEN CGM contributes to the development of 'personalized' medicine, with the potential to revolutionize healthcare.

The **RIKEN Research Center for Allergy and Immunology** (RCAI) is involved in international collaborations aimed at identifying mechanisms that develop, maintain and regulate the immune system toward the development of therapies for common allergies, autoimmune diseases and cancer.

Also at Yokohama is the **RIKEN Bioinformatics And Systems Engineering division** (BASE), where researchers develop methods to link phenome to genome using a high-speed phenotype mapping system.

The **RIKEN Center of Research Network for Infectious Diseases** (CRNID) networks Japanese institutions with a group of overseas research centers established as part of the reemerging infectious diseases program supported by the Japanese government.

Harima Institute

The Harima campus, west of Kobe in central western Japan, is internationally renowned as the location of RIKEN's **SPring-8** (8 GeV 'super photon ring') synchrotron radiation facility, one of the most advanced facilities of its class in the world. Coupled with the **RIKEN SPring-8 Center** (RSC), the facility aims to become the world's leading center of excellence for synchrotron science. The RSC promotes cutting-edge,

advanced research toward the development of innovative high-energy light sources, such as the soon-to-be-completed **X-ray Free Electron Laser** (XFEL), as well as interdisciplinary photon science research.

Kobe Institute

Situated on an artificial island in Kobe Bay is the Kobe Institute, home to the **RIKEN Center for Developmental Biology** (CDB) and the **RIKEN Center for Molecular Imaging Science** (CMIS). Researchers at the RIKEN CDB have provided the world with insights into the processes that see a single-celled fertilized egg develop into a complex system of functioning tissues and organs. The interdisciplinary nature of RIKEN CDB research relies on close collaboration among scientists in embryology, developmental cell biology, neural developmental biology, stem cell and tissue regeneration research, evolutionary biology and genome research. The RIKEN CMIS is another multidisciplinary center that gathers researchers from diverse backgrounds and areas of expertise to collaborate on the development of molecular imaging for biological applications toward diagnosis and therapeutic applications. RIKEN CMIS researchers aim to advance the drug discovery process in Japan through activities ranging from the design and synthesis of novel molecular probes to the development of new imaging technologies.

The Kobe site is also home to the **Next-Generation Supercomputer**, which is currently under construction and due for completion in 2012. Initiated under a directive of the Japanese government as a key technology of national importance, the new RIKEN supercomputer will be among the most advanced supercomputers in the world, 250 times faster than Japan's Earth Simulator.

Tsukuba Institute

The RIKEN Tsukuba campus has been a center of life sciences research since 1984, but from 2001 the site took on a new significance with the establishment of the **RIKEN BioResource Center** (BRC), now one of the world's most important repositories and distribution centers for many biological materials for life sciences research in Japan and abroad. The center's distinguished position partly lies in its capacity to handle a wide range of living strains of experimental animals (mice), experimental plants (*Arabidopsis*), cell lines of human and animal origin, genetic materials, microorganisms and lines of human induced pluripotent stem (iPS) cells.

Sendai Facility

The RIKEN ASI maintains laboratories as part of the Terahertz Wave Research Program at the Sendai Facility on Japan's Pacific Coast. The program aims to expand terahertz research and establish it as a key technology in practical and industrial applications.

Nagoya Facility

The RIKEN–TRI Collaboration Center for Human-Interactive Robot Research (RTC) at the Nagoya Facility is a collaboration between RIKEN and Tokai Rubber Industries Ltd (TRI) aimed at developing human interactive robots for direct contact with humans at care facilities and in the home.

RIKEN around the world

In addition to its research divisions in Japan, RIKEN maintains a strong presence overseas through its many joint research projects and facility and offices. In the US, RIKEN runs a collaborative research center with Brookhaven National Laboratory (BNL) in New York through the **RIKEN BNL Research Center**. The center is dedicated to the study of high-energy particle interactions, such as lattice quantum chromodynamics, and physics based on experiments at the Relativistic Heavy Ion Collider, including spin physics. Also in the US is the **RIKEN–MIT Center for Neural Circuit Genetics** at the Massachusetts Institute of Technology (MIT) in Cambridge, Massachusetts. The center carries out cutting-edge research in areas such as neural circuit genetics, neuroscience of learning and memory, and multiphoton imaging of synaptic plasticity.

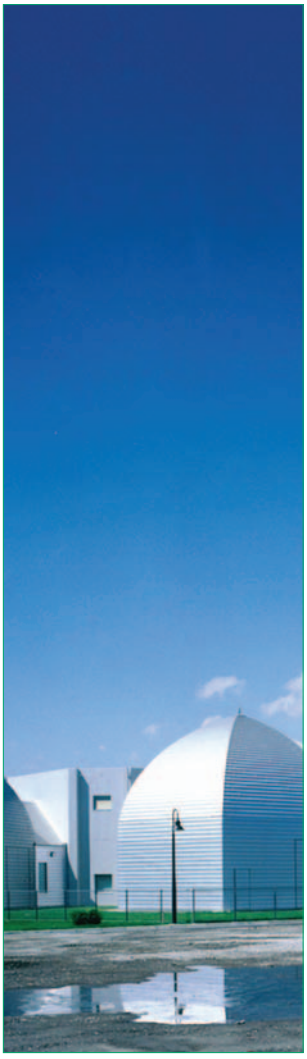
In Europe, RIKEN shares the facilities of the Rutherford Appleton Laboratory (RAL) in Oxfordshire, UK, under the coordination of the **RIKEN Facility Office at RAL**. Working with colleagues from RAL, scientists from the RNC in Japan have constructed the **RIKEN–RAL Muon Facility**—the world's premier muon source and a hub for international muon research.

In Asia, RIKEN in partnership with Hanyang University (HYU) in Seoul, Korea, supports fusion research on 'flucto-order functions' through the **RIKEN–HYU Collaboration Research Center**. The center, working closely with researchers from the RIKEN ASI in Japan, aims to establish a real-time research network in the Asian region for the development of fusion and 'post-nano' technologies, unconventional information-processing technologies and new functional materials. RIKEN also maintains collaboration offices in Singapore through the **RIKEN Singapore Representative Office**, and in China through the **RIKEN China Office**.

Governance

Charting the future course of RIKEN

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**, composed of experts from both within and outside RIKEN, discuss and advise on the overall direction of research activities. This committee prioritizes research areas deemed to be of highest importance, and develops proposals for resource allocation and the systems necessary for carrying out research.

The **Institute and Center Director Committee**, composed of the institute directors and center directors of the five RIKEN campuses, provides a forum for directors responsible for research to exchange information and opinions and share common knowledge on research and management.

The **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 undertakes self-evaluation based on governmental guidelines regarding research themes and the performance of individual scientists. 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 management of the research institutes at RIKEN, providing guidance on future research strategies and improvements to management structures. The most recent RAC meeting in April 2009 was RIKEN's seventh such appraisal.

The **Center and Institute Advisory Councils** are bodies set up within each research center and institution to receive recommendations from eminent Japanese and international scientists in their respective fields of research. The closer integration of the roles of these advisory councils and the RAC began with tabling of shared consultation plans by the president to the seventh RAC meeting in 2009. The council recommendations form an integral part of the ongoing appraisal of RIKEN's performance as a scientific research organization.

The 2009 RAC meeting report is available for download from the RIKEN website at: www.riken.go.jp/engn/r-world/info/report/rac/pdf/7report.pdf

Members of the 2009 RIKEN Advisory Council

RAC core members

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Neuroscience
Emeritus Vice Chancellor, University of California, San Francisco, USA

Hiroo Imura
Vice-Chair
Medicine, endocrinology
President, Foundation for Biomedical Research and Innovation, Japan
Principal Fellow (Chair), Center for Research and Development Strategy, Japan Science and Technology Agency, Japan

Yuan Tseh Lee
Vice-Chair
Chemistry
President Emeritus and Distinguished Resarch Fellow, Academia Sinica, Taiwan
1986 Nobel Laureate

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

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Distinguished University Professor, Center for Bioinformatics and Computational Biology, University of Maryland, USA

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

Toshiaki Ikoma
Electronics
Executive Vice-President and Chief Technology Officer, Canon Inc., Japan

Biao Jiang
Chemistry
Director, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, China

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

Karin Markides
Chemistry
President, Chalmers University of Technology, Sweden

Hans L. R. Wigzell
Medicine, immunology
Director, Center for Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Sweden

Rainer E. Metternich (Absentee participant)
Drug discovery
Vice President, Basic Research and Site Head, W.P., Biomedical Research Administration, Merck Research Laboratories, USA

RAC members and advisory council chairs

Allan Bradley
Cluster of Life Science Platform
Genetics
Director, Wellcome Trust Sanger Institute, UK

Max D. Cooper
Research Center for Allergy and Immunology
Medicine
Professor, Department of Pathology and Laboratory Medicine, Emory University, USA

Hidetoshi Fukuyama
Advanced Science Institute
Basic solid state science
Professor, Department of Applied Physics, Faculty of Science, Tokyo University of Science, Japan

Sydney Gales
Nishina Center for Accelerator-Based Science
Nuclear physics
Director, Grand Accelerateur National D'Ions Lourds, France

Sten Grillner
Brain Science Institute
Neuroscience
Professor and Director, Nobel Institute for Neurophysiology, Karolinska Institutet, Sweden

Wilhelm Gruissem
Plant Science Center
Plant biotechnology
Professor, ETH Zurich, Institute of Plant Sciences, Switzerland

Jean-Louis Guenét
BioResource Center
Veterinary medicine, mouse genetics
Director, Unité de Génétique des Mammifères, Institut Pasteur, France

Jerome Hastings
RIKEN SPring-8 Center
Applied physics
Professor, Photon Science, SLAC National Accelerator Laboratory, USA

Bengt Långström
Center Molecular Imaging Science
Biochemistry
Professor, Department of Biochemistry and Organic Chemistry, Uppsala University, Sweden

Mark Lathrop
Center for Genomic Medicine
Gene science
Director General, Center National de Genotypage, France

Austin Smith
Center for Developmental Biology
Stem cell biology
Medical Research Council Professor and Director, Wellcome Trust Centre for Stem Cell Research and Institute for Stem Cell Biology, University of Cambridge, UK

The SPring-8 Center in Harima

THE YEAR IN RESEARCH

Research highlights from *RIKEN RESEARCH*

RIKEN supports thousands of researchers at numerous institutes and centers throughout Japan and the world. Every year, these researchers together publish several hundred research articles in top scientific and technical journals across a broad spectrum of disciplines—physics, chemistry, biology, medicine, engineering and many areas of technology.

The very best of this research is highlighted in *RIKEN RESEARCH*—an online and print publication showcasing RIKEN's scientific, engineering and technological achievements. The following selection of research highlights from 2009 demonstrates the caliber of research conducted at RIKEN. All of the year's research highlights and more, including the latest news and developments, can be found at the *RIKEN RESEARCH* website and in the monthly print magazine.

www.rikenresearch.riken.jp

Physics & engineering

Tapping the cosmic pulse (*RIKEN RESEARCH*, Jul. 2009)

Physics & engineering

New stars on the horizon

From raising fundamental questions about the universe to unearthing novel electronic materials and providing new clues to medical treatments, physics experiments and discoveries at RIKEN during 2009 continued to break new ground at the forefront of contemporary research.

The universe around us

The vastness of space holds surprises for physicists as they press for a better understanding of the laws and processes that govern our Universe. In the search for further discoveries, researchers are now using the orbiting Fermi Gamma-Ray Space Telescope launched by NASA in 2008 to record the high-energy gamma-ray radiation. Nobuyuki Kawai and colleagues from the RIKEN Advanced Science Institute (ASI) are participating in this research effort (*Pinpointing pulsars*, Jul. 2009). From data yielded by the telescope, they have already made a major discovery, identifying a new class of pulsar—the remains of dying stars that collapse in giant supernova explosions.

Typically, pulsars are identified by their oscillating signal at radio frequencies, but the newly identified class emits intense gamma-rays at short intervals. The finding suggests that a much larger variety of pulsars await discovery. This will be an ongoing task for the team at RIKEN and their international collaborators.

The life and death of stars are catalysts for the creation of all the elements in the Universe. Yet, fundamental questions remain as to why the relative quantity of elements is as we observe it. The balance between positively charged protons, which determine the character of an element, and the electrically neutral neutrons, which determine the isotope of an element, are subject to ongoing scientific research.

Pieter Doornenbal and Heiko Scheit from the RIKEN Nishina Center for Accelerator-Based Science and colleagues are working on this nuclear physics question using the recently completed Radioactive Isotope Beam Factory, the world's most powerful ion accelerator (*Too many neutrons break the rules*, Sep. 2009). Using the rare and exotic atomic isotopes generated by the new facility, the researchers upturned the long-standing assumption that isotopes containing exactly 20 neutrons or protons form 'magic number' nuclei—isotopes that are particularly stable against radioactive decay. This surprising discovery poses new questions regarding our understanding of the structure of atomic nuclei.

A new spin on applications

Over the past year, topological insulators have come to the fore as a hot topic of research in the field of condensed matter physics. These compounds have unusual electronic quantum states that allow more stable exploitation of an electron's spin compared with conventional materials. Importantly, the electronic properties of topological insulators provide unique advantages for dealing with electron spin that could lead to new applications in the rapidly advancing field of spin electronics.

The discovery of topological insulating properties in selenium- and tellurium-based semiconductor compounds by international research teams triggered renewed interest in topological insulators

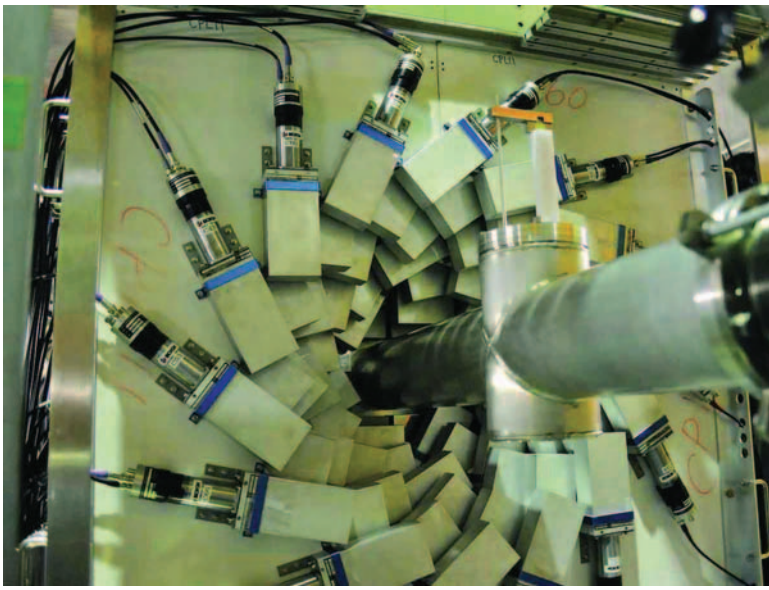
in the past year, sparking a new crop of research activities at RIKEN. A new experimental X-ray scattering technique developed by Hidenori Takagi and colleagues from the RIKEN ASI, for example, is allowing the magnetic and electronic properties of a material to be determined with unprecedented precision (*Magnetic x-ray vision*, Jul. 2009, see p. 24). Amongst several other uses in the study of magnetic materials, this technique is also suited to identifying topological insulator candidates from among many complex oxides. The successful candidates could be of great importance for device applications as their stronger insulating nature promises topological insulating behavior up to room temperature—unlike all other known compounds.

Multiferroic materials—in which electric and magnetic properties are coupled—are another example of intriguing new electronic materials. 'Multiferroics' have potential applications in sensing or electronic devices where electric (magnetic) fields control magnetic (electric) properties. Yusuke Tokunaga, Yoshinori Tokura and colleagues from the RIKEN ASI not only discovered the multiferroic compound $GdFeO_3$, but also showed that the magnetoelectric coupling in this compound is very strong at low temperature (*All together now*, Aug. 2009). Moreover, the researchers revealed that the coupling is facilitated by the domain walls that separate the regions of different magnetic and electric orientations within the material. This means that the domain walls drive the switching of electric and magnetic fields, an insight that will be important in the design of future applications. Their work highlights the importance of interfaces across or within materials, where the careful engineering of material properties may lead to novel practical applications.

The physics of biological systems

As large molecules often consist of hundreds of thousands atoms, understanding the many complex proteins that control biological functions is a daunting research field. RIKEN physicists are making inroads on this front by analyzing the structure of complex proteins through high-resolution X-ray scattering experiments using RIKEN's SPring-8 synchrotron.

Systems composed of more than one protein, however, represent a particularly significant challenge for these experiments. Among the cellular sensory processes that plants, bacteria and fungi use to sense external conditions are 'two component systems' consisting of two specific proteins. Through detailed X-ray scattering analyses, Yoshitsugu Shiro and colleagues revealed the mechanistic details of the interaction between these proteins (*Seeing the sense in it all,* Jan. 2010, see p. 25). This information could lead to the development of new antibacterial drugs aimed at disturbing the interaction between these proteins, which provide essential functions for bacteria but not humans.



The DALI2 detector array (shown here during construction) at the Radioactive Ion Beam Factory allows RIKEN researchers to study a range of exotic isotopes (*Too many neutrons break the rules*, Sep. 2009).

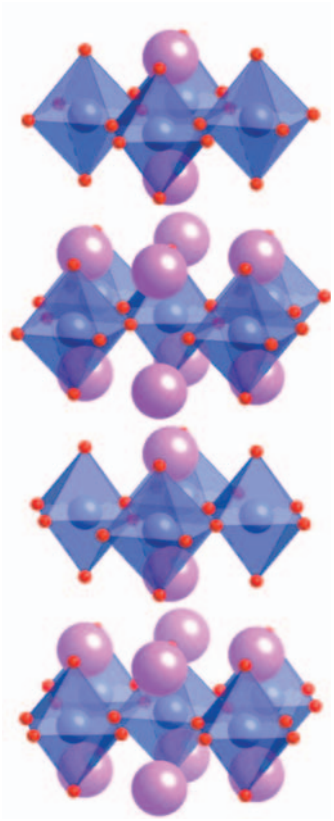
Whether contributing to the understanding of fundamental processes, such as the death of stars and the stability of atomic elements, or to applied research, such as novel electronic devices and new therapeutics, physics research at RIKEN continues to remain strong across a wide range of disciplines. ■

Related highlights from *RIKEN RESEARCH*

- *The single photon switch,* Feb. 2009
- *A tale of two excitations,* Apr. 2009
- *Spin lattices enter a new phase,* May 2009
- *The pairing habits of superconductors,* Jun. 2009
- *Capturing electrons in action,* Sep. 2009
- *Netting new physics from a stellar collapse,* Oct. 2009
- *Sifting out the sources of spin*, Dec. 2009

Magnetic x-ray vision

Enhancements to an experimental technique reveal novel magnetic materials



Crystal structure of Sr_2IrO_4 (pink, Sr; red, O; blue, Ir).

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

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

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

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

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

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

Seeing the sense in it all

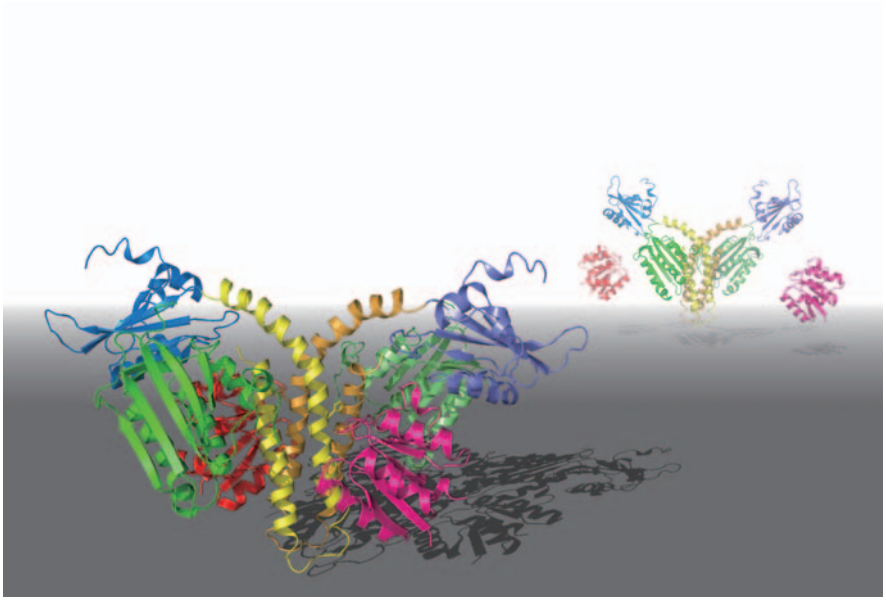
Structural details of an environment-sensing protein complex could guide development of new drugs to direct plant growth or combat bacterial infection

Plant, fungal and bacterial species all rely on cellular sensory processes known as 'two component systems' (TCS) to monitor external conditions and deliver instructions on how to respond to fluctuations. "TCS can sense and respond to a variety of environmental changes related to osmotic pressure, oxygen, amino acids, metal ions, nutrients, light, hormones, and so on," explains Yoshitsugu Shiro of the RIKEN SPring-8 Center in Harima.

Each TCS is composed of two proteins: a histidine kinase (HK), which is the outward-facing receptor, and a response regulator (RR), which transmits HK signals within the cell. Following activation by an external stimulus, HK picks up a phosphate group from an adenosine triphosphate (ATP) molecule, which it subsequently transfers to the RR in order to activate it.

Many mysteries remain about TCS signaling mechanisms, partly because the proteins involved are complicated and contain floppy, mobile regions that make structural analysis arduous. Shiro and his colleagues recently achieved a breakthrough on this front, however, by assembling a high-resolution reconstruction of the ThkA/TrrA TCS complex from *Thermotoga maritima*[1]. This bacterium is normally found within geothermal vents, and its proteins exhibit greatly enhanced stability at working temperatures, making structural analysis more feasible.

The HK component, ThkA, assembles in pairs through interactions at a 'dimerization domain', which also contains the histidine amino acid that receives—and eventually transfers—the phosphate group. Accordingly, Shiro's team found that the TrrA 'phosphoacceptor' aligns closely with this residue, with its orientation governed primarily by three points of interaction between the two proteins. However, they also noted that ThkA's sensor domain appears to interact with the catalytic domain, blocking access to the phosphate-receiving histidine and thereby preventing activation. Since ThkA/TrrA is similar to another bacterial signaling TCS, FixL/FixJ, which undergoes physical rearrangements in the presence of oxygen, they hypothesize that this blocked configuration might represent the 'off state' of a switch that enables selective activation (pictured). "The mode of interaction between the sensor and catalytic domains of HK reveals the signal-transduction pathway at an atomic level," says Shiro.



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Model of the ThkA/TrrA TCS complex. The structure in the foreground may represent the 'off' state for this system, where the catalytic domain is physically blocked from interaction with the receptor phosphorylation site. In the background is a proposed structure of the system in its 'on' configuration.

Encouraged by these and other mechanistic insights, Shiro's team is now moving on to study the TCS governing plant response to the growth hormone ethylene, but he sees other potential benefits from this work. "Structural information from TCS could help the development of antibacterial drugs without undesirable side effects," says Shiro, "because TCS is essential for the bacterial life cycle, but not present in humans."

1. Yamada, S., Sugimoto, H., Kobayashi, M., Ohno, A., Nakamura, H. & Shiro, Y. Structure of PAS-linked histidine kinase and the response regulator complex. *Structure* **17**, 1333–1344 (2009).

A prototype accelerator for the X-ray Free Electron Laser at the Harima Institute

Chemistry, nanotechnology & materials

Casting a new light on chemical reactions

In many ways, 2009 was the year when chemists finally attained a detailed view of what was happening inside their test tubes. Whether smashing molecules together at breakneck speeds, blasting them with high-energy X-rays, or making them dance using ultrashort-pulse lasers, RIKEN researchers have developed ingenious ways to observe chemical reactions as they occur.

Eyeing reactions

When DNA strands within our bodies absorb ultraviolet light, their electrons become excited and jump to higher energy states; this excess energy must be quickly released, otherwise destructive free radicals form that break DNA apart, leading to ailments such as skin cancer. A better picture of this process would help in the fight against cancer, but because the excited electrons move so fast—within a trillionth of a second—detecting these events has been difficult.

Toshinori Suzuki of the RIKEN Advanced Science Institute (ASI) and colleagues have developed a technique to track electrons excited by ultraviolet light using lasers that emit light faster than atoms can move (*Chemistry gets a new set of eyes*, Sep. 2009). After initiating a photochemical reaction in a molecule known as pyrazine, the researchers used a special two-dimensional detector to map the real-time distributions of excited electrons. This is a valuable new tool to image how and why multifaceted chemical reactions take place.

Although many of life's most important processes take place in water, directly observing how water molecules participate in important reactions, such as acid–base transitions, is extremely challenging. Shik Shin and colleagues have used the powerful X-rays of RIKEN's SPring-8 synchrotron to measure, for the first time, the quantum signals of acetic acid in aqueous solutions (*Stability reigns*, Dec. 2009).

As acetic acid in aqueous solution is in dynamic equilibrium, chemists previously believed that acetic acid switched frequently between two different forms, either neutral or ionized, through forward and backward elementary reactions. However, the X-ray experiments revealed that water molecules play an unexpected role: they prevent any dynamic switching between acetic acid states, likely by forming a stabilizing 'shell' around each molecule. The surprising influence of water in this reaction should spur further investigations into poorly understood solvent effects.

Better routes to flexible lighting

Molecules that generate their own illumination are playing a central part in new lighting technologies. Organic light-emitting diodes (OLEDs) use a polymer film, sandwiched between transparent electrodes, to produce display types that are lighter, more flexible and more efficient than liquid-crystal materials. Within the polymer film are phosphorescent metal complexes that emit bright radiation when stimulated by low voltages. However, these complexes create difficulties during OLED manufacturing: if strict concentration limits are not followed, the metal centers clump together and deactivate one another.

Mass production of OLEDs could become easier thanks to a new chemical strategy developed by Zhaomin Hou of the RIKEN ASI

and colleagues (*Organic lighting offers a bright future*, Aug. 2009, see p. 28). The researchers modified a phosphorescent iridium complex with nitrogen-bearing molecules known as amidinates that bind tightly to the metal centers. Because the amidinates stop the metals from aggregating together, a wide range of concentrations—from 7 to 100% phosphorescent materials—can be used to produce OLEDs with bright yellow–green emissions, with more colors on the way.

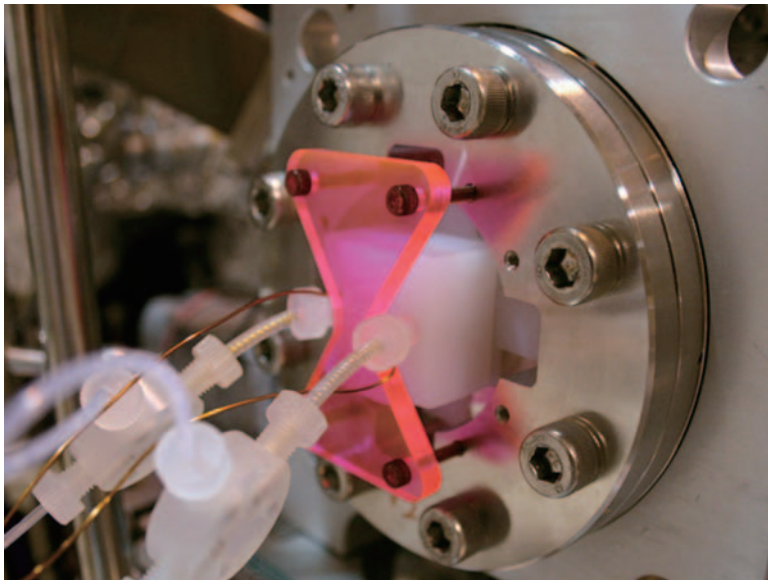
Natural creations

Many important pharmaceutical compounds are sourced from natural products—chemicals manufactured by living species. The complex and unusual structures of these biological molecules are difficult for chemists to reproduce, and often require new synthetic approaches. Mikiko Sodeoka of the RIKEN ASI and colleagues' success in producing an essential fragment of the natural product, called physalin B (*Natural products: Cage closed*, Sep. 2009), is an achievement that has eluded researchers for more than 50 years.

Physalin B, isolated from a tropical plant known as ground cherries, is a steroid-type molecule with potent anti-tumor activity. Researchers believe that these medicinal effects arise from the unique structure of this molecule, especially a cage-like component made up of four interconnected rings. By employing a multi-step domino reaction—a cascading series of chemical transformations that occur under mild conditions—Sodeoka and her team synthesized the molecular cage using a single reaction vessel. This new synthetic method will aid scientists in understanding how nature can use simple inputs to make intricate molecules with therapeutic properties.

Nanoscale coordination

Expertise from multiple disciplines—such as biology, chemistry, and engineering—is being combined in the emerging field of nanotechnology to produce new devices that function on an atomic scale. Establishing control over complex natural molecules like DNA, however, demands innovative techniques and state-of-the-art analytical tools. By developing a novel DNA complex that can be switched between single and duplex strands using the power of light, Shinzi Ogasawara and Mizuo Maeda of the RIKEN ASI have achieved the reversible control needed to further advance DNA nanomachines and architectures (*Making the switch for DNA*, Mar. 2009, see p. 29).



RIKEN's SPring-8 synchrotron has been used to measure the quantum signals of acetic acid in aqueous solution using a liquid reaction cell (*Stability reigns*, Dec. 2009).

To make their nanoscale switch, the researchers attached molecules known as photochromic nucleosides (PCNs)—biochemical compounds that contain a light-sensitive functional group—to DNA duplexes. When irradiated with light, the PCNs undergo a geometric transformation known as a cis–trans isomerization, which expands the PCN structure, splitting the DNA duplex apart. Applying a different frequency of light to this material switches the isomerization and brings the DNA strands back together into a duplex.

Through cutting-edge experiments that reveal how molecules detect, generate and interact with light, RIKEN researchers are gaining crucial insight into previously hidden chemical actions. Such explorations are leading to breakthroughs in pharmaceutical synthesis, ultra-bright materials and DNA-based nanotechnology—achievements that are set to continue throughout 2010. ■

Related highlights from *RIKEN RESEARCH*

- *Nanoparticles get svelter in the heat,* Apr. 2009
- *Seeing molecules move in real-time,* May 2009
- *Smashing pictures,* May 2009

Organic lighting offers a bright future

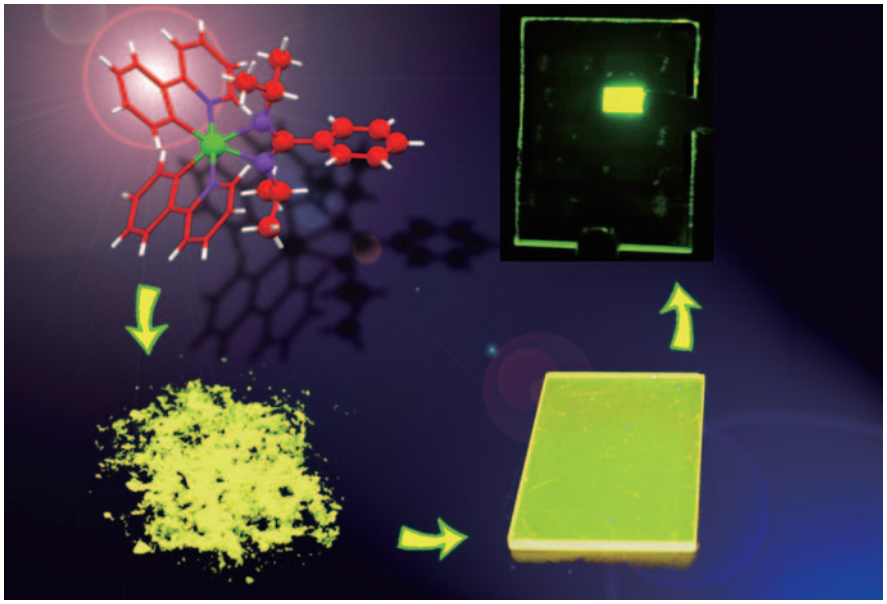
New phosphorescent complexes improve manufacturing of high-efficiency light sources

Organic light-emitting diodes (OLEDs) are set to revolutionize lighting technology, ushering in an era of thin, flexible, and ultra-bright devices. At the heart of recent OLED devices are phosphorescent metal complexes that, when stimulated by an electric voltage, produce a sustained emission of light with higher efficiency than other sources. Furthermore, because OLEDs create their own light, they eliminate the need for backlights used in liquid crystal displays, and therefore consume low amounts of power.

Although the advantages of OLEDs are impressive, manufacturing these devices remains a challenging and expensive process. Phosphorescent OLEDs are normally fabricated by via a process known as 'doping' where metal complexes are added into a host matrix under strict concentration requirements. If the metal concentration is too high, the complexes interact and quench each other's phosphorescent abilities.

Now, a team of scientists led by Zhaomin Hou from the RIKEN Advanced Science Institute in Wako has developed a way to eliminate precise doping limits from the OLED manufacturing process[1]. By using a metal dopant containing molecular groups that block the self-quenching interactions, the scientists have, for the first time, fabricated high-efficiency OLEDs with a wide range of doping concentrations.

Hou and colleagues modified a phosphorescent iridium metal complex with a class of molecules known as amidinates. These molecules bind to iridium through a nitrogen atom that localizes electrons near the center of the metal complex. Bulky carbon groups on the edges of the complex are inert and prevent the materials from attaching and self-quenching their phosphorescence.



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A phosphorescent iridium–amidinate complex (top left) serves as an excellent emitter (bottom), enabling the first successful fabrication of highly efficient non-doped phosphorescent OLEDs (top right).

Prototype OLED devices made with the iridium–amidinate complex exhibited a bright yellow-green emission (pictured) using very low driving voltages. The scientists found that a wide range of doping concentrations—from 7% to 100%—could be used to produce the OLED devices.

"One of the research projects in my group led to an efficient synthesis of various amidinates," says Hou. "We envisioned that a geometrically hindered amidinate group might overcome the problems encountered previously in phosphorescent metal complexes."

According to Hou, the iridium complex itself possesses charge-transport ability, removing the need for a host matrix. Moreover, because of the excellent performance and the ease of synthesis, the iridium–amidinate phosphorescent complexes should have high potential in practical applications such as flat-panel displays and organic lighting.

"We are now applying the amidinate molecules to phosphorescent metal complexes that emit light at different wavelengths," says Hou. "This will allow us to produce new high performance OLED devices with different colors." ■

1. Liu, Y., Ye, K., Fan, Y., Song, W., Wang, Y. & Hou, Z. Amidinate-ligated iridium(III) bis(2-pyridyl)phenyl complex as an excellent phosphorescent material for electroluminescence devices. *Chemical Communications* **25**, 3699–3701 (2009).

Making the switch for DNA

New switches could lead the way in controlling DNA duplex formation with potential nanotechnology applications

Two RIKEN researchers have developed a switch to control the formation and separation of DNA duplexes that may have implications in many biological processes, such as gene regulation.

Formation of complexes of our genetic building blocks, the nucleic acids, underlies many biological events. Hybridization of the nucleic acids, through interactions known as base pairing, forms the intricate complexes responsible for the formation of DNA duplexes. The ability to control hybridization, and consequently whether biological events take place, is a very important goal for scientists.

Now, Shinzi Ogasawara and Mizuo Maeda at the RIKEN Advanced Science Institute, Wako, have developed a light-controlled switch that directs the formation and destabilization of a series of DNA duplexes[1].

They designed the photoswitch, a photochromic nucleoside (PCN), with several fundamental properties and benefits. The switch can be easily incorporated into a DNA strand and its physical conformation can be altered reversibly when irradiated by an external light source. Change of the physical conformation, by isomerization, disrupts and destabilizes the hybridization of two DNA strands. Another benefit of the PCN switch is that installing it into DNA has little influence on the structure of the duplex when it forms. Further, the PCN can be used as molecular trace label because it is fluorescent. This PCN photoswitch is therefore easy to track in the body and could be used in living cells without disruption.

The researchers irradiated a series of reaction mixtures containing PCN-modified DNA duplexes, which were fluorescent, with light at 370 nm for 5 minutes. After this time, only a slight fluorescence was seen. The PCN fragments had isomerized and the duplex broken. They then irradiated the mixtures at 254 nm for 2 minutes and the fluorescence returned, indicating a change back in conformation of the PCNs and importantly, hybridization to re-form the duplexes (pictured). This switching showed good reversibility over two cycles.

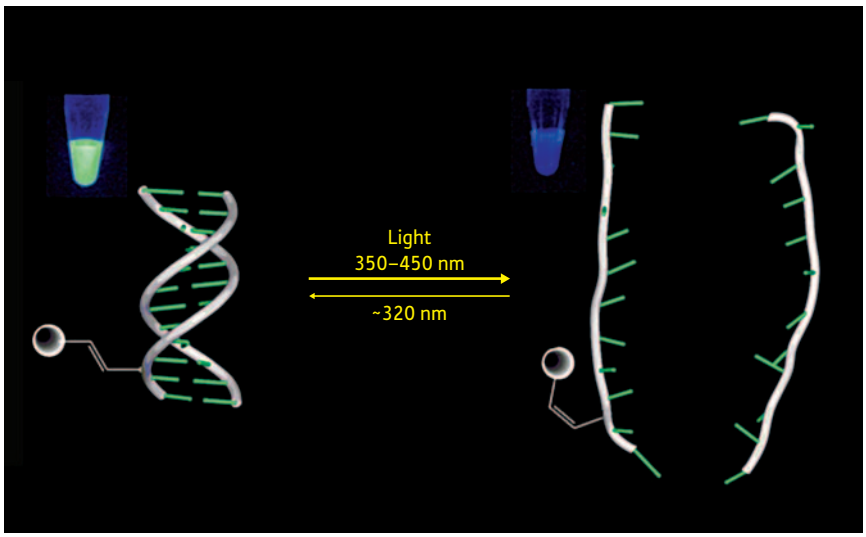


Illustration showing the reversible formation and destabilization of a DNA complex by a photochromic nucleoside (PCN) that changes formation under differing light conditions. The changes are monitored by fluorescence.

Surprisingly, this easy switching system also works below room temperature. Ogasawara is naturally pleased with the current results. "There were no particular problems we had to overcome," he says. However, the synthesis of the PCNs was not as straightforward as they would have liked.

Ogasawara and Maeda now want to build on the results of this current study. "We plan to apply this technology to gene regulation such as antigene, antisense and siRNA," says Ogasawara. "We think that this light-switching technique can be applied to nanotechnology, for example [using] light [to] control DNA nanomachines and architectures." ■

1. Ogasawara, S. & Maeda, M. Straightforward and reversible photoregulation of hybridization by using a photochromic nucleoside. *Angewandte Chemie International Edition* **47**, 8839–8842 (2008).

Genomics

Genomics

Reading between the letters

Next-generation sequencing technologies are now broadly accessible to both scientists and the public, but a genome is more than just the sum of its sequences and there remain many mysteries to be untangled. By effectively mining the wealth of sequencing data, researchers at RIKEN are making valuable progress in exploring the deeper mysteries of gene structure, function and regulation.

Pattern recognition

The Functional Annotation of the Mammalian Genome (FANTOM) Consortium is an international research collaboration spearheaded by the RIKEN Omics Science Center in Yokohama. FANTOM has addressed diverse genomic questions over the past decade, but it is currently focused on the complex regulatory processes governing gene activity. In three landmark articles published in April 2009, the consortium—now known as FANTOM4 and headed by RIKEN scientists Harukazu Suzuki and Yoshihide Hayashizaki—described the use of a technique called 5' cap analysis of gene expression (CAGE) to precisely determine sites where gene expression begins, and thereby characterize adjacent binding sites for expression-modulating transcription factors (*Filling out the map*, Jun. 2009). Their analysis revealed unexpected complexity, with gene expression dependent on tightly coordinated activity from multiple regulators rather than just a few 'master' controllers. They also uncovered a surprisingly active role for retrotransposons; these self-replicating DNA sequences scattered throughout mammalian genomes were previously considered passive 'hitchhikers', but instead appear to directly modulate gene expression. More mysteriously, the team also came across a new class of tiny, non-protein-coding RNA that localizes near start sites, but with as yet unknown functionality.

Genomic data is also a powerful tool for identifying disease risk factors. By identifying DNA sequence variations that are genetically associated with a specific condition within a given population, scientists can spotlight chromosomal regions that may contain causative genes. These segments can include hundreds of genes, each requiring further analysis, but Tetsuro Toyoda and colleagues at the RIKEN Bioinformatics And Systems Engineering division (BASE) in Yokohama have developed a tool that takes some of the pain out of this process (*Innovation via genetic 'googling'*, Nov. 2009).

Decades of genetic research have produced a bounty of published articles and databases containing information that could help scientists connect genes with diseases—if they only knew where to look. PosMed is a sophisticated search engine based on the principles of neural networks, which combs through over 17 million scientific documents and flags candidate genes from humans, mice and rats based on explicit or inferred disease associations. The resulting hits within a chromosomal region of interest are then ranked to help scientists focus their resources more productively.

Genomics goes green

PosMed isn't just for mammals, however; Toyoda's team has also developed a version containing data from rice (*Oryza sativa*) and thale cress (*Arabidopsis thaliana*), popular genetic model organisms, offering the potential to reveal genes that could facilitate agricultural solutions to global hunger, environmental problems and more.

Kazuo Shinozaki and colleagues at the RIKEN Plant Science Center in Yokohama have also achieved a valuable breakthrough in this area through their work with the ubiquitous soybean, *Glycine max* (*Building a soy gene catalogue*, Jun. 2009). Shinozaki's team participated in the multinational consortium that sequenced the *G. max* genome, and one valuable by-product of this effort was a catalog of over 6,500 genes expressed by this plant under a variety of environmental conditions. Many of these have never been characterized, and more than 4.8% have no known counterpart in any other plant species. In an effort to accelerate analysis and application of these data, Shinozaki and his collaborators have posted the data publicly, and the genes identified in this study have already been incorporated into commercially available tools for gene expression analysis.

Put to good use

With a large collection of cloned genes in hand, the next challenge is finding ways to characterize function. Brewer's yeast, *Saccharomyces cerevisiae*, is a simple eukaryote with a fully sequenced genome, and a valuable model for genetics and cell biology. To further extend its utility, Minoru Yoshida of the RIKEN Advanced Science Institute in Wako partnered with Canadian researchers to develop a yeast gene library suitable for a wide variety of functional and drug characterization studies (*Cellular insights via barcoded yeast genes*, Aug. 2009, see p.32).

They cloned 90% of *S. cerevisiae* genes—nearly 5,000 in total—into special DNA vectors containing unique nucleotide sequence 'barcodes', which considerably simplify experiments in which large numbers of genes are being screened. By introducing this library into yeast with mutations that increase resistance to an otherwise toxic compound, researchers can identify barcodes that disappear when the yeast are treated with the drug—thereby revealing target genes that mediate its deadly effects.

In spite of the staggering diversity of genetics, scientists sometimes crave access to proteins with properties not found in nature. This can be achieved by manipulating the enzymes that help cells translate the genetic code, yielding proteins that incorporate synthetic amino acids beyond the standard 20. Shigeyuki Yokoyama's team at the RIKEN Systems and Structural Biology Center in Yokohama found success with such techniques, but realized that these manipulated enzymes tend to make mistakes that reduce their overall efficiency (*Staying true to the code*, Mar. 2009, see p.33).

The cloning of species such as rice to acquire stronger and more productive crops could be made easier thanks to the intelligent search engine PosMed-plus (*Innovation via genetic 'googling'*, Nov. 2009).

Further engineering solved this problem; Yokoyama's team appended a 'proofreading' domain onto these enzymes, which greatly boosted their specificity. This breakthrough improves prospects for other researchers looking to move beyond the constraints of the genomic code but also, like the work of other RIKEN researchers, represents valuable progress towards understanding how to unlock the power hidden behind the genome's seemingly endless strings of the letters A, G, T and C. ■

Related highlights from *RIKEN RESEARCH*

- *Double trouble*, Feb. 2009
- *Stay of execution*, Mar. 2009
- *Dividing the photosynthetic spoils*, Apr. 2009
- *Unearthing the diversity of plant chemicals*, May 2009
- *Shortening the generation of generations*, Jul. 2009
- *Cellular secrets exposed in living color*, Nov. 2009
- *A beacon of change*, Dec. 2009
- *The simple truth*, Dec. 2009
- *Putting the brakes on cell death*, Dec. 2009

Cellular insights via barcoded yeast genes

A newly created yeast gene archive will enable efficient analysis of the function of bioactive compounds with potential pharmaceutical use

By establishing a library of individual yeast genes, each cleverly tagged with its own molecular barcode, an international team of molecular geneticists has designed a valuable resource for pharmaceutical research with advantages over previous approaches.

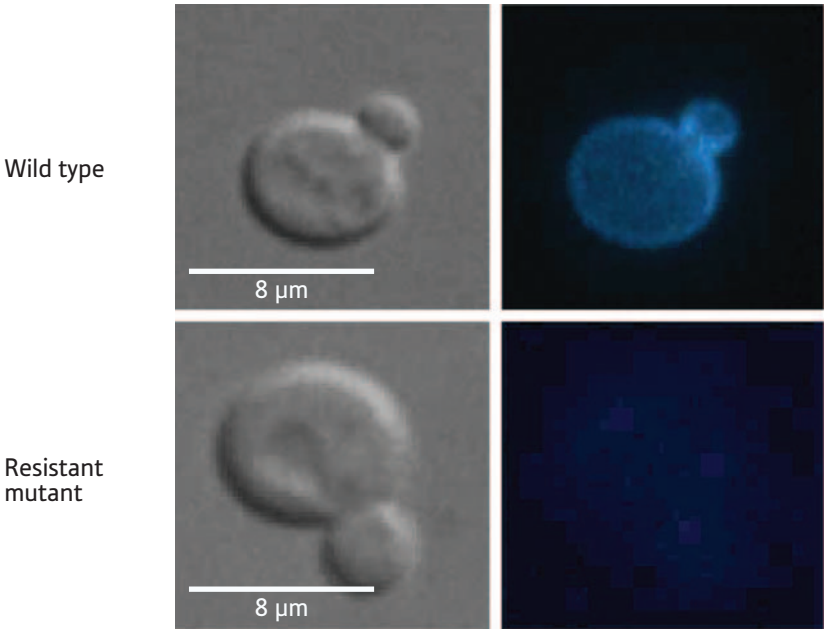
The research team, including Minoru Yoshida at the RIKEN Advanced Science Institute in Wako, and Charles Boone at the University of Toronto, Canada, developed the library in which each yeast gene is copied and attached to two unique single stranded DNA molecules that act as barcodes. This enables researchers to efficiently identify each gene.

The yeast-based chemical-genomics approach, presented recently in *Nature Biotechnology* by Yoshida and colleagues[1], is useful because many medicinally important drugs target fundamental biological processes that are conserved between yeast cells and higher organisms.

Using the team's approach, all the gene-carrying units, or plasmids, in the yeast are carefully constructed individually, as opposed to conventional genomic libraries that are created from random fragments of DNA. Each plasmid carries a single yeast gene as well as two 20-nucleotide barcodes that identify it. The library comprises plasmids for almost 5,000 genes and covers approximately 90% of the yeast genome.

Other approaches to examine the genetic influence of potential drugs have limitations such as needing high volumes of test compound, which can be of limited availability, or being labor intensive.

Most significantly, the newly created gene catalogue will enable researchers to identify at the genetic level the precise modes of action of specific compounds that are being screened as potential pharmaceuticals. The library can be used to efficiently identify mutant genes that confer resistance to a test drug by comparing cells that show resistance and susceptibility to the compound. Determination of the mutant genes leads to the identification of the functional impact of a potential drug.



Localization of a novel antifungal compound (left) visualized by fluorescent microscopy (right). The upper panels show normal (wild type) cells and the lower panels show a cell containing a mutant gene resistant to the compound.

In a demonstration of the usefulness of the library, Yoshida and colleagues identified the gene responsible for conferring resistance to a novel class of compounds with pharmaceutical potential (see image). Identifying this gene enabled the team to characterize the mechanism of action of these molecules and to determine that they are antifungal compounds, a property not detected by other techniques.

An essential but challenging step in the development of small molecules into therapeutic drugs is identification of their cellular target. "Using this library, our group intends systematically to study chemical–genetic interactions in which an altered gene dosage or gene mutation leads to a change in cellular response to a bioactive compound," says Yoshida. ■

1. Ho, C.H., Magtanong, L., Barker, S.L., Gresham, D., Nishimura, S., Natarajan, P., Koh, J.L.Y., Porter, J., Gray, C.A., Andersen, R.J. *et al.* A molecular barcoded yeast ORF library enables mode-of-action analysis of bioactive compounds. *Nature Biotechnology* **27**, 369–377 (2009).

Staying true to the code

By turning enzymes into better editors, Japanese scientists achieve improved results in protein engineering

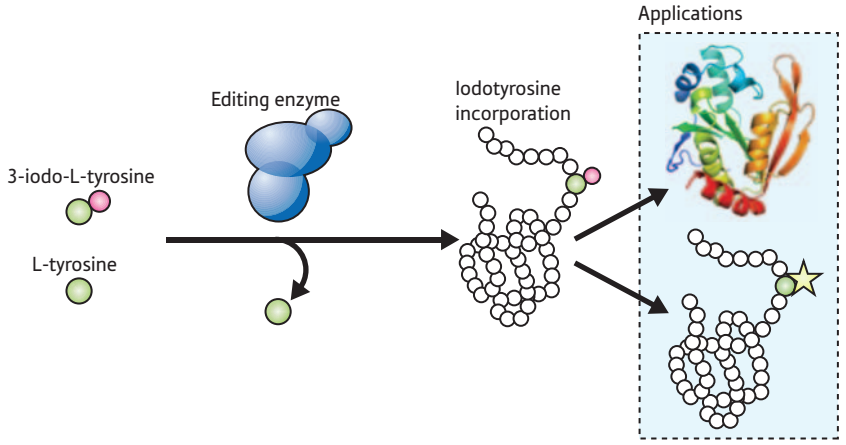
Cells achieve astonishing protein diversity with a fairly limited palette: just 20 naturally occurring amino acids. However, there is sufficient flexibility inherent in the protein-coding and -translation processes that has allowed enterprising scientists to develop clever means for introducing additional, unnatural amino acids into otherwise normal proteins.

As cellular translation machinery reads an RNA transcript, it identifies nucleotide triplets known as codons that indicate what amino acid is needed—these are then delivered through the assistance of a family of enzymes called aminoacyl-tRNA synthetases, which ensure proper placement of the proper molecule.

In previous work, Shigeyuki Yokoyama from the RIKEN Systems and Structural Biology Center in Yokohama and colleagues demonstrated that these enzymes can be engineered to introduce alternative amino acids into proteins[1]—in this case, substituting L-tyrosine with 3-iodo-L-tyrosine, a synthetic analog with uses in imaging and structural biology applications.

Unfortunately, this approach was not a total success, as the mutated synthetase enzyme (iodoTyrRS) still processes L-tyrosine at a reduced, but still significant, frequency. "Any further changes made in the amino-acid-binding pocket [of the enzyme] could not reduce the error rate," explains Kensaku Sakamoto, a member of Yokoyama's team. "We had to change the approach to achieve satisfactory selectivity."

The team's solution was to teach iodoTyrRS to be a better proof-reader. In new work, Yokoyama and colleagues have further engineered a version of the synthetase, one that incorporates a transplanted enzymatic domain that specifically recognizes and purges L-tyrosine[2].



Schematic of the synthetase editing functionality. Synthetase enzymes with a clear preference for 3-iodo-L-tyrosine will occasionally introduce L-tyrosine by accident. The integration of an editing domain prevents this by cutting L-tyrosine molecules loose, so that proteins synthesized from RNAs containing the appropriate codon will consistently incorporate only the modified amino acid.

They began by analyzing various synthetase enzymes that exhibit this editing functionality, in an effort to zoom in on the domains that confer this ability. Once these had been identified, they grafted these domains onto different sections of iodoTyrRS. One of the variants, iodoTyrRS-ed, showed strong specificity for 3-iodo-L-tyrosine alone (pictured), while the original iodoTyrRS enzyme and other variants would regularly make use of L-tyrosine when the synthetic amino acid was no longer available. This specificity was greatly reduced when the editing domain was inactivated by mutation, indicating that this functionality is highly important for establishing strict amino acid preference.

The team is now looking to move their modified enzymes out of the test tube and into living cells, but they are generally quite pleased with this demonstration of grafting two sophisticated enzymatic activities together seamlessly. "Our approach may facilitate developing other enzymes required for incorporating non-natural amino acids into proteins site-specifically," says Sakamoto, "so that the list of available non-natural amino acids can thus be further extended." ■

1. Kiga, D., Sakamoto, K., Kodama, K., Kigawa, T., Matsuda, T., Yabuki, T., Shirouzu, M., Harada, Y., Nakayama, H., Takio, K. *et al. Proceedings of the National Academy of Sciences USA* **99**, 9715–9720 (2002).
2. Oki, K., Sakamoto, K., Kobayashi, T., Sasaki, H. & Yokoyama, S. Transplantation of a tyrosine editing domain into a tyrosyl-tRNA synthetase variant enhances its specificity for a tyrosine analog. *Proceedings of the National Academy of Sciences USA* **105**, 13298–13303 (2008).

Medicine

Medicine

Moving forward on multiple fronts

Progress in medicine that will advance human health and herald new and improved treatments for disease all starts with basic research in a wide range of fields, from imaging and genetics to immunology. The convergence of these fields at RIKEN has led to important biomedical discoveries in 2009.

Finding disease genes

The discovery of genetic variation linked to human disease can lead to mechanistic insight into how diseases are induced and how they progress. This understanding may in turn lead to novel therapeutic approaches to eradicate disease. Heart attack, or myocardial infarction, is a common disease on the radar of geneticists taking this approach. In early 2009, Toshihiro Tanaka and colleagues at the RIKEN Center for Genomic Medicine in Yokohama published findings showing that variation in the *BRAP* gene is linked to heart attack in Asians (*Homing in on heart attacks*, Jun. 2009). The research was performed in collaboration with scientists from other institutes in Japan and Taiwan.

Tanaka and colleagues decided to focus on the *BRAP* gene after finding that the BRAP protein binds to the protein galectin-2. They had already discovered that the gene for galectin-2 is also linked to increased risk of heart attack. BRAP seemed to regulate inflammatory signaling in cardiac blood vessels, suggesting that targeting inflammation may be a promising strategy to prevent and treat heart attack.

The researchers reported that the genetic variants in the *BRAP* gene linked to heart attack are found in Japanese and Taiwanese populations—but not in African or North American populations. Because different ethnic groups may harbor different susceptibility genes for a given illness, the findings emphasize the importance of examining genetic links to disease in multiple ethnic populations.

The picture of health

Scientists and clinicians use imaging technologies to look non-invasively inside the living body. Magnetic resonance imaging scans, for example, can determine areas of damaged brain after stroke. Some of these technologies use radioactive tracer molecules, but these can only be used one at a time, limiting the amount of information that doctors can obtain at one time during a patient's illness.

Shuichi Enomoto, Shinji Motomura and colleagues at the RIKEN Center for Molecular Imaging Science in Kobe and Wako established a way to visualize up to three different radioactive tracers at a time in living mice using a special imaging tool called a semiconductor Compton camera (*Many tracers make light work*, Jan. 2009). This camera is a gamma-ray imaging device used previously in astrophysics studies. If the Compton camera can be developed for clinical use, it could enable doctors to non-invasively gain information about multiple physiological processes at once within their patients.

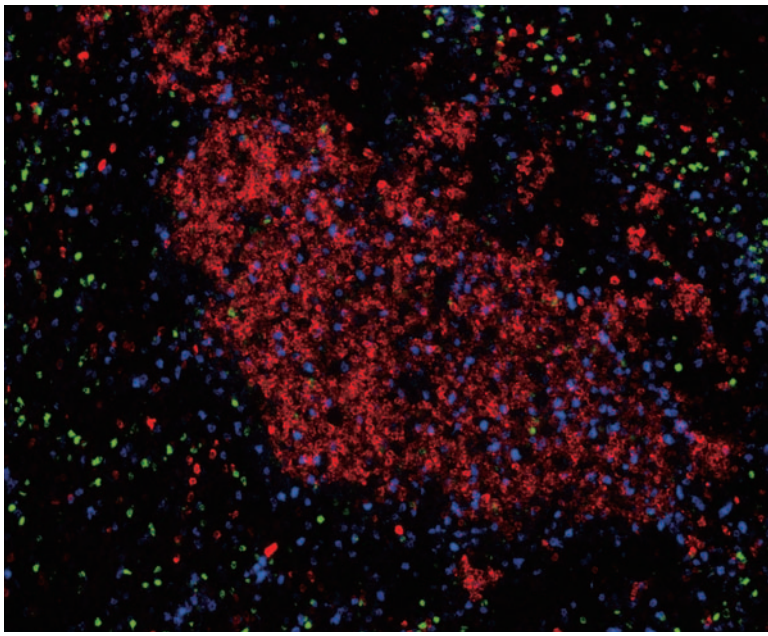
The immune environment

Deciphering how the immune system protects the body from foreign invaders—whether viruses, bacteria or fungi—presents opportunities to develop new therapeutics. Takeshi Saito from the RIKEN Research Center for Allergy and Immunology (RCAI) and his team may have taken the first step in developing suitable treatments against *Malassezia* fungal species (*Fungal recognition*, Jul. 2009, see p.36). These fungi reside on skin and can cause severe infections if they invade the bodies of people with weak immune systems, such as premature infants.

After identifying the Mincle protein as a surface receptor for *Malassezia* fungal species, the researchers found that immune cells increase their expression of the Mincle protein when exposed to these fungi. This receptor seemed to be required for initiating the consequent inflammatory responses, because immune cells lacking Mincle were unable to mount a response to *Malassezia* fungi. Saito and his colleagues intend to investigate whether this inflammatory response is indeed beneficial to the infected host.

Keeping foreign organisms, such as gut bacteria, in their proper place in the body is another important job of the immune system. Cells known as 'T_{FH} cells' are involved in stimulating the immune system to fight bacteria if they stray from their rightful place within the gut lumen by, for example, invading the lining of the gastrointestinal tract and causing inflammation. Collaborative work between Sidonia Fagarasan and Shohei Hori from two laboratories at the RIKEN RCAI determined that these immune-stimulating T_{FH} cells are actually derived from immunosuppressive regulatory T cells (*Plotting a career change*, Jul. 2009). This surprising switch in role from suppressing the immune system to activating it, when needed to fight bacterial invasion of the gut, may have important implications in understanding why immune cells sometimes react inappropriately, such as during the induction of autoimmune diseases.

The immune system needs not only to fight invading pathogens, but also to avoid mounting responses to harmless antigens in the environment, such as pollen or dust. These 'allergic' immune reactions are driven by T_H2 cells. In collaboration with scientists in the United States, Masato Kubo and colleagues at the RIKEN RCAI discovered a protein called Mina that regulates the formation of T_H2 cells from more immature immune cells (*Tipping the balance of immune response*, Oct. 2009, see p.37). The Mina protein binds to the gene that encodes interleukin-4, a key player in T_H2 maturation.



Labeled T cells in a Peyer's patch—a cluster of immune cells (*Plotting a career change*, Jul. 2009)

When the researchers overexpressed Mina in mice, it led to a reduction in the expression of interleukin-4. Small changes in the Mina gene sequence could account for disparities in T_H2 cell production in different lines of mice. If this variation in the *Mina* gene exists in humans, it could explain why some individuals are more prone to develop allergies.

These important findings made at various RIKEN institutes working in biomedical research will aid in our understanding of how the body works, and what may go wrong during disease, paving the way for future therapeutic discoveries. ■

Related highlights from *RIKEN RESEARCH*

- *How the body senses tissue damage,* Jan. 2009
- *Sights set on immunization target,* Jan. 2010
- *Immune cell activation under the microscope,* Mar. 2009
- *Neutralizing spurious associations,* Apr. 2009

Fungal recognition

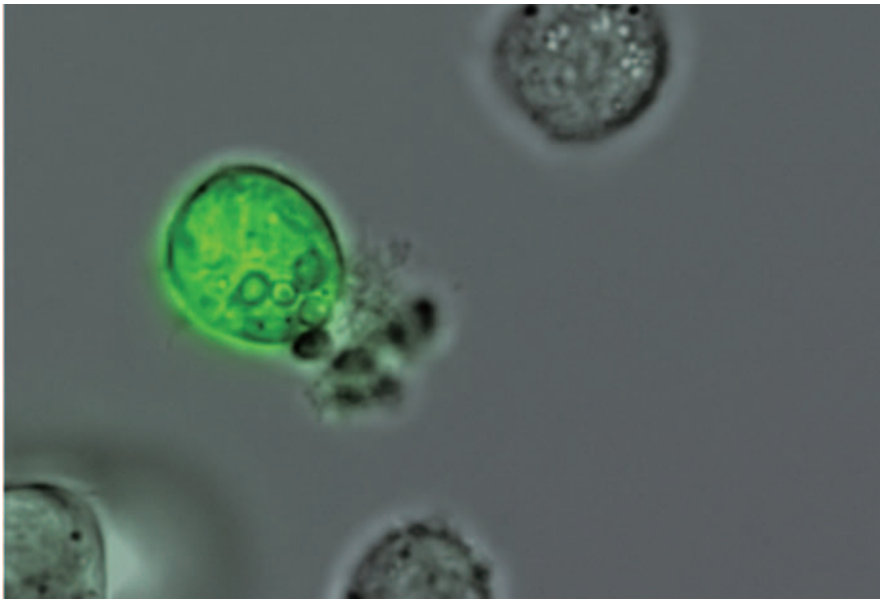
Mincle, a protein expressed on immune cells, is a receptor that recognizes Malassezia fungal species and mediates inflammatory responses

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

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

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

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



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Activation of Mincle signaling causes a specially engineered reporter cell to fluoresce green when it binds to *Malassezia* fungal species.

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

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

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

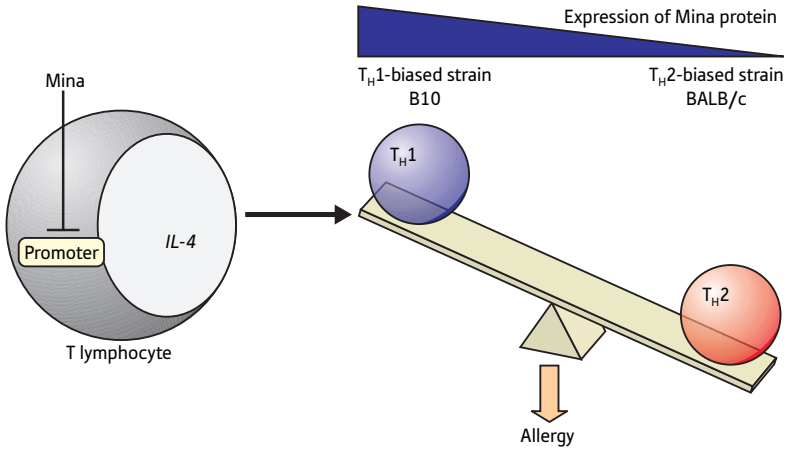
Tipping the balance of immune response

Hybrid mice help researchers zoom in on a gene with a potential role in controlling allergic responses

When the immune system encounters a potential threat, antigen-presenting cells deliver chunks of protein from the invading pathogen to naive helper T cells. These naive cells respond by differentiating into one of two classes of mature helper T cells: T_H1 cells, which mobilize the immune system against viruses and other intracellular pathogens, and T_H2 cells, which drive the response against blood-borne threats, such as the parasitic disease leishmaniasis.

Interleukin-4 (IL-4), one of a class of signaling factors known as cytokines, drives T_H2 differentiation and triggers secretion of additional IL-4, resulting in a positive feedback loop that fuels T_H2 production while suppressing T_H1 production. The degree of initial IL-4 production varies considerably between individuals and the resulting 'T_H2 bias' can have serious clinical implications. "T_H2 bias is thought to be a mirror of allergic response, because many T_H2 cytokines tightly associate with pathology of allergy," says Masato Kubo, of the RIKEN Research Center for Allergy and Immunology in Yokohama.

T_H2 bias also varies between different mouse strains, a fact that Kubo, Mark Bix of St. Jude's Children's Research Hospital in Memphis, USA, and colleagues exploited in a recent effort to identify determinants for this trait[1]. It was known that BALB/c strain mice have a high T_H2 bias—producing large quantities of IL-4 following T cell activation—while B10.D2 mice have a 50-fold lower bias. However, a hybrid BALB/c strain generated by Kubo and Bix that contains a chunk of chromosome 16 from the B10.D2 strain also exhibited low bias, suggesting that this segment includes a gene pertinent to this characteristic.



Schematic showing the role of the Mina protein in T_H2 bias. The extent to which the *IL-4* gene is being inhibited by Mina protein (left) affects the maturation of naive T lymphocytes (right). Low levels of Mina mean a greater bias towards T_H2 production, as in BALB/c mice, while higher levels lead to relatively higher T_H1 production, as in B10 mice. Strong T_H2 bias is thought to be a risk factor for allergy.

Closer analysis spotlighted the *Mina* gene as a likely suspect; analysis of various mouse strains revealed that Mina gene activity and levels of Mina protein were inversely correlated with T_H2 bias. Bix and Kubo's team subsequently determined that Mina assembles into a larger multi-protein complex that directly binds to and inhibits the gene encoding IL-4, supporting a key role for this factor in T_H2 bias (see image).

The team's analysis also identified nearly two dozen sequence variations in *Mina* that correlate with gene activity levels. These so-called single-nucleotide polymorphisms (SNPs) could provide useful diagnostic tools, and Kubo and Bix are now exploring this potential. "We have already done large-scale SNP analysis with Japanese and US populations," says Kubo. "The human *Mina* locus has several SNPs, and some of them have weak correlation with atopic asthma in the Japanese population, but not in the US [population]." ■

1. Okamoto, M., van Stry, M., Chung, L., Koyanagi, M., Sun, X., Suzuki, Y., Ohara, O., Kitamura, H., Hijikata, A., Kubo, M. & Bix, M. Mina, an IL4 repressor, controls T helper type 2 bias. *Nature Immunology* **10**, 872–879(2009).

Neuroscience

Neuroscience

Unraveling the brain's signals and sensory systems

In 2009, researchers from the RIKEN Brain Science Institute used state-of-the-art techniques to probe the mechanisms of neuronal signaling and to advance our knowledge of smell and taste—the least understood sensory systems. The basic principles of neuronal signaling are well understood, but the sheer number of neurons in the brain make studying the brain's signaling mechanisms a formidable task. New research has provided fresh insights into the complexity of neuronal signaling.

Inhibiting inhibition

In the brain, neurons synthesize chemical messengers called neurotransmitters, which are stored at nerve terminals in structures called vesicles. When a cell becomes active, the vesicles fuse with the nerve terminal membrane and the neurotransmitters are released, diffusing across the synapse to bind to receptors on the neighboring cell and thereby alter its activity.

Neuronal activity is modulated by receptor trafficking, which involves the shuffling of receptors to and from synapses. Learning and memory are widely believed to be dependent on increases in the efficiency of signaling, which occur when a receptor known as AMPA, which mediates fast signaling by the excitatory neurotransmitter glutamate, is transported to synapses in response to neuronal activity.

In mid-2009, an international team of researchers including Hiroko Bannai of the RIKEN Brain Science Institute (BSI) discovered a novel form of trafficking using recently developed methods based on nanobiotechnology (*Roaming receptors*, Oct. 2009, see p. 40). They showed that neuronal activity reduced the number of receptors for the inhibitory neurotransmitter GABA at synapses, lowering the efficiency of inhibitory neurotransmission. Paradoxically, however, the total number of GABA receptors at the cell surface remained unchanged.

To investigate this further, the researchers labeled individual GABA receptors with light-emitting nanocrystals called quantum dots so that their movements could be tracked. This revealed that neuronal activity causes the receptors to diffuse away from synapses. The findings could lead to a better understanding of epilepsy, which is characterized by excessive excitatory neurotransmission.

Shedding light on receptor activation

Metabotropic glutamate receptors mediate slow excitatory neurotransmission and act in pairs at the membrane by forming a 'venus fly trap' module that clamps shut when bound to glutamate. This causes a conformational change that brings the intracellular domains of the two receptors together, leading to activation of biochemical signaling cascades within the cell.

Although the mechanisms of metabotropic glutamate receptor activation have been studied extensively, very little is known about the kinetics of the process. Thomas Knöpfel and colleagues at the RIKEN BSI, in collaboration with Païkan Marcaggi from University College London, elucidated the dynamics of these receptors in real time with unprecedented precision (*Intercepting the transmission*, Oct. 2009). Using a sophisticated imaging technique involving genetically

encoded fluorescent sensors, the researchers found that metabotropic glutamate receptors can be activated within 10 milliseconds of binding glutamate, faster than any other known metabotropic receptor. Deactivation, however, takes approximately 50 milliseconds.

Complex communications

Star-shaped cells called astrocytes, long thought to merely provide structural and nutritional support to neurons, have emerged as key players in the brain. By showing that astrocytes modulate neuronal network activity by secreting a protein called S100B, which binds to receptors for advanced glycation end-products (RAGE), Hajime Hirase and colleagues at the RIKEN BSI have provided further evidence of the important role of astrocytes in neuronal activity (*Reciprocal communication*, Apr. 2009). The researchers demonstrated that S100B released from astrocytes is modulated by the activity of neurons, and were able to describe, for the first time, a novel pathway for reciprocal communication between the two cell types.

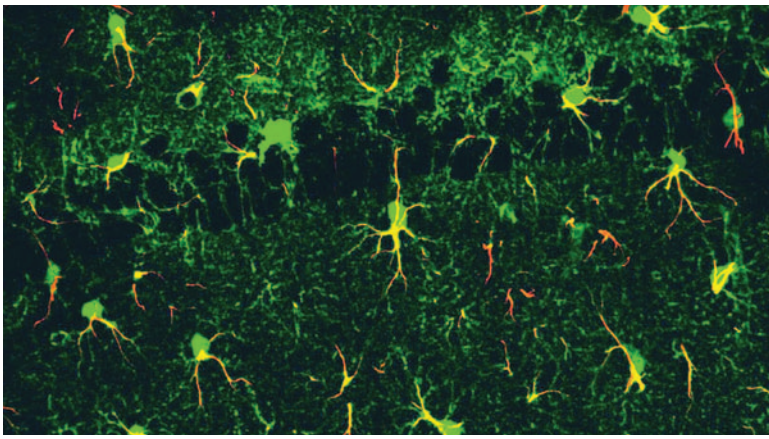
A taste of differentiation

The mechanisms of taste receptor activation are understood in some detail, but much remains to be discovered about the development of taste bud cells. The RIKEN BSI's Takashi Kondo and colleagues have identified an unusual molecular mechanism underlying the differentiation of taste bud cells (*A matter of taste*, Aug. 2009). The researchers used a combination of experimental and computational techniques to identify a protein called HES1 as a key regulator of genes that are critical for taste bud development. Their results suggest that HES1 maintains stem-cell identity in the tissues that give rise to taste buds, and that export of the protein from the nucleus to the cytoplasm is an early step in taste bud differentiation.

Scent tracking

On the surface of the olfactory bulb, an 'odor map' develops, by which different components of smells are spatially segregated. Just how the map is represented in higher brain centers lingers as a major question in this area of research, and answering that question requires a detailed analysis of the fine structure of the neurons that transmit information beyond the olfactory bulb.

Using a genetic method for fluorescently labeling specified cells, and applying it to zebrafish, Yoshihiro Yoshihara and his team at the



An S100B positive cell (green) labeled with an astrocyte-specific protein (red). S100B protein is secreted by astrocytes to modulate neuronal network activity.

RIKEN BSI visualized the axon trajectories of mitral cells, which project axons from the olfactory bulb to the higher olfactory centers (*The path to olfaction*, Aug. 2009, see p. 39).

Surprisingly, they found that one particular population of mitral cells in both the right and left olfactory bulbs sends axon branches directly and asymmetrically only to the right side of the brain—to a structure called the right habenula. Because the habenula controls emotional and social behaviors, this may mean that zebrafish could show a left/right preference in eliciting certain olfactory behaviors, such as an innate escape response evoked by alarm pheromones.

Together, these studies provide a solid basis for further research into the development and organization of the systems of taste and smell, which are both poorly understood. The findings also suggest that the zebrafish olfactory system could be a useful model for future investigations of the mysterious asymmetries in structure and function observed in the vertebrate brain.

The inroads forged across varied, but important, aspects of brain research at the RIKEN BSI during 2009 will guide future research into the fundamental processes that underlie all aspects of brain function. ■

Related highlights from *RIKEN RESEARCH*

- *Memory maintenance,* Apr. 2009
- *From robotics to animal motor-control systems,* May 2009
- *Sense of attraction,* Sep. 2009

Roaming receptors

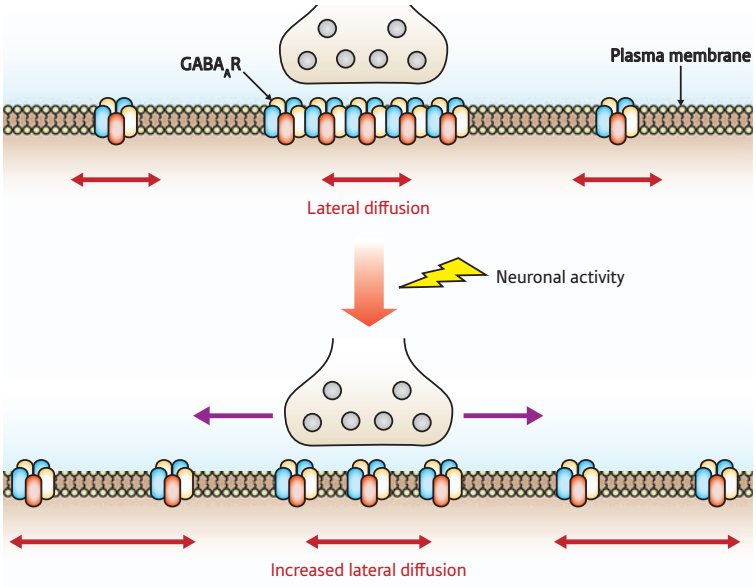
Neurons communicate more efficiently when neuronal activity causes inhibitory receptors to diffuse away from the synapse

Changes in the synaptic strength of neurons, effected by repeated neuronal activity, drive important behavioral processes such as learning and memory. Continuous simulation of a neuron, for example, can alter the signaling or molecular architecture at its synapses, and make it easier—or harder—for that neuron to activate other neurons with which it communicates.

Synaptic efficacy can be enhanced by increasing the process known as excitatory neurotransmission, or by decreasing its opposing process, inhibitory neurotransmission. These processes trigger or halt the firing of neurons, respectively. Now, an international team of researchers, including Hiroko Bannai at the RIKEN Brain Science Institute in Wako, has shown that neuronal activity drives inhibitory neurotransmitter receptors to diffuse away from the synapse, which substantially reduces inhibitory neurotransmission at those synapses[1].

In many parts of the brain, inhibitory neurotransmission is mediated by a molecule called γ-aminobutyric acid (GABA) binding to its receptors at synapses. When the researchers induced neuronal activity in cultured neurons, they found fewer GABA receptors—and fewer GABA receptor scaffolding molecules—at the synapses of these neurons. This resulted in less efficient inhibitory neurotransmission owing to smaller inhibitory electrical currents through these receptors.

To respond to GABA molecules, GABA receptors must be on the surface of the neuron. But neuronal activity did not change the levels of GABA receptors that were on the surface or that were inside the neuron. Instead, when the researchers labeled the GABA receptors and watched them move, they found that induction of neuronal activity enhanced the diffusion of the receptors along the surface of the neuron. Importantly, it seemed that greater GABA receptor diffusion caused by neuronal activity reduced the amount of time that the GABA receptors spent at the synapse (see image). This could explain why neuronal activity caused a decrease in inhibitory neurotransmission.



A new molecular mechanism to explain the modulation of synaptic strength via lateral diffusion. The diffusion of GABA receptors (GABA$_A$R) away from the synapse reduces the number of receptors (blue, red and yellow clusters), without changing the receptor number on the plasma membrane.

The investigators obtained these results in neurons from the hippocampus, a part of the brain involved in spatial learning. However, other reports have shown that neuronal activity can reduce diffusion and enhance synaptic targeting of receptors for a different inhibitory neurotransmitter called glycine in neurons from the spinal cord. This suggests that different cell types—and different receptors—may respond to neuronal activity in totally different ways.

These findings indicate that "lateral diffusion, regulated through interactions between receptors and their scaffolding proteins, could provide a simple mechanism for rapid and reversible activity-dependent modulation of synaptic strength," says Bannai. "Next, we plan to elucidate the detailed molecular mechanisms controlling receptor diffusion dynamics." ■

1. Bannai, H., Lévi, S., Schweizer, C., Inoue, T., Launey, T., Racine, V., Sibarita, J-B., Mikoshiba, K. & Triller, A. Activity-dependent tuning of inhibitory neurotransmission based on GABA$_A$R diffusion dynamics. *Neuron* **62**, 670–682 (2009).

The path to olfaction

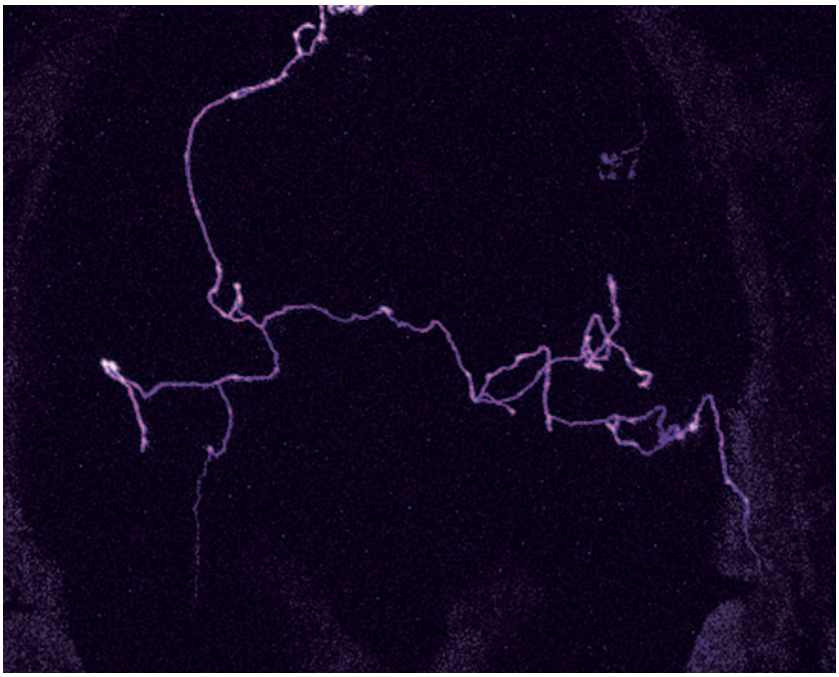
Neurons conveying information about smell from the olfactory bulb communicate with multiple regions of the brain

Olfactory signals are transmitted through the nose to the olfactory bulb, where information about distinct odors is spatially separated, leading to the formation of an 'odor map' in that structure. To determine how this information is sent to other parts of the brain, a team of researchers led by Yoshihiro Yoshihara and Nobuhiko Miyasaka at the RIKEN Brain Science Institute in Wako used genetic fluorescent labels to visualize the axon trajectories of mitral cells, the output neurons of the olfactory bulb, within small vertebrates called zebrafish.

They report in *The Journal of Neuroscience* that these neurons transmit information to several brain structures on both sides of the brain, but the odor map is not maintained intact in these higher brain structures[1].

The researchers found, for example, that information from one part of the odor map is sent in a divergent manner to many different higher brain structures. At the same time, information from many parts of the odor map can converge onto a single brain structure. This mixing of olfactory information in higher brain regions could serve to control the behavioral and hormonal responses of the zebrafish to multiple odors in their environment, according to the researchers.

Axons that project long distances within the central nervous system tend to cross the midline only once before reaching their targets. But, surprisingly, Yoshihara, Miyasaka and colleagues found that some of the mitral cells they labeled crossed the midline twice, sending information along the way to as many as three brain regions on both sides of the brain (see image). This suggests that multiple brain regions simultaneously respond to identical olfactory information from a single mitral cell.



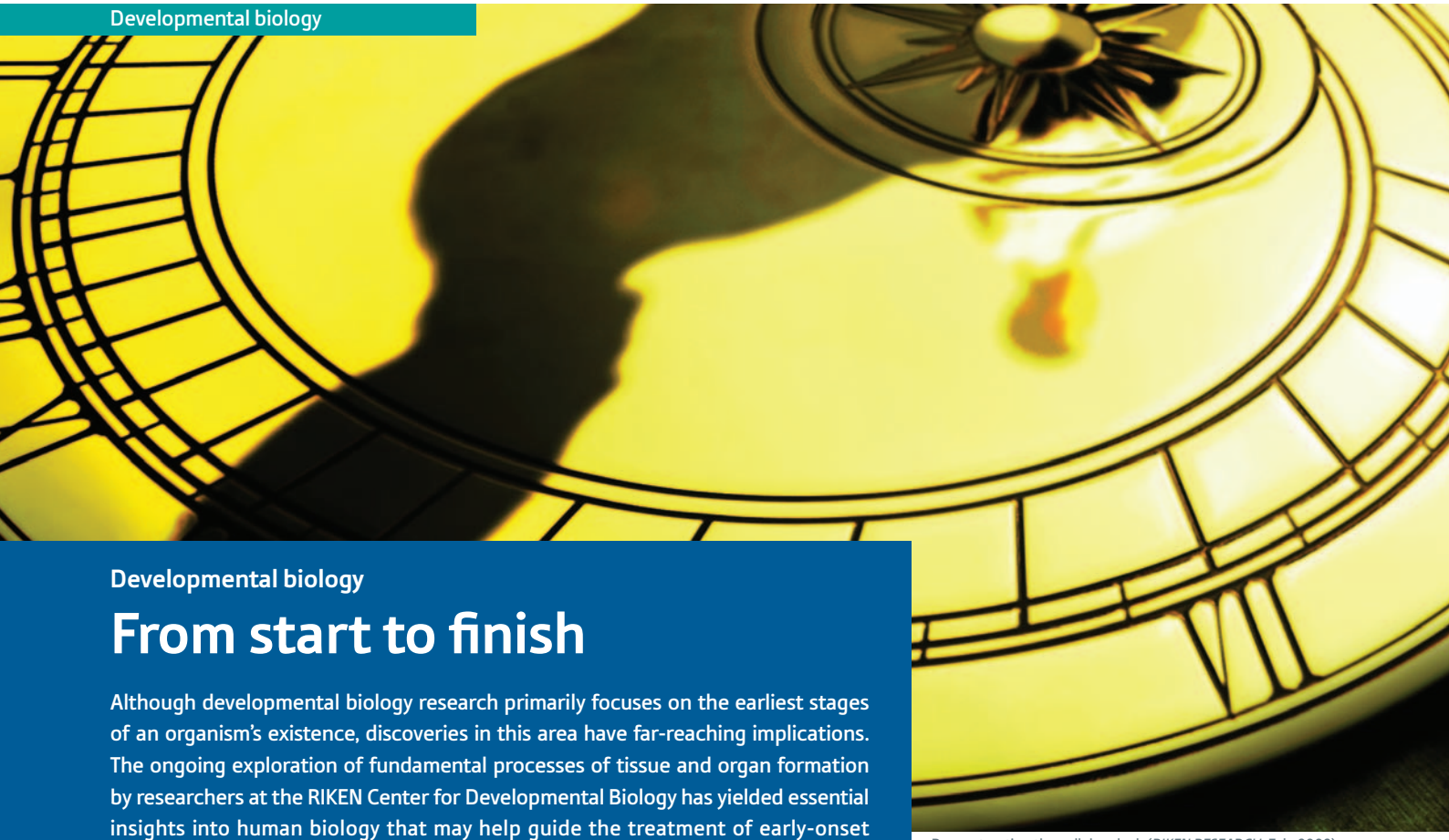
A fluorescently labeled mitral cell in a zebrafish. This mitral cell projects its axon to three different parts of the brain, with its axon finally terminating within the right habenula.

Projection neurons on one side of the brain tend to send their axons—and therefore to control—bodily functions on the other side of the body. But the researchers found unexpectedly that one particular population of mitral cells in both the right and the left olfactory bulb project their axons directly and asymmetrically only to the right side of the brain—to a structure called the right habenula. Because the habenula controls emotional and social behaviors, this may mean that zebrafish could show a left/right preference for exhibiting olfactory behaviors, such as an innate escape response.

As the next step in this research, Yoshihara says "we now aim to dissect olfactory neural circuits mediating various odor-induced behaviors, such as attraction, escape, memory, and social behaviors."

1. Miyasaka, N., Morimoto, K., Tsubokawa, T., Higashijima, S., Okamoto, H. & Yoshihara, Y. From the olfactory bulb to higher brain centers: genetic visualization of secondary olfactory pathways in zebrafish. *Journal of Neuroscience* **29**, 4756–4767 (2009).

Developmental biology



Developmental biology

From start to finish

Although developmental biology research primarily focuses on the earliest stages of an organism's existence, discoveries in this area have far-reaching implications. The ongoing exploration of fundamental processes of tissue and organ formation by researchers at the RIKEN Center for Developmental Biology has yielded essential insights into human biology that may help guide the treatment of early-onset developmental disorders as well as clinical problems that arise in adulthood.

Reconstructing the cellular clock (*RIKEN RESEARCH*, Feb. 2009)

Keeping their options open

Intensifying interest in embryonic stem cells is increasing the importance of developmental biology research. Embryonic stem cells are maintained in an immature 'pluripotent' state, which enables them to develop into any cell type in the body—giving them remarkable potential for tissue replacement, among other applications.

Recent work by scientists at Kyoto University and elsewhere has shown that the expression of key genes that establish pluripotency can even reprogram adult cells into embryonic-like 'induced pluripotent stem cells', although the actual reprogramming mechanisms remain unclear.

Hitoshi Niwa of the RIKEN Center for Developmental Biology (CDB) and colleagues made important progress on this front by revealing details about the regulatory circuitry activated by leukemia inhibitory factor, a protein that acts as a primary driver for pluripotency in mouse embryonic stem cells (*Joining the dots on stem cell signaling*, Oct. 2009, see p. 44). They identified two parallel signaling pathways activated by leukemia inhibitory factor, which trigger the cascade of gene activation needed to maintain pluripotency and embryonic stem cell self-renewal through two intermediate transcription factors. The complexity of the resulting network makes it robust against disruption. The details obtained by Niwa's team could guide the development of more effective stem-cell cultivation techniques.

Even after cellular differentiation and embryonic development are underway, a subset of cells called primordial germ cells retain some measure of pluripotency in order to confer reproductive capabilities to the mature animal. Primordial germ cells form early in development, long before their eventual maturation into spermatozoa or ova; work by Mitinori Saitou from the RIKEN CDB and collaborators revealed how the protein Blimp1 triggers this process by reprogramming a small region of the embryo (*How it all begins*, Jul. 2009).

More recently, Saitou's group clarified the basis of Blimp1 activation, demonstrating that although primordial germ cell formation is normally governed by the interplay of several stimulatory and inhibitory signals, only a single activating factor is strictly necessary to initiate this process in cultured embryonic cells. Primordial germ cells derived by this approach developed into properly functioning spermatozoa upon transplantation into mice—the first demonstration of experimental production of functional gametes, and an achievement that could benefit future studies exploring human infertility.

Building a body

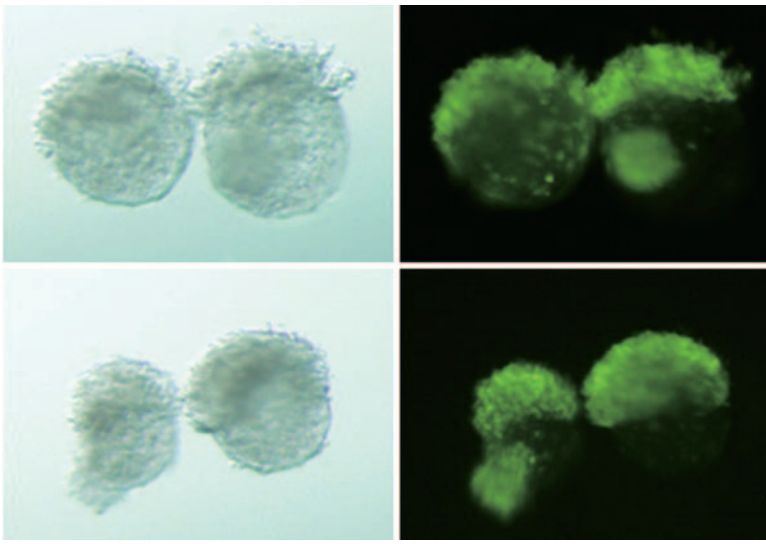
Some of the most important events in early embryonic development involve the determination of the various axes that will guide body patterning, including proper development of organs and

limbs. The dorsal–ventral axis, which establishes an embryo's 'front' and 'back' side, is generated via signals from bone morphogenetic protein signaling factors; activity of these factors on one side of the embryo promotes ventral development, while inactivation by the Chordin protein on the other side leads to dorsalization. Yoshiki Sasai's team at the RIKEN CDB recently discovered a key regulator of this process, a protein called ONT1. This protein confers an important layer of stability to the axis determination program by delivering Chordin to enzymes that subsequently break it down and thereby ensure that the extent of dorsalization is appropriately limited (*Balancing act*, Feb. 2009, see p. 45). These findings represent an important step towards reconstructing the complex flow of regulation that enforces tight control over body patterning.

Indeed, developmental biologists are still coming to terms with the vast amount of information that must be processed in the developing body to ensure that everything is positioned and connected correctly. The brain is a prime example, as inappropriate assemblage of the neural wiring between different regions can prove catastrophic, even if the rest of the body has developed properly. The cerebellum, for instance, receives two different types of inputs from other regions of the brain, each of which is selectively connected to a specific class of cerebellar cells. The RIKEN CDB's Masatoshi Takeichi and colleagues recently demonstrated that this selectivity is achieved even in *in vitro* cultures; cerebellar granule cells can transiently form synapses with both mossy fibers—their proper partner—and climbing fibers, when they meet each other (*Know who your friends are*, Nov. 2009). However, only the former will trigger the full range of structural changes required for the development of functional synapses, suggesting that these cerebral neurons recognize specific 'instructions' on their target cells that ensure the formation of appropriate connections.

The dawn of time

Other aspects of organism development are considerably more subtle than body patterning or organ formation, but no less essential. Many animals have an internal cellular 'clock' that establishes their circadian rhythm. This cellular clock plays an essential role in behavior and metabolism, and is even believed to influence disease progression and response to therapeutic interventions in humans. Hiroki Ueda's group at the RIKEN CDB identified several of the genes that establish cellular timing, but only recently has the group been able to formally model how fluctuations in the expression



Fluorescently labeled induced primordial germ cell-like cells (*How it all begins*, Jul. 2009).

of these genes produce such highly structured rhythms (*Setting the cellular clock*, Feb. 2009). By establishing synthetic circadian circuits in cultured cells, they were able to recapitulate phases of gene expression equivalent to the 'night' and 'day' states observed in nature, as well as intermediate states such as 'dawn' and 'dusk'.

Further progress in this area could contribute significantly to the treatment of circadian disorders, but will also—as with the rest of the work now underway at the RIKEN CDB—represent an important stride towards understanding the essential molecular events that contribute to the development of a properly formed, fully functioning animal or human. ■

Related highlights from *RIKEN RESEARCH*

- *Decoding the rhythm of life, Apr. 2009*
- *Building new connections, Jun. 2009*
- *Day in and day out, Sep. 2009*
- *Solving the riddle of the turtle shell, Nov. 2009*
- *Embryonic development—lost in space?, Dec. 2009*
- *Keeping the circadian clock ticking, Dec. 2009*

Joining the dots on stem cell signaling

Hierarchical networks of transcription factors maintain self-renewal of mouse embryonic stem cells

Transcription factors, the proteins that control the activity of genes, can be part of a hierarchy of signaling compounds, RIKEN molecular biologists have shown. They have also demonstrated such a hierarchy among the transcription factors and that they keep mouse embryonic stem cells from specializing or differentiating.

The study is important because the role of transcription factors in switching genes on and off is now recognized as a significant part of genetic function. For instance, researchers are now able to turn specialized cells back into a stem cell-like form—induced pluripotent stem cells—through applying transcription factors. Better understanding of how these factors themselves are activated should further this work.

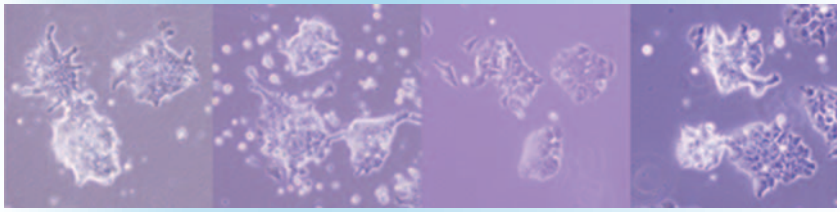
Mouse embryonic stem cells in culture remain in an undifferentiated or pluripotent state if treated with the cytokine or extracellular hormone known as leukemia inhibitory factor (LIF). Inside the cell, such pluripotency is known to be directly associated with three transcription factors, *Oct3/4, Sox2* and *Nanog*. In the past, other researchers have determined the involvement of the intermediate signaling compounds Jak and Stat3, and shown that pluripotency could be maintained without LIF by activating *Nanog* or Stat3 alone. How all these pieces fit together was unknown.

Hitoshi Niwa and colleagues from the RIKEN Center for Developmental Biology in Kobe set about tracing the signaling pathways, and detailed the results of their work in the journal *Nature*[1].

By analyzing data on compounds associated with the key transcription factor *Oct3/4*, they tracked down two other transcription factors, *Klf4* and *Tbx3*. Either of these genes when artificially stimulated is capable, like *Nanog*, of maintaining pluripotency without LIF (see image). The researchers then created transgenic cells in which each of *Klf4*, *Tbx3* and *Nanog* was activated, so they could study the impact of these transcription factors on levels of other key compounds.

Their work revealed parallel signaling pathways stimulated by LIF of a hierarchical nature. The pathway involving Jak and Stat3 turns out to activate *Klf4* and through it *Sox2* and *Oct3/4*. *Tbx3* is part of another pathway which stimulates *Nanog* and *Oct3/4*. Other signaling compounds are known to connect into this latter pathway. They also found that transcription of all these factors is regulated by the core of *Oct3/4*, *Sox2* and *Nanog*. The complexity of the network confers stability, the researchers say.

"Based on this picture, we will try to establish a precise quantitative model of the transcription factor network that will be applicable for computational simulation," Niwa says. ■



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Examples of mouse embryonic stem cells grown without LIF, but with the transcription factors *Klf4* (left), *Nanog* (middle) and *TBx3* (right).

1. Niwa, H., Ogawa, K., Shimosato, D. & Adachi, K. A parallel circuit of LIF signalling pathways maintains pluripotency of mouse ES cells. *Nature* **460**, 118–122 (2009).

Balancing act

A recently discovered protein works behind the scenes to confer much-needed stabilization to an essential developmental pathway

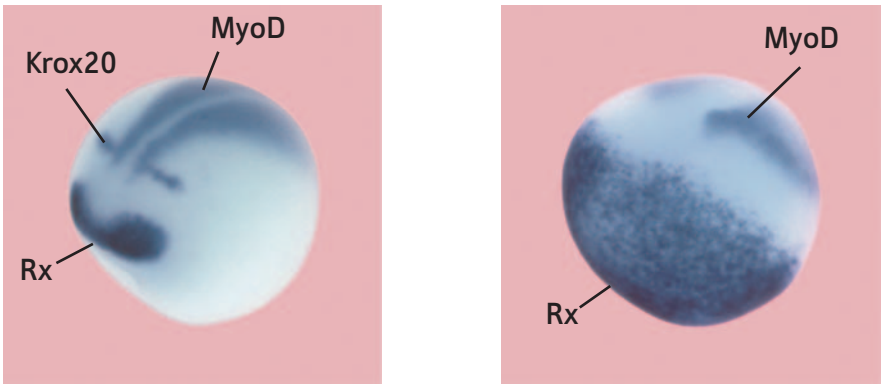
Early in development, embryos transition from being simple spheres of cells into more structured forms in which the foundations of body patterning—such as distinct dorsal (back) and ventral (front) sides—have been established.

Dorsal–ventral patterning is primarily established by BMP signaling factors, which exhibit a gradient of activity along the length of the embryo: elevated BMP activity induces ventral development, while reduced BMP signaling induces dorsality. Reduction in BMP activity is mediated by a structure known as the Spemann organizer, which secretes factors like Chordin, which inactivates BMP and drives dorsalization.

However, BMP also represses Chordin expression, creating a seemingly fragile regulatory situation in which transient upregulation of Chordin could trigger a chain reaction of uncontrolled Chordin upregulation, with catastrophic results for body patterning.

This isn't the case; in fact, this process is surprisingly robust. Yoshiki Sasai of the RIKEN Center for Developmental Biology in Kobe, suspected that additional failsafe mechanisms must exist to stabilize Chordin–BMP regulation, and decided to investigate the involvement of a protein recently discovered by his team, ONT1, which they thought might play a role in body patterning[1].

ONT1 is produced and secreted by cells in the dorsal region of the embryo, where it appears to directly regulate Chordin function, and Sasai's team found that frog embryos with reduced ONT1 activity are far more vulnerable to excessive dorsalization in the presence of abnormally elevated Chordin levels (see image). "We were really surprised to see how drastically the stability collapsed after knocking down ONT1 function," he says.



From Fig. 1. Reproduced with permission. © 2008 Elsevier

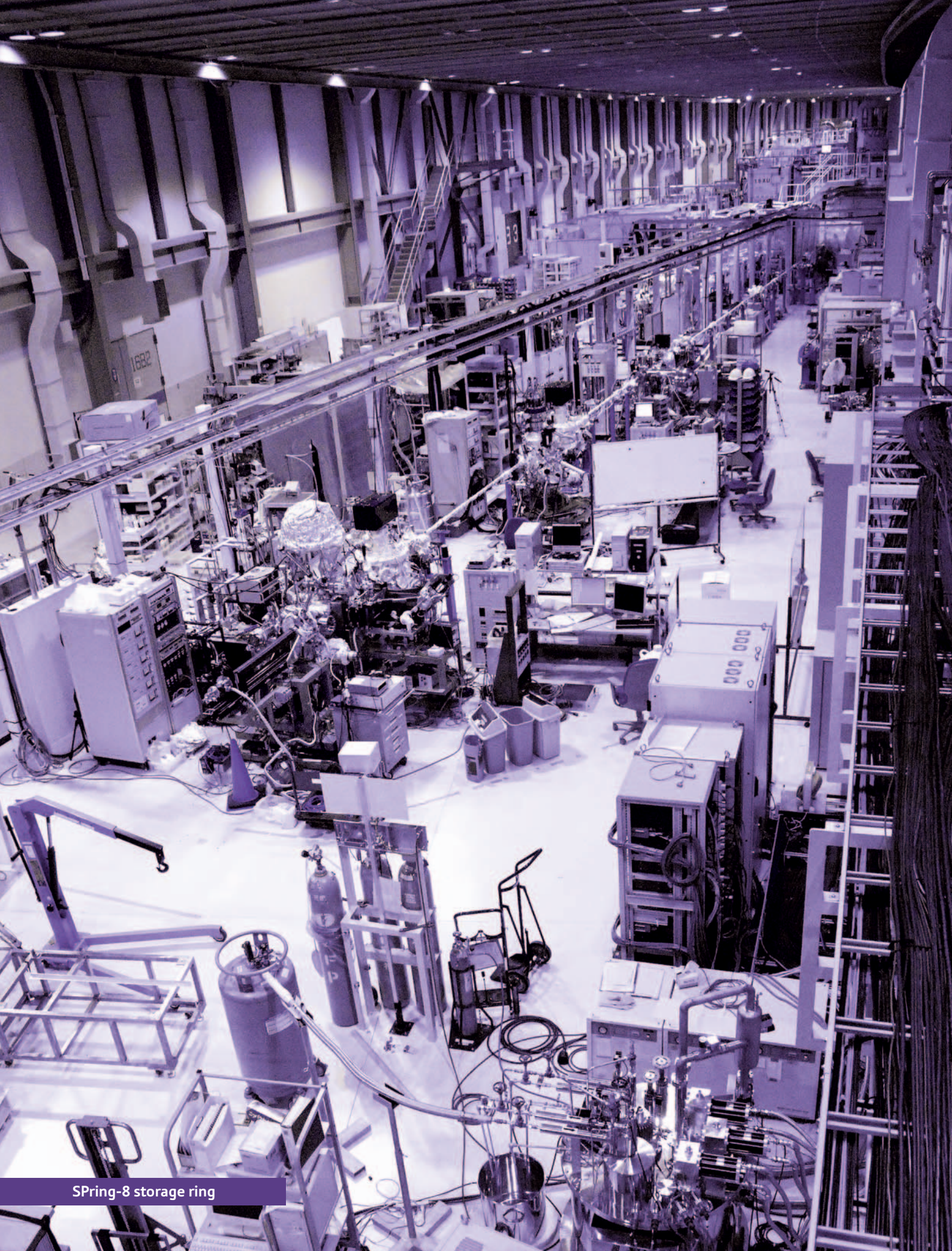
Frog embryos stained to reveal alterations in gene expression patterns in a normally patterned embryo (left) and in an embryo subjected to elevated Chordin levels under conditions of artificially reduced ONT1 activity (right). The latter embryo exhibits signs of profound dorsalization, as evidenced by expansion of the zone of expression for dorsal marker Rx, and reduction or loss of expression of ventral markers *MyoD* and *Krox20*.

They determined that ONT1 not only interacts directly with Chordin, but also binds to an enzyme known to degrade Chordin, and came to the surprising conclusion that ONT1 acts as a bridge that links the two proteins and thereby expedites destruction of the dorsalization signal. "There are a number of examples of intracellular scaffolds," says Sasai, "but ONT1 is a rare example of a secreted scaffold for enzymes."

There is another recently identified pathway for the regulation of dorsal–ventral patterning, mediated by ADMP, a protein that reduces Chordin levels by activating BMP receptors, and ONT1 and ADMP appear to regulate parallel but independent pathways for ensuring robust control of dorsalization in the embryo.

The researchers now hope to delve deeper into this more complex model of organizer regulation. "One important approach will be to establish a mathematical model for this integrated view of organizer function," says Sasai, "particularly to explain these phenomena in a spatial and real-time fashion." ■

1. Inomata, H., Haraguchi, T. & Sasai, Y. Robust stability of the embryonic axial pattern requires a secreted scaffold for Chordin degradation. *Cell* **134**, 854–865 (2008).



SPring-8 storage ring

HISTORY

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.

Founding scientists

The formative years

RIKEN has a proud history of scientific achievement, from its original establishment in 1917 as a private research foundation, known in Japanese as *Rikagaku Kenkyusho*, to its restructuring following the Second World War and rebirth in the twenty-first century as a government-supported independent administrative institution. RIKEN researchers include some of the most respected scientists of modern times, and it is at RIKEN that scientists have made some of the most remarkable and influential scientific breakthroughs. The foundations for these achievements were laid by RIKEN's first scientists and luminaries, whose 'RIKEN Spirit' lives on to this day.

Founded in Tokyo's Bunkyo Ward in 1917 with funding from an imperial donation, government subsidies and private contributions, RIKEN emerged as a major research institute in Japan under the leadership of the foundation's third president, Masatoshi Okochi, formerly a professor of mechanical engineering. Okochi oversaw a restructuring of RIKEN's research program that culminated in 1922 with the establishment of 14 autonomous laboratories headed by leading scientists of the time. Traditional divisions between physics and chemistry divisions were abolished in the new program and the structure of research overhauled with the aim of giving researchers more freedom and flexibility. Okochi's strong entrepreneurial spirit further led to the establishment of the 'RIKEN konzern', a group of companies that applied RIKEN's research to the development of commercial products.

The scientists that presided over these new laboratories would become RIKEN's founding scientists, and many emerged as icons of the Japanese scientific community. One of these scientists was Hantaro Nagaoka, director of RIKEN's physics division and a pioneer of physics research in Japan. Nagaoka's work in fields from theoretical and atomic physics to experimental physics, geophysics and magnetism paved the way for Japan's later achievements in these fields. Likewise, Nagaoka's junior colleague Kotaro Honda, a physicist specializing in metallurgy and magnetism, raised the profile of Japanese magnetism research to an international level as head of the RIKEN–Honda Laboratory at Tohoku Imperial University, the first in a long line of RIKEN laboratories operated through collaborations with universities. Honda is particularly renowned for his skill as an educator, mentoring world-famous scientists such as Shoji Nishikawa, Hakaru Masumoto and Seiji Kaya.

Some of the founding scientists of RIKEN. Clockwise from top left: Masatoshi Okochi, Hantaro Nagaoka, Umetaro Suzuki, Kotaro Honda.

Agricultural chemist Umetaro Suzuki, another of RIKEN's founding scientists, is known today as the father of vitamin research in Japan. His most important achievement was the isolation of vitamin B1 from rice bran, which proved to be an effective cure for a debilitating disease known as 'beriberi'. Suzuki's research on nutrition and food led to the invention and development of products such as 'RIKEN Vitamin', a commercial product that made RIKEN a household name in Japan.

In 1927, recognizing the need to transform its inventions and discoveries into commercial products of benefit to society, RIKEN began establishing venture businesses. By 1939, the organization was at the core of an industrial group consisting of 63 companies and 121 manufacturing facilities.

It was also in the 1930s that physicist Yoshio Nishina rose to prominence following the publication of his 1928 theory on quantum physics. Nishina's arrival at RIKEN in 1931 fostered an expansion of research on nuclear physics, cosmic rays and elementary particle physics that lead to the construction of Japan's first particle accelerator, ushering in a new era of accelerator science. In the years following the Second World War, Nishina went on to serve as president of RIKEN, a post that he retained until he passed away in 1951. In his time, Nishina oversaw remarkable achievements that reinvigorated Japanese research, particularly in nuclear physics. These achievements included the awarding in 1949 of Japan's first Nobel Prize to Hideki Yukawa for his 1935 meson theory, and the publication in 1943 of Shin-ichiro Tomonaga's 'super-many-time theory' that reconciled quantum mechanics with the theory of relativity, for which Tomonaga would be awarded a Nobel Prize in 1965.

RIKEN's influence in the Japanese and international scientific communities is a testament to the spirit of freedom and curiosity-driven research championed by RIKEN's founding scientists in the first half of the twentieth century and to the many distinguished scientists that followed—a spirit that lives on into the twenty-first century.

Historical perspective

Overcoming postwar difficulties

The use of particle accelerators for physics research has been one of RIKEN's core strengths since the 1930s. RIKEN's Yoshio Nishina, Japan's top nuclear physicist at the time, actively applied knowledge acquired from the West to develop Japan's first, albeit small, cyclotron in 1937. He later designed a larger cyclotron and conducted preliminary experiments using its first beam in 1944. But Japan's prowess in particle physics, and RIKEN itself, would be severely tested by war.

The end of the Second World War marked a major turning point in Japanese history, but it also precipitated a major setback for Japanese science.

The US-led General Headquarters of Allied Forces (GHQ), which was placed in control of postwar Japan, feared the country had the capability to build nuclear weapons, and suspected that RIKEN's two cyclotrons would be used to develop them. The cyclotrons were seized by the GHQ following an inspection of Nishina's laboratory at RIKEN, and were later disposed of in Tokyo Bay.

The actions of the GHQ dismayed both Japanese scientists and their counterparts in the US, where the loss of the cyclotrons was widely criticized within the research community. US scientists successfully protested to then-president Harry Truman, prompting the GHQ to ask the Department of the Army to recruit scientific advisors so as not to repeat the same mistake in the future.

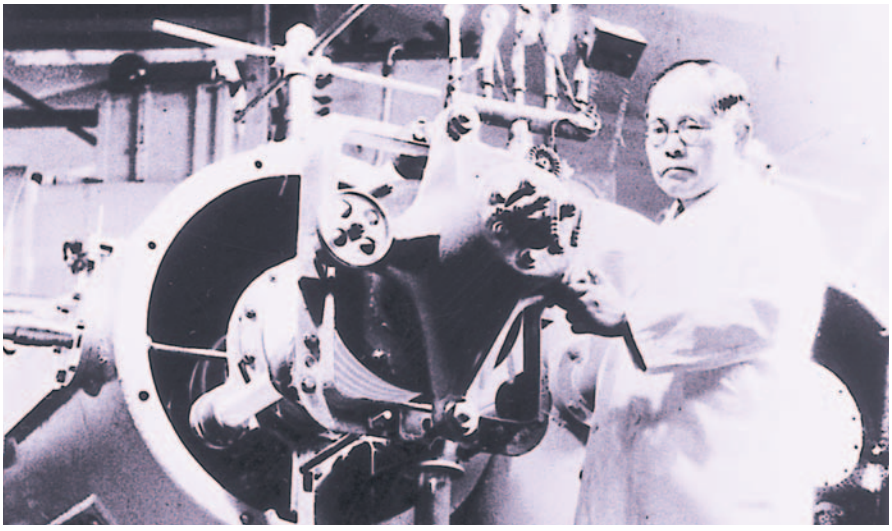
Young US scientists, including Harry Kelly from the Massachusetts Institute of Technology, were chosen to work for the GHQ's Scientific and Technical Division. Soon after he arrived in Japan in January of 1946, Kelly came to the conclusion that Japan would not prosper without its scientists and engineers. He subsequently played a vital role in reconstructing scientific research in post-war Japan.

Under the GHQ's governance in the period up to 1952, Japan faced many restrictions on its activities, including a ban on nuclear physics and other areas of scientific research. The GHQ also ordered the liquidation of the powerful business conglomerates that dominated Japan's economy, an action that had a major effect on RIKEN, which had formed a group of flourishing venture companies in the 1930s and '40s. Not only did the GHQ dissolve RIKEN's business group, it also considered abolishing RIKEN itself.

In his early days in Japan, Kelly met many top-class scientists at RIKEN and came to appreciate its importance for Japan's future. Kelly began work with Nishina, who had influence in the setting of government scientific policy, and the two built a close relationship of trust that eventually developed into a strong friendship. Backed by a passion to save the moribund RIKEN, the two men scrambled to negotiate with tough government officials from the Allies and Japan, spending two years persuading officials to keep the research institute alive.

In 1947, RIKEN made a fresh start as Japan's first incorporated research institute, with Nishina appointed as its first president. In his inauguration speech, Nishina praised Kelly, proclaiming that "Today's RIKEN is indebted to efforts by the GHQ's Dr Kelly, and this fact should be long remembered in our institute's history." Bowen C. Dees, a colleague of Kelly at the GHQ, predicted that without the efforts of Kelly and his Japanese colleagues, RIKEN would have met the same fate as its cyclotrons.

In 1950, Kelly completed his mission and left Japan to work for the US National Science Foundation, where he promoted the US-Japan Scientific Cooperation as the co-chair of its Steering Committee. Although no longer working together, the close bond between Kelly and Nishina nonetheless remained strong even after Kelly's return to the US. RIKEN flourished in the years that followed and now stands as one of the largest scientific organizations in the world—a testament to Nishina and Kelly's perseverance and solidarity at a time of upheaval and hardship.



Yoshio Nishina is renowned as the founder of modern physics in Japan

THE YEAR IN FIGURES

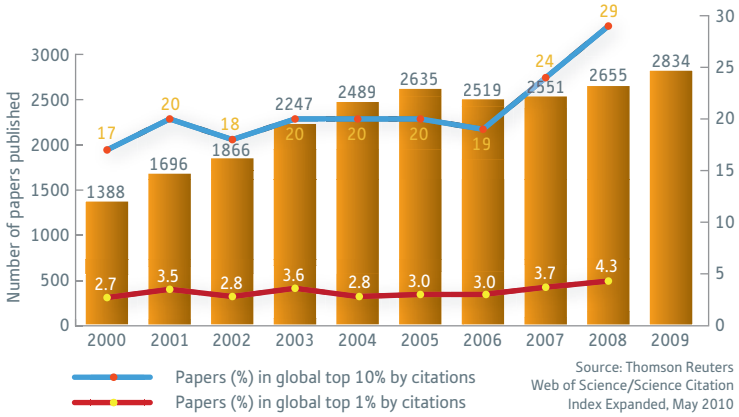
As an independent administrative institution, RIKEN is primarily funded by the Japanese government, and in return is responsible for securing additional revenue streams, implementing strategic administrative reforms, promoting international collaboration and serving society through the application of research outcomes. As shown in this section, the 2009–2010 financial year marked another twelve months of impressive progress in all of these areas against a background of global economic uncertainty.

Research output

World-class research at RIKEN in 2009

Innovative, high-quality research is the lifeblood of RIKEN. In fiscal 2009, both the quality and quantity of research carried out at RIKEN continued to improve, ensuring that RIKEN maintained its place as a leading international research organization. Over the period, RIKEN scientists published 2,834 papers in the primary literature—a 6.7% increase on the previous twelve months. The proportion of papers published by RIKEN rated in the top 10% and 1% of the most highly cited articles* continued its upward trend.

*Citation data for papers published globally in 2008



Source: Thomson Reuters Web of Science/Science Citation Index Expanded, May 2010

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 (left), 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 along with lively feature articles that introduce the people, facilities and programs that make up RIKEN's daily life. In fiscal 2009, the website was visited by readers from 163 countries and registered 22% more visits than the previous year, whilst the number of people registering for the email alert service rose by 34%. Over the same period, issues of the *RIKEN RESEARCH* monthly print magazine featuring research highlights covering 114 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 commerce together

RIKEN actively promotes the transfer of its scientific achievements into commercial products through partnerships with private industry. Taking its name from the place in a relay race where one team member hands off the baton to another, 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. The Baton Zone initiative is composed of the following two major parts:

Integrated Collaborative Research Program with Industry

Projects on topics suggested by private industry are undertaken at 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 seven active collaborative teams.

Industry–RIKEN Collaboration Centers

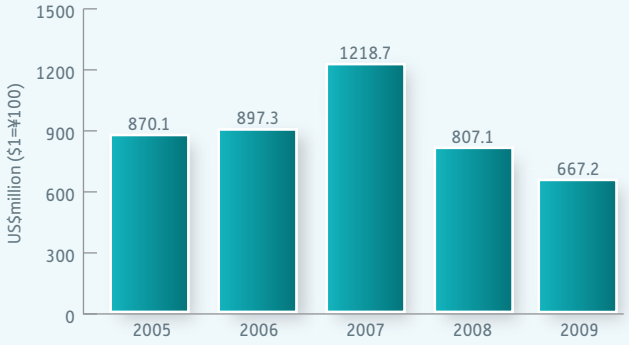
Collaboration centers are set up within RIKEN institutes based on proposals made by private industry to provide a research environment where a comprehensive relationship between the two parties accelerates the realization of medium- to long-term projects. The collaboration program aims to cultivate emerging fields and to train experts able to work in both the scientific and business worlds. Three centers are currently in operation.

Technology transfer

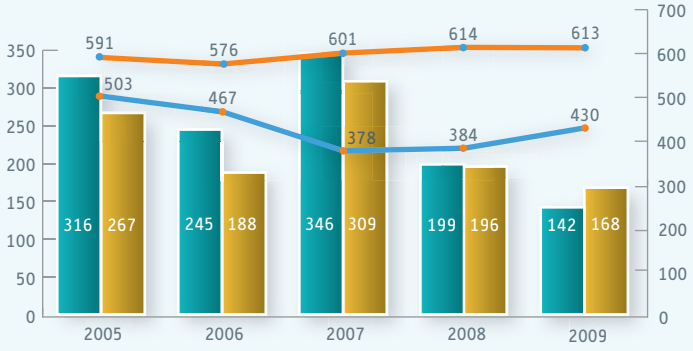
Patent activity in 2009

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 Center for Intellectual Property Strategies (CIPS), which functions as a conduit between RIKEN and the private sector. The CIPS is responsible for licensing of intellectual property, collaboration with industry and the acquisition of external and competitive funding. It also supports RIKEN's growing number of venture capital companies, which are established by its scientists to develop practical applications for their research.

RIKEN patent portfolio income

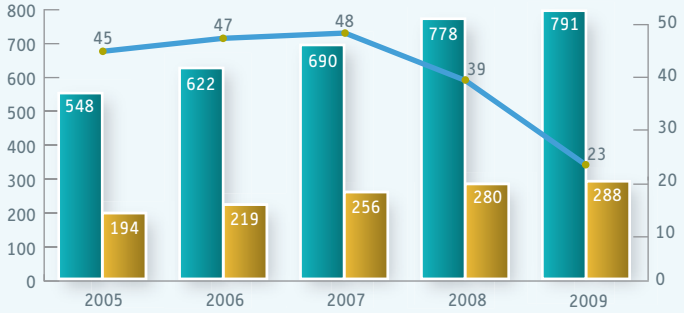


Patent applications and registrations

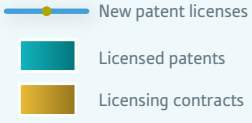


In fiscal 2009, RIKEN continued to build up its patent rights portfolio. By the end of the period, RIKEN held the rights to a total of 1,043 patents, representing an increase of over 4.5% on the previous year. Of the total, approximately two-thirds related to patents of overseas origin. In the same period, over 300 patent applications were made, over 50% of which were filed overseas.

Patent licenses and contracts



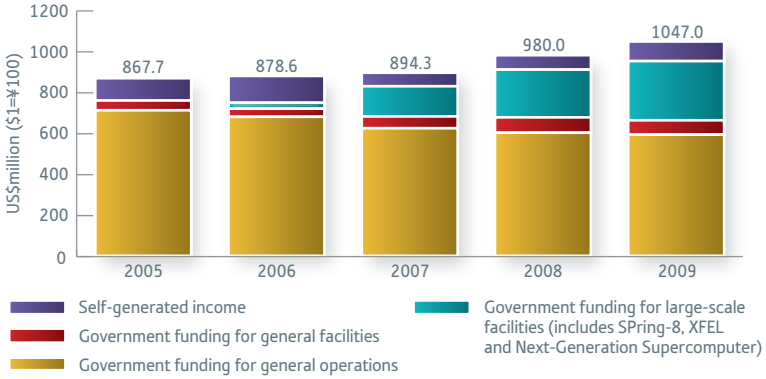
During fiscal 2009, growth in patent licenses and contracts entered into by RIKEN continued steadily. By the end of 2009, the number of patents licensed by RIKEN reached an all-time high of 791, and the number of licensing contracts entered into by the organization edged higher to 288. The current total number of patent licenses and contracts issued by RIKEN has grown by 45% since 2005.



Budget profile

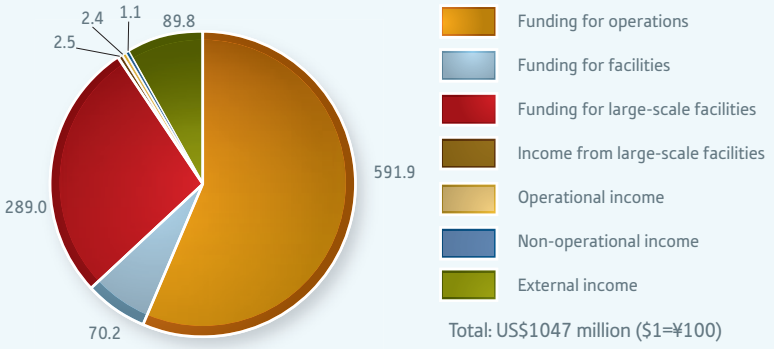
Income—diversifying funding streams

As in previous years, RIKEN continues to draw the majority of its funding from the Japanese government. Despite recent difficulties in the world economy, funding for RIKEN increased in 2009 topping US$1 billion ($1=¥100) for the first time. This was largely as a result of increased grants for large-scale facilities and the maintenance of public funding for general operations at levels close to those of preceding years, although self-generated funding also rose in absolute terms compared with 2007–08. Ever conscious of the importance of diversifying its funding streams, RIKEN continues to work hard to obtain funding from other sources.



Income by source

The single biggest source of income at RIKEN comes in the form of direct grants from government. This provides funding for operations and maintenance of RIKEN facilities, while funding for large-scale facilities such as the SPring-8 synchrotron radiation facility, the X-ray Free Electron Laser (XFEL) and the Next-Generation Supercomputer account for another sizable portion. An important fraction comes from externally generated income, which this year accounted for over 8.5% of the total.



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.

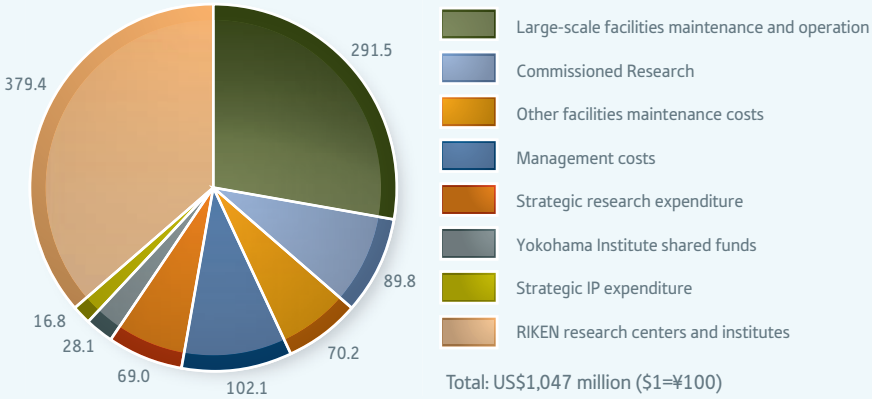
Category		FY2007	FY2008	FY2009
		US$million ($1=¥100)		
1. Competitive funds	Grants-in-Aid for Scientific Research	32.66	37.28	37.90
	Grants-in-Aid for Scientific Research (Ministry of Health, Labour and Welfare, and Ministry of Environment)	1.57	0.82	2.29
	Special Coordination Funds for the Promotion of Science and Technology	1.84	0.37	0.65
	Projects funded by organizations that fund science and technology	12.25	17.11	25.35
	Basic Research Programs (JST)	22.13	29.25	61.93
	Other publicly supported projects	4.39	3.93	4.84
	Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST)	–	–	5.65
Sub-total		74.84	88.76	138.61
2. Non-competitive funds	Government commissioned research	43.37	36.82	26.85
	Government-related commissioned research	3.30	2.38	2.46
	Government grants	1.18	1.70	6.62
	Private grants	0.97	2.23	1.50
	Contributions	2.22	1.67	1.52
Sub-total		51.04	44.80	38.95
Total		125.88	133.56	177.56

Expenditure—prioritizing research

In common with other independent administrative institutions in Japan for which the government is the primary financial supporter, RIKEN is responsible for deciding how to allocate its funds for operation. Although granting a broad degree of latitude as to how funds are disbursed by RIKEN, the government reviews the use to which public money is put closely. RIKEN's first priority is always to develop its research capacity, and its network of campuses, facilities, research centers and collaborations, both domestic and international is unparalleled in Japan. Government funding for facilities is used by RIKEN for capital projects such as building construction. Government grants also fund the majority of maintenance costs for RIKEN facilities. Costs incurred in the of maintenance and operation of large-scale facilities such as SPring-8 synchrotron radiation facility, the X-ray Free Electron Laser (XFEL) and the Next-Generation Supercomputer are shared with the government under a legal framework that guarantees the use of such facilities for the public good.

Expenditure by category

RIKEN devotes the great majority of its income to funding its primary research activities at the RIKEN research centers and maintaining its facilities including its large-scale facilities—SPring-8, XFEL and the Next-Generation Supercomputer—at its five main sites in Japan. It also invests considerable sums in strategic research, while management costs account for less than 10% of total expenditure.

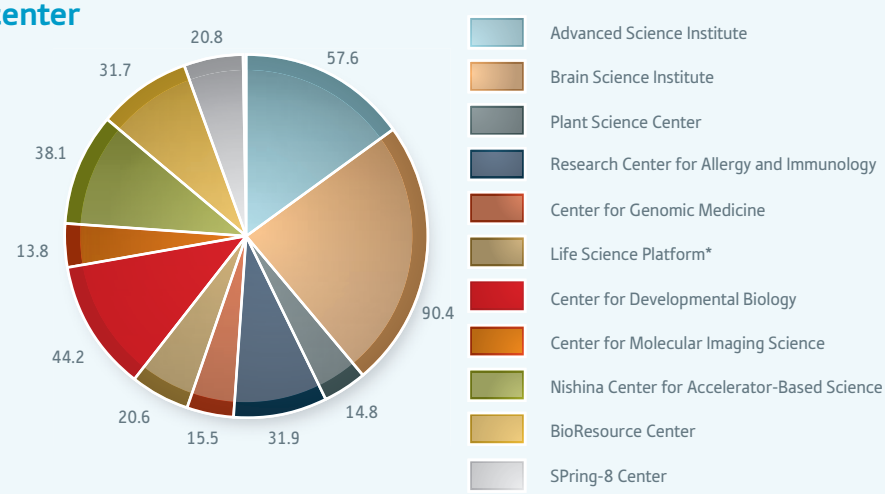


Total: US$1,047 million ($1=¥100)

Expenditure by research center

RIKEN spends more of its budget—over 36% of total income—on the 13 main research centers* maintained by RIKEN in Japan. Over a quarter of this money is allocated to the Brain Science Institute with other centers such as the Advanced Science Institute, Center for Developmental Biology and the Center for Genomic Medicine also claiming sizable portions.

*The Life Science Platform includes the Omics Science Center, the Systems and Structural Biology Center, and the Bioinformatics And Systems Engineering division (BASE).

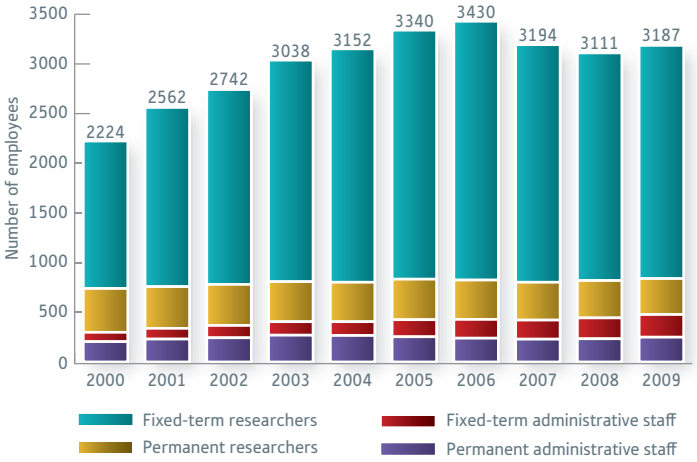


Total: US$379 million ($1=¥100)

Personnel

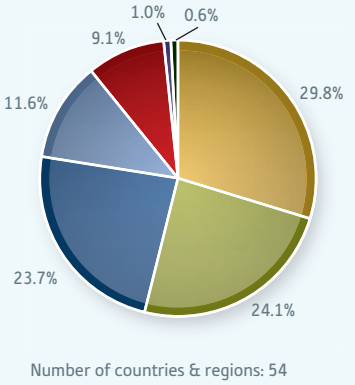
Excellence and diversity

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 slightly in 2009 compared with the previous twelve months, although the proportion of tenures and fixed-term staff remained essentially unchanged at 20% and 80%, respectively. 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.



International research staff at RIKEN

In 2009, RIKEN hosted researchers from 54 countries and regions around the world, with the majority from China and Korea. The number of non-Japanese research staff increased by almost 22% on the previous year, now accounting for 14% of all researchers at RIKEN.

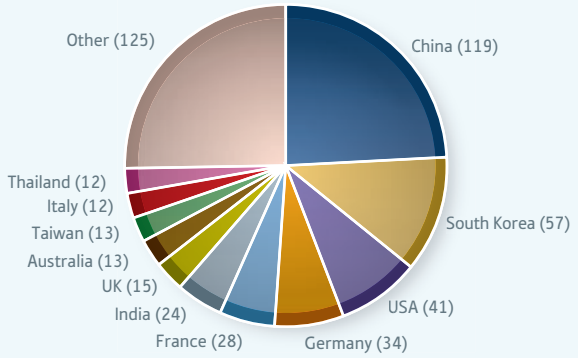


Number of countries & regions: 54

International staff by region

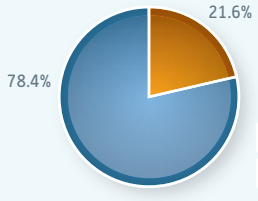
- Europe
- China
- Asia–Pacific (excluding China and Korea)
- South Korea
- USA & Canada
- South America
- Africa

International staff by country/region including visiting researchers (as of October 1, 2009)



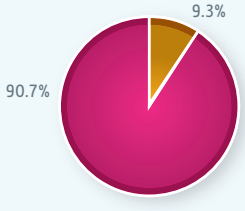
Diversity at RIKEN

Research staff employed by RIKEN (as of March 31, 2010)



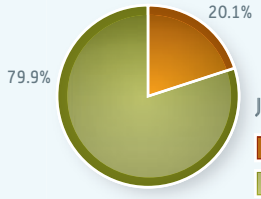
Male: 1,593

- Principal Investigator
- Other



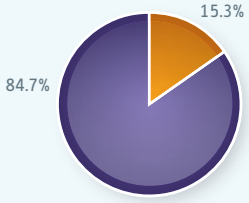
Female: 333

- Principal Investigator
- Other



Japanese: 1,658

- Principal Investigator
- Other



Non-Japanese: 268

- Principal Investigator
- Other

RIKEN Directory

Japan

RIKEN Headquarters and Wako Institute
Advanced Science Institute
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Nishina Center for Accelerator-Based Science
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RIKEN Research Cluster for Innovation
RIKEN Innovation Center
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RIKEN Biomass Engineering Program
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Yokohama Institute
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Center for Genomic Medicine
Research Center for Allergy and Immunology
Omics Science Center
Systems and Structural Biology Center
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Fax: +81-78-306-0101

Center for Molecular Imaging Science
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