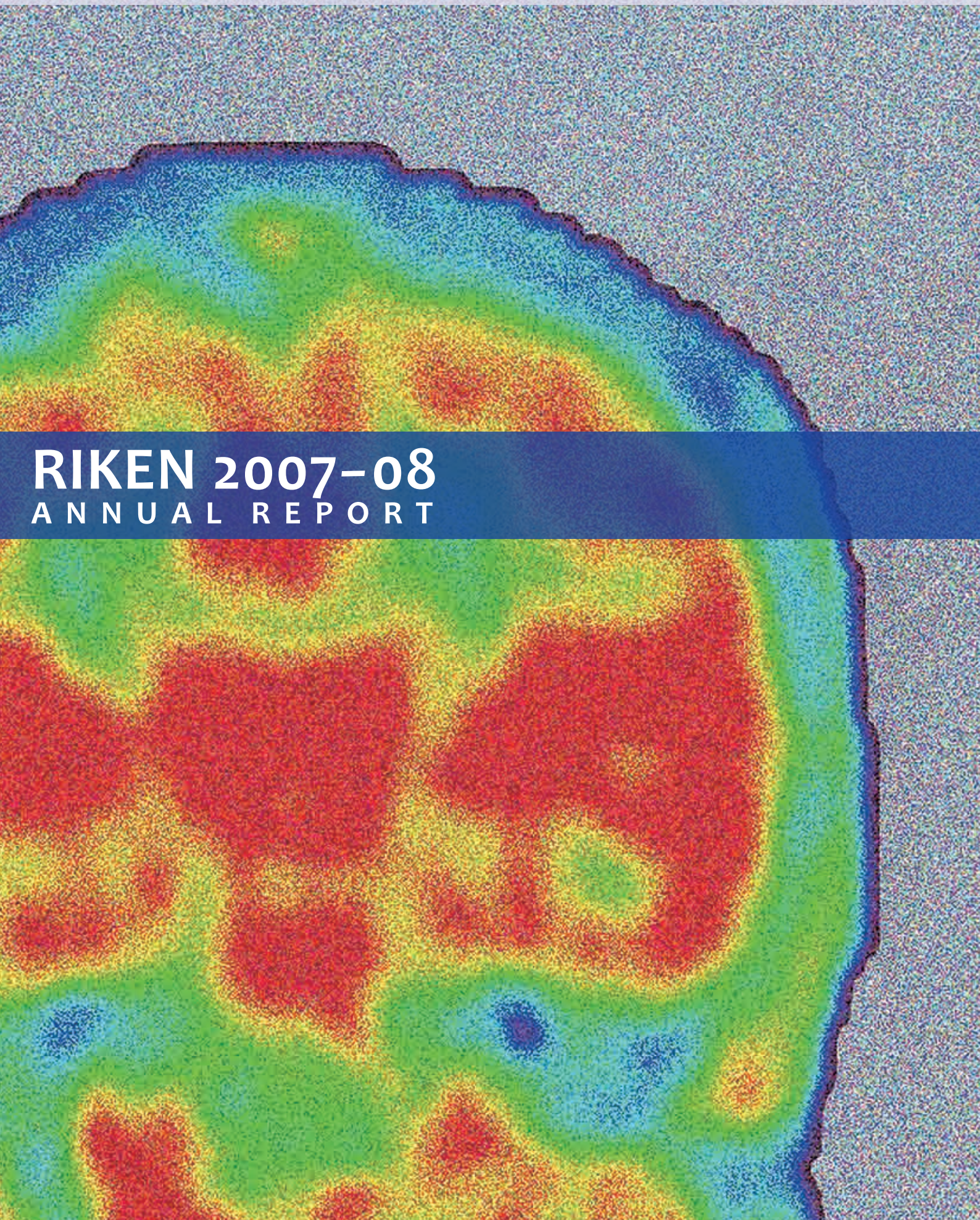


RIKEN 2007–08
ANNUAL REPORT

RIKEN Strives to be Indispensable to Society

By

Making significant advances in science and technology

Contributing to society and being worthy of its trust

Establishing a globally recognized brand image

Why do we pursue science? This is because humans instinctively seek to understand their environment. Knowledge is fundamental to culture, and technology based on scientific knowledge is the foundation of civilized society. In fact, progress in science and technology has pushed the average life expectancy in developed countries from 45 to 80 over the past century. Many people have access to a sufficient food supply, and the world's population has expanded to 6.6 billion despite the hardships some face to make a living. Freed from the need to carry out simple manual tasks, many people today enjoy considerable leisure time in their daily life, and advances in communication technology have made it possible to communicate directly with people on the other side of the earth, or even outside the earth. Modern civilization has come this far. But it shouldn't run wild to such an extent that it threatens our culture, the foundation of our spirituality. Science and technology should not just satisfy the desire of the present generation, but should contribute more for the betterment of future society.

RIKEN seeks to make itself indispensable to the society of tomorrow. With the RIKEN Spirit—appreciation of nature and a legitimate view of society nurtured by our predecessors at RIKEN over the past 90 years—we intend to work with all our efforts to contribute to society in all its aspects and to meet its expectations.

This *RIKEN Annual Report* summarizes our research results for Fiscal Year 2007. We hope that it will give you an idea of our activities, and we earnestly wish for your ever increasing support for RIKEN.

NOYORI Ryoji (D.Eng.)
President

March 2008

CONTENTS

Profile of RIKEN

With a 90-year history of cutting-edge research in the natural sciences, RIKEN is the only fully comprehensive research institute in Japan. RIKEN conducts basic and applied research covering a diverse range of fields including physics, chemistry, engineering, biology, and medical science. Not only does RIKEN participate in research collaborations with universities and corporations and undertake commissioned research projects, it also actively disseminates its scientific and technological findings and facilitates the transfer of technology to industry.

Mission

RIKEN's mission is to conduct research that extends the boundaries of science and technology. The aim is to produce internationally recognized results and maximize the social benefits of those results, making full use of RIKEN's unique research environment. This includes the pioneering of new research fields reflecting society's needs, and taking the initiative in undertaking research in particularly important areas.

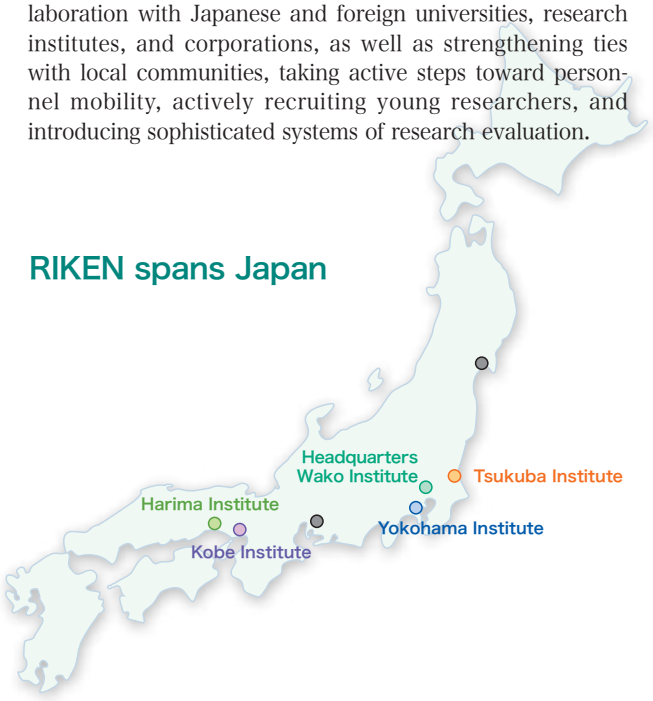
History

RIKEN was established in Tokyo in 1917 as a private research foundation. After the Second World War, RIKEN was restructured as a private corporation named the Science Research Institute Ltd. (KAKEN), but in 1958, it became a semi-public corporation and was again called RIKEN. In 1967, RIKEN shifted its main headquarters out of Tokyo to its current location in Wako, Saitama. With the continued expansion of RIKEN's research activities, its research facilities are increasing in number and now, in addition to those located across Japan, RIKEN has established research centers in the United Kingdom and the United States. In October 2003, RIKEN underwent another administrative restructuring to become an Independent Administrative Institution (IAI).

Expectations

RIKEN encourages active research by fostering a competitive environment and further developing its international character through the recruitment of researchers from various parts of the world. RIKEN is expected to maintain a process of constant self-improvement and to take the lead in renovating science and technology systems through collaboration with Japanese and foreign universities, research institutes, and corporations, as well as strengthening ties with local communities, taking active steps toward personnel mobility, actively recruiting young researchers, and introducing sophisticated systems of research evaluation.

RIKEN spans Japan



RIKEN's distinguished scientists

Hantaro Nagaoka
Physicist

Nagaoka proposed the Saturnian theory, postulating a planetary model of the atom as a nucleus with orbiting electrons. He was also the architect of Japan's platform for physical sciences and the director of the RIKEN foundation's Physics Division.

Kotaro Honda
Magnetic physicist

Honda pursued the study of metallurgy and magnetism, and raised the level of Japanese research in these fields to international standards with the invention of KS steel, a type of magnetic resistant steel, and an enhanced NKS steel.

Umetaro Suzuki
Agricultural chemist

The founder of vitamin research in Japan, Suzuki successfully isolated vitamin B1 from rice bran, calling it oryzanin. Vitamin B1 proved effective in preventing and treating the vitamin deficiency disease beriberi, which was flourishing at the time. He was also instrumental in inventing and developing other products including "RIKEN Vitamins," which financed much of the RIKEN foundation's activities.

Organizational structure of RIKEN in fiscal 2007

*Reorganized in April 2008 (see page 84)

Headquarters

- Research Priority Committee • Policy Planning Division • Public Relations Office
- General Affairs Division • Personnel Division • Finance Division • Contract Management Division
- Facilities and Utilities Division • Safety Division • Auditing and Compliance Office
- Internal Communications and Systems Support Office
- Center for Intellectual Property Strategies • Advanced Center for Computing and Communication
- Next-Generation Supercomputer R&D Center • XFEL Project Head Office

Wako Institute

- DRI/FRS Promotion Division • Brain Science Promotion Division

- **Discovery Research Institute** • **Frontier Research System**
- **Brain Science Institute** • **Nishina Center for Accelerator-Based Science**
- **Research and Development Program for Next-Generation Computational Research**

Tsukuba Institute

- Tsukuba Research Promotion Division • Tsukuba Safety Center

- **BioResource Center**

Harima Institute

- Harima Research Promotion Division • Harima Safety Center

- **RIKEN SPring-8 Center**

Yokohama Institute

- Yokohama Research Promotion Division • Yokohama Safety Center

- **Genomic Sciences Center** • **Plant Science Center**
- **SNP Research Center** • **Research Center for Allergy and Immunology**
- **Center of Research Network for Infectious Diseases**

Kobe Institute

- Kobe Research Promotion Division • Kobe Safety Center

- **Center for Developmental Biology**
- **Molecular Imaging Research Program**

Terahertz-Wave Research Program (Sendai)
Bio-Mimetic Control Research Center (Nagoya)

Masatoshi Okochi

Scientist and executive

While promoting original, atypical basic research, Okochi sought ways to nurture emerging research achievements into full-fledged industries, founding the RIKEN Industrial Group (RIKEN Konzern) in the process. He is credited with creating RIKEN's unique environment as a "scientist's paradise" during his term as the RIKEN foundation's third director.

Yoshio Nishina

Physicist

His Klein-Nishina formula, derived with Oskar Klein, opened the door to a new kind of physics, and his laboratory in RIKEN inspired many scientists with its emphasis on researcher interaction and collaboration. He was president of the Scientific Research Institute Ltd. (KAKEN) after the war.

Shin-ichiro Tomonaga

Theoretical physicist

Tomonaga's RIKEN career began when he joined Nishina's laboratory in 1932. He shared the Nobel Prize in Physics with Richard Feynman and Julian Schwinger in 1965 for his contribution to quantum electrodynamics theory.

Hideki Yukawa

Theoretical physicist

Yukawa also joined Nishina's laboratory in 1940 and later became a RIKEN Chief Scientist from 1961 to 1965, working on the properties of elementary particles. His prediction of meson particle existence earned him the Nobel Prize in 1949, making him the first Japanese national thus decorated.

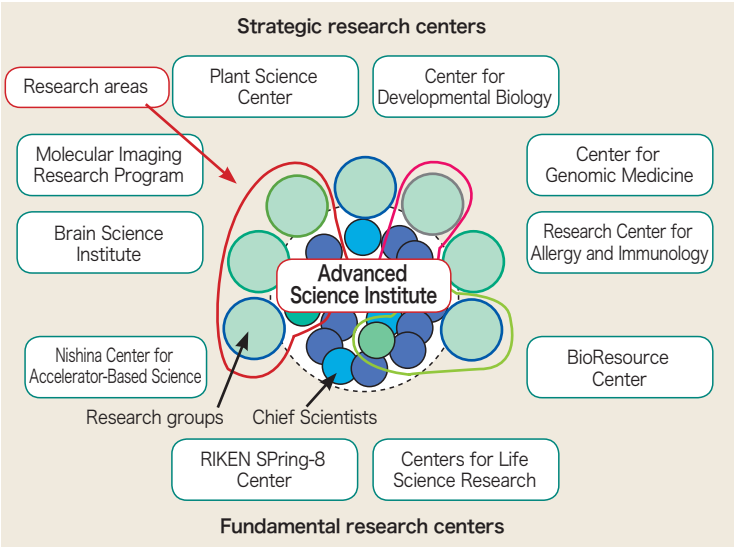
Reorganization in Fiscal 2008

Wako Institute and Yokohama Institute will begin to take a step toward a new stage on April 1, 2008.

Wako Institute

Discovery Research Institute (DRI) and Frontier Research System (FRS), at the Wako Institute, will merge into the Advanced Science Institute (ASI) on April 1, 2008. DRI has been making new research fields by conducting a wide range of basic research focused on freewheeling ideas. FRS has developed these research fields into advanced research areas.

ASI will aim to develop research projects, originating from its two forebears, into the world's top-class research schemes, by strategically operating these projects as integrated and time-limited plans in the boundary and multidisciplinary fields. ASI will also try to realize its potential as a dynamic research institute, with researchers from both within and outside Japan exchanging actively by stepping up cooperation with not only RIKEN's strategic research centers, but also other Japanese and foreign institutes.



Raison d'être of the Advanced Science Institute

ASI will play the main role in creating new strategic and fundamental research centers, by strengthening its ability to develop new research areas through the fusion of various basic scientific researches. This research will be based on freewheeling ideas (DRI) and research projects aimed at developing new scientific technologies (FRS).

Yokohama Institute

Genomic Sciences Center (GSC) will be reorganized and developed into three research departments. The purpose of this is to build a common foundation in Japanese life science research and effectively putting such a foundation to use; the reorganization will also apply research results achieved at the center over the past 10 years, since its establishment, and the characteristics of each research group at the center. Its mouse mutagenesis-related operations will be transferred to the Tsukuba Institute and the system biology-related research to ASI, as part of the center's reorganization.

SNP Research Center (SRC) will be renamed Center for Genomic Medicine (CGM) to more accurately reflect SRC's emphasis on medical science and its activities thus far. A pharmacogenomics research group and international collaboration team will be set up at CGM to promote joint research with Japanese and foreign institutes, in order to establish Japan-originated personalized and preventative medicine.

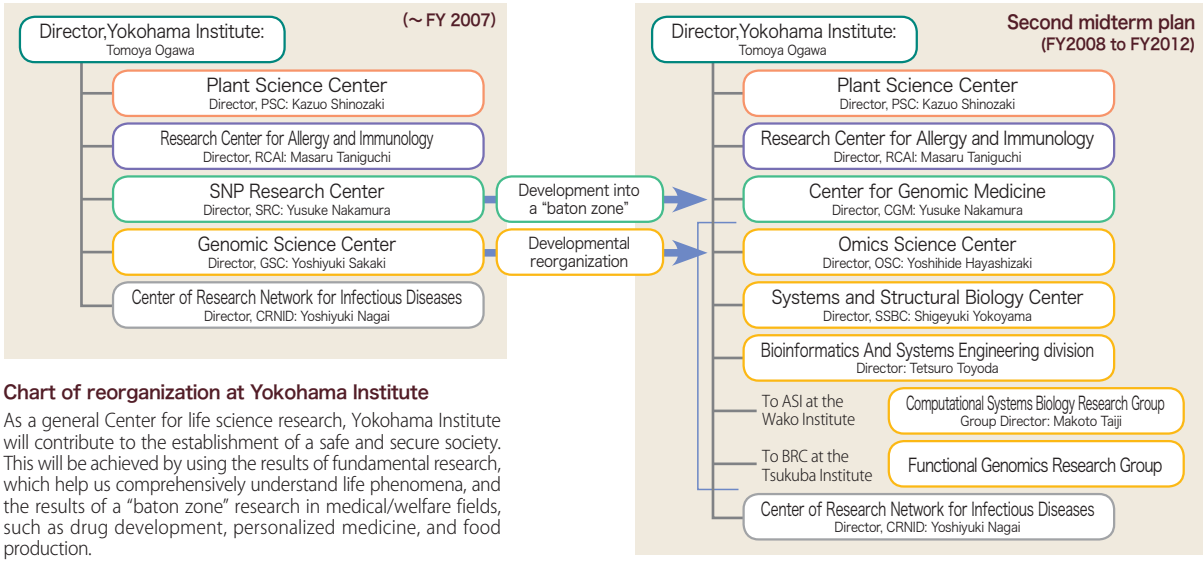


Chart of reorganization at Yokohama Institute

As a general Center for life science research, Yokohama Institute will contribute to the establishment of a safe and secure society. This will be achieved by using the results of fundamental research, which help us comprehensively understand life phenomena, and the results of a "baton zone" research in medical/welfare fields, such as drug development, personalized medicine, and food production.

PROJECT

Remarkable progresses in the development of "key technology of national importance"

"Key technology of national importance"
... Research or technology that the entire nation must tackle intensively

World's most advanced XFEL facility under construction

RIKEN is currently building an X-ray Free Electron Laser (XFEL) facility in Harima Science Garden City, near Osaka, jointly with the Japan Synchrotron Radiation Research Institute (JASRI). Lasers with wavelengths in the X-ray band can help researchers clarify the three-dimensional structure of even a single protein molecule. A joint project group of RIKEN and JASRI succeeded in making a prototype laser generate EUV (Extreme Ultra Violet) laser light in 2006, amid fierce competition with rival groups around the world. The group's XFEL facility is scheduled to start in 2010 generating 'dream light' X-ray lasers, which are expected to help develop entirely new scientific fields.

Acquiring 'dream light'

Just as the invention of telescopes helped people understand the universe more deeply, microscopes have helped clarify the world of micro-scale substances that make up various materials. Clearly, scientific instruments for observing objects of various sizes are indispensable for making technological progress. Very soon, a new type of light source, XFEL, is expected to make a significant contribution to scientific technology by giving scientists the ability to instantaneously capture atomic-scale events.

X-rays, with their very short wavelengths, have more than 1,000 times more energy than visible light. With X-rays, we can see the internal structures of various objects. X-rays can also be used to differentiate atoms. The SPring-8 (Super Photon Ring 8Gev) synchrotron radiation facility next to the XFEL facility construction site is used for examining the structures and properties of materials at the atomic/molecular level using extremely bright X-rays.

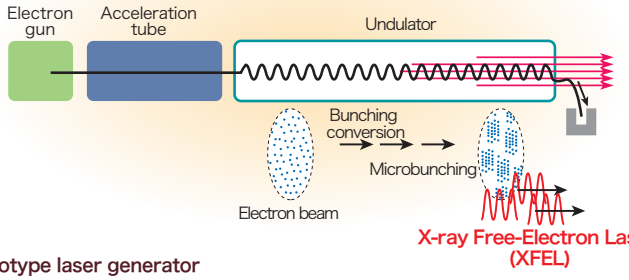
Before X-ray examination at SPring-8, the objects to be observed must be crystallized to freeze the element positions of structures for long exposure of the light, because of the intensity of a coherent X-ray component picked up from various wavelengths is low. But the XFEL's light is intensive and its wave phases are aligned. Thus, Noritaka Kumagai, deputy director of the XFEL project, stresses that there is no need for crystallization of the objects, due to the coherence of XFEL X-rays.

Moreover, the XFEL will be 1 billion times brighter than the X-rays generated by SPring-8, so objects will be able to be observed for a short time, because of its peak intensity, and with much more precision, because of its coherency. Most membrane proteins, which are key *in vivo* substances, for instance, are hardly crystallized. With XFEL, it will be possible to observe the three-dimensional structure of even a single molecule of membrane protein in the *in vivo* environment. XFEL light will also help researchers observe objects for 100 femtoseconds (1 femtosecond = 1,000 trillionth of a second). This will make it possible to observe ongoing chemical reactions in cells or materials like watching a film frame by frame.

Elaborate building of XFEL facility

XFEL is based on three key technologies: the 'monocrystal cerium boride (CeB_6) thermionic electron gun,' the 'C-band accelerator' and the 'in-vacuum undulator.' Project members call these technologies the 'three sacred treasures,' after the three main Imperial regalia of the Japanese emperor.

Principles of the X-ray Free Electron Laser



An electron beam is accelerated to near the speed of light, and passes through undulators, a series of permanent magnets with alternating polarity. These sinusoidally deflect the electrons' path with their magnetic fields, causing the interaction between the electrons and generated light. This light and the electron beam repeat their interaction in the undulator many times, generating a free electron laser.

Photo of the prototype laser generator


Thermoelectron gun


C-band acceleration tube


In-vacuum undulator

Aerial photo of the construction site
The XFEL facility (the area surrounded by red lines) is being built next to the SPring-8 Storage Ring (the circular facility). SPring-8, completed in 1997, is the world's premier synchrotron radiation facility, and is capable of generating extremely bright X-rays. SPring-8 has been used for research in a wide range of fields such as life science and materials science, in addition to a variety of applications to various industrial activities.

To stably emit laser light, the performance of the electron gun must be high. Monocrystal cerium boride (CeB_6) was used as the material for the gun's 3mm-wide muzzle, because CeB_6 can keep its surface evenly and a high brightness electron beam can be emitted from the muzzle of the gun. In addition, the path of the beam must be as straight as possible. "Lasers are not generated unless an electron beam of 30μm in diameter travels straight with an error of up to 4μm per 70 meters of the undulator section. So, correcting the beam's orbit precisely is necessary along the accelerator after the beam is emitted from the gun, and especially required for the undulator section," said Yuji Otake, team leader of the Beam Diagnosis Team and the Timing and Low-level RF System Team. Such correction should be done within several tens of micrometers. Furthermore, the pulse width of the beam is several femtoseconds, therefore, the measurements related to the pulse width must also be made with the same time resolution, Otake is developing a clock even more precise than the highly accurate atomic clocks currently in use.

The project group has sharply reduced the project's construction costs by miniaturizing various types of high-performance equipment without compromising their performance. In the case of the C-band accelerators, the team has halved the length of their acceleration areas by doubling the frequency used for acceleration. Permanent magnets, which are usually put outside the undulators, are now contained inside the in-vacuum undulators. As a result, the gap (beam aperture) necessary for generating lasers inside the undulators has become narrow and they can generate a strong magnetic field.

Kumagai metaphorically describes the current stage of building the facility as the harvest time after his group grew its project into a large tree with firm roots. Completion of the XFEL facility will cap their long-term efforts to challenge limitations.

Construction with millimeter accuracy

It would not make sense if the facility were built on an unstable foundation, even if equipment at the site had an accuracy of several tens of femtoseconds and a few μm. At the construction site, where the ground is soft, 52-meter-long piles were driven down to bedrock to secure a stable foundation. Kazuo Ohshima, team leader of the Facilities Construction Team, explained that the facility has to be constructed with an accuracy of millimeters. In the buildings and foundation of the facility, even the slightest expansion or shrinkage in the concrete is unacceptable.

XFEL facility under construction

Thanks to the group's extensive preproduction planning and high level of technical expertise, construction of the 700-meter-long facility has advanced steadily. Researchers are now considering linking the facility to SPring-8 to improve the quality of the beams generated there. RIKEN also plans to connect the new facility with the Next-Generation Supercomputer to be set up in Kobe (see page 16) to speedily process the huge volumes of data generated at the facility.

XFEL light will soon be produced with the support of RIKEN's rich resources. And new scientific technologies to be created thanks to the XFEL facility are just around the corner.

(from right)

Noritaka Kumagai Deputy Director, XFEL Project Head Office

Yuji Otake Team Leader, Beam Diagnosis Team, Timing and Low-level RF System Team(conc.)

Kazuo Ohshima Team Leader, Facilities Construction Team

World's fastest computation power — Supporting Japan's scientific research and industry

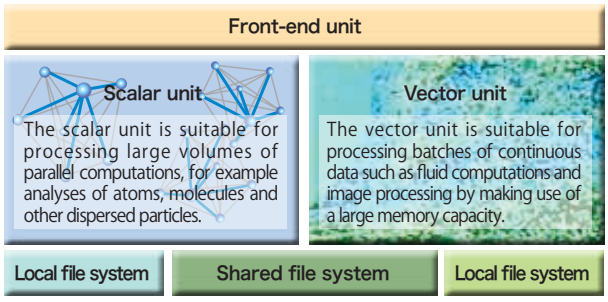
RIKEN Next-Generation Supercomputer R&D Center (NSC) is developing the world's fastest Next-Generation Supercomputer for computational scientific applications. After completion of this multipurpose supercomputer, with a calculation speed of 10 petaflops (10^{16} floating-point operations per second) in 2012, it is expected to not only help develop Japan's computer technology but also be a powerful tool for researchers and engineers in many scientific and industrial fields, including medicine, life sciences, manufacturing, nanotechnology and materials science. RIKEN plans to install the machine at a research facility on Kobe Port Island, Hyogo Prefecture, near Osaka.

The challenge: to develop a faster and more widely applicable next-generation supercomputer

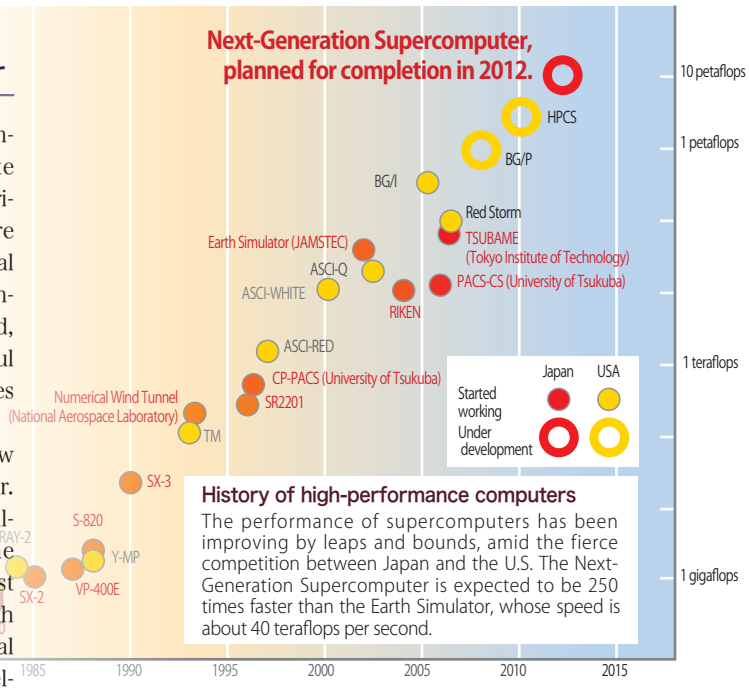
As scientific technology gets more advanced and complicated, researchers demand more and more accurate prediction and verification of objects that are hard to experiment with and observe. Computer simulations, which are numerical experiments carried out by computer, are crucial for satisfying such needs. Like developing theories and conducting experiments, simulations are a key research method, and the Next-Generation Supercomputer will be a powerful R&D tool in this regard, capable of processing large volumes of data with the world's fastest number-crunching power.

High-speed calculation is not the only reason for the new computer being called a "next-generation" supercomputer. Tadashi Watanabe, project leader of the NSC, is a specialist in high-speed calculations, and was involved in the development of the Earth Simulator,* the world's fastest supercomputer at the time it was built. "Unlike the Earth Simulator, which was developed exclusively for geophysical computations, our next-generation machine is being developed as a general purpose computer," Watanabe said. "And while the new machine will be able to handle a wide range of scientific calculations, its performance will be continually improved." The Next-Generation Supercomputer will be able to support diverse applications because of its novel system configuration combining two types of processors. The combination of vector and scalar processors will make it possible to efficiently carry out any type of computation.

* The Earth Simulator, developed by Japan's NEC Corp., was the world's fastest computer from 2002 to 2004.



System configuration
While the processors share calculation data, each processor performs computations that are suitable for it. This parallel processing configuration makes it possible to realize a faster and more widely applicable machine.



History of high-performance computers
The performance of supercomputers has been improving by leaps and bounds, amid the fierce competition between Japan and the U.S. The Next-Generation Supercomputer is expected to be 250 times faster than the Earth Simulator, whose speed is about 40 teraflops per second.

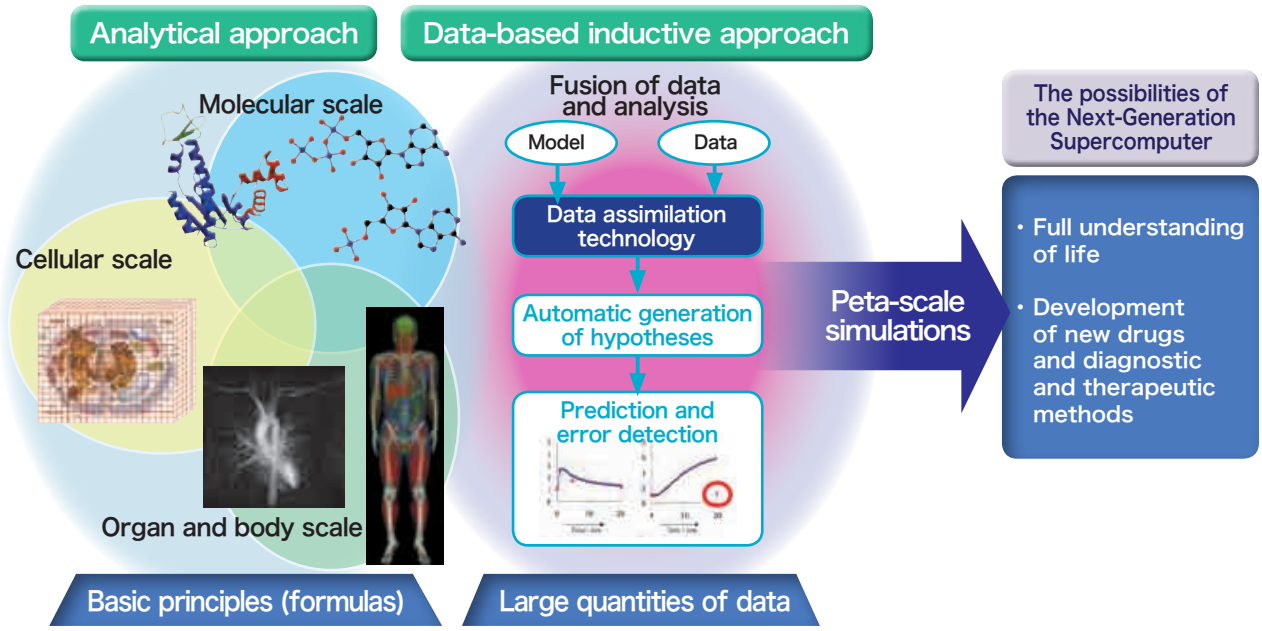
Application software to address diverse needs

RIKEN's next-generation machine will be capable of simulating blood circulation in an entire body, collision analysis of a whole car and other phenomena in their entirety, making the most of its high speed and multipurpose calculation power. The development team also aims to apply the computer to systematic understanding of life by integrating different levels of simulations, such as those of proteins, cells and organs.

As a major life science research institute in Japan, RIKEN is also developing application software to run on the new

Role of Next-Generation Supercomputer in life sciences

The new supercomputer will help researchers systematically understand *in vivo* phenomena at various scale levels through simulations from two approaches – basic principles (formulas and models) and analysis of experimental data. Another role of the machine in life sciences will be in developing application software, which will apply systematic methods to medical diagnoses, drug development and health sciences



machine, with emphasis on applying the machine to scientific results and industrial activities. Researchers have high expectations for the software's contributions in the medical and pharmaceutical fields. Selecting chemical compounds for pharmaceutical use involves an enormous volume of calculations, which include analyses of the structures of various proteins and chemical interactions between compounds and proteins. The new supercomputer will be able to process such computations extremely accurately. At the Institute for Molecular Science, atomic- and molecular-level simulations, including calculations of electron orbits, are instrumental in developing new materials and catalysts in nanotechnology.

Technology and people necessary for developing the world's fastest supercomputer

The new machine's performance per unit of power consumed will be more than 50 times more efficient than the Earth Simulator, according to the development team's plan. Given the power and space constraints, the key to developing such a high-performance machine is technological innovation in microprocessors — the heart of arithmetical processing — and data communications. The finer the circuit lines of a semiconductor become, the less power is consumed and the more powerful the semiconductor becomes. But technological challenges such as difficulty in creating such fine lines and preventing of current leaks must be overcome. RIKEN will try to reduce the circuit linewidths from the current 65 nm to 45 nm by overcoming these challenges.

Moreover, data communications between the various parts of the supercomputer system will be made faster by adopting optical interconnections. These will also make the wiring of the system shorter and simpler. Watanabe said: "Optical interconnections do not affect other electronic devices, as optical signals are not susceptible to noise. In addition, having less wiring will help save energy." These technological innovations, developed through the supercomputer project, will be applicable to other areas as well.

Improvement of hardware alone is not enough to make the new supercomputer perform at its true capabilities — new software custom-made for its system configuration will also be required. The basic software for running the machine must first be developed, and then tuning of the application software will be needed to efficiently run such software on the high-speed machine.

Watanabe emphasizes the need for involving experts from a wide range of fields in developing computer technology. "I think developing the Next-Generation Supercomputer is very important," he said. "The development processes are also crucial, as technology and human resources are developed through the participation of experts from various fields in creating something new." He plans to promote sharing of the new machine with researchers in a variety of areas, and will carry out the development project by deepening collaboration with universities, research institutes and local communities, in hopes that the new supercomputer center will become a key research and educational facility for computational science.

Tadashi Watanabe
Project Leader
Next-Generation Supercomputer R&D Center

Outline of the program — X-ray Free Electron Laser project (XFEL)

The search for a novel type of light — Pioneer a new field in science with an X-ray Free Electron Laser —

An X-ray Free Electron Laser (XFEL) is a laser beam with an X-ray wavelength. This is an ultimate beam, which no one else has achieved. The XFEL at SPring-8, a large scale radiation light facility, is one billion times brighter than a synchrotron radiation X-ray. The XFEL is increasingly expected to become the world's top performance research infrastructure, allowing instant calculation of ultrafine structures at the atomic level, as well as ultrafast changes in chemical reactions.

The importance of developing the XFEL was recognized by the Government of Japan. In the Third Science and Technology Basic Plan, the XFEL project was appointed as a "Key Technology of National Importance", to be dealt with in the long-term national strategy. In addition to Japan, this scientific field is also being developed in the US and Germany; hence, realizing XFEL has become a global competition.

RIKEN collaborates with JASRI in organizing the SPring-8 Joint Project for XFEL, and is promoting its development with the aim of commencing the shared operation of the facility in fiscal 2011. This unprecedented X-ray laser can be used in elucidating the structure and function of membrane proteins that are important in drug discoveries, developing new materials that can adsorb gases, and developing micro-fabrication technology with ultra-precision at the nano-level. Through this project, RIKEN expects to pioneer new research areas in various scientific fields, such as life sciences, nano-technology, and materials, and derive findings ahead of other competing countries.

Number of full-time personnel: 27 (as of March 31, 2008)

The Third XFEL Symposium on January 16, 2008.
"The power and future of the unprecedented XFEL"

Outline of the program — Next-Generation Supercomputer project (NSC)

Targeting the world's fastest and highest performance

Computational science and technology, along with theory and experimentation, have established strong positions as approaches to take in modern scientific technology. A Next-Generation Supercomputer is something that can contribute to the further development of computational science and technology. Similarly to XFEL, the Next-Generation Supercomputer is positioned as a "Key Technology of National Importance," to be dealt with in the long-term national strategy.

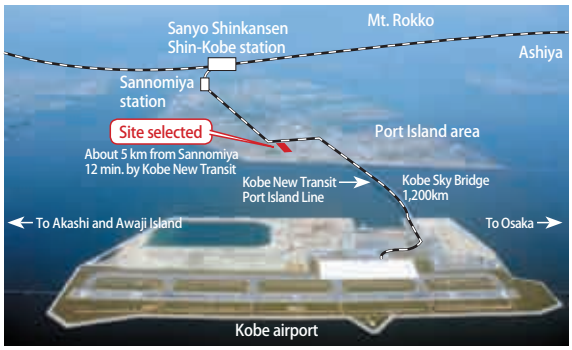
"The Next-Generation Supercomputer project" was introduced by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) in fiscal 2006. Through developing computational science and technology and providing an infrastructure that allows extensive use across a broad range of fields in scientific technology/academic research and industry, the project's goals include enhancing the competitiveness of Japan, producing research results that will contribute to society in various ways such as developing new materials and medicine, and maintaining and strengthening the technical capabilities that will support the development of supercomputers in Japan.

Specific goals include

- development and improvement of the world's fastest high performance Next-Generation Supercomputer*;
  *10 petaflops class
- development and distribution of software (also referred to as Grand Challenge Applications) that can make the most of the Next-Generation Supercomputer;
- establishment of the world's highest standard supercomputing research and education facility, based around the Next-Generation Supercomputer;

Under the MEXT initiative, these goals will be promoted by RIKEN (the developer), taking the lead in collaboration with industry, academia, and government. The targeted completion of the Next-Generation Supercomputer is in 2012.

Number of full-time personnel: 28 (as of March 31, 2008)



Kobe's Port Island where the Next-Generation Supercomputer facility will be built

RESEARCH

Fourteen outstanding scientific achievements

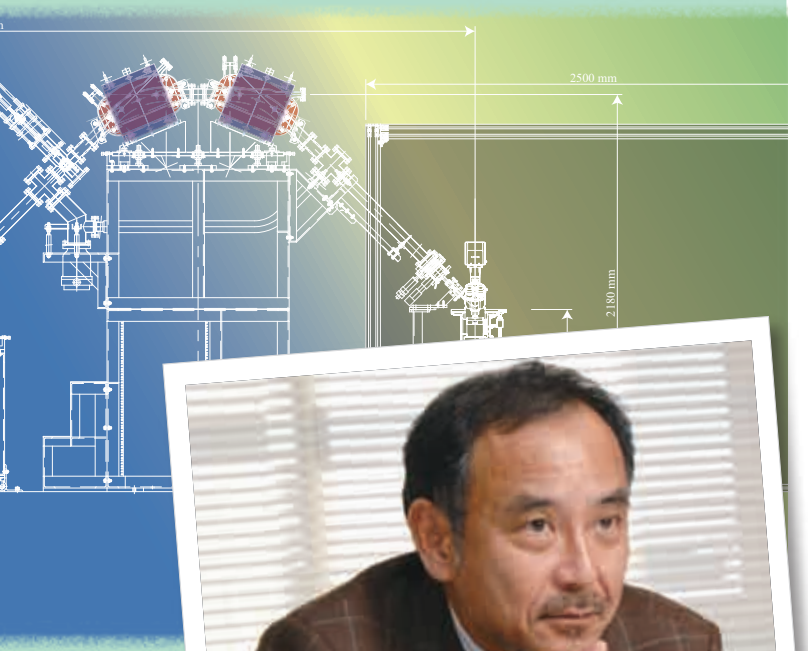
W A K O

Discovery Research Institute

Cell surgery with ion beams

A team of RIKEN researchers has found that an ion beam of usual quality can converge into a very fine one as it travels inside a long, tapered, glass capillary, and pass through a lid covering the tip of the capillary. The beam can then be injected from the tip directly into a liquid in which the capillary is placed, with no liquid flowing into the capillary. This new technology can be used in irradiating a very limited spot within a cell, and the team expects it to be used to study the structures of cells and functions of subcellular organelles.

In April 2008, the DRI was reorganized into the Advanced Science Institute (ASI)



Yasunori Yamazaki Chief Scientist
Atomic Physics Laboratory

Converging ion beam with a tapered glass capillary

The team, led by Yasunori Yamazaki, chief scientist of the Atomic Physics Laboratory, has studied the interaction between particles, such as atoms and ions, and material surfaces. About 15 years ago, the team conducted the world's first experiment to investigate the interaction between ions and surfaces of very fine metallic capillaries bundled in a honeycomb structure. Since then, the team has been carrying out experiments involving the injection of particles into fine capillaries. "A German researcher, a colleague of mine, started experiments with a bundle of insulator capillaries and got some very interesting results," Yamazaki said. "We decided to study the behavior of a single tapered glass capillary instead of the bundle of fine capillaries."

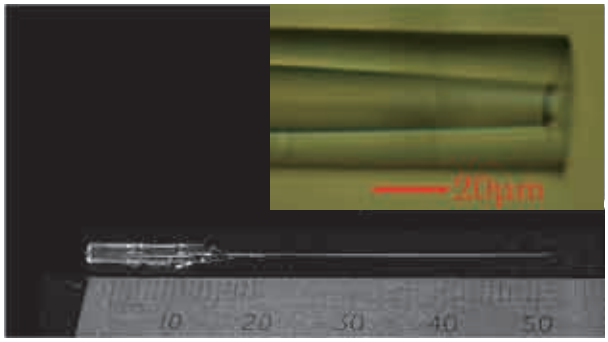


Photo of glass capillary and enlargement of its tip

Extending and tapering a glass capillary is known to help guide energetic particles through it. The team found that while the beam traveled along the capillary, it converged and the density was enhanced by a factor of 1,000 as compared with the incident beam. (http://www-ap.riken.go.jp/nanobeam/) "Electric and/or magnetic lenses are usually used, but it is quite difficult to focus an ion beam to a diameter in the micrometer range. It was a surprise for us to discover that ion beams of usual quality can be automatically focused with a tapered glass capillary," Yamazaki said. The diameter of the tip of such a glass capillary is controllable from several hundred nanometers to several micrometers.

Applying basic physics to biology

Even when the tip of such a capillary is capped with a glass lid, the beam traveling along the capillary can still pass

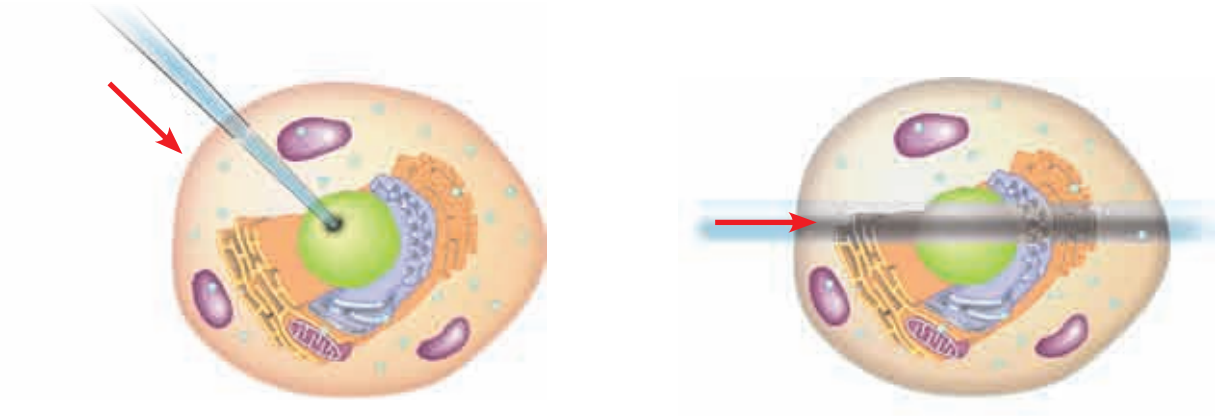


Illustration of beam irradiating cell

Using conventional technology (right), a high-energy beam passes through the cell and damages it along the beam's track. But the combination of the tapered glass capillary and a relatively low-energy beam allows precise bombardment and causes pinpoint damage in the cell (left).

through it. The team considered applying this technology to biological research. Even if the capillary is inserted into a cell, no contents of the cell will flow into it when the lid caps the capillary. Such a direct irradiation of a beam in a cell has not been realized so far. "One of the advantages of working at RIKEN is having researchers in various fields around you," Yamazaki noted. "Such an environment prompted us to consider applying this technology to biology. We are basic physics researchers and we happen to have biologists next door. So we came up with the idea of applying our new method to biological research."

To advance this research, Yamazaki's team cooperated with the Discovery Research Institute's Imamoto Cellular Dynamics Laboratory and Beam Application Team, as well as the Iwasaki Advanced Meson Science Laboratory at the Nishina Center for Accelerator-Based Science.

Using ion beams on cells actually has a long history. Researchers have been studying the functions of various parts of a cell through either destroying or changing the parts with ion beams and observing what happens after irradiation. But with conventional technology, only a high-energy beam of ions can be focused to a sufficiently fine beam suitable for cell irradiation. Such high-energy beams pass through the cell and cause damage along the beam's track. Moreover, with the conventional method, the beam's focus deteriorates and the point of the beam that hits the target becomes less accurate because the beam is extracted from the vacuum capillary via a relatively thick window in air and then shoots into a cell in a liquid.

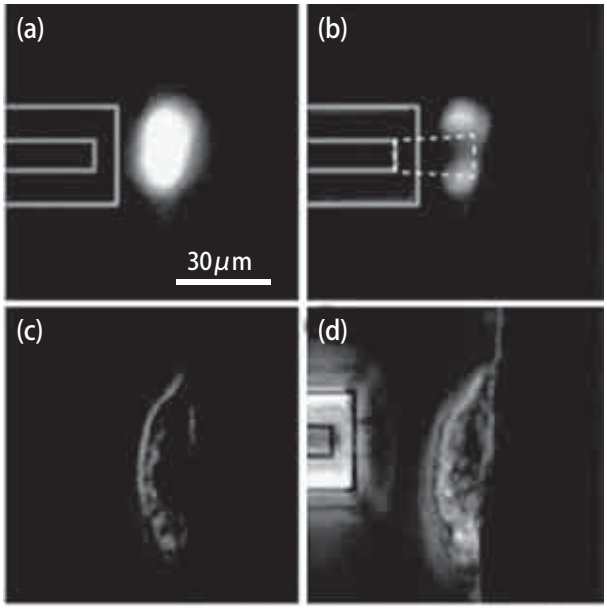
Beam accurately irradiates target inside cell

In the glass capillary-based method, the ion beam can irradiate inside a cell directly, so the beam size is kept focused at the target point. In addition, the beam can be accurately positioned to the targeted spot as the tip of the capillary can be seen through an optical microscope. As a typical animal cell is about 50μm in diameter and the sizes of the cell organelles range from 100nm to 1μm, the tip of the glass capillary can be accurately aimed at the organelles.

The new technology can also effectively converge a beam even if its energy is about one-100th that of beams now used in biological research. This is important, because a low-energy beam does collateral damage to other parts of a cell much less than a high-energy one. "We can control the range of the beam, the distance it travels from the lid of the glass capillary, by changing its energy," Yamazaki said. Conventional methods involve the use of an ion beam that damages cell structures along its track inside the cell, while the new technology can precisely induce damage only to the targeted spot.

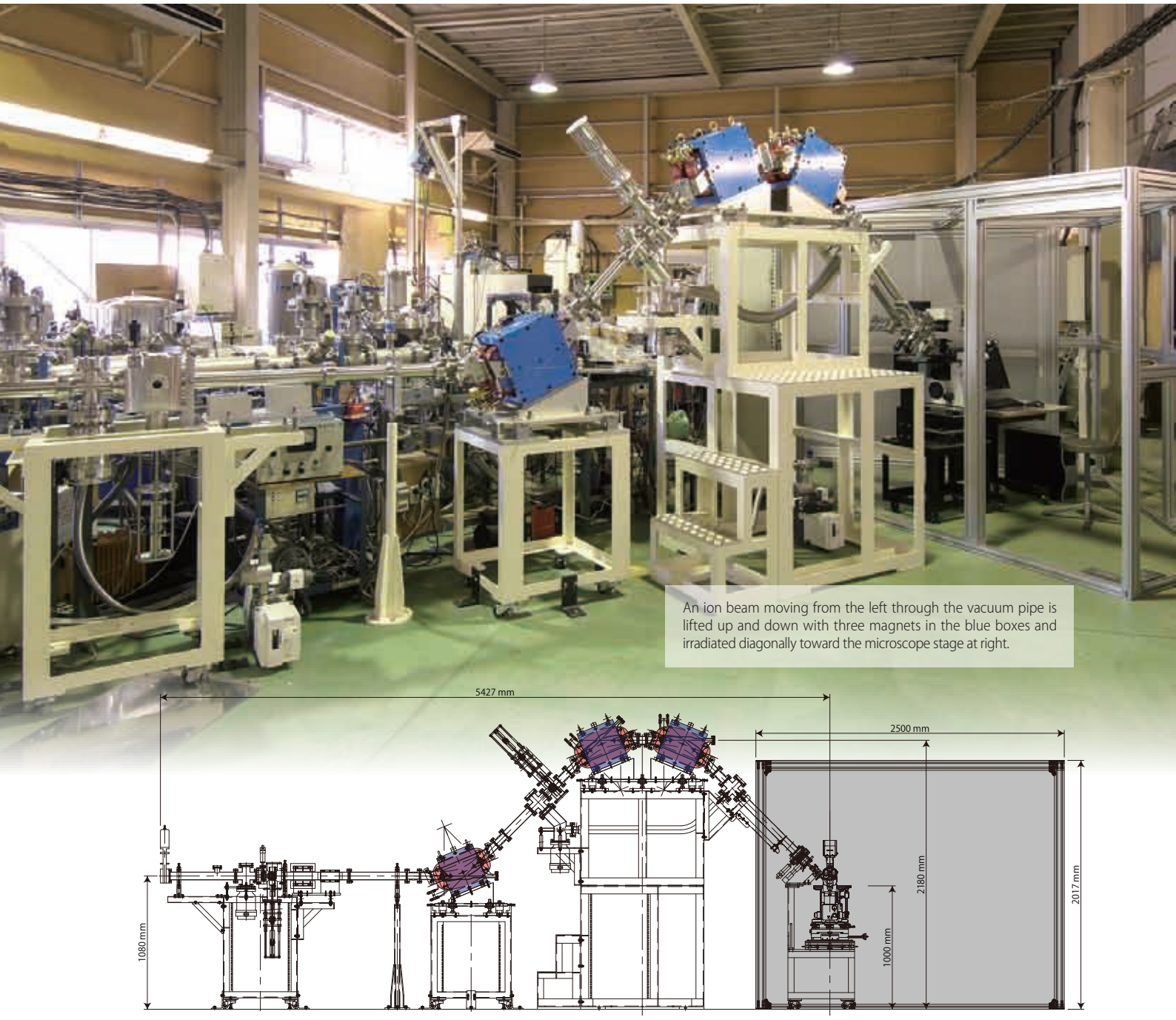
The team has observed that when an ion beam was irradiated from a glass capillary to the nucleus of a HeLa cell (a human cancer cell) that was labeled by a fluorescent molecule, the irradiated volume was optically inactivated after irradiation. This shows that the beam irradiated a very limited area of the nucleus.

Test results of beam irradiation of HeLa cell



Before (a) and after (b) ion beam irradiation
A 4MeV helium ion beam was injected in a HeLa cell from a capillary with an inside diameter of 9.6μm at the tip and a 7.3 μm-thick lid.
At first glance, there appears to be no change to the cell's surface before irradiation (c) and after (d), suggesting that only a limited area was damaged.

Newly developed equipment for cell surgery



An ion beam moving from the left through the vacuum pipe is lifted up and down with three magnets in the blue boxes and irradiated diagonally toward the microscope stage at right.

Promoting applications of the new technology

New equipment dedicated to cell surgery was completed in April 2008 for conducting full-scale research. A beam provided by ordinary irradiation equipment travels horizontally, but it is very difficult to use such a horizontal beam to irradiate a cell in a liquid medium. The new beam equipment at RIKEN has a unique beam line. A series of magnets bend the beam first upward and then downward so that the focused beam from the tapered capillary irradiates a cell placed on a microscope from an angle of 45 degrees. The team plans to study how much damage is induced by such a beam to each internal organelle by changing the beam's energy and the duration of its radiation. With the damage data, the team will optimize irradiation conditions for cell research.

According to a simulation, a glass capillary with an outlet diameter of 100nm and a 100nm-thick lid can irradiate a volume of about $100nm^3$ inside the cell with an ion beam having energy about one-100th the present one. Just a compact beam acceleration system is enough to generate such a low energy beam. The team plans to miniaturize the equipment to the desktop level so that it can be widely used at universities and research laboratories.

Discovery Research Institute (DRI)

Japan's Greatest Integrated Basic Science Institute — The Heart of RIKEN —

One of the greatest features of Discovery Research Institute (DRI) is the "chief scientist system"—the unparalleled research system introduced to promote the development of unique research. This system introduced in 1922 by RIKEN's third president, Masatoshi Okouchi, in 1922 offers a flexible research environment by granting total authority—the setting of the research theme, budget planning, member selection, etc.—to a certain number of research leaders (so-called "chief scientists") who have displayed excellent research capabilities. A number of inventions and discoveries have been achieved through this innovative system, which has also produced a number of outstanding human resources, including, among others, Shin-ichiro Tomonaga from Nishina Laboratory and Katsumi Takahashi from Umetaro Suzuki's research team.

Since DRI was organized in 2002, it has adopted various research systems, including the "associate research scientist system," in order to promote a dynamic new research environment. In DRI, chief scientists from various fields actively exchange opinions while mutually selected representatives intervene in its administration under the supervision of the director. The policy of not drawing any boundaries between different research fields triggers constraint-free research cooperation, and thereby nourishes the germination of new research projects.

DRI is Japan's greatest integrated basic science institute and has the reputation of being "the Heart of RIKEN." For over 90 years, DRI has been contributing to the development of national industries and to the improvement of our daily lives. DRI will become an Advanced Science Institute from the next fiscal year and will continue to operate as the core of RIKEN. We are determined to increase our efforts and assume a leadership role as the front-runner in a wide range of natural science and engineering fields, and also become a global base for creating new scientific fields.

Number of full-time personnel: 414 (as of March 31, 2008)

Director's Message

Unique achievements gained through an interdisciplinary research system

Koji Kaya, Director, Discovery Research Institute

Q. Which project did you particularly focus on in fiscal 2007?

A. An alliance agreement was concluded with the Research Institute for Electronic Science, Hokkaido University, in demonstrating the first model of an "alliance laboratory." This alliance will be used as a driving force in enhancing the alliance laboratory division, and will be aimed at further development for university, industrial, and international collaboration. To this end, the Alliance Laboratory of the Research Institute for Electronic Science, Hokkaido University, was established in DRI in order to conduct collaborative research on molecular-informational life science.

Q. What are some of the noteworthy achievements of fiscal 2007?

A. Aurelia aurita and Nemoplema nomurai are types of jellyfish that float on tidal currents. The mass-emergence of these jellyfish near the Japanese coast can cause serious damage. We, however, turned the potential disaster into an advantage and developed a useful resource from studying jellyfish.

Kiminori Ushida, the research unit leader of RIKEN's Eco-Soft Material Research Unit, and his colleagues discovered a new type of mucin — a glycoprotein — in the jellyfish. This new mucin has a similar structure to the human mucin, which is a major component of human gastric fluid. This finding is expected to contribute to the development of medicines, cosmetics, and food additives.

Q. What are your future prospects?

A. DRI will be integrated with FRS to form an Advanced Science Institute (ASI), and will be germinating new research fields based on basic science research supported by the free-thinking of researchers. These new research fields will then be strategically developed into viable research areas, with the institute being their core research base. In order to achieve these roles, we are determined to go beyond any specific field, organization, and country.

Jellyfish (Nemoplema nomurai)
The body can grow up to two meters long.

Frontier Research System

Controlling the coupling between quantum bits: a crucial step in developing quantum computers

Researchers at the RIKEN Frontier Research System (FRS) have demonstrated that the coupling of quantum bits, or qubits, which are the basic data-processing units of quantum computers, can be controlled. This is a significant step for realizing quantum computers — dream machines that might be able to solve problems in under a minute that would take existing supercomputers many years. If they can be developed, quantum computers could play a significant role in cryptography technologies, retrieving information from databases and simulating various phenomena to solve problems.

In April 2008, the FRS was reorganized into the Advanced Science Institute (ASI)

Franco Nori Laboratory Head
Digital Materials Laboratory

Jaw-Shen Tsai Laboratory Head
Macroscopic Quantum Coherence Laboratory

The power of quantum computers

The basic units used by conventional computers are bits, which can be in either a '0' or a '1' state. Such computers convert information into binary digits for processing. The basic units of quantum computers are qubits, which can also be in either the '0' or '1' state — or both simultaneously, in what is called a superposition state. Moreover, if two qubits in a superposition state are put into an entangled state, in which their quantum states are linked together so that one qubit cannot be described without its counterpart — even though the individual qubits may be spatially separated, quantum computers will be able to compute four combinations of calculations simultaneously. With N qubits, such a machine will be able to calculate combinations of the Nth power of 2 in parallel at the same time. Quantum computers are expected to be much more powerful than existing supercomputers in solving certain problems involving calculations of huge numbers of combinations.

The word 'quantum' originally meant the smallest unit of a material that has the properties of both wave and particle. Typical quanta include electrons and photons. One of the quantum's properties is that its energy levels sometimes take discrete values. Electrons in atoms move around their nuclei at very high speeds. As there are gaps in energy levels between orbits, electrons in one orbit do not jump to the next. But if energy corresponding to an energy gap between two orbits is added, electrons can move back and forth between these two energy levels. These oscillations create quantum superposition and quantum entanglement.

Difficulties trying to couple quantum bits

Franco Nori, laboratory head of the Digital Materials Laboratory, has been proposing various ideas about circuit designs for quantum computers. Recently, he came up with a new idea to generate quantum entanglement by using microwaves. Such entanglement involves mutual interactions of two coupled qubits.

Quantum computers will perform calculations by combining two types of operations — independent manipulation of the state of a single qubit and making two coupled qubits interact — in accordance with quantum algorithms. In these operations, the interactions between two coupled

qubits must be controlled. However, Nori says, "Controlling the coupling between qubits is difficult."

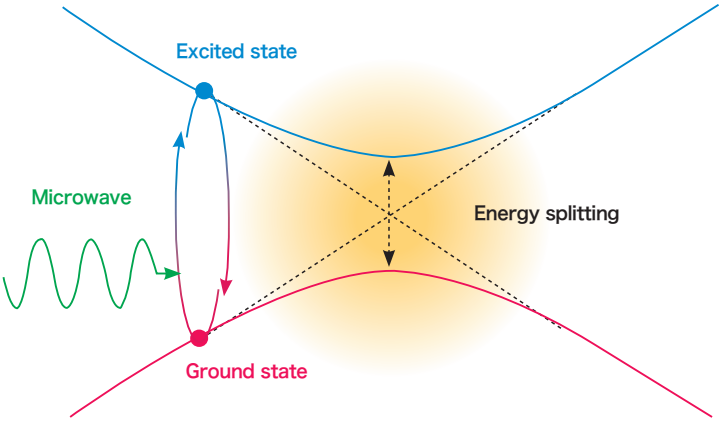
Nori's research team studies superconducting qubits based on Josephson devices. These can be used for controlling quantum states using applied electrical and magnetic fields, including microwaves. The wave properties of quanta usually appear at a microscopic scale. Some relatively large structures that can be designed and manipulated possess such properties. Josephson devices are such structures.

Nori's team has pioneered several research results in superconducting qubits including: coupling qubits to a quantized electromagnetic field inside a cavity, the first study of quantum tomography in solid state systems, quantum thermodynamics, cooling qubits, photon-generation on demand, qubit-based micro-masers, coupling with mechanical qubits, quantum transducers, and how to best couple qubits.

Using microwaves with different frequencies

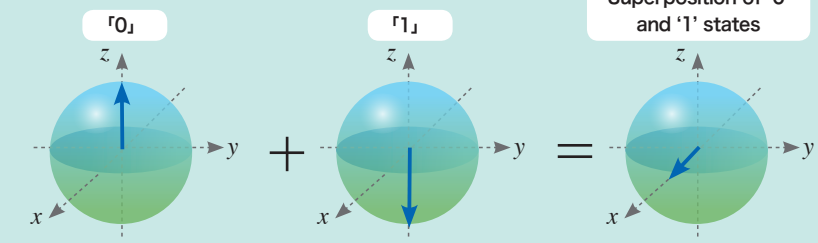
Josephson devices are circuit components made of superconducting materials containing Josephson junctions, in which two superconductors are linked by a non-conducting barrier. As Jaw-Shen Tsai, laboratory head of the Macroscopic Quantum Coherence Laboratory, says, "These circuit components have many electrons, which move freely under normal circumstances. But when they are cooled to very low temperatures, they become superconductive and their electrons fall into a macroscopic quantum state in which they behave like a single wave." As Josephson device specialists, Tsai's team has been making significant contributions toward

Controlling quantum states by using microwaves



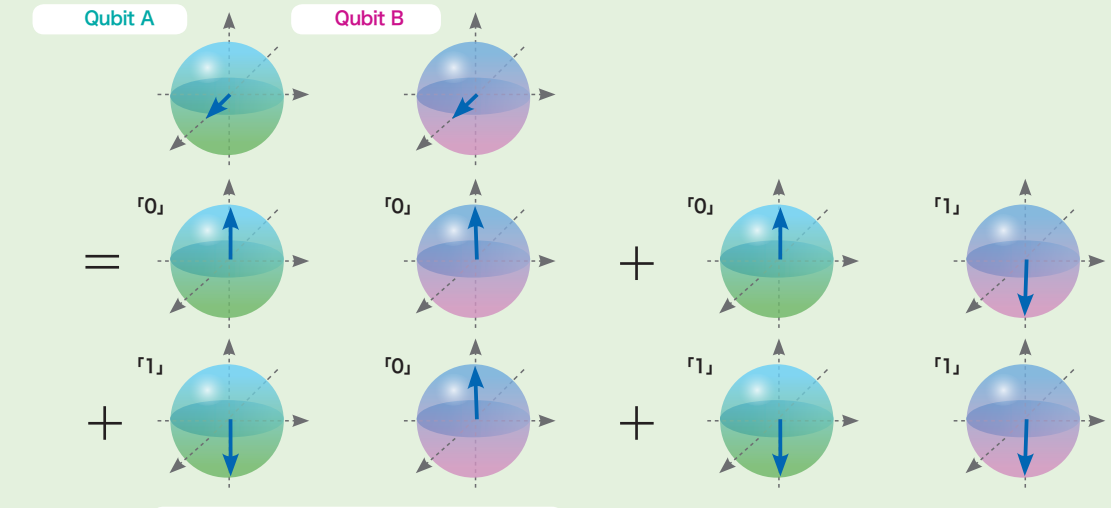
Microwaves have energies corresponding to their frequencies. Microwaves with an energy corresponding to the gap between the two specific states of a particle can induce oscillations between these two states.

Not only '0', but also '1' simultaneously

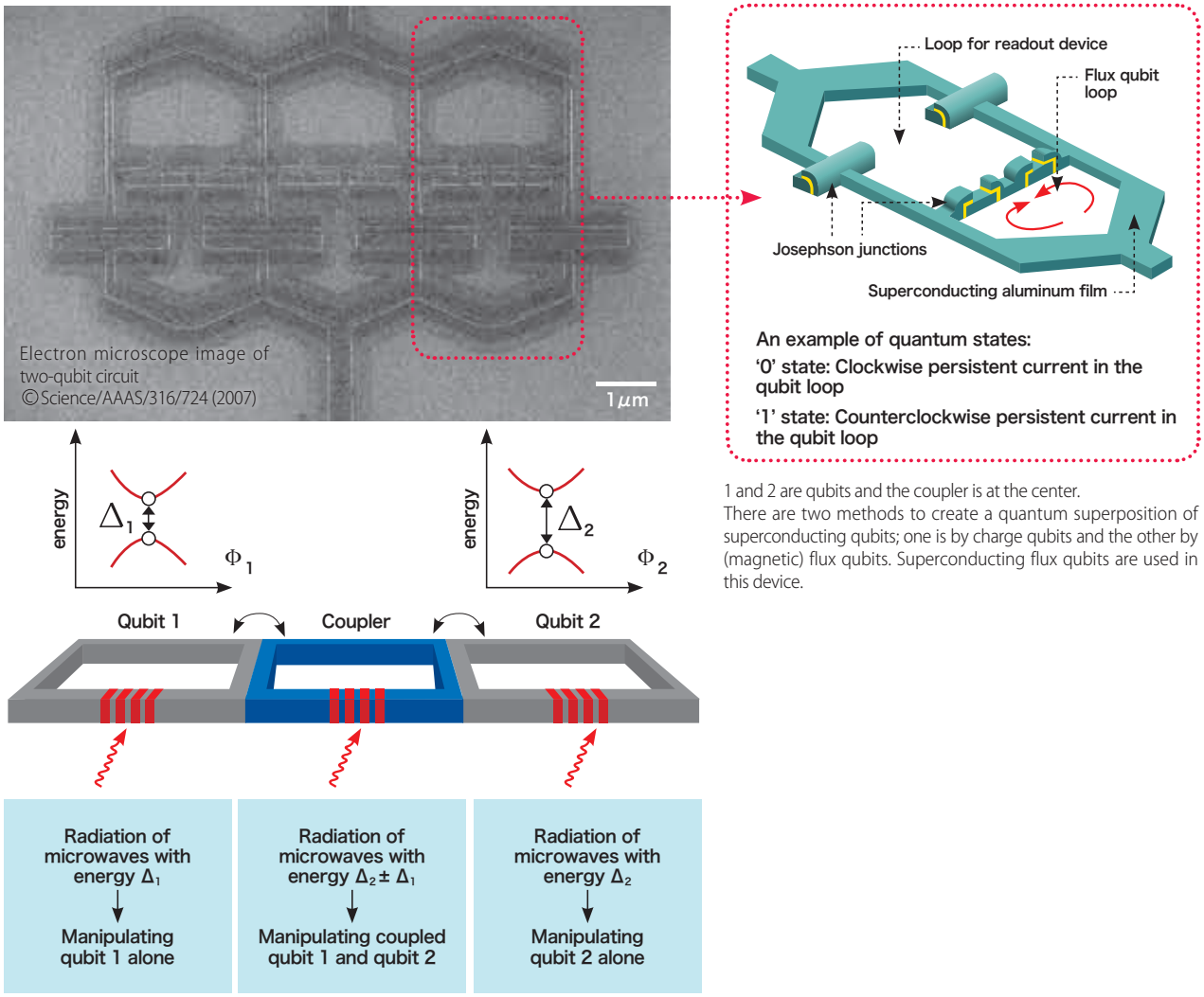


The state of a qubit can be expressed with an arrow pointing to a certain point on a spherical surface. If the north pole is '0' and the south pole is '1', a qubit could take any point on the surface, depending on the degree of the superposition of the '0' and '1' states. If the superposition with the probability of the '0' state is 50% and the '1' is 50%, the arrow indicates a point on the equator.

If the two qubits in the superposition state are entangled ...



Two-qubit circuit with tunable coupling



1 and 2 are qubits and the coupler is at the center.
There are two methods to create a quantum superposition of superconducting qubits; one is by charge qubits and the other by (magnetic) flux qubits. Superconducting flux qubits are used in this device.

realizing quantum computers. As shown schematically in the above figures, electrons in the macroscopic quantum state flow in the loops clockwise or anticlockwise as a resistance-free persistent current. The clockwise current can be used as '0' and the other current as '1' because the energy states of these two types of currents are different.

Tsai's team has designed and produced a quantum computer circuit using three Josephson devices. In the figure above, the loops on the right and the left are qubits, while the central loop is a coupler to magnetically connect the two qubits. Each qubit can be operated independently by irradiating it with microwave frequencies corresponding to the energy of the selected or target qubit. The circuit is designed so that each qubit has a different energy level. Tsai's team has also demonstrated for the first time anywhere that the two qubits can be coupled and made to interact when the central circuit is irradiated with microwaves with frequencies corresponding either to the sum or the difference of the energy gap of the two qubits. The coupling of two superconducting qubits can be controlled by changing the frequencies of the microwaves and the length of time they are applied.

For realizing future quantum computers

Tsai's quantum computer circuit might be suitable for producing large-scale circuits by connecting many qubits because its qubits and the coupler have the same structure. Tsai's team has also succeeded in maintaining the quantum superposition and entanglement states for a world-record-long 10 microseconds. This period is thought to be almost long enough for operating a quantum computer. "We radiated microwaves three times in our experiments." Tsai says, "We think that quantum algorithms will be executed by radiating about 10 times. If the algorithms are carried out, we will have developed a prototype quantum computer consisting of two qubits. That is our next goal."

Nori's team has already started examining other ideas and approaches. He says, "Since the study of quantum computers has just started, it's too early to tell whether the superconductive circuits we're studying will be more fruitful for this task in the long run. Several possibilities are still open. Therefore, at this point this is a very exciting area of research." Researchers at RIKEN are searching for a way to develop quantum computers through close cooperation between the theoretical and experimental teams.

Frontier Research System (FRS)

– The Fountainhead of RIKEN's Vitality –

Frontier Research System (FRS) was established in October 1986, initially as the Frontier Research Program. Using clear targets, excellent researchers were then recruited from various fields, under the fixed-term system. This novel research system, with limited term research projects, had an impact on the Japanese research system, which had traditionally been staffed by full-lytenured research personnel. In 1997, Brain Science Institute was established through this research system, and since then, other research organizations, both within RIKEN and externally, have followed suit, establishing research organizations using FRS as a model. This indicates the height to which this research system has been evaluated and has attracted interest.

Out of the many other limited-term RIKEN research organizations, FRS is the only existing organization with no specific research field in its appellation. This characterizes FRS's mobility, flexibility, and the expectations it bears to serve as an incubator for new interdisciplinary projects and to test new research system operations.

FRS has played a pivotal role in germinating new research fields, in line with the future planning of RIKEN. At present, we are integrating with Discovery Research Institute (DRI), which promotes creativity-based, free-thinking basic research in a variety of fields; we are also taking a new step forward as Advanced Science Institute (ASI), from fiscal 2008. By taking advantage of our comprehensive research institute, we will do our best to fulfill our role as an Advanced Science Institute that promotes advanced cross-disciplinary research in extensive fields, through a flexible and borderless research system.

Number of full-time personnel: 172 (as of March 31, 2008)

Director's Message

– The Fountainhead of RIKEN's Vitality –

Kohei Tamao, Director, Frontier Research System

Q. Which projects did you particularly focus on in fiscal 2007?

A. Studies on the supra-biomolecular system and spatio-temporal function materials, both of which commenced in October 1999, were successfully concluded with a number of notable achievements. Reports from the Spatio-Temporal Function Materials Research Group and the Supra-Biomolecular System Research Group were heard on September 14 and September 20, respectively, and were well attended by many concerned parties. In October 2007, the Cross-Correlated Materials Research Group, the Responsive Matter Chemistry & Engineering Research Group, and the Systems Glycobiology Research Group were launched and began their research.

Based on RI-MAN, a lifestyle-support robot developed by the Bio-Mimetic Control Research Center, the RIKEN-TRI Collaboration Center for Human-Interactive Robot Research was established in August in order to realize the practical use of human interactive robots, which can be trusted and relied upon when they are used at care facilities.

Q. What are some of the noteworthy achievements of fiscal 2007?

A. The Single Quantum Dynamics Research Group, which commenced its studies in October 2001, obtained a number of findings in 2007 and held four press conferences. Specifically, and worthy of special mention, the Macroscopic Quantum Coherence Team successfully demonstrated the world's first controllable coupling between quantum bits. On December 12, Akira Tonomura, group director of Single Quantum Dynamics Research Group, was appointed as a member of the Japan Academy, due to his remarkable academic achievements.

Q. Where there any movements in the research system in fiscal 2007?

A. Some of the achievements of the Supra-Biomolecular System Research Group have been succeeded by the Systems Glycobiology Research Group for further development. Using the high-performance nano membrane technology — developed by the Topochemical Design Laboratory (Toyoki Kunitake, director and laboratory head) in the Spatio-Temporal Function Materials Research Group — as a business foundation, NanoMembrane Technologies, Inc. was established on September 14, 2007, and conducts R&D as a RIKEN venture company.

Q. What are your future prospects?

A. In the Advanced Science Institute, which will be launched in fiscal 2008, researchers from various fields will work together on creative and leading research projects under the flexible and borderless research system. ASI will play a critical role in the research process, which circulates from germinating new research to strategically nurturing research fields and developing a core research base.

We believe that this process will result in great scientific and technological progress, and contribute to the development of human society.

W A K O

Brain Science Institute

Discovery of genetic defect linked to autism RIKEN researchers unlock the mechanism of cerebellar development

Autism is a developmental disorder whose cause is unknown, though researchers have long suspected that it may be genetic. Researchers at RIKEN Brain Science Institute (BSI) have discovered genetic abnormalities that are expected to help clarify how autism develops, and have started examining the possibility of applying their discovery to early diagnosis of the disorder. Autism specialists expect RIKEN's new finding to lead to the development of medications and other treatments for the disorder. Functional analysis of the abnormal gene suggests that autism may be caused by improper formation of neural circuits.

Teiichi Furuichi Laboratory Head
Laboratory for Molecular Neurogenesis

Clue may clarify autism's development mechanism

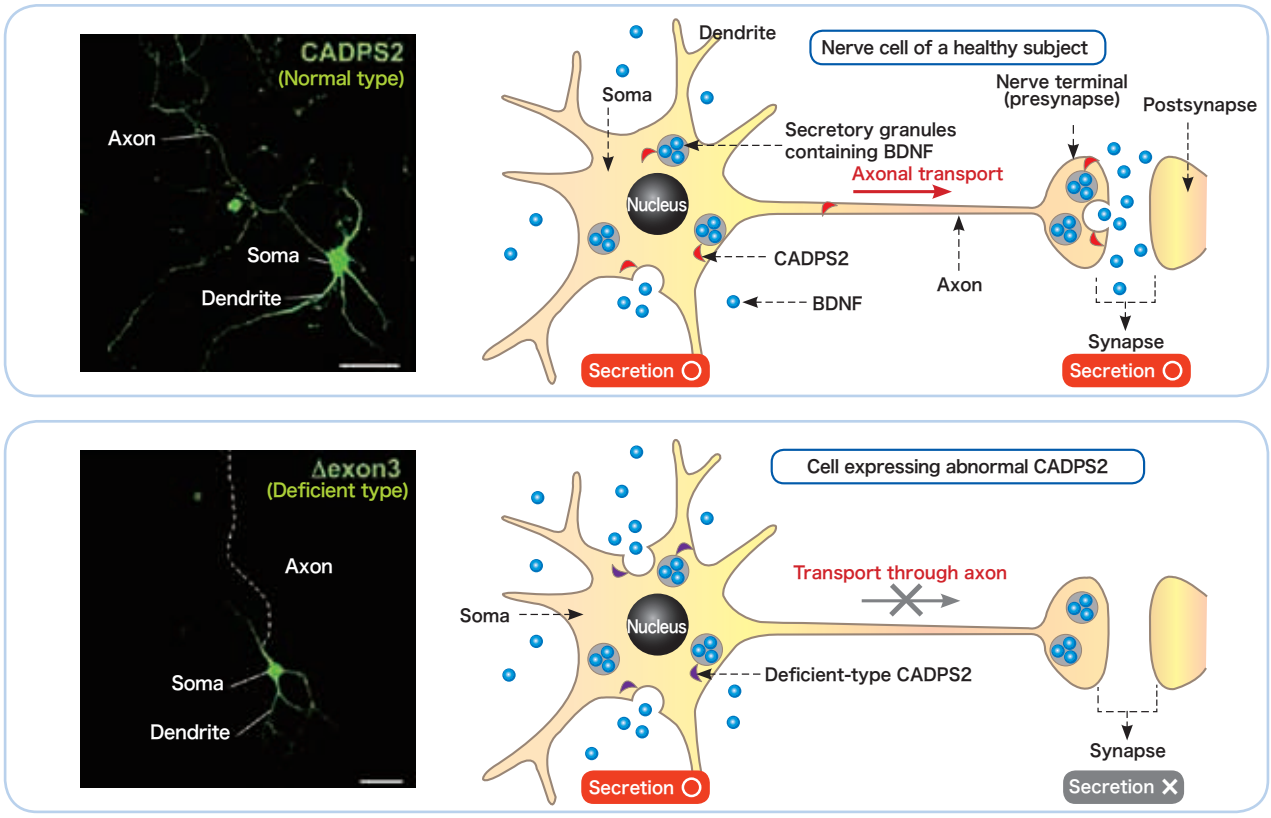
Autism is a disorder characterized by unique behavioral patterns among its sufferers, including serious problems with social interaction and communication with other people, and repetitive behavior. The disorder is relatively common, occurring at a rate of one in 1,000 people during infancy. There is great variation in the severity of these features. Studies indicate that if broader diagnostic criteria are applied (autism spectrum disorder, ASD), the rate of ASD could be as high as 6 in 1,000. But the underlying cause of autism has not been found, and no cure has been developed. Some autistic patients' aberrant behavior and function improve to some extent through special training and treatment early in life. But identifying the root cause and establishing a basic therapy are urgent tasks in light of the relatively high occurrence of the disorder and the impact on patients' families.

In recent years, researchers have suspected the involvement of genes that could be a clue to clarifying the autism development mechanism. When an identical twin has autism, the probability of the other twin also suffering it is 60-92%. In the case of fraternal twins, whose genetic information is different, the rate falls to 0-10%. Researchers have identified potentially important candidate genes that they believe are linked to autism, but they lack conclusive evidence. The genes in question were found in less than 1% of all cases and model mice with most genes did not develop autism-like phenotypes. Now the RIKEN researchers are investigating the possibility that the Ca^{2+}-dependent activator protein for secretion 2 (CADPS2) gene may be involved in causing the disorder. CADPS2-deficient mice have shown behavioral patterns similar to those of autistic patients. In addition, aberrant splicing of CADPS2 transcript has been identified in four of 16 autistic patients and seven single nucleotide variations in CADPS2 gene have been identified by analyzing genomes of 252 patients.

Hypothesis formulated through testing on knockout mice

Neural circuits in the cerebellum usually develop as the individual grows. But Teiichi Furuichi, laboratory head of

CADPS2 protein and BDNF release



Axonal localization of CADPS2 protein
(Top) While normal CADPS2 is distributed from the dendrite and soma to the tip of the axon (synapse), the deficient-type CADPS2 is not transported to the axon (dotted line) and is localized only around the dendrite and soma (below).

The CADPS2 protein promotes the release of BDNF, which regulates the formation of neural circuits and memory and learning functions. The normal CADPS2 protein is transported to the axon and BDNF is released from the presynaptic terminal. But CADPS2 lacking exon3, which is produced due to aberrant alternative splicing, is not transported to the axon. As a result, BDNF is not secreted from the presynaptic terminal.

the Laboratory for Molecular Neurogenesis, studying the genetic process of cerebellar development, and Tetsushi Sadakata, a member of his team, have found that when the CADPS2 gene has abnormalities, these circuits are not properly formed. "We created CADPS2-deficient knockout mice, and found that the release of the brain-derived neurotrophic factor (BDNF) was reduced in comparison with that of their wild-type littermates. As a result, we concluded that the CADPS2 protein is involved in BDNF secretion," Furuichi said. BDNF, which promotes neuronal differentiation and survival, regulates functions crucial for synaptic plasticity and connectivity. The brain develops by wiring and rewiring of neural circuits through the individual's learning and experience. A BDNF shortage may cause developmental deficits in neural circuit underpinning social behaviors, Furuichi said, adding, "Through detailed examination of the knockout mice, we found that they displayed aberrant cellular and behavioral phenotypes that were reminiscent of the features that characterize autistic patients."

Autistic patients are sometimes found to have underdevelopment (hypoplasia) in a particular region of their cerebella. The team found that their knockout mice had hypoplasia in the same region of the cerebellum as autistic patients do. The number of specific neuron types in the cerebrum and hippocampus as well as the cerebellum is decreased. But the cell numbers can be recovered if BDNF is administered, demonstrating that a BDNF deficit causes such reduction of neuron number. The knockout mice were normal in basic visual, olfactory and auditory functions, but showed problems with social interaction and response to unfamiliar environments and exhibited hyperactivity. These behavioral problems appear to be autistic-like symptoms, Furuichi said. "We hypothesized that autism may be caused by improper development of neural circuits during infancy, a very critical brain development stage. Such improper wiring may prevent the brain from working properly."

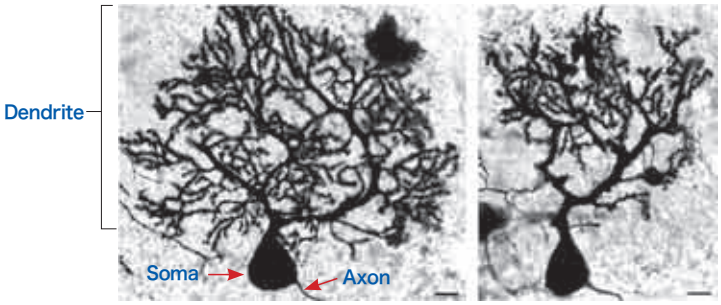
Genetic abnormality also identified in humans

The human CADPS2 gene exists within the chromosomal region that is thought to be associated with autism susceptibility. Furuichi said his team decided to find out whether CADPS2 gene in autistic patients has abnormalities. The team found a shorter transcript (mRNA) encoding the deficient type of the CADPS2 protein in the blood of four of 16 autistic patients. This type of protein is not identified in the blood of healthy people. Sequencing the short mRNA also showed that when the CADPS2 gene is transcribed, the third exon (exon3) of all 28 exons* is skipped. Moreover, the team clarified the importance of the exon3 in its interaction with a protein involved in transporting CADPS2 through axons. Furuichi noted: "The exon3-deficient CADPS2 is not transported from soma (cell body) to the tips of axons (the synapses). As a result, I think that the synapses may not

*Exon ··· protein-encoding sequence

Aberrant cerebellar development and abnormal behaviors of the CADPS2 knockout mouse

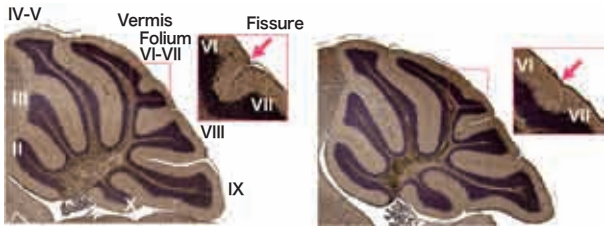
Comparison of dendrite morphology in cerebellar Purkinje cells



Normal mouse

Knockout mouse (abnormal dendrite formation)

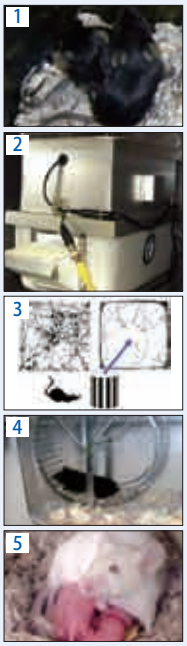
Comparison of formation of intercrural fissures in cerebella



Normal mouse

(Absence of intercrural fissure in cerebellar vermis)

Behavioral tests of normal and knockout mice



1. Social interaction: A pair of mice was placed in a neutral cage to observe their social interactions such as physical contact and grooming. The wild-type (normal) mice often made contact, while the knockout mice did so much less frequently.

2. Home-cage activity: The horizontal movements of mice in their home cage were measured by counting how many times an infrared beam was interrupted. The test found that the knockout mice moved actively (hyperactivity), an autistic symptom, was observed.

3. Response to unfamiliar environment: The knockout mice tended to avoid unfamiliar objects placed in an open field (novel environment). Low adaptation and/or increased anxiety to the unfamiliar environment were observed.

4. Intrinsic sleep-wake regulation (circadian rhythm): The wild-type mice behaved in accordance with their intrinsic biological clocks in a dark environment all day long. But such cycles of their knockout counterparts was impaired.

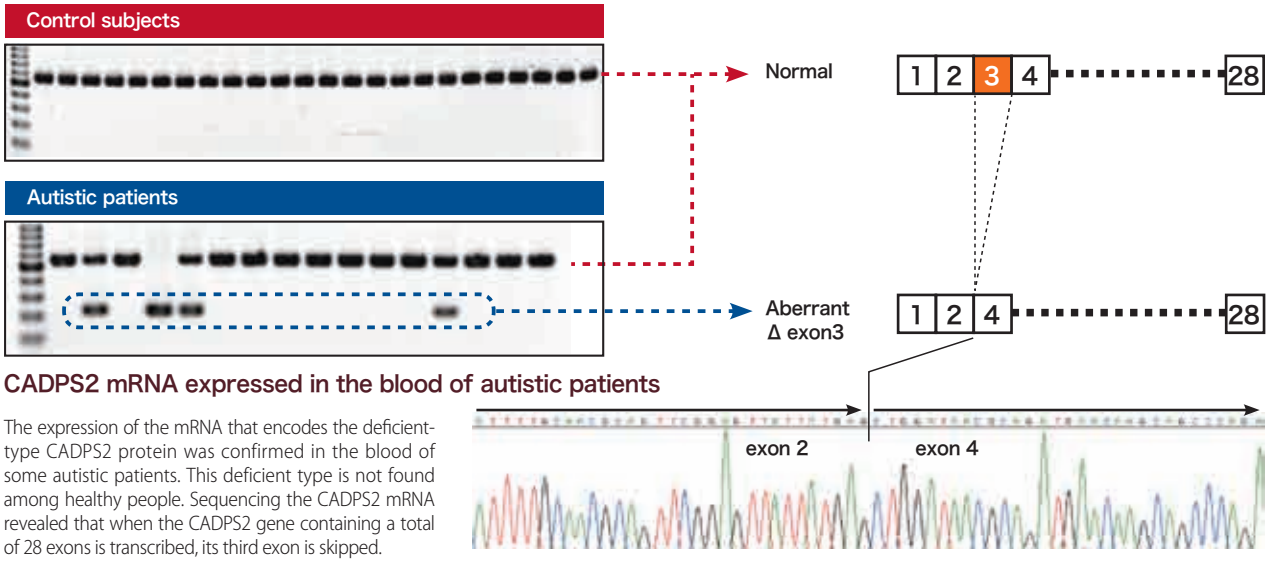
5. Maternal behavior: The ratio of mothers who did not raise their offspring was higher among knockout mice than among their wild-type littermates.

release BDNF and that neural circuits may not be formed properly, due to a lack of local BDNF action at synapses."

It is crucial to start providing proper training and treatment for autistic patients as early as possible. Early diagnosis could lead to the formation of educational and treatment programs for autistic infants. Furuichi and his team have already obtained a patent on deficient-type CADPS2-based early autism diagnosis. "Although combined action of multiple interacting genes is implicated in autism, identifying what genes are involved and studying their functions could lead to the development of drugs and treatments. We want to collect more data about CADPS2 gene from patients," he said. He is enthusiastic about applying his team's discovery to future drugs and therapies for autistic patients.

Results derived from study on 'genetic design of cerebellum'

Furuichi and his team have created a database that could be called a "genetic design of the cerebellum," by investigating when and how certain genes are expressed in developing mouse cerebella. He and his team have already mapped about 9,000 such genes, which they posted on the Internet. Furuichi stressed that basic research has led to a clue to clarifying the development mechanism of autism, and stressed that he and his team do not focus on studying autism alone. Further research on gene functions may lead to the discovery of the involvement of other genes in the development of other disorders and diseases. The team's research is expected to greatly contribute not only to understanding of the human brain but also treatment of a variety of medical problems.



CADPS2 mRNA expressed in the blood of autistic patients

The expression of the mRNA that encodes the deficient-type CADPS2 protein was confirmed in the blood of some autistic patients. This deficient type is not found among healthy people. Sequencing the CADPS2 mRNA revealed that when the CADPS2 gene containing a total of 28 exons is transcribed, its third exon is skipped.

Brain Science Institute (BSI)

Aiming at a new height

Ten years have passed since Brain Science Institute (BSI) was first established in October 1997, as a core national brain science research organization. In order to study the brain, researchers and engineers from various fields, including medical science, biology, physics, engineering, information science, mathematical science, and psychology, have assembled; the intention of this collaboration is to carry out extensive theoretical and experimental research in an integrated manner. Thanks to a number of research achievements and the contribution of human resource development, today, BSI has gained worldwide fame and trust.

Over the past 12 months, even more remarkable research achievements have come to light: the elucidation of the high order mechanism of the brain that learns through conceptualizing right and wrong, etc.; the development of genetic technology that breaks and recovers specific neural circuits; the elucidation of the pathogenic mechanisms involved in ALS, schizophrenia, Alzheimer's disease, etc.; the establishment of a tool-using rodent model; the development of real-time observation technology for use in DNA replication and cell division; and many others.

In fiscal 2007, we also actively addressed collaborations with industry and increased communication with the public; we have also enhanced the development of human resources, in the field of brain science research, through activities such as internationalization, collaborations with research institutes at home and abroad, conducting summer programs, and holding a series of tutorials. As expectations and demands on brain science and its responsibility to society increase, the role of BSI becomes ever more important. We will continue to create new comprehensive human sciences and streams of knowledge so that brain science can meaningfully contribute to society.

Number of full-time personnel: 495 (as of March 31, 2008)

Director's Message

Aiming to jump higher

Shun-ichi Amari, Director, Brain Science Institute

Q. Which project did you particularly focus your attention on in fiscal 2007?

A. Ever since BSI was established in 1997, it has been assuming a leading role in the development of brain science research in Japan with a long-term perspective in mind. In fiscal 2007, our 10th anniversary, I believe that we reached a major turning point.

One of the reasons for this turning point is that a brain science committee, which discusses national brain science strategies, was established at the Ministry of education culture sports science and technology (MEXT) despite the fact that brain science research budgets are being cut back. This event has shown just how important brain science is at the national level.

The second reason is that an element of brain science has reached the stage at which it can be put to practical use, and, as a result, it is gradually being tightly bound to society. Another notable achievement was the establishment of two collaboration centers within BSI: the RIKEN BSI-OLYMPUS Collaboration Center and the RIKEN BSI-TOYOTA Collaboration Center. A research project on the brain activity of people playing Shogi also commenced, in cooperation with Fujitsu Limited and the Japan Shogi Association.

The third reason for the turning point is that a 10th anniversary event was held. To enable more people to understand brain science and BSI's activities, we conducted a range of activities, including an event called Brain Science Park and the creation of a Dreaming Brain Science Map, in cooperation with experts from various fields. These activities resulted in a large influx of feedback from society.

Q. What are the center's future prospects?

A. BSI's strongest points are its comprehensive interdisciplinary nature and its challenges in merging cross-cutting researches. From fiscal 2008, we intend to remove the current boundaries between fields and aim at further evolution through reorganization into four core areas of research: Mind and Intelligence Research Core, Neural Circuit Function Research Core, Disease Mechanism Research Core, and Advanced Technology Development Core — all of which will be increasingly important for the future of brain science research.

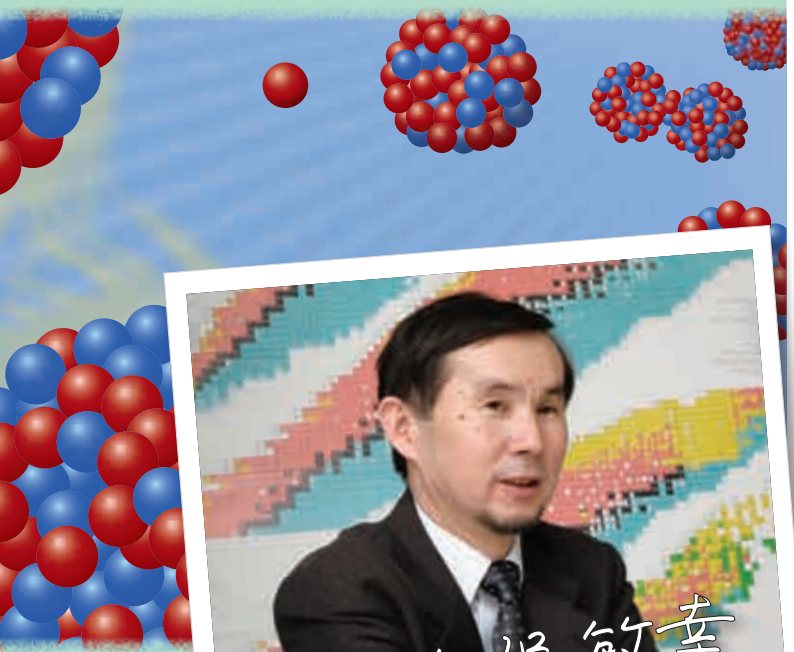
BSI is also an organization that is very advanced in regard to internationalization. It not only accepts a number of foreign researchers but also actively promotes collaborations with the Massachusetts Institute of Technology, Harvard University, and a number of other universities. We are successfully obtaining the world's leading researchers.

In addition, BSI has developed advanced technologies that can act as a foundation for brain science and is making them available to the rest of the world. It is currently leading the world in the fields of fluorescent proteins, imaging technology, and neuroinformatics technology, and is making significant contributions to the research activities of the national brain science community.

Nishina Center for Accelerator-Based Science

New radioisotope discovered at RI Beam Factory

The new RI Beam Factory at the RIKEN Nishina Center for Accelerator-Based Science (RNC) began its working life in style last year— researchers there discovered a new isotope of palladium (Pd 125) in June 2007, shortly after the facility started operations. The achievement clearly demonstrated that the RIBF, which was designed to generate known radioisotopes (RIs) as well as discover new ones, can already deliver the world's most advanced performance of any facility of its type. Various research projects are already being implemented at the as-yet unfinished RIBF, which is targeted for completion in 2012.



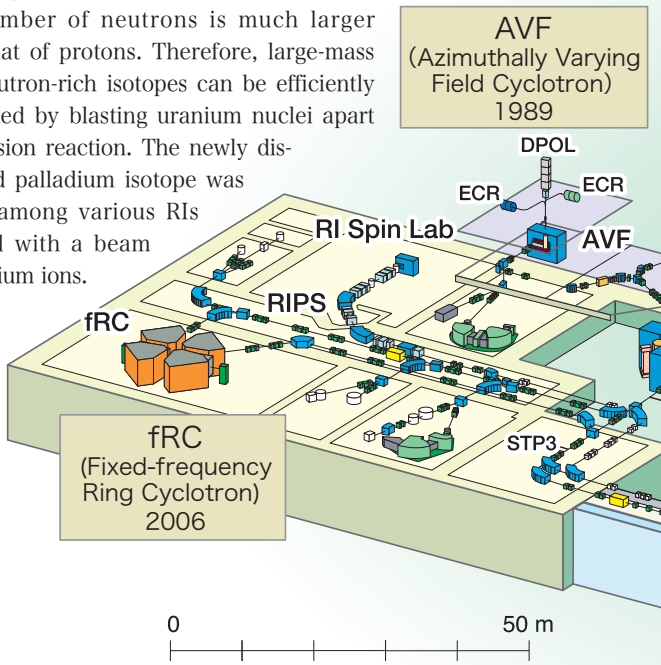
Toshiyuki Kubo Group Director
Experimental Installations Operation Group

Studying the origins of elements

Scientists understand the basics of how the lighter, naturally occurring elements, from hydrogen to iron, were created after the Big Bang — the birth of the universe — though the process is still being clarified. But how elements heavier than iron formed remains a mystery, and radioisotopes hold the key to resolving this question.

The atomic nuclei of elements that occur naturally are usually stable. Nuclei consist of neutrons and protons, and when the number neutrons becomes excessive or that of protons becomes much smaller, the nuclei become unstable and as a result decay quickly after their creation. These unstable nuclei are called radioisotopes. The generation and observation of RIs that do not occur naturally is indispensable for learning about the origins of heavy elements and clarifying their structures.

RIs are generated as a result of the fragmentation, or fission, of nuclei when they collide at extremely high energies with target nuclei. At the RIBF, the world's first five-stage acceleration system became available in 2006 with the completion of a superconducting ring cyclotron (SRC) with the world's most advanced acceleration performance. The RIBF is capable of accelerating uranium ions to about 70% of the speed of light. Uranium, the heaviest naturally-occurring element, exists in a state in which the number of neutrons is much larger than that of protons. Therefore, large-mass and neutron-rich isotopes can be efficiently generated by blasting uranium nuclei apart in a fission reaction. The newly discovered palladium isotope was found among various RIs created with a beam of uranium ions.

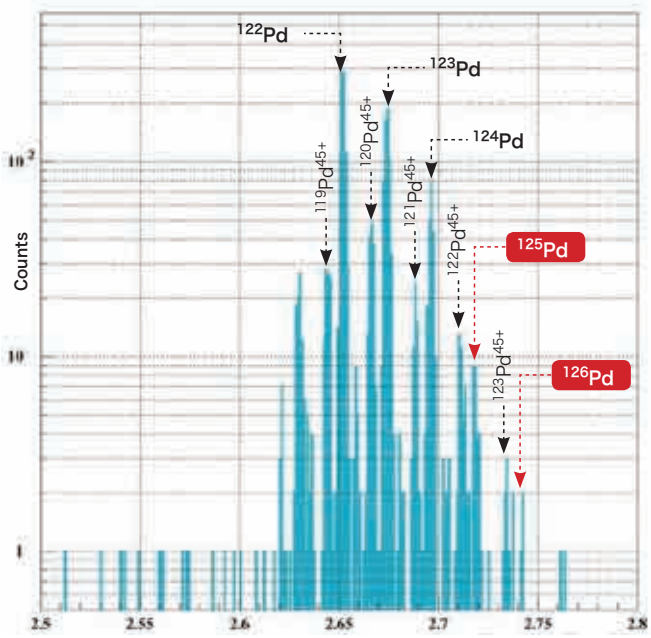


Discovery of Pd 125, a new RI

Creation and separation of radioisotopes are carried out at the RIKEN in-flight RI beam separator (BigRIPS), completed in February 2007 at the RIBF. Toshiyuki Kubo, group director of the Experimental Installations Operation Group, was in charge of developing BigRIPS and led an experiment to find new radioisotopes. "We carried out full-scale trial experiments from May 16th to June 3rd to discover new RIs," he said. "In the first half of the project, we conducted tests to confirm BigRIPS's performance and in the second half started experiments for finding new radioisotopes by using a uranium beam."

In the experiment to create RIs, his team bombarded a beryllium target with a beam of uranium ions accelerated to 70% of the speed of light. For the first time, 43 events of palladium 125 were discovered among the RIs obtained in the experiment. Pd 125 is a palladium isotope containing 15 more neutrons than palladium 110, the heaviest naturally-occurring palladium atom.

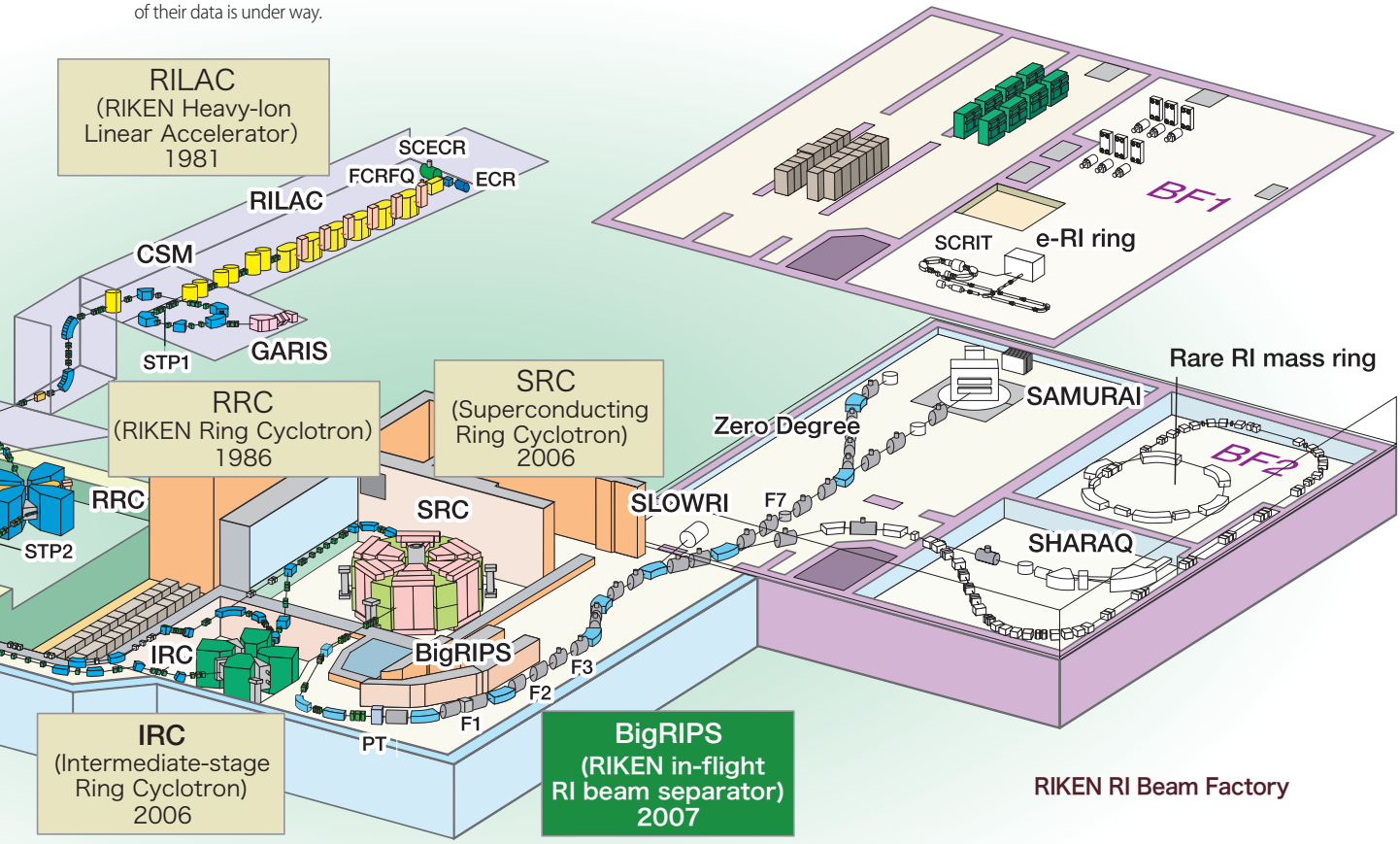
It is widely known that atomic nuclei become especially stable when they contain specific "magic numbers" of protons and neutrons, for example 50 protons and 82 neutrons. Many researchers are paying close attention to the structure of the newly discovered palladium 125, with its 46 protons and 79 neutrons, because these numbers are close to the magic numbers. The discovery was immediately reported at the International Nuclear Physics Conference INPC 2007, on June 6, 2007, and highly praised by nuclear physicists around the world.



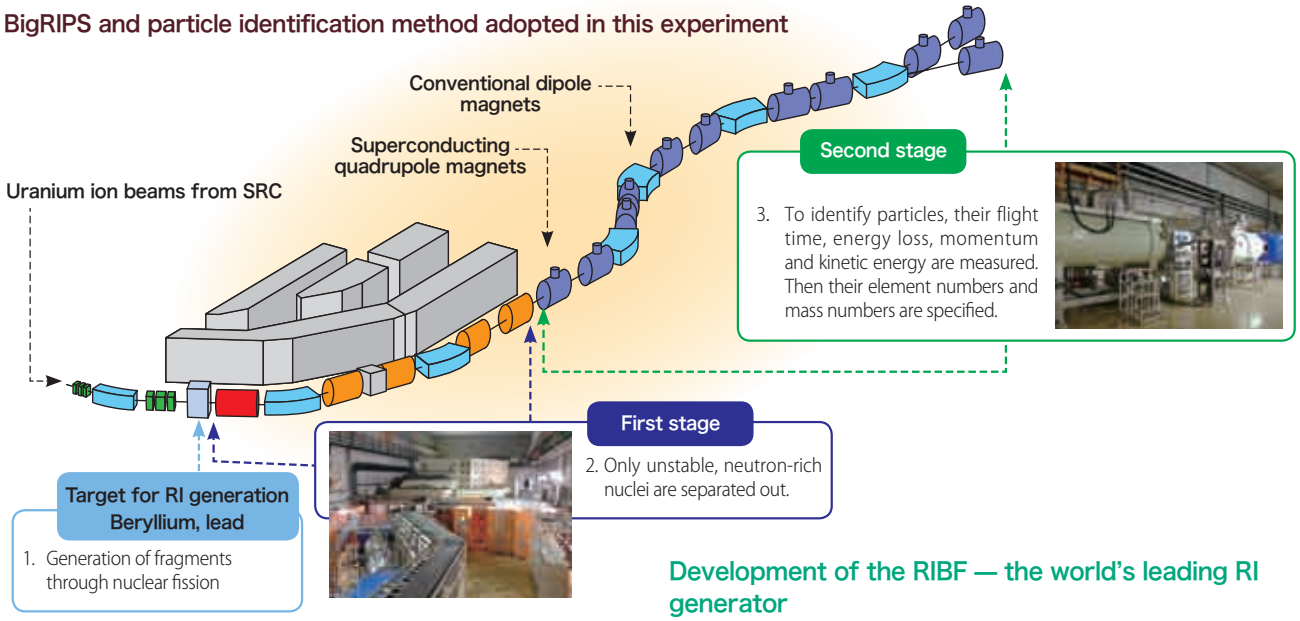
Discovery of a new radioisotope, Pd 125
Palladium radioisotopes were separated from RIs generated through collisions of uranium and target nuclei. They were then plotted according to the ratios of mass number and charge. Forty-three events of Pd 125 were confirmed. Four events that appeared to be palladium 126 were also observed. Detailed analysis of their data is under way.

High RI identification and generation capabilities of BigRIPS

The discovery was due to the advanced capabilities of BigRIPS, which was designed specifically to handle uranium ion beams. BigRIPS has a two-stage tandem structure: the first stage is for collecting and separating radioisotopes, and the second is for identifying them. Its high radioisotope identification performance stems from this two-stage structure. As the RIBF can rapidly generate RIs at intervals of



BigRIPS and particle identification method adopted in this experiment



100 billionth of a second, it is possible to observe them for a relatively long time before they decay. As a result of the smashing of the uranium atoms, nucleus fragments fly off in wide directions. BigRIPS can collect about 50% of all generated RIs not only by widening the diameter of the beam line through which the beams pass, but also by converging the beams with powerful superconducting quadrupole magnets. Some RIs that appear to be close to the target radioisotope are separated out from the collected RIs and sent to a second stage, where the separation criteria include the ions' radius of curvature when they move in a magnetic field, and energy loss when passing through a metal plate.

In the second stage, the RIs are identified by their flight time and energy loss, and their elements and their degree of neutron richness are specified. Kubo explained, "We change the strength of the magnetic field and thickness of the metal plate or adjust the RI detectors, according to the target radioisotope. After a name tag is attached to each separated RI, they are sent to the next facility beyond BigRIPS." In addition to palladium 125, Kubo's team also found four events that appeared to be Pd 126, and they are currently analyzing the data to confirm this.

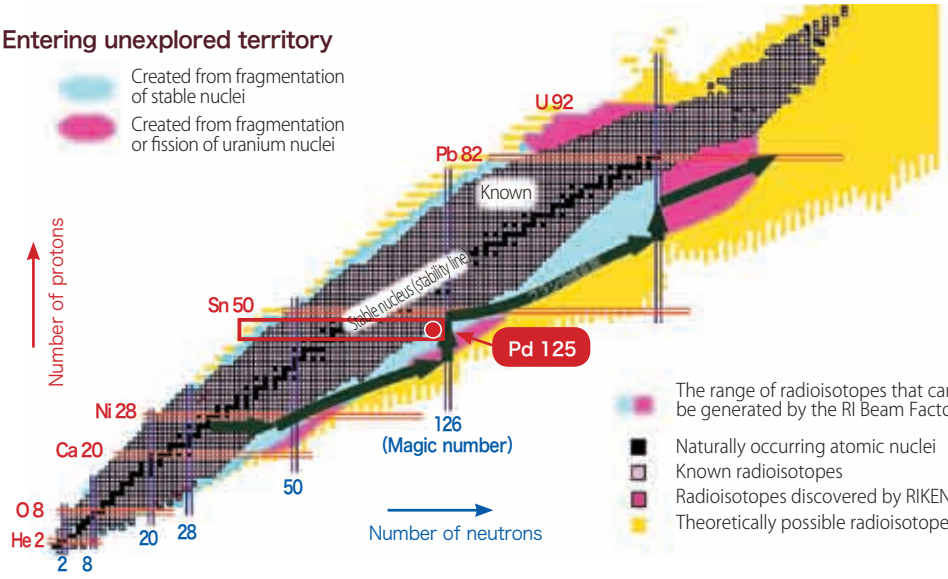
Development of the RIBF — the world's leading RI generator

The experiment to discover new RIs was carried out in collaboration with other laboratories outside RIKEN, with the participation of American, French and German researchers. Kubo said: "The U.S. and European countries are developing their own large particle accelerators. In that sense, they are our competitors. But international cooperation is crucial to make the most of very high-performance facilities like the RIBF by overcoming various challenges."

The RIBF can generate about 4,000 different kinds of RIs, including about 1,000 never before seen. The facility has already succeeded in creating two kinds of unknown radioisotopes even at 100,000th the beam strength it eventually aims to achieve, demonstrating that the RIBF has the world's highest RI generation capability. RIKEN plans to solicit proposals from researchers around the world for experiments to resolve a host of unsettled issues in nuclear physics.

Construction of new experimental equipment linked with BigRIPS began in April 2008. RIKEN will continue development activities to complete the RIBF in 2012 to keep its lead over its European and U.S. rivals in the competition to develop RI beam generation facilities.

Entering unexplored territory



The vertical axis is the number of protons and the horizontal axis is the number of neutrons. Each small square represents an atomic nucleus. There are about 270 naturally-occurring stable atomic nuclei. Around these are many unstable nuclei (radioisotopes). The RI Beam Factory can use uranium or other heavy-ion beams to generate about 4,000 kinds of radioisotopes, including about 1,000 that were previously unknown. In this way it enables researchers to find new radioisotopes and study the origin of the elements.

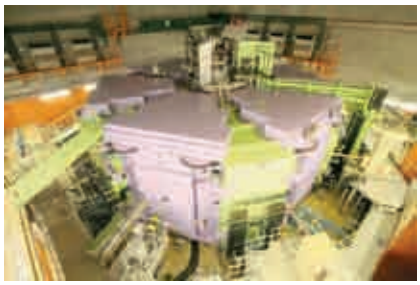
Nishina Center for Accelerator-Based Science (RNC)

Leading the world through tradition and innovation
– Tradition and innovation –

Approximately 70 years have passed since Japan's first, and the world's second, cyclotron was constructed by Yoshio Nishina, in 1937. Since then, RIKEN has been promoting accelerator science year in and year out, and has maintained its position as a global front-runner.

RIKEN Nishina Center for Accelerator-Based Science (RNC) was established in 2006 in order to comprehensively promote accelerator science at RIKEN, and was named after Yoshio Nishina, "The father of modern Japanese physics." The center has bases at Brookhaven National Laboratory in the United States and Rutherford Appleton Laboratory in the United Kingdom, and has been promoting the development of the RI Beam Factory (RIBF), a next-generation accelerator facility. The mission of the center is to elucidate the mystery of material creation by thoroughly investigating the entity of the atomic nucleus and the elemental particles and to further develop technologies that can use the power of the atomic nucleus in industries such as agriculture and medicine.

The RIBF, currently being developed at the Wako Institute, is an advanced research facility, equipped with the world's first Superconducting Ring the cyclotron (SRC)—a collection of fundamental accelerator construction technologies. The construction of the main facility was completed in 2007 and will soon be in full operation and conducting experiments.



Superconducting Ring Cyclotron

By utilizing the RIBF, which was acquired over time using advanced technologies, and overseas research bases that promote international collaborations, RNC will continue to change the face of the new history of accelerator science as a global front-runner.

Number of full-time personnel: 141 (as of March 31, 2008)

Director's Message

The time has come to launch the RIBF, a collection of fundamental accelerator construction technologies

Yasushige Yano, Director, Nishina Center for Accelerator-Based Science

Q. Which project did you particularly focus your attention on in fiscal 2007?

A. The development of the main RIBF facility, which has been promoted by the Wako Institute since 1997, was completed in 2007, and an initial experiment has just begun.

In June 2007, the largest international conference in the field of nuclear physics (International Nuclear Physics Conference (INPC)) was held in Japan for the first time in 30 years. On this occasion, we created a report titled "The discovery and creation of a new isotope of palladium 125," based on the first research achievement made in the RIBF; for this, we received praise from nuclear physicists from a variety of countries. Since the development of the main facility was only just completed in March 2007, it was an enormous challenge to have equipment adjusted and conduct experiments in order to gain research achievements within two months, since the international conference was held in June. However, we did successfully deliver our first research achievements to the world at the best opportunity to do so, as a result of the concerted effort made by the center researchers.

Q. What are some of the noteworthy achievements of fiscal 2007?

A. Makiko Nio, contract researcher (currently a research scientist) from Theoretical Physics Laboratory, as well as her colleagues, successfully calculated the electromagnetic force of a single electron to an accuracy of parts per trillion using RIKEN's RSCC supercomputer. This finding demonstrated a new determination of a fine structure constant to the world's highest accuracy. It will be the foundation for further understanding of the roots of natural phenomena.

Q. What are your future prospects?

A. We believe the RIBF, having the world's highest performance, should be international common property that can be used to generate new knowledge. The center is also promoting creative research through organic bidirectional collaborations. As part of the responsibility of being an organization that has been entrusted with a world-leading research facility (similar to the aforementioned), we plan to open the RIBF's doors to the rest of the world and continue to develop a smooth system to accept external research institutes establishing their research bases.

W A K O

Center for Intellectual Property Strategies

Highly efficient ultraviolet LEDs being developed through "baton zone" between RIKEN and industry

The High-Power UV-LED Laboratory, a research team within the RIKEN Center for Intellectual Property Strategies (CIPS), has been developing ultraviolet light emitting diodes (UV-LEDs) for commercialization. The team has succeeded in emitting UV light of very short wavelengths through the development of a new mixed crystal technology. UV-LEDs are expected to be used as a new light source to replace fluorescent lamps. They will also be used for medical and environmental purposes. This team was set up as part of the Integrated Collaborative Research Program with Industry — an industry-academia collaboration program run by CIPS. The program is aimed at realizing speedy commercialization of research results through joint research with industry. In this joint research at RIKEN, emphasis is put on corporate leadership.

Kenji Tsubaki Team Leader
Integrated Collaborative Research Program with Industry High-Power UV-LED Laboratory

Hideki Hirayama Deputy Team Leader
Integrated Collaborative Research Program with Industry High-Power UV-LED Laboratory

Wide range of potential applications of UV-LEDs

The wavelengths of visible light range from 400nm (violet) to 800nm (red). Ultraviolet has shorter wavelengths and higher energy levels than violet, and various applications of UV are under consideration based on its wavelengths and high energy.

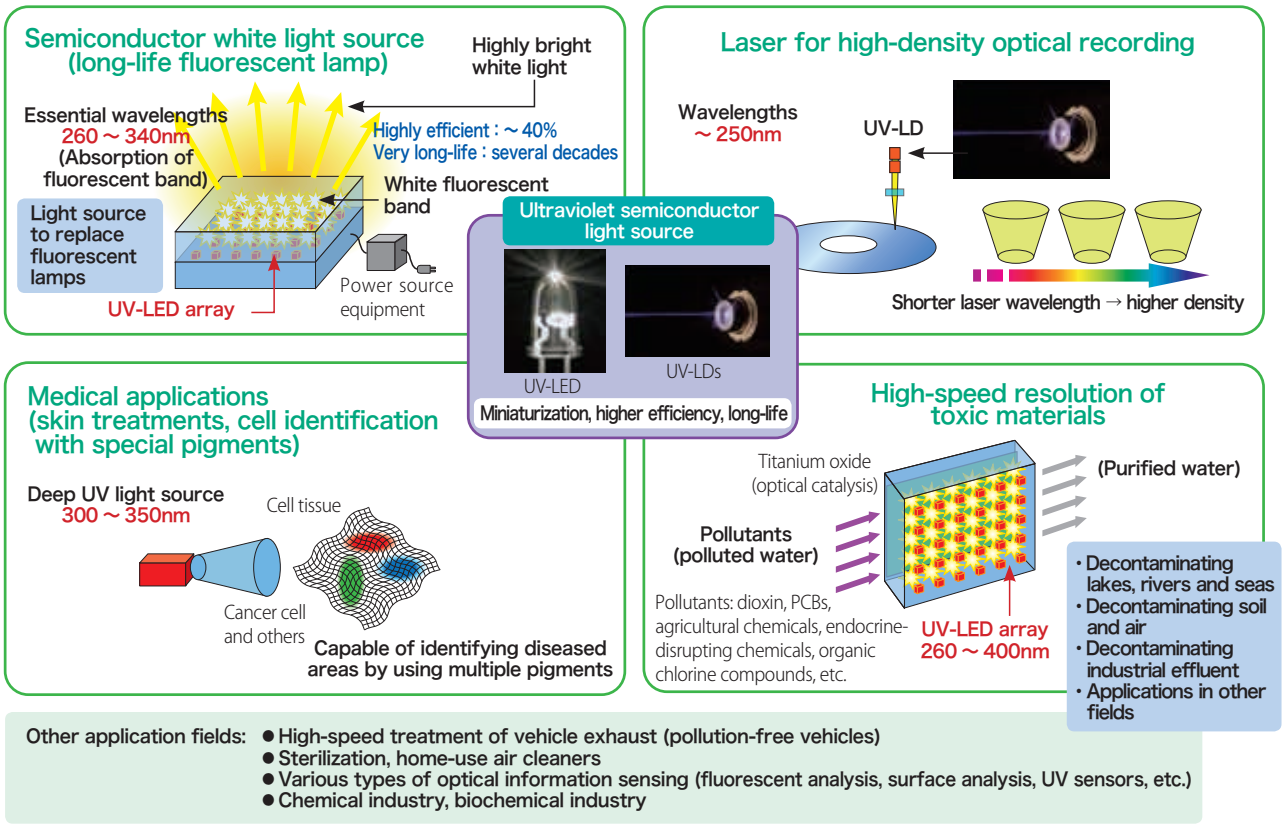
If highly efficient ultraviolet LEDs with wavelengths of 260 to 340nm are developed, it will be possible to create various types of light — including types that are gentle on the eyes or that mimic sunlight — through blending of many colors of fluorescent materials. Ultraviolet of 300 to 350nm has high potential for medical applications. Ultraviolet can be used to detect cancer cells and other diseased areas by injecting special pigments into the body and irradiating them with UV light to illuminate those parts. Furthermore, UV of around 265nm can effectively sterilize bacteria.

The High-Power UV-LED Laboratory has been conducting joint research with Matsushita Electric Works Ltd. as part of the Integrated Collaborative Research Program with Industry of the Center for Intellectual Property Strategies (CIPS) at RIKEN. The research has been implemented in combinations of RIKEN's crystal growth and device processing technologies with Matsushita's excellent device-mounting technology. Hideki Hirayama, deputy team leader of the Integrated Collaborative Research Program with Industry High-Power UV-LED Laboratory, summarized his team's goal in developing the new LEDs: "Our team has been trying to develop semiconductors for emitting UV light, which has more energy than blue light."

High efficiency from quaternary mixed crystals

When voltage is applied to semiconductor layers, electrons inside move from their original layer to a layer at a lower energy level. As a result, light corresponding to the energy gap (band gap) between the layers is emitted. This explains how an LED emits light. The larger the band gap, the shorter the emitted light's wavelength becomes. In 1993, Shuji Nakamura developed blue LEDs based on indium gallium nitride (InGaN). At that time, development of blue LEDs was believed to be impossible. Since his successful development, very bright, low-power-consuming blue LEDs have been spreading rapidly in various applications, such as traffic signals and billboards.

Applications of ultraviolet LEDs

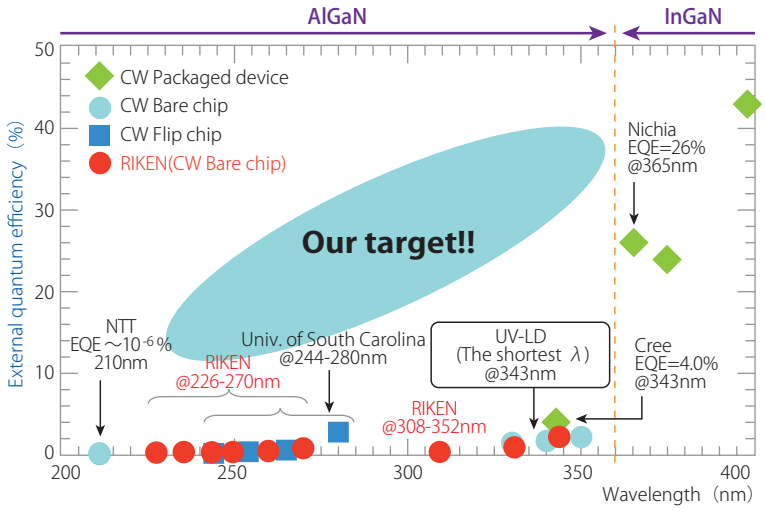


Other application fields:
- High-speed treatment of vehicle exhaust (pollution-free vehicles)
- Sterilization, home-use air cleaners
- Various types of optical information sensing (fluorescent analysis, surface analysis, UV sensors, etc.)
- Chemical industry, biochemical industry

Development of UV-LEDs, which can emit light with higher energy, began around 1997. Researchers have been using aluminum gallium nitride (AlGaN) as an LED material, but its output is 0.02 microwatts — too small for use in commercial applications, according to published reports. In September 2007, a joint group of the Terahertz Quantum Device team, led by Hirayama at RIKEN, and Saitama University developed a high-power LED that emitted 0.15 milliwatts of light with a wavelength of 227.5nm. The group also developed LEDs capable of emitting 1mW of 253nm light, 1.65mW of 261nm and 3.3mW of 273nm. These wavelengths are in the band where UV is effective in killing germs. Behind the success is the use of new LED materials and improvement in quality of the basic layer (buffer layer).

In 2000, Hirayama developed a material based on quaternary mixed crystal composed of AlGaN and a small volume of indium. His new material can emit light several hundred times stronger than other similar substances. LEDs are produced through the metal organic chemical vapor deposition (MOCVD) method, in which gasified organic materials containing LED elements are used to grow LED crystals on the substrate. It had been difficult to produce such quaternary mixed crystal because the temperature at which indium can be added to AlGaN crystal is 400 degrees lower than that at which stable AlGaN crystal can be developed. But Hirayama discovered that if the volume of aluminum gas flow is increased during development of LED crystal, indium can be added at a much higher temperature. “After the discovery, through much trial and error, we tried to find a better combination of gas flow volume, temperature and material composition to improve the light output of our LEDs,” he said.

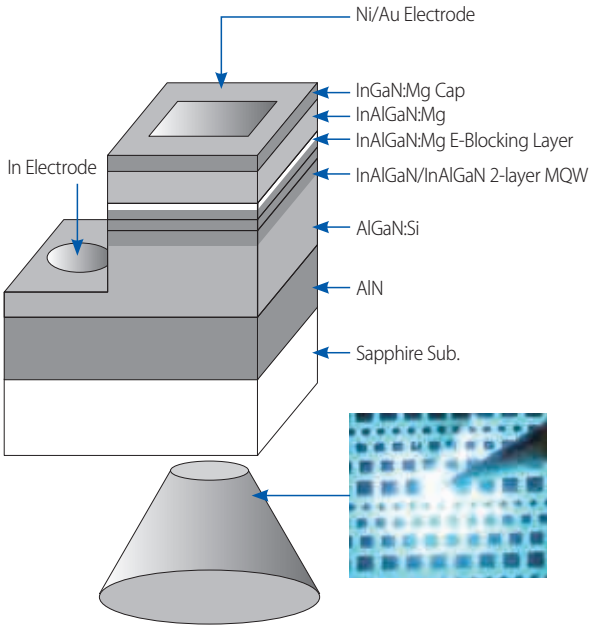
In order to develop clear crystal, a stable foundation is indispensable. The group began to improve the quality of



External quantum efficiency of nitride-based UV-LEDs
The external quantum efficiency is the ratio of the number of photons emitted from the light-emitting device to the number of electrons injected into the light-emitting layer. In the wavelengths region shorter than 360nm, the external quantum efficiency stands at only several percent overall. The research team aims at improving the efficiency of LEDs in this wavelength band.

Structure of 340nm-band LED

A buffer layer as the foundation was initially formed on a sapphire substrate. An n-type layer, light emitting layer, p-type layer and others were formed on top of the buffer layer. The light-emitting layer is quaternary mixed crystal. The challenge the team is facing is to find a way to effectively dope the p-type layer with substances.



the aluminum nitride (AlN) crystal of the buffer layer for that purpose. The group has developed the ammonia pulse-flow multilayer growth method to develop high-quality AIN crystal as the buffer layer on a sapphire substrate. In the new MOCVD-based method, AlN crystal is developed through the continuous supply of aluminum material gas and pulsed supply of ammonia gas. In addition, another layer is developed through the continuous supply of the aluminum material and ammonia gases. The layer formed through the pulsed supply reduces gaps in atom positions between crystal lattices with different inter-atomic distances on the substrate, while the layer made through the continuous supply keeps the flatness of layers in the atomic level. The alternate development of the two types of layers also helps prevent cracks. As a result of these efforts, Hirayama's team has raised the emitting intensity of LEDs by another 50 times.

Equipment handmade by Hirayama to evaluate light emission properties

'Baton zone' between RIKEN and companies

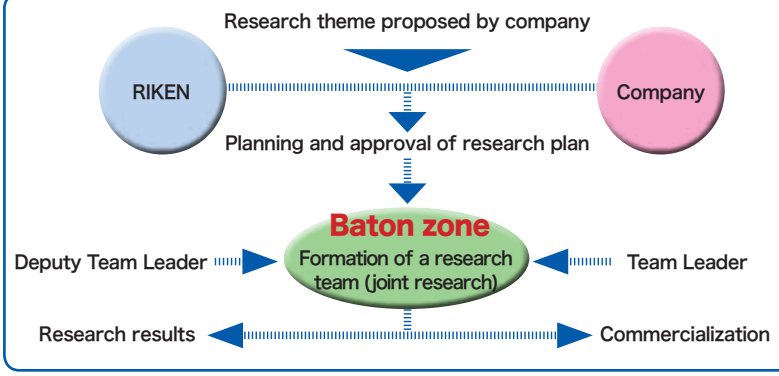
Industry-academia collaboration via existing Technology Licensing Organizations (TLOs) can be quite difficult, not only in the speedy exchange of experienced-based knowledge but also when commercializing scientific results. RIKEN's industry-academia collaboration programs consist of joint research with industry, in which corporate partners take the lead. This is the first time in Japan for companies to take the lead. Introduction of the 'baton zone,' in which research activities and commercialization efforts run in parallel, is aimed at smoothly commercializing research results.

Kenji Tsubaki, team leader of the Integrated Collaborative Research Program with Industry High-Power UV-LED Laboratory, said: "Matsushita Electric Works Ltd. is conducting this joint research to use RIKEN's UV-LED development technology to develop not only the company's lighting equipment business but also new business opportunities. RIKEN is flexible and provides an environment for us to conduct the research without restraints." Hirayama also stressed the merits of the baton zone approach, saying that RIKEN's original technology can be merged with the rich background technology owned by its corporate partner, which helps accelerate research activities.

"Our challenge is to improve the emitting efficiency of the LEDs. Their internal quantum efficiency has reached 50%. But the overall efficiency of the equipment stands at a few percent. The overall rate should be raised to 30-50%," Hirayama said. Tsubaki added: "We aim at commercializing UV-LEDs in the near future. We also want to accumulate more technology necessary for commercial production of LEDs through this project."

RIKEN and its corporate partner will continue tackling these challenges.

Integrated Collaborative Research Program with Industry



- High-Power UV-LED Laboratory
- Terahertz Biological Sensing Research Laboratory*
- Elastomer Precision Polymerization Laboratory
- Next Generation Mobile Communications Laboratory
- Applied Mass Spectrometry Laboratory*
- Nanoparticle Characterization Laboratory
- Nanofunctional Materials Laboratory
- Innovative Nanopatterning Laboratory

Eight teams in total are conducting joint research.
(as of March 31, 2008)

* The project was complete as of March 31, 2008.

Center of Intellectual Property Strategies (CIPS)

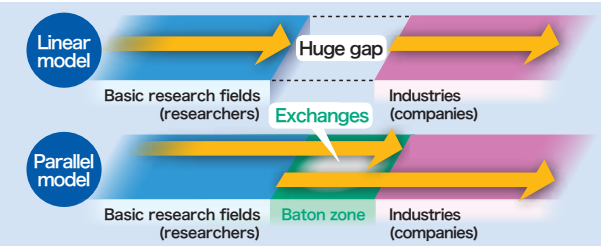
Using a "baton zone" to make RIKEN that is useful to the world

The Center of Intellectual Property Strategies (CIPS) was established in April 2005 in order to implement one of the Noyori Initiative policies, namely that of making "RIKEN that is useful to the world." The objective of the center is to efficiently create intellectual property from RIKEN's excellent research achievements and effectively feed it back to society in cooperation with industry.

CIPS acts as a gateway between RIKEN and society, and has functions which are significant throughout RIKEN's activities, such as the creation of intellectual property from research achievements, cooperation with industry through licensing and collaborative research, etc., and the acquisition of external and competitive funding. In addition, the center is working on the establishment and implementation of a "baton zone"; this is an even faster and more efficient technology transfer scheme.

As part of the "baton zone" implementation program, "Integrated Collaborative Research Program with Industry" and "Collaboration Centers Program" commenced in 2004 and 2007, respectively. Both focus on the needs of companies and promote collaborative research in problem solving projects initiated by companies.

Number of full-time personnel: 97 (as of March 31, 2008)



"Baton zone" depiction

As a scheme to transfer research achievement technology, RIKEN established the system of providing a "baton zone," where researchers from companies and RIKEN can maintain close cooperation with each other. It is a parallel model mechanism wherein companies and RIKEN can work alongside each other. Smooth technology transfer and development of talented researchers are the expected achievements of this "baton zone."

Director's Message

Feedback of research achievements to society, and contributing socially through research

Shigekazu Saitou, Director, Center for Intellectual Property Strategies

Q. What are some of the noteworthy achievements of fiscal 2007?

A. Public research organizations, like RIKEN, conduct activities to assert the rights of research achievements as patents, and then offer the use of those patents to companies. These days, universities are also making a strong effort to conduct these kinds of activities. However, a problem arises when thinking about how to use an invention after it has already been created—this delay means it can be too late for the invention's effective use. In order to promote the world's most cutting-edge research and make excellent achievements, it is necessary to overcome this difficulty. Moreover, as research themes and researchers themselves are inseparable, it is probably natural that researchers occasionally put in less effort on a research theme that they are reluctant to investigate. Nevertheless, in order to make research achievements useful to society, I consider it necessary for a research institute to have a policy or a character of targeting research themes that can be useful to society. You could say that it is a type of social contribution through research.

By RIKEN efficiently adopting the research themes and resources of companies, CIPS has been able to focus its energy on facilitating and operating a research system that pleases both RIKEN and companies. This is what the "baton zone" between RIKEN and industries is intended for.

Through the "baton zone," where companies and RIKEN share common objectives and move in the same direction to transfer research achievements and technologies in daily research cooperation, remarkable progress was made in 2007 including the following:

1. The establishment of three collaboration centers (Olympus Optical Co., Ltd.; Tokai Rubber Industries, Ltd.; and, Toyota Motor Corporation).
2. The implementation of business that puts RIKEN technologies (such as SNP typing and molecular imaging) into practice in cooperation with companies.
3. The completion of the "RIKEN-WAKO Incubation Plaza." This facility is located adjacent to RIKEN and is used as a "baton zone" where research ideas for use in RIKEN ventures are made available to RIKEN by companies.
4. The creation of a strong baton (drug patent)— commencing a baton zone development in the field of drug discovery.

Q. What are your future prospects?

A. We will continue to provide feedback regarding our excellent research achievements to society based on a trusting relationship with individual researchers. Likewise, using our continued trusting relationship with companies as the cornerstone, we would like to further improve our organizational coordination and social contribution, with a view to developing new industrial areas.

BioResource Center

SABRE opened to the public Database enables searching of plant gene resources

The RIKEN BioResource Center (BRC) developed an integrated database called SABRE (Systematic consolidation of Arabidopsis and other Botanical Resources) to enable searching of different plant gene resources and allowed public Web access to it starting in June 2007 (http://saber.epd. brc.riken.jp/sabre7/SABRE0101.cgi). Users can use genetic information on the model plant *Arabidopsis thaliana* as keywords to search four different resources of plant gene data, as if skewering the data on a saber. Retrieving crop genes that are similar to useful genes of Arabidopsis enables users to develop high-yield crop breeds. Hopes are high that the resulting breed improvement will help solve food problems.

Kaoru Fukami Head
Bioresource Information Division

Mitigating food crisis with breed improvement

The world's population is expected to grow from the current 6.7 billion to 8 billion by 2025, and to over 9 billion by 2050. The rapid growth is expected to exceed the increase in food production, leading to aggravation of already serious food shortages. So-called super crops, with high yields and strong resistance to arid and cold conditions, are one way to avert such shortages.

Recent studies suggest that genes are responsible for determining plant characteristics. Researchers are focusing on exploring genes that make fruit larger and plants stronger against extreme environments, thereby boosting production. Global plant research efforts evolve around Arabidopsis, which has small white flowers, because the plant is easy to grow and has a short life cycle and limited number of genes. Researchers have already sequenced the entire genetic map of the plant, ahead of other plant species. They already know the functions of many of the genes that make up the Arabidopsis genome.

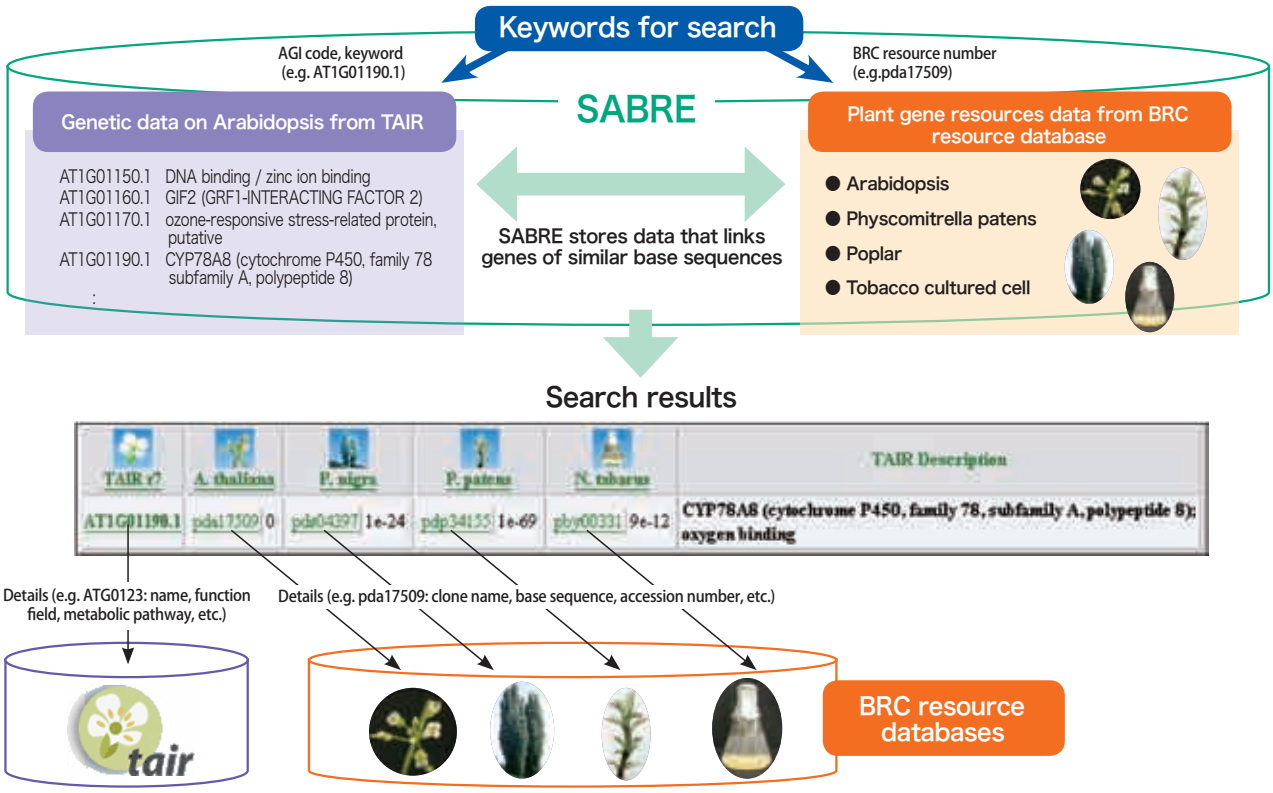
In many cases, genes that make plants resistant to dry climates are similar across different species. Given the small number of genes in Arabidopsis, researchers believe they all occur in many plant species with much larger numbers of genes. That means success in Arabidopsis research provides important clues for research on other plant species. The development of the SABRE database started with an assumption made by Kaoru Fukami, senior scientist, head of the Bioresource Information Division, and her colleagues. They assumed a comparison between Arabidopsis and other plant species would enable researchers to apply the results of Arabidopsis studies to other plant species.

Retrieving genetic resources of homologous sequences

In the U.S., a database called TAIR (The Arabidopsis Information Resource) has been built and made available to the public. TAIR integrates and manages genetic and molecular biology data on the model plant Arabidopsis, and receives an average of 30,000 hits per month. RIKEN's BRC also has its own database, which accumulates data necessary for collecting, preserving and distributing genetic

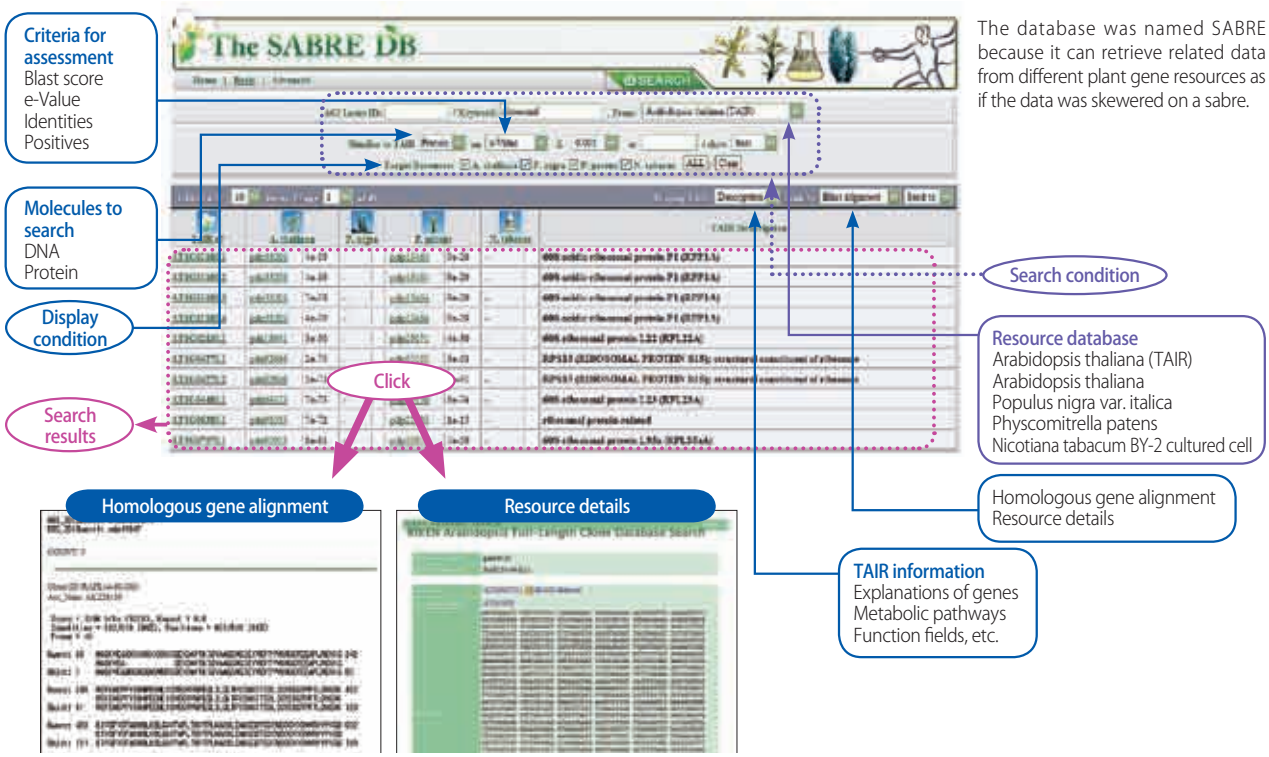
Structure of the SABRE database

SABRE stores data that links BRC plant gene resources based on Arabidopsis gene sequences registered in TAIR. The database has a simple structure that is easy to expand and maintain.



resources of Arabidopsis, the moss *Physcomitrella patens*, poplar, tobacco and other plants. SABRE combines these two databases. After a researcher enters a BRC resource number, an AGI code (an ID number assigned to each Arabidopsis thaliana gene), or the name of a protein, SABRE can retrieve TAIR and BRC resources with similar genetic sequences. In other words, SABRE uses genetic data on Arabidopsis provided by TAIR to instantly retrieve genetic resources of Arabidopsis, Physcomitrella, poplar and tobacco that have homology, or similar sequences.

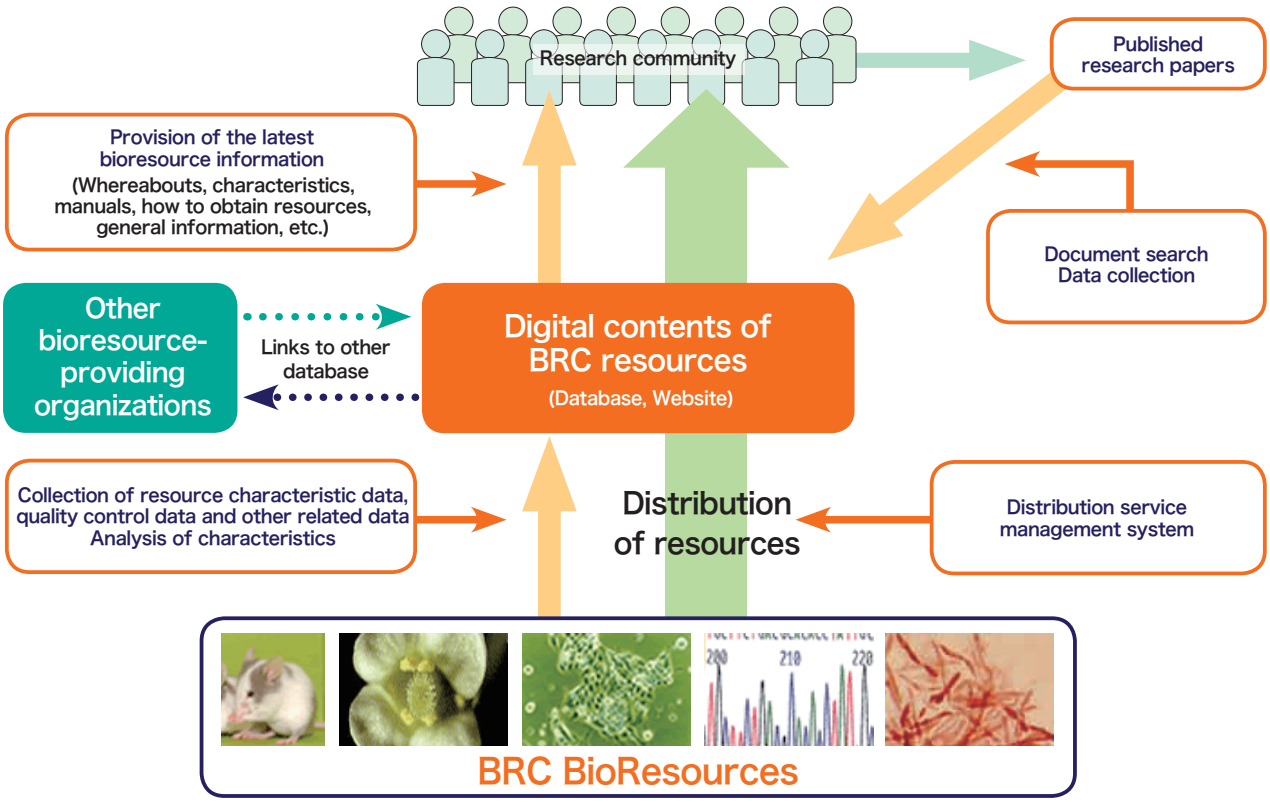
SABRE's search window



The database was named SABRE because it can retrieve related data from different plant gene resources as if the data was skewered on a sabre.

The role of Bioresource Information Division in BRC

The Bioresource Information Division plays the role of BRC's information hub which distributes, in a digital format, the latest resource data collected, maintained and provided by BRC to the research community.



Since many of the functions of Arabidopsis genes are already known, the results of the research will give clues about genetic functions of the plant resources of various studies. The names of enzymes and genes may differ from one species to another, but SABRE's search function based on genetic sequences enables researchers to find enzymes and genes with functional similarities.

BRC's Bioresource Information Division is preparing to provide resource information of such food crops as cassava and Chinese cabbage in SABRE, in addition to the four species whose gene resources are already available. BRC hopes the addition of genetic data on food crops to SABRE will help develop high-yield vegetables and fruits.

BRC has a long-term vision to develop an animal version of SABRE for public use based on its experience with the plant-version. Fukami says her team will explore the possibility cautiously, because animals' genome sizes and the reliability of their genetic information are quite different from those of plants.

Making SABRE easy to use

Fukami explains what went through her mind when developing SABRE: "I carefully considered how we could keep a database from becoming obsolete. Our answer was to design a system to accommodate an ever-increasing volume of data." For example, if base sequences of all species are cross-referenced, the amount of work required to update the database will increase with the square of the number of species. SABRE links resource species only to TAIR because that is enough to link all the species, and the structure prevents exponential increase in the workload for updating the database. In this way, Fukami's team can ensure that SABRE users always access up-to-date information, no matter how many more species are added to the database. This was made possible by Fukami's strong wish that SABRE remain a viable tool for users for years to come.

It is also important from the standpoint of maintenance to keep the data registered in the database to a minimum. Data that do not necessarily have to be in the database should be kept somewhere else. Details of genes linked by SABRE can be found by jumping to links to the TAIR and BRC resource databases for further reference.

Fukami compares her role in providing the database to a soccer player feeding an accurate pass to a striker aiming at a goal. "That's my and BRC's current role," she says. Feedback from users is indispensable for making SABRE even more convenient to use. "I'd appreciate users sharing their thoughts and requests with us," Fukami adds.

BioResource Center (BRC)

Maintaining the world's highest standard of bioresources in the development of life sciences

Since its establishment in 2001, RIKEN BioResource Center (BRC) has been operating as a core bioresource facility in Japan with the mottos of "Trust," "Sustainability," and "Leadership." In order to solve the problems that humans face, such as health enhancement, food production, and environmental conservation, BRC has been engaging in the maintenance of bioresources (biological research materials), which are indispensable in life science studies and bioindustry. Unlike the Jackson Laboratory and the Global Bioresource Center (ATCC) in the United States, or the Nottingham Arabidopsis Stock Centre (NASC) in the United Kingdom, BRC is a multidisciplinary center that handles a wide range of bioresources, including human samples, model animals and plant individuals, as well as cells and genes.

In close collaboration with other related institutions and organizations, both within and outside of Japan, the center collects, preserves, and distributes the following: (1) experimental animals (mice), (2) experimental plants (Arabidopsis), (3) cell lines of human and animal origin, (4) genetic materials, and (5) microorganism materials, as well as related information on all of the above. The "RIKEN BRC Brand" is currently being established as a source for the most globally advanced and reliable bioresources.

In striving to provide resources of the highest quality, BRC is developing new bioresources and new technologies necessary for quality control, and further, for the characterization of bioresources. BRC also offers advanced training courses in order to provide the research community with more effective and efficient utilization of our resources.

Furthermore, in order to promote international collaborations and the international assignment of bioresources, the center plays a key role in the international community. For the purpose of improving the standard of science in Asia, the center is creating an Asian network and has signed collaborative research agreements with other related institutions. Through these activities, the center is promoting life science studies and bioindustry both in Japan and overseas.

Number of full-time personnel: 85 (as of March 31, 2008)

Director's Message

Cornerstone of the century: Life sciences

Yuichi Obata, Director, BioResource Center

Q. Which project did you particularly focus your attention on in fiscal 2007?

A. BRC has been carrying out strict quality control of bioresources with our motto of "Trust." Having obtained ISO9001, the International Quality Management Standard, we conduct quality control tests as per its recommendations for cellular and microorganism materials—bioresources that are very much in demand in industry. Therefore, we can now expect the reliability of our resources to increase even more with further utilization.

Q. What were some of the noteworthy achievements of fiscal 2007?

A. The second term of the National BioResource Project (NBRP), established by the Minstry of Education, Culture, Sports and Technology (MEXT), commenced in fiscal 2007. In addition to the research centers concerning mice, Arabidopsis, human, and animal cells, as well as DNA from the first term project, the center was appointed and begun operating as a core facility for microorganisms in the second term. Furthermore, three BRC themes were adopted in the NBRP fundamental technology development program as well as in the genomic analysis program.

Q. What are your future prospects?

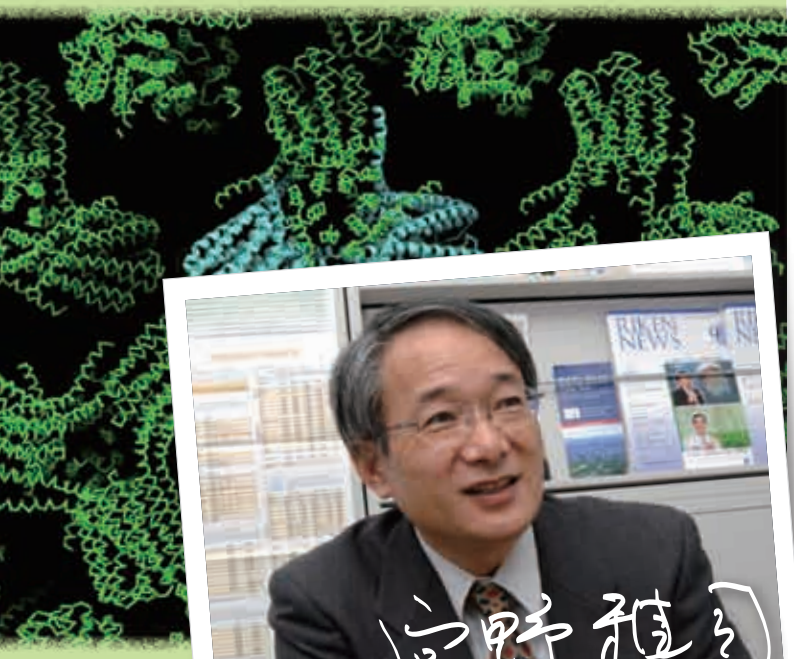
A. The iPS cells created by Shinya Yamanaka, a professor at Kyoto University, are increasingly expected to lead the way in regenerative medicine, with mouse iPS cells already being deposited at BRC in July 2007. They will be available to general researchers from March 2008. In addition, human iPS cells will be the next to be deposited.

Moreover, the Center for Genomic Medicine (CGM) will be dissolved into a new organization at the end of fiscal 2007, wherein the group that had been involved in the mouse mutagenesis project at CGM will be transferred to BRC from fiscal 2008. Due to this integration, BRC's R&D capabilities will significantly increase and thus, accelerated improvement of our intellectual foundation can be expected.

RIKEN SPring-8 Center (RSC)

Clarifying the 3D structure of membrane protein involved in allergic reaction

A research team at the RIKEN SPring-8 Center (RSC) has clarified the structure of leukotriene C_4 synthase (LTC_4S), a human integral membrane protein known to work as a catalyst for synthesizing leukotriene C_4 (LTC_4), which causes allergic reactions. The team's structural analysis of this membrane protein has shown that a V-shaped cavity formed by three LTC_4S molecules plays the key role in its activity. The possibility of developing new allergy medicine targeting this cavity is under examination.



Masashi Miyano Chief Scientist
Structural Biophysics Laboratory

Membrane protein supporting body functions

The human genome sequence has already been clarified, and we know that the human genome consists of 3 billion base pairs. But we cannot understand the mechanism of our life system without identifying the functions of various types of protein. Protein, which is synthesized *in vivo* based on one-dimensional genomic information in genome, has a three-dimensional structure comprising folded polymer strings made up of amino acids. In recent years, researchers have been paying attention to protein structures as a clue to understanding their functions.

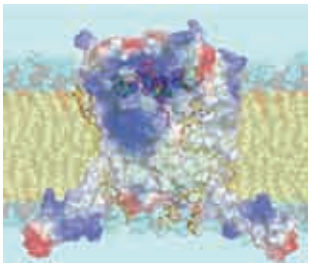
Masashi Miyano, chief scientist of the Structural Biophysics Laboratory, has clarified the stereo-structure of LTC_4S, a membrane protein in cell membranes, in collaboration with a group at Harvard University's Brigham Women's Hospital in the U.S. Membrane protein, which is involved in exchanging information and nutrients between the outside and inside of cells, is a crucial protein that is also deeply implicated in disease. LTC_4S is membrane protein involved in causing allergic reactions. When an antigen enters the body and cells related to immunity and inflammation are activated, LTC_4S begins working as a catalyst to promote a reaction between the fatty acid LTA_4 and glutathione for producing LTC_4, a lipid mediator. LTC_4 and its metabolites (leukotriene D_4 and leukotriene E_4) cause bronchus constriction or increased mucous membrane secretion. When allergic reactions such as these symptoms occur excessively, a life-threatening anaphylactic shock may be triggered.

The clarification of LTC_4S's three-dimensional structure has provided a clue to unraveling how an allergic-reaction-causing chemical is synthesized. According to the team's finding, further examination of the mechanism to suppress allergic reaction is expected to lead to the development of more effective medicine for asthma, hay fever and other chronic allergies.

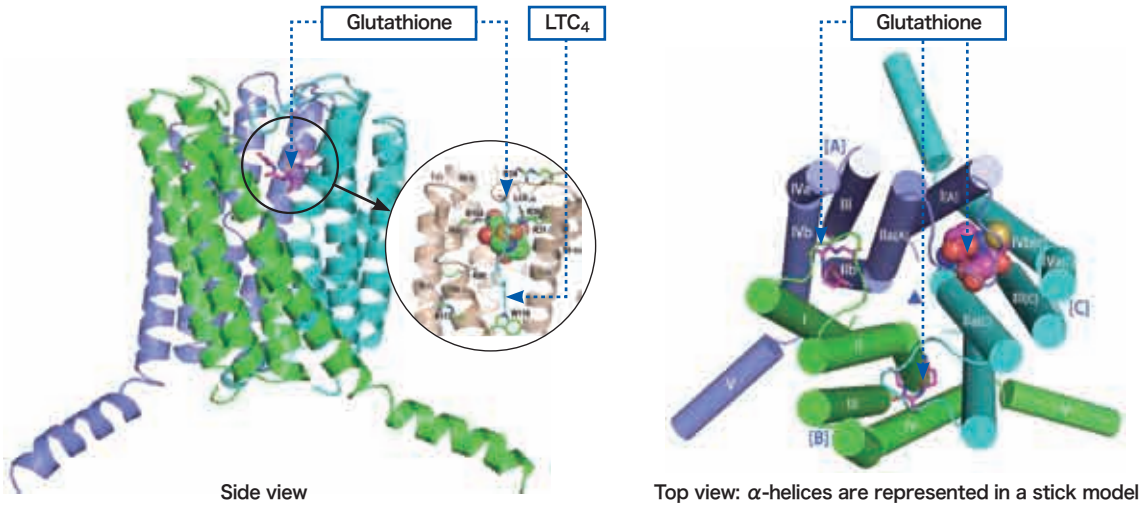
3D structure is source of activity

The structural analysis of LTC_4S shows that it consists of five amino-acid spiral chain rods (α-helices). Amino acids are the building blocks of protein. Of the five helices, four are trans-membrane. A remarkable thing about LTC_4S's structure is that three LTC_4S molecules get together to form a trimer,

A combination of three LTC4S molecules forms a V-shaped cavity



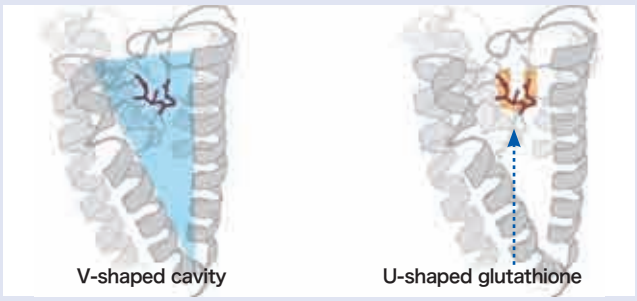
LTC4S embedded in the cell membrane



Side view

Top view: α-helices are represented in a stick model

LTC4S consists of five α-helices, four of which are transmembrane helices. Three LTC4S molecules aggregate to form a trimer, with each molecule at a vertex of the triangle. A V-shaped cavity is formed at the interface between two neighboring LTC4Ss. Glutathione in a U-shape is bound deep inside the cavity with the charge of amino acid residues. LTC4, represented in front of the glutathione, is produced as the enzyme reaction proceeds through binding of the substrate LTA4, another reaction material.



V-shaped cavity

U-shaped glutathione

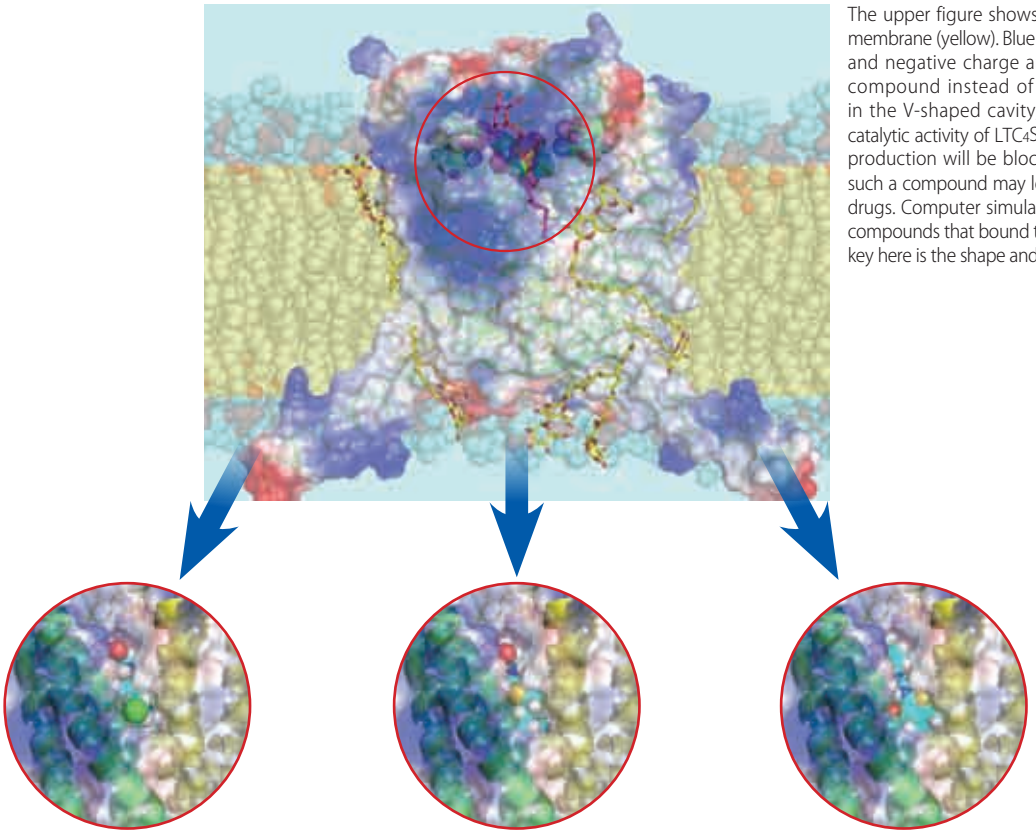
with each molecule at a vertex of the triangle, and that a V-shaped cavity is formed at the interface between two neighboring molecules. In addition, all amino acid residues, which have been considered to be involved in the function of LTC4S, face the cavity. "We have found that glutathione, a material for LTC4, is fixed with the charge of amino acid residues deep inside the cavity and that glutathione resides in a U-shaped conformation in the cavity," Miyano says. "This cavity is the very active site of LTC4S." He was surprised to find that LTC4S's catalytic function is derived from the three-dimensional structure of three combined molecules, not from two molecules.

Key to structural analysis: crystallization

The X-ray crystal structural analysis of LTC4S was carried out at SPring-8, a large synchrotron radiation facility run by RIKEN. Extremely accurate structural analysis data can be obtained with highly bright X-rays generated at the synchrotron radiation facility. The most challenging issue in the analysis is crystallization of protein (see page 10). The type of precipitation agent used and optimum pH conditions must be investigated each time, depending on the protein to be tested. Membrane protein is in the cell membrane, so it must be taken out without damaging the protein. In addition, a surfactant used for dissolving the cell membrane makes the crystallization conditions of the targeted membrane protein more complicated.

Miyano and his colleagues first produced a large volume of human LTC4S by making fission yeasts express it. They have succeeded in crystallizing LTC4S in the suitable form for crystal analysis after four to five years' effort. "We have confirmed that LTC4S removed from the cell membrane worked as a catalyst for producing LTC4, which is made from LTA4 and glutathione. As long as we can take out LTC4S without damaging its function as protein, it can keep its function after the removal," he says. A surfactant and inhibitor used for extracting the protein instead of a substrate also helped crystallize LTC4S bound in the cavity. This successful crystallization of LTC4S has lead to its structural analysis.

Example of docking simulations on a computer



The upper figure shows LTC_4S embedded in the cell membrane (yellow). Blue and red areas indicate positive and negative charge areas, respectively. If another compound instead of glutathione, which resides in the V-shaped cavity, is bound in the cavity, the catalytic activity of LTC_4S may be suppressed and LTC_4 production will be blocked as a result. Investigating such a compound may lead to development of allergy drugs. Computer simulations were carried out to find compounds that bound to the cavity (lower figure). The key here is the shape and charge of the compound.

Analyzing protein structure will lead to new drug development

Researchers have been reporting that LTC_4S gene-deficient mice tend not to suffer chronic allergy symptoms, indicating that an inhibitor of LTC_4S may become an allergy drug. Miyano and his colleagues have confirmed that when LTC_4S is combined with S-hexyl-glutathione, which is known as a compound to suppress catalytic reaction but weakly, the compound enters LTC_4S's V-shaped cavity for suppressing reaction. Miyano says, "Compounds that can successfully be bound selectively in this cavity have potential to become allergy medicines." His team has been conducting computer simulations about what compounds can reside in the cavity, in collaboration with the Advanced Computational Sciences Department of RIKEN's Genomic Sciences Center (From April 2008, the department belongs to the Advance Science Institute). The simulations are called virtual screening.

Miyano says the structure of protein determines its functions. Since the functions of a protein can be controlled based on its structure, research on the protein structures can lead to the development of new drugs. Miyano clarified the three-dimensional structure of rhodopsin extracted from cow retinas, in collaboration with the University of Washington in 2000. Last year, he and his colleagues identified the structure of human integral membrane protein prepared in different organism like yeast for the first time. In 2007, research teams around the world also announced that they had clarified the structures of various types of membrane protein. "It will take a long time to verify the medical efficacy of candidate compounds for medicine after they are found," he said. "I want to help shorten that long verification stage." He is enthusiastic about identifying the structures of protein, which is expected to be useful for developing new drugs.

Number of articles citing the RIKEN's paper on rhodopsin exceeded 2,000
– Press release on Feb. 21, 2008 –

Rhodopsin in the retina is a protein involved in detecting light. Rhodpsin belongs to a group of membrane proteins called G-protein coupled receptors (GPCRs). About half of all drugs target GPCRs. This demonstrates that GPCR is closely implicated in developing diseases and the group is an important target of drug discovery. Bovine rhodopsin was the first GPCR whose structure was clarified. By early 2008, more than 2,000 articles had cited the RIKEN's paper on rhodopsin as GPCR model template. The number is the highest among all articles written by RIKEN scientists as responsible authors.

URL : http://www.riken.jp/r-world/info/info/2008/080221/index.html

RIKEN SPring-8 Center (RSC)

A group of photon science pioneers
— Colligation of the world's highest performing light sources —

RIKEN SPring-8 Center (RSC) involves itself in advanced research in areas such as life sciences and material sciences using a high-intensity Synchrotron Radiation (SR) beam; it also engages in R&D on the fundamental technologies of unprecedented SR technology and the next-generation light source. A feature of RSC is SPring-8, the largest-scale SR facility. RIKEN has seven beamlines dedicated to research at SPring-8. They are designed, upgraded, and tailored for efficiency according to the content of the intended research. The center has developed a device that automatically replaces test samples of protein crystal as well as large-scale measuring instruments for specific purposes, and is, therefore, able to deliver new research achievements through the development of research techniques — something unrealizable at other institutes. In comparison to the researchers that visit SPring-8 as general users, we have the enormous advantage of being able to reflect our research ideas in the development of devices faster than anyone else.

Developing a light source for the creation of a new type of light is also one of our missions. In order to complete this achievement by fiscal 2010, we are currently working on the development and construction of an "X-ray Free Electron Laser" (XFEL), which is a completely new type of light that will play a major role in the next generation. A prototype of the XFEL, which was successfully demonstrated in June 2006, has been improved so that it can now be used as a laser source of sufficient intensity in ranges other than that of vacuum-UV light. It will be available for use in research in fiscal 2008.

RSC is group of pioneers in photon science. It is creating the new type of light, developing a new research field using light, and making light more useful. As a key SR facility in the Asia-Oceania region, it is active in cooperative research and exchanges.

Number of full-time personnel: 105 (as of March 31, 2008)

Director's Message

Being a vanguard of global light science to date and in the future

Tetsuya Ishikawa, Director, RIKEN SPring-8 Center

Q. Which project did you particularly focus your attention on in fiscal 2007?

A. Being our 10th anniversary, 2007 was a milestone year for SPring-8. In commemoration, we held a ceremony and symposiums in order to proceed with further development. During the ceremony, the past 10 years were reviewed with particular attention given to the fact that SPring-8 had progressed unremittingly. Since our establishment, synchrotron radiation has increased its stability and its brightness has increased tenfold. Its base of users has expanded from research institutes to industry, with a subsequent total of over 78,000 people using the facility. At the symposium, discussions were held involving representatives from overseas radiation facilities, and the event turned into an occasion where the future roles of SPring-8 could be contemplated.

Two symposiums concerning the XFEL, which is being constructed adjacent to SPring-8, were also held. We hope to maintain the center's global lead by further expanding SPring-8 and completing the development of the XFEL on the same campus as SPring-8.

Q. What are some of the noteworthy achievements of fiscal 2007?

A. One would be the Structural Biophysics Laboratory's achievement, as featured in this report, of elucidating a protein that could lead to the development of new anti-inflammatory and anti-allergy drugs, which could potentially be used to treat chronic allergy diseases.

Another would be the achievement in observing an optical phenomenon in which one "parent" photon of an X-ray interacts with electrons within a material and separates into two photon "sisters." Since the probability of generating these two photons is 1 in 100 billion, and their intensities are weak (100 billionth that of the parent photon), it has been extremely difficult to accurately measure until now. However, one of the weak sister photons was finally measured with high accuracy through the use of our unique measuring instrument. This achievement is only the first step in the nonlinear optics of the X-ray region, and even more progress is expected in the various nonlinear X-ray optics with the completion of the XFEL.

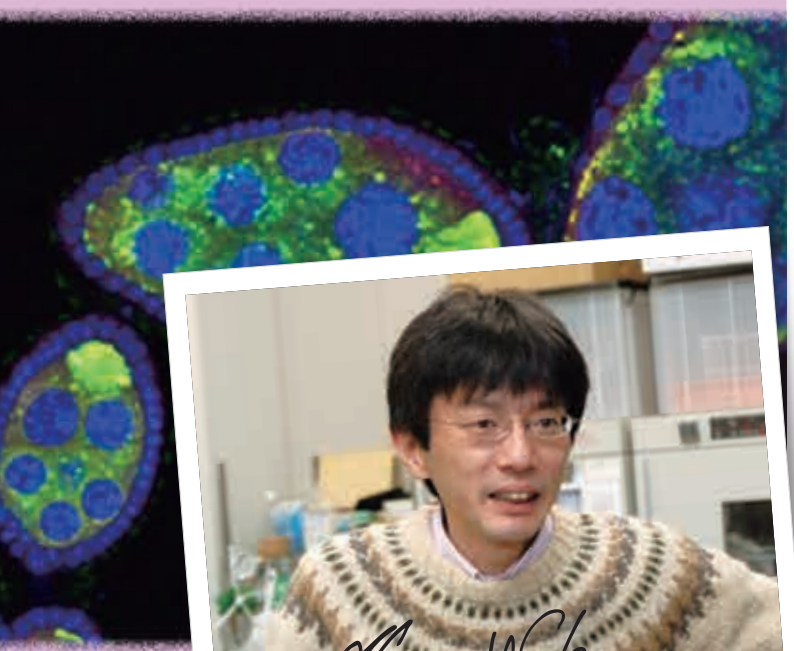
Q. Were there any newly launched research projects in fiscal 2007?

A. Quantum Order Research Group was launched in 2007, aiming to discover new material functions by studying quantum orders such as spin, the energy excited state, and the space distribution of electrons in materials at the nano-scale. In the spirit of ignoring the constraints of traditional techniques, we are seeking new utilization methods for SPring-8 and its measurement technologies. The group is also establishing a close network with RIKEN in-house organizations, other than SPring-8 Center, and is actively involved in revolutionary research.

Center for Developmental Biology

Discovery of protein that assures differentiation of germ cells

The cells of multicellular organisms are largely divided into two types: somatic and germ. Somatic cells form the organism's body, while germ cells develop into sperm or egg cells. A research team at the RIKEN Center for Developmental Biology (CDB) has clarified using *Drosophila* that a protein called Pgc prevents cells that are supposed to become germ cells from developing into somatic cells by repressing the expression of genes that promote somatic cell differentiation. Although different types of proteins are involved, a similar mechanism has also been suggested for mice and nematodes, indicating that it may be common to all multicellular animal species.



Akira Nakamura Team Leader
Laboratory for Germline Development

Pole cells: Cells destined to become germ cells

Akira Nakamura, team leader of the Laboratory for Germline Development, has been studying the enigma of germ cell differentiation. "Germ cells, which develop into sperm or egg cells, are indispensable for sexually reproducing organisms," he said. "Germ cells can be thought of as immortal in the sense that they can create new individuals. They are crucial from the viewpoint of evolution because changes made to them are handed down to the next generation."

Germ cells of *Drosophila*, or fruit flies, can be distinguished from other cells at an early developmental stage. At the posterior pole of the embryo is a specialized cytoplasm called the germ plasm. Some cells take in germ plasm to develop into pole cells, which are destined to become germ cells.

While pole cells are being formed, somatic cells rapidly differentiate. Proper development of pole cells into germ cells must be unaffected by genes that are robustly expressed to promote the differentiation of somatic cells. It is already known that RNA polymerase II (RNAPII), which transcribes genes, is repressed in pole cells and does not activate the somatic genes, so that pole cells can develop properly into germ cells. But what represses RNAPII's activity was unknown until now.

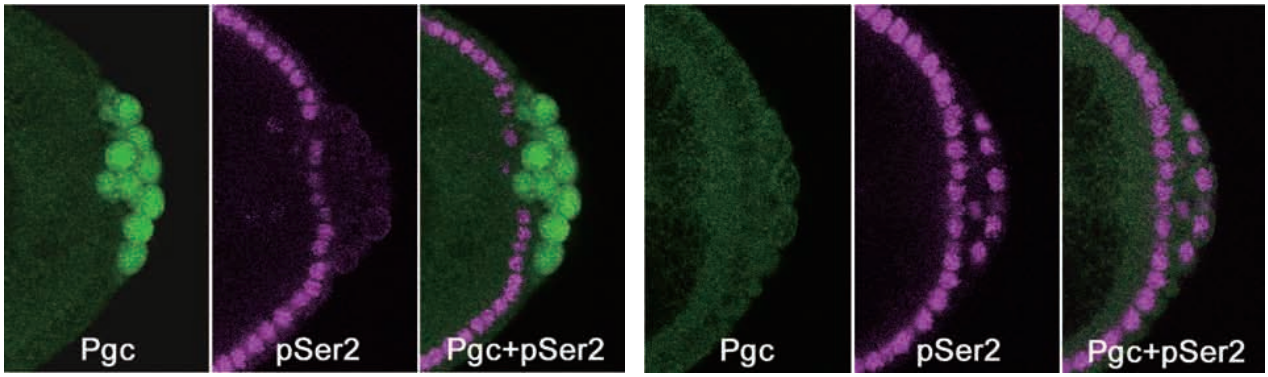
Discovery of Pgc protein as repressor of RNAPII

Nakamura has been searching for factors indispensable for forming germ cells by focusing on proteins and RNA contained in germ plasm. His team has found that the protein called Pgc represses the activity of RNAPII in *Drosophila* pole cells.

Ten years ago, Nakamura found the *polar granule component (pgc)* gene, which encodes the Pgc protein, as an indispensable factor for forming *Drosophila* germ cells. But he suspected that the messenger RNA (mRNA) produced by the *pgc* gene might have been a new type of RNA that did not synthesize protein. This suspicion was based on not only the gene's irregular structure, but also the possibility that its mRNA might have a very complex secondary structure. So he did not identify the functions of the *pgc* gene.

Nakamura later found that all 12 *Drosophila* species

Illustration of how the Pgc protein represses RNAPII



In the wild-type pole cell (left) where the Pgc protein (green) is expressed, phosphorylation of CTD serine2 (magenta) is repressed. In the pole cell without the Pgc protein (right), phosphorylation of serine is not inhibited.

have genes corresponding to the *pgc* gene and that these genes produce short proteins. The Pgc protein is robustly expressed in newly formed pole cells. In this embryonic development stage, activity of RNAPII is repressed in pole cells, while the genes are actively expressed in somatic cells. When the Pgc protein disappears in a later stage of embryogenesis, activation of RNAPII is also observed in pole cells, showing that there is an inverse association between the expression of the Pgc protein and activity of RNAPII — the more strongly the Pgc protein is expressed, the less active RNAPII becomes.

Pgc inhibits P-TEFb activity

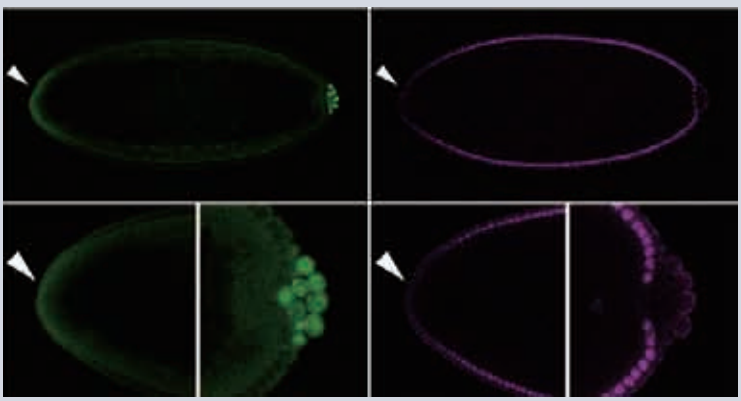
During observation of mutants without the *pgc* gene, RNAPII was not repressed in their pole cells, so that the genes to promote the differentiation of somatic cells were expressed, as predicted. Moreover, when the *pgc* gene was expressed in somatic cells at the embryonic heads, where the gene is not supposed to be expressed, RNAPII activity was repressed, and the somatic gene was expressed to a lesser degree. The same results were observed in cultured *Drosophila* cells. It was confirmed in these experiments that the Pgc protein represses RNAPII activity in any cells where the protein is expressed and that, as a result, mRNA transcription is suppressed. Then which of the factors involved in transcription by RNAPII does the protein target?

RNAPII has a specialized domain called the carboxyl-terminal domain (CTD), where a sequence of seven amino acids is repeated multiple times. When serine at the second amino acid of each repeat (CTD serine2) is phosphorylated, RNAPII is fully activated and begins transcriptional elongation. The positive transcription elongation factor b (P-TEFb) complex, which is composed of two molecules (Cdk9 and CycT), has been known to phosphorylate CTD serine2. Nakamura said, "We thought that if the Pgc protein inhibited the function of P-TEFb, CTD serine2 would not be phosphorylated. We found that the Pgc protein binds to the Cdk9 of P-TEFb and inhibits P-TEFb's function."

This may be a common mechanism of organisms to repress transcription.

Put simply, it appears that the Pgc protein inhibits P-TEFb's function by repressing the enzymatic activity of Cdk9. But Cdk9 does not lose its activity even after associating with the Pgc protein. The question is how P-TEFb is repressed. "We have found that the Pgc protein does not repress the enzymatic activity of P-TEFb, but inhibits the recruitment of P-TEFb to RNAPII," Nakamura said. In pole cells where the Pgc protein is expressed, P-TEFb is not carried to RNAPII, so that RNAPII does not begin efficient transcription, although RNAPII is located to the transcription initiation regions of the somatic genes.

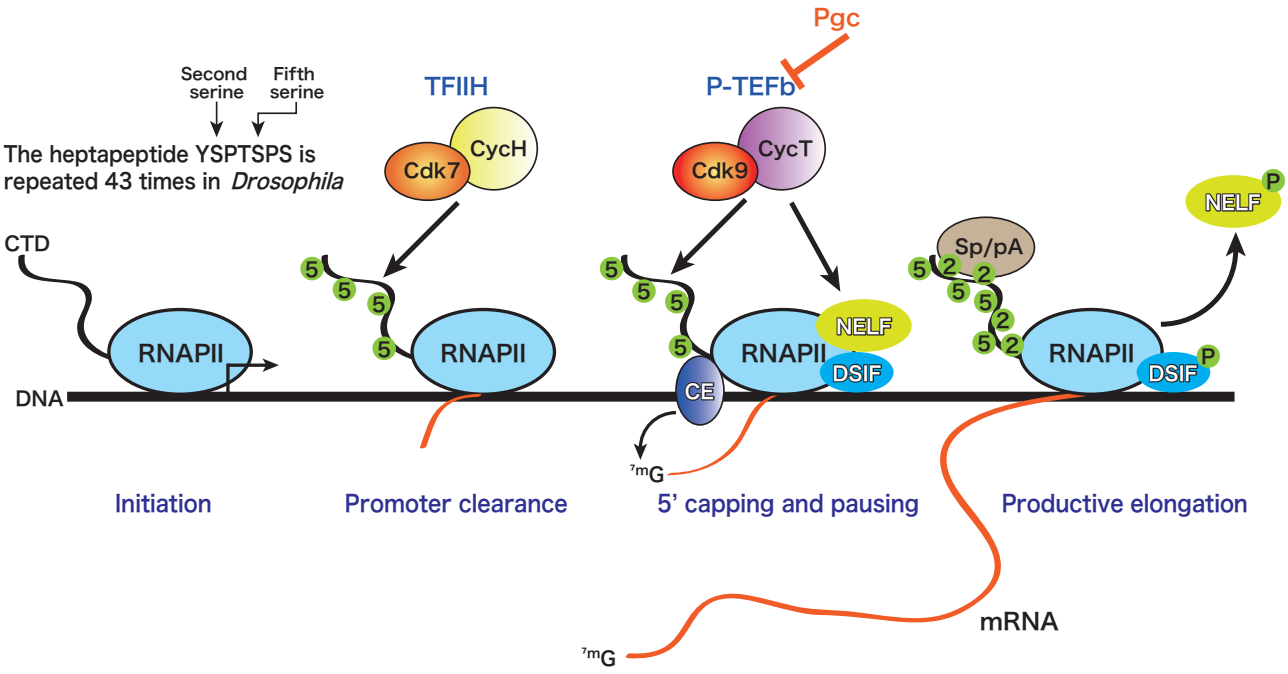
The mechanism works even in somatic cells



When the Pgc protein (green) is expressed (white arrows) in the embryonic anterior, which is supposed to develop into somatic cells, phosphorylation of CTD serine2 (magenta) is inhibited as in the case of pole cells.

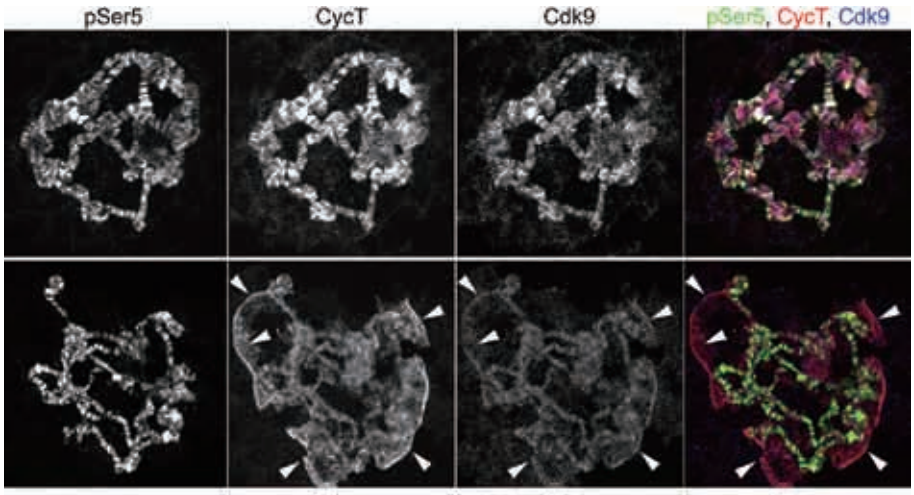
The Pgc protein inhibits transport of P-TEFb to RNAPII

When RNAPII is connected to the transcription initiation region of DNA, the fifth serine of CTD is first phosphorylated, and RNAPII then stops transcribing temporarily after transcribing a very short region. P-TEFb then phosphorylates the second serine, and full-scale transcription begins. But when the Pgc protein is present, the second serine is not phosphorylated and transcription does not start because P-TEFb cannot reach RNAPII.



"It is also known that a factor indispensable for somatic cell differentiation is inhibited in cells of nematodes or mice that are supposed to develop into germ cells," Nakamura said. "Researchers have reported that in the case of nematodes, a protein called PIE-1 interacts with P-TEFb. The Pgc and PIE-1 proteins are quite different factors, and have evolved independently. It is very interesting that the two proteins target the same factor, P-TEFb. Inhibiting P-TEFb activity appears to be a very significant step in regulating the transcription process."

From the fact that P-TEFb is excessively expressed in patients with cancer or cardiac hypertrophy, P-TEFb may be related to promoting the transcription of genes associated with diseases. It is already known that P-TEFb is indispensable for proliferation of the HIV/AIDS virus. The Pgc protein may be used in medicines to repress excessively expressed P-TEFb. The team's discovery of the protein may one day contribute to the development of new drugs.



Distribution of RNAPII, Cdk9 and CycT, the components of P-TEFb, in the *Drosophila* salivary gland chromosome were examined. In the absence of the Pgc protein (upper), Cdk9 and CycT joined around RNAPII (the white parts on the chromosome), which stopped transcribing temporarily after the fifth serine was phosphorylated. In the presence of the Pgc protein (lower), Cdk9 and CycT are outside the chromosome (the white arrows), so that they cannot access RNAPII.

Center for Developmental Biology (CDB)

Aiming at elucidating the mystery of life and applying it in regenerative medicine

The Center for Developmental Biology (CDB) was established in April 2000 as an institute where comprehensive basic and model research can be performed; the aim was to elucidate animals' developmental systems and realize regenerative medicine. CDB encompasses various developmental biology research fields, ranging from basic embryology — including classic embryology, molecular cell biology, neural development biology, evolutionary biology, functional genomics, and bioinformatics — to studies that can be applied to medical science, such as stem-cell research. The scale at which it conducts intense developmental biology studies is globally unprecedented.

One of the features of CDB is that the research center is completely accessible to outsiders. It has an open day every year for the general public, and also contains an exhibition room in which people can experience simulated experiments. These are just some of our efforts to promote scientific communication. From the perspective of fostering next-generation researchers, the center is actively enrolling graduate students. An intensive two-day course is also held every summer within the framework of the Collaborative Graduate Studies Program and has proved very popular, as it offers people a real sense of the research workplace. CDB and the adjacent Institute of Biomedical Research and Innovation both share a central role in the "Kobe Medical Industry Development Project," which investigates the possibility of applying basic biology achievements in regenerative medicine.

Number of full-time personnel: 307 (as of March 31, 2008)

Director's Message

Looking back over the past twelve months

Masatoshi Takeichi, Director, Center for Developmental Biology

Q. Were there any major movements in the research system in fiscal 2007?

A. Carina Hanashima has been appointed as the team leader of the Laboratory for Neocortical Development. The laboratory is analyzing the formation mechanism of the cerebral cortex, which is composed of cells of the highest diversity among multicellular organism tissues. Hanashima says, "As CDB is actively promoting both internal and external intellectual exchanges, I would like to make the most of its excellent research environment to elucidate the mechanisms underlying the development of the cerebral cortex."

One of the features of CDB is the mobility of its researchers. In fiscal 2007, the decision was made to transfer team leader Kiyoji Nishiwaki to Kwansei Gakuin University as a professor. When Nishiwaki first arrived at RIKEN, it was the first time he had his own laboratory. Looking back on his life as a researcher at CDB, he notes, "I was able to extensively develop the research in which I was really interested. And as a result, a number of research papers were published with my name listed as the final author. This experience gave me a lot of confidence in being the laboratory leader. CDB is a rare institution that incorporates many laboratories for invertebrates, such as nematodes and flies. My wish is that this kind of depth in research will remain and that it will continue to be a world-class basic research center."

Q. What were some of the activities on which the center focused its attention on in fiscal 2007?

A. CDB includes a public relations and internationalization office, which ensures that activities are held to make science available to the general public. In fiscal 2006, the "Life science hands-on learning program for high school students" was trialed in cooperation with high schools with which we had already had some interactions in the past. In fiscal 2007, this activity was extended to other high schools; and, as a result, a total of 28 students (more than the capacity for which we had initially planned) attended. This hands-on program was a day-long event that included a tour of the research facility, a lecture by a group of directors, laboratory visits, and hands-on practice in fluorescent immunostaining using cultured cells. Many of the students who had previous hands-on experience in advanced science were very excited to be participating.

As a new endeavor for fiscal 2007, we conducted a training course for high school science teachers with a total of 24 participants. The purpose of this training course was to provide practical educational tools and make them available to teachers for actual use in high schools. In consideration of the high school curriculum, it used nematodes — a model organism that is easy to deal with — in the lecture and practical activities. We look forward to even more opportunities to pass on the fascination of developmental biology through contributing to the enhancement of high school science classes in the future.

Cutting-edge Program

Molecular Imaging Research Program

Successful development of cerebral receptor-binding compound may lead to new medicines

Molecular imaging is a technology that allows researchers to observe the activities of drugs and other bioactive compounds and of biopolymers such as proteins in living organisms. A group of researchers at the RIKEN Molecular Imaging Research Program (MIRP) has developed not only a compound (15*R*-TIC) with the function of protecting the central nervous system, but also a new labeled chemical reaction (rapid [^{11}C]methylation). Moreover, the group has successfully observed the activities of 15*R*-TIC in human and monkey brains with high resolution by using the latest imaging analysis technology. The program, aimed at reinvigorating drug development and disease diagnosis through molecular imaging research, is attracting attention from researchers, and the group won the Erwin von Bälz Prize in fiscal 2007.

Drawing out specific function by changing compound's structure

Prostaglandin (PG) is a group of biomolecules that help maintain homeostasis in the human body. Prostaglandin E helps make the body more active by generating heat upon waking up. Prostaglandin D causes sleepiness by lowering body temperature. Prostacyclin is the most effective of the PG molecules in helping platelets aggregate and blood vessels expand. Researchers are paying attention to its role in the brain as well. Prostacyclin is so unstable *in vivo* that it was difficult to identify whether it affects the peripheral or central nervous system. MIRP has started tackling this issue by developing a fine molecular design technique based on their original synthetic method.

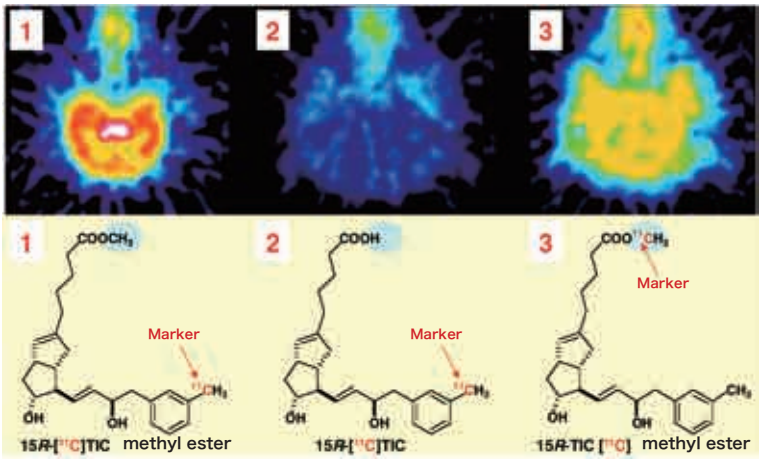
Hisashi Doi, who studies labeled chemical reactions, is deputy team leader of the Molecular Probe & Drug Design Laboratory. "Prostaglandin usually has the S configuration of a hydroxyl group at C-15 within the molecules," he said. "Researchers used to believe that prostaglandin with a different configuration did not become active inside the body. Masaaki Suzuki, team leader of the Molecular Probe & Drug Design Laboratory, and his colleagues changed its configuration to *R*, the mirror image of the *S* configuration. As a result, they created 15*R*-TIC, a new, highly active compound that can bond only with the central nervous system.

Clear visualization of activity in brain

One of the program's key research themes is to inject a compound labeled with ^{11}C, a carbon radioisotope, into living organisms and observe how the compound moves and changes inside the body. The compound can be observed by detecting the gamma rays emitted by the carbon radioisotope through positron emission tomography (PET). Since the amount of gamma rays emitted by ^{11}C with half-life of 20 minutes, a target compound should be quickly labeled with ^{11}C. "We set our goal at 5 minutes to complete the labeling," Doi said. "It took five years for us to develop such a quick labeling method." The group's hard work has resulted in the development of a novel chemical reaction.

The program's PET-based research has revealed that 15*R*-TIC is taken in the brain in the form of methyl ester and binds with cerebral receptors as carboxyl acid after it is hydrolyzed in the brain (see figure). The findings have demonstrated the importance of where ^{11}C is labeled. Clear PET images that reflect a compound's activities in the living body were obtained by labeling the compound's carbon

Obtaining clear images by labeling the carbon frameworks of the target compound with ^{11}C



By labeling the mother nucleus with ^{11}C, PET images can be obtained showing that 15*R*-TIC is localized at the receptors.

As long as it remains carboxylic acid, it cannot be taken up into the brain.

When the methyl ester is labeled with ^{11}C, it is affected by metabolism in the brain and its localization cannot be monitored.

frameworks with ^{11}C. This methyl ester is a prodrug capable of penetrating into the brain, and its importance has been demonstrated in this PET-based research. Furthermore, the group has confirmed that 15*R*-TIC can protect cranial nerves. The new compound may someday be used to treat cerebral infarction or other brain diseases.

Yasuhiro Wada, research scientist of the Molecular Probe Dynamics Laboratory, and expert on PET image analysis, emphasized the effectiveness of the new compound this way: "Compounds are affected by metabolism of the body and change immediately after they enter the body. As we can now place ^{11}C anywhere we want in a compound, our target compound can be efficiently put into the brain. We have succeeded in clearly imaging how quickly the compound is metabolized in the brains of living organisms."

Developing drugs safely and speedily

The 15*R*-TIC cannot reach the brains of rodents, as the animals quickly metabolize the compound. The group was able to develop the compound because they conducted the research on primates, which are closely related to humans. Some compounds that are effective for rodents do not work in humans. In that sense, the ordinary drug development processes for testing new drugs, from rodents to primates and finally to humans, may not be the most effective or efficient. Because of this flow of processes, developing new drugs may require a great deal of time and involve huge costs.

It has become possible to monitor the effectiveness of a compound even if its dose is very small, thanks to developments in PET technology. "Our micro-dose clinical tests are aimed at watching the distribution of a radioactive drug in the body by administering less than one-hundredth the normal pharmacological dose (one-ten-thousandth of a gram) to people for whom this volume has no negative effects," Wada noted. In micro-dose clinical tests, a candidate compound for a drug can be directly administered in people to evaluate its effectiveness, so that new drugs may be speedily developed. An official panel on this issue is discussing the implementation of micro-dose clinical tests in Japan (rules or guidelines on the tests were announced in June 2008). RIKEN will soon set up a system for conducting such clinical tests at MIRP.

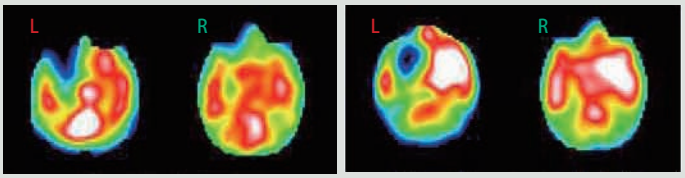
(from left)

Hisashi Doi
Deputy Team Leader Molecular Probe & Drug Design Laboratory

Yasuhiro Wada
Research Scientist Molecular Probe Dynamics Laboratory

Cranial nerve protection by 15*R*-TIC

One side of the middle cerebral arteries of a crab-eating monkey was ligated to temporally cause cerebral infarction. Later, the ligation was released. When 15*R*-TIC was administered, a fall in the [^{15}O] oxygen metabolism and a drop in the [^{18}F] glucose metabolism caused by the ligation were prevented. The red areas are where the metabolism recovered. These PET images demonstrate the effectiveness of 15*R*-TIC in protecting cranial nerves.



Oxygen metabolic rate in the brain Glucose metabolic rate in the brain

Left: No administration Right: 15*R*-TIC was administered

Outline of the program — Molecular Imaging Research Program (MIRP)

For creating new sciences and drug development processes

Molecular Imaging Research Program (MIRP) was set up in September 2005 as a base project for finding medicinal candidate substances under a life science research and development scheme of the Ministry of Education, Culture, Sports, Science and Technology (MEXT). The ministry started the scheme also called "Molecular imaging research program" to address social needs. RIKEN began the MIRP in the fiscal year beginning in April 2007 as a full-fledged project.

Molecular imaging is technology that quantitatively identifies the behavior of genes, proteins, other biologically functional molecules, and medicine molecules *in vivo* without intruding into the body. Biological and medical studies that have been carried out on animals will be implemented using humans as subjects as this non-invasive technology has no serious or adverse effects on human health. Experts have high expectations that MIRP will contribute greatly to life science development. As a base project to search for new drug candidate materials, we plan to drastically reform the new medicine development process. To achieve this innovation, we intend to drastically shorten the period from finding new drug candidates to conducting clinical tests by efficiently shortlisting them at a very early stage in drug development efforts.

RIKEN started offering an educational course named PET Science Academy for researchers at companies as part of the MIRP in the fiscal year starting in April 2007. The course is aimed at helping spread molecular imaging technology by systematically providing lectures for corporate researchers pa rticipating in the program.

We aim to establish an "all-Japan" research system composed of top Japanese experts in molecular imaging by expanding the MIRP team and upgrading the MIRP project to a key research center in the field.

Number of full-time personnel: 38 (as of March 31, 2008)

Genomic Sciences Center

Different mutations of same gene enable development of model mouse strains for schizophrenia and depression

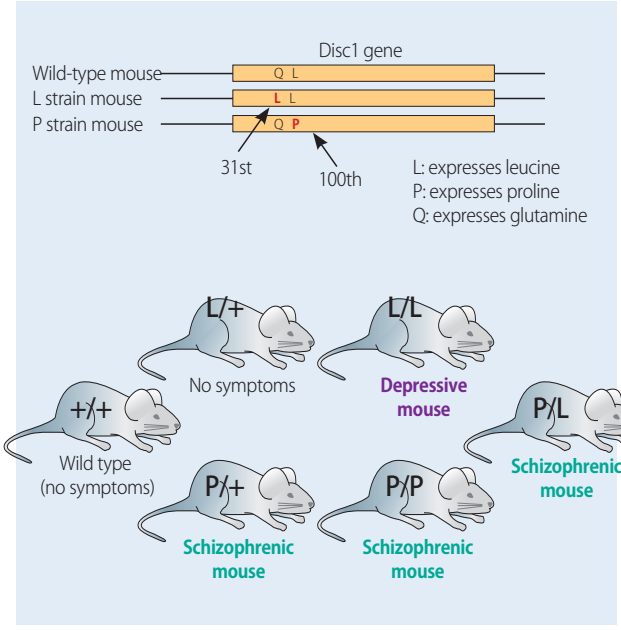
RIKEN Genomic Sciences Center (GSC) has succeeded in developing two model mouse lines carrying mutations of the same gene. One mouse strain developed schizophrenia, the other depression. The mechanisms for the onset of these disorders are still unclear, as both environmental and inherited factors contribute and interact in complex ways. It is hoped that the new model mouse strains will aid in learning how the disorders arise and in the development of new treatments and medicines.

In April 2008, the GSC was reorganized into three units.
- *Omics Science Center*
- *Systems and Structural Biology Center*
- *Bioinformatics And Systems Engineering division*

Yoichi Gondo Team Leader
Population and Quantitative Genomics Team (Until March 2008)
BRC Mutagenesis and Genomics Team (From April 2008)

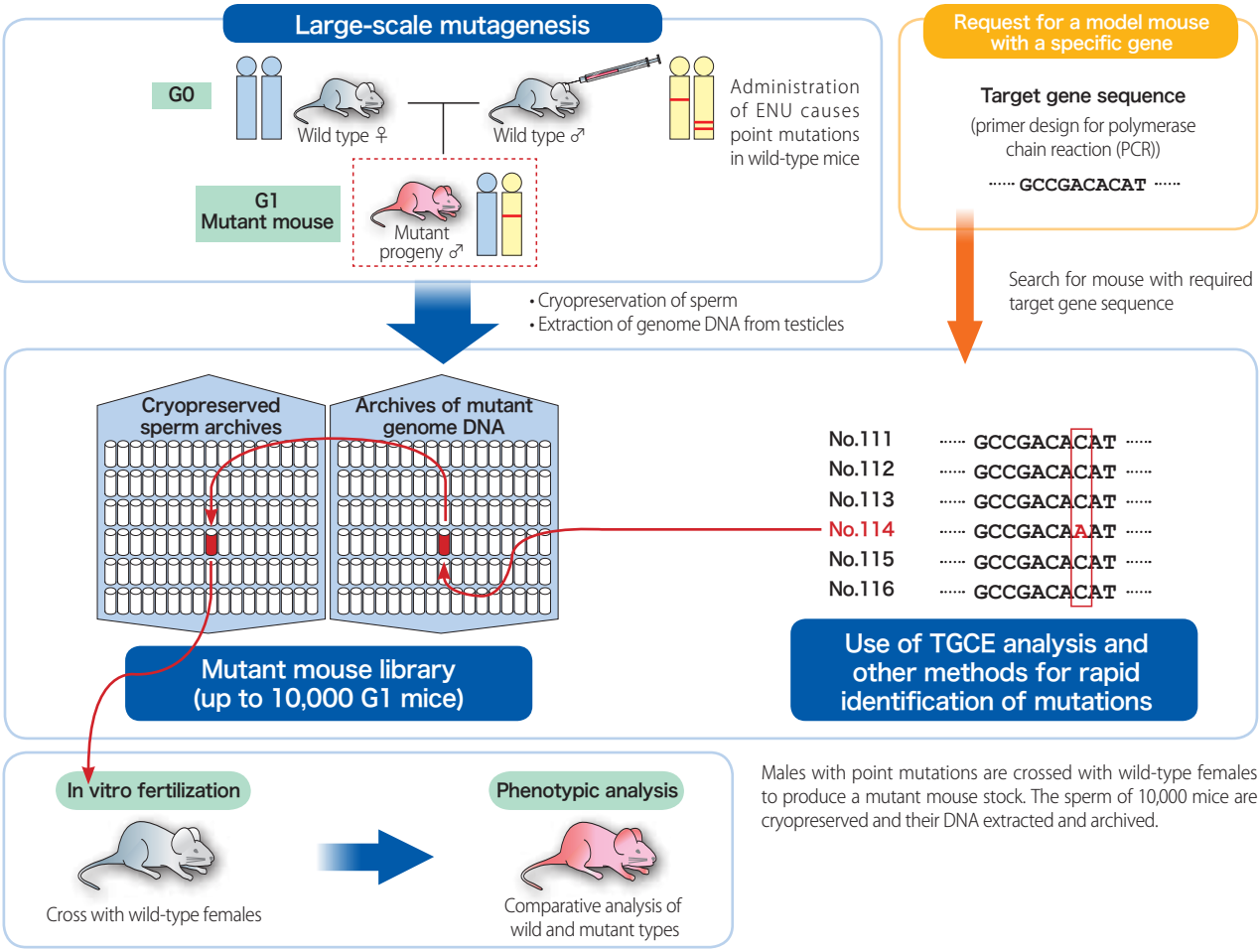
Analyses of point mutations in mice lead to unexpected discovery

The team headed by Yoichi Gondo, team leader of the Population and Quantitative Genomics Team, was commissioned by the research institute of Mount Sinai Hospital in Toronto, Canada, to develop mutated mouse lines in the 31L and 100P mutations expressed from the Disc1 gene. Together with researchers from Edinburgh University in Scotland, the Canadian research team analyzed these mouse strains. It was found that the P strain mice were unable to cope well with external stimulation and manifested other symptoms consistent with schizophrenia as a dominant trait; while in the L strain mice, symptoms of depression such as shorter swimming time in a hopeless condition, passivity in social interaction, and lack of reward responsiveness, emerged as a recessive trait. In addition, mice in both lines exhibited the reduction in brain volume characteristic of both diseases.

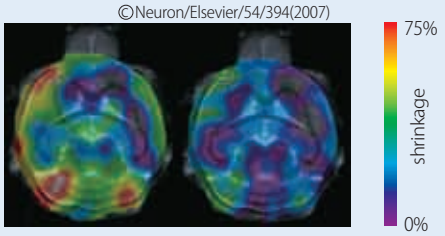


Point mutations and onset of mental disorders
The Disc1 gene causes the 31st glutamine to be exchanged for leucine in the L strain; the 100th amino acid is exchanged from leucine to proline in the P strain. The gene combination inherited from the parent causes different disorders in the progeny.

RIKEN ENU Gene-driven mouse mutagenesis system



The Disc1 gene had been linked to schizophrenia in previous studies, but its connection to the onset of depression was completely unexpected. Gondo said, "It was revealed that one base change in a gene could cause two different disorders. This new discovery was made possible by analyzing point mutations in mice."



Schizophrenic model mouse
13% contraction of brain in P strain mutations

Depressive model mouse
6% contraction of brain in L strain mutations

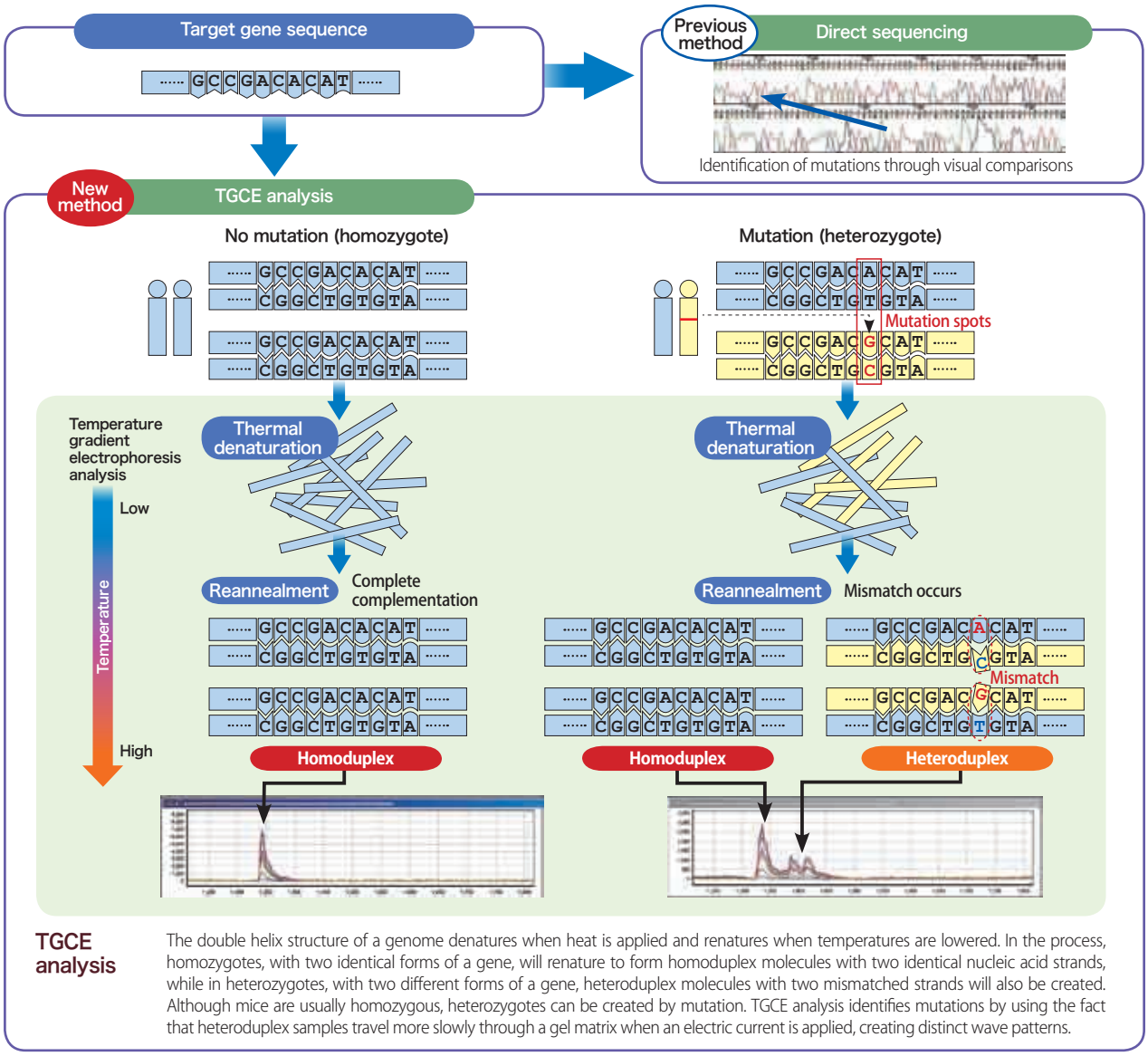
Changes in the brain volume of mutant mice

Magnetic resonance imagery (MRI) was used in analysis of the brains of the mutated mice. Each strain exhibited a contraction of tissues in certain areas of the brain characteristic of schizophrenia. In particular, the contraction of the cerebellum tissue seen in all the mice are traits of both depression and schizophrenia.

Model mouse lines expedite research

The international project team also tested for medicinal reactions. The administration of antipsychotics mitigated the symptoms of schizophrenic mice. Of the depressed mice, those treated with the antidepressant bupropion experienced an improvement in symptoms, but the administration of rollipram had no effect. Rollipram inhibits the activity of PDE4B, which is a binding partner of the Disc1 protein. It was found that in the brains of the L strain homozygous mice, PDE4B protein activity had decreased by half. The drug may have not been effective because of deficiency of PDE4B. Gondo is confident that the new model mouse can be used for a multitude of studies that were not possible with the other models.

Schizophrenia afflicts about 1% of the world's population and depression about 10%, and the development of effective treatments and preventive measures are much desired. Both disorders are believed to manifest as a result of a combination of environmental and genetic factors, but the actual mechanism of onset has not yet been discovered. To understand why this disorder occurs, we must learn more about environmental influences and the effects of medication. Model mice with the disorder will prove useful in acquiring not only experimental data, but also clinical data. This could be a breakthrough in resolving the mechanism of onset of this disorder.



TGCE analysis

The double helix structure of a genome denatures when heat is applied and renatures when temperatures are lowered. In the process, homozygotes, with two identical forms of a gene, will renature to form homoduplex molecules with two identical nucleic acid strands, while in heterozygotes, with two different forms of a gene, heteroduplex molecules with two mismatched strands will also be created. Although mice are usually homozygous, heterozygotes can be created by mutation. TGCE analysis identifies mutations by using the fact that heteroduplex samples travel more slowly through a gel matrix when an electric current is applied, creating distinct wave patterns.

Deciphering genomes using the model mouse

The new model mouse is the result of the RIKEN ENU Gene-driven Mouse Mutagenesis System headed by Gondo. This system cryopreserves the sperm of mutant mice. Random point mutations are induced in the mice through administration of the alkylating mutagen N-ethyl-N-nitrosourea (ENU). These male mice are bred with wild-type females to produce mutant offspring. All of the sperm are cryopreserved, and a library of their genomic DNA is assembled. If a certain gene is desired for analysis, DNA information is retrieved from the archives, and a live mutant mouse can be produced through *in vitro* fertilization of the cryopreserved sperm. Gondo explains that these mice are different from knockout mice, in that knockout mice lack a certain gene altogether while in the ENU-mutagenesis-based mouse, gene sequences can be identified down to a single base level. The RIKEN mutagenesis system has been made available to researchers since 2002, and its use is spreading in both Japan and other countries.

Providing research opportunities

ENU induces a point mutation for every million bases. Since the mouse genome has three billion bases, every mouse should have an average of 3,000 point mutations. RIKEN's library contains about 10,000 G1 mouse samples, so the cost and effort of finding a specific mutation can be horrendously difficult. The usual method of identifying base changes through visual examination has proved too inefficient. By adopting the temperature gradient capillary electrophoresis system (TGCE), which can screen for base changes quickly and accurately, the efficiency of the mutagenesis system improved drastically. The system could not be developed without the progress in genetic analysis technology.

"Previous research studies were limited in scale and number, and themes tended to be similar or overlap with those of others," Gondo said. "Our genome project began when we decided to try to create a center in which the material and data could be assembled on a large scale, to be utilized by all researchers." He feels that they have only started, and that there is still much useful data waiting to be discovered in their library. They hope more researchers will use their archives for further breakthroughs in science.

Genomic Science Center (GSC)

GSC — Challenging the elucidation of the "life strategy"

Genomic Science Center (GSC) named the space containing layers of life activities from genome to phenome (the phenotypic characteristics of an individual) the "omic space." GSC has been aiming to elucidate the "life strategy" with this comprehensive perspective as the main axis. The "genome network," which is interwoven in every direction of the omic space, contains the knowledge of how life survived for over 4 billion years, and represents the accumulation of life strategies. The objective of GSC is to elucidate the whole picture of the "life strategy," which controls complex life phenomena. Within GSC, five research groups are cooperating with each other to elucidate the "life strategy" by integrating the aforementioned layers using informatic methodologies, while also continuing with research specific to their own area.

As a result, GSC has played an important role in many of the world's most advanced large-scale projects, which include the International Human Genome Project (the global project of completing the sequencing of the human genome chromosome 21), the Genome Network Project, the Protein 3000 Project, and the National BioResources Project, and has obtained successful outcomes from these projects, yielding global-scale achievements.

In the future, by using these achievements as a foundation, we plan to further utilize the existing large-scale analysis systems and resources; we will also developmentally expand our research into new areas by reflecting the characteristics of each individual group and by cooperating with each other.

Number of full-time personnel: 314 (as of March 31, 2008)

Director's Message

The expectation of new genome science developments while recapitulating on 10 years of activities

Yoshiyuki Sakaki, Director, Genomic Sciences Center

Q. Which project did you particularly focus your attention on in fiscal 2007?

A. Fiscal 2007 was GSC's 10th anniversary. While recapitulating on our 10 years of activities, we focused on the activities through which we can expect further development from past activities. In particular, while holding commemorative events, such as a 10 year anniversary symposium, we promoted activities directed toward new developments, including making the existing NMR (Nuclear Magnetic Resonance) facility available to external researchers, revising the formation of our activities, establishing proposals for restructuring activities, etc., and commencing collaborative research with Tata Consultancy Services (TCS) in India

Q. What are some of the noteworthy achievements of fiscal 2007?

A. Although there are a number of research achievements, I would like to pay particular attention to the schizophrenic model mouse that was developed by Yoichi Gondo's team, as featured in this report. A variation was found in the Disc1 gene, and it can be expected to open a path for systematically analyzing complex diseases. In addition, a research team of senior scientists, Yasushi Totoki and Atsushi Toyoda, has elucidated the control mechanism of microRNA and introduced an innovative perspective in controlling the early development of mammals. This achievement has contributed to elucidating the "life strategy," the research theme of GSC.

Q. What are the center's future prospects?

A. Over the past 10 years, GSC has involved itself in sequencing the human genome, completing the Mouse Genome Encyclopedia, establishing the Protein Structural Analysis Pipeline, and conducting tests on several hundred model mice. All of these achievements fall into the category of "genomic science"—a new discipline created by GSC. GSC has brought innovation to the style of life science research in Japan. Ahead of us lies the necessity of establishing a system that will raise the entire research level in Japan by sharing technologies, human resources, facilities, know-how, and many other resources that have been developed by GSC and the scientific community. The opening of the NMR facility to external researchers will be just one of such models.

In addition, a large amount of various data and information are rapidly being accumulated in the field of life sciences due to the development of genomic science. In order to understand the essence of life that lies within that pile of information, it is necessary to develop an appropriate information processing system and a mathematical scientific approach for use in revealing any regularities or particular characteristics of a phenomenon. The Computational and Experimental Systems Biology Group within GSC will be established for that purpose. From fiscal 2008, the group will create a new discipline— computational biology— and will operate using the petaflops computer (to be deployed in Kobe in the future), aiming at opening a new frontier in life science.

Plant Science Center

Identifying genes controlling biosynthesis of cancer-preventing compounds in Brassica vegetables

Researchers at the RIKEN Plant Science Center (PSC) have identified a gene necessary for generating cancer-preventing sulforaphane contained in plants of the family Brassicaceae. The gene, *PMG1*, holds the key to regulating the production of glucosinolates (GSLs), from which sulforaphane is derived. The gene could pave the way for the development of vegetables that are highly effective in preventing cancer. The success of the research was due to what is known as the Omics method, which integrates information from many areas of biology.

Masami Hirai Unit Leader
Metabolic Systems Research Unit (Until March 2008)
Team Leader, Metabolic Systems Research Team (From April 2008)

Pungency of daikon radish can keep cancer in check

It is often said that pungency in daikon radishes helps fight cancer. Glucosinolates (mustard oil glycosides), or GSLs, are chemical compounds present in plants of the family Brassicaceae. GSLs turn into a pungent chemical called isothiocyanate when grated or chewed and degraded by myrosinase, an enzyme in vegetables' cells. Sulforaphane is a type of isothiocyanate that helps enhance enzymatic activity to help detoxify carcinogens.

GSLs have several different biosynthetic pathways. Different pathways produce isothiocyanate with different physiological functions. In order to boost effectiveness in controlling cancer, it is necessary to specifically increase the amount of methionine-derived GSLs. Getting a handle on regulating the amount and pathways of GSL biosynthesis would pave the way to developing vegetables with many health-enhancing functions. But until today, how GSL biosynthesis is controlled in plant cells has been largely a mystery.

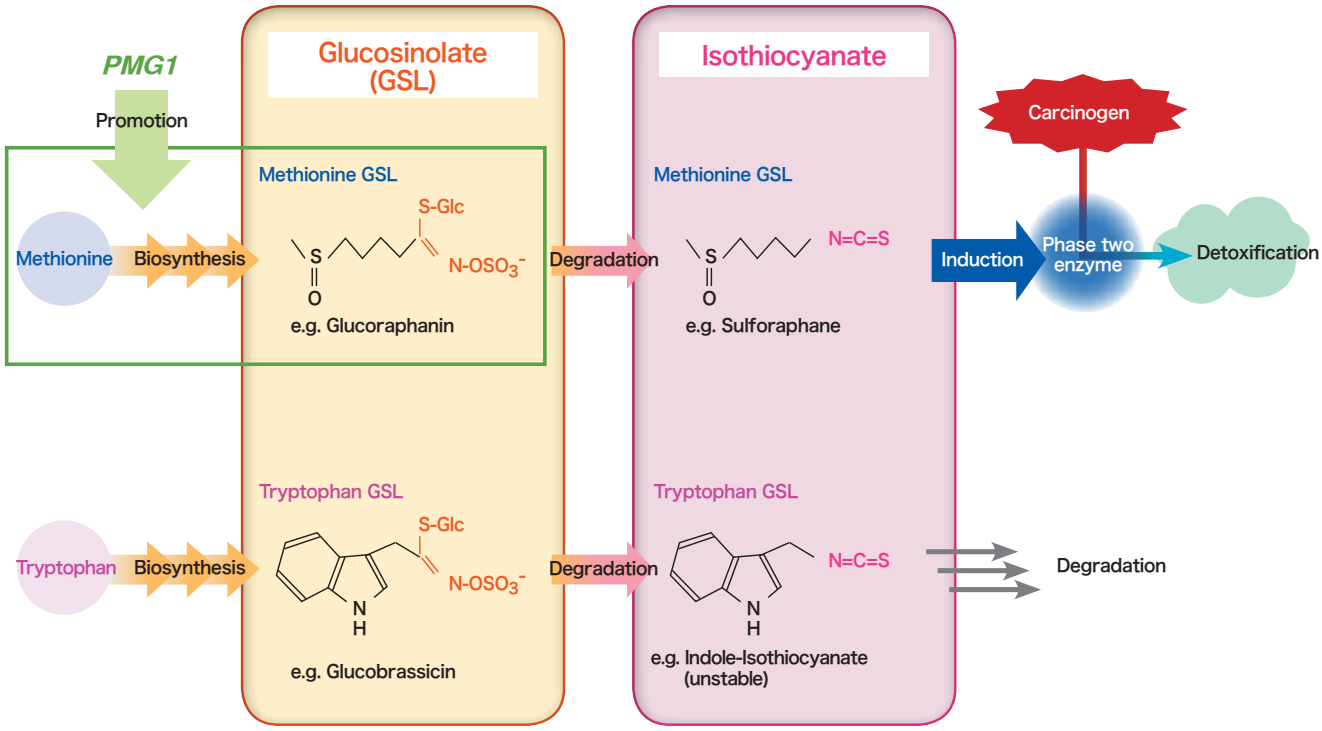
Omics helps to understand biosynthesis as a whole

In April 2007, Masami Hirai, unit leader of the Metabolic Systems Research Unit, identified a gene that selectively regulates biosynthesis of methionine-derived GSLs, which turn into sulforaphane. She named the gene *PMG1*.

Instead of using the traditional method of verifying a hypothesis with experiments to identify the gene, she used the comprehensive analysis of biological information called Omics. Hirai describes Omics as a data-driven methodology to set up a hypothesis based on a large amount of data. In this study, she combined data obtained by transcriptomics, which analyzes genetic expression (transcription factors), and metabolomics, which analyzes such low-molecular metabolites as sugar and amino acids. Through the analysis, her team studied correlations between the genes and metabolic pathways. In doing so, she successfully identified *PMG1*.

Functions of *PMG1* gene

Arabidopsis thaliana has about 30 types of GSLs, each synthesized from different compounds. GSLs turn into isothiocyanates when they are degraded by an enzyme called myrosinase. Isothiocyanates derived from methionine-derived GSLs contains sulforaphane, which detoxifies carcinogens. This study reveals that the *PMG1* gene can selectively control the production of methionine-derived GSL. PMG stands for Production of Methionine-derived Glucosinolate.



Identifying genes by proving a hypothesis

Hirai has been intensively studying sulfur metabolism in plants. Sulfur, she noted, is an essential element that helps maintain the structure and activity of proteins. When soil lacks sulfur, plants adjust to give priority to more critical chemical reactions by switching metabolic pathways. To understand this mechanism, Hirai chose to combine transcriptomics and metabolomics. Her team grew *Arabidopsis thaliana* (thale cress) in a sulfur-deficient culture medium for about one week. The team took samples several times during the course of cultivation and conducted transcriptome and metabolic analyses on the samples.

When analyzing the samples, they used the BL-SOM (Batch-Learning Self-Organizing Map) developed by Shigehiko Kanaya, a visiting senior researcher and professor at the Nara Institute of Science and Technology. The mapping helped the team understand clusters of genes and metabolites that go through similar changes over time. The analysis also identified several groups in relation to the genes. Among them was a cluster containing genes responsible for GSL biosynthesis. The cluster also contained many other genes with unknown functions. One of them was *Myb28*.

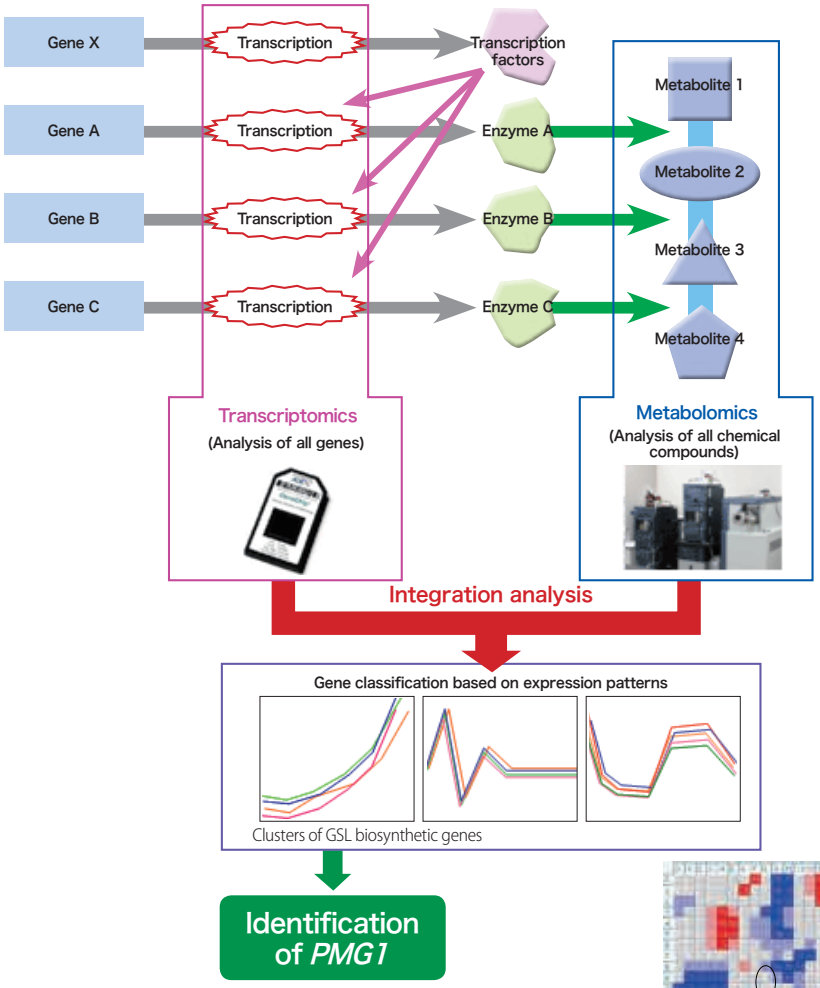
"*Myb28* is thought to be involved in the biosynthesis of GSLs," Hirai said. "The cluster contained genes that help the biosynthesis of both methionine-derived and tryptophan-derived GSL. So we tried to find out which pathways the gene is involved in." By referring to publicly available data, the team compared *Myb28* with expression patterns of genes responsible for GSL biosynthesis. Hirai said the comparison led her to hypothesize that the *Myb28* gene is responsible for regulating biosynthesis of methionine-derived GSL. To prove the hypothesis, the team grew Arabidopsis whose *Myb28* function had been knocked out. The team saw suppressed expression of genes responsible for biosynthesis of methionine-derived GSL and reduced GSL accumulation, while finding no noticeable changes in the expression of genes regulating tryptophan-derived GSL and the amount of GSL accumulation. Over-expression of *Myb28* in cell cultures of Arabidopsis that do not normally synthesize GSLs resulted in a similar amount of GSL accumulation as seen in the knockout plant. The experiments led the team to believe that *Myb28*is capable of selectively controlling biosynthesis of methionine-derived GSL. The gene was named *PMG1*.

Huge potential in Omics analysis

The research has not only unraveled part of the mystery involving the genes but also helped make Omics a viable analytical tool. The method can now be used to identify genes with particular functionalities.

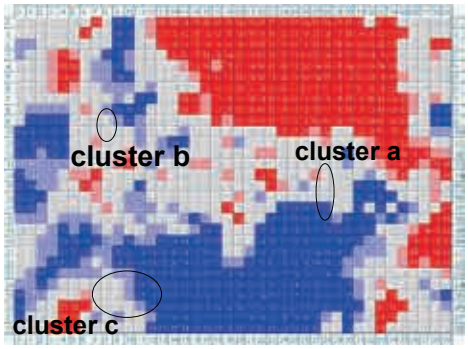
"I was not certain that this combination of transcriptomics and metabolomics for a comprehensive analysis would

Identification of gene functions using the Omics method



The research looked into correlations between genes and metabolic pathways by combining transcriptomics on gene expressions (transcription factors) and metabolomics on sugar, amino-acid and other low-molecular metabolites.

work," Hirai noted. "But in about one year, my team was able to prove that it would work in the *PMG1* and other individual projects. We are now confident that we chose the right method. We might see unintended achievements like this in our future research. We will focus on the development of a new analysis method in addition to the identification of unknown genes." Hirai's challenge clearly does not end here.



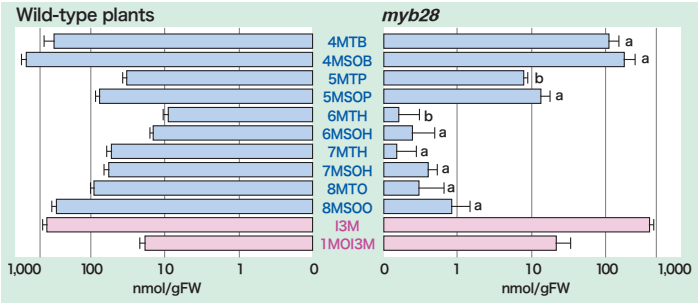
BL-SOM (Batch-Learning Self-Organizing Map)

The colors in the squares show changes in the relative accumulation of metabolites and relative amount of gene expression, with red signifying an increase and blue a decrease.

Genes and metabolites that go through similar patterns of change over time are placed in the same or adjacent squares. The mapping shows that genes and metabolites in the same cluster are synchronizing and likely have similar functions. The mapping helps researchers induce functions of unknown genes. As for clusters of GSL-related metabolites and genes, clusters a, b and c were identified on the map. Cluster c contained genes involved in GSL biosynthesis and *Myb28* (*PMG1*) was found there.

Myb28 (*PMG1*) influences the amount of GSLs produced.

Arabidopsis whose *Myb28* had been knocked out saw a decrease in the amount of methionine-derived GSLs (blue bars) but no change in the amount of tryptophan-derived GSLs (pink bars).



Plant Science Center (PSC)

Making a social contribution by improving both quantitative and qualitative plant productivity

A rapid increase in population accompanied by rapid industrialization in Asia has caused imbalances in food and energy supplies, leading many to predict global food, energy, and environmental crises. The Plant Science Center (PSC) was established in 2000 in response to this need, as plant-science based research and development will be extremely important in averting such crises. In its first five years, PSC garnered success researching plant hormone metabolisms and information signaling, amalgamating chemistry, biochemistry and molecular genetics, and compiling Arabidopsis genome information and resources.

Currently in our second five-year phase and looking 15 years into the future, PSC is promoting plant science research and development that will contribute to solving the food and energy crises envisioned by 2020 and alleviating environmental problems associated with global warming. Specifically, we are promoting research on functional genomic (e.g., transcriptome, proteome, metabolome) analyses in model plants in order to elucidate the control mechanisms for growth, morphology, photosynthesis, metabolism, and environmental response in the context of whole organisms. We also aim to identify the genes that lead to improved plant production in terms of both quality and quantity, and applying this knowledge to food and timber crops.

Specifically, we promote plant science research through domestic and international collaborations with other research institutes, universities, and companies. PSC also actively employs and nurtures young research talent to promote plant science and plant biotechnology.

We aim to use PSC research achievements to ensure a reliable supply of food, materials, and energy, and to contribute to the establishment of a sustainable society.

Number of full-time personnel: 119 (as of March 31, 2008)

Director's Message

Contributing to the establishment of a sustainable society through improving plant productivity

Kazuo Shinozaki, Director, Plant Science Center

Q. Which project did you particularly focus on in fiscal 2007?

A. We realized a significant achievement with developing infrastructures for metabolome analysis and hormonome analysis. In terms of international collaborations, we signed agreements for research exchange with the Max Planck Institute and the Leibniz Institute in the area of metabolome research, and an agreement with Nanjing Forestry University on timber biotechnology research. We also launched collaborations in crop genome research and systems biology.

In addition, we laid out a framework for implementing bioinformatics, recruited excellent bioinformatics researchers, and prepared for the construction of an informatics infrastructure and a database for metabolome and genomic analysis.

Q. What are some of the noteworthy achievements of fiscal 2007?

A. In terms of contribution to human health, we discovered a transcription factor gene that could be a key to the biosynthesis of mustard oil glycoside (glucosinolate), a substance found in vegetables of the Brassicaceae family. This research received global attention as it was achieved using a metabolome analysis technique. In addition, PSC published the results of our research on the role of a nitrogen compound ammonia transporter involved in plant growth and an analysis of a transcription factor related to the formation of root hairs involved in nutrient absorption. In terms of comparative genome studies, we published a well-received article on the full-length complementary DNA (cDNA) libraries for cassava and poplar. Another notable achievement is that according to Thomson ISI, PSC research papers were among the most cited worldwide

Q. What were some newly launched research projects in fiscal 2007?

A. Our Collaborative Graduate Studies Program with Yokohama City University, which aims to expanding our research of crops such as wheat, is now in full operation. It is important work that will expand research achievements from model plants to crops. We also launched two significant domestic collaborative research projects with the National Institute of Agrobiological Sciences (rice metabolome research) and the Japan International Research Center for Agriculture (development of genetically modified, drought-resistant rice and wheat) that has expanded from model plants to crops. And we have initiated new research on a molecular mechanism that determines the size of plant cells and the size of the plant; we expect this research to lead to an increase in crop yields.

Q. What are your future prospects?

A. We will continue with our research and development goals of improving the quantitative productivity and the qualitative functionality of plants in order to contribute to solving environmental concerns related to biomass production, food production, and global warming. We will also apply our research achievements and the knowledge and intellectual properties generated thereof to improve the production of food and timber crops.

SNP Research Center

Discovery of gene associated with development and aggravation of Kawasaki disease

A research team of the SNP Research Center (SRC) at RIKEN has found that the inositol 1,4,5-trisphosphate 3-kinase C (ITPKC) gene is associated with the development and aggravation of Kawasaki disease, a relatively common feverish disorder among babies and infants. The team made the finding by using RIKEN's genotyping method in a joint research project with the University of California at San Diego in the U.S. Experts hope the team's finding will help quickly clarify Kawasaki disease, paving the way for not only preventing the illness from progressing but also developing treatments suited to each patient.

In April 2008, the SRC was reorganized into the Center for Genomic Medicine (CGM)

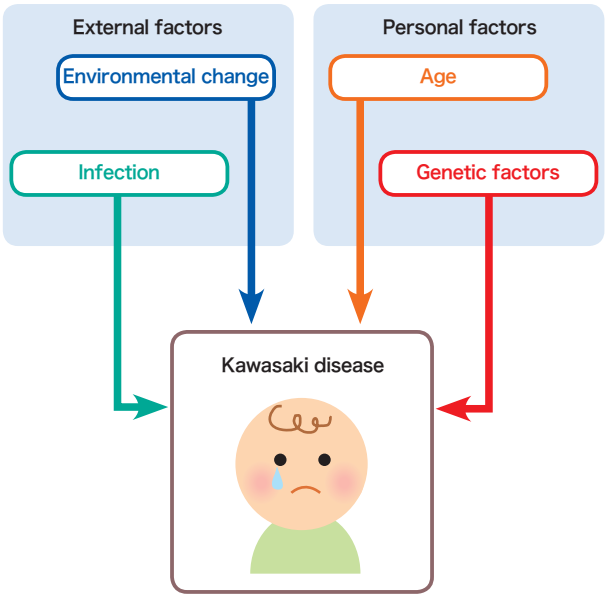
Yoshihiro Onouchi Senior Scientist
Laboratory for Gastrointestinal Diseases (Until March 2008)
Laboratory for Cardiovascular Diseases (From April 2008)

Genetic factor behind high incidence of Kawasaki disease among Japanese

Japanese pediatrician Tomisaku Kawasaki first reported cases of Kawasaki disease in 1967. The disease is characterized by fever and skin rashes caused by inflammation of midsize and small arteries of babies around 12 months old. The basic cause of the disease remains unknown, although specialists believe it may be induced by hyper-reaction of the immune system. They suspect the disease may be caused by involvement of genes, as it is more common in Asian countries than in other areas and affects more boys than girls. More than 10,000 small children suffer the disorder annually in Japan. About 20-25% of the patients, if not properly treated, develop complications such as coronary artery aneurysms.

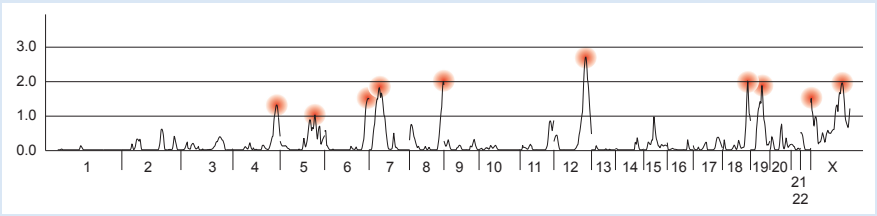
Yoshihiro Onouchi, senior scientist of the Laboratory for Gastrointestinal Diseases, is one of the discoverers of the ITPKC gene, and is also a pediatrician. He said, "In the belief that the disease should not be taken lightly, researchers have been trying to clarify the cause of the disease for

Multiple factors linked to Kawasaki disease



Although various factors are suspected to be involved, the basic cause of Kawasaki disease has remained unidentified for 40 years since the first case was reported.

Linkage analysis



By analyzing patients, chromosomal regions where suspected causal genes exist were roughly identified. These regions are on chromosomes 4, 5, 6, 7, 8, 12, 18 and 19 and chromosome X.

forty years. Intravenous injection of a large dose of gammaglobulin is an effective treatment for the disease, but cannot prevent complications in some patients. So a new therapy to tackle the root cause is urgently needed."

Rough grasp of cause before elaborate examination

Onouchi adopted a three-stage approach — linkage analysis, association analysis and function analysis — to identify suspected genes (susceptible genes) associated with the disease. He thought he would initially use linkage analysis to roughly grasp where suspected genes are located in chromosomes. Association analysis would then be employed to precisely identify the chromosomes and regions where the suspected genes are located. Finally, function analysis would clarify the functions of the genes.

In the first stage, he conducted linkage analysis of test samples donated by 80 sibling pairs of Kawasaki disease patients. He examined genetically identical parts of sibling pairs and checked whether such identical parts could be found in other pairs. He found 10 chromosomal regions where he believes the susceptible genes reside.

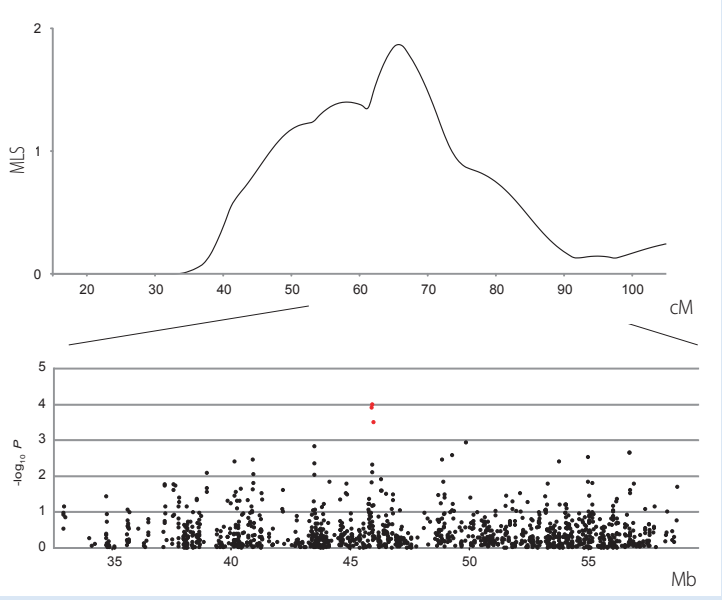
In the second stage, he further narrowed the suspected regions through association analysis based on genotyping. Existing in each region are single nucleotide polymorphisms (SNPs), in which only one base in the DNA sequence is replaced with another. Onouchi compared each SNP with those of 640 people (the test group) who have had the disease, and 1,000 people (the control group) who have not. He found nine SNPs on chromosome 19 that showed statistically significant association with Kawasaki disease.

RIKEN's genotyping technology, called the invader method, worked very well in Onouchi's association analysis. "Manual analysis of a single SNP takes a whole day to complete, but as many as 100 SNPs can be analyzed very speedily and accurately using the invader method," he said. "The method is very efficient in terms both of time and cost."

Association analysis was also carried out on test samples collected from some 200 American Kawasaki disease patients and their parents. The University of California collected the samples from European Americans, Asian Americans, Hispanic Americans and other ethnic groups in the U.S. Onouchi compared the analysis results of the U.S. samples with those of the nine SNPs he had identified. He found four common SNPs among Japanese patients and U.S. patients. These four SNPs are shared by patients of various ethnic groups.

Gene affects regulation of immune response

Function analysis was used to identify the key SNP among the four in the third stage. A disease model covering the functions of a gene to the development of Kawasaki disease

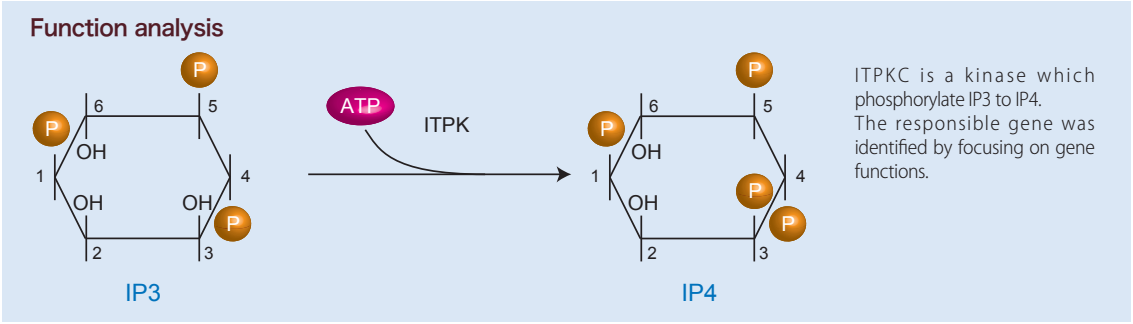


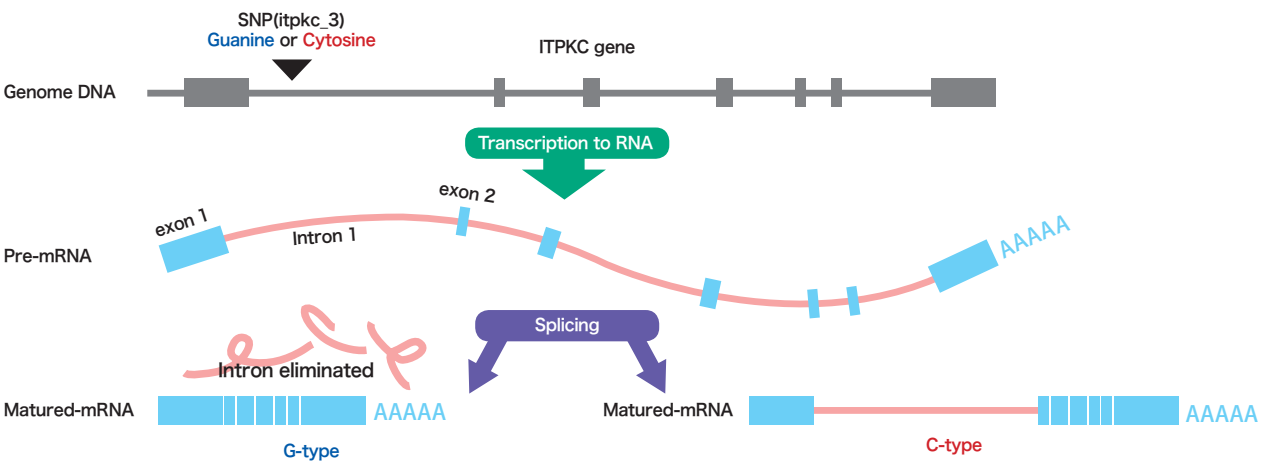
Association analysis

Association analysis of a group of patients was systematically compared to that of healthy people using SNPs as markers. As a result, the regions where the responsible polymorphisms exist were narrowed.

The upper graph indicates the possibility of linkage of chromosome 19 as a whole. The bottom figure is the peak area of the upper graph. In the figures, the higher a value on the vertical axis, the higher the significance of linkage or association between the suspected gene and the disease.

The three red dots are SNPs, which are closely associated with Kawasaki disease. They exist in regions around the ITPKC gene. Close examination of these regions around ITPKC shows that nine SNPs in total have statistically significant association with the disease.





In the case of people with the C-type SNP, intron 1 is not efficiently eliminated, so the volume of the transcribed ITPKC protein decreases.

should be established and the characteristics of the susceptible gene must match the model. Onouchi looked at ITPKC, one of the four genes in which the associated SNPs had been found. ITPKC, which is kinase, converts inositol trisphosphate (IP3) to inositol tetrakisphosphate (IP4). Onouchi hypothesized that ITPKC controls signal transduction of cells by phosphorylating IP3.

He found in experiments that ITPKC plays a significant role in T cells, an important element in the body's immune system. When the ITPKC expression in a T cell line was decreased, the output of interleukin-2, which stimulates T-cells for activating the immune response, increased. This matches the fact that the thickness level of interleukin-2 inside the body of a Kawasaki disease patient rises just after the patient develops the disease. The level further increases in patients with serious complications.

The key SNP associated with Kawasaki disease exists in an intron (a part that is transcribed but has no genetic information) of ITPKC. Such an SNP has cytosine (C-type) instead of guanine (G-type), which the corresponding SNP of healthy people has in that position. Onouchi also found the mechanism that due to decrease in the splicing efficiency (separating introns and connecting necessary parts) in the area called intron 1, the volume of the transcribed ITPKC protein decreases in people with the C-type SNP.

Early treatment prevents disease from progressing

It has become clear that people with the C-type SNP tend to exhibit hyper-immune response more than G-type people because the volume of ITPKC expression in C-type people is smaller. Not all C-type people develop the illness, but Japanese with the C-type SNP are 1.89 times more likely to develop Kawasaki disease than are G-type people.

Onouchi's research has produced results that may be directly applied to treating patients. Those with serious coronary artery complications have a closer association with the C-type SNP than the G-type (2.05 times more among Japanese and 3.36 times more among Americans). This strongly indicates that the C-type SNP is not only associated with the susceptibility of the disease, but also aggravates it. Moreover, the analysis of data on the American patients shows that those who have not positively reacted to gammaglobulin, the key medicine in treating the disease, are 4.67 times more likely to have the C-type than the G-type.

"We need to continue studying the disease to accumulate more data," Onouchi said. "If we can find more SNPs associated with aggravation of the disease, we will be able to treat patients more intensively by assessing the risk that their condition will become severe when they are admitted to hospital." While viruses and other causes have been suspected, Onouchi said his discovery of a single firm factor encourages him to continue researching. He aims to find more genes associated with Kawasaki disease to clarify the whole picture of its development mechanism.

SNP Research Center (SRC)

Toward the realization of personalized medicine

SNP Research Center (SRC, renamed Center for Genomic Medicine (CGM) in April 2008) was launched as part of the Millennium Genome Project initiated by the late former Prime Minister, Keizo Obuchi, in April 2000. The high-throughput SNP (single nucleotide polymorphism) genotyping system developed at SRC and a disease-gene identification method using case-control genetic association studies covering the entire genome have enabled us to discover genes for myocardial infarction, osteoarthritis, spinal disc herniation (slipped disk), diabetic nephropathy, rheumatoid arthritis, diabetes, asthma, and so on. SRC is also the largest contributor to the International Hapmap Project, a global consortium to map human genetic variations, and has contributed about 25 percent of the genotyping data. We have also carried out association studies on examining the effectiveness or side effects of various drugs, such as the anticoagulant warfarin and anti-cancer drugs. To reduce the risk of serious drug adverse reactions (ADRs), we have developed a system for predicting an individual's risk for ADRs from various anti-cancer drugs. Our many achievements have made us one of the leaders in the field of SNP research.

In addition to our research on the systematic SNP genotyping of the entire genome, we will extend the area of our research to include gene expression analysis and systematic proteome analysis of serums and tissues. Our ultimate goal is to investigate every aspect of genomic studies that may affect the development and progression of diseases. Toward this goal, SRC was renamed the Center for Genomic Medicine.

In order to fulfill our initial mission to develop personalized treatments and preventive measures for each individual, we will continue our systematic case-control studies and test different approaches to treat diseases. We hope to discover more about the application of SNP genotyping to evaluate individual differences on the effectiveness of drugs and risks of ADRs, and to apply those results to clinical treatments.

Number of full-time personnel: 108 (as of March 31, 2008)

Director's Message

Personalized medicine is our goal

Yusuke Nakamura, Director, SNP Research Center

Q. Which project did you particularly focus on in fiscal 2007?

A. We will change the name of SRC in fiscal 2008 to the Center for Genomic Medicine. In fiscal 2007, to promote our expanded range of research interests, we held a summer seminar program on medical genetics for scientists in the medical and pharmacological fields; we also conducted a joint workshop titled "Pharmacogenomics in Drug Development," in cooperation with the US National Institute of Health Pharmacogenetics Research Network (NIH-PGRN).

In addition, we held study sessions with the NIH-PGRN and the Japanese Society for the study of Xenobiotics (JSSX) to initiate the Global Alliance for Pharmacogenomics (GAP) in which American and Japanese scientists can collaborate on researches for the genetic factors that influence individual responses to various drugs.

Q. What are some of the noteworthy achievements of fiscal 2007?

A. SNP association studies identified genes concerning spinal disc herniation and Kawasaki disease.

In another important study, we used data from our BioBank (described below) to evaluate 19 anti-cancer drugs known to have severe drug adverse reactions (SDAR). SNP analysis enabled the identification of SNPa associated with the risk of SDAR. There is also an ongoing study with our Thai collaborators to find genes that influence patients' reactions to HIV treatment. The identification of such genes will enable us to predict individuals' risk of ADRs prior to the treatment.

Another achievement was the opening of the Laboratory for Biomarker Development in June 2007. Proteomic analysis of serum samples will help to find biomarkers that can be used to screen and prevent diseases.

Q. What are the center's future research prospects?

A. The International HapMap Project published its Phase II Map in 2007, providing SNP data for European, Asian, and African populations. This has provided a solid basis for SNP research and has accelerated whole genome association studies in the world, especially in Europe and the United States. The center has been in a leading position in this field, and in fact, first discovered genetic variants related to certain diseases using whole genome association studies and was a major contributor to the International HapMap Project. However, many research institutions and pharmaceutical companies in Europe and the United States have also begun large-scale SNP research.

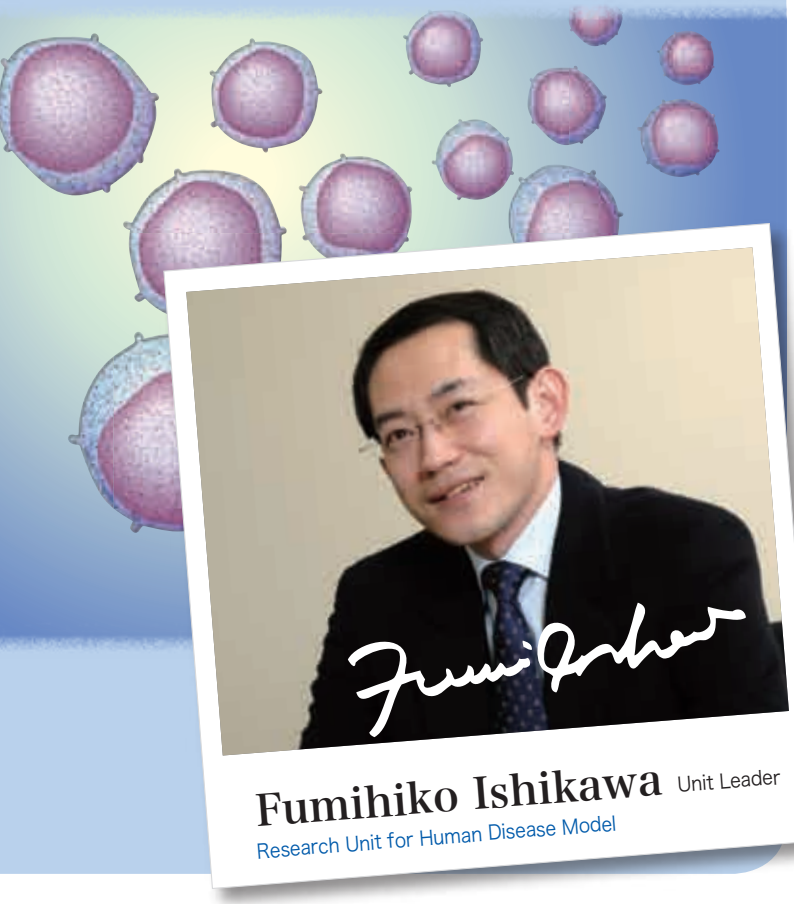
At present, and as an important part of the Personalized Medicine Project by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), we have constructed a BioBank in which DNA, serum, and clinical data from more than 300,000 cases have been collected. We should use this resource to our full advantage to make further contributions in the field of medical science.

The field of genomic medicine should not be just a part of science studies, but should be one of the key elements of a nation's health policy.

Research Center for Allergy and Immunology

Clarifying the causes of human leukemia relapse

Researchers at the RIKEN Research Center for Allergy and Immunology (RCAI) have succeeded in inducing human acute myelogenous leukemia (AML) in mice, and discovered that slowly multiplying leukemia stem cells are responsible for AML relapse. The stem cells show resistance to existing cancer drugs, and stem cells that survive chemotherapy begin to again produce large numbers of leukemia cells. These findings are the result of the researchers' joint study with other research organizations, including Jackson Laboratory in the U.S. and Kazusa DNA Research Institute in Chiba Prefecture, near Tokyo. Identification of the basic cause of AML relapse is the first step toward developing a new therapy to eradicate leukemia.



Fumihiko Ishikawa Unit Leader
Research Unit for Human Disease Model

Leukemia stem cells producing leukemia cells

White blood cells attack and remove germs and viruses that have entered the body. Leukemia is a disease in which white blood cells begin to multiply abnormally and become cancer cells, and the body can no longer produce normal blood cells and immuno-cells. Some patients can fully recover from leukemia through bone marrow transplants or chemotherapy. But patients with AML tend to relapse much more frequently than those with other types of leukemia, and the disease is very difficult to treat effectively.

Fumihiko Ishikawa, unit leader of the Research Unit for Human Disease Model, has been conducting leukemia research. He treated leukemia patients until 2006, when he began to concentrate on research. "I began researching the disease because I wanted to save as many patients as possible," he said.

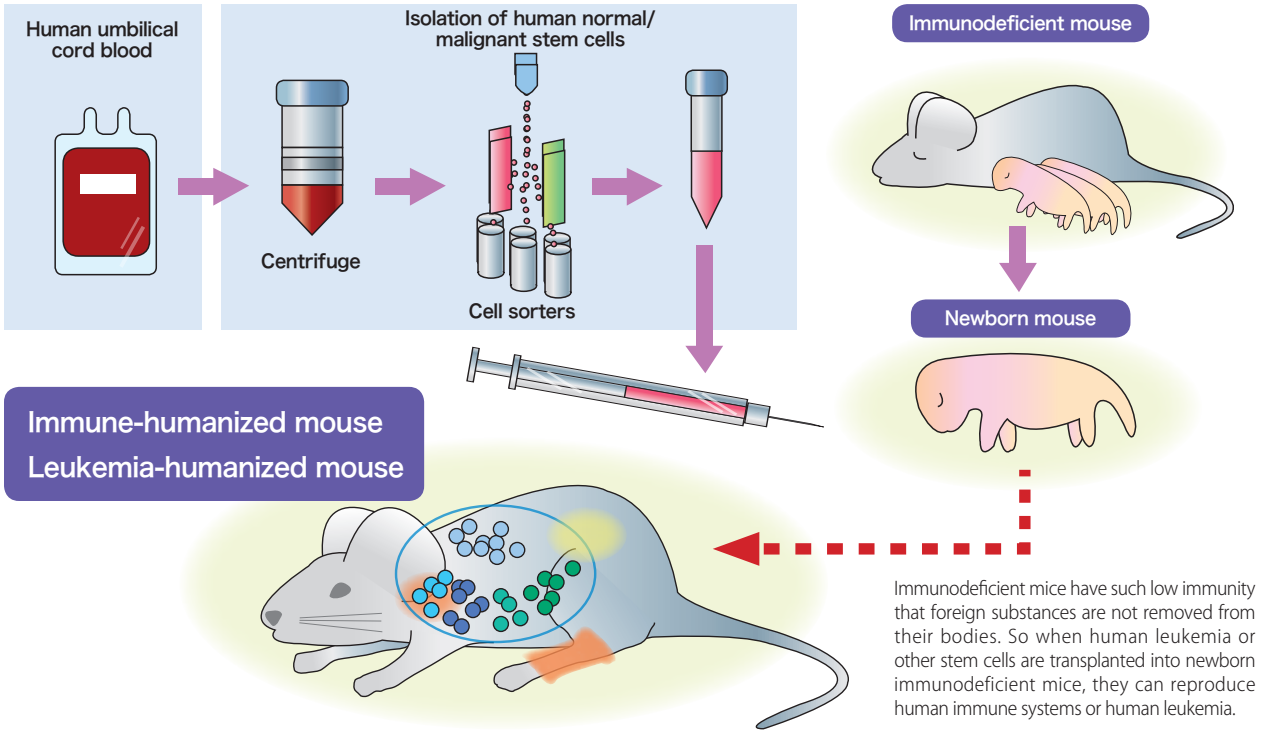
Various types of leukemia cells exist in AML patients. It was recently found that such cells contain a small number of leukemia stem cells, which have been found to produce other leukemia cells.

Studying leukemia by using leukemia-humanized mice

Ishikawa started trying to create leukemia-humanized mice to study the development and relapse of the disease. "When human stem cells are transplanted into healthy mice, the animals' immune systems identify the stem cells as foreign substances and immediately remove them," he said. "But when such stem cells are transplanted into mice whose immunity is very low, human immune systems and diseases can develop in them." Ishikawa started studying immunodeficient mice in 1998 in the U.S. Four years later, he succeeded in creating the first immunity-humanized mice, in which the human immune system can be reproduced. His team created leukemia-humanized mice by injecting leukemia stem cells taken from the bone marrow of AML patients into blood vessels of newborn immunodeficient mice. The team thus succeeded in developing human leukemia in these mice.

The mice have multiple types of leukemia cells in their blood, indicating that they developed leukemia through leukemia stem cell injections. But they did not develop the disease when injected with leukemia cells other than stem

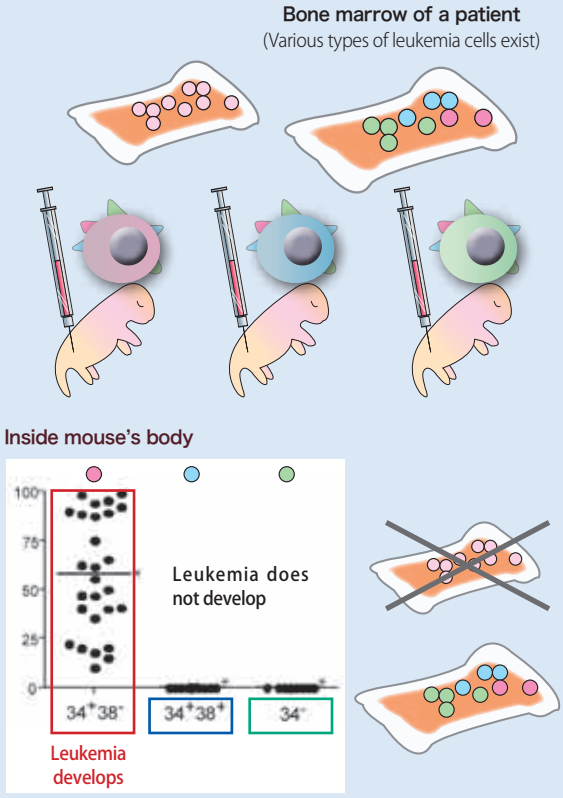
Creation of humanized mouse



Immunodeficient mice have such low immunity that foreign substances are not removed from their bodies. So when human leukemia or other stem cells are transplanted into newborn immunodeficient mice, they can reproduce human immune systems or human leukemia.

What are leukemia stem cells?

Cancer was once thought to be an illness in which a single type of cell multiplies abnormally. But various types of leukemia cells exist inside the bodies of patients with leukemia, which is a type of blood cancer. Leukemia stem cells, which can produce multiple types of leukemia cells, exist among leukemia cells. This research demonstrates that the recipient develops leukemia only when these stem cells are transplanted.



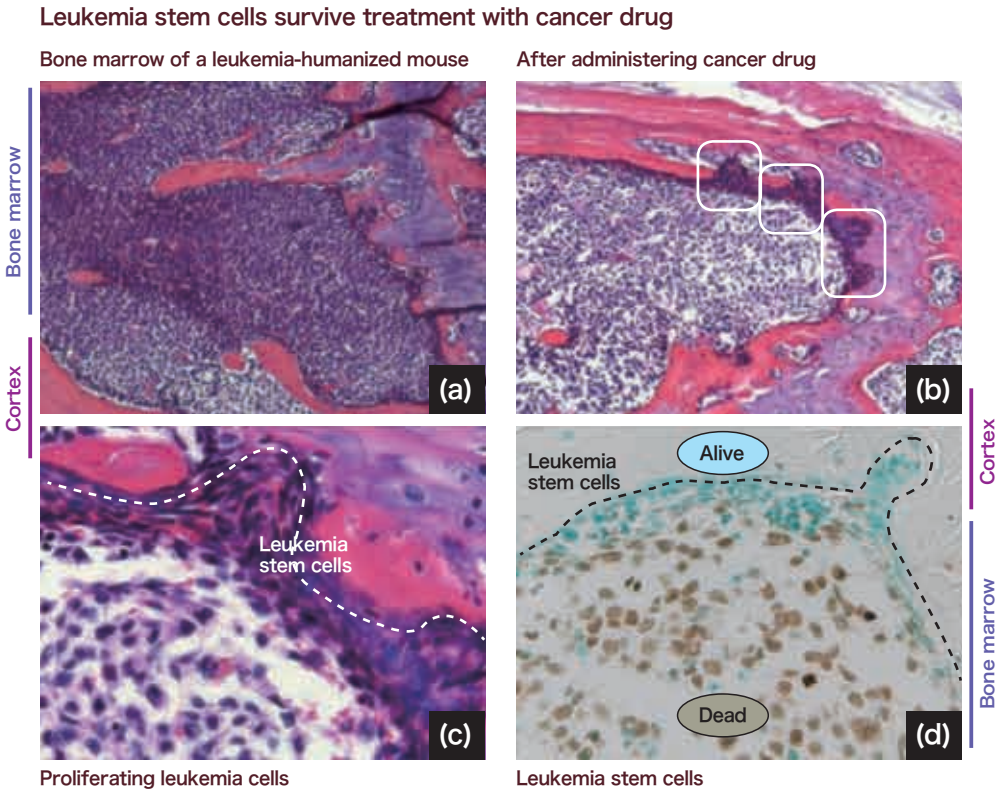
cells. This shows that such stem cells not only multiply but also produce other types of leukemia cells, and are the cause of the disease.

Slowly multiplying stem cells cause leukemia relapse

When cancer drugs are given to mice with leukemia, they effectively kill most leukemia cells, but 70 to 80 percent of the leukemia stem cells survive. Existing cancer drugs cannot completely eliminate stem cells. Those that survive produce large numbers of leukemia cells, causing the disease to redevelop. This shows that leukemia stem cells that are resistant to cancer drugs are the key cause of leukemia relapses.

The research team also found that leukemia stem cells multiply more slowly than other leukemia cells. Cancer cells generally multiply faster than normal cells, so to effectively fight cancer, drugs are designed to attack cells that multiply more quickly than normal cells. However, since leukemia stem cells multiply more slowly than normal cells, cancer drugs are not effective against them.

The team also found that unlike other leukemia cells, stem cells exist only in the areas that border the cortex at either end of bone marrow. Ishikawa believes this localization may be the key to why stem cells multiply slowly and keep their functions. If the reason for the localization is clarified, it may become possible to develop new therapies aimed at leukemia stem cells. These would include development of molecular-targeted drugs aimed at cells that multiply slowly, and of agents that speed up the multiplication of leukemia stem cells to make existing



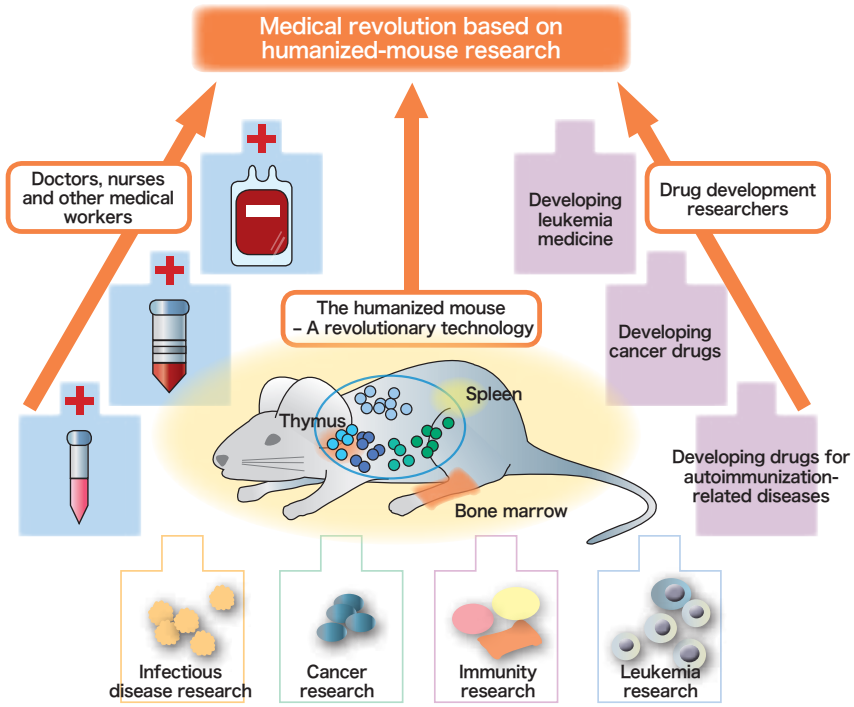
(a) Bone marrow of a mouse that developed leukemia caused by leukemia stem cells. The leukemia cells (purple) have multiplied and spread widely in the bone marrow.
(b) and (c) When a cancer drug is injected into a leukemia-humanized mouse, many of the leukemia cells die, and there are relatively wide spaces in the central bone marrow. But there are purple areas bordering the cortex (red). This indicates that leukemia stem cells exist.
(d) Using a special dye, the dead cells are colored brown and living ones blue. It was confirmed that leukemia stem cells near the cortex survived after the cancer drug was administered.

cancer drugs more effective against them. In the near future, researchers are expected to develop new therapies for eradicating AML.

Looking beyond 10 years

Research based on leukemia-humanized mice is expected to lead to the development not only of new medicines targeting leukemia stem cells but also treatments tailor-made for individual leukemia patients. "Our next goal is to develop a therapy to prevent relapses," Ishikawa said. "In the new therapies, conventional cancer drugs will be used first to reduce the number of leukemia cells other than stem cells, and then it will be followed by a treatment to destroy the stem cells." His team has already started developing new medicine to attack leukemia stem cells. The team is also trying to identify, by using humanized mice, causes of leukemia other than AML and those of primary immunodeficiency syndrome, whose patients congenitally have very low immunity.

When Ishikawa started his research on humanized immunodeficient mice in the U.S. in 1998, his superiors told him the research would be so tough that he would not be able to produce any tangible results even in 10 years of effort. Ten years later, "I'm beginning to think that my research has finally produced results that may be able to help people," he said. He will continue to strive to eradicate leukemia, following his principle that research should be carried out to help patients.



Research Center for Allergy and Immunology (RCAI)

Working to control allergies and immune system diseases

The immune system is not an organ like the brain or liver, but a collection of mechanisms in which more than one trillion cells work together to protect the body. A malfunction in this highly intricate system results in autoimmune diseases, allergies, and immunodeficiency disorders, while an active immune system keeps the body fit by eliminating tumor cells and infectious pathogens. Understanding the mechanisms of the structure, function, and breakdown of the immune system is one of the central themes in medicine and life sciences.

Incidences of allergic diseases such as asthma, pollen allergy, and atopic dermatitis have increased rapidly over the last 20 years, largely in developed countries. In Japan, for example, the number of asthma patients has doubled, and the number of people afflicted with atopic dermatitis has nearly tripled. Approximately one-third of Japanese citizens have some kind of allergy, according to a comprehensive 2003 health survey by the Ministry of Health, Labour and Welfare. Pollen allergies affect about 20 percent of the population, with the resulting medical expenses and financial losses from the decline in work performance estimated at about 286 billion yen, according to a 2000 study by the former Science and Technology Agency. Atopic dermatitis, the next most common allergy in Japan, is seen in about five percent of the population. Asthma claims about 4,000 lives each year. Some 700,000 people suffer from autoimmune diseases, with the economic expense from transplant operations totaling one trillion yen. The development of a permanent cure for allergies and immune system diseases is greatly needed.

RCAI is committed to protecting human health by developing treatments and preventive measures through our studies of the immune system.

Number of full-time personnel: 192 (as of March 31, 2008)

Director's Message

Preparations underway to apply our research for the good of society

Masaru Taniguchi, Director, Research Center for Allergy and Immunology

Q. Which project did you particularly focus on in fiscal 2007?

A. One example of RCAI's efforts to benefit society is our project on primary immunodeficiency disease (PID) in which genetic disorders cause dysfunctions in the immune system and increase the risk of viral and bacterial infection. PID is often accompanied by other complications such as tumors, autoimmune diseases, and allergies. RCAI has signed a joint research agreement with 13 Japanese universities and the Kazusa DNA Research Institute for the construction of a database, collective management of research samples, DNA diagnostic analyses, and a specialist consultation system, aimed at identifying the genes that cause PID and elucidating the disease's mechanisms. This project has been recognized by the Jeffrey Modell Foundation, a nonprofit organization in the US; in January 2008, the RIKEN Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiencies was founded, becoming one of 36 such centers around the world.

Q. What are some of the noteworthy achievements of fiscal 2007?

A. We made progress in the development of a pollen allergy vaccine with reduced risk of anaphylactic shock, and mouse experiments have indicated that it is safe and effective for treatment and prevention.

We also conducted Phase II clinical studies on 20 patients with lung cancer by treating them with NKT cells (natural killer T cells, which are types of immune cells). The initial treatment alone raised the 3 year survival rate to over 60 percent and extended life expectancy to 19 months, compared with 4.6 months after chemotherapy treatment. We are now looking for a pharmaceutical company to help us develop a medicine based on these studies.

In the four years since RCAI was launched, our team leaders and unit leaders have made remarkable progress. I am very proud that these leaders, many still in their forties, published in such prestigious publications as Nature and Science in fiscal 2007. A total of eight articles were published in such top-rated journals.

Q. What are your future prospects?

A. The Immunology Frontier Research Center at Osaka University, launched in 2007 as a premier world-class research facility, has designated RCAI as its sole satellite facility in Japan. I hope this new partnership will spark further progress in our research by encouraging active exchange and innovation among our excellent team of specialists.

Center of Research Network for Infectious Diseases

To Asia and Africa: Twelve overseas research centers in eight countries

In 2005, RIKEN established the Center of Research Network for Infectious Diseases (CRNID), which supports the Program of Founding Research Centers for Emerging and Reemerging Infectious Diseases launched by the Ministry of Education, Culture, Sports, Science and Technology (MEXT). In fiscal 2007, the midpoint of the five-year project, the research network expanded with the addition of new overseas research centers, and many of our research results were published in scientific periodicals.

Yoshiyuki Nagai Director
Center of Research Network for Infectious Diseases

Confronting threats of infectious disease

In Japan and other developed countries, there is a mistaken impression that infectious disease is no longer a serious threat. But since the 1950s, epidemics of new infectious diseases have occurred in many developing countries, and the risk of spreading to other countries has increased along with the development of transportation. The recent appearances of SARS (Severe Acute Respiratory Syndrome) and avian influenza have shown us that such epidemics do pose a serious threat to Japan as well. Under the program, research centers are being established in countries where the outbreaks of infectious diseases will likely take place, and Japanese researchers are stationed in these centers to carry out the research continuously. The role of CRNID is coordination and support of research activities at these overseas centers.

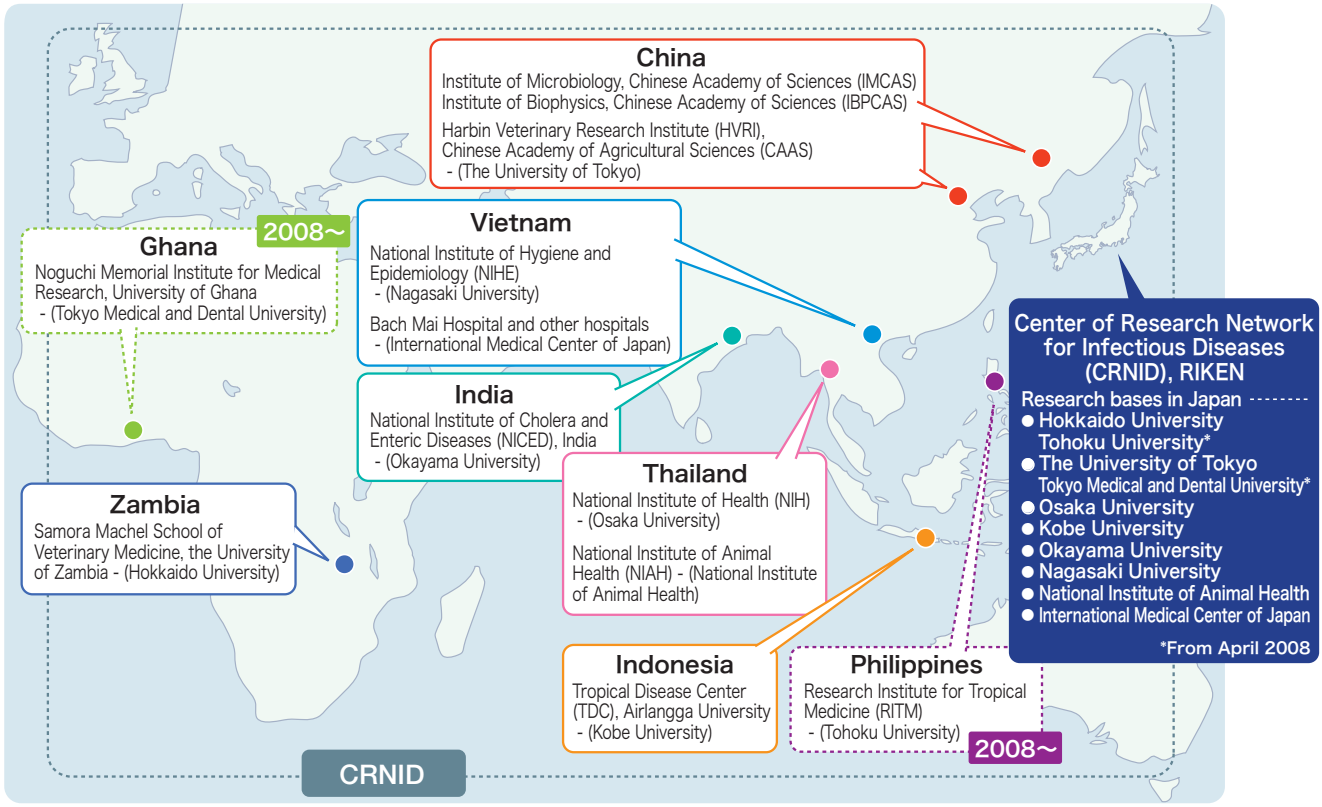
At the start of the program, overseas research centers located only in China, Vietnam and Thailand, but in 2007 we were able to establish centers in India, Zambia and Indonesia. We also began negotiations to establish research centers in the Philippines and Ghana. In fiscal 2008, research centers in those two countries will be added to our program, for a total of 12 research centers in eight countries, under the management of eight Japanese universities and two research institutions.

Yoshiyuki Nagai, director of the CRNID, said: “With the increase in the number of research centers, our international network is finally taking the form that the program is meant to achieve. Compared with other institutions with similar objectives, such as the Pasteur Institute and Oxford University, our network falls short in size, but it has strengthened Japan’s presence in this scientific field.” By fiscal 2007, many research articles had been published in scientific journals. “Publication of so many research results at this juncture makes conditions favorable for further development and enlargement of the network in the next five-10 years,” he added.

Passing on state-of-the-art Japanese technologies to our overseas partners

Fiscal 2007 was dedicated to applying new Japanese technologies for research and diagnosis at our overseas research centers. As an example, a new DNA amplification

CRNID oversea research centers and its network



(March 2008)

Three new overseas research centers

National Institute of Cholera and Enteric Diseases

Samora Machel School of Veterinary Medicine, the University of Zambia

Tropical Disease Center, Airlangga University

method called LAMP (Loop-mediated Isothermal Application) has shortened the time needed to diagnose tuberculosis from two weeks, the length of time needed to grow a culture from a sample, to just one hour. Preparations have begun to enable this new technique to be used throughout the research network. The LAMP method proved very useful in the 2007 cholera epidemics in Vietnam and Thailand.

A similar undertaking is the development of a kit for a speedy diagnosis of H5N1-type avian influenza that was tried in Vietnam with good results. Although outbreaks were sporadic, three out of five people who manifested the disease died, so the development of successful treatment methods is an urgent issue. A new Japanese influenza drug, T-705, has produced very good results in pre-clinical animal tests against the H5N1 virus, and clinical testing in Vietnam is now being considered. According to Nagai, if a pandemic occurs, this new drug may be our best hope. In terms of saving lives, this may be as significant as the development of induced pluripotent stem (iPS) cells. He is eager to demonstrate Japanese cutting-edge technology to the world.

Importance of preparing for emergencies

Epidemics of new infectious diseases may occur anytime, anywhere in Japan. We must prepare, in terms of both knowledge and technology, for such contingencies. But scientists confined within Japan cannot collect raw data. Access to overseas facilities is essential. Doctors must be able to diagnose and treat infectious diseases, such as cholera, typhoid fever, dengue fever and AIDS if they appear in Japan. The establishment of overseas centers enables the sharing of knowledge and research with our counterparts there. To this end, we must take the time and effort to build relationships of mutual trust.

In the future, we hope to utilize overseas research centers in graduate school education and encourage the participation of clinical specialists who can diagnose and analyze actual cases.

Publicizing the program in Japan and abroad, strengthening ties with other facilities

The activities of CRNID include publicizing research outcomes in Japan and other countries, and enlightening people about the program. Nagai hopes that in fiscal 2008 Japanese will become more aware of the program and its importance, and more willing to provide support. For example, in Thailand, where many Japanese companies have offices, we hold lectures on preventing and countering the risk of infectious diseases for Japanese residents, and would like to hold similar events in other countries as well.

In order to learn from prominent institutions and with possible future partnerships in mind, we held an exchange of opinions with them for the first time at the Asian Science and Technology Forum sponsored by the Japan Science and Technology Agency (JST) in October 2007. The forum was a good opportunity to make our research network known in other countries and to encourage the sharing of information with other research facilities. And in January 2008, the annual Asian Research Forum on Emerging and Reemerging Infections was held in Osaka, where researchers in all of the member countries came together.

CRNID Newsletter

Asian Research Forum on Emerging and Reemerging Infections – January 28-29, 2008, Osaka

Nagai has been active in visiting the overseas research centers and exchanging views on what kinds of research would be the most valuable. "The ability and manpower to cope with unprecedented circumstances are vital in dealing with infectious diseases," he said. "Research on infectious diseases encompasses a wide range of subjects, from fundamental medicine and field studies to treatment of patients. Its results have a tremendous impact on society."

Center of Research Network for Infectious Diseases (CRNID)

Activities of CRNID

1. Collection and circulation of information, coordination of joint projects

- Hosting the annual Asian Research Forum on Emerging and Reemerging Infections, publication of pamphlets and newsletters, and enlightening people with information on infectious diseases via the website
- Coordinating joint research projects between overseas research centers and with other organizations such as the various RIKEN research facilities

2. Supporting the operations of research centers

- Supporting the establishment of collaborative overseas research centers at universities and research facilities, and participating in their management

3. Promoting the program as a whole

- Utilizing research results to aid society, and planning and managing the program from a long-term standpoint
- Assisting MEXT board to promote research on infectious diseases, and holding meetings with research center heads to discuss program management

About the Program of Founding Research Centers for Emerging and Reemerging Infectious Diseases

The program started in 2005 as an entrusted program by MEXT to set up research centers in countries where outbreaks of infectious diseases are taking place or will likely take place. Japanese scientists will be able to work regularly at such facilities in cooperation with local research establishments while reinforcing the support system within Japan.

Through concentrated and continued research in these centers, the program aims to learn more about infectious diseases, nurture human resources, and contribute to the safety and health of the Japanese people, the citizens of our partner countries, and the world.

Number of full-time personnel: 12 (as of March 31, 2008)

FACTS & FIGURES

RIKEN's administration and management: fulfilling our responsibilities to society

Transformation into an Independent Administrative Institution

Setting mid-term objectives and drafting mid-term and annual plans

In October 2003, RIKEN's status changed to an Independent Administrative Institution (IAI). The Japanese government established mid-term objectives for new IAIs to meet within three to five years, and it now oversees their efforts toward achieving these objectives.

IAIs were required to draft mid-term plans describing how they would achieve their objectives, and to get these approved by the ministry in charge, which in RIKEN's case is the Ministry of Education, Culture, Sports, Science and Technology (MEXT). RIKEN also has to submit a plan to MEXT each fiscal year. Committees appointed by the government conduct evaluations of IAIs each year and at the end of the terms for their mid-term objectives. Based on the outcomes of its evaluations, RIKEN makes changes as necessary.

Summary of the mid-term plan

Category	Target
1. Improvement of operations	
1) Publication and utilization of research results	
Publish original results	1,820 or more papers annually
Publish in journals that are highly regarded in the relevant fields	50% or more
Register intellectual property	610 applications in fiscal 2007
License patents	12%
Issue press releases	40 per year
Publish RIKEN News	12 times per year
2) Training and development of researchers and technical staff	
Special Postdoctoral Researchers	Maintain constant level of 200 researchers
Initiative Research Scientists	10 researchers by fiscal 2007
Junior Research Associates (JRA)	Maintain constant level of 140 JRAs
2. Improvement of operational and managerial efficiency	
Increase operational efficiency	Reduce expenditure by 1% annually
Increase procurement efficiency	Reduce expenditure by 2% annually
Increase managerial efficiency	Reduce administrative costs by 15% (before taxes)

The Noyori Initiative

On becoming the first President of RIKEN as an Independent Administrative Institution, NOYORI Ryoji issued the for the future of the institute.

Through the Noyori Initiative, RIKEN is putting into practice its mid-term plan and continuing to pursue scientific research at the very highest levels.

1. Visibility of RIKEN	・Improve and strengthen RIKEN's public image ・RIKEN staff should be committed to informing the public of the importance of science
2. Maintaining RIKEN's outstanding history of achievement in science and technology	・Sustain and deepen RIKEN's research spirit ・Emphasize RIKEN's consistently high level of research output ・Increase intellectual property activities and provide scientific knowledge and achievements to industry and society
3. RIKEN that motivates researchers	・Promote research driven by curiosity ・Seek unique, risky projects ・Develop talent
4. RIKEN that is useful to the world	・Find and foster ties with industry and society ・Produce science and technology that will support science in a more fundamental way than simply working with industry
5. RIKEN that contributes to culture	・Increase RIKEN's cultural level ・Provide information to the humanities and social sciences

Research Priority Committee

The Research Priority Committee is advises the President on all aspects of RIKEN's managerial policy. It discusses issues related to the management of RIKEN, such as the direction of future research and prioritization of the research projects and areas.

RIKEN promotes Strategic Programs for R&D (funded by the President's Discretionary Fund) based on the advice of the Research Priority Committee. In order to take a strategic approach, research projects that convene workshops and study meetings—aimed at establishing collaborations across all organizations—in a top-down manner are conducted. In addition, collaborative research projects between research institutes/centers or between research fields, and original and novel strategic research projects are screened with public participation and then implemented. These practices contribute to the excellent research management at RIKEN.

RIKEN Science Council

The objective of the RIKEN Science Council is to respond to inquiries from the President and report its findings to the President. The council consists of approximately 30 members, including Directors, Chief Scientists, and Group Directors. It has lively debates on topics such as the broad and long-term issues of what fields RIKEN should research and formulating a vision for researchers at RIKEN.

Eight meetings were organized during fiscal 2007. Discussions were held on the research institutes that are to be built at RIKEN in the next year, plans for the basic research areas, and on the issue brought forward by the President, namely, "How basic science can help solve the energy problem."

Major awards for 2007

Japan Academy Prize

Japan Academy Prizes are awarded to persons who have achieved notable research landmarks or who have authored particularly outstanding academic papers or books. An award ceremony has been held every year since 1911, and since 1949, the ceremony has been graced by the presence of His Majesty the Emperor of Japan. Since 1990, both the Emperor and Empress have attended the award ceremony.

Kohei Tamao

(Director, Frontier Research System)
(awarded jointly with Hisashi Yamamoto, Professor, The University of Chicago)
For "Exploitation of Chemical and Physical Properties of Main-group Element Compounds based on Flexibility for High Coordination (Joint Research)"

Yoshiyuki Nagai

(Director, Center of Research Network for Infectious Diseases)
For "Elucidation of the Molecular Basis of Paramyxovirus Pathogenicity and Generation of a Novel Class of Expression Vector"

Medal with Purple Ribbon

The Medal with Purple Ribbon is a medal of honor awarded by the Japanese government to individuals who have contributed to academic and artistic developments, improvements, and accomplishments.

Yoshihide Hayashizaki

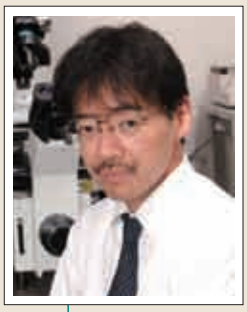
(Project Director, Genomic Sciences Center)
For "Development of large-scale gene analyses of higher life forms and a standard international platform for life sciences"

Satoshi Kawata

(Chief Scientist, Discovery Research Institute)
For "Outstanding contribution to the advancement of science and technology"

MEXT commendations for achievements in science and technology

Prize for Science and Technology in the Development Category



Atsushi Miyawaki

Atsushi Miyawaki
(Group Director, Brain Science Institute)

Satoshi Karasawa
(Visiting Technician)
For "Development of fluorescent protein for application in bioimaging technology"

Satoshi Karasawa
Keiji Tanaka
Maki Kawai
Zhaomin Hou
(From left)

Prize for Science and Technology in the Research Category

Maki Kawai
(Chief Scientist, Discovery Research Institute)
For "Research on the chemical reaction resulting from the adsorption of a single molecule on a solid surface"

Zhaomin Hou
(Chief Scientist, Discovery Research Institute)
For "Research on the development of high-performance rare earth polymerization catalysts"

Keiji Tanaka
(Deputy Director, Brain Scientist Institute)
For "Research on the brain's mechanisms for looking at and recognizing objects"

Strengthening scientific governance

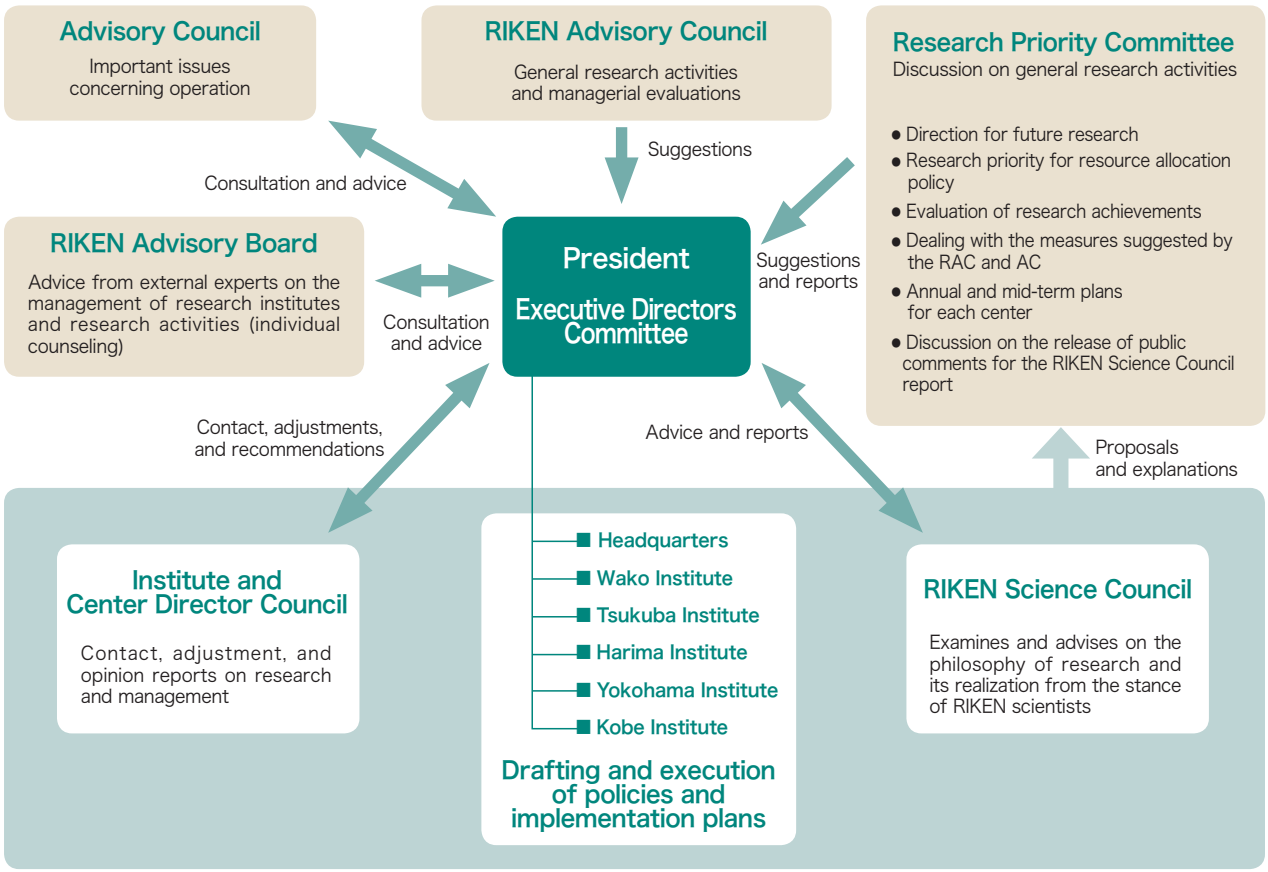
The RIKEN Advisory Council (RAC) is an advisory to and evaluation body for the President that is composed of external experts. On June 2004, the 5th RAC meeting was held for the first time since RIKEN became an Independent Administrative Institution. In the meeting, the council recommended that RIKEN practice scientific governance management and strengthen the roles of the President. The advisory functions of the President have since been strengthened.

The organization of RAC, given in the chart below, is composed of world-famous scientists from various research fields of domestic and international repute as well as people with managerial experience in research institutes. This organization provides suggestions on both general research activities and the management of the research institutes at RIKEN.

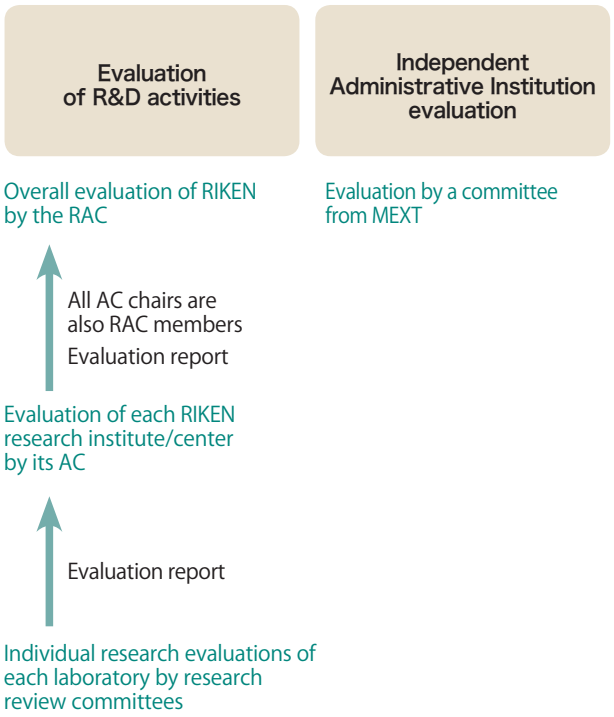
The Research Priority Committee is also composed of experts from both within and outside of Japan and it discusses the overall direction of research activities for RIKEN with a view toward the future. This committee deals with general research activities such as the prioritizing of research subjects and areas that are deemed the most important, the systems necessary for carrying out research, and resource allocation.

The Institute and Center Director Committee provides a forum where a board of the members and center directors who are responsible for the research at RIKEN exchange opinions and share common knowledge of the research and management at RIKEN.

The Advisory Council (AC) offers advice on important issues concerning the operation of RIKEN. The RIKEN Advisory Board, experts from inside and outside Japan, provides council on the management of the research institutes and research activities. Moreover, the RIKEN Science Council consists of officials chosen from the excellent scientists who carry out research activities over the broad fields outlined by RIKEN. The objective of the RIKEN Science Council is to examine suggestions made on the research fields that should be studied and the policies required for promoting research with a long-term yet broad perspective from the stance of scientists and to advise the President.



Evaluation at RIKEN



Overall evaluation of RIKEN

Established in 1993, the RIKEN Advisory Council (RAC) is an advisory body for the whole of RIKEN. The council comprises distinguished members from the national and international scientific and academic communities. RAC conducts thorough reviews of RIKEN's research and management activities and advises the President accordingly.

Evaluation of research institutes and centers

Each institute and center within RIKEN has its own advisory council (AC), which observes and assesses its research activities. International experts from the relevant areas of research are invited to sit on these councils.

Evaluation of research at the laboratory level

Research groups and laboratories are assessed independently by panels of external experts.

Governmental evaluation

A MEXT committee evaluates the extent to which RIKEN has met its mid-term objectives.

The report of the 6th RIKEN Advisory Council: "RIKEN: Leading Japanese Science to Global Pre-eminence"

RAC serves as an external advisory body and evaluates RIKEN's scientific and administrative activities for the President. The RAC is composed of highly influential and successful people from outside RIKEN. The 6th RAC meeting was held in June 2006. In the report of that meeting, "RIKEN: Leading Japanese Science to Global Pre-eminence" (available on the RIKEN website at http://www.riken.jp/engn/r-world/info/report/rac/pdf/ 6report.pdf), RIKEN was praised highly for having taken its place among the most prestigious international scientific research organizations. The organizations cited in the report include the National Institutes of Health (USA), the Weizmann Institute (Israel), the Max-Planck Society (Germany), the British Medical Research Council, and the French national research organizations CNRS and INSERM. Furthermore, the report analyzes RIKEN's management style and praised its current management initiatives and reforms, stating; "The President has established a strong system of advisory committees and a transparent, broadly-based governance regime that balances 'top-down' and 'bottom-up' management."

For further development of the organization, and in order to play a leading role in the international scientific community, RAC recommended that RIKEN strengthen its recruiting efforts by seeking talented personnel from around the world, create a strong international RIKEN brand, increase its international visibility, and cultivate scientific relationships with other countries in Asia. Additionally, with regard to RIKEN's role in providing scientific infrastructure, it recommended that RIKEN become "a source of innovative science," and that its relationships with universities and other research institutions be enhanced.

RIKEN has taken those suggestions very sincerely and reflected them in its second mid-term plan, which commenced in 2008. In addition, the 7th RAC is to be held on April 2009.

Endeavoring to diversify funding

The government remains RIKEN's primary financial supporter

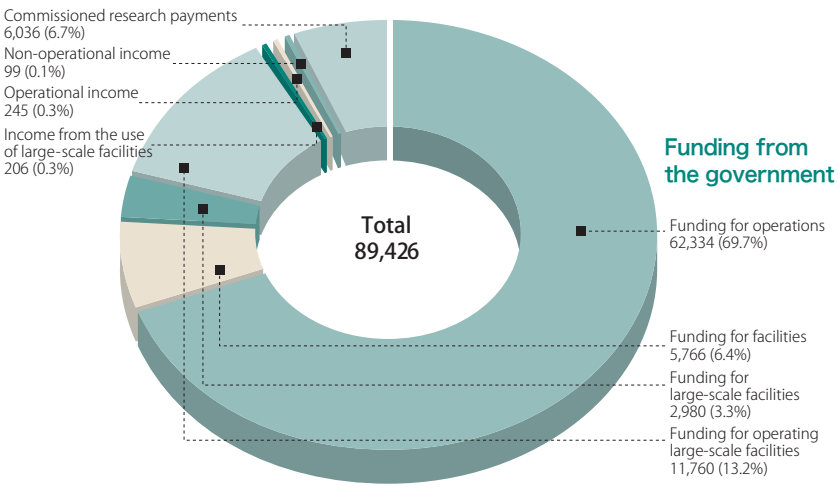
Like other Independent Administrative Institutions, RIKEN is responsible for deciding how to distribute the funds it receives from the government. While the government does not impose requirements on how its funds are used at RIKEN, it does monitor and evaluate spending closely.

The subsidies for the facilities that RIKEN receives from the government can only be used for acquiring tangible assets, such as for the purchase of land or for constructing buildings. Costs for the maintenance and operation of SPring-8 and the Next-Generation Supercomputer R&D Center are shared with the government under a law related to the use of such advanced facilities for the benefit of the public. RIKEN also works hard to obtain funding from other sources to reduce its dependency on government subsidies. These other types of funding include the following:

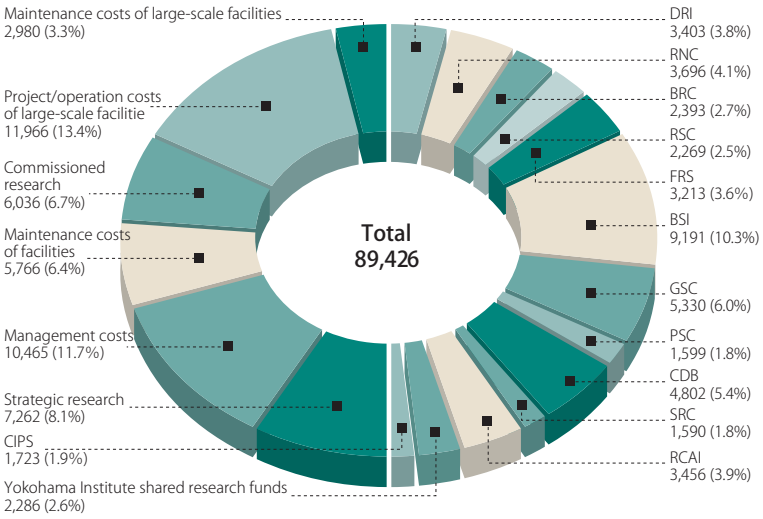
1. Operational income earned through licensing, patent royalties, or through the distribution of research materials
2. Non-operational income from real estate, rental income, and earned interest
3. Payment for research that RIKEN is commissioned to conduct
4. Income from the use of large-scale facilities: Income from the use of SPring-8

Projected 2007 budget

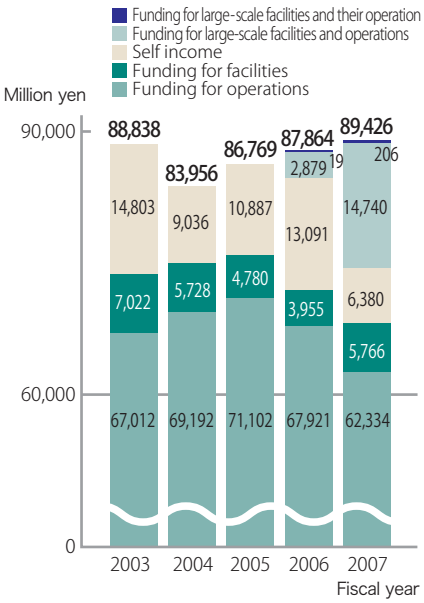
Income (unit: million yen)



Expenditure (unit: million yen)



Recent budgets (initial budgets)



External funds

RIKEN also acquired funds from various government bodies, including MEXT, as well as public and private organizations in fiscal 2007.

Acquisition of external funds

Category	Description		FY2005 million yen	FY2005 cases	FY2006 million yen	FY2006 cases	FY2007 million yen	FY2007 cases
1. Competitive funds	Grants-in-aid for Scientific Research		2,538	484	2,634	574	3,266	626
	Grants-in-aid for Scientific Research (Ministry of Health, Labour and Welfare and Ministry of Environment)		133	4	38	2	157	4
	Special Coordination Funds for the Promotion of Science and Technology		417	8	328	6	184	4
	Projects funded by organizations that fund science and technology		1,318	64	1,228	65	1,225	79
	Basic Research Programs (Japan Science and Technology Agency)		556	2	544	4	2,213	18
	Other publicly supported projects		277	14	354	18	439	22
Sub-total			5,239	576	5,126	669	7,484	753
2. Non-competitive funds	Commission	Government-commissioned research	9,488	27	10,136	39	4,337	35
		Government-related commissioned research	263	28	261	30	330	42
	Grants	Government grants	76	13	90	15	118	22
		Private grants	51	36	115	57	97	59
	Collaborative research	Contributions	127	20	267	19	222	22
Sub-total			10,006	124	10,870	160	5,104	180
Total			**15,245**	**700**	**15,996**	**829**	**12,589**	**933**

Acquisition of external funds, grouped by center

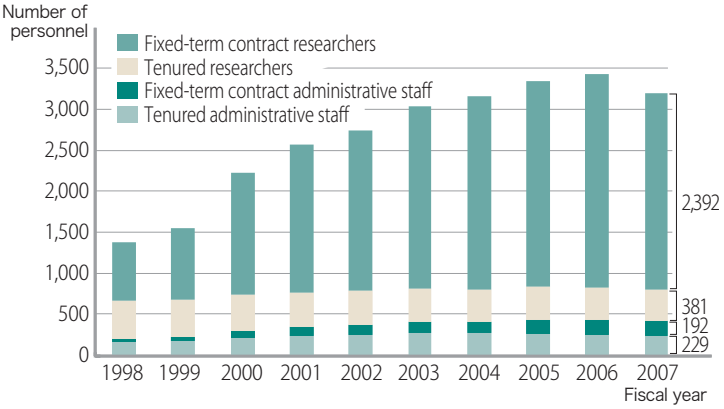
Center/Institute		FY2005 million yen	FY2005 cases	FY2006 million yen	FY2006 cases	FY2007 million yen	FY2007 cases
Wako Institute	Discovery Research Institute (DRI)	2,302	245	2,391	261	2,531	274
	Frontier Research System (FRS)	703	48	955	62	573	72
	Brain Science Institute (BSI)	579	122	792	153	1,015	192
	Center for Intellectual Property Strategies (CIPS)	25	7	50	6	26	8
	Nishina Center for Accelerator-Based Science (RNC)	0	0	97	19	499	34
	Next-Generation Supercomputer R&D Center (NSC)	0	0	287	3	1,237	3
	Others	243	23	0	0	0	0
Sub-total		3,852	445	4,573	504	5,881	583
Tsukuba Institute	BioResource Center (BRC)	131	28	147	27	199	30
Harima Institute	RIKEN SPring-8 Center (RSC)	2,043	25	1,896	37	631	40
Yokohama Institute	Genomic Sciences Center (GSC)	5,792	35	5,476	51	1,829	53
	Plant Science Center (PSC)	200	27	486	47	387	53
	SNP Research Center (SRC)	1,730	12	1,616	13	1,445	19
	Research Center for Allergy and Immunology (RCAI)	488	65	453	74	407	69
	Center of Research Network for Infectious Diseases (CRNID)	170	1	293	1	270	1
Sub total		8,380	140	8,323	186	4,337	195
Kobe Institute	Center for Developmental Biology (CDB)	839	62	1,058	75	987	75
	Molecular Imaging Research Program (MIRP)	0	0	0	0	554	10
Sub total		839	62	1,058	75	1,540	85
Total		**15,245**	**700**	**15,996**	**829**	**12,589**	**933**

Enabling the best people to achieve the best results

At RIKEN, tenured employees with mandatory retirement age are mostly employed in laboratories headed by Chief Scientists and in administrative departments. Scientists working on fixed-term projects are usually fixed-term contract employees, with one-year renewable contracts.

To stimulate innovative research, a bonus system has been introduced for researchers, and annual salaries are determined based on the original evaluation standard established in each research center. By constructing a transparent, fair, and satisfying employment system, RIKEN is working to forge employment policies that will encourage scientists in their endeavors.

RIKEN personnel



Fixed-term contract researchers

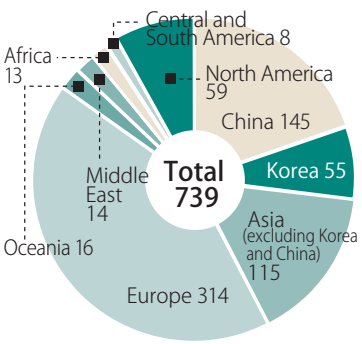
(number of personnel)

	FY2003	FY2004	FY2005	FY2006	FY2007
Discovery Research Institute (DRI)	223	206	212	200	198
Frontier Research System (FRS)	134	175	168	217	172
Nishina Center for Accelerator-Based Science (RNC)	-	-	-	62	65
Brain Science Institute (BSI)	457	499	531	540	494
BioResource Center (BRC)	37	45	53	52	50
SPring-8 Center (RSC)	97	117	93	86	64
Genomic Sciences Center (GSC)	396	390	408	393	314
Plant Science Center (PSC)	92	99	94	134	119
SNP Research Center (SRC)	131	131	115	115	108
Research Center for Allergy and Immunology (RCAI)	163	177	238	229	192
Center for Developmental Biology (CDB)	269	293	308	318	307
Center for Intellectual Property Strategies (CIPS)	-	-	51	68	61
Molecular Imaging Research Program (MIRP)	-	-	-	-	38
Next-Generation Supercomputer R&D Center (NSC)	-	-	3	12	14
XFEL Project, Head Office (XFEL)	-	-	-	6	22
Other	231	218	233	174	174

International diversity

International cooperation is a cornerstone of scientific research, and RIKEN employs many researchers from abroad. Various services are provided to help them and their families adjust to living and working in Japan. Foreign employees receive a handbook called "Life in RIKEN" and a monthly English-language newsletter called ICO News, and English-speaking staff are available in the ICO Room and other offices.

Foreign researchers at RIKEN by area of origin (includes visiting researchers)



Foreign researchers by center/institute (includes visiting researchers)

Center/program	Number of personnel	Center/program	Number of personnel
DRI	140	SRC	15
FRS	90	RCAI	22
RNC	75	CDB	41
BSI	201	CIPS	20
BRC	8	MIRP	4
RSC	36	CSRP *1	3
GSC	48	XFEL	4
PSC	19	IRU *2	13
		Total	**739**

*1 : Computational Science Research Program
*2 : Initiative Research Unit System

New salary system

For Japanese science and technology to advance, RIKEN believes that an appropriate degree of mobility is necessary so that scientists can acquire experience in a wide range of work settings. RIKEN also believes that appropriate remuneration for outstanding achievements is one way to motivate and encourage young scientists.

With these objectives in mind, a new annual salary system was introduced for Chief Scientists in fiscal 2005. It includes a retirement package designed to encourage mobility, and incentive bonuses for outstanding achievements. As this system is more widely applied at RIKEN and other organizations, we hope that it will stimulate greater mobility among young Japanese scientists, making them more internationally competitive and raising the standards of science and technology in Japan.

Fostering the development of young researchers

■ Junior Research Associate Program

The Junior Research Associate (JRA) program employs young doctoral candidates to work at RIKEN laboratories as part-time staff. The intent of the program is to foster the next generation of researchers. The JRA is expected to complete his or her doctoral degree within the contract term.

Contract term: one year
(renewable subject to evaluation up to a maximum of three years)
Total number of JRAs in FY2007: 135

■ Special Postdoctoral Researcher Program

RIKEN's program for Special Postdoctoral Researchers (SPR) was instituted in fiscal 1989 to provide young and creative scientists with the opportunity to be involved in autonomous and independent research. Candidates must possess natural sciences or equivalent research capability, and must independently and responsibly pursue a research topic of their own choosing at RIKEN.

Contract term: one year
(renewable subject to evaluation up to a maximum of three years)
Total number of SPRs in FY2007: 177

■ Initiative Research Unit Program

The purpose of this new program is to recruit young, creative scientists and give them the opportunity to pursue independent research to open up hitherto unexplored fields. Initiative Research Scientists are selected based on the originality of their research and the validity and feasibility of their proposals. They serve as the leaders of Initiative Research Units, which conduct independent research. Beginning in fiscal 2007, RIKEN is recruiting Initiative Research Scientists internationally, especially in fields we consider to be strategically important.

Beginning in fiscal 2008, the attempt will be made to improve the quality of the young researchers that supervise units and their effective operations at the Advanced Science Institute (ASI), which was established as a result of merging FRS and DRI. As of March 2008, there are eight active units.

Contract term: one year
(renewable subject to evaluation up to a maximum of five years)

- Kishi Initiative Research Unit
  Investigating ubiquitin regulation of the cell cycle
- Nishii Initiative Research Unit
  Performing molecular and genetic analysis of embryo morphogenesis in Volvox
- Iwawaki Initiative Research Unit
  Investigating ER stress and its roles in vivo
- Nakagawa Initiative Research Unit
  Examining the molecular mechanisms that control cell behavior in the central nervous system
- Manabe Initiative Research Unit
  Developing a new catalytic system for novel organic synthesis
- Okamoto Initiative Research Unit
  Designing functional biopolymers on an atomic scale using organic synthesis
- Miyagishima Initiative Research Unit
  Identifying and characterizing novel organelle division proteins (in chloroplasts and mitochondria) that are contributed by the eukaryotic host
- Song Initiative Research Unit
  Atomic resolution coherent X-ray diffraction imaging by utilizing the X-ray Free Electron Lazer (XFEL)

■ Sponsored laboratories

RIKEN uses only corporate and other private funds. As of March 2007, the Abe Laboratory is studying physiologically active substances produced by hornets.

To build stronger bonds between RIKEN and industry, RIKEN has created the Sponsored Laboratory Program, whereby an invited scientist can establish a laboratory at RIKEN using only corporate and other private funds.

Sponsored Laboratory: Abe Laboratory
(Studied the physiologically active substances produced by hornets. Completed in September 2007.)

Communicating with the scientific community and the general public

The publication of papers and oral presentations are important ways of conveying RIKEN's activities to the international scientific community. For particularly noteworthy achievements, RIKEN holds press conferences to get the news to as wide an audience as possible. RIKEN Symposiums provide a forum for research activities that are of special interest in academic and industrial circles, and give RIKEN scientists the opportunity to discuss their work with as many people as possible. The Research Ethics Committee meets with well-informed members of the community to solicit opinions and exchange ideas on the advancement of science in general. RIKEN also opens up it campuses to the public on open days, and hosts a variety of scientific lectures and other activities to encourage greater understanding of its science and technology.


RIKEN Gallery, Wako

Research presentations in FY2007

Center/ Institute	Original papers published		Articles in journals		Oral presentations		Total
	English	Japanese	English	Japanese	Overseas	In Japan	
Discovery Research Institute (DRI)	526	18	43	147	580	1,408	**2,722**
Frontier Research System (FRS)	222	103	19	41	209	358	**952**
Nishina Center for Accelerator-Based Science (RNC)	131	8	3	14	105	139	**400**
Brain Science Institute (BSI)	374	29	48	134	511	490	**1,586**
BioResource Center (BRC)	58	3	4	26	39	116	**246**
SPring-8 Center (RSC)	139	2	29	33	108	310	**621**
Genomic Sciences Center (GSC)	138	3	15	49	165	392	**762**
Plant Science Center (PSC)	78	2	12	20	133	225	**470**
SNP Research Center (SRC)	26	0	4	20	27	67	**144**
Research Center for Allergy and Immunology (RCAI)	84	0	3	28	61	144	**320**
Center for Developmental Biology (CDB)	99	3	17	32	111	168	**430**
Center for Intellectual Property Strategies (CIPS)	17	15	5	20	51	79	**187**
Others	7	0	7	28	21	166	**229**
Total	**1,899**	**186**	**209**	**592**	**2,121**	**4,062**	**9,069**

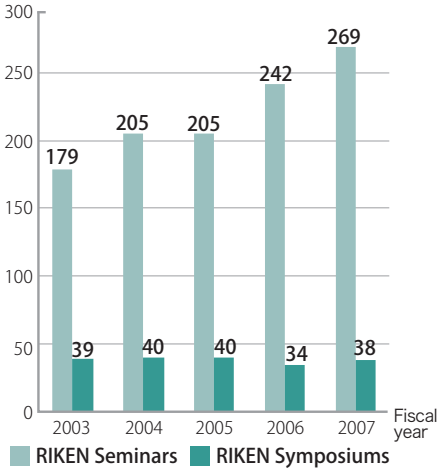
Articles do not include the original papers that have been published.

Data for citations (January 1998 to February 2008)

Fields	Total number of citations	Number of citations per paper	Number of citations per paper within Japan
Biology and Biochemistry	39,956	17.72	12.90
Physics	41,386	9.06	7.42
Molecular Biology and Genetics	46,773	29.07	20.82
Chemistry	19,412	9.27	9.15
Neuroscience and Behavior	19,635	20.33	12.71
Plant and Animal Science	18,370	22.40	6.22
Clinical Medicine	12,110	16.19	9.17
Immunology	9,919	41.68	20.23
Microbiology	5,262	11.54	10.57
Engineering	5,176	4.57	3.18
Materials Science	2,521	6.78	5.33

Source: Thomson Reuters (Essential Science Indicators ™)

RIKEN Seminars and Symposiums



Press release

In fiscal 2007, RIKEN made 99 research related press releases (including ones for RIKEN-initiated joint research with other organizations) and 18 press releases regarding other matters. Additionally, there were 28 press releases related to joint research initiated by other organizations, and reference materials were distributed on 37 occasions.

"Nishina Zao" created at RNC (left)
(Announced on October 31, 2007)

Number of press releases initiated by RIKEN

Enhancing RIKEN's public image

Open day visitors

(number of visitors)

		FY2006	FY2007	
Wako Institute		6,664	Apr 21	6,464
Tsukuba Institute	General Open Day	622	Apr 18	355
	Special Open Day	481	Apr 21	569
Kobe Institute		1,010	Apr 21	1,227
Harima Institute		2,898	Apr 22	3,449
Yokohama Institute		1,644	June 23	1,820
Bio-Mimetic Control Research Center (Nagoya)		61	Aug 25	731
Terahertz-Wave Research Program (Sendai)		583	Oct 20	47
Total		13,963		14,662

Miniature SL running inside the Wako Institute
(With the cooperation of the Japan Miniature Railway Club (JMRC))

RIKEN FY2007 Science Lectures

Theme: **Immunity opens up the future**
Date: February 2, 2008 Venue: Marunouchi Building Hall, Tokyo Audience: 435
Lectures: **"Mice with humanized immune systems are the foundation of a medical revolution"**
Fumihiko Ishikawa (Unit Leader, RCAI)

"The pursuit of unimolecule and solving the mystery of immunity"
Takashi Saito (Deputy Director, RCAI)

"Can allergies be overcome?"
Masaru Taniguchi (Director, RCAI)

"Antibody therapy for autoimmune diseases"
Tadamitsu Kishimoto
(Visiting Professor, Graduate School of Frontier Biosciences, Osaka University)

Full house

Research Ethics Committees

Researches targeting humans include investigations with not only human subjects but also blood and cells collected from humans and information such as the medical records of specific patients. With recent advances in life sciences research, RIKEN performs a considerable amount of research targeting humans.

Research Ethics Committees have been established at four RIKEN institutes (Wako Institute, Tsukuba Institute, Yokohama Institute, and Kobe Institute) to review each research subject in terms of research ethics and scientific pertinence.

In order to ensure objectivity, RIKEN invites a well-informed person from external organizations to be a member of the committees. Moreover, RIKEN attempts to maintain transparency in the committee discussions through measures such as disclosures of all committee review summaries on our websites.

Institute	Number of committee meetings held	Total number of cases reviewed
Wako	20	77
Tsukuba	4	12
Yokohama	16	122
Kobe	3	11

(fiscal 2007)

Working to make RIKEN that is useful to the world

On April 1, 2005, the Center for Intellectual Property Strategies (CIPS) was established for the purpose of making RIKEN's research results, its intellectual property, more readily available to industry and society as a whole, in line with President Noyori's call for making RIKEN useful to the world.

CIPS is responsible for the licensing of intellectual property produced through research activities, collaboration with industry through joint research, and the acquisition of external and competitive funding. Through these functions, CIPS acts as a gateway between RIKEN and the outside world for intellectual property matters. In addition to this, there are three research projects directly under the auspices of CIPS to assist industry with technology transfer.

1. Acquiring patents

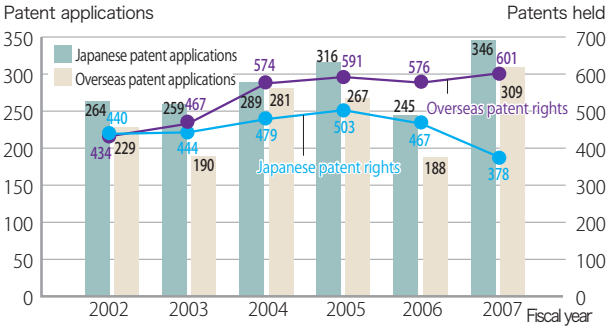
RIKEN works with its researchers to identify patentable intellectual property and provides advice on patenting inventions. It also holds patent seminars and provides instruction on inventions and intellectual property tailored to specific fields of science and technology and projects being conducted at RIKEN. These efforts have been rewarded by increased awareness of both intellectual property issues and the patent application process, and the number of patent applications being made from all RIKEN campuses has risen.

Overseas patent applications: The possibilities of applying in other nations for inventions for which Japanese applications have already been completed are also thoroughly investigated.

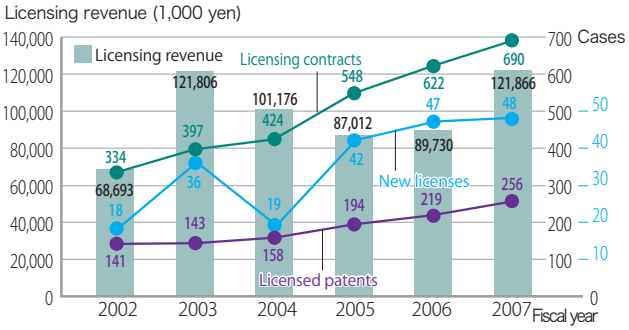
Patent rights: The licensability of patent rights possessed by RIKEN or its scientists or collaborators are also regularly checked and verified to efficiently manage them as necessary.

Applications filed in FY2007: 655 patents, 4 plant breeders' rights
(in FY2006: 433 patents, 2 trademarks)

Patent applications and registrations



Patent income, licenses and license contracts



2. Technology transfer for practical applications

Collaboration Center with Industry

The Collaboration Center with Industry is a completely new collaborative model established in response to various collaborative issues that include research support and technology deployment, which are not dealt with in simple joint research. RIKEN and a company enter into a contract based on a proposal made by the company and a center is established within RIKEN with the name of the company attached as the prefix. The Collaboration Center with Industry is a program for mutual collaboration on various themes and has a broad range of objectives, which include fostering new fields and nurturing talented personnel.

The system was introduced in February 2007, and a total of three Collaboration Centers were established in fiscal 2007.

- RIKEN BSI-Olympus Collaboration Center
- RIKEN-Tokai Rubber Industries (TRI) Collaboration Center for Human-Interactive Robot Research
- RIKEN BSI-Toyota Collaboration Center

RIKEN - WAKO Incubation Plaza

In February 2007, RIKEN - WAKO Incubation Plaza was launched within the Wako Campus as a collaboration between RIKEN and Saitama Prefecture, Wako City, and the Organization for Small and Medium Enterprises and Regional Innovation Japan (SMRJ). The purpose of this facility is to conduct RIKEN's research activities and establish partnerships with next-generation venture companies and with small and medium enterprises. Seventeen companies have opened offices and begun to conduct research and development in cooperation with RIKEN.

This facility will strengthen RIKEN's new cooperative ties with municipalities such as Saitama Prefecture and Wako City and other related organizations and carry out technical transfer activities, which can contribute to the industries and economical development of the region.

E-mail newsletter on collaboration with industry

In fiscal 2006, RIKEN launched an email newsletter on its collaboration with industry. The newsletter provides information on new inventions and events related to technology transfer. The main subscribers to this newsletter are companies interested in incorporating technological advances in their products and operations.

Subscribers: 285 companies, 587 personnel

New type of RIKEN venture

Established in October 2007, RIKEN Genesis Co., Ltd., was formed with the objective of promoting RIKEN's SNP genotyping technology and contributing to the medical welfare of citizens. RIKEN Genesis Co., Ltd. is a spin-off formed on the basis of an activity performed at the Yokohama Institute and became the 28th RIKEN venture.

3. Supplying bioresources

Bioresources are collected and maintained at the RIKEN BioResource Center (BRC) in Tsukuba, and recorded in a database to actively promote supply to outside users.

FY2007 (as of March 31, 2008)	
Laboratory animals (mice)	3,172 strains
Laboratory plants (seeds, DNA, cultured cells)	544,235 strains (including clones)
Cell bank	8,167 cell lines
DNA samples	1,605,396 clones
Microorganisms	17,667 strains

4. Research collaboration

In fiscal 2007, RIKEN concluded a strategic cooperative agreement with Peking University to develop research education centered on the Joint Graduate School Program described below and nuclear physics. RIKEN also concluded a cooperative agreement with Kyushu University, Hokkaido University, and Osaka University to promote research on molecular life sciences. Riken cooperates with Japanese and overseas research institutions as well as with various industrial, academic, and governmental institutions.

Joint Graduate School Programs

It has always been RIKEN's policy to promote collaborative relationships with universities by accepting university students into its laboratories as trainees. This policy was expanded in 1989 with the launch of a joint RIKEN-Saitama University graduate program, the first time such a program was introduced in Japan. As of fiscal 2006, RIKEN has joint programs with the 24 universities listed below.

Saitama University
University of Tsukuba
Tokyo University of Science
Toyo University
Tokyo Institute of Technology
Tohoku University
Rikkyo University
Chiba University
University of Hyogo
Tokyo Denki University
The University of Tokyo
Yokohama City University
Kyushu Institute of Technology
Kobe University
Kyoto University
Nara Institute of Science and Technology
Toho University
Kwansei Gakuin University
Niigata University
Tokyo Medical and Dental University
Nagaoka University of Technology
Osaka University
Hokkaido University
Ritsumeikan University
Tokyo Metropolitan University
Waseda University
Gunma University

International Associate Program

The International Associate Program was established in 2006 in cooperation with Japanese and overseas graduate schools with the objectives of accepting foreign doctoral candidates at RIKEN, contributing to the nurturing of excellent young researchers, and building an international research collaboration network.

At present, RIKEN has concluded agreements with the University of Tokyo Graduate School (Graduate School of Frontier Sciences), Tokyo Medical and Dental University Graduate School, Tokyo Institute of Technology Graduate School, Saitama University Graduate School, Peking University, Xi'an Jiaotong University, Galati University, and Lanzhou University. RIKEN intends to enhance this program.

Asian Joint Graduate School Program

In order to encourage the promotion of science in the wider Asian region, a network was established in 2001 with a number of Asian universities to promote the educational opportunities of doctoral students throughout Asia.

The network consists of cooperative relationships between RIKEN and Pusan National University (S. Korea), Peking University (China), University Sains Malaysia (Malaysia), Kasetsart University (Thailand), Hanoi University of Science (Vietnam), and National Chiao Tung University (Taiwan).

Organizational structure of RIKEN

(as of April 1, 2008)

Senior Advisors

President
Executive Directors

Auditors

President
NOYORI Ryoji

Executive Directors
Kenji Okuma
Shin Ohkouchi
Kenji Takeda
Yoshiharu Doi
Takao Kuramochi

Auditors
Takanobu Hashimoto
Tasaburo Masuda

Headquarters
- Research Priority Committee
- Policy Planning Divison
- Public Relations Office
- General Affairs Division
- Personnel Division
- Finance Division
- Contract Management Division
- Facilities and Utilities Division
- Safety Division
- Auditing and Compliance Office
- Internal Communications and Systems Support Office
- Center for Intellectual Property Strategies
- Advanced Center for Computing and Communication
- Next-Generation Supercomputer R&D Center
- XFEL Project Head Office

Wako Institute
- Advanced Science Institute
- Nishina Center for Accelerator-Based Science
  - Advanced Research Promotion Division
- RIKEN Brain Science Institute
  - Brain Science Promotion Division
- Computational Science Research Program

Tsukuba Institute
- BioResource Center
  - Tsukuba Research Promotion Division
  - Tsukuba Safety Center

Harima Institute
- RIKEN SPring-8 Center
  - Harima Research Promotion Division
  - Harima Safety Center

Yokohama Institute
- Plant Science Center
- Center for Genomic Medicine
- Research Center for Allergy and Immunology
- Omics Science Center
- Systems and Structural Biology Center
- Bioinformatics And Systems Engineering division
- Center of Research Network for Infectious Diseases
  - Yokohama Research Promotion Division
  - Yokohama Safety Center

RIKEN Kobe Institute
- Center for Developmental Biology
- Molecular Imaging Research Program
  - Kobe Research Promotion Division
  - Kobe Safety Center

Executives (as of April 1, 2008)
From left: Tasaburo Masuda, Takao Kuramochi, Kenji Takeda, Kenji Okuma, Ryoji Noyori, Yoshiharu Doi, Shin Ohkouchi, Takanobu Hashimoto

RIKEN facilities

Japan

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Advanced Science Institute
Brain Science Institute
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Fax +81-48-462-4713

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Fax +81-29-836-9109

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Fax +81-791-58-0800

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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 +81-3-5223-6060

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RIKEN-MIT Neuroscience Research Center
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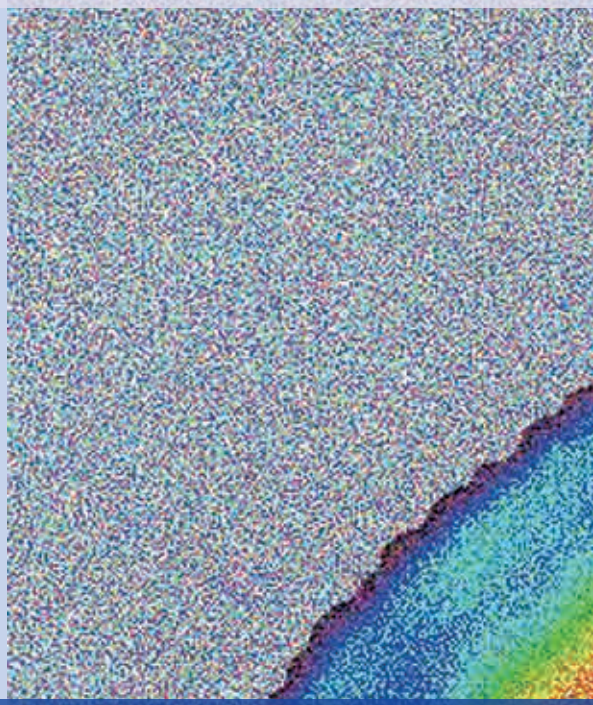

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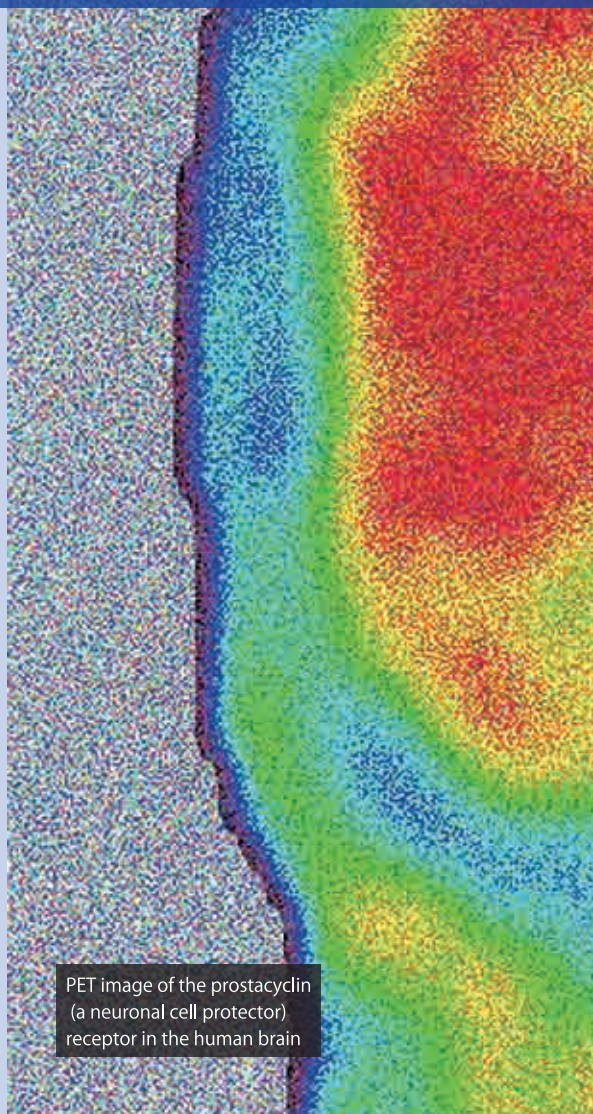
koho@riken.jp



PET image of the prostacyclin (a neuronal cell protector) receptor in the human brain

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