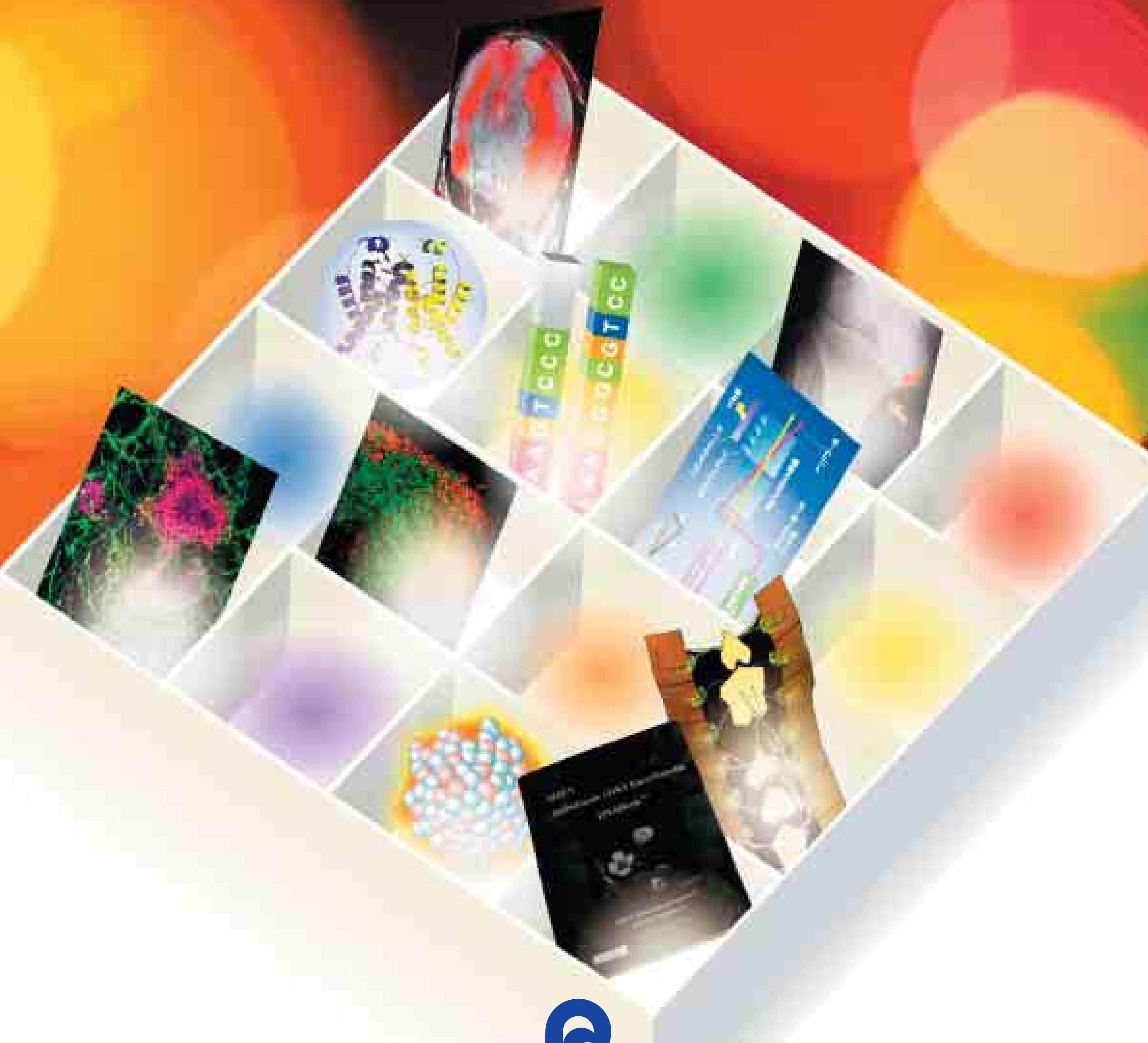
A N N U A L   R E P O R T

RIKEN 2004



RIKEN

http://www.riken.jp/

ANNUAL REPORT

RIKEN2004

Contents

Tradition and renovation
— RIKEN creates brilliance

RIKEN, inaugurated in 1917 as the Institute of Physical and Chemical Research, celebrates its 88th birthday this year. This is beiju, a pinnacle event in Japan that marks longevity.

RIKEN's enduring presence and organizational evolution as a comprehensive research institute are significant testaments to the role it has played in nurturing Japanese advances in natural sciences. Yet, a research organization does not survive in isolation. It thrives only when it accepts its social responsibilities and transforms itself to address the demand that are imposed by an ever changing society. In Japan, we say fueki-ryukou, to express the relationship between constancy and change, that the roots never change. The saying reminds us of the balance between valuable traditions and beneficial modifications. Today's RIKEN is a product of the efforts made by its previous occupants, who clearly understood this and were able to forge an organization that is open, flexible and with a mind towards a promising future.

I inherited RIKEN's leadership in October 2003. I am proud of RIKEN's output, which testifies to the abundance of intelligence and intuition in our researchers. The breadth of the research and the creative advances made are inspiring, and I feel they should be truly appreciated by society as a whole.

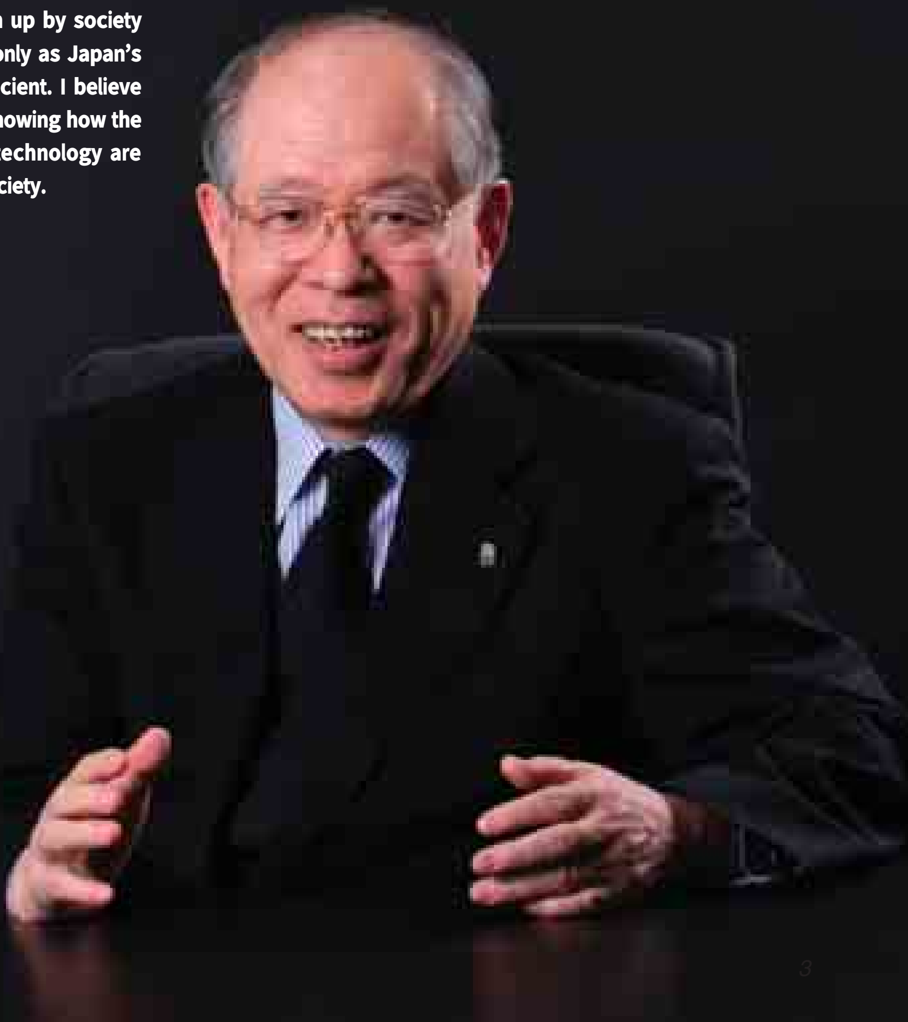
Without question, RIKEN's primary mission is to achieve superb research results that can be taken up by society in one way or another. However, serving only as Japan's flagship research organization is not sufficient. I believe that RIKEN should also be committed to showing how the continued contributions of science and technology are essential to ensure a sustainable global society.

Cultivating interest in science for the younger generations, gaining social acceptability for new technologies and securing a strong financial base are the keys to vitality for the 21st century research community. Without public understanding and support, scientific research will not survive. Therefore, our activities need to garner the highest approval from the broadest of audiences. This means that, for the sake of science, we scientists must become its missionaries and spreading their knowledge throughout the world.

RIKEN wants to create everlasting brilliance. To achieve this, RIKEN should radiate an intense light and yet also be illuminated in various ways and from various sources. This Institute exists within a broader social context that enlightens others. This illuminating process reveals RIKEN to many people who in turn cast light over us.

This annual report has been prepared to bring to light RIKEN's diverse activities and attract increasing interest. I sincerely hope that a closer inspection of our research efforts deepens your appreciation of the beauty and wonder of science while revealing its value to society.

June, 2005
Ryoji Noyori, President



An unrivaled research institute

Japan's only comprehensive approach to investigating the natural sciences

With more than 80 years of research in the natural sciences, RIKEN is unique in Japan. It conducts cutting edge research covering a diverse range of fields that include physics, chemistry, engineering, biology and medical science. Research spans basic investigations to practical applications. RIKEN actively disseminates its scientific and technological findings, encourages research collaborations between research institutes, and facilitates the transfer of technology into industry.

Objectives: To conduct thorough research investigations that extend the boundaries of science and technology (excluding only human and social sciences).

Mission: To produce internationally recognized results that fully exploit all the benefits of RIKEN's research environment, and to maximize the social benefits of those results. This will be possible by pioneering new fields for research and undertaking research in important areas based on social need.

RIKEN's distinguished scientists

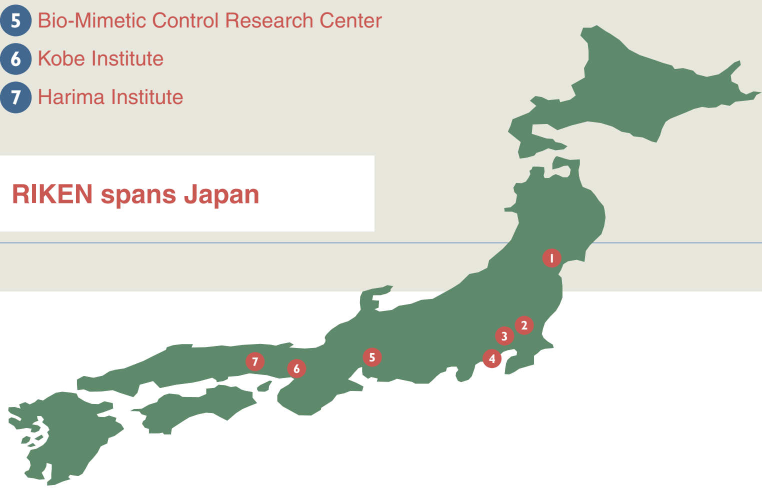
Hantaro Nagaoka
Physicist
With his Saturnian model of an atom, Nagaoka said that atoms look like the planet, with rings of electrons circling a positively charged core. He was also the architect of Japan's physical sciences and the Director of the Physics Division for the RIKEN Foundation.

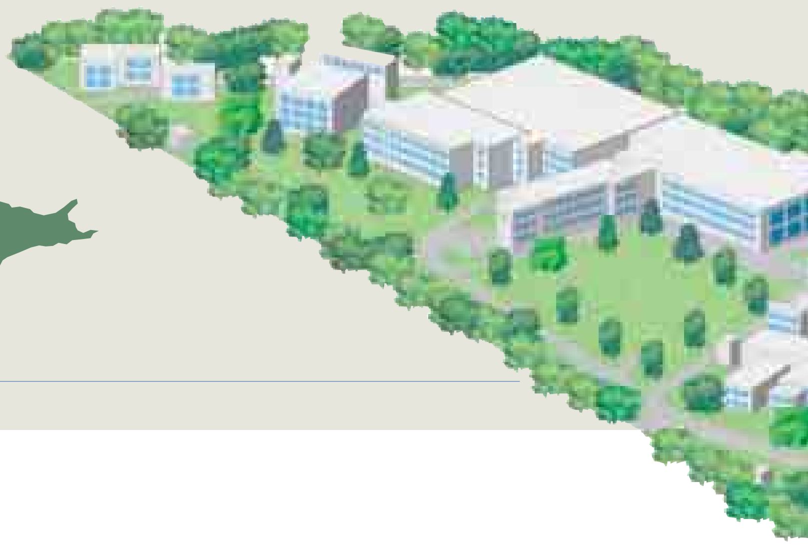
Kotaro Honda
Magnetic physicist
His investigations in metallurgy and magnetism contributed to raising the international status of Japanese work in these areas. He invented and studied K.S. magnet steel, the world's strongest permanent magnet.

Umetaro Suzuki
Agricultural chemist
The founder of vitamin research in Japan, Suzuki successfully isolated vitamin B1 from rice bran, calling it oryzanin. It was effective in preventing and treating the related vitamin deficiency disease, beriberi. He was also instrumental in inventing and developing other products that were marketed by RIKEN Vitamin and financed much of RIKEN's activities as the RIKEN Foundation.

1. Photodynamics Research Center
2. Tsukuba Institute
3. Wako Institute, RIKEN Headquarters
4. Yokohama Institute
5. Bio-Mimetic Control Research Center
6. Kobe Institute
7. Harima Institute

RIKEN spans Japan





Expectations: For 88 years, RIKEN has sought to extract tangible and intangible goods from its research results. It is expected to sustain its success through continuous self-improvement that maintains RIKEN's leading role and drives scientific and technological innovations. Our tactics include efforts to recruit young, outstanding researchers from across the globe to work in a highly charged, competitive, international and fluid environment that is designed to encourage active research. Increasing collaborations with universities and research institutes within Japan and internationally, and deepening ties with our local communities, will also inspire advanced investigations. Finally, a superior evaluation system of research activities will guide researchers and ensure that their efforts exceed expectations.

History: RIKEN was established in 1917 as a private research foundation in the northwest area of Tokyo. After World War II, it was restructured and renamed the Science Research Institute Ltd. or KAKEN, which become a public corporation, RIKEN, in 1958. In 1967, the main headquarters moved out of Tokyo to its current location in Wako so that it could expand its research activities. With continued expansion of it research activities, other facilities were established in Tsukuba, Harima, Yokohama, Kobe, Sendai, Nagoya, the United Kingdom, and the United States. In the fall of 2003, RIKEN under went another administrative restructuring. It operates now as an Independent Administrative Institution.

Masatoshi Okochi

Scientist and executive

While promoting original, atypical basic research, Okochi sought ways to nurture emerging results into industries, founding the RIKEN Industrial Group (RIKEN Konzern) in the process. He is credited with creating RIKEN's unique environment as a researcher's haven during his term as the RIKEN Foundation's third president.

Yoshio Nishina

Physicist

His Klein-Nishina formula, derived together with Oskar Klein, opened the way to a new physics and his laboratory in RIKEN inspired many scientists by emphasising researcher interaction. His tenure as the President of the Scientific Research Institute Ltd. (KAKEN) was marked by particle physics investigations. The Nishina crater on the moon is named after him.

Shin-ichiro Tomonaga

Theoretical physicist

Tomonaga's RIKEN career started when he joined Nishina's laboratory in 1932. There he determined how a group of the same type of particles interacted. He shared the Nobel Prize in Physics with Richard Feynman and Julian Schwinger for their quantum electrodynamics theory.

Hideki Yukawa

Theoretical physicist

Another alumnus of Nishina's laboratory, Yukawa joined that laboratory in 1940 and later became a RIKEN chief scientist from 1961 to 1965, working on the properties of elementary particles. His prediction of the meson particle existence earned him the Nobel Prize in 1949, making him the first Japanese national to be so decorated.

Highlights in 2004

RIKEN's activities in 2004 are divided into three sections: Research, Organization, and Data & Information, which highlights RIKEN's management practices.

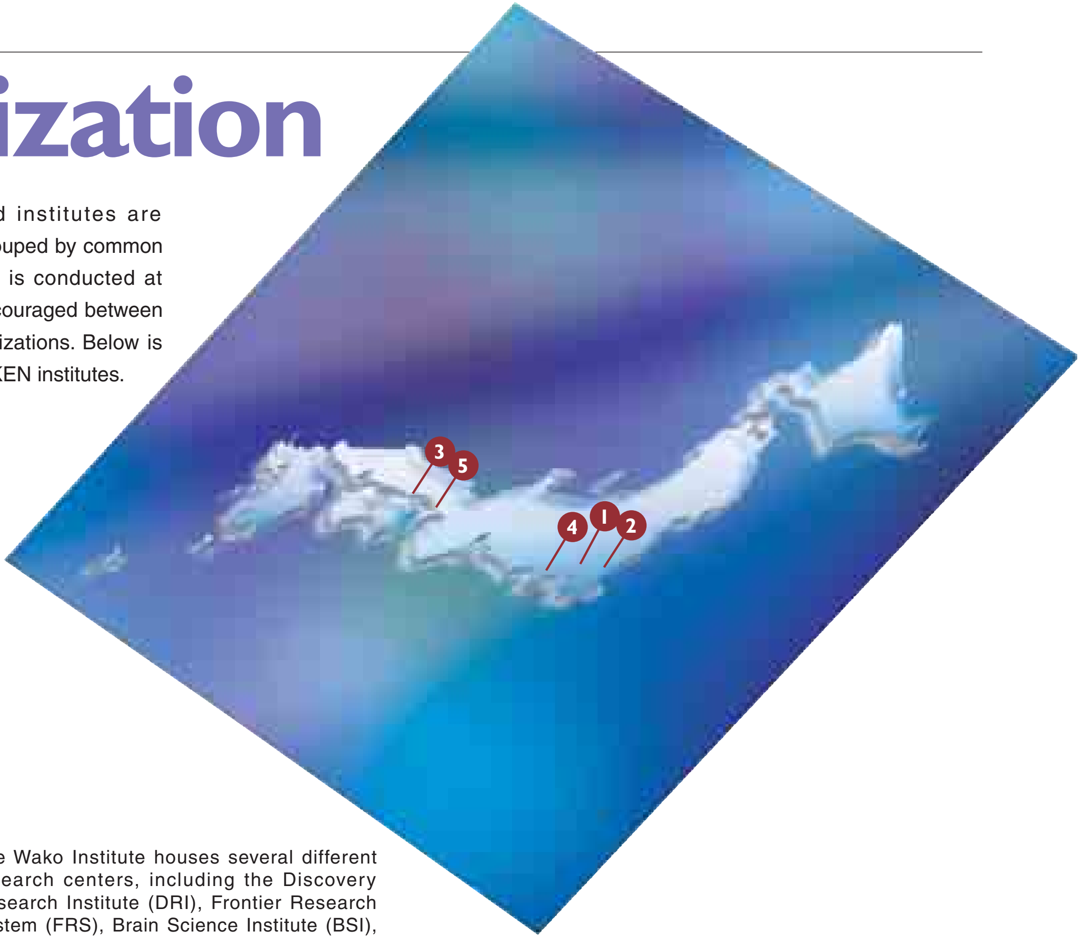
Research

Research, naturally, is the most important aspect of RIKEN. Ten of the most popular findings of 2004 are presented here and described in detail later.

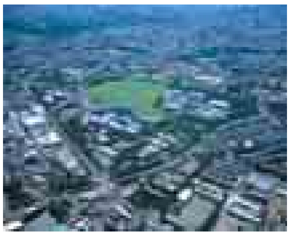
1. RIKEN discovers its first new element
2. MRI's revealing the signs of Alzheimer's disease
3. The 3-D structure of the protein regulating the biological clock revealed
4. Chimpanzees are not humans
5. DNA is the newest bookworm?
6. Creating soft-bodied robots
7. Teraherz lights illuminating a new world
8. A new method to coach ES cells into becoming higher level neurons
9. Development of the world's first artificial lymph nodes
10. Identifying genetic links to osteoarthritis.

Organization

RIKEN's research facilities and institutes are distributed throughout Japan and grouped by common areas of research. Novel research is conducted at each location with collaborations encouraged between other RIKEN and non-RIKEN organizations. Below is simply a short introduction to five RIKEN institutes.



1 Wako Institute



The Wako Institute houses several different research centers, including the Discovery Research Institute (DRI), Frontier Research System (FRS), Brain Science Institute (BSI), Initiative Research Units, and sponsored laboratories. In 2004, element 113 emerged from a long-term research project in DRI and FRS created a new system for research under a new mission. BSI continued to expand international ties with several nations as it continued to pursue a broad range of activities in brain science.

2 Tsukuba Institute

The BioResource Center (BRC) at this institute supports research by preserving and distributing bioresources and developing technologies that support research activities. In the past year, BRC has expanded its available resources and developed a training program to ensure that their resources are used effectively and efficiently.

3 Harima Institute

Spring-8 (Super Photon ring-8 GeV) the largest third generation synchrotron radiation facility in the world is located at the Harima Institute, which incorporates the facility into its research activities. International attention focused on Harima in 2004 with the construction of the X-Ray Free Electron Laser prototype.

4 Yokohama Institute

To promote life science research that can open up new industries, four research centers are grouped together in Yokohama: Genomic Sciences Center (GSC), Plant Science Center (PSC), SNP Research Center (SRC), and the Research Center for Allergy and Immunology (RCAI). The GSC's second phase of activities started in 2004 while PSC and SRC closed it first phase with remarkably, with results that more than justify phase two. With the completion of the new research building, RCAI began operations and set Yokohama's activities into full swing.

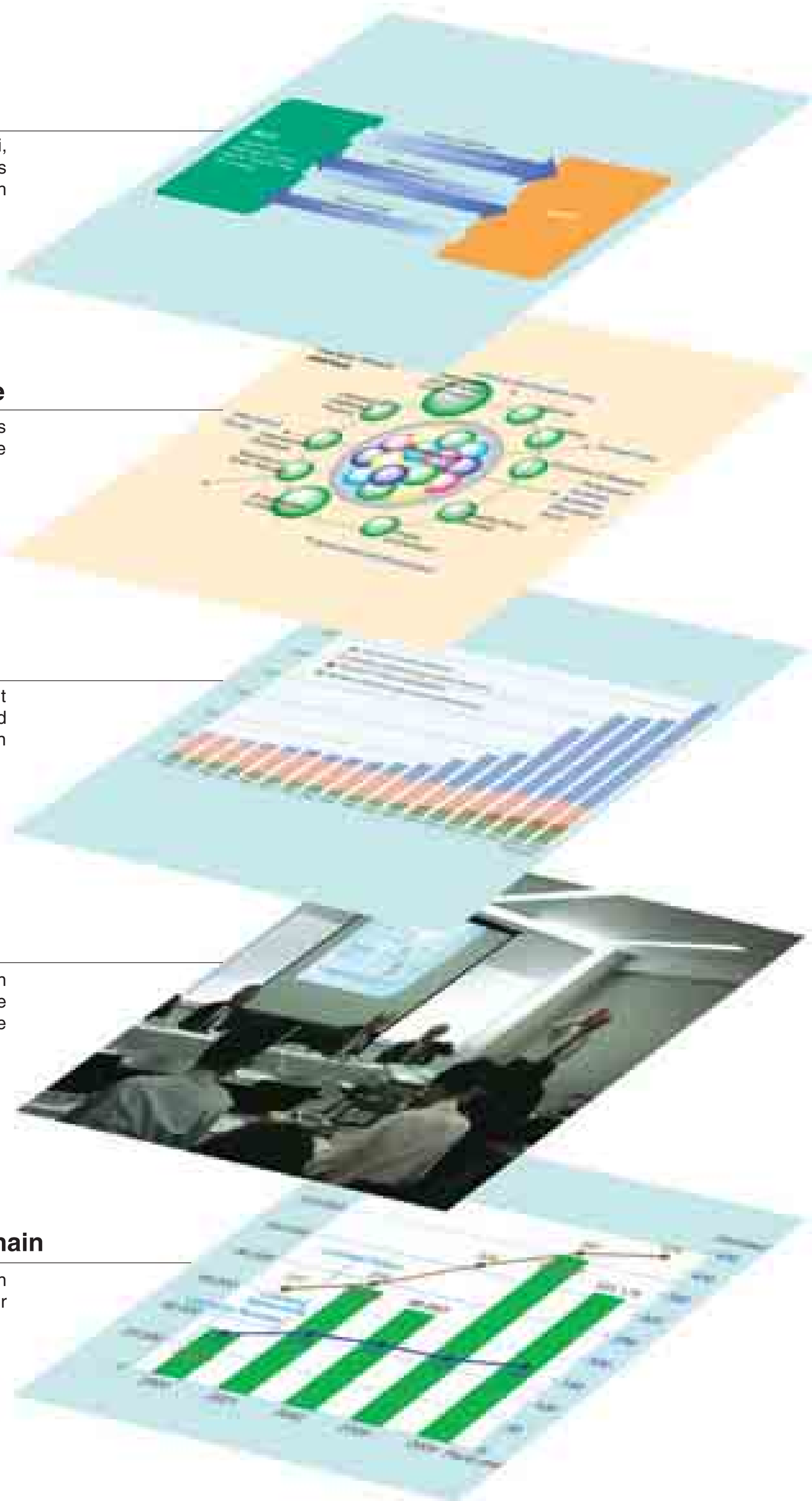
5 Kobe Institute

The Center for Developmental Biology (CDB) at Kobe Institute researches various aspects of developmental biology. 2004 was a good year for CDB. Many research findings were well received internationally and the center earned many rewards for its diverse activities.

Highlights in 2004

Data & Information

In October 2003, RIKEN was restructured and became an Independent Administrative Institution. With this transformation, management practices and activities also evolved. Below is a brief summary of some of the key activities throughout RIKEN to provide some insight into how its management functions to support research.



"Noyori Initiative"

The first president of the new organization, Ryoji Noyori, introduced the Noyori Initiative. This document outlines RIKEN's goals and highlights some the tactics by which those goals will be attained.

Strengthening of scientific governance

Upon the RIKEN Advisory Council recommendations in July 2004, RIKEN took measures to improve the performance of RIKEN's scientists.

Personnel

In 2004, RIKEN employed 685 full-time permanent and 1,557 contract staff, including both researcher and administrative personnel, in its effort to establish an optimal system for researcher activities.

Public understanding of science

RIKEN researchers published 1,946 original papers in English and issued 55 press releases based on those results. These results attracted 13,844 people to the RIKEN campuses for RIKEN Open Days.

Transfer of science into the public domain

RIKEN earned 101 million yen from patent revenues in 2004 and will continue to expand our efforts to transfer technology to industry.

RIKEN 2004

Ten major achievements in 2004

Research

Filling a space in the Periodic Table
The first new discovery of an element by Japanese

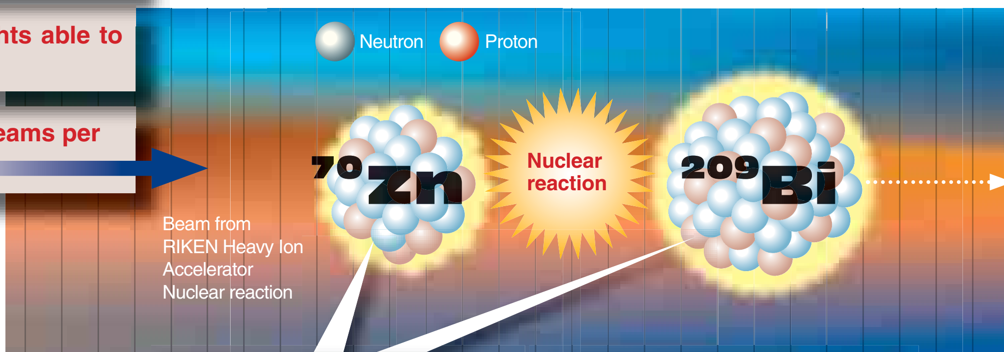
Did you know that there are many spaces in the periodic table starting with hydrogen, helium, …?
The group headed by Senior Research Scientist Kosuke Morita of the Cyclotron Center synthesized the heaviest element: number 113.
This is the first time a Japanese research group has discovered a new element and a Japanese-originated element's name may appear in the periodic table.

La	Ce	Pr	Nd	Pm
57	58	59	60	61

Keywords

1. Some spaces left in the periodic table
2. Search for a super heavy element which does not exist in the natural world
3. Are historical naming rights able to be acquired?
4. Irradiation of 2.5 trillion beams per seconds for 80 days

How a nuclear reaction advances



1 Projectile

Smash the beam of zinc (^{70}Zn) of atomic number 30 and mass number 70 which has been accelerated to one tenth of the light speed by the linear accelerator RILAC, into the target nuclei, bismuth (^{209}Bi) of atomic number 83 and mass number 209.

2 Target nuclei

2.5 trillion nuclei of zinc per second were irradiated to the target. Total irradiation time was 1920 hours, i.e. 80 days. Totally 1700 ten-million billion (1.7 x 10^{19}) zinc nuclei irradiated the target and consequently, one new element was synthesized.

The Voice of Researchers

Kosuke Morita
Discovery Research Institute
Cyclotron Center

Capturing the 2nd and 3rd events of element No. 113, I wish that we could discover a larger element ahead of them.

If we can discover the 2nd event in the same method as we have discovered the 1st event, we can prove with more certainty the existence of the 1st one. Therefore, how many days it may take to discover the 2nd one and, furthermore, when the 3rd one is discovered will show the probability of the emergence. Even though the same method may be employed for each of the experiments, these experiments are very exciting, each representing a new meaning.

Although the same method as was used for No. 113 may also be used in order to synthesize No. 114 ahead of it, it becomes necessary to develop other beams. Since an accelerator facility exists in the Institute and as it is possible to carry out these activities in collaboration with this facility, it is also possible to aim for the next steps. Among the world scientific community, this should be possible with RIKEN only.

Take a look at the spaces in the periodic table!

Atoms are particles of matter consisting of negatively charged electrons revolving around the nuclei, which contains almost the entire volume of atomic mass. The nuclei consist of protons having positive electrical charges and electrically neutral neutrons, and are electrically positive. The atoms show electrical neutrality since the electrons' and protons' electrical charges usually exist in equal proportions.

The number of protons contained in the nuclei is called the atomic number, it is shown from elements arranged in order of atomic number that there is periodicity in the change of the nature of elements.

In the natural world, very few elements heavier than uranium with an atomic number 92 have been discovered. Neptunium, with an atomic number 93, and the subsequent elements were created artificially based on reaction of the nuclei. The periodic table is the result of efforts by many researchers to fill its spaces.

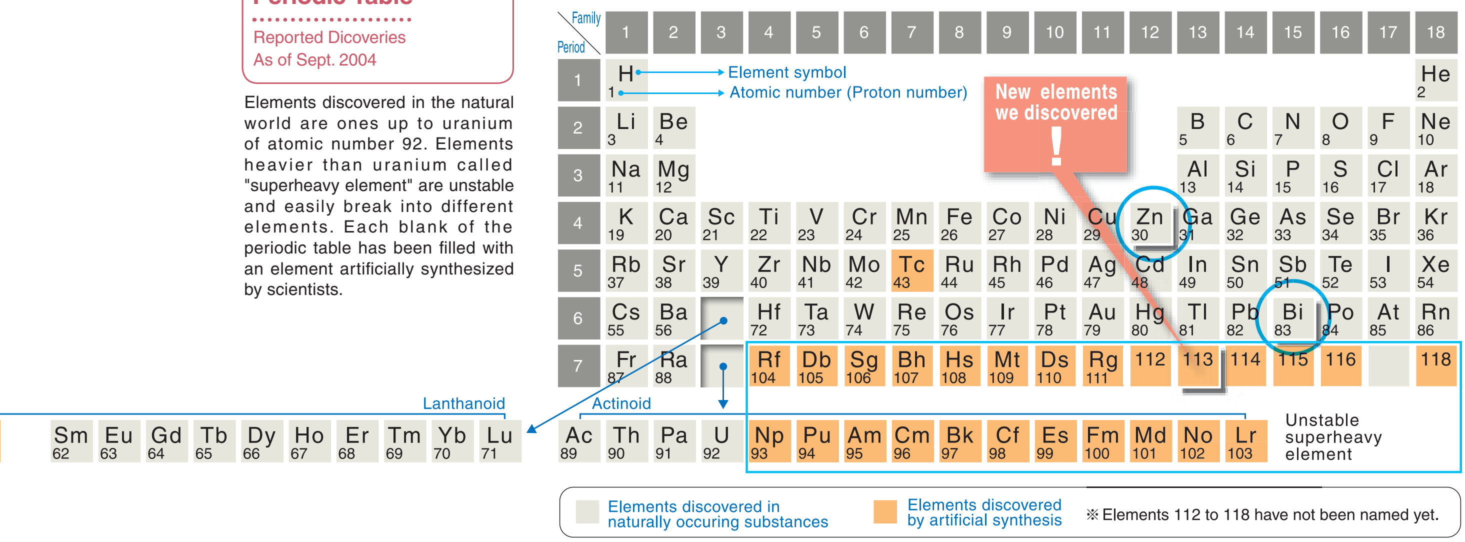
Establishment of a new element with a 0.0003 second life.

The newly synthesized element resulted from irradiating the nuclei of zinc (^{70}Zn) containing 30 protons, with 2.5 trillion beams per second for 80 days in order to

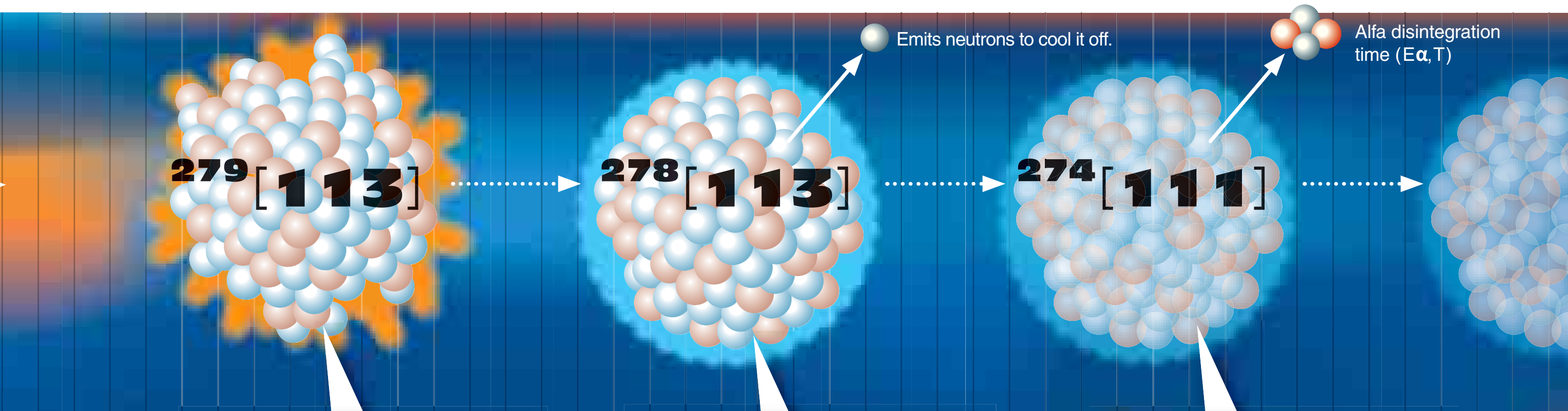
Periodic Table

Reported Dicoveries
As of Sept. 2004

Elements discovered in the natural world are ones up to uranium of atomic number 92. Elements heavier than uranium called "superheavy element" are unstable and easily break into different elements. Each blank of the periodic table has been filled with an element artificially synthesized by scientists.



Natural Science Chronology Prepared with reference to achievements in 2004



3 Compound nucleus in the excited state (high temperature)

Compound nucleus in the excited state (at high temperature) (atomic number 113, mass number 279)

4 Nucleus in the ground state

The nucleus of our interest in the ground state (low-energy state) (atomic number 113, mass number 278) after emitting neutrons to cool off

5 Daughter nuclei of ^{278}[113]

Disintegrations by four alpha decays followed by spontaneous fission. The fourth alpha decay and the spontaneous fission decay were known decays of ^{266}Bh and ^{262}Db. By tracing back three alpha decays we could conclude the first one was that of ^{278}[113].

make the zinc protons run into the nuclei of bismuth (^{209}Bi), a heavy metal element containing 83 protons.

The isotope of the confirmed element with atomic number 113 is expressed as ^{278}[113], which resulted from one neutron jumping out of the nuclei produced when bismuth and zinc were completely fused. Only one atom of ^{278}[113] was observed with a life of only 0.0003 seconds. However, since the entire process of decays of ^{278}[113] (see figure) was observed and determined without contradiction, it was recognized as nuclei of which atomic and mass numbers were determined on an experimental basis for the first time as the isotope with atomic number 113.

RIKEN-original world's highest atomic number

There were two key points that led researchers to success. First, a stable supply of high-intensity beams was available. Using the heavy ion linear accelerator (RILAC), which provides beams of the highest known intensity, together with RIKEN-original units, beams were accelerated up to a level at which super heavy elements (with atomic numbers of 110 or higher) can be produced.

Another point was the subjectivity to detect only the nuclei of our interest with extremely low probability separating them from the huge amount of unwanted particles. To deal with this problem, the group manufactured a gas-filled recoil separator (GARIS), consequently achieving a level 100 times or more than the same types of separator used by other research institutes.

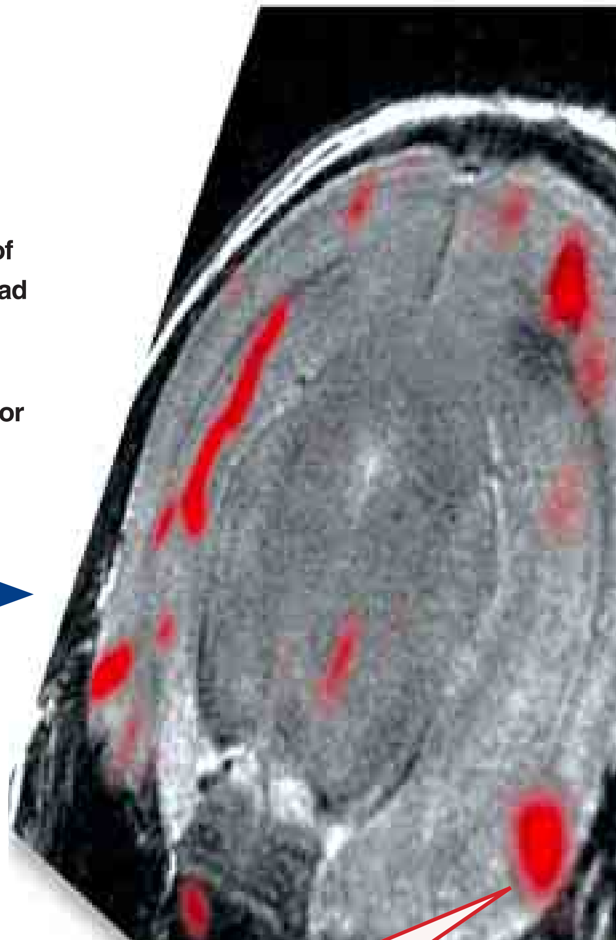
If the newly discovered data is authenticated, the group will be certified as having been the first to discover the element and authorized to suggest a name for the new element. Though 111 types of elements have been named up to today, this is the first time that a Japanese team have discovered a new element. The discovery by the group will leave its footprints in the history of new element discovery in Japan.

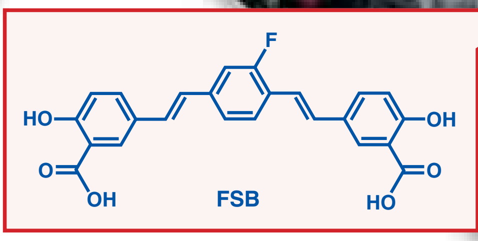
Observation of amyloids in the brain Diagnosis of Alzheimer's disease now enabled

The onset of Alzheimer's disease is triggered by excessive deposition of amyloid-β peptide (Aβ) in the brain. A group headed by Laboratory Head Takaomi C. Saido of the Laboratory for Proteolytic Neuroscience, Brain Science Institute, succeeded detecting amyloid deposition in the brain of a living mouse with Magnetic Resonance Imaging (MRI) for the first time in the world. This method is expected to lead to establishment of presymptomatic diagnosis of Alzheimer's disease.

Keywords

1. Amyloid deposition, the cause of Alzheimer's disease
2. Observation of amyloid plaques in the brain with MRI
3. Synthesis of an MR-compatible compound that binds to amyloid plaques with high affinity
4. Opening the way for a new stage in the study of Alzheimer's disease





^{19}F-containing amyloidophilic compound FSB (Fluoro Styryl Benzene) .

A new compound that binds to "amyloid-β plaques" (a pathological hallmark of Alzheimer's disease) with high affinity and avidity was designed and synthesized. Because ^{19}F nucleus is MR-compatible, it was expected that this compound would allow us to detect amyloid-β plaques *in vivo* (in living animals).

The Voice of Researchers

Takaomi C. Saido
RIKEN Brain Science Institute Laboratory for Proteolytic Neuroscience

Development of preventive medicine for Alzheimer's disease would allow a drastic decrease the number of patients.

Our major aim is to elucidate the pathological mechanism of the disease development and thereby to establish clinical means to prevent and treat Alzheimer's disease.

For this purpose, we are working on a project, in which we search for diagnostic biomarker(s) of the disease using amyloid imaging.

Our approach is that we develop and utilize pathophysiologically relevant mouse model that reconstitutes all the pathological features of Alzheimer's disease. This model would be a "second generation" mouse model which is less artificial than the "first generation" models used worldwide presently.

Detection of amyloid plaques in living animals

Deposition of amyloid-β peptide in the brain upon aging is considered to be the primary cause of Alzheimer's disease. Because formation of amyloid plaques in the brain takes place many years prior to the actual disease onset, non-invasive detection of the plaques *in vivo* would contribute to establishing presymtomatic diagnosis.

For this reason, amyloid imaging has been one of the major strategic target in the Alzheimer research community. PET (positron-emission tomography), which has been most extensively studies for this purpose, has not been quite successful. The advantages of MRI technology include its relatively high resolution, moderate cost-effectiveness, long-term storability of the probes, no requirement of contrast enhancers, and removal of the danger of exposure to radiation.

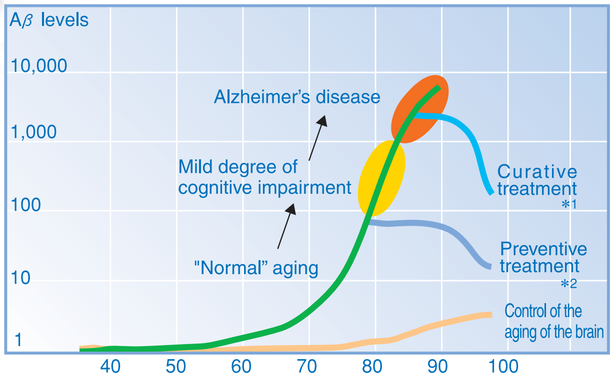
Successful application of MRI to amyloid imaging

Since MRI (magnetic resonance imaging) is safer, more cost-effective and provides higher resolution than PET, Saido Group explored its applicability in a unique way. As previously demonstrated, the ^{1}H MRI that detects general

1 MR images were taken after intravenous administration of FSB to a mouse model of Alzheimer's disease

The red-pseudo colored signals represent the FSB-derived MR images that correspond to amyloid-β plaques. We have also discovered that FSB enhances ^{1}H-derived MR signals in amyloid-β plaques, implying that it may become possible to detect amyloid-β plaques *in vivo* using a resonator for ^{1}H-MRI that is already in use by a number of hospitals.

The quantity of amyloid-β peptide in the brain increases upon aging



*1 At this point, because of the irreversibly progressed neurodegeneration, a complete cure is deemed difficult.

*2 To make preventive medicine possible, it is indispensable to establish presymptomatic diagnosis.

2 The quantity of amyloid-β peptide in the brain increases upon aging

Human brains generally start to accumulate amyloid-β peptide after the age of 40, and the amount increases gradually as the individual ages. The mechanism of this aging-dependent accumulation of amyloid-β peptide is also being studied by Saido Group. The ultimate goal of the research is to reduce the number of Alzheimer patients to 10% and also to control aging by regulating the metabolism of amyloid-β peptide.

hydrogen nucleus does not capture amyloid plaques in a specific manner.

To overcome this problem, FSB, a new compound that contains fluorine (^{19}F), a signal source for MRI, and binds to amyloid with high specificity and avidity, was designed and synthesized (Fig. 1). This strategy has led to specific *in vivo* detection of amyloid plaques by MRI for the first time in the world. Fig. 2 clearly demonstrates that this technology can quantitatively detect amyloid burdens that increase upon aging. Further detailed analyses of the model mice carrying different amyloid burdens indicated that the MR signals correlate with the amyloid burdens in a statistically significant manner.

Presymptomatic diagnosis for preventive medicine

With this new technology, a number of goals which have previously been unattainable have now become possible. For example, it is now possible to continuously observe pathological changes in Alzheimer's disease model mice without sacrificing animals at each time point. This will facilitate discovery of new diagnostic markers. It will also enable the tracing prognosis after a medical treatment over time. If this can be applied to human beings hopefully in the near future, it will be effective not only for the presymptomatic diagnosis of Alzheimer's disease but also for the development of prevention and treatment of the disease by reducing the brain amyloid-β peptide levels. Aside from the above, the Laboratory for Proteolytic Neuroscience has announced success in the development of a gene therapy to control the pathology of Alzheimer's disease using "neprilysin", an enzyme that breaks down amyloid-β peptide. In ways like these, the Laboratory for Proteolytic Neuroscience is leading the way world research community of Alzheimer's disease.

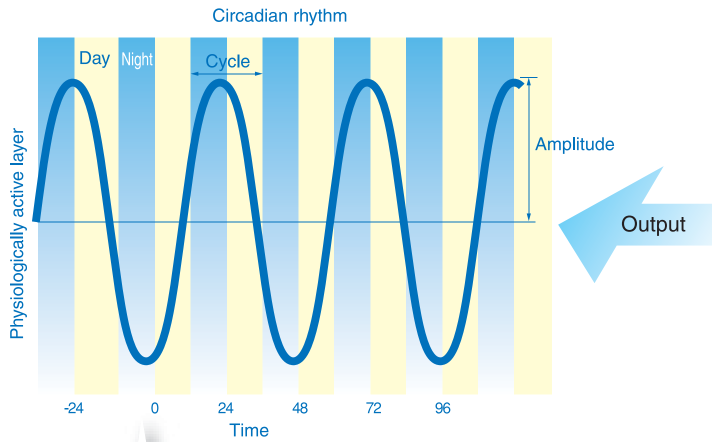
Harima Institute, Membrane Dynamics Research Group Kinetic Crystallography Research Team

Elucidation of structural basis for proteins responsible for the biological clock Determination of biological clock structure and functions at the atomic level

Organisms on the Earth ranging from bacteria to mammals have an internal (or biological) clock to measure time 24 hours a day. A group headed by Team Leader Hiroaki Kato and Research Scientist Toru Nakatsu of the Membrane Dynamics Research Group, Harima Institute, has succeeded in atomic level elucidation of the three-dimensional structure and functions of proteins which function as the biological clock of cyanobacteria carrying out photosynthesis.

Keywords

1. Organisms have an elaborate 24-hour clock
2. Proteins are responsible for the biological clock
3. Structure determination was carried out on SPring-8
4. The structural changes of the protein influence the accuracy of the biological clock



1 Biological clock oscillation mechanism of the cyanobacteria and 3-D structure of the KaiA protein

It has been known that there are three types of biological clock controlling proteins, namely KaiA, KaiB and KaiC. Among these three types, the 3-D structure of the KaiA (Upper right side drawing) has been determined in this time. The three different types of proteins, KaiA, KaiB and KaiC are making mutual interactions among themselves. KaiA works to stimulate the gene expression and production of KaiB and KaiC whereas KaiC works to repress its own production. This is thought to be the essence of the biological clock oscillations. Also, KaiA reacts to KaiC to enhance phosphorylation of KaiC. It is supposed that this phosphorylation is possibly regulating the lifetime of KaiC.

The Voice of Researchers

Hiroaki Kato
Harima Institute
Membrane Dynamics Research Group
Kinetic Crystallography Research Team

Unless the structure is determined, the true functions will not be revealed.

The proteins which work as the biological clock include KaiC and KaiB - not only KaiA of which the structure has been determined. In particular, KaiA and KaiC will exhibit the biological clock function only when they bind together. Then, we would like to clarify how they are interacting together and how they are functioning.

As for the biological clock, the biological phenomenon and its gene only were known but its molecular mechanism had not been revealed. Proteins which are formed by the expression of the clock genes should exist and have functions. We are aiming to elucidate the whole pictures from genes to bio-phenomena through visualization of the structures of proteins.

Organisms have an elaborate 24-hour clock

The Earth has an approximately 24-hour cyclic movement with alternating day and night. Thus, the "24 hours a day" cycle, namely the circadian rhythm, has been influencing various internal functions of living organisms since the moment they arose.

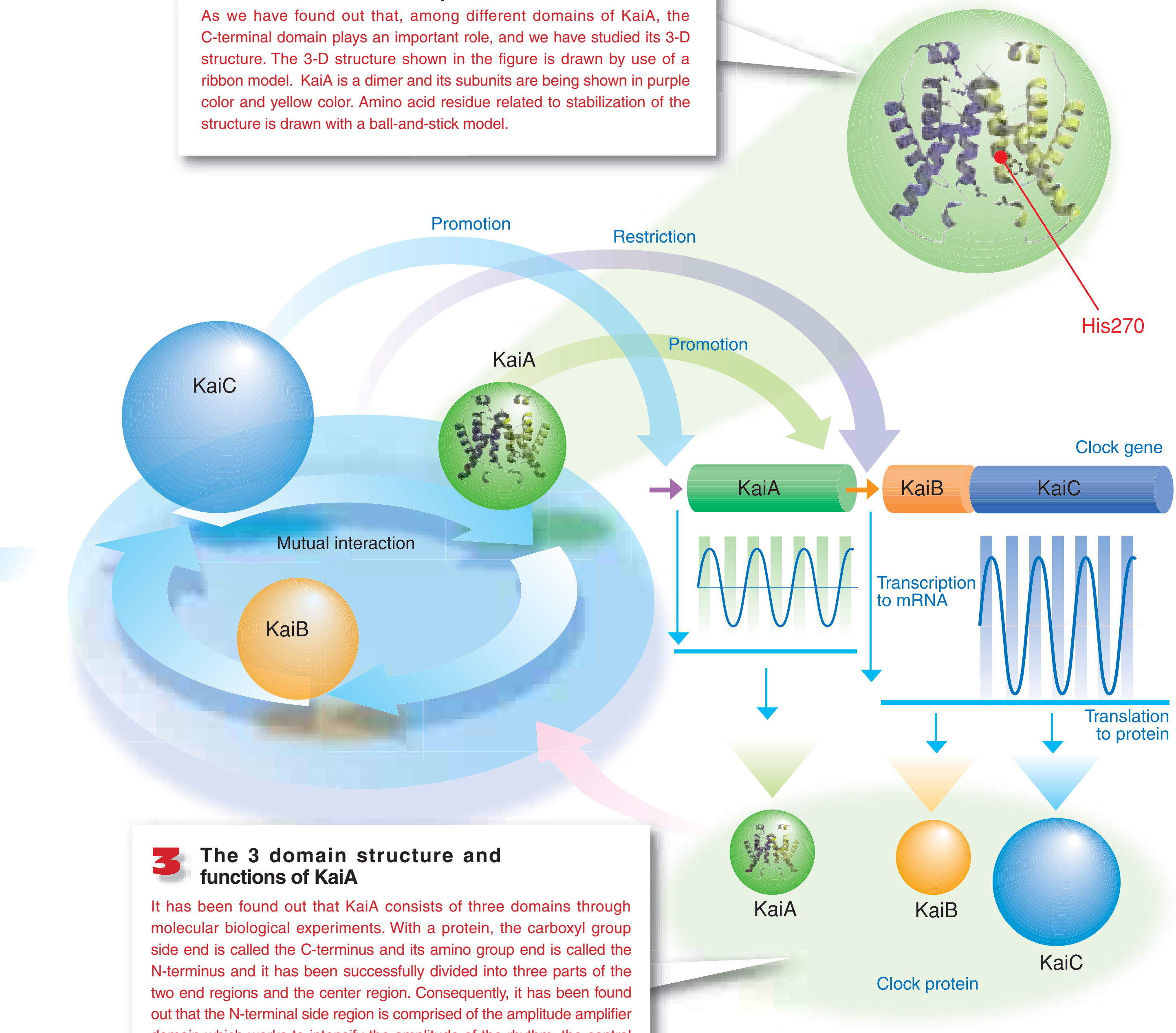
This system is called the biological clock and has some important characteristics. First, it is less susceptible to the environment such as weather and temperature changes, and functions stably even in the bodies of heterothermic animals. Second, it is a system that works autonomously regardless of the actions and discretion of the animal. Third, taking a cue from light, it can adjust for errors. Fourth, even bacteria, which separate several times in a day and consequently grow into the next generation, inherit the circadian rhythm from the previous generation. Similar to this, the biological clock has interesting characteristics, many of which have not yet been explained, and which continue to attract the interest of biologists.

The biological clock contains components of specific protein molecules

Cyanobacteria are the lowest form of animals

2 3-D structure diagram of the C-terminal domain of the KaiA protein

As we have found out that, among different domains of KaiA, the C-terminal domain plays an important role, and we have studied its 3-D structure. The 3-D structure shown in the figure is drawn by use of a ribbon model. KaiA is a dimer and its subunits are being shown in purple color and yellow color. Amino acid residue related to stabilization of the structure is drawn with a ball-and-stick model.



3 The 3 domain structure and functions of KaiA

It has been found out that KaiA consists of three domains through molecular biological experiments. With a protein, the carboxyl group side end is called the C-terminus and its amino group end is called the N-terminus and it has been successfully divided into three parts of the two end regions and the center region. Consequently, it has been found out that the N-terminal side region is comprised of the amplitude amplifier domain which works to intensify the amplitude of the rhythm, the central region is comprised of the period-adjuster domain which works to adjust the cycle to 24 hours and the C-terminal side region is comprised of the clock oscillar domain which works to control the clock signal emission.

in which the existence of a biological clock has been recognized. It has also been demonstrated that there are clock proteins Kai (A, B, and C) formed by the expression of corresponding genes in cyanobacteria.

The elucidation achieved by the group is the atomic shape of the clock protein KaiA and how it provides clock oscillation. The study of the clock gene clarified that KaiA consists of three domains: the "amplitude amplifier domain" that enhances the amplitude of the rhythm, the "period-adjuster domain" located at the center that adjusts the cycle to approximately 24 hours, and the "clock oscillator domain" that is responsible for oscillation of the clock.

Three-dimensional structure has been determined at SPring-8

For structural analysis of the protein, high-performance X rays provided by SPring-8, the Japanese third-generation synchrotron radiation facility, were utilized. The analysis clarified that the KaiA's clock oscillator domain structure consists of general α-helices, and the overall shape of the molecule is like a concave lens. Based on the structural analyses, the group discovered that the 270th histidine residue located near the center of the concave surface is essential to KaiA's clock oscillation function.

It was also revealed that mutations that could cause the structural disruption of KaiA altered the rhythm to such a great degree as to cause an acycle, long-period, or low-amplitude cycle. Mutations with less influence on the structure had little effect on the clock oscillation other than to lengthen it slightly.

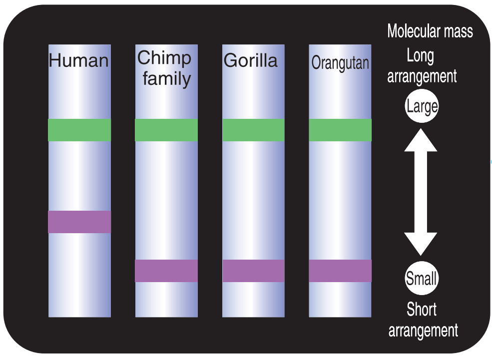
The achievement by the group made considerable strides towards understanding how the mechanism of the biological clock, with its many sophisticated functions, works on a molecular level.

Humans and chimpanzees
Their genes and proteins are considerably different

It is thought that humans and chimpanzees have differences in genetic information of approximately 1.23 percent. "The International Chimpanzee Genome Sequencing Consortium" established by RIKEN Genomic Sciences Center and other institutes, sequenced chimpanzee chromosome 22 with a 99.998% degree of accuracy. When compared with human chromosome 21, it was revealed that in addition to the difference of 1.44%, caused by base-substitution, there exists the considerable difference caused by so-called "insertion-deletion".

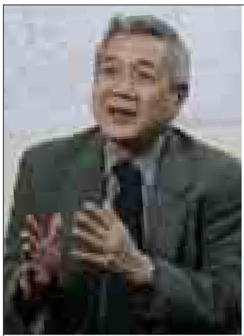
Keywords

1. Comparison between human and chimpanzee genomes
2. Sequencing of the entirety of the chimpanzee chromosome with a high degree of accuracy
3. Greater-than-expected difference in the genetic information
4. 80% of proteins have some differences between human and chimpanzee



Counting these kinds of insertions and deletions resulted in 68,000 findings in chromosome 22 of 33 million base pairs.

The Voice of Researchers



Yoshiyuki Sakaki
Genomic Sciences Center

Human beings can be appreciated as human beings when some other comparisons are made.

By comparing the genes of chimpanzee with the genes of human being, it becomes possible to measure not only the differences between these genes, but also the changing speed of the genes. We believe we may be able to discover what is occurring during the course of evolution by examining what is being assumed by the genes that defy change and what is being formed by the manifestation of the genes that tend to make changes.

To find out what has been changed and what has been stored during the course of evolution will lead researchers to find out what makes a human being a human being and the common factors between chimpanzees and humans.

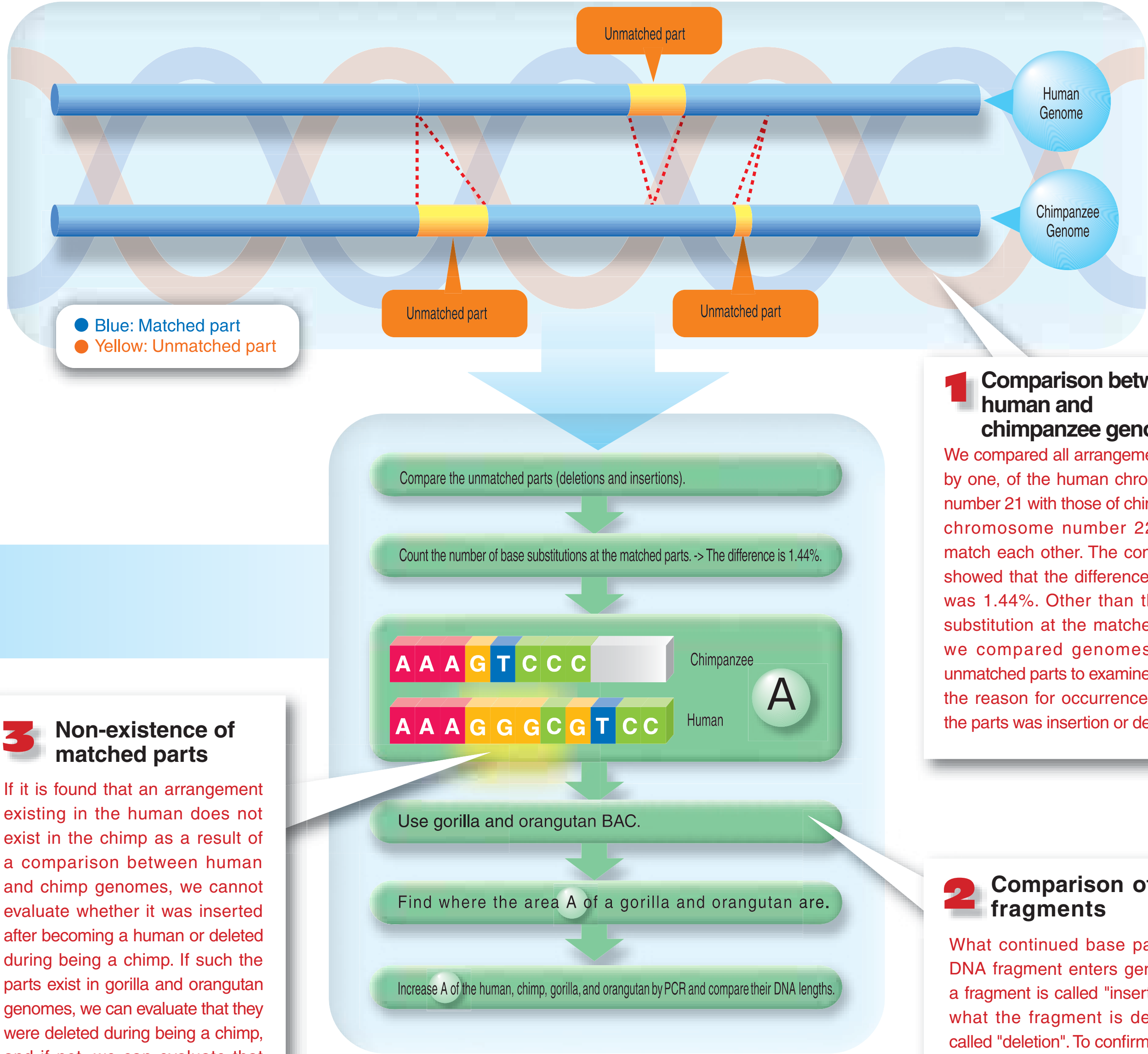
Deciphering the human genome should not be deemed as an accomplishment point but should be deemed as the starting point of these research activities.

Genome, chromosome, and DNA

Genetic information of animate beings is written in DNA in a sequence of four types of base pairs (base sequence). The entire base sequence of a certain animate being is called a genome. DNA in the nucleus of a cell forms an aggregate, called a chromosome. A human being has 24 types of chromosomes and a chimpanzee has 25. It is considered that human chromosome number 21 is close to chimpanzee chromosome number 22. The consortium made a comparison between these two.

Observation of the chimpanzee genome

Genome-wide sequence differences between humans and chimpanzees have not been studied methodically nor on a large scale in the past; it has been considered that their morphological and behavioral differences depended on a slight genetic difference. In 2001, RIKEN took a leading role in forming "The International Chimpanzee Genome Sequencing Consortium" in cooperation with the National Institute of Genetics, Primate Research Institute, Kyoto University and with the participation of various countries such as Germany, China, Korea, and Taiwan. The main purpose of establishing the consortium was to clarify morphological and dynamic differences between humans and chimpanzees at the genomic level, by sequencing the entire genetic information of



1 Comparison between human and chimpanzee genomes

We compared all arrangements, one by one, of the human chromosome number 21 with those of chimpanzee chromosome number 22 which match each other. The comparison showed that the difference in base was 1.44%. Other than the base substitution at the matched parts, we compared genomes at the unmatched parts to examine whether the reason for occurrence of such the parts was insertion or deletion.

2 Comparison of DNA fragments

What continued base pairs of a DNA fragment enters genome as a fragment is called "insertion" and what the fragment is deleted is called "deletion". To confirm whether the reason for occurrence of the unmatched parts was insertion or deletion, we used gorilla and orangutan genomes.

3 Non-existence of matched parts

If it is found that an arrangement existing in the human does not exist in the chimp as a result of a comparison between human and chimp genomes, we cannot evaluate whether it was inserted after becoming a human or deleted during being a chimp. If such the parts exist in gorilla and orangutan genomes, we can evaluate that they were deleted during being a chimp, and if not, we can evaluate that they were inserted after becoming a human.

the chimpanzee (chimpanzee genome) and comparing it with the human genome since it is a primate the most closely related to humans.

In 2002, a research team headed by RIKEN made an announcement based on the rough scanning of the entire chimpanzee genome, that the difference between human and chimpanzee genomes was predicted to be 1.23%.

Larger-than-expected difference holding surprises

On July 1, 2003, the International Chimpanzee Genome Sequencing Consortium achieved success in the determination of all sequences across 33.5 Mb (33.5 million base pairs) of the chimpanzee chromosome number 22 with a 99.998% degree of accuracy and deciphering the information. Using this data in May 2004, the Consortium made an announcement that the sequence difference between the chimpanzee chromosome number 22 and the human chromosome number 21 is 1.44%. Aside from this, it was shown that certain DNA fragments including those called a transposon do not exist in human DNA, but do exist in chimpanzee DNA, and vice versa; such differences were found surprisingly in 68,000 sites. Some researchers assume that combining these two results, the difference in base pairs reaches 5%. In addition, the comparison showed that more insertions of transposons are seen in human DNA than in chimpanzee DNA. This suggests that human's process of evolution occurred more rapidly.

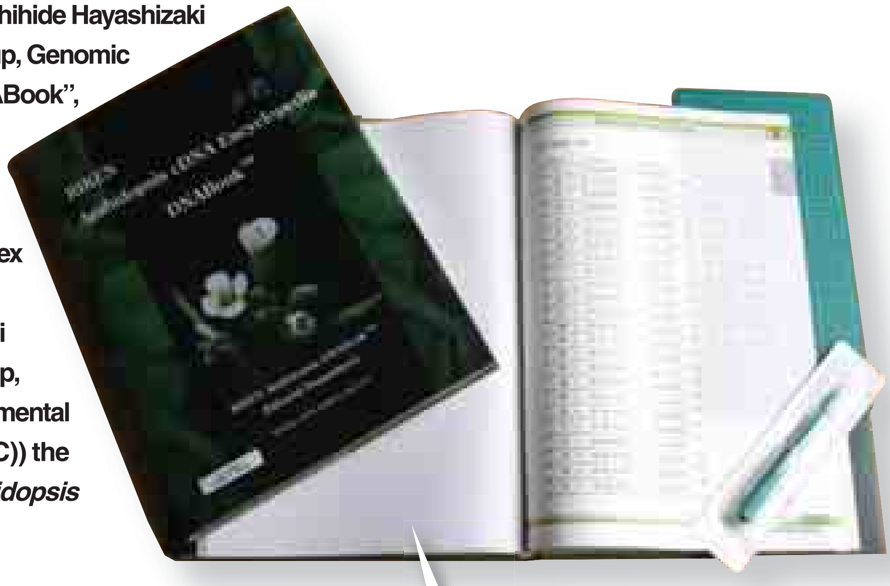
Also, a sequence comparison on 231 protein-coding genes comprising 1% of the entire number was carried out and as a result, it was determined that 83% of them are somehow different in DNA sequences. It is thought that these differences in DNA may cause differences in certain functions of proteins that are produced.

This was the first time in the world that the entirety of the chimpanzee chromosome was deciphered with such a high degree of accuracy and that its characteristics were quantified like this.

Genomic Sciences Center, BioResource Center

Easy and simple distribution of DNA samples as DNABooks, now also available for *Arabidopsis thaliana*

In the past the process of sending DNA samples to other research groups presented a logistical challenge: it was expensive and time-consuming with the ever-present risk of damage to both tubes and plates during transport . To avoid these problems, Dr. Yoshihide Hayashizaki and Dr. Jun Kawai (Genome Research Group, Genomic Science Center(GSC)), developed the "DNABook", a new revolutionizing method to store and transport DNA. The technique has already been used for mouse, human and flatfish DNA and now the turn has come to the complex genomes of plants. In collaboration with Dr. Kazuko Shinozaki and Dr. Motoaki Seki (Plant Functional Genomics Research Group, GSC) and Dr. Masatomo Kobayashi (Experimental Plant Division of BioResource Center(BRC)) the group has produced a DNABook for *Arabidopsis thaliana*.



Keywords

1. The development of a technology that enables the storage of DNA at ambient temperatures
2. The possibility to physically attach relevant DNA material to a corner of a research paper
3. An exceptionally convenient way of transporting DNA samples
4. The first easily distributed cDNA collection of a complex plant genome — *A. thaliana*

1 Distribution of samples using the DNABook

The DNABook may look like an ordinary hard cover handbook, but every page is suffused with cDNA samples in distinct patches. Easy to store and easy to use, just punch out the selected sample with the accompanying pen tool and dissolve in water to retrieve the DNA.

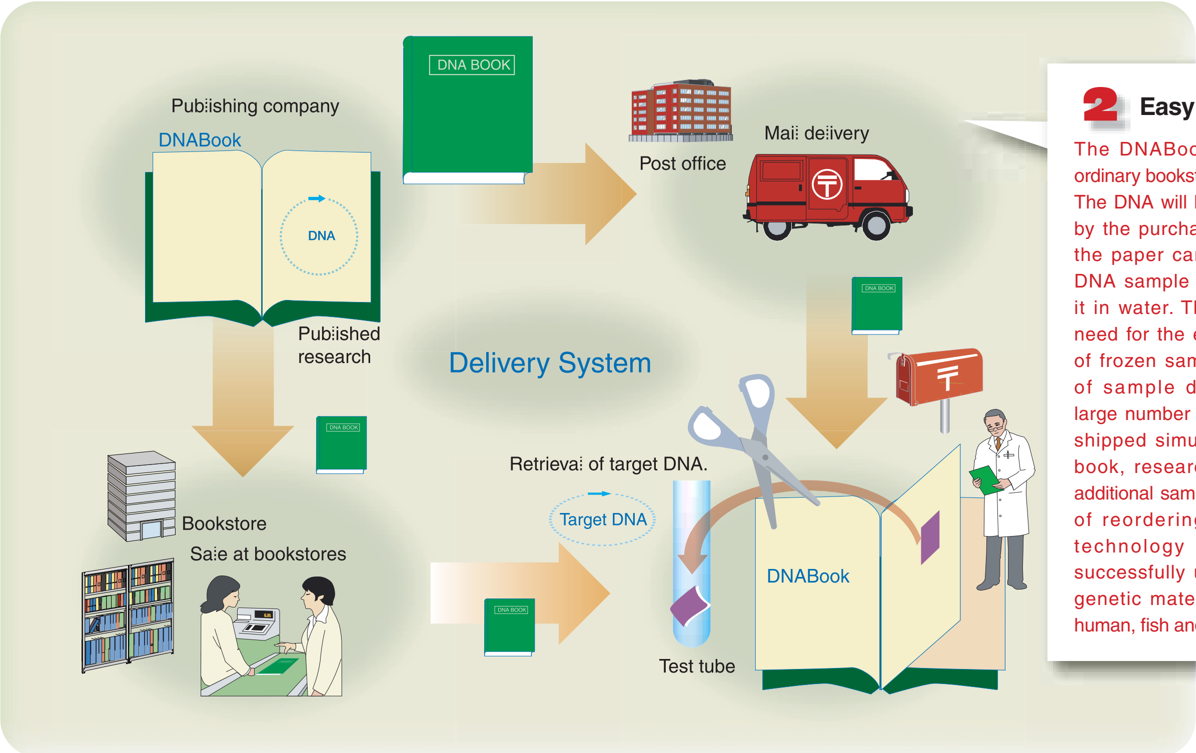
A new era in genome deciphering

Advancement in the techniques available for DNA deciphering has rapidly increased the number of available DNA sequences and taken genome interpretation to a new level, a major advancement in the collection of cDNA: the parts of genes used for protein synthesis.

RIKEN, the core research institute for full-length cDNA from *A. thaliana*, has through Dr. Kazuo Shinozaki and Dr. Motoaki Seki (Plant Functional Genomics Research Group, GSC), collected ~ 18.000 independent full-length cDNA from A. thaliana (~70% of the total number of genes) together with an additional number of 10,000 clones provided by Dr. Masatomo Kobayashi (Experimental Plant Division, BRC), to be used as a standard gene resource in the plant research community. The logistical problems arising for all global research communities is the actual sharing of the available DNA material, shipping and storage have so far been a tedious trial without guaranteed success.

Sending a book of DNA

The DNABook were developed by a research group lead by Dr. Yoshihide Hayashizaki and Dr. Jun Kawai (Genome Exploration Research Group, GSC) to solve this storage and transport problem. In the past, all handling of DNA required special treatments; today, the DNABook enables long term storage (~ six months) of DNA at ambient temperatures and easy shipping. The DNA suffused paper has proven to withstand temperature changes (- 40°C for 14 hours to + 114°C for 5 seconds), high



2 Easy DNA handling

The DNABook can be sold in ordinary bookstores or sent by mail. The DNA will be easily recovered by the purchaser by cutting out the paper carrying the desired DNA sample and then dissolve it in water. This eliminates the need for the extensive handling of frozen samples and the risk of sample damage. Since a large number of samples can be shipped simultaneously in one book, researchers can access additional samples directly instead of reordering. The DNABook technology has so far been successfully utilized for storing genetic materials from mouse, human, fish and now plants.

The DNABook has already been used for a great variety of organisms.

In the past the problem of packing DNA for transportation were not trivial.

pressures (17MPc) and exhibits a DNA recovery level of 95%.

This opens up the opportunity for researchers to attach the subject DNA samples to the research papers. The recipient can easily obtain the DNA of interest by cutting out the suffused area and dissolve the paper in water, eliminating the time and cost of additional shipping.

Plants next in line

Following the "Human DNABook","Mouse DNABook"(containing 60,000 full-length cDNA), and the "AquaBook"(containing flatfish microsatellite markers and materials necessary for diagnosing fish disease), RIKEN now presents the first plant DNABook, "The RIKEN Arabidopsis cDNA Encyclopedia DNABook™". Containing 1,069 transcription factors from *A. thaliana* it is the first of its kind. This book will be distributed among the researchers in collaboration with RIKEN, and the research community. Together with the RIKEN RART database (RIKEN Arabidopsis Transcription Factor Database: http://rarge.gsc.riken.jp/rartf/), the Book of *A. thaliana* DNA will make a great contribution to the field of plant science.

The Voice of Researchers

Yoshihide Hayashizaki
Genomic Sciences Center Genome Exploration Research Group

Kazuo Shinozaki
Genomic Sciences Center Plant Functional Genomic Research Group

Masatomo Kobayashi
BioResource Center Experimental Plant Division

One of the greatest inventions since Gutenbergs moving types: How to share common DNA by pages in a book.

Since the first DNABooks, which were produced manually in 120,000 copies (causing aching muscles and shaky hands), a system is being developed to carry out the process of applying the DNA to the pages mechanically. Our goal is to continually improve the process, for example to extend the long-term storage ability of cDNA. The invention of storing DNA in the pages of a book is analogous to the development of Gutenbergs typographic printing machine.

Robots with flexible bodies
Slithering along using artificial muscles

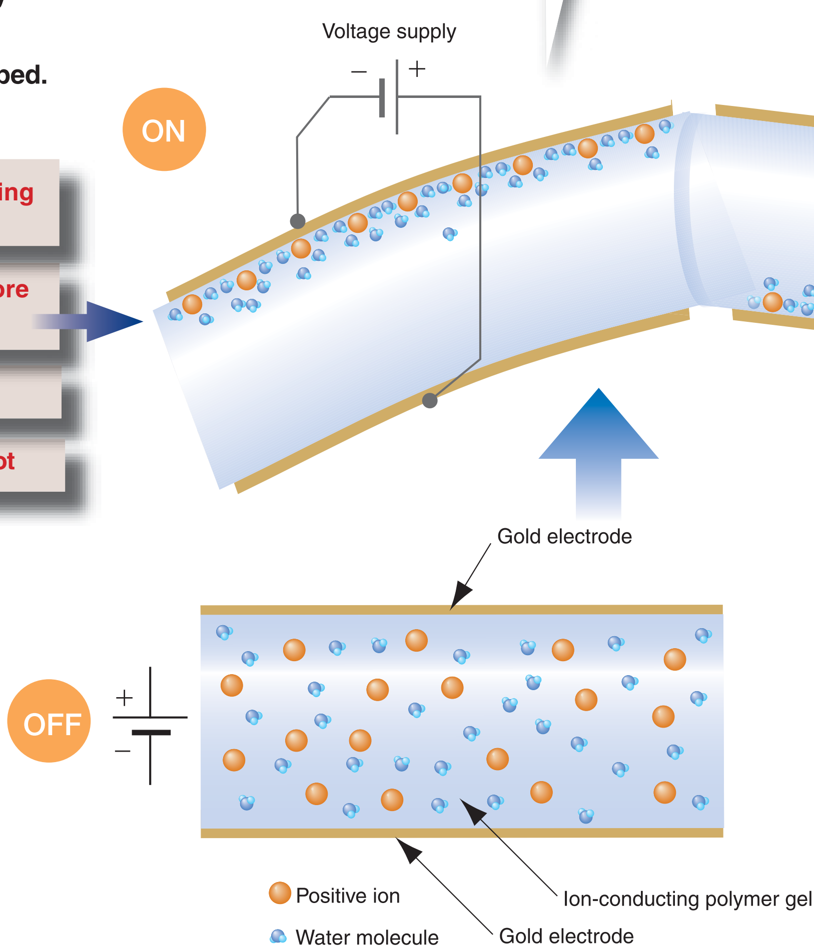
Is it possible to produce a robot that can make flexible movements like an animate being?
Team Leader Toshiharu Mukai and other researchers of the Biologically Integrative Sensors Laboratory, Bio-Mimeteic Control Research Center, manufactured a "snake-like robot" with a flexible body that uses an artificial muscle made from polymer gel.
The world's first totally flexible robot has been developed.

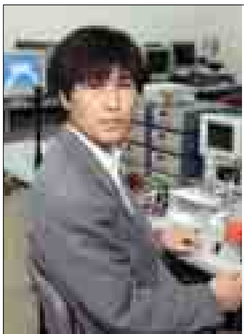
Keywords

1. Movement using artificial muscles involving application of polymer gel
2. Smaller, noiseless, more flexible, and more light-weight than electromagnetic motors
3. "Snake-like robot" swimming in the water
4. Toward miniaturization and stand-alone robot

1 Principle of operation of artificial muscle

Carrying electricity allows positive ions and water molecules in polymer gel to gather disproportionately at the negative pole of the gold electrodes coated on the polymer gel. Since the side where positive ions and water molecules increased expands and the side where they decreased shrinks, the entire of the artificial muscle bends.





The Voice of Researchers

Toshiharu Mukai
Bio-Mimetic Control Research Center Biologically Integrative Sensors Laboratory

We want to have robots operate inside a living body by automating and down-sizing.

Our next target is to automate and to make it into a cordless robot. We believe that we can automate it by exercising ingenuity such as adhering to an ultra-small computer and a button battery, or feeding the electric current from an external source via a wireless circuit. Once we succeed in automating and down-sizing, and taking advantage of its soft features, we are planning to let it play the role of creating the motive force for a device to work within the living body such as blood vessels and the gastrointestinal tract, or the acting portions thereof.

Additionally, we believe that, taking advantage of its paper-like shape, we may be able to create robots that can function after having been folded like origami (the Japanese art of folding a square sheet of paper into various shapes) or after having been bent.

Actuator using polymer gel

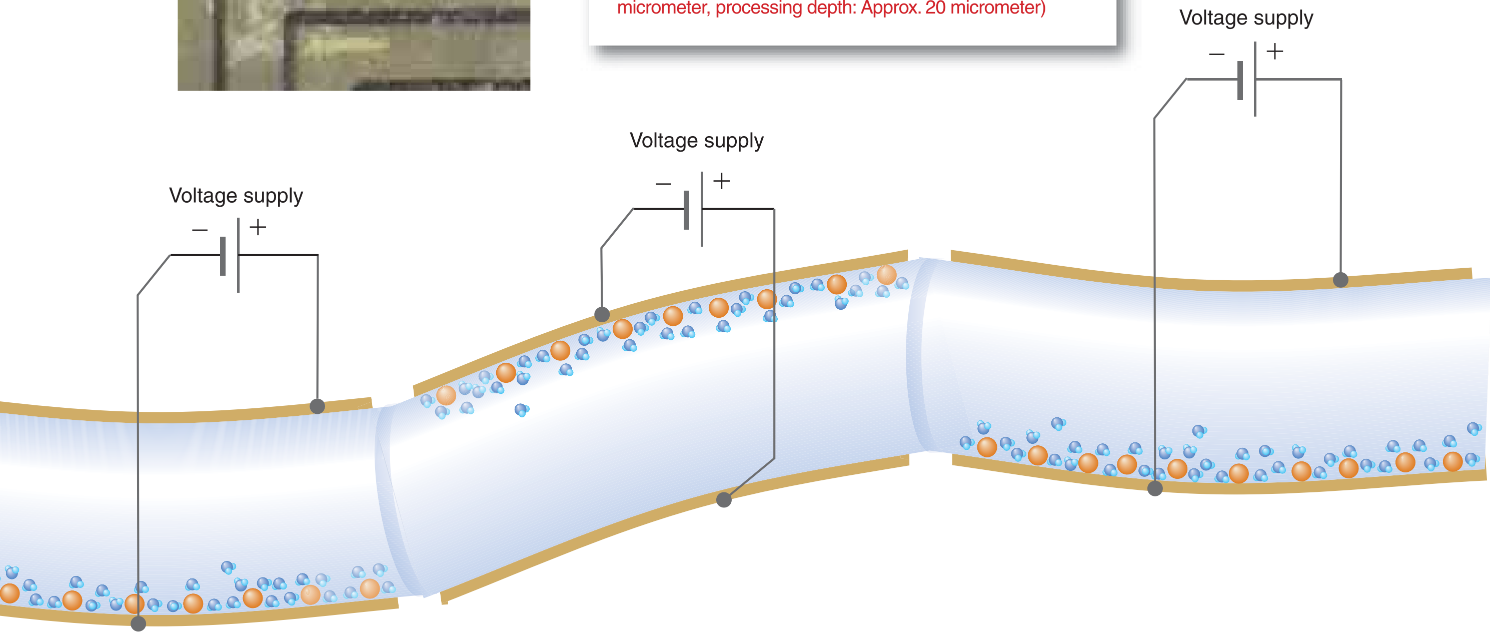
In modern robots, an electromagnetic motor is generally used to power movable parts. However, they cannot exhibit flexible movement such as those enabled by human muscles. Although flexibility can be provided by manipulation of controls, designers are still confronting a large problem. The solution to this problem lies in the use of actuators consisting of artificial muscles.

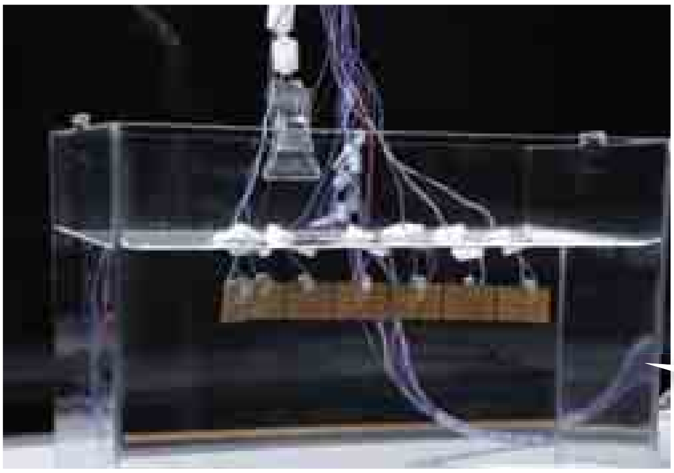
One of the solutions is the IPMC actuator that uses ion-conducting polymers (high-polymer electrolyte gel). IPMC stands for Ionic Polymer Metal Composite and the nature of this material enables it to bend when a voltage of approximately 2V is applied between electrodes situated on both sides of a polymer gel film.

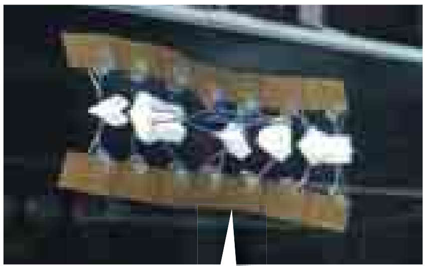
The principle of the bending process is as follows: positive ions move when a voltage is applied to them, water molecules move as the ions move, one side of the gel expands and the other side constricts, and as a result, bending occurs. When compared with conventional electromagnetic motors, the IPMC actuator exhibits not only flexibility but also various other features such as being light-weight, noiseless and stable, and the ability to operate even when wet, although its force is still small and cannot be used in large-size robots.

2 Enabling multiple degrees of freedom by patterning

Dividing the electrodes of one artificial muscle into multiple areas gives complex movements. The photo shows patterning using laser. (Min. processing line width: 50 micrometer, processing depth: Approx. 20 micrometer)







3 Enabling the robot to swim by controlling each area

Connect cords to each part from the above and control respective voltages, and it advances in the water windingly.

Complex movements based on patterning

Because one IPMC actuator simply bends according to the voltage applied, it cannot produce complex movements in the robot. However, the IPMC actuator cannot be connected easily. To solve this problem, a method was developed to electrically divide the electrodes of one IPMC actuator. This is called "patterning" and enables partial and independent bending of the electrodes.

Patterning allows production of robots using one IPMC actuator, resulting in simplification of the structure. Therefore, it is assumed that miniaturization is also able to be facilitated.

"Snake-like robot" swimming in the water

As a first step, one IPMC actuator was divided into seven areas to fabricate a 14-cm long robot able to swim with a similar winding motion as a snake (Fig. 3). The robot makes snake-like movements when a sine curve voltage with a phase shifted to respective areas is applied, and consequently it swims using the motion as a propelling force. The robot moves at a speed of 4.22 mm per sec. Its back-and-forth symmetrical structure allows the robot to move in a backward direction when the voltage phase is reversed. In addition, applying a bilaterally-asymmetric "saw-tooth" wave enables rotational movements.

At present, an external computer is connected to the robot to provide control ability and electric power. As for a final target, the team is aiming to manufacture stand-alone robots by mounting an ultra small control computer and a small battery or wireless powering system in the robots. The development by the team gives some indication of the future possibilities of developing a working robot that can move freely inside a fragile tube such as a blood vessel.

Kawase Initiative Research Unit

Terahertz light to open a new, rich image world

The study of the terahertz light region existing between radio waves and visible light has remained untouched for a long time, resulting in a delay in development in this area. Kawase Initiative Research Unit created a system to beam clear terahertz light in a wide range of frequencies by developing an innovative desktop sized light source

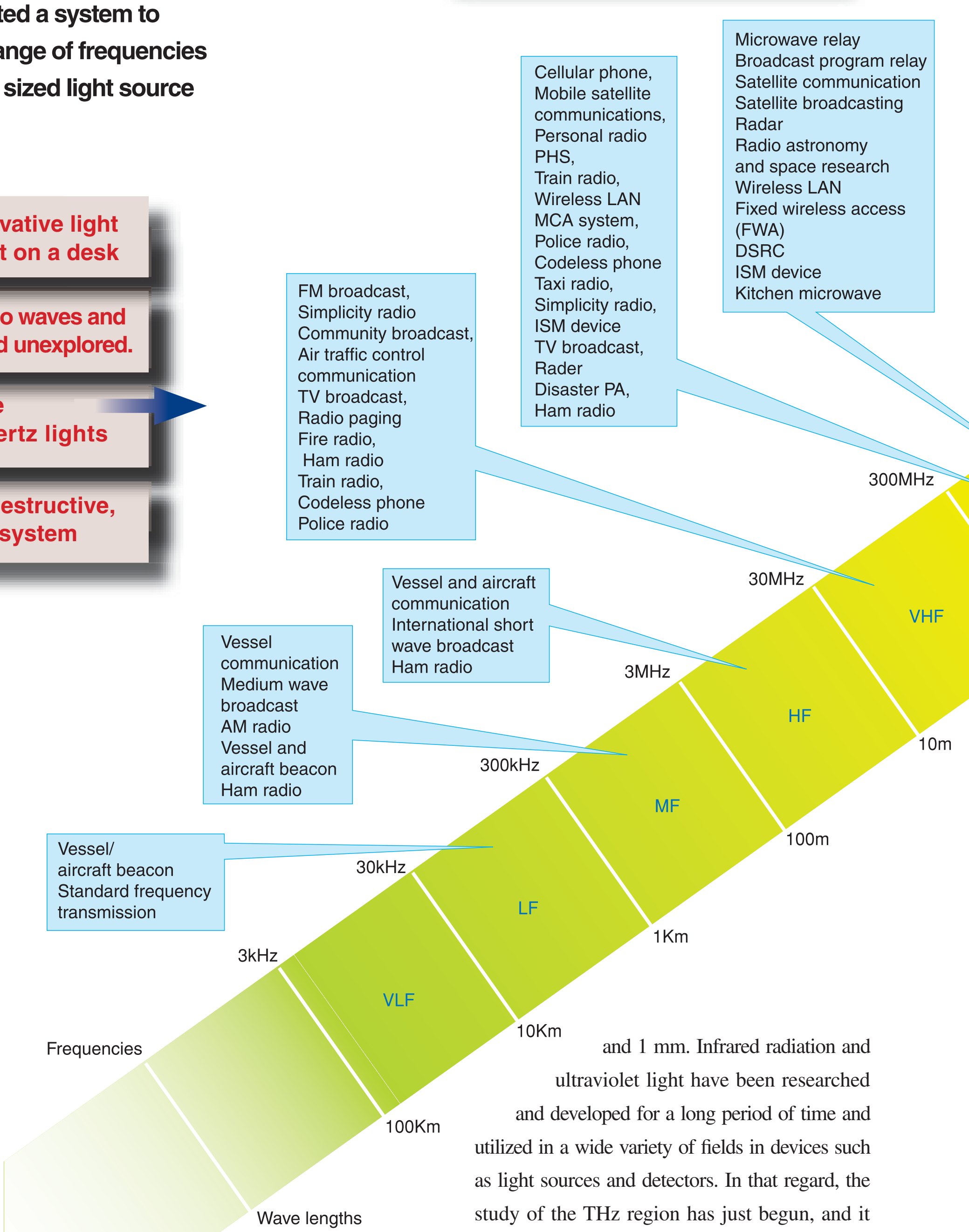
Keywords

1. Development of an innovative light source which can be put on a desk
2. Frequencies between radio waves and visible light have remained unexplored.
3. Observation of animate beings using the terahertz lights
4. Development of a non-destructive, non-contact inspection system

1 Features of terahertz waves and their application fields

Terahertz waves are being positioned in the border range of electric waves and light waves, in other words, between the infrared rays and millimetric waves

Being in the border range of electric waves and light waves, the terahertz wave range has thus been a region where studies were insufficient or a underdeveloped electromagnetic wave region.



The Voice of Researchers

Kodo Kawase
Kawase Initiative Research Unit

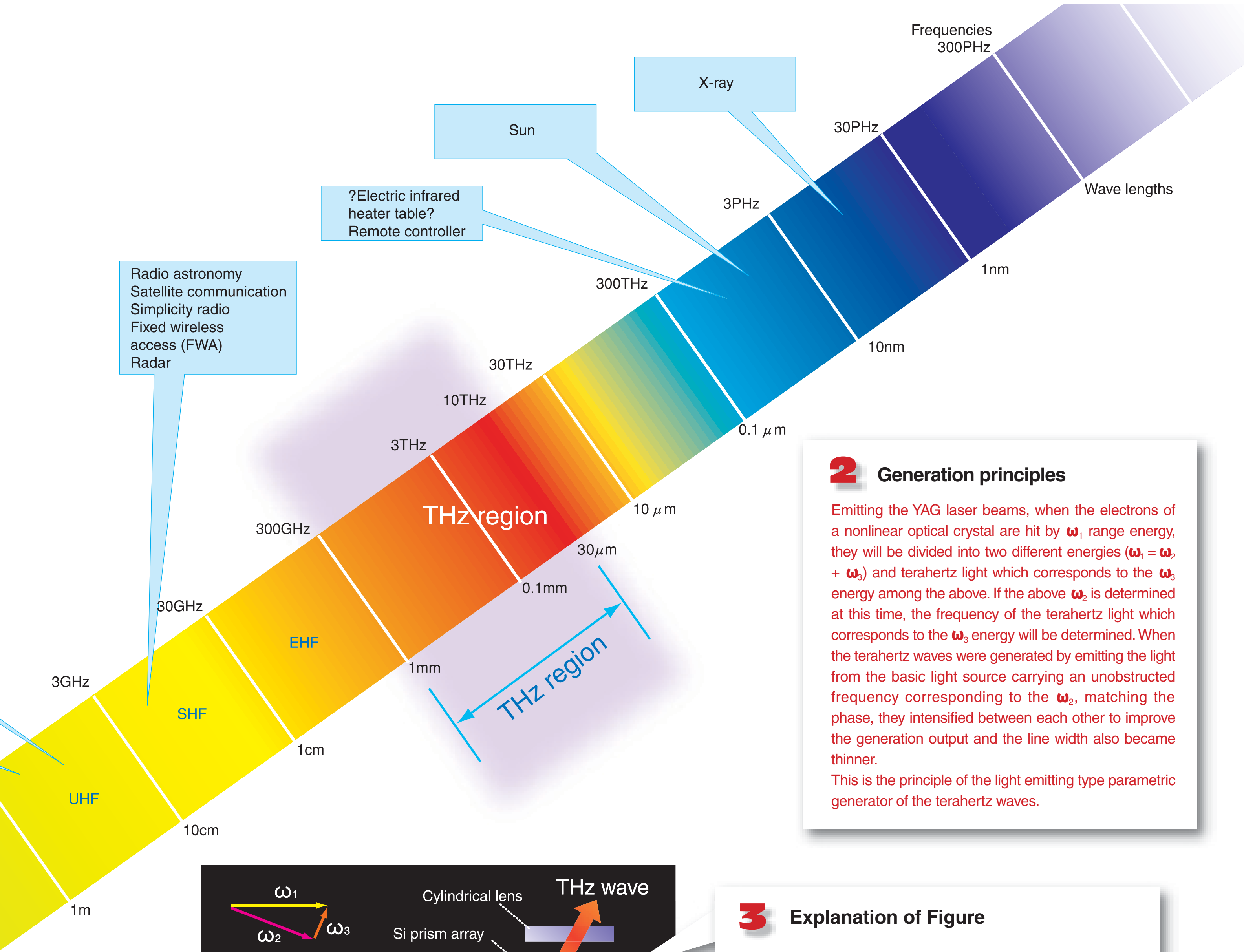
What can be done by the use of terahertz lights? We believe this should be our next task.

Terahertz lights have thus far been a field where insufficient research has been carried out. I am still thinking of proving the hypothesis of letting proteins inside the living body find the reactive opponent out of countless numbers of substances using resonant vibrations being described in the article by Frohlich titled "The cell surface membranes are resonating in harmony like a crystal oscillator" which I read when I was a senior at University. As for my research into terahertz lights, I began this research work since a light source that can emit terahertz lights in a broad band was necessary in order to find out the frequencies to create resonance inside a living body. Although the probability of successful proving this may be 20 to 30 percent, I am determined to continue this research as one of the important themes of my work.

Terahertz field has not been explored

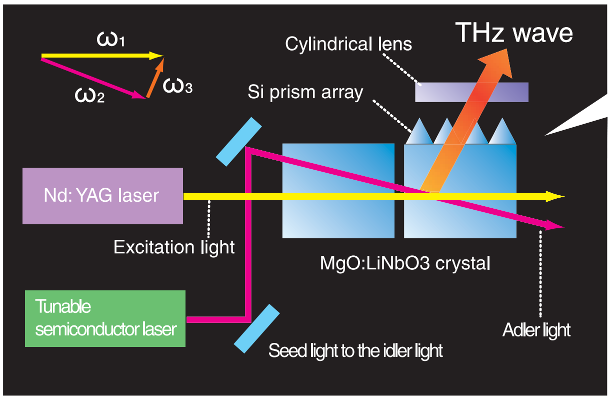
Terahertz (THz) is 10 raised to the 12th power hertz, and THz lights are electromagnetic waves with a frequency in the region between far-infrared radiation and extremely high frequency waves. To be precise, they lie between 0.3 to 10 THz which corresponds to wavelengths of between 30μm and 1 mm. Infrared radiation and ultraviolet light have been researched and developed for a long period of time and utilized in a wide variety of fields in devices such as light sources and detectors. In that regard, the study of the THz region has just begun, and it can be considered that the THz region is the last frontier of electromagnetic spectra. As to the main reasons this area has remained untouched, the following reasons can be deduced; it was difficult to fabricate a strong and reliable THz wave generator (light source), and no sensor to efficiently detect the novel emitted lights was available.

Kawase Initiative Research Unit have shrunk a huge and difficult-to-use THz light source down



2 Generation principles

Emitting the YAG laser beams, when the electrons of a nonlinear optical crystal are hit by ω_1 range energy, they will be divided into two different energies ($\omega_1 = \omega_2 + \omega_3$) and terahertz light which corresponds to the ω_3 energy among the above. If the above ω_2 is determined at this time, the frequency of the terahertz light which corresponds to the ω_3 energy will be determined. When the terahertz waves were generated by emitting the light from the basic light source carrying an unobstructed frequency corresponding to the ω_2, matching the phase, they intensified between each other to improve the generation output and the line width also became thinner.
This is the principle of the light emitting type parametric generator of the terahertz waves.



3 Explanation of Figure

Nonlinear optical crystal (lithium niobate crystal on which doping of magnesium oxide has been executed)
Cutting the single cell silicon on a prism, these cut single cell silicon slices are being pressured bonded in a lined up order on the surface of the nonlinear optical crystal.
Pump light Nd:YAG laser beam (Wave length: 1.064μm)
The emitting light to the idler is a tunable semiconductor laser beam (Wave length: 1.068 – 1.074μm)

to desktop size.

Detection of illicit drugs hidden inside an envelope using THz lights

Kawase Initiative Research Unit developed a system to detect the type of chemical material in an envelope by irradiating THz lights at various frequencies. This method takes advantage of a feature based on the fact that many chemical materials show a distinguishing absorption characteristic called "spectral fingerprints" in the THz region.

In addition, the THz light can penetrate a package (paper, cardboard, textiles, plastics, wood, ceramics, semiconductors, and dry or frozen material). Combining these two features enabled a non-destructive and non-contact inspection of the contents of an envelope.

By using a technique called the principal component analysis for measurement data analyses, the density and distribution of a particular chemical material using spectral fingerprints can be drafted even if some chemical materials are mixed (Figure).

IC circuit inspection with the Laser-Terahertz Emission Microscope (LTEM)

If an IC chip is irradiated by a femtosecond laser beam with an extremely short time-width (femto is 10 raised to the -15th power) when a voltage is applied, a tiny amount of THz light is generated due to back scattering. Its intensity is almost proportional to the voltage applied to the wiring. The IC was scanned with the femtosecond laser, and a comparison between the image of the intensity of the generated THz light and the normal IC image showed some places with weak THz light, which were damaged parts. Like this, the use of the emission microscope enables configuration of a completely non-contact inspection system.

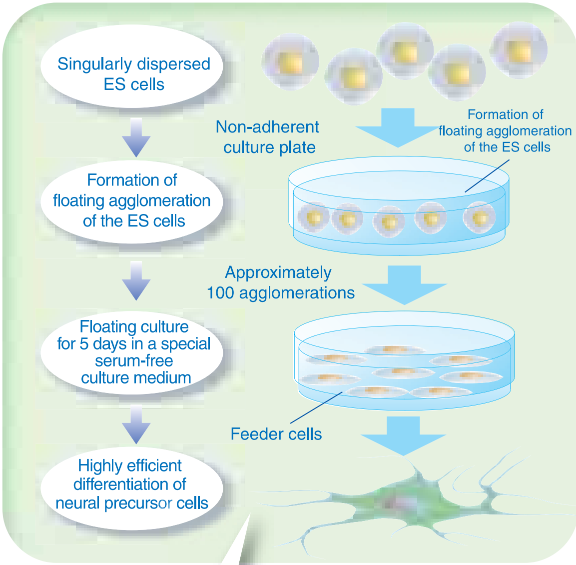
Aside from the above, the development of THz lights is advancing in a wide range of applications from food-related to bio-related inspections and areas of medical science. Further developments are awaited.

Creating brain cells from the ES cell Development of a technique to differentiate cerebral precursor cells

The ES cell differentiates to turn into cells to form various kinds of organs. A group headed by Group Director Yoshiki Sasai and research workers including Kiichi Watanabe of the Laboratory for Organogenesis and Neurogenesis, Center for Development Biology, has developed the world's first technique to preferentially differentiate the ES cell of a mouse to cerebral precursor cells in a test tube, namely the SFEB method.

Keywords

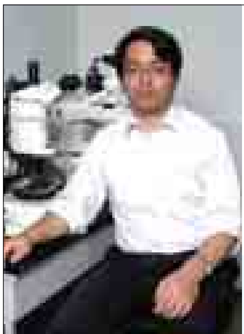
1. A method for preferential differentiation of the ES cell has been established
2. The cerebral precursor cells differentiate between various brain cells
3. A large number of brain cells can be generated in a test tube
4. It is expected this process can be applied to Parkinson's and Huntington's diseases



1 Neurotrophy from the ES cells by use of the SFEB method (Serum-free Floating culture of Embryoid Body)

Although it has been a usual custom to add serums which stimulates differentiation into a culture fluid, we were able to create a state where no external stimulation factor is being involved by removal as far as possible of these stimulating factors and by use of an inhibitory agent against the factors which stimulate differentiation of the neural precursor cells. Under such state, differentiation of the neural precursor cells has been induced by making out an agglomeration state of around 100 pieces.

The Voice of Researchers



Yoshiki Sasai
Center for Developmental Biology
Laboratory for Organogenesis and Neurogenesis

If brain or cerebrum cells can be made out systematically, we can expect to be able to use them in applications for medical treatments.

If cerebrum cells can be made out easily by applications using this method, we believe that these cells can be used effectively for the screening work of curative medicines for Alzheimer's disease, etc. Furthermore, in future, if it becomes possible to systematically make out several hundred types of cells in the cerebrum, it may lead to the realization of a transplanting curative treatment for cerebrum related diseases.

As basic research, we were able this time to reproduce the mechanism of their generation by use of the ES cells. That is to say, it has been discovered that the ground state of anaplastic cells of mammals are progenitor cells of the cerebrum. This is a very interesting finding for a study of the generation.

Creating nerve cells from the ES Cell

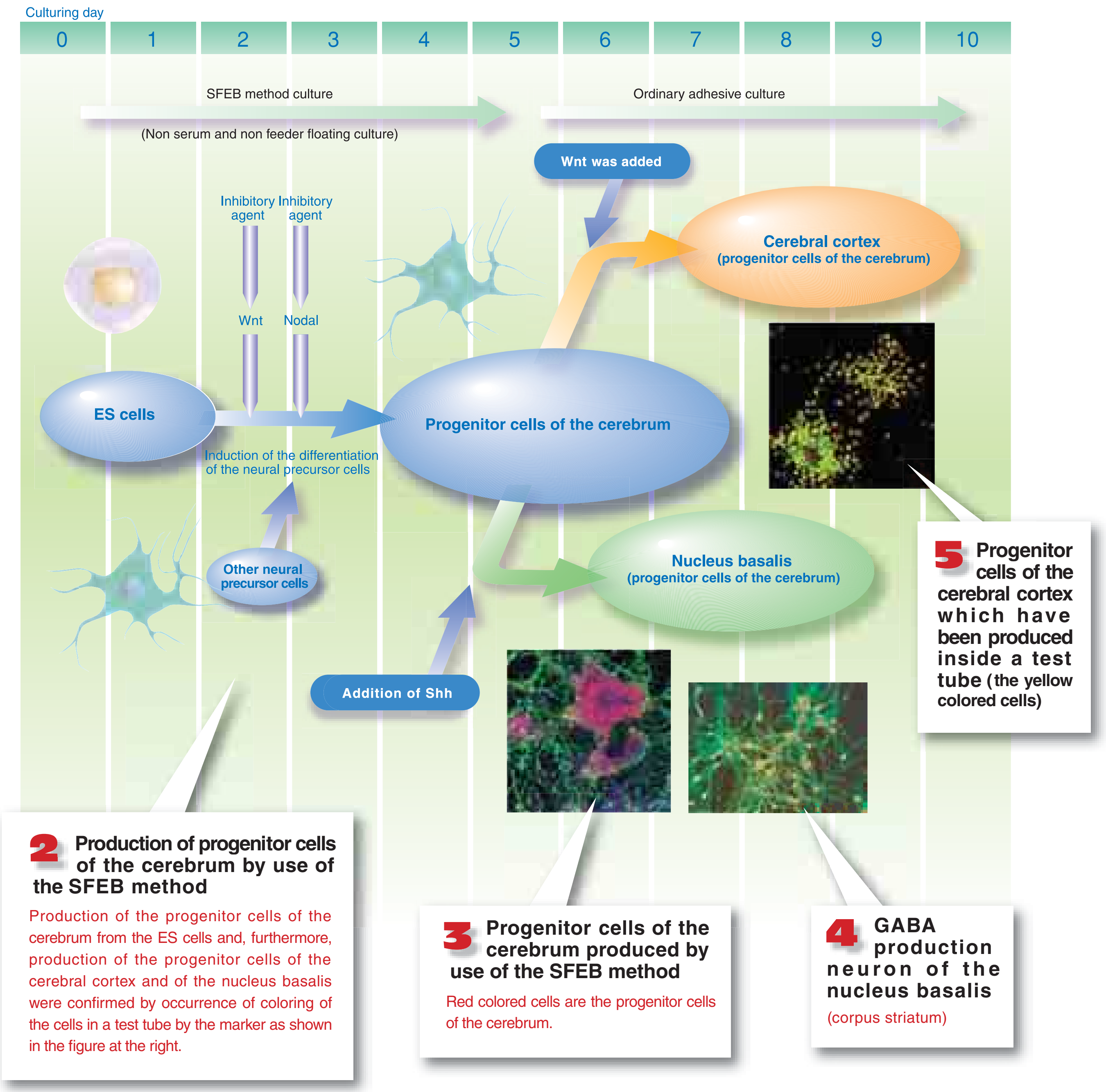
ES cells stand for Embryonic Stem Cells obtained at the stage after a fertile egg (embryo) has divided several times, and precursor cells refers to cells at the stage before they are differentiated and matured.

It is already known that the ES cell turns into cells of various kinds of organs depending on how it is stimulated. Using such a characteristic, a method to create cells of difficult-to-sample organs on an experimental basis is being studied.

Kiichi Watanabe and other research workers of the Laboratory for Organogenesis and Neurogenesis Group have established, as shown in Fig. 1, a system to efficiently differentiate an ES cell to nerve cells using a certain method, which is based on culture with a small aggregate of an ES cell floating in a special serum free culture solution (called the SFEB method).

Reproducing cerebrum cells in a test tube

In addition, as shown in Fig. 2, induction to nerve cells has been nearly preferentially inducted by temporarily controlling the activity of two secretor factors, Wnt and Nodal, which restrict



differentiation to nerve cells. In fact, these nerve cells are exactly the cerebral precursor cells which have been deemed to be difficult to produce. This is the first time in the world that preferential differentiation of the ES cell to cerebral cells and tissues has been achieved.

Application of the SFEB method is now being extended toward the differentiation and induction of tissues of different areas of the cerebrum as well as the cerebral precursor cells. As shown in Fig. 2, it will be implemented by adding a soluble signal factor to the cerebral precursor cells. The soluble signal factor such as Shh is known as being capable of controlling generation of each area of the fetal cerebrum. It was added to the test tube based on this fact and as a result, differentiation of each area of the cerebrum was reproduced in it.

Expected applications in the medical field

From the point of view of medical research, application of the SFEB method to the human ES cell provides two significant advantages. First, it is possible to elucidate the cerebral disease generation mechanism in a test tube; this will facilitate development of a new medicine effective against the disease. In the case of Alzheimer’s disease or BSE, for example, it is possible to efficiently elucidate the disease contraction mechanism by making full use of cerebral cells produced in the test tube. It should be considerably useful for development of medicines to control the death of nerves and functional disorder.

Second, it will open the door for medical treatment of cerebral diseases from the point of view of generative medicine. For example, Huntington's disease, one of the genetic diseases, denatures corpus striatum nerve cells to inhibit voluntary movement. However, a new medical treatment method can be provided if test-tube corpus striatum nerve cells can be transplanted.

Making full use of the immune function in living organisms
Completion of the world's first artificial lymph node

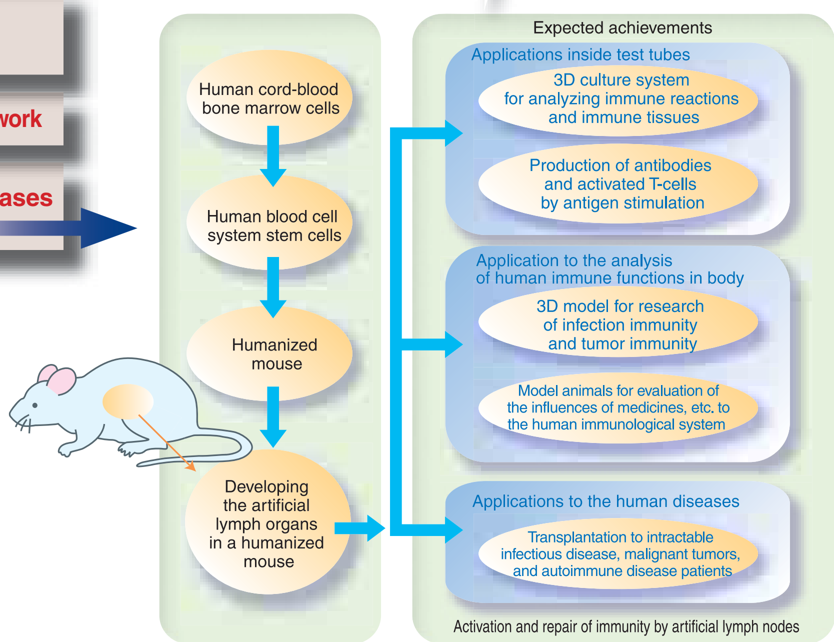
Development of new techniques for the treatment of infectious diseases and cancer is in progress. Unit Leader Takeshi Watanabe and researchers including Sachiko Suematsu of the Research Unit for Immune Surveillance, Research Center for Allergy and Immunology, have for the first time in the world manufactured a structure extremely similar to that of a natural lymph node using high-polymer materials, and confirmed that its immune functions operate fully using a mouse.

Keywords

1. A lymph node works as a barrier to protect the body
2. A lymph node is a condominium for immune cells
3. Achievement using an artificial framework
4. Useful for serious infectious diseases and the treatment of cancer

1 Future plan

1) Building of an artificial lymph nodes which function specifically to antigens such as pathogenic microorganism and cancer cells or specifically to immune responses such as helper T-cells, control T-cells, and killer T-cells in the mouse.
2) Enhancement and regulation of the immune functions by artificial lymphoid tissues in mouse and human.
3) Building and application of the human lymph node built based on human immune cells for treatment of various diseases.



The Voice of Researchers

Takeshi Watanabe
Research Center for Allergy and Immunology
Research Unit for Immune Surveillance

To understand immune functions working in 3D, we must undertake research in 3D. Otherwise, we will have something beyond our comprehension.

Artificial lymph nodes provide a new environment for research of immune functions. Conventionally, immune responses have been researched based on planar culture in a test tube. However, use of artificial lymph nodes allows reproduction of an immune reaction which actually occurs in a living organism, in the 3D structure.

In addition, I think the artificial lymph node can be used for medical treatment as a device to activate, repair, or control the immune functions. Transplanting artificial lymph nodes to patients with their immune functions weakened can activate their immune functions. Besides, I think that artificial lymph nodes having an antigen-specific function will protect us effectively from particular diseases such as infectious diseases and cancer.

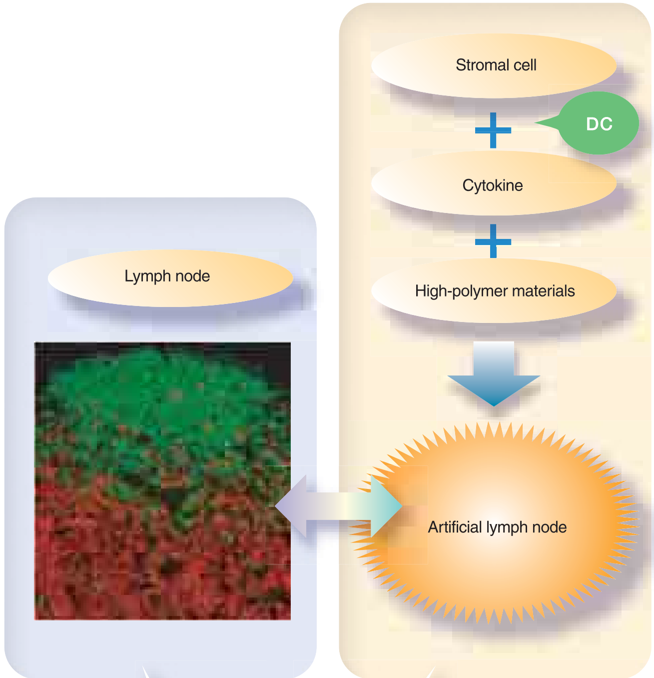
It might become possible to control autoimmune diseases or severe allergy by artificial lymph nodes enriched the regulatory cells.

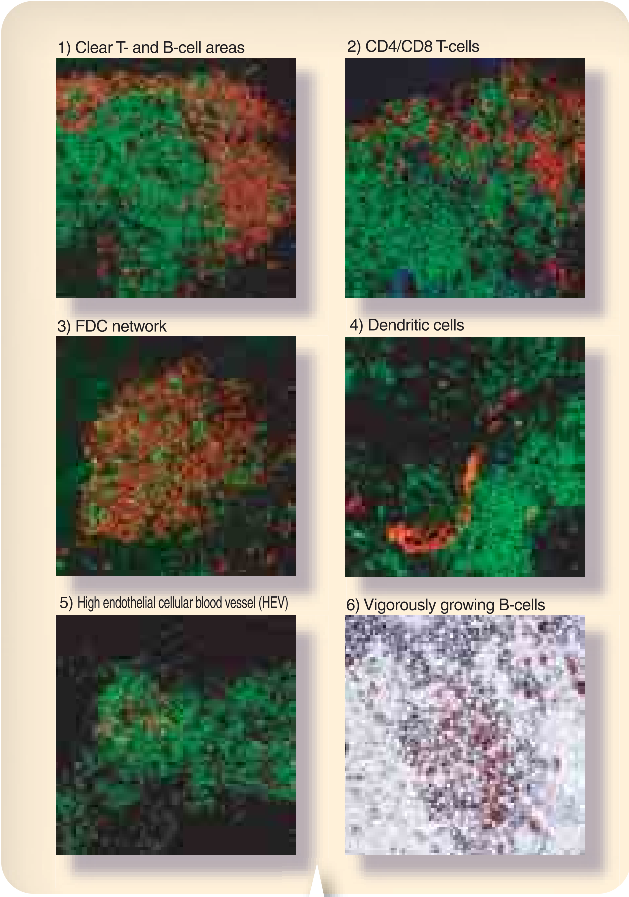
A lymph node works as a barrier to protect the body from infectious diseases and cancer cells

Other than the blood vessel, the human body has an important tube running through it called a lymph channel. Lymph fluid containing waste matter passed out from cells, nutrients, cells responsible for immunity, and depending on circumstances, infectious microorganisms or cancer cells, flows through the lymph channel. The lymph node is positioned at pivotal points along the lymph channel like a barrier, and exist throughout the body. The lymph node detects bacteria and harmful substances or cells that have entered the body and triggers an immune reaction against them. It also plays a role in aiding the body to acquire the immune strength to eliminate them. Simply put, the lymph node is a tissue that surveys the entire inside of the body and plays a central role in generating immune strength to eliminate abnormal cells and other material generated inside the body.

The lymph node is a structure in which various immune cells are segregated

To unlock the secret of how the lymph node is structured and what factors relate to its structure, Unit Leader Takeshi Watanabe and other researchers are going to carry out a detailed examination of the lymph node by manufacturing





2 Secondary lymph node and artificial lymph node

An "artificial lymph node", which has a structure similar to a natural secondary lymph node and is integrated in an area where B-cells and T-cells are efficiently and clearly distinguished (follicle is formed), has been built by combining stromal cells, biocompatible high-polymer materials, dendritic cells, chemokine, etc. As biocompatible materials, collagen matrix was used. As a place to build an artificial lymph node, the space under the renal capsule of a mouse was used.

3 Tissue structure of the artificial lymph node

The newly built artificial lymph node revealed the following.
1) Clearly distinguished T-cell and B-cell areas exist and follicles are formed.
2) Dendritic cells exist together with both T-cells and B-cells.
3) CD4 and CD8 positive T-cells are distributed in the T-cell area in the same condition as in a natural secondary lymph node.
4) Blood vessels are formed.
5) A follicular dendritic cell network is formed.
6) A formed germ center where active division growth of B-cells is in progress is observed as an image

an artificial lymph node. A small organ called a lymph node has a three-dimensional structure in which various kinds of cell masses are organized in a sophisticated way. It is like a condominium that is comfortable to live in, and makes full use of its functions by causing each immune cell mass having different functions to be segregated and distributed in various places. The unit headed by Watanabe has succeeded in building a structure much like that of a natural lymph node using an artificial framework which does not cause a rejection response even if it is placed inside the body, a stromal cell, or a cytokine, which is a protein to activate various immune cells. When the unit transplanted the artificial lymph node inside the mouse's body, a strong immune reaction was induced, and consequently they could confirm that it worked as an immune tissue. Moreover, after carrying out further experiments using a mouse in which the immune function did not work, the unit discovered that the artificial lymph node had the ability to trigger a strong immune reaction against serious infectious diseases and cancer. If an artificial lymph node specific to a regulatory T cell, which can control immune cells, can be manufactured, it is likely to be applicable in the treatment for autoimmune diseases and allergies.

Artificial lymph node, from a mouse to a human

The experiments into the artificial lymph node were conducted on a mouse. As a future target, plans are underway to develop an artificial lymph node available for a human.

A method to produce human-originated immune cells by introducing human hematopoietic stem cells to a genetically engineered newborn mouse has been developed, increasing the feasibility of the creation of a human lymph node. Moreover, there are plans to build a system to produce material that plays an important role in immune functions such as a cytokine, and an antibody from an artificial lymph node manufactured in a test tube using cells which base immune cells produced in a human body.

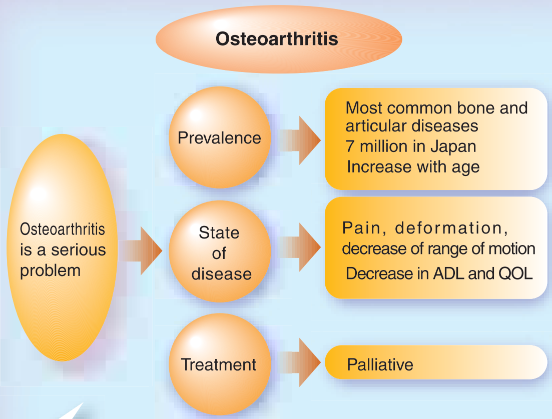
SNP Research Center, Laboratory for Bone and Joint Diseases

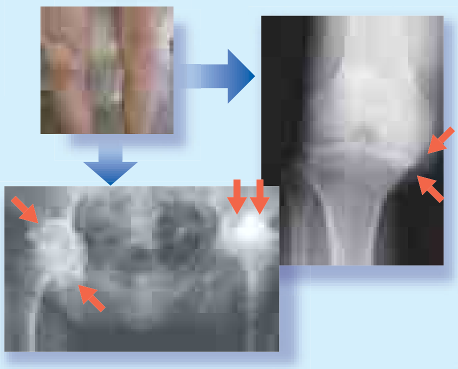
Good news for 7 million patients
Discovery of the causative genes of osteoarthritis

Osteoarthritis is a common disease with which 7 million people are diagnosed just in Japan; however there has been no medical treatment available since the mechanism that causes this disease had not been clarified. Although it had been thought that multiple causative genes were related to the disease, they had not been clearly identified. However, the causative gene of osteoarthritis has now been identified for the first time in the world by Team Leader Shiro Ikegawa and researchers including Hideki Kizawa at the Laboratory for Bone and Joint Diseases, SNP Research Center.

Keywords

1. The cause of osteoarthritis is the asporin gene
2. Genetic polymorphism of asporin correlated to the disease
3. Asporin controls TGF-β
4. Asporin represses regeneration of cartilage





1 Osteoarthritis

Osteoarthritis is a disease wherewith the arthrodial cartilages will disappear. Osteoarthritis will develop in knee joints and hip joints and the osteoarthritis is the disease with the largest number of patients among various bone and joint diseases. 30% of the people with the age of 70 or more are being affected with this disease.

The Voice of Researchers

Shiro Ikegawa
SNP Research Center
Laboratory for Bone and Joint Diseases

Research results to be of great assistance to patients. Research to be carried out by doctors should seek to make such achievements.

Since I am a doctor, researching is just one way to treat my patients. As for the results of this time as well, I am hoping that I can make use of them for actual diagnoses and curative treatments, as the next step.

If it becomes possible to make genetic diagnoses, we will be able to let our patients appreciate the risks and persuade them to improve their life style thus helping them effectively prevent various diseases.

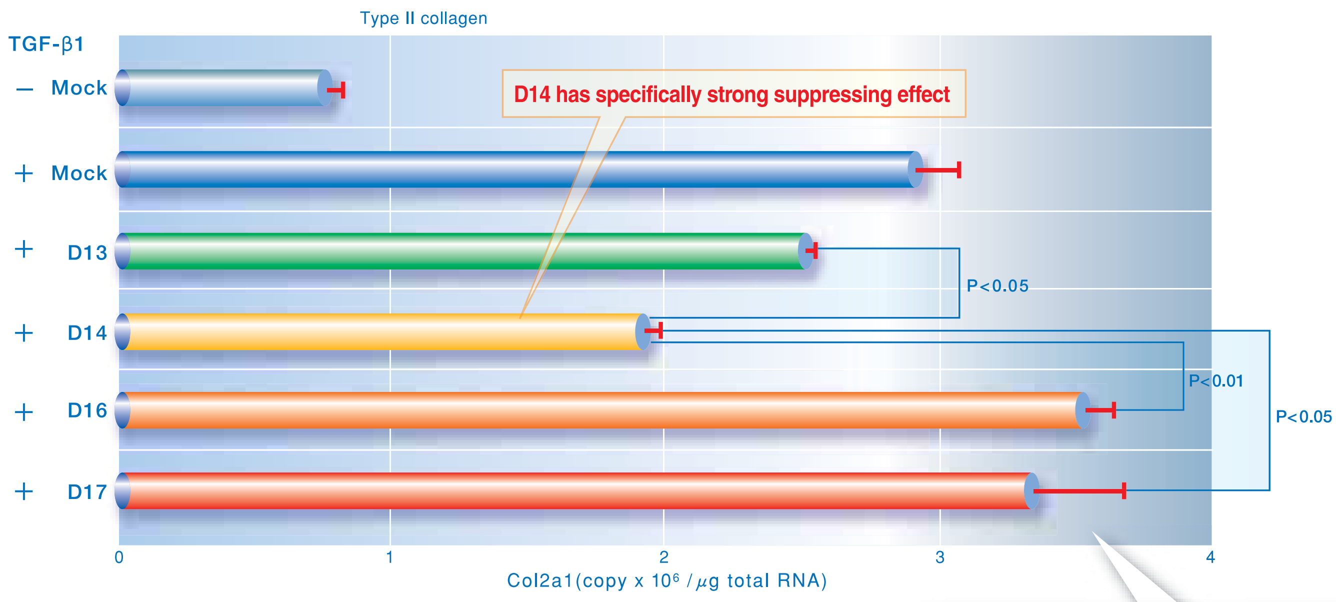
Furthermore, we are willing to found out epoch making treatment methods and curative medicines on the basis of the genetic information thus found. Since the mechanisms to cause diseases have been clarified, we are willing to find out the right methods to control them and to make full use of the results thereof.

What is osteoarthritis?

As people get older, their joints begin to stiffen and frequently cause pain. You often hear that elderly people describe symptoms such as swelling and feelings of pain in their joints. The most common cause generating these kinds of symptoms is osteoarthritis. This is an extremely common disease and 7 million people are diagnosed with this disease just in Japan. In joints between bones, tissues called articular cartilage exist, which are precisely formed so as to aid smooth movement of the joints. The condition in which this particular cartilage gradually vanishes is called osteoarthritis.

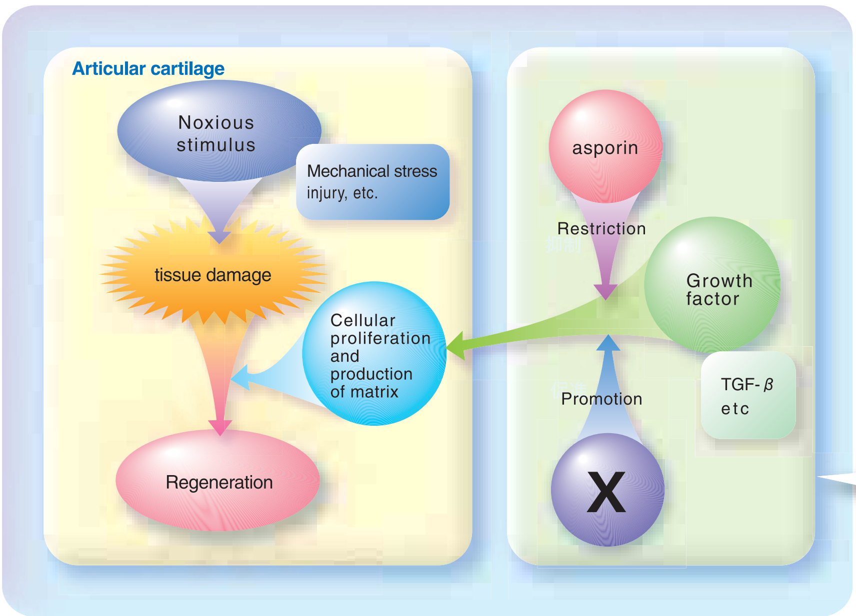
Genetic polymorphism of asporin correlated to the disease

To examine the cause of this disease, research to compare genetic difference between osteoarthritis patients and normal people was carried out. Human genomes are identical at a rate of 99.9%, however there is a slight difference between individuals. Individual differences of these gene sequences are called genetic polymorphisms, of which the relation



2 The effects of asporin is specific with D14

It has been found out that among the asparatic acid being included in asporin, the asparatic acid with 14 times of the sequence repetitions are more tending to cause osteoarthritis. The suppressing effect against the growth factors is specifically strong with the asporin containing the asparatic acid with 14 times of the sequence repetitions seems to be causing the osteoarthritis. In normal case, the number of times of repetitions is 13 and the point is not whether the number of times of repetitions is large or small but it has been found out that it is specific with 14 times of the repetitions.



3 Articular cartilage organizing mechanism mainly with asporin

When the growth promoting substances run out of control, cellular proliferations will expand to cause ossification of cartilages and generation of tumors. When action of growth factors stops by excessive asporin, bones cannot be formed any more and transformation will occur. → osteoarthritis will develop.

to the disease has been actively researched in recent years, primarily at the SNP Research Center. The Laboratory for Bone and Joint Diseases has found that there was a difference in genetic polymorphism between patients and healthy individuals. This was discovered by conducting an analysis based on genetic polymorphism data acquired at the SNP Research Center and using a high-speed, high-volume typing system.

In asporin, a base encoding asparagine is repeated 10 to 19 times. This analysis unraveled the fact that people having 14 repeat in their asporin were twice as vulnerable to this disease as people having 13 repeat which was most commonly observed .

Asporin controls TGF-β

In the affected areas of osteoarthritis patients, a large amount of substances called TGF-β and asporin are produced. TGF-β plays a central role in regenerating cartilage. However, it is not beneficial if the cartilage grows too much due to the TGF-β , and therefore, some repression of regeneration at the right level by controlling TGF-β is required. Analysis of TGF-β functions in cartilage cells clarified that asporin was the repressor of TGF-β . If repression of the asporin is overly effective, regeneration of cartilage does not work, and as a result, people becomes susceptible to osteoarthritis.

Future expectation

Since an osteoarthritis-causing body substance and the genes that produce it were discovered, it is expected that medical treatment for this disease will see major progress. This will be delightful news for a great many osteoarthritis patients in the world. Taking a cue from this discovery, we hope to unlock the second and third causal agent genes.

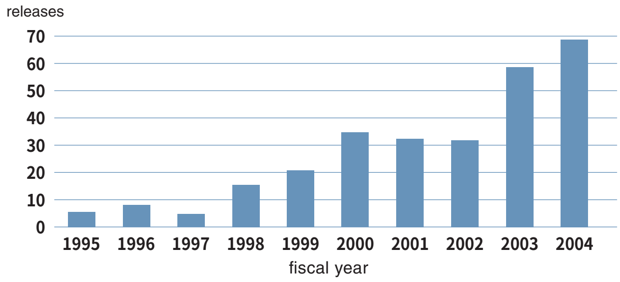
Press releases

In FY2004, RIKEN issued 69 press releases on its research results and research laboratory activities.
Below is a list highlighting those reports by date, title, institute, laboratory, reseacher and venue.

2004

Date	Title	Institute	Laboratory	Researcher	Journal / Conference
Apr. 1	RIKEN launches the Integrated Collaborative Research Program with Industries	FRS	DRI/FRS Research Promotion Division		
5	Public release of the E-Cell2D	DRI	Computational Astrophysics Laboratory	Toshikazu EBISUZAKI	
7	On-site Day-care for Kids opens in Wako Campus	Headquarters	Genral Affairs Division		
8	Elucidation of important work in Bone Morphogenetic Protein (BMP) signaling in hair formation	BSI	Yamada Research Unit	Masahisa YAMADA Munehiro YUHKI	Development 131, 1825-1833 (2004)
9	Conclusion of an inclusive agreement between University of Tokyo and RIKEN	Headquarters	Policy Planning Division		
14	RIKEN Research Center for Allergy and Immunology begins operating at the RIKEN Yokohama Institute	Yokohama Institute	Yokohama Research Promotion Division		
15	Formation mechanism of an intermediate mass black hole	DRI	Computational Astrophysics Laboratory	Toshikazu EBISUZAKI	Nature 428, 724 - 726 (2004)
21	Activation mechanism of homologous recombination hotspot	DRI	Genetics Dynamics Research Unit	Kunihiro OHTA	The EMBO Journal 23, 1792–1803 (2004)
21	RIKEN Super Combined Cluster System has a execution performance of 8 TFLOPS	Headquarters	Advanced Center for Computing and Communication	Ryutaro HIMENO	
23	Appointment of Yoshiyuki Sakaki as the Director of Genomic Sciences Center (GSC) and the Fifth Anniversary Symposium of the GSC	Yokohama Institute	Yokohama Research Promotion Division		
30	Elucidation of structual basis for transcription regulation	Harima Institute	Structural and Molecular Biology Laboratory	Shigeyuki YOKOYAMA	Cell 117, 299-310 (2004)
May. 1	Elucidation of molecular mechanism controlling allergic symptoms	RCAI	Laboratory for Cell Signaling	Takashi SAITO	Nature Reviews Immunology 4, 323 (2004)
7	Determination of the three-dimensional structure of a protein, which plays a central role in DNA recombination	GSC	Protein Research Group	Takashi KINEBUCHI	Molecular Cell 14, 363-374 (2004)
17	Highly sensitive small gene analysis equipment developed	DRI	Bioengineering Laboratory	Mizuo MAEDA	
19	Lamprey Hox genes and the evolution of Jaws	CDB	Laboratory for Evolutionary Morphology	Shigeru KURATANI	Nature 428 (2004); doi:10.1038/nature02616
25	Realization of minute line width of 50 nm exceeding conventional limitations using visual rays	FRS	Exciton Engineering Laboratory	Teruya ISHIHARA	Applied Physics Letters, 84, 4780–4782 (2004)
26	Elucidation of difference in genetic information between humans and chimpanzees	GSC		Yoshiyuki SAKAKI	Nature 429, 382 - 388 (2004)
27	Elucidation of structural basis for proteins responsible for the biological clock	Harima Institute	Kinetic Crystallography Research Team	Hiroaki KATO	Nature Structural & Molecular Biology 11, 623 - 631 (2004)
Jun. 3	The 5th RIKEN Advisory Council held	Headquarters	Research Planning Division		
18	Elucidation of the conformation of the protein that plays an important role in the translation process of genes	GSC	Protein Research Group	Mikako SHIROUZU Shun-ichi SEKINE	PNAS 101,9595-9600 (2004)
28	High-resolution analysis of the movement of protein on genome	GSC	Human Genome Research Group	Katsuhiko SHIRAHIGE	Nature 430, 573 - 578 (2004)
Jul. 9	Elucidation of the three-dimensional structure of phosphomannomutase	Harima Institute	Highthroughput Factory	Naoki KUNISHIMA	The Annual National Meeting of the American Crystallographic Association, ACA, 2004
15	Discovery of the gene for Juvenile Myoclonic Epilepsy	BSI	Laboratory for Neurogenesis	Kazuhiro YAMAKAWA	Nature Genetics 36, 842 - 849 (2004)
16	Computing the seismic wave propagation in the earth's lowermost mantle	DRI	Computational Astrophysics Laboratory	Toshiaki IITAKA	Nature 430, 442 - 445 (2004)
Aug. 2	Success in generating the world's strongest carbon ion beams	DRI	Computational Astrophysics Laboratory	Masahiro OKAMURA	LINAC 2004 - Proceedings, Lübeck, Germany

Annual Press Releases



Date	Title	Institute	Laboratory	Researcher	Journal / Conference
Aug. 3	Release of TraitMap: a genetic-map database combining multigenic loci and biomolecular networks	GSC	Genomic Knowledge Database Research Team	Tetsuro TOYODA	Bioinformatics 20, i152 - i160 (2004)
3	Elucidations of transcription factors interactions	Harima Institute	Structural and Molecular Biology Laboratory	Shigeyuki YOKOYAMA	Cell 118, 297-309 (2004)
19	Results of the 5th RIKEN Advisory Council	Headquarters	Policy Planning Division		
20	Development of world's fastest LSI	Yokohama Institute	High Performance Biocomputing Research Team	Makoto TAIJI	Hot Chips 16, 2004
24	Discovery of new atomic nuclei with superhigh density	DRI	Advanced Meson Science Laboratory	Masahiko IWASAKI	Physics Letters B 597, 263-269 (2004)
Sep. 1	Joint research agreement for development of novel technologies of SNP typing for personalized medcine	SRC	Research Group for Pesonalized Medicine	Yusuke NAKAMURA	
1	Visualization of morphological change of the neuronal circuit in memory formation	BSI	Laoboratory for Molecular Mechanisms of Hippocampal Long-Term Potentiation	Yasunori HAYASHI	Nature Neuroscience 7, 1104 - 1112 (2004)
7	Elucidation of molecular mechanism for Intracellular Tumor Necrosis Factor (TNF) signaling	GSC	Protein Research Group	Shigeyuki YOKOYAMA	Structure 12, 1719-1728 (2004)
8	Identification of a novel lead compound for SARS antiviral drugs	GSC	Protein Research Group	Shigeyuki YOKOYAMA	
8	A new mechanism in the regulation of mesenchymal-epithelial transitions	CDB	Laboratory for Body Patterning	Yoshiko TAKAHASHI	Developmental Cell 7, 425-438 (2004)
17	Elucidation of the mechanism how the Cytotoxic Amphidinolide H Suppresses the Tumor Cell Growth	DRI	Antibiotics Laboratory	Takeo USUI	Chemistry & Biology 11, 1269-1277 (2004)
24	Visualization of the nervous neural activity of the retina	BSI	Laboratory for Integrative Neural Systems	Manabu TANIFUJI	Investigative Ophthalmology and Visual Science 45, 3820-3826 (2004)
24	Discovery of the 113th element	DRI	Cyclotron Center	Kosuke MORITA	Journal of the Physical Society of Japan 73, 2593-2596 (2004)
29	The 1st Korea-RIKEN Workshop on Nanoscience and Nanotechnology	FRS	DRI/FRS Research Promotion Division		
Oct. 1	New research projects in Integrated Collaborative Research Program with Industries started	FRS	DRI/FRS Research Promotion Division		
8	The 2004 RIKEN Public Lecture	Headquarters	Public Relations Office		
18	Elucidation of a new aspect of the pathogenesis of epilepsy	RCAI	Laboratory for Epithelial Immunology	Hiroshi OHNO	Journal of Cell Biology 167, 293-302 (2004)
20	Publication of the paper, "Finishing the euchromatic sequence of the human genome"	GSC		Yoshiyuki SAKAKI	Nature 431, 931 - 945 (2004)
26	Conclusion of an inclusive agreement with Karolinska Institutet	Headquarters	Technology Transfer and Research Coordination Division		
28	Development of short-time analyzing technique in reduced time of the conformation of protein	DRI	Computational Astrophysics Laboratory	Toshikazu EBISUZAKI	Super Computing 2004
Nov. 2	Development of a high efficiency storage method for positrons under ultracold temperature and ultrahigh vacuum	DRI	Atomic Physics Laboratory	Yasunori YAMAZAKI	Phys. Rev. Lett. 93, 195001 (2004)
12	Elucidation of melanin pigment transport mechanism	Headquarters	Fukuda Initiative Research Unit	Mitsunori FUKUDA	Nature Cell Biology 6, 1195 - 1203 (2004)
16	Development of a rewritable optical memory using a new fluorescent protein	BSI	Laboratory for Cell Function Dynamics	Atsushi MIYAWAKI	Science 306, 1370-1373 (2004)
Dec. 3	Successful creation of a plant immune to dry environment	DRI	Plant Molecular Biology Laboratory	Kazuo SHINOZAKI	PNAS 101, 17306-17311 (2004)
6	Development of the RIKEN Arabidopsis cDNA Encyclopedia DNABook™	GSC BRC	Plant Functional Genomic Research Group Genome Exploration Research Group Department of Biological Systems	Kazuo SHINOZAKI Yoshihide HAYASHIZAKI Yuichi OBATA	27th Annual Meeting of the Molecular Biology Society of Japan
14	Experience-dependent pruning of dendritic spines in visual cortex by tissue plasminogen activator	BSI	Neuronal Circuit Development	Takao K. HENSCH	Neuron 44, 1031-1041 (2004)

2005

Date	Title	Institute	Laboratory	Researcher	Journal / Conference
Jan. 7	Identification of the gene for Osteoarthritis, the most common bone and joint disease	SRC	Laboratory for Bone and Joint Diseases	Shiro IKEGAWA	Nature Genetics 37, 138 - 144 (2005)
12	Elucidation of the receptor mechanism of a plant growth hormone at the molecular level	PSC	Laboratory for Growth Regulation	Hideharu SETO	Nature 433, 167 - 171 (2005)
13	Discovery of a redox sensor protein capable of recognizing the oxidation stress of organisms and elucidation of part of the stress control mechanism	BSI	Laboratory for Developmental Neurobiology	Katsuhiko MIKOSHIBA	Cell 120, 85-98 (2005)
14	Success of the large number of cold antiproton accumulation	DRI	Atomic Physics Laboratory	Yasunori YAMAZAKI	Phys. Rev. Lett. 94, 023401 (2005)
19	Investigation of mechanisms for brain asymmetry	BSI	Laboratory for Developmental Gene Reguration	Hitoshi OKAMOTO	Current Biology 15, 238-243 (2005)
20	Conclusion of an inclusive agreement with Saitama Prefecture	Headquarters	Policy Planning Division		
25	Joint research on the identification system of DNA types with National Research Institute of Police Science	SRC	Research Group for Pesonalized Medicine	Yusuke NAKAMURA	
27	Elucidation of a part of molecular mechanism on the olfactory nerve circuit formation	BSI	Laboratory for Neurobiology of Synapse	Yoshiro YOSHIHARA	Development 132, 751-762 (2005)
Feb. 1	Success in the preparation of cerebral precursor cells from embryonic stem cells	CDB	Laboratory for Organogenesis and Neurogenesis	Yoshiki SASAI	Nature Neuroscience 8, 288 - 296 (2005)
2	Successful observation of a non-linear optical phenomenon in the X-ray region	DRI	Laser Technology Laboratory	Katsumi MIDORIKAWA	Phys. Rev. Lett. 94, 043001 (2005)
14	Transition of an insulating organic crystal to a metallic state by one shot of light irradiation	DRI FRS	Condensed Molocular Materials Laboratory Exciton Engineering Laboratory	Reizo KATO Teruya ISHIHARA	Journal of the Physical Society of Japan 74, 511-514 (2005)
15	Development of a method to search for unidentified target proteins using a non-natural amino acid	GSC	Protein Research Group	Shigeyuki YOKOYAMA	Nature Methods 2, 201 - 206 (2005)
23	Identification of Robo2 as a crucial gene for neural circuitry formation in the Zebrafish olfactory system	BSI	Laboratory for Neurobiology of Synapse	Yoshiro YOSHIHARA	Development 132, 1283-1293 (2005)
Mar. 3	Development of snake-shaped robot moving with artificial muscle	FRS	Biologically Integrative Sesors Laboratory	Toshiharu MUKAI	12th SPIE Annual International Symposium on Smart Structures
14	Invasive visualization of the accumulating condition of a causative substance of Alzheimer's disease	BSI	Laoboratory for Proteolytic Neuroscience	Takaomi SAIDO	Nature Neuroscience 8, 527 - 533 (2005)
19	Discovery of a new therapeutic target for Alzheimer's disease	BSI	Laoboratory for Proteolytic Neuroscience	Takaomi SAIDO	Nature Medicine 11, 434-439 (2005)
24	Elucidation of the structure of causative agent of hyperglycinemia	Harima Institute	Advanced Protein Crystallography Research Group	Nobuo KAMIYA	Phys. Rev. Lett. 94, 103904 (2005)
25	New non-linear optical phenomenon revealed with photonic crystals	FRS	Nanoscience Research Program	Shin-ichiro INOUE	The EMBO Journal 24, 1512-1522 (2005)

Classification

Category	RIKEN Press releases	Press releases issued by jointly but initiated by another institute	References
Research Results	55	10	8
Others	14	5	4
Total	**69**	**15**	**12**

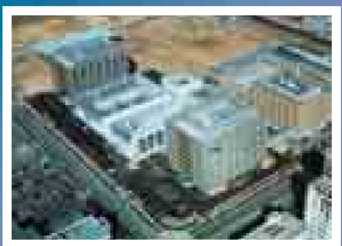
Organization	RIKEN Press releases	Press releases issued by jointly but initiated by another institute	References
Discovery Research Institute (DRI)	15	4	1
Frontier Research System (FRS)	6		1
Brain Science Institute (BSI)	12	1	1
Initiative Research Unit (IRU)	1		
BioResource Center (BRC)		1	1
Harima Institute	5		1
Genomic Sciences Center (GSC)	11	5	
Plant Science Center (PSC)	1		
SNP Research Center (SRC)	3	1	2
Research Center for Allergy and Immunology (RCAI)	2		2
Center for Developmental Biology (CDB)	3	1	
Others	10	2	3
Total	**69**	**15**	**12**

Research institutes and centers

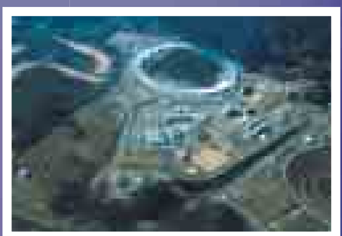
Organization

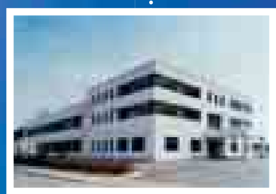
RIKEN spans across Japan

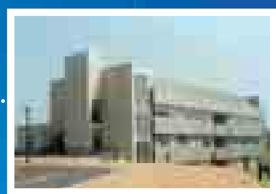
RIKEN currently has five institutes and two research centers at various locations in Japan. They conduct research on a broad range of subjects and seek to collaborate whenever possible. Activities are coordinated at RIKEN Headquarters located on the Wako campus.

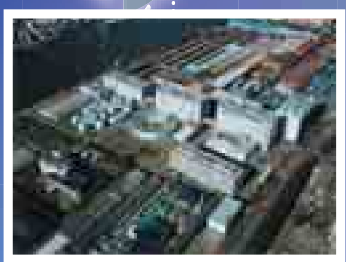

Kobe Institute

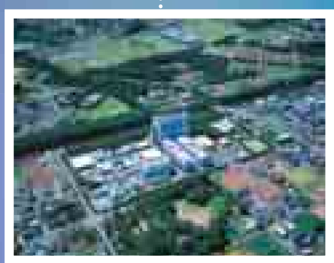

Wako Institute


Harima Institute
(SPring-8)


Photodynamics Research Center (Sendai)


Bio-Mimetic Control Research Center (Nagoya)


Yokohama Institute


Tsukuba Institute

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- Research Collaborative Group

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Harima Research Promotion Division
Harima Safety Center
- Institute Laboratories
- Division of Bio-Crystallography Technology
- Synchrotron Radiation Research Network
- Advanced Protein Crystallography Research Group
- Research Collaborative Group

RIKEN Yokohama Institute
Yokohama Research Promotion Division
Yokohama Safety Center
- RIKEN Genomic Sciences Center
- RIKEN Plant Science Center
- RIKEN SNP Research Center
- RIKEN Research Center for Allergy and Immunology

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

Wako

The facilities in Wako contain cutting edge technologies

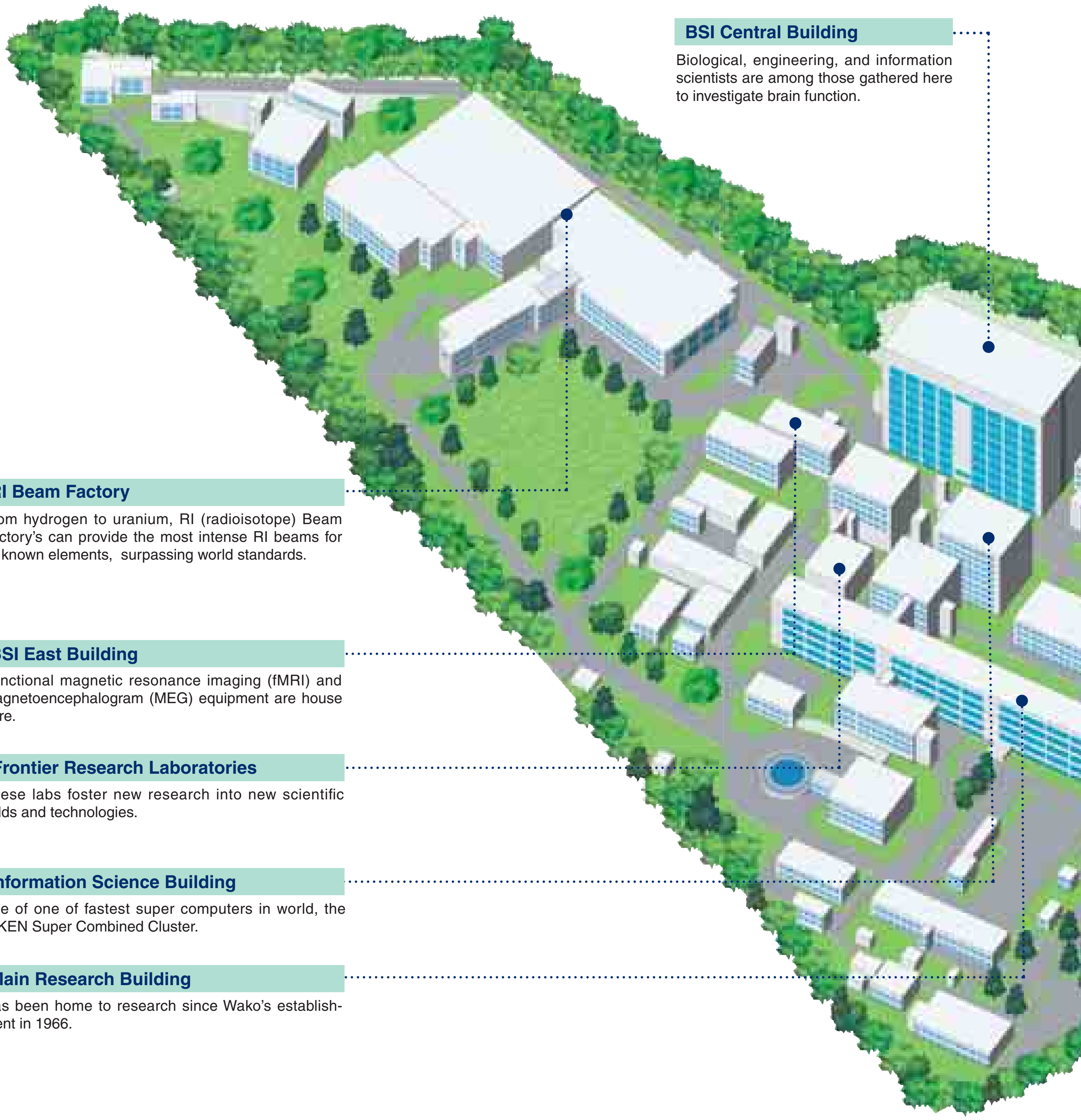
The campus also houses RIKEN Headquarters and the Wako Institute, which incorporates Discovery Research Institute, Frontier Research System, Brain Science Institute, Initiative Research Units, and Sponsored Laboratories.

1917

RIKEN Foundation established in Tokyo. Komagome Building No.1 is shown here.

1938

60-inch Cyclotron completed.



BSI Central Building

Biological, engineering, and information scientists are among those gathered here to investigate brain function.

RI Beam Factory

From hydrogen to uranium, RI (radioisotope) Beam Factory's can provide the most intense RI beams for all known elements, surpassing world standards.

BSI East Building

Functional magnetic resonance imaging (fMRI) and magnetoencephalogram (MEG) equipment are house here.

Frontier Research Laboratories

These labs foster new research into new scientific fields and technologies.

Information Science Building

Site of one of fastest super computers in world, the RIKEN Super Combined Cluster.

Main Research Building

Has been home to research since Wako's establishment in 1966.

1967

Wako campus opened.

1987

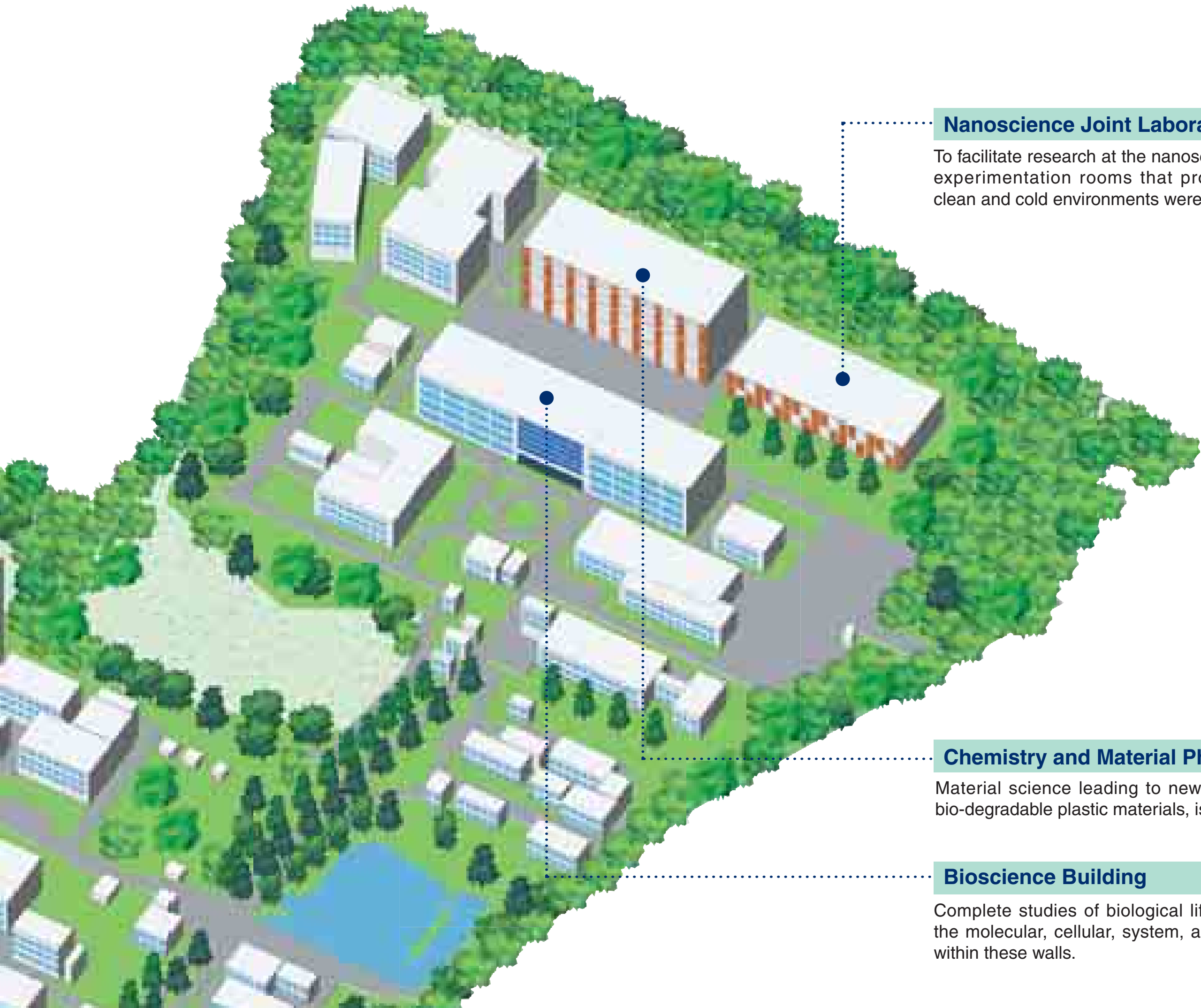
Ring cyclotron completed.

1992

Japan's Emperor visited Wako Institute.

2005

RI Beam Factory being built.



Nanoscience Joint Laboratories

To facilitate research at the nanoscale, advanced experimentation rooms that provide suitably clean and cold environments were built.

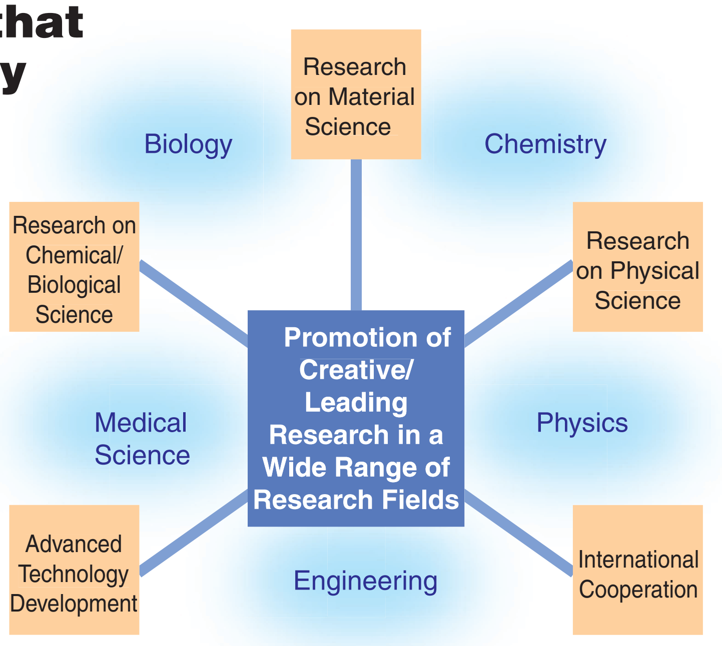
Chemistry and Material Physics Building

Material science leading to new materials, such as bio-degradable plastic materials, is conducted here.

Bioscience Building

Complete studies of biological life are conducted at the molecular, cellular, system, and organism levels within these walls.

The research system that has created the history of RIKEN



The Discovery Research Institute (DRI) houses Chief Scientist System-based curiosity-driven laboratories (Chief Scientist Laboratory) under a flexible cross-disciplinary approach operation, and is promoting creative and groundbreaking research.

The basic policy behind the Institute's research activity is to promote topical research in frontier science and technology by giving each laboratory free reign to explore its own ideas in the competitive environment of RIKEN. Additionally, the goal is to encourage a collaborative structure for cross-disciplinary research in pulling together the achievements of each of the laboratories, to give rise to new cross-disciplinary and integrated fields of research, and to germinate the seeds for commercial application out of basic scientific experimentation (research of next generation nanoscience technology to elucidating physical phenomena in the nanoscale world and research on the molecular level conducive to environmental protection).

The Cyclotron Center is promoting heavy ion science research using the accelerator equipment presently in place and providing technical support for it. The Discovery Research Institute, furthermore, is in the process of building an RI beam factory (RIBF) that will be a next-generation heavy ion accelerator for generating RI beams of all the elements from hydrogen to uranium covering the widest range of elements with beam intensities far exceeding the current global standard.

message

Director
Koji Kaya
Discovery Research Institute

The past year and the future of the Discovery Research Institute

One and a half years have past since RIKEN was reestablished as an Independent Administrative Institution. The Discovery Research Institute is a comprehensive research institute with an 88 year history since RIKEN was established. It has been playing a role as a pioneering research institute to undertake out-of-the-box research based on researchers' creativity. With RIKEN's re-establishment as an Independent Administrative Institution, we have initiated major organizational reforms that will encourage outstanding young scientists to freely pursue creative research while at the same time giving our chief scientists the higher status and solid foundation they need to become world-class leaders in their respective fields of endeavor.

Thinking back over the past year of the Discovery Research Institute, we could release reports in a wide variety of study results: creation of a new element (atomic number 113) by researchers including Senior Scientist Morita, Cyclotron Center, observation of local electronic geometry which will lead to the unlocking of the mechanism of high-temperature superconductivity (by researcher Hanaguri, Magnetic Materials Laboratory), observation of nonlinear effect using soft X-ray laser (Chief Scientist Midorikawa, Laser Technology Laboratory), elucidation of protein translocation mechanism in cells (researcher Sato, Molecular Membrane Biology Laboratory). All these results gave great impact on their related fields. Particularly, the creation of the new element was an innovative result which attained the ultimate of the root element of the matter. It was achieved based on long-term dedicated research.

The Cyclotron Center was separated from the Discovery Research Institute in 2005. It will be relocated to the Frontier Research System to reach maturity as a center, and after that, will start independent operation. It is exciting to think about the future of the heavy ion accelerator science Center as it evolves into the world's leading ion accelerator facility.

It is considered that huge equipment-based research will be referred to the Heavy Ion Accelerator Science Center and the Harima Institute. Thus, they should be operated depending on their severity according to their respective situations. For research conducted in the Discovery Re-

The Advanced Development Supporting Center is developing advanced research infrastructure tools and also providing advanced technical and analytic support.

For research cooperation with overseas institutes, the Institute built a muon generation facility as an ancillary facility of the world's highest proton accelerator ISIS in the Great Britain's Rutherford Appleton Laboratory (RAL), undertaking muon science research. In addition, it built an experimental work facility in the Relativistic Heavy Ion Collider (RHIC) which is in the United States' Brookhaven National Laboratory (BNL), and established the RIKEN BNL Research Center (RBRC) using research potential of both Japan and US to implement frontier research including research of spin physics.

Overseas strongholds

1 RIKEN Facility Office at RAL U.K.

Based on the international research cooperation agreement on muon science research entered into with the Great Britain's SERC (current CCLRC), it built a muon generation facility in the Great Britain's Rutherford Appleton Laboratory (RAL) as an ancillary facility of the world's highest proton accelerator ISIS. Simultaneously with the completion of the facility, it opened RIKEN RAL to undertake full-scale muon science research.

2 RIKEN BNL Research Center(RBRC) U.S.A.

Based on the international research cooperation agreement entered into with the United States' BNL, it installed an experimental work facility in the world's only Relativistic Heavy Ion Collider (RHIC) in BNL. In addition, it opened "RIKEN BNL Research Center" in 1997, a new research system using research potential of both Japan and US. Under this system, it is promoting frontier research including spin physics research.

search Institute, Harima Institute, and Heavy Ion Accelerator Science Center, intrusive, cooperative and flexible discussions should be constantly carried out based on shared responsibility under the Chief Scientist System. We should not forget that their common duty is to take the head of Japan's basic research by smoothly separating operational independency and research-related collaborative activities.

Project-based research of life science in RIKEN is supported as national strategic research. It has achieved advanced results, some of which should be continued on a long-term basis without completing them as just projects. It is one of the important challenges for the next year that the Discovery Research Institute operated under the Chief Scientist System works as a pillar of research promotion based on a long-range outlook across RIKEN to build a research system without being constrained to the retirement and fixed-term systems by raising continuance of excellent research as a common issue.

Main activities in FY 2004

2004 [Review committee]	
Nov. 16-17	RBRC Scientific Review Committee
Nov. 18-20	RIBF International Advisory Committee
2005 [RIKEN conference]	
Feb. 15-17	Partial Restoration of Chiral Symmetry In Nuclei and Nuclear Matter
2004 [RIKEN symposium]	
June 29	The First Environmental Molecular Science Symposium
Nov. 29-30	Molecular Ensemble 2004
2005 [RIKEN symposium]	
Feb. 4	The Second Chemical Biology Symposium
March 8	Simulation Research on Biodynamic
March 9	Research on Digitalization of Living Organism's Shape and Building a Database
March 10	The Second Environmental Molecular Science Symposium

(A total of 28 symposiums were held including the above.)

Opening new fields through project-oriented research

Research Activities of the Frontier Research System

Multiple-field
- Supra-Biomolecular System Research Group
- Spatio-Temporal Function Materials Research Group
- Single Quantum Dynamics Research Group

Linking with Regional Potential
- Photodynamics Research Center
- Bio-Mimetics Control Research Center

Collaboration within RIKEN
- Nanoscience Research Program

Linkage with Industry
- Integrated Volume-CAD System Research Program
- Integrated Collaborative Research Program with industry

The Frontier Research System (FRS), originally established in October 1986 as the International Frontier Research Program, is a pioneering, project-oriented research organization that seeks to gather the very best domestic and overseas research talent on a limited contract basis for goal oriented, time limited research projects covering a wide range of fields. Its establishment came about as a result of a consideration for the need for a flexible, project-oriented research organization able to respond swiftly to the most recent trends in research worldwide. In 1997, RIKEN's Brain Science Institute was spun off from FRS as a separate institute, and since then a number of new, project-oriented research organizations have been established on the FRS model both within RIKEN and without. These facts serve to show the high acclaim that the FRS organization model has received and the amount of attention that it is getting.

In addition to the organizational model that FRS was built around, it has also been the mission of FRS to link up RIKEN's research potential with that of the outlying regions of Japan by establishing research centers there. Centers in Sendai and Nagoya were established in 1999 and consolidated with the main Wako campus Frontier organization to create FRS as we know it today. Starting in April 2004 FRS' flexibility allowed it to add on two new programs which continue to operate in a multifaceted and flexible manner.

The first, the Nanoscience Research Program, got its start as the Nanoscience Research Program Promotion Division, established in December 2002. With the construction of the Nanoscience Joint Laboratory, fully equipped with state-of-the-art equipment, researchers from all over RIKEN, including FRS, can propose research projects, join nanoscience research sub-teams and participate in leading-edge nanoscience research. The second program was the Volume-CAD System Research Program.

Once again, in 2004 a new trial program was begun that aimed to link research with industry, called the Integrated Collaborative Research Program. This program provides a unique platform for the development of industrial technology, one that is hoped will contribute to the development into the 21st century of Japan's industrial technology.

message

Director
Ei'ichi Maruyama
Frontier Research System

Frontier research activities during 2004-5

In 2004, the Frontier Research System (FRS) added to its existing research groups several new initiatives. It established the Integrated Collaborative Research Program and the Nanoscience Research Program, and took over the Volume-CAD System Research Program with the aim of clarifying a policy of closer integration with industry both within RIKEN and without.

However, FRS was then advised by both its own Frontier Advisory Council (FRAC) and the RIKEN Advisory Council (RAC) that these moves should cause it to reexamine its mission, which it did. Led by its executive board, RIKEN looked once again at FRS, and decided that FRS should concentrate on a) integrated, collaborative research toward opening new fields or investigating new issues in science and technology, and b) the incubation of new research centers. As a result of this, in 2005 a new initiative called the Center for Intellectual Property Strategies was created for deepening ties with industry, further clarifying FRS' mission to incubate and spin off new centers.

While all of FRS' research projects have produced solid results, among the more impressive has been the terahertz imaging project conducted in the Photo Dynamics Center in Sendai; much is to be expected of the non-intrusive, safe imaging that has been shown possible in the terahertz waveband. In the Bio-Mimetics Control Research Center as well, a "snake" robot and other robotics technology has been developed worthy of exhibition at the Expo 2005 in Aichi Prefecture, increasing the expectant anticipation of the technology being developed there.

This year, 2005, represents the 100th anniversary of the miracle year in which Einstein published three research papers which changed the world, and as such has been designated "International Physics Year." FRS, for its part, is contributing toward the furtherance of Einstein's work through its Single Quantum Dynamics Research Group, doing basic research toward the eventual realization of a quantum computer. In the Supra-Biomolecular Research Group, work continues on elucidating the roles of glycochains and lipids, knowledge which will form the foundation of new disease treatments.

Japan's nanoscience research contributes to strengthening the industrial base by developing key technologies in the parts and materials industries. This field is being advanced at FRS in

History of the Frontier Research System

Mission of FRS at inception: The advancement of basic research into unexplored, leading edge areas of science and technology

1986 Frontier Research Program established
(name changed to Frontier Research System in 1999)

1990 Photodynamics Research Center established in Sendai, Japan

1993 Bio-Mimetic Control Research Center established in Nagoya, Japan

1997 FRS Brain Science Research programs spun off to create RIKEN Brain Science Institute

1998 Earthquake Disaster Mitigation Research Center in Miki, Japan established;
transferred in 2001 to National Research Institute for Earth Science and Disaster Prevention

Mission expanded: Strengthen linkage with industry

2004 April Volume-CAD System Research Program* transferred to FRS, and Nanoscience Research Program inaugurated

Oct Integrated Collaborative Research Program* inaugurated

Mission reevaluated:
- Integrated, collaborative research toward opening new fields or investigating new issues in science and technology
- The incubation of new research centers

Toward a new FRS

New framework for calling for proposals from the various research centers of RIKEN
(development of new, strategic fields, reorganization of existing research organizations and assets)

*These two organizations transferred to the Center for Intellectual Property Strategies in 2005

spatio-temporal functions and materials research, which focuses on utilizing self-organization to elucidate functional dynamics throughout the range from the nano- to the micro-scales.

All of FRS current research projects will soon reach or have already passed their halfway points, and continue to work to not only clarify their own research objectives, but to make more easily visible and transparent contributions to society.

Main activities in FY 2004

2004	
April 1	- FRS reorganized with addition of the Volume-CAD System Research Program and inauguration of Nanoscience Research Program - Integrated Collaborative Research Program with Industry inaugurated and call for project proposals issued
April 7-8	Frontier Research System Advisory Council held
Oct. 1	- Seven proposals selected from among those received in April for initiation as Integrated Collaborative Research Program with Industry projects - Specific rules established for the development of strategic fields and the reorganization of research organizations and assets
2005	
Feb. 15	Second RIKEN Nanoscience Symposium

To better understand humankind, the Institute investigates the mysterious workings of the brain

The expectations for advances in brain science, as one of the last remaining frontiers of the natural sciences, in the 21st century are high. Anticipated advances include developing an understanding of higher level mental functions, approaches to treat or prevent difficult diseases such as Alzheimer's disease, and computer systems modeled on the brain that may lead to new technologies and industries.

Therefore, in October 1997, those laboratories researching the brain and neuron function as part of RIKEN's Frontier Research System became the first laboratories of the Brain Science Institute. This institute was, and is, charged with conducting broad investigations of the brain. Research at BSI is interdisciplinary, international, and innovative.

The brain is the source of all mental function, or the mind. Hence, approaches in brain science seeking to understand the complexities of mental function must be interdisciplinary. This is why life, information, and social sciences are all integral elements of the neuroscientific investigations at BSI.

Good science transcends national borders. As a leading international neuroscience institute, BSI established English as its common language. One-fifth of its research staff and laboratory and unit leaders are non-Japanese. Hence, BSI is well positioned to negotiate international collaborations and partnerships on Japan's behalf.

BSI pursues innovative research in part by employing younger researchers under a fixed-term contract. Researchers are typically in their mid-thirties and they work together to achieve their goals. BSI will continue to encourage interdisciplinary collaborations between its researchers in the hope that this cross-fertilization will yield new approaches, methods, materials and technologies that push brain science forward.

The research system at BSI focuses these larger elements into four targeted research areas: "Understanding the brain", "Protecting the brain", "Creating the brain", and "Nurturing the brain". Listed on the next page are some of the 2004 achievements to emerge from these areas.

RIKEN MIT Neuroscience Research Center

Established in 1998 on the MIT Campus as a collaborative agreement between RIKEN BSI and the Massachusetts Institute of Technology (MIT) to accelerate progress in brain science, this center nurtures cross-pollination of ideas through annual joint seminars and researcher transfers.

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message

Director
Shun-ichi Amari
Brain Science Institute

The last year at BSI

In 2004, BSI firmly established its international name in brain science. Over the year, its research activities exceeded the standards set by the international community and earned the Institute increased recognition for its unique international and interdisciplinary research system. Of all its achievements, three stand above the rest for their broad contributions.

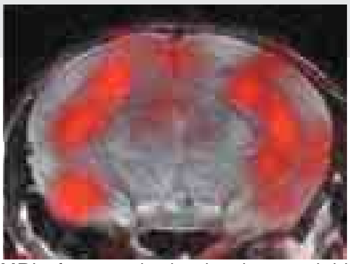
First, investing the causes of Alzheimer's disease, Takaomi Saido and his research team in the Laboratory for Proteolytic Neuroscience in "Protecting the brain" successfully advanced our understanding of amyloid beta's contribution to the disease. A few years ago, they identified neprilysin's protective role in preventing the build up of amyloidal plagues in the brain, one of the pathological hallmarks of Alzheimer's disease. This finding created international waves. The lab then found a ligand that activates this protective enzyme that might lead to a promising pharmacological therapy.

Second, researchers in "Nurturing the brain" in the Laboratory of Takao Hensch, succeeded in uncovering the mechanisms regulating development of the visual cortex. Through this work, they identified several of the proteins essential to the morphological changes and provide a new insights into normal brain development.

The final achievement came out of the Laboratory for Cell Function Dynamics, led by Atsushi Miyawaki, in BSI's unique research group, Advanced Technology Development Group. This group was created to research and develop the technologies and materials needed to support the cutting-edge research of the laboratories working in BSI's four research areas. Miyawaki's team followed up their successful development of *Kaede*, a fluorescent protein that is widely used around the world, with *Dronpa*. This new fluorescent protein can rapidly switch between its active and inactive states to enable selective imaging of cells and their functions.

International cooperation also expanded in 2004. A research agreement with a laboratory at the Ècole normale supèrieure in France which will also facilitate graduate student training. Through a RIKEN wide agreement, collaborative investigations with Karolinska Innstitutet in Sweden are also underway. Other agreements with Harvard University for periodic graduate school training, the OECD for an International Neuroinformatics project, and a Pacific Rim Re-

BSI's 2004 research activities and areas


MRI of mouse brain showing amyloid plaques.

"Understanding the brain"
The complex weave of over 100 billion neurons governs how the brain functions, and the two research groups in this area investigate how these neurons do what they do. The Neuronal Circuit Mechanisms Research Group studies the brain's basic mechanisms and the structures and functions of neural circuits. The structure and functions of the cerebral cortex, which is responsible for higher cognitive processing especially in humans, is studied by the labs of the Cognitive Brain Science Group using magnetic resonance imaging (MRI) and other imaging technology. The Laboratory for Integrated Neural Systems in this group successfully imaged the retinal responses of macaques in response to light stimulus. Their study was the first study in primates.

"Protecting the brain"
This area seeks to uncover the causes of neuropsychiatric diseases and the aging of the brain. There are three research groups in this area. The Molecular Neuropathology Group searches for the genes associated with brain diseases, and the Aging and Psychiatric Research Group investigates the molecular mechanisms of Alzheimer's disease and mental disorders. The final group, the Neural Growth and Regeneration Research Group, is looking for ways to repair damage to neurons. The laboratories in this area have made significant contributions in understanding and treating various disorders, including Alzheimer's and Parkinson's diseases.

"Creating the brain"
The ultimate goal of the laboratories in this area is to create a computer that can think spontaneously, like a living brain. Labs here have successfully developed a model system showing the relationship between thought and memory, and revealed how information integration occurs during cognitive and emotional acts. Another lab used a


Image of MRI used to detect amyloid plaques using a novel technique developed at BSI.

robot that may explain how a neural system might process language.

"Nurturing the brain"
The brain and mind grow as the human new born becomes a child and later an adult. The laboratories in this area are working to understand how a healthy brain develops. Visual stimulation can reconfigure the connections within neural circuits in an animal's brain when that stimulus occurs during particular time windows in early development, called critical periods. As the Laboratory for Neuronal Circuit Development has successfully manipulated the time course of this process by drug administration, they provide new insights into brain development.

search Cooperation project involving the United States, China, Australia, and Japan are now nearing completion.

2004 was an important year for "Creating the brain", which underwent an international review. The committee praised BSI's pioneering step, leading the world in establishing a computational neuroscience group to understand the brain and incorporate their results into innovative information technologies. It then recommended increasing industrial cooperation and further developing the area.

Main activities in FY 2004

2004	
4/12-4/14	BSI Advisory Council meeting
6/28-8/27	BSI Summer Program Internship Course
7/6-7/16	BSI Summer Program Lecture Course
9/13-9/14	The Fourth CDB-DRI-BSI Joint Forum
9/22-9/24	The Fourth RIKEN-MIT Symposium
9/28	"Creating the brain" International Workshop
9/29-10/1	"Creating the brain" Research Review
10/4-10/6	BSI Retreat
11/18-11/20	Japan-Korea-China-India Workshop
2005	
3/12	World Brain Awareness Week 2005—special event

Foundation for Discoveries and Access to the Future

The Tsukuba Institute started as the Tsukuba Life Science Research Center in 1984 and has been involved in cutting-edge research and development concerning genes.

The facility was renamed the RIKEN Tsukuba Institute in April 2000, and began housing a BioResource Center in January 2001 for undertaking the collection, preservation and distribution of biological resources, and the development of novel technologies for exploiting these resources.

BioResource Center

Biological resources (bioresource) such as experimental animals and plants, cellular material, microorganisms and genetic material are essential elements for advancement of life science research.

The BioResource Center (BRC) has been conducting its activities in close collaboration with domestic and overseas institutions; it collects and preserves a wide range of bioresource, provides strictly quality-controlled bioresource and relevant information for domestic and overseas researchers. It also develops novel bioresource and technologies for quality control and analysis, and provides training cources for handling bioresource.

In the National BioResource Project launched in 2002 by the Ministry of Education, Culture Sports, Science and Technology, the Center was selected as a core facility for experimental animal (mouse), experimental plant (Arabidopsis), human and animal cell materials, and genetic material, and since then it has been committed to be a driving force of the National Project.

message

Director
Kazuo Moriwaki
BioResource Center

Track of the RIKEN BioResource Center

After an investigation for over a year by the Sugano Preparatory Committee, RIKEN BioResource Center was established in Tsukuba Research Institute in 2001 as a full-scale independent institution designed for developing an intellectual basis for life science. There are only a few full-scale centers for bioresources in Japan of course and in the world.

Since its foundation, this center has been managed under three basic guiding principles of trust, sustainability and leadership. The enterprise activities of the center were centered on two pillars. The first pillar deals with collection, conservation and provision of the five resources consisting of live stocks of mouse, Arabidopsis (thaliana), cells and genetic materials of humans, animals and plants, microorganisms and information on the resource characteristics and location. The second pillar is research and development on the resource characteristics and their conservation technologies.

In 2002, our center participated to the National BioResource Project sponsored by Ministry of Education, Culture, Sports, Science and Technology (MEXT) as the core organization for the five resources. We have achieved the expected results including the collection of 1,500 strains of mice, 250,000 stocks of Arabidopsis, and the cells of 2,300 strains for the development of an intellectual basis for Japan's life science. In recent years, we have been recognized as an important resource center together with the Jackson Laboratory of U.S. and the EMMA Group in Europe in the field of the mouse.

In the sphere of development and research, this center has achieved valuable results closely associated with its target resources. They include genetic analysis of wild mouse strains of Asian origin, technical development of microscopic fertilization of mouse embryos and nucleus transplantation, technical development of trace constituent analysis of plant organisms, and resolution of the stem cell differentiation mechanism. Moreover, for the mouse, Arabidopsis and microorganisms, this center is carrying out resource collection and characteristic development by making the most of its regional identity in Asia.

In view of the fact that this center obtains resources from all over Japan as the principal object of collection and development, a review committee has been established for each resource and meetings are held periodically to hear the opinions of Japanese researchers involved in the management of the resources. In addition, an advisory council (BRAC) meets every two years and reports are prepared with the purpose of giving guidance and advice to the management of this center from a broader point of view. This report is forwarded to the RIKEN Advisory Council (RAC). In 2004, RAC fully recognized

BRC in FY 2004

BRC, the heart of the Tsukuba Institute conducts the collection, preservation, development, characterization of bioresources and relevant information, and provides them for research institutes in Japan and overseas as describe above. In recent years, as sequencing of DNA has advanced, the central aim of the research is shifting to learn functions of genes. To meet such demands, BioResource Center carries out the collection and preservation of live stocks, cells, genetic materials, and relevant information in order to provide important bioresources required for the research. In addition, development of new bioresources and technologies for preservation is carried out in BRC. Furthermore, the BRC has started to give training courses to promote the efficient use of bioresources.

In the Tsukuba Institute, there are three research collaborative groups to enrich bioresources.

Shinozaki Research Collaborative Group undertakes the production of an mutant Arabidopsis by engineering or partially destroying its genes to analyze the function of plant genes at an individual organism level.

Ishii Research Collaborative Group undertakes the research on the function of transcription factors of mainly mouse and drosophila models. Transcription factors control development, growth and illness of animals and also play an important role in protection from diseases, and the process behind how it is generated as an egg and grows into an adult.

The third, Shiroishi Research Collaborative Group, undertakes the innovation of fundamental generic technology mainly using a mouse in the production of allelic mutants, and gene function analyses based on the allelic mutants produced.

BRC also handles human materials such as cells and DNA. In 2004, it started to provide cord-blood stem cells for research as exemplifies these bioresource. Like this, the Institute is to handle research materials significantly involved in the ethics issues, i.e., human and animal genes. From this point of view, the Institute is expending all possible means to assure safety, environmental protection, and bioethics such as nonproliferation of genetically-engineered organisms, the ethical review of research using human materials, and planning of experiments without causing pain to animals.

the importance of this center. Having become an independent administrative institution, this center is assessed by the Independent Administrative Institution Assessment Board of MEXT.

It was favorably assessed by the Board for fiscal 2004. Furthermore, every year, this center is required to explain its annual projects to the Council for Science and Technology Policy. The rating for this center was "S" for the fiscal 2004 and "A" for 2005.

We are determined to carry on steady and recurring activities in the center's areas of collection, conservation and provision in the future. At the same time, we will be required to undertake anew development by setting our sights on new needs from the research community, such as human stem cells and normal cells and genetic materials of the living species representing principal taxonomical phylla. We will be required to make efforts in achiheving higher added-value for the resources in our development and research activities. It is our fervent desire that this center will continue to carry on activities as the intellectual basis of life science in Japan for a long time in the future.

Main activities in FY 2004

2004	
March 19	"Experimental Animal (Mouse) Symposium in National BioResource Project-Achievement report and International Circumstances Surrounding Experimental Model Mouse" (Tokyo).
April. 16-19	Open House.
July 1	Japan Collection of Microorganisms under control of the Discovery Research Institute was integrated into the BioResource Center as the Microbe Division.
Sep 29	National BioResources Project Arabidopsis Symposium (Tokyo).
Oct	Technical training courses started (on experimental animals and plants).
Nov. 19-21	Participated in the 1st Mouse Resource Centers Round Table.
Nov. 29 to Dec. 2	Participated in OECD Global BRC Network Conference (France).
Dec. 8-11	Participated in the Molecular Biology Society of Japan and presented achievements (Kobe). Panel exhibition (Dec. 8-11). National BioResource Project Symposium (Dec. 9).
2005	
Jan.11-20	Resource Committees (six committees on experimental animal, experimental plant, cell material, genetic material, microbial material, and information) (Tokyo).
March 22	BRC symposium "Thoughts on BioResources" (Tsukuba).

Creating new light, performing observations with invisible light

The Harima Institute was established in Oct. 1997 to collectively promote frontier research into synchrotron radiation obtained by the large-scale synchrotron radiation facility (SPring-8). SPring-8 constructed jointly with the Japan Atomic Energy Research Institute at the Harima Science Garden City in Nishi Harima, Hyogo Prefecture, has the largest capacity in the world, boasting beam energy of 8 billion electron volts and is widely accessible facility shared by universities, government research institutions, and private industry.

The Institute undertakes the research of structural biology for gaining a deeper understanding of the mechanism of bio-phenomena by unlocking the three-dimensional structures of living organism-composing proteins with the use of synchrotron radiation. Moreover, it promotes the physics of the generation of coherent X-rays and their applications. In this way, SPring-8's potential as a next-generation synchrotron radiation emitter can be fully exploited in giving rise to new fields of research.

The Institute since 1999 has also been a hub for collaborating with universities in consolidating the research potential of SPring-8 and pioneering new and groundbreaking fields of experimentation with synchrotron radiation.

Additionally, since 2002, the Advanced Protein Crystallography Research Group has been utilized in cooperation with the RIKEN Yokohama Institute as part of RIKEN Structural Genomics/ Proteomics Initiative in undertaking the cyclopedic analysis of protein structure.

What is SPring-8?

SPring-8 is the world's largest third-generation synchrotron radiation facility. Its construction began in 1991 by RIKEN in collaboration with the Japan Atomic Energy Research Institute. It took approximately six years before completion, and in October 1997, it began operations as a widely opened public facility. A great number of users gather here to promote frontier research bearing into the 21st century.

To promote public use of SPring-8, the Japan Synchrotron Radiation Research Institute (JASRI), which is specified by the government as a synchrotron radiation-based research promotion organization, is responsible for the management, operation and development of the facility.

SPring-8 is the nickname of the large-scale synchrotron radiation facility, with its origin in Super Photon ring-8 GeV in English.

Super = super (supersmart), Photon = light quantum, ring = storage rings, GeV = giga electron volt (the unit of kinetic energy of electrons) (1 GeV = 10^9 eV = 1 billion electron volts)

Synchrotron radiation is electromagnetic waves generated when the traveling direc-

message

Director
Tetsutaro Iizuka
Harima Institute

Thinking back over 2004

One and a half years have quickly passed since I assumed the Director's post of the Harima Institute in October 2003 simultaneously with the reestablishment of RIKEN as an Independent Administrative Institution.

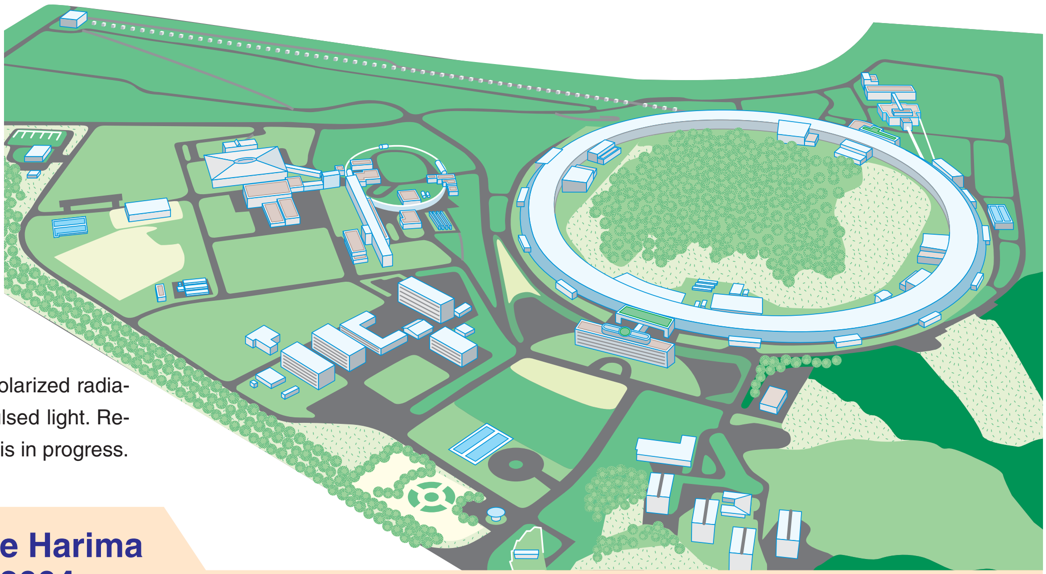
Thinking back over the past year, I have been very busy and have faced many unexpected incidents. Especially the damage of the Storage Ring building by typhoons Nos. 16 and 18 in August and September greatly shocked us. However, everyone at the site including the staff at JASRI took prompt and appropriate action, reassuring me with their competence. I would like to express my sincere appreciation to everyone who devotedly supported us on these issues.

Despite such shortcomings in this year, the conformation analysis of many important proteins successfully took place at SPring-8. Those proteins were, for example, a Protein relating to gene transcriptional control (by Chief Scientist Shigeyuki Yokoyama), a Protein related to oscillation generation of the biological clock (by Team Leader Hiroaki Kato) and a Protein that causes hyperglycinemia (by Group Director Seiki Kuramitsu).

Also in physics research, Chief Scientists Hideo Kitamura, Tetsuya Ishikawa and Tsumoru Shintake have been developing elemental technology for the XFEL (the X-ray Free Electron Laser) for a long time. Currently they have started to construct its new prototype. Selected as one of the 10 national critical technologies, the XFEL is attracting worldwide attention for bringing in an "epoch in light".

Regarding the differences between physics and biology researchers, the Harima Institute provides an excellent environment that allows them to consult with each other for their own benefit. For instance, a beamline-related problem brought up by a biology researcher can be investigated immediately by a physics researcher. Not only the researchers, but also the staffs from both RIKEN and JASRI inspire each other for further improvement.

In October 2005, the Harima Institute at SPring-8 is being challenged by important transitions such as the withdrawal of the Japan tion of electrons, which go straight at close to the speed of light, is altered by a magnet or the like.The features of synchrotron radiation are: extreme brightness, the ability to focus it down into fine ray, difficulty in diffusing it, inclusion of a wide range of wavelength areas from X-rays to infra-red radiation, polarized radiation, and repetition of short pulsed light. Research utilizing these features is in progress.



Activities of the Harima Institute in FY 2004

In the Harima Institute, various research is in progress in nine institute laboratories and four research groups, supported by the Division of Synchrotron Radiation Instrumentation.

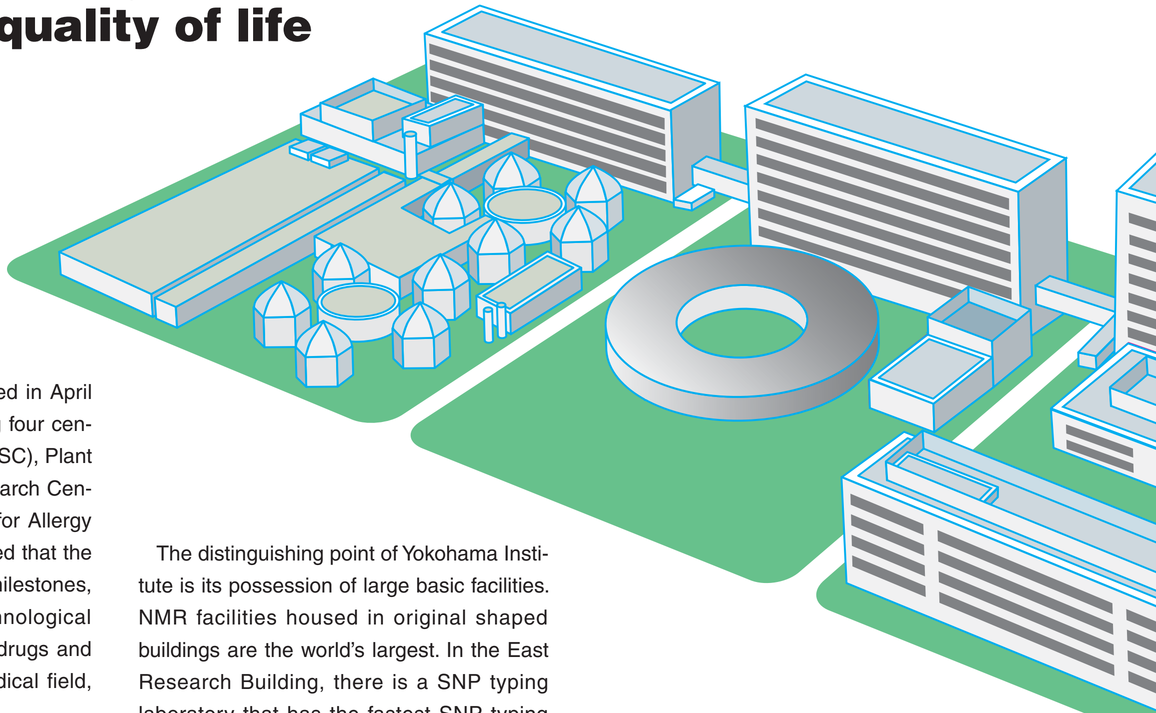
One of the achievements of 2004 was the three-dimensional structural analysis of the clock protein KaiA related to oscillation of the biological clock conducted jointly with Nagoya University. We elucidated the three-dimensional structure which serves as the oscillation function of the clock protein controlling the biological activity at a circadian rhythm, using SPring-8 RIKEN beamline BL26B1 and BL26B2. This provided big base for understanding of the mechanism at the atomic level to clarify how the biological clock of sophisticated molecular device oscillates. Other than the above, the Harima Institute has made a number of discoveries regarding the determination of the protein structures relating to living organism functions.

Atomic Energy Research Institute from the SPring-8 management. We will continue to promote further development of our independent research, and in addition, will advance together with the world's largest synchrotron radiation facility SPring-8.

Main activities in FY 2004

2004	
April 24	SPring-8 Open House.
May 21-22	Quantum Materials Research Group Workshop.
June 25	RIKEN RAL Introduction Seminar - Muon Science and Application.
July 30 to Aug. 1	RIKEN Seminar “The 3rd Annual Meeting of Structural-Biological Whole Cell Project of *Thermus thermophilus* HB8”
Sept. 5-7	SAXS in the 21st Century.
Sept. 7-11	BSR2004 (the 8th International Conference on Biology and Synchrotron Radiation)
Sept. 9	Structural Biology with Angstrom X-ray Lasers.
Oct. 8	The Harima Institute - CDB Joint Seminar.
Nov. 14-16	The 2nd PICS Workshop on High Energy Spectroscopies in *d* and *f* Electron Systems and RIKEN Workshop on Quantum Materials Research Group.
Dec. 6-7	RIKEN Symposium "Use of Complex Dynamical Systems and SR/FEL"
2005	
Jan. 14	RIKEN Symposium "National Center/RIKEN Harima Institute Joint Symposium"
Jan. 27-28	RIKEN Symposium "Structural Biology - New Tools for Structural Biology in Future"
March 9	RIKEN Symposium "Research and Development of X-ray Free Electron Laser (XFEL)"
March 29-31	RIKEN Symposium "Pressure and Protein Dynamics"

Research for a brighter future and a better quality of life



Yokohama Institute was established in April 2000 and consists of the following four centers: Genomic Sciences Center (GSC), Plant Science Center (PSC), SNP Research Center (SRC), and Research Center for Allergy and Immunology (RCAI). It is hoped that the research will achieve academic milestones, and at the same time be a technological platform for development of new drugs and personalized medicine in the medical field, and giving rise to new industries.

In addition, through a graduate university program with Yokohama City University sited in its premises, the Institute has close research relationships with the University.

The distinguishing point of Yokohama Institute is its possession of large basic facilities. NMR facilities housed in original shaped buildings are the world's largest. In the East Research Building, there is a SNP typing laboratory that has the fastest SNP typing system in the world. Laboratories for high-throughput DNA sequencing are in the West Research Building. In the top floors of the Central Research Building and the East Research Building, there are high-tech experimental greenhouses. The North Research Building is owned by Research Center for Allergy and Immunology.

Director
Tomoya Ogawa
Yokohama Institute

Yokohama Institute in FY 2004

1 Start of the second phase of Genomic Sciences Center, and end of the first phase of Plant Science Center and SNP Research Center

Genomic Sciences Center entered the second phase, and in April, a science lecture commemorating the fifth anniversary was held with the attendance of Director Sakaki. Plant Science Center and SNP Research Center that were established as a millennium project ended its first phase. These Centers held symposiums in their respective centers to report their research achievements.

2 North Research Building Completion Ceremony (April)

The North Research Building, a research facility of Research Center for Allergy and Immunology established in 2001, was completed and the opening ceremony was held on April 14. Approximately 150 people participated in the ceremony, and commemorative lectures were delivered by Special Advisor Kiminari Ishizaka and a member of the Council for Science and Technology Policy, Tadamitsu Kishimoto.

3 Establishment of a library (May)

On the second floor of the Central Research Building, an ID card-controlled library available at all hours was opened. Based on the characteristics of Yokohama Institute's research fields, its book stock consists primarily of books relating to life sciences.

4 Open Day (June)

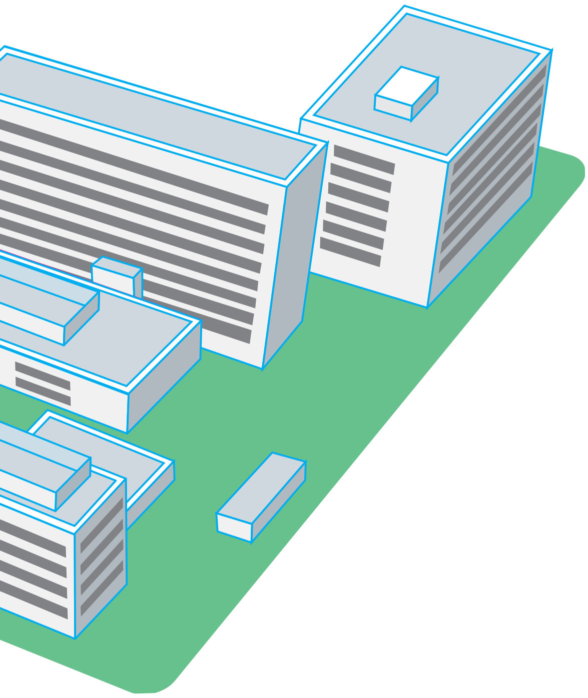
All our research centers held the Open Day in June 26 for the first time. Approximately 1,600 people visited Yokohama Institute, which is approximately 600 people more than the previous year, and many families participated in the events including the special lecture delivered by Team Leader Masahiro Sakaguchi, Research Center for Allergy and Immunology, and Group Director Yusuke Nakamura, SNP Research Center.

5 Introduction of Yokohama Institute at an overseas booth in BIO2004 (June)

In BIO2004 held in June last year in San Francisco, California (June 7-9, 2004, at Moscone Center), Yokohama Institute showed its exhibition as a part of the Yokohama City Booth of the Japan Pavilion. Yokohama Institute showed

Symposium and other events in FY 2004

2004	
April 16	Opening ceremony of the new research building of RCAI research facility
May 8	PSC Citizen Lecture "Power of plants supporting living and human life-What is the result of the Millennium Project Research?" (at the University of Tokyo)
May 24	GSC Fifth Anniversary Symposium "Future Prospects of Genome Sciences" (at Keidanren Hall in Tokyo)
May 31	SRC Symposium "Elucidating affected genes based on the SNP" (at Sankei Hall in Tokyo)
June 26	RIKEN Yokohama Institute Open Day
Dec. 2-3	PSC: Millennium Plant Science Symposium 2004 "Expected Plant Science Research in 21st Century" (at Kokuyo Hall in Tokyo)
2005	
March 18	GSC Symposium "Establishment and utilization of mouse models for human common diseases" (at Japan Center for Cities in Tokyo)
March 22	GSC: First Symposium of Genome Network Project (at Tokyo Kokusai Kaikan)
March 28	SRC Symposium "Elucidating affected genes based on the SNP" (at Sankei Hall in Tokyo)



International symposium

2004	
July 20	GSC: 30th Mouse Functional Genomics Seminar (at Main Office Building Hall)
Sept. 10-14	GSC: FANTOM3 Meeting (at Main office Building Hall)
Sept. 14-16	PSC: International workshop on Tobacco BY-2 cells (at Main Office Building Hall)
2005	
Jan. 17	GSC First Meeting of The RTK Consortium (at Main Office Building Hall)
Feb. 18	First RCAI Workshop "Spatio-temporal Regulation of Architecture and Responses in Immune System" (at North Research Building Conference Hall)

its research activities using panels and video images as a characteristic government funded research institution among many biotech companies.

6 Start of a salon concert (September -)

Since September 2004, a "Salon Concert" has been held every month. This was started to provide the Institute's staff with opportunities to perform music in a salon-like environment with an aim to promote exchange and relaxation among the centers and laboratories beyond each research center. It is expected that active participation of many people working in Yokohama Institute, for example, as performers, audiences, people enjoying their meals, and people to support operation of the concert, will stimulate Yokohama Institute and improvement of the research environment, and have a dramatic effect on producing achievements.

7 Completion of the Outdoor Multi-Purpose Area (October -)

Lawn was planted in an empty space in the south of the Central NMR Complex and the Outdoor Multi-Purpose Area for sports and recreation was built. Benches and summer houses were built around the square people use as a place for relaxation.

8 Holding laboratory management seminars (October -)

Since October, four seminars have been held to provide an expert's advice to management-level employees regarding precautions on operating a laboratory. It will also be held in 2005 to develop the management ability of management-level employees.

9 Placement of a consulting room for responding to staff's concerns (November)

Aiming at improving the working environment, a consulting room was opened to respond to various business-related concerns and complaints of people working in Yokohama Institute. In this room, consultors can take counsel from former members of the Institute with experience in research and research support business.

10 Entire visitors to Yokohama Institute

The number of visitors was 1,161 in total, which consisted of 255 from government and other public offices, 134 from private companies, 247 from associations and academic societies, 284 from teaching institutions, and 241 from others. Many of them visited on study tours held by super science high schools, local communities, or companies. As guests from abroad, we received a visit from Chairman Henry Freesen, the RIKEN Advisory Council, delegates of European, American, and Swedish BIO MISSION sponsored by JETRO, and researchers from the Human Science Frontier Program. In December, Yasufumi Tanahashi, Minister of State for Science and Technology Policy and in February Nariaki Nakayama, Minister of Education, Science, Sports and Culture visited the Yokohama Institute.

11 Award winners

Fifteen award winners were reported in FY 2004, including winners of Medal with Purple Ribbon, Group Director Yusuke Nakamura, SNP Research Center and Director Masaru Taniguchi, Research Center for Allergy and Immunology, and a winner of Osaka Citizen Prize, Director Kumao Toyoshima, SNP Research Center.

Benefiting society by unraveling the successful life strategies acquired through the life evolution over more than 4 billion years

DNA (genes, genomes) and proteins are at the root of functions and involved in all sorts of life phenomena.

The systematic and focused research into the structure and function of these materials should give the international initiative in the field of life science, and produce major breakthroughs in new medical technology, environmental conservation technology and food production technologies crucially impacting a wide range of industries.

To respond to this expectation, Genomic Sciences Center (GSC) was established in October 1998 and relocated in Yokohama in 2000. Since then, it has produced world-acclaimed activities in the research field of genes, genomes and proteins.

At present, the Institute is mainly undertaking the study of (1) clarifying strategies of life, (2) development and application of advanced technologies, (3) development of various human disease model animals, and (4) centralized analysis of genome functional information.

It is also proactive in undertaking various national projects such as "The International Human Genome Project (Determination of the sequence of human genomes), "Protein 3000 Project (The structural and functional analysis of approximately 3000 kinds of proteins)", "National BioResource Project (regarding a mouse)", "Genome Network Project (Unraveling of the gene network related bio-phenomena and diseases)".

GSC in FY 2004

In 2004, GSC released important news in genome science such as the completion of the sequence of chimpanzee chromosome 22 and the development of the "DNABook" of Arabidopsis transcription factors. Regarding the former, it was reported largely in newspaper and TV that there were a great many differences called “insertion-deletion” (68,000 places) between humans and chimpanzees other than those of the base sequence, and more than 80% of approximately 200 genes that were compared were different in sequences, which might cause differences of some kinds in the functions of proteins. This demonstrated the high level of interest existing among the public. The latter is a technology developed by RIKEN which enables the easy tool and transportation of DNA at ambient temperature by having DNA adsorbed into paper. This is expected to contribute greatly to the research of post-genome in future.

message

Director
Yoshiyuki Sakaki
Genomic Sciences Center

Thinking back over 2004

Also in 2004, GSC published a great number of research papers in *Nature* and other high impact journals. Papers which had a strong impact on society included one about the research and analysis of the genome sequence comparison of humans and chimps published in *Nature*, and the discovery of a lead compound for the SARS antiviral drugs of which paper has not yet been published. The former clarified that there was a difference between human and chimp genomes greater than what has been discovered before, and the genomes changed in the evolutive process much more drastically than expected. The latter is expected to lead to development of powerful medicine against SARS.

The most distinctive GSC activity in 2004 was that the "Genome Network Project", which is taking a leading part in post-sequence genome science, was started under GSC as a core institute. This fact clearly demonstrates that GSC is taking the lead of domestic and overseas genome research as a core center of genome science.

GSC has been characterized by having taken the lead in domestic and overseas genome research by successfully building a framework of genome science, such as deciphering of the human genome and full-length cDNA. As well in 2005, we are going to undertake an important role in the Protein 3000 Project and National BioResource Project to lead the world by creating a new framework for development of genome science.

Main activities in FY 2004

2004	
Apr.1	Dr. Yoshiyuki Sakaki assumed the Director, GSC.
May 24	GSC Fifth Anniversary Symposium "Future Prospects of Genome Sciences"
July 20	30th Mouse Functional Genomics Seminar.
Sept. 10-14	FANTOM3 Meeting.
2005	
Jan. 17	First meeting of The RTK Consortium.
March 18	GSC Symposium "Establishment and utilization of mouse models for human common diseases"
March 22	First Symposium of Genome Network Project.

Exploring the potential function of plants for a better life, better food and better living

Plants are indispensable as food and for conserving the earth's environment. An important challenge we face involves enhancing infrastructure technology essential for solving food and environmental problems in the future by clarifying plant functions, dynamically improving these functions, and developing breeds that produce larger yields and/or that are environmentally and disease resistant.

Plant Science Center (PSC) is progressing to clarify the potential abilities and control mechanisms of plants from the aspects of genes and bio-molecules using the most advanced facilities and experimental techniques of genome science. Moreover, PSC returns the results and profits from this research to society, performing its activities as a center of excellence in the field of plant science in Japan and the rest of the world.

Cultured cells of *Zinnia* introduced with fluorescent proteins

PSC in FY 2004

In PSC, six research groups are advancing the world's highest-level research about the abilities of plants under the main themes of "body architecture" and "useful compound production". PSC is also working to develop a new environmental purification method by elucidating the ability of immotile plants to adapt to various environments.

PSC is making a concerted effort to analyze genes of laboratory model plants in use worldwide. In 2004, PSC succeeded in analyzing the sequence of tobacco DNA on a huge scale with regard to the protein-creating component, and published the results. Since tobacco is a plant that humans have been using through the ages, it has been utilized in research as an experimental plant. The information obtained from this large-scale analysis is boosting hopes for the development of source material for medical products.

In addition, RIKEN is also proceeding to research genome sequencing of a higher plant *Arabidopsis thaliana.* PSC has undertaken research into how seeds wake up from dormancy, and eventually they found a master gene to awake seeds using *Arabidopsis thaliana.* They also clarified the function of four blue light sensors in plants. Furthermore, they unlocked the receptor mechanism of the plant hormones. This achievement will aid future research into increasing crop yields of agricultural products.

message

Director
Tastsuo Sugiyama
Plant Science Center

The past year of the Plant Science Center

PSC was created in April 2000 with the aim of establishing the Millennium Plant Science Project. 2004 was a very busy year for the staff, in particular for those working under the fixed-term system since it was the last year for the project. They were expected to produce results toward the termination of the project and had to spend a lot of time job hunting for 2005 and subsequent years.

Under such circumstances, some world-class achievements were realized in PSC. A noteworthy achievement resulting from the Millennium Plant Science Project was the discovery by the Kamiya Group and the Nambara Team of a master gene controlling dormancy and seed budding. "Learn from Plants, Utilize Plants - this is the motto of PSC, for which their research is very appropriate. There is no doubt that it contributes to the basic research of physiological functions in plants. Not only that, it has the possibility to reduce seed germination in a spike (spike germination) that reduces a grain crops'yield in conventionally-pluvious Japan. This possibility can lead to the development of agricultural technology to secure the yield.

As such, 2004 was the year in which we could produce results from a great deal of research that had been developed since the start of the Project. The research into the biosynthesis of plant hormones and their signal transduction mechanisms received recognition as world-class achievements. Other world-class results were: unlocking of reception of light stimulus most important in response to plant's external environment, model-plant-based elucidation of the tree formation mechanism important for accumulation of carbon dioxide, and the creation of crops having power to remove so-called endocrine disrupters in soil. I say with certainty that the achievements of this basic research will lead to “a better life”, “better food” and “better living”in a much improved way in future.

PSC has consistently produced steady results, and established assessment as a hub of world-wide plant science research. Plant science should contribute to society, and it is the Center's effort to realize this. I believe that the assessment we obtained from experts worldwide is the first step toward obtaining recognition of plant science research among citizens.

Main Activities in FY 2004

2004	
May 8	Citizen Lecture "Power of plants supporting living and human life - What is the result of the Millennium Project Research?"
Sept. 14-16	International workshop on Tobacco BY-2 cells.
Dec. 2-3	Millennium Plant Science Symposium 2004"Expected Plant Science Research in the 21st Century"

Aiming at establishment of personalized medicine by examining gene information which relates to factors such as lifestyle-related diseases and medicines' effects and side effect

The phenomena of genetic information varying among individuals are called genetic polymorphism. Individual differences of constitution depends on genetic polymorphism. Systematically mapping the link between genetic polymorphism and the disorders and drug responsiveness of lifestyle-related diseases can lead to discovering genes that are related to the disorders and clarifying the effect genetic polymorphism has on the functions of these genes, and is expected to lead to the realization of personalized medicine.

SNP Research Center (SRC) has targeted single nucleotide polymorphisms (SNP) among genetic polymorphisms in analyzing and identifying disorder-causing genes by supplying genetic polymorphism data necessary for the research of each disorder-causing gene in full use of the high-speed and high-precision SNP analysis method developed by SRC.

The research of genetic polymorphism is crucial for providing personalized medicine less harmful to the body. SRC has the world's fastest analytical instrument to identify what bases a test object person has in regard to the part having genes varying between individuals. SRC is also making an effort to develop effective curative medicine for cardiac infarction, diabetes, osteoarthritis, allergy, and adipositas by establishing respective research teams to analyze related genes.

SRC in FY 2004

In 2004, SRC entered into a joint research agreement with TOPPAN PRINTING CO., LTD. and Shimadzu Corporation to develop new technology enabling the analysis and diagnosis of genetic polymorphism at hospital. If genetic polymorphism can be analyzed using the extracted blood without separating DNA, we can come significantly close to the realization of personalized medicine. As other achievement of SRC, the group headed by Team Leader Toshihiro Tanaka found the galectin-2 gene related to cardiac infarction, and published the results in the UK science magazine *"Nature"*. The method of this research is considered to be a clue not only for opening the way to medical treatment but also for unraveling genetic aspects of other diseases of which patient count is greater than the cardiac infarction patient count.

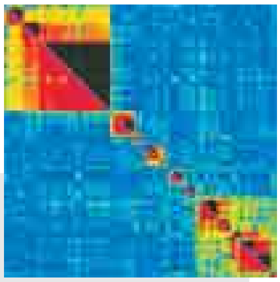
message

Director
Kumao Toyoshima
SNP Research Center

Thinking back over 2004

2004 was the final year of the Millennium Genome Project. For the past five years, SRC has been showing step by step that screening of single nucleotide polymorphisms (SNP) across the entire genome area with a focus on the gene area is most effective for analyzing multifactorial disorders such as lifestyle-related diseases and is most appropriate for practical use. As such, the basic issues cannot be studied in a short time such as one year, and in that sense, I feel that the five years set for this project was appropriate. I hope that I may be able to spare some space to provide a detailed explanation about it.

Following identification of genes relating to cardiac infarction (in 2002), rheumatoid arthritis (in 2003), addition of cardiac infarction, and the start of diabetic nephropathy, the group headed by Team Leader Ikegawa succeeded in identification of a gene relating to the start of osteoarthritis in 2004. This is also the world's first identification of a new lifestyle-related disease gene. The asporin that resulted is one of the proteins existing in extracellular composition; the polymorphism of direct repeat of asparagine in it relates to the formation of cartilage in joints. Asporin as well as lifestyle habits like handling heavy goods were fingered as factors for osteoarthritis seizure. It is considered that these fingered factors show the research will give a marker for prevention and medical treatment of osteoarthritis, of which patient count has been rapidly increasing in the aging society.



Linkage disequilibrium, haplotype block

The Tsunoda Team made a presentation of the haplotype and linkage disequilibrium map of Japanese by organizing vast amounts of SNP data. Creation of the world's first SNP-based detail map will provide a meaningful contribution to research into future diseases, effects and side effects of medical agents, and human genetics by identifying, on the genome, the existence of SNP bearing an important role for Japanese genetics analyses and a position where a high frequency of homologous recombination is yielded at the time of meiosis for creating generative cells.

Main activities in FY 2004

2004	
May 31	Elucidating affected genes based on the SNP/Symposium
Sept. 1	A joint research agreement was entered into between TOPPAN PRINTING CO., LTD and Shimadzu Corporation.
2005	
Jan. 25	A joint research agreement was entered into with National Research Institute of Police Science, JAPAN.
March 28	Elucidating affected genes based on the SNP/Symposium

RCAI is undertaking general research on regulatory mechanisms in immunological and allergic diseases caused by malfunctions of the immune system, and including studies that are aimed at the development of new treatment strategies

Immunity is a highly complex defense system that protects the body against illness. Based on our understanding of this intricate system, an important challenge for the 21st century is to develop successful treatment strategies for increasingly common immunological disorders, such allergies, autoimmune diseases, or the rejection of implanted cells and tissues.

In order to address this issue, in 2001 RIKEN established the Research Center for Allergy and Immunology (RCAI) with the intention to create a veritable center for immunological research in Japan and to accelerate the transfer of new findings into clinical applications. Research activities at RCAI span virtually all areas of immunobiology yet share a common interest in the study of regulatory mechanisms within the immune system, today one of the major fundamental questions in immunology. The study of regulatory mechanisms is directly to relevant clinical applications. It is the explicit goal of RCAI to contribute to society through the development and evaluation of novel treatment regimes for immunological disorders and, to this end, RCAI has created the "Strategic Research Program" which, comprises three units specialized in allergy, cell therapy, and autoimmune diseases.

RCAI in FY 2004

The RCAI research facilities were completed in early 2004 and at the beginning of April 2004 RCAI started operations as the 4th research center at the RIKEN Yokohama Institute. Some 153 researchers and technicians have started working at the center's new building in early 2004.

It is believed that around 30% of the Japanese population is now suffering from allergic disorders, such as asthma, allergic dermatitis, or cedar pollen allergy, or else immunological disorders such as rheumatoid arthritis. For most of these diseases no veritable treatment strategy exists at present. For example, in the case of cedar pollen allergy the allergy causing agent and the symptomatic mechanisms are now well characterized, yet to date there is no veritable therapy for cedar pollen allergy.

In order to open up new opportunities for treatment strategies against common allergies and autoimmune disorders, RCAI is focusing on the elucidation of the basic mechanisms of immune regulation. Also, various vaccination strategies against pollinosis using CpG and liposome vaccines are presently under evaluation. Highly promising results have been obtained in animal tests with a CpG vaccine. In accord with the road map for cedar pollinosis research decided by the Council for Science and Technology Policy (CSTP), RCAI now plans clinical studies on the safety and effectiveness of the vaccine.

And, despite its relatively short time in operation, investigators at RCAI have already made a number of important contributions to our understanding of the immune system. For example, Takashi Saito's group at the Laboratory for Cell Signaling has clarified the mechanisms behind the molecular switch that controls allergic symptoms. Also, the first successful demonstration of a tissue engineered secondary lymphoid organ that fulfills important immunological functions by Takeshi Watanabe and Sachiko Suematsu, published in Nature Biotechnology, has met with considerable interest.

message

Director
Masaru Taniguchi
Research Center for Allergy and Immunology

This year at RCAI

In order to promote curiosity driven research, we have created an organization with a minimum degree of hierarchy all while providing laboratory heads with a maximum of discretion over important management decision and the use of resources. In the short time since its creation, RCAI has already contributed important new insights on the workings of the immune systems and has lead the way in the development of important new treatment strategies in allergy, autoimmune regulation, and cell therapy.

In order to promote translational and preclinical research, RCAI has set-up three special research units and has created an internal funding scheme to support application oriented projects that are of strategic importance to the center. Also, we have set-up collaboration agreements with a number of external partners, including the Clinical Research Center at the Sagamihara National Hospital, a special treatment facility for allergic disorders, and the Chiba University Medical School.

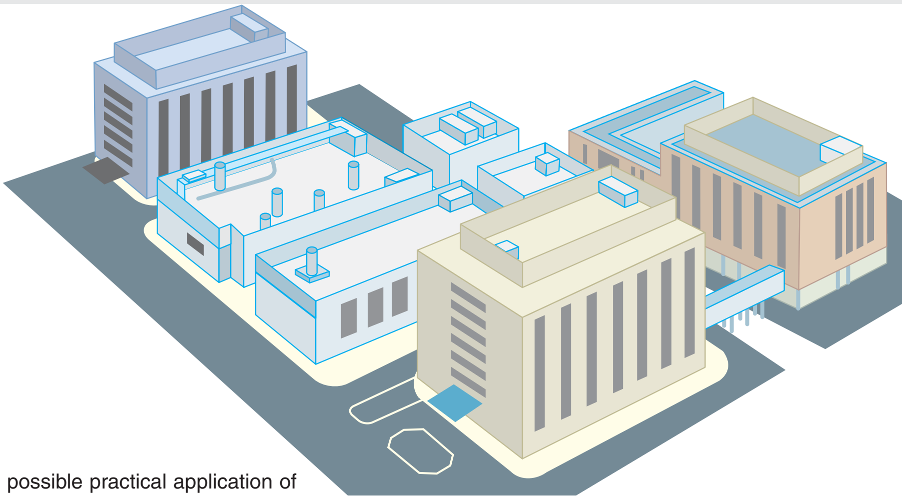
Within the framework of the strategic research program we also support important areas in fundamental research and technology development that are crucial to the center.

As a large-scale, publicly funded research center focused entirely on immunology RCAI is unique—not just in Japan, but around the world. RCAI has the potential to become an important international center for research in immunology and, I believe, it is our responsibility to work towards that goal. Further, in order to speed up the transfer of new knowledge toward the clinic and in order to link basic science with clinical applications, building an ever stronger network with university hospitals and medical research organizations is crucial. RIKEN has no prior experience with applied medical research, and efforts to build an infrastructure to support translational and preclinical studies at the institute is face many difficulties. Yet, our goal is to design an approach that can serve as a model for other research organizations in Japan.

Main activities in FY 2004

2004	
April 14	RCAI starts operations at the new facility at the RIKEN Yokohama Institute.
April 16	Opening ceremony of the new RCAI research facility.
2005	
Feb. 18	First RIKEN Workshop on "Spatio-temporal Regulation of Architectures and Responses in the Immune System"

Seeking to reveal developmental and regenerative mechanisms and their application to regenerative medicine



Kobe Institute

The RIKEN Kobe institute was established in 2002 as the home of the Center for Developmental Biology, which aims to promote basic research into developmental biology, as well as to conduct basic and model research into cell therapy and organ regeneration for use in medical applications.

Center for Developmental Biology

The Center for Developmental Biology (CDB) was launched in April 2000 to conduct basic and model research into developmental and regenerative systems in animals, and to consider the possible practical application of these systems to regenerative medicine. As the core research institute of the Kobe Medical Industry Development Project, the Kobe institute is located adjacent to the Institute of Biomedical Research and Innovation and forms one part of the industry-government-academic complex which is seeking to develop new advances in medicine for the 21st century.

CDB fosters research not only into areas of basic developmental biology such as classical embryology, molecular cell biology, neurogenesis, evolutionary biology, functional genomics and bioinformatics, but also into areas of medical research such as regenerative medicine and stem cell research.

To cover this wide range of research activities, the Center employs a number of talented researchers from both Japan and overseas, placing great importance on their originality and independence and respecting the independence of each research team.

One of the key features of the Center is that innovative thinking in both basic research in developmental biology and in the field of medical science can be carried out in the same institute. It is expected that close interaction between these different areas will help develop the world of developmental biology and produce innovative contributions to life science in the 21st century.

message

Director
Masatoshi Takeichi
Center for Developmental Biology

Looking back on the past year

The past year has been an important one for CDB and one that has seen many changes, the great majority of which represented real progress. In June of this year, CDB advisory council met to review the Center's performance and to make recommendations for the future. The positive nature of the council's findings, from the organizational level to individual labs, gave us a high degree of confidence in the operating of this institute.

2004 has also been a fine year for research activities. A number of excellent papers were published, including "Directed differentiation of telencephalic precursors from embryonic stem cells" (*Nature Neuroscience* 8, 288-296, 2005) by Group Director Yoshiki Sasai of the Laboratory for Organogenesis and Neurogenesis, and "Shisa promotes head formation through the inhibition of receptor protein maturation for the caudalizing factors, Wnt and FGF" (*Cell*, 120, 223-235, 2005) by Group Director Shinichi Aizawa of the Laboratory for Vertebrate Body Plan. These research achievements contributed to making the final year of the Millennium Project especially fulfilling.

Upon the completion of the Millennium Project, Group Leader Kiyokazu Agata left to take up a position as a professor at Kyoto University, while Team Leader Shigeru Kondo also took a professorship at Nagoya University. It gave me great pleasure to see researchers who have matured at CDB being given such prestigious appointments, as well as contributing to the exchange of personnel between RIKEN and universities.

Affiliations with a number of local graduate schools keep our labs open to grad students, many of whom joined us for a well received summer school in September. From 2005 the Osaka University Graduate School of Medicine will join our existing affiliated universities (Kobe University, Nara Institute of Science and Technology, Kyoto University and Kwansei Gakuin University) to further strengthen educational exchanges with universities in the Kansai region. Public relations activities at CDB continue to expand and achieve greater public awareness and understanding of our research mission and achievements. Visitors to the Center can now experience mock experiments in the Center's gallery to gain hands-on familiarity with actual model organisms as they are used in CDB.

Entering a new phase in CDB's history the institute is moving to meet the challenges of

CDB in FY 2004

Although genomic sequencing in various organisms has been advancing rapidly, it is still not known how an individual cell is able to give rise to a wide variety of differentiated cells. In addition, the complete function of any particular gene has so far only been revealed in model organisms.

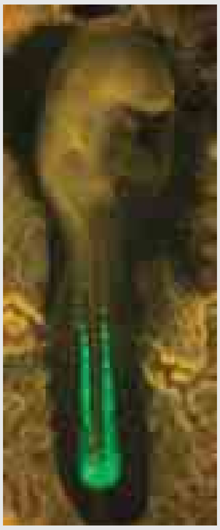
The 30 research teams in CDB are divided into three distinct groups consisting of the core research program, creative research promoting program and supporting laboratories. In addition, translational research, which applies research results to humans after satisfying vigorous safety and ethical standards, is also a goal of the Center's work.

In 2004, CDB labs published several pioneering studies with far-reaching implications. These ranged from the successful induction of cortical precursor cells, to the development of technology to maintain an infertile mouse line. Other significant research achievements included the clues toward the genetic basis of the lamprey's failure to develop a jaw, and a method capable of detecting individual body time and diagnosing circadian disorders.

CDB was also the recipient of many awards during the past year, beginning with a television program on the life and scientific research of Group Director Kiyokazu Agata, which was awarded the MEXT Minister's Prize in the Educational Video category at the 45th Science and Technology Film/Video festival. Center Director Masatoshi Takeichi was also elected to the American Academy of Arts and Sciences as a Foreign Honorary Member, as well as being named a "Person of Cultural Merit", one of Japan's highest honors, in recognition of his discovery of the cadherin family of cell adhesion molecules, and subsequent work in characterizing cadherin structure and function. The French Ministry of Education also acknowledged Takeichi's work by honoring him with the l'Ordre des Palmes Academiques.

One distinctive feature of CDB is its openness to the outside world, demonstrated by its yearly symposium attended by both domestic and foreign researchers; numerous scientific seminars; affiliations with both domestic and foreign universities, and the annual open house which allows members of the public to explore CDB. One particular area of focus this year was the Asia-Pacific region, and in April 2004 Team Leader Teruhiko Wakayama helped organize the inaugural meeting of the Asian Reproductive Biology Society (ARB), held in Ho Chi Minh City, Vietnam under the auspices of Nong Lam University (Vietnam) and CDB.

the next generation of developmental biology. CDB is currently involved in various activities focusing on the Asia-Pacific region, and we look forward to the continuation of this trend as a means of encouraging new relationships in the region and helping CDB achieve its goal of becoming a world leader in the field of developmental biology.



Somites forming in 2-day chiken embryo

Main activities in FY 2004

2004	
April 12-14	First Asian Reproductive Biology meeting in Vietnam co-hosted by CDB.
April 16	Television program on Kiyokazu Agata wins MEXT Minister's prize at Science and Technology Film/Video Festival.
April 17	Open House.
May 12	Center Director Takeichi elected to American Academy of Arts and Science as Foreign Honorary Member.
June 28-July 1	East Asia C.elegans meeting.
Sept. 6-7	Intensive lecture program for affiliated graduate school students.
Oct. 7	JSPS summer program for young foreign researchers.
Oct. 18-19	The third annual CDB Retreat.
Oct. 20-24	Joint workshop on regenerative medicine.
Nov. 3	Center Director Takeichi named "Person of Cultural Merit"
Nov. 8	Asia-Pacific Developmental Biology Research Symposium.
Nov. 15	Center Director Takeichi awarded l'Ordre des Palmes Academiques by France's Ministry of Education.
Nov. 15-16	Asia-Oceania Fish Meeting.
Nov. 25	Team Leader Hiroki R. Ueda awarded Japan Innovator Award.
2005	
Jan. 13	Center Director Takeichi awarded 2005 Japan Prize.
Feb. 2-3	CDB Meeting: Diversity of Developmental Mechanisms in Invertebrates.

RIKEN's unique research system extends the range of research

Sponsored Laboratory

To stimulate research within RIKEN that can build ties between basic research and industry, RIKEN developed the Sponsored Laboratory Program. Under the system, corporate and private funds are used to invite eminent scientists to RIKEN and to manage a laboratory.

Two such laboratories had been established by the end of FY2004.

- Ikawa Laboratory, headed by Dr. Yoji Ikawa, conducts the research on the physiological functions of cancer suppressor genes and its medical applications.
- Abe Laboratory, headed by Dr. Takashi Abe, conducts the research on new bioactive compounds derived from hornets and the analysis of their functional mechanisms.

(*Sponsored Laboratories became a part of the Center for Intellectual Property Strategies from April 2005.)

Initiative Research Unit

The Initiative Research Unit system provides competent, young scientists the opportunity to engage in creative research at RIKEN that opens hither to unexplored fields of research. Each Initiative Research Scientist must be under 40 years of age and have completed at least three years of research experience following the completion of his or her doctorate in the natural sciences. The Unit Leader is solely responsible for staffing and managing her or his Initiative Research Unit.

There were six Initiative Research Units as of the end of FY2004.

- Kawase Initiative Research Unit
  (Development of the terahertz imaging system)
- Masai Initiative Research Unit
  (Mechanisms underlying neuronal differentiation and the formation of neural circuits in the vertebrate developing retina)
- Imakubo Initiative Research Unit
  (Development of novel organic conductors with supramolecular structure and multifunctionality)
- Fukuda Initiative Research Unit
  (Role of synaptotagmin-like proteins in intracellular membrane trafficking)
- Kishi Initiative Research Unit
  (Cell cycle regulation by the ubiquitin system)
- Nishii Initiative Research Unit
  (Molecular and genetic analysis of morphogenesis in Volvox embryo)

RIKEN 2004

Trends of RIKEN

Data & Infomation

The transformation into an Independent Administrative Institution

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

RIKEN became an independently administered organization in the fall of 2003. With the transformation, the Japanese government established mid-term objectives for projects that should be completed in three to five years, and it oversees the efforts to meet them. To this end, the new organizations were required to draft mid-term plans detailing how designated objectives would be accomplished, and to secure approval from the ministry in charge of the organization: the Ministry of Education, Culture, Sports, Science and Technology (MEXT). An annual plan must also be submitted to MEXT for each fiscal year. Annual evaluations will assess RIKEN's achievements by a committee appointed by the government of Japan. At the end of the mid-term period, another evaluation will take place. Based on its outcome, RIKEN will make the necessary revisions or to its operation procedures.

Summary of mid-term plan

Category	Target
1. Improvement of operations	
1) Research dissemination and transfer	
• Publish original results	1,800 or more papers annually
• Publish in high impact journals for respective research fields	50% or more of 1,800 papers
• Register intellectual property	600 applications/fiscal year in 2007
• License materials	12%
• Issue press releases	40 a year
• Publish RIKEN News	12 a year
2) Develop research & technical staff	
• Special Postdoctoral Researchers	Maintain constant level of 200 researchers
• Initiative Research Scientists	10 researchers by 2007
• Junior Research Associates (JRA)	Maintain constant level of 140 associates
2. Improvement of operational efficiency	
• Increase project efficiency	Reduce expenses by 1% annually
• Increase procurement efficiency	Reduce expenditure by 2% annually
• Improve managerial efficiency	Reduce administrative costs by 15% (before taxes)

Noyori Initiative

Upon becoming the first president of the newly organized RIKEN, Ryoji Noyori issued the "Noyori Initiative", which outlines how RIKEN will meet its mid-term targets. He also prescribed the direction the research institutes should take to pursue science to its highest levels of achievement.

Noyori Initiative

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 • Knit science, industry and society together by transferring research results
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 • Disseminate results widely; include humanities and social sciences

Research Priority Committee

Since October 2003, the Research Priority Committee has been advising the President on ways to improve the managerial policies for RIKEN. The committee consists of RIKEN and non-RIKEN individuals who meet regularly to discuss and prioritize research activities and to direct those activities into the future.

The Committee also explores possible strategic research development projects that enable the fluid incorporation and management of key experimental studies. It highlights expected developments in these areas.

RIKEN Scientists Association

This association was established in January 2005 to be the voice of RIKEN's researchers. In the three meetings held in fiscal year 2004, representatives from all the institutes and centers met to discuss research-related issues and draft research proposals that outlined expected outcomes.

Strengthening scientific governance

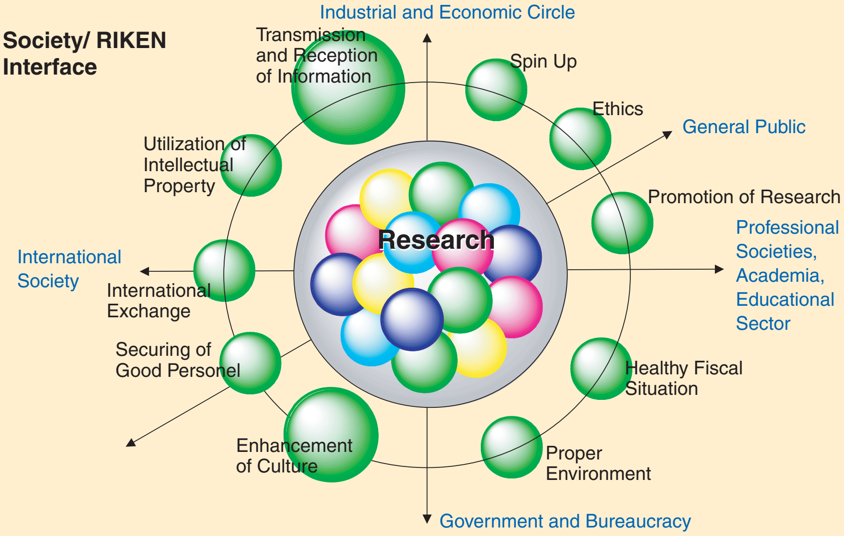
Recommendations from the RIKEN Advisory Council and RIKEN's responses

The RIKEN Advisory Council (RAC) serves as an external advisor and evaluator of science and administrative activities for the RIKEN President. This council is made up of highly influential and successful non-RIKEN individuals.

The first RAC under the new organizational structure took place in June 2004. The results of that session are available on the RIKEN web site at http://www.riken.jp/r-world/info/release/press/2004/040819/index/html. RAC highly praised RIKEN's operational policies, and research activities and the Noyori Initiative. They also recommended unifying the organization according to the anticipated directions of science to make it stronger, and toughening scientific governance.

RIKEN quickly developed concrete measures to address the concerns of the Advisory Council. It established Ten Important Managerial Items and study groups to investigate ways to tackle them, implement the Noyori Initiative, and develop appropriate governance of scientific activities. These groups, staffed mainly by more junior members of RIKEN, have already affected the way resources will be allocated in fiscal year 2005 and thereby strengthened RIKEN's role in generating science in line with its stated objectives.

Fig. 1 Ten Important Managerial Items



Study group visit outside RIKEN
(Transmission and Reception of Information Team)

Fig. 2 RIKEN Evaluations

Evaluation of R&D Activities

Evaluation of R&D Organization: Comprehensive evaluation
RIKEN Advisory Council (RAC)

↑ All AC chairman to be RAC members
Report the results of evaluations

Evaluation of R&D Organizations: Research-unit evaluation
Advisory Council (each research center)

↑ Report the results of evaluations

Evaluation of R&D themes: laboratories and research units
Research Review Committee

Evaluation of Independent Administrative Institutions

Governmental evaluation by MEXT (Ministry of Education, Culture, Sports, Science and Technology) Evaluation Committee for Independent Administrative Institutions

Evaluation of R&D organization: comprehensive evaluation of RIKEN

Established in 1993, the RIKEN Advisory Council (RAC) acts as an advisory body for the whole of RIKEN. Members represent some of the most distinguished members of the national and international scientific and academic communities. The council conducts thorough reviews of RIKEN's research and management activities, and provides advice to the RIKEN President.

Evaluation of R&D organization: institutes and research centers

Each RIKEN Institute and research center establishes its own Advisory Council (AC) that observes and accesses the development of science within the organisation. International experts in the relevant areas of research are invited to sit on these councils.

Evaluation of R&D themes: laboratories and research units

Research groups and laboratories receive independent assessments by a panel of external experts.

Governmental evaluation

Upon reaching its mid-term point, RIKEN must undergo a governmental evaluation by the MEXT Evaluation Committee for Independent Administrative Institutions to assess the degree to which RIKEN has met is mid-term objectives.

RAC's key findings

The results of the 5th RAC are summarized below.

Level of research

There can be no doubt that RIKEN has evolved into one of the world's top research institutes, and its newest research centers have significantly contributed to the establishment of its international status.

Management

In order to provide RIKEN with the support it will need as it continues to grow, the current management structure will need to be improved. The five points of the Noyori Initiative provide an appropriate and powerful framework to address many of the issues facing RIKEN.

The management structure should be analysed in light of the suitable support it can provide to RIKEN's scientific activities and to those of its President. It would be wise to focus on fostering research collaborations domestically, within and beyond RIKEN, and internationally. Efforts should also be made to increase the caliber of staff, develop a more efficient system for technology transfer, and attract more foreign scientists.

Members of the 5th RAC

Chair
Dr.Henry G. Friesen
(Medicine: endocrinology)

Chair, Board of Directors, Genome Canada, Canada
Distinguishd Professor Emeritus, Senior Fellow of Centre for Advancement of Medicine, University of Manitoba, Canada

Prof. Hidetoshi Fukuyama
(Basic solid states science)

Professor, Institute for Materials Research, Tohoku University, Japan
Former Director, Institute for Solid State Physics, the University of Tokyo, Japan
Chair of Institute Laboratories Advisory Council (ILAC)

Prof. Toshiaki Ikoma (Electronics)

Guest Professor, Graduate Scool of International Corporate Strategy, Hitotsubashi University, Japan
Former President, Texas Instruments Japan Ltd.
Chair of Frontier Research System Advisory Council (FRAC)

Dr. Zach W. Hall (Neuroscience)

Senior Associate Dean for Research, Keck School of Medicine, University of Southern Carifornia, USA
Former Director, National Institute of Neurological Disorders and Stroke, NIH, USA
Chair of Brain Science Institute Advisory Council (BSAC)

Prof. Yoshitaka Nagai (Biochemistry)

Honory President, Mitsubishi Kagaku Institute of Life Sciences, Japan Advisor, the Mitsubishi Chemical Corporation, Japan
Professor Emeritus, the University of Tokyo, Japan
Chair of BioResource Center Advisory Council (BSAC)

Dr. Susumu Nishimura (Biology)

President Emeritus, Banyu Tsukuba Research Institute, Banyu Pharmaceutical Co., Ltd, Japan
Chair of Genomic Science Center Advisory Council (GSAC)

Prof. Shang Fa Yang (Plant science)

Professor Emeritus, Dept. of Vegetable Crops, University of California, Davis, USA
Chair of Plant Science Center Advisory Council (PSAC)

Prof. Fumihiko Sato
(in place of Prof. Yang)

Professor, Dept. of Plant Gene and Totipotency, Division of Integrated Life Science, Graduate Scool of Biostudies, Kyoto University, Japan

Dr. Mark Lathrop
(Gene science)

Directeur Général, Centre National de Génotypage, France
Chair of SNP Research Center Advisory Council (SRAC)

Dr. Max D.Cooper (Medicine)

Investigator, Howard Hughes Medical Institute, University of Alabama at Birmingham, USA
Chair of Research Center for Allergy and Immunology Advisory Council (AIAC)

Dr. Igor B. Dawid (Biology)

Chief, Laboratory of Molecular Genetics, National Institute of Child Health and Human Development, NIH, USA
Chair of Center for Developmental Biology Advisory Council (DBAC)

Prof. Shigehiko Hasumi
(French literature)

Former President, the University of Tokyo, Japan

Prof. Hiroo Imura
(Medicine: endocrinology)

Chair, Foundation for Biomedical Research and Innovation, Japan
Former Member, Council for Science and Technology Policy, Japan
Former President, Kyoto University, Japan

Prof. Junjiro Kanamori
(Condensed matter)

Director, the International Institute for Advanced Studies, Japan
Former President, Osaka University, Japan

Dr. Geraldine A. Kenney-Wallace
(Chemistry, physics)

Director, e-Strategy & Learning, City & Guilds, UK

Dr. Yuan Tseh Lee
(Chemistry)

President, Academia Sinica, Taiwan

Prof. Guy Ourisson (Chemistry)

Membre (Ancien Président), Academie des Sciences, France

Prof. Hans L. R. Wigzeil
(Medicine: immunology)

Director of Center for Medical Innovation, Karolinska Institute, Sweden
(Former President)

Dr. Paul R. Williams (Nuclear physics)

Former President, Council for the Central Lab. of the Research Councils, UK

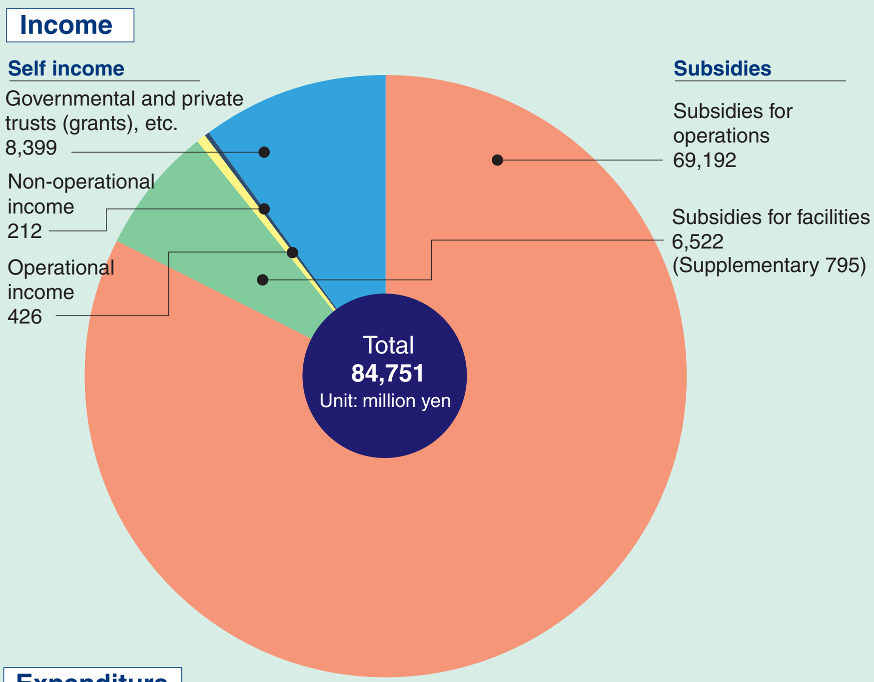
RIKEN Advisory Council Members and Executive Directors

Finding diversity in research by developing diversity in funding

The government remains RIKEN's primary financial supporter

- Like other Independent Administrative Institutions, RIKEN is responsible for determining how to distribute the funds it receives from the government. Yet, while the government does not impose requirements on how its funds are used at RIKEN, it does monitor and evaluate management spending activities closely.
- The government has also supported building renovation and construction that are or will become RIKEN assets.
- As an Independent Administrative Institution, RIKEN also develops other sources of funding to reduce its dependency on government subsidies. These include:
  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. Governmental and private trusts (grants)

Fig. 1 Projected 2004 Budget



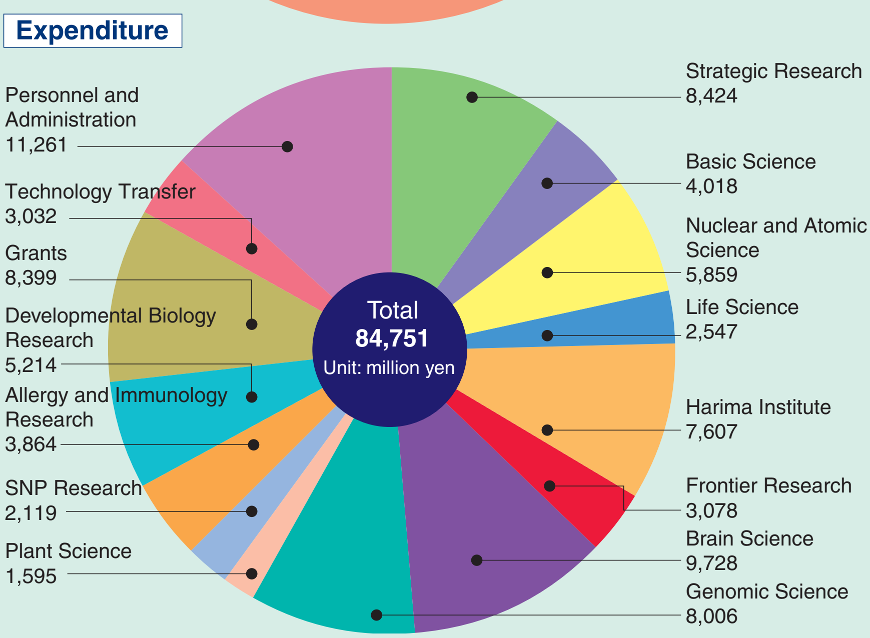
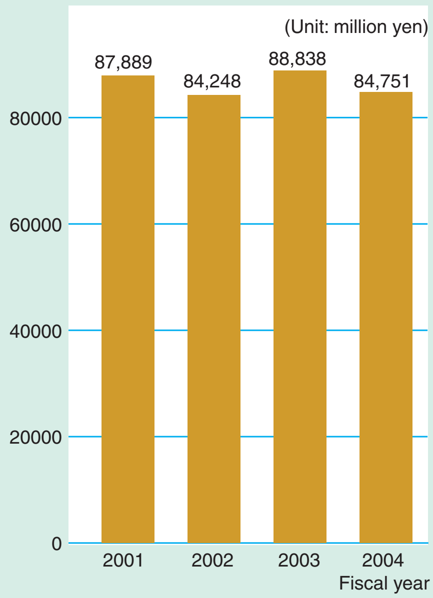


Fig. 2 Recent budgets



External funds

RIKEN also acquired funds from various government bodies, including MEXT (Ministry of Education, Culture, Sports, Science and Technology), as well as public and private organizations, in fiscal year 2004.

Table 1 Acquisition of external funds

Category	Description		FY2001 thousand yen	FY2001 cases	FY2002 thousand yen	FY2002 cases	FY2003 thousand yen	FY2003 cases	FY2004 thousand yen	FY2004 cases
1. Competitive Funds	Grant-in-aids for Scientific Research		1,041,815	297	1,837,863	338	1,966,905	367	2,457,819	426
	Grant-in-aids for Scientific Research (Ministry of Health, Labour and Welfare, and Ministry of Emvironment)		120,500	3	122,250	4	113,180	4	60,828	2
	Special Coordination Funds for the promoting of Science and Technology		1,586,523	33	1,038,847	27	712,442	16	534,383	10
	Basic Research Programs (Japan Science and Technology Agency)		714,077	41	1,150,782	56	1,212,054	63	1,457,174	70
	Others		78,150	2	188,408	9	196,874	12	208,099	8
Sub-total			3,541,065	376	4,338,150	434	4,201,455	462	4,718,303	516
2. Uncompetitive Funds	Commission	Government commissioned research			12,005,981	16	26,282,726	35	8,278,807	25
		Government-related commissioned research	1,425,479	12	1,010,093	15	1,040,228	25	148,179	25
	Subsidy	Government subsidy	111,486	39	102,320	39	127,533	33	97,880	31
		Private grant	30,720	18	61,321	29	66,696	33	60,750	46
	Collaborative Research	Defrayment	8,500	2	23,450	3	78,743	10	114,366	14
Sub-total			1,576,185	71	13,203,165	102	27,595,926	136	8,699,982	141
Total			5,117,250	447	17,541,315	536	31,797,381	598	13,418,285	657

Including defrayments from the Japan Science and Technology Agency (JST) and advanced funds from the Japan Society for the Promotion of Science (JSPS)

Table 2 Acquisition of external funds (grouped by center)

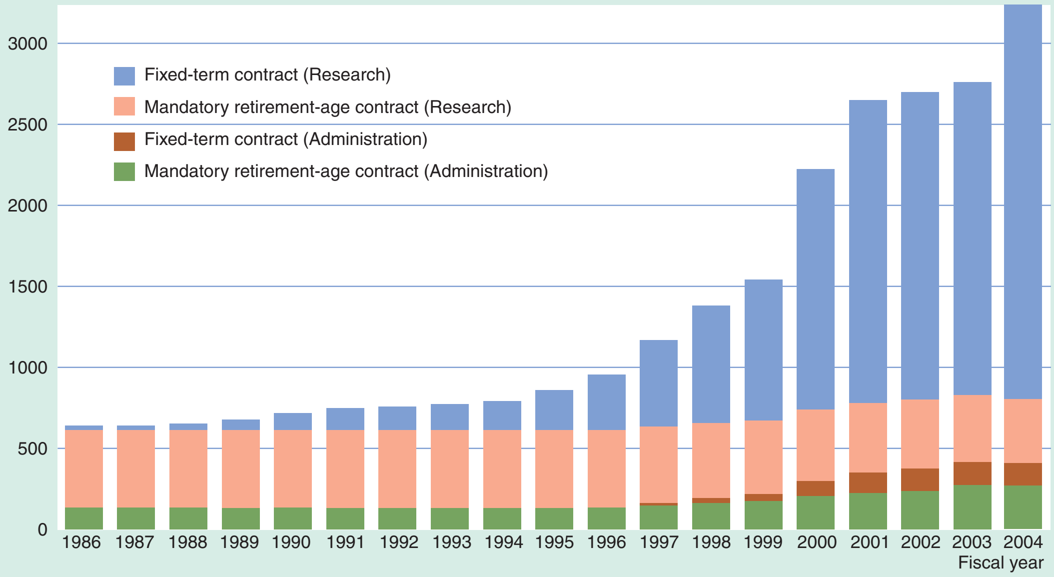
(Unit: thousand yen)

	FY2001	FY2002	FY2003	FY2004
Discovery Research Institute	2,201,388	2,440,603	3,749,040	2,240,683
Frontier Research System	132,278	208,400	435,395	200,382
Brain Science Institute	741,323	701,134	736,577	814,459
BioResource Center	150,776	1,514,407	1,570,676	126,100
Harima Institute	254,393	1,015,737	1,197,356	1,272,522
Genomic Sciences Center	1,405,248	9,442,410	12,711,837	5,627,079
Plant Science Center	28,500	19,900	390,843	97,743
SNP Research Center	26,845	1,424,265	6,732,818	1,239,500
Research Center for Allergy and Immunology	1,425	158,711	187,817	496,433
Center for Developmental Biology	155,550	592,367	3,734,828	1,115,550
Others	19,524	23,381	350,194	187,834

Enabling the best people to achieve the best results

RIKEN uses a two-tiered employment system. One is a mandatory retirement-age contract system that provides permanent employment at RIKEN. The other system is a fixed-term contracting system that employees staff on one-year renewable contracts. After exceptional researchers working under the latter expressed concerns about long-term job security, RIKEN implemented a new system in February 2004 called the Long-Term Principle Investigator. Under this system, a researcher is guaranteed five years of employment at RIKEN. In addition, RIKEN is stepping up efforts to attract foreign staff that will help establish the organization as an international center of excellence.

Fig. 1 RIKEN personnel



Mandatory retirement-age employment

While the government has ordered a reduction in staff employed under this category, RIKEN's rapid growth under the other system put pressure on the existing administrative personnel. With government approval, RIKEN increased the number of mandatory retirement-age administrative personnel to compensate for that growth.

Fixed-term employment

Since it was first implemented in 1986 with the start of the Frontier Research System, the number of staff employed under such contracts has steadily increased. This system has since become the primary employment system throughout RIKEN.

Table 1 Mandatory retirement-age contract employment Trends

Fiscal year

Category	2000	2001	2002	2003	2004
Research	441	430	426	413	413
Administration	204	225	237	272	272
Total	645	655	663	685	685

Table 2 Fixed-term contract employment trends

Fiscal year

Category	2000	2001	2002	2003	2004
Frontier Research System	140	145	191	137	156
Brain Science Institute	426	459	499	527	532
BioResource Center	–	17	17	17	17
Genomic Sciences Center	250	335	276	214	226
Plant Science Center	64	97	100	100	100
SNP Research Center	50	74	81	81	81
Research Center for Allergy and Immunology	–	105	153	153	153
Center for Developmental Biology	203	243	243	243	243
Others	–	–	16	24	49

Long-term Principal Investigator system

To enable greater researcher mobility, RIKEN adopted a fixed-term contract employment system. However, because contracts were renewed annually following evaluation and no assurances of renewal were provided, some concerns about job security arose. The same system also inhibited long-term research planning.

Therefore, the Labor Standards Law was revised in January 2004, and RIKEN become able to offer researchers contracts for periods of up to five years. Exceptional fixed-term researchers can also be guaranteed a five-year term, under the Long-Term Principal Investigator system. Currently there are four such researchers at RIKEN: two in the Brain Science Institute, one in the Plant Research Center, and one in the SNP Research Center.

Fostering Young Researchers

Special Postdoctral Researcher program

Under this program, creative young researchers under 35 years of age may initiate their own research activity. Those with Ph.D.'s in the natural sciences or who have demonstrated sufficient research capacity are able to design and conduct original research at RIKEN for a period of one year. Following a successful review, a researcher will be invited to extend that work for up to two more years. There were 208 Special Postdoctral Researchers at RIKEN during the fiscal year 2004.

Junior Research Associates (JRA)

The JRA program fosters the next generation of researchers by inviting doctoral course students to work in laboratories as part-time staff and thereby participate in on-going research. JRA fellows are employed under one-year contracts that may be renewed twice, or upon completion of their doctoral course. They essentially do the research for their doctoral degrees at RIKEN. There were 139 JRAs in RIKEN in fiscal year 2004.

International personnel

Acknowledging the value of international cooperation, RIKEN recruits researchers from around the world. Various services are provided to help these researchers and their families adjust to life and work in Japan. The International Cooperation Office publishes a handbook called "Life in RIKEN" and a monthly newsletter called "ICO News." There are also three offices that have been set up to support international staff: ICO Room (RIKEN-wide), International Relations and Communications (Brain Science Institute), and the Office of Science Communications and International Affairs (Center for Developmental Biology).

Fig. 2 Number of foreign researchers in RIKEN (as of March 1, 2005)

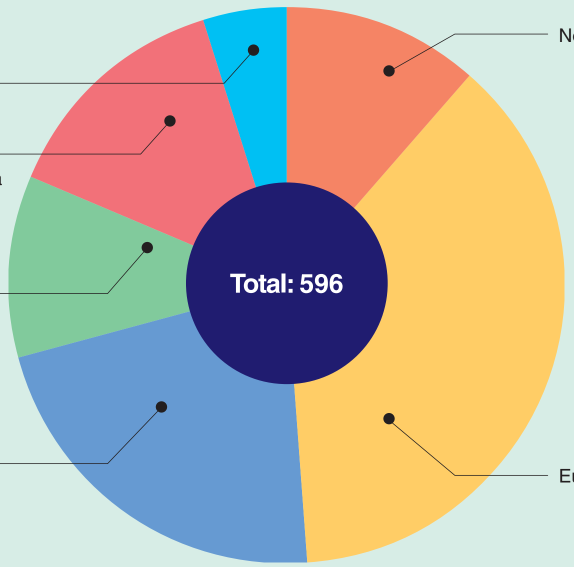


Table 3 Number of foreign researchers by research center

Discovery Research Institute	219
Frontier Research System	55
Brain Science Institute	125
BioResource Center	8
Harima Institute	53
Genomic Sciences Center	52
Plant Science Center	5
SNP Research Center	5
Research Center for Allergy and Immunology	15
Center for Developmental Biology	31
Others	19
Administration	9

RIKEN's activities 4 **Promoting public understanding**

Emphasis on public relations

Paper publications and conference presentations maintain connections between RIKEN and the international research community. Yet, for results to have an impact on society as a whole, other communication must also take place. RIKEN disseminates research broadly by issuing press releases on research activities and organizing events such as RIKEN Symposia on interesting research areas. The Research Ethics Committee meets with well-informed members of the community to solicit opinions and exchange ideas on the course and adoption of science at large. Finally, public lectures and Open Days invite the public to engage directly with the researchers about their work at RIKEN.

RIKEN Gallery (Wako Institute)

Table 1 Published original papers (Fiscal year)

		2001	2002	2003	2004
Discovery Research Institute	European Languages	577	636	694	637
	Japanese	33	22	38	38
Frontier Research System	European Languages	78	200	202	278
	Japanese	21	57	65	76
Brain Science Institute	European Languages	245	266	253	334
	Japanese	40	20	20	24
BioResource Center	European Languages	12	32	36	87
	Japanese	0	3	1	4
Harima Institute	European Languages	103	166	122	191
	Japanese	7	7	0	3
Genomic Sciences Center	European Languages	62	105	135	102
	Japanese	2	9	3	2
Plant Science Center	European Languages	44	61	43	63
	Japanese	0	0	0	1
SNP Research Center	European Languages	18	33	5	40
	Japanese	0	4	0	1
Research Center for Allergy and Immunology	European Languages	6	58	67	94
	Japanese	0	2	1	4
Center for Developmental Biology	European Languages	2	48	76	85
	Japanese	0	0	0	4
Others	European Languages	22	59	69	35
	Japanese	4	12	20	20
Total	European Languages	1,169	1,664	1,702	1,946
	Japanese	107	136	148	177

Table 2 Conference presentations (Fiscal year)

		2001	2002	2003	2004
Discovery Research Institute	Overseas	660	532	763	791
	Domestic	1,349	1,068	1,403	1,466
Frontier Research System	Overseas	141	232	290	342
	Domestic	229	268	302	413
Brain Science Institute	Overseas	275	288	268	394
	Domestic	326	445	360	473
BioResource Center	Overseas	16	26	19	42
	Domestic	56	100	95	117
Harima Institute	Overseas	85	159	130	214
	Domestic	180	293	308	330
Genomic Sciences Center	Overseas	149	197	156	167
	Domestic	221	365	276	239
Plant Science Center	Overseas	24	66	88	87
	Domestic	75	150	101	140
SNP Research Center	Overseas	1	6	6	28
	Domestic	6	11	21	48
Research Center for Allergy and Immunology	Overseas	0	56	40	92
	Domestic	0	124	121	209
Center for Developmental Biology	Overseas	11	51	52	50
	Domestic	16	100	75	47
Others	Overseas	17	62	64	60
	Domestic	73	166	143	104
Total	Overseas	1,379	1,675	1,876	2,267
	Domestic	2,531	3,090	3,205	3,586

Table 3 RIKEN and Japanese average citation rate comparison

Field	Total number of RIKEN papers	RIKEN citations per paper	Japanese average citations per paper
BIOLOGY & BIOCHEMISTRY	30,258	15.88	11.56
PHYSICS	26,919	7.28	6.44
MOLECULAR BIOLOGY & GENETICS	24,003	21.90	18.23
CHEMISTRY	16,251	8.69	7.42
NEUROSCIENCE & BEHAVIOR	14,682	20.00	11.14
PLANT & ANIMAL SCIENCE	10,895	16.89	5.08
CLINICAL MEDICINE	5,962	12.29	7.89
MICROBIOLOGY	4,246	10.56	9.37
ENGINEERING	3,531	3.68	2.63
MATERIALS SCIENCE	1,393	4.44	4.10

(Source: Thomson ISI Essential Science Indicators™)

Table 4 RIKEN Seminars and Symposia (Fiscal year)

	2001	2002	2003	2004
RIKEN Seminar	106	142	179	205
RIKEN Symposium	39	37	36	40

Press releases

In the 2004 fiscal year, 55 science-related and 14 RIKEN-related press releases were issued. Joint press releases that were initiated by other organizations totalled 15. 12 reference materials were also distributed. (Detailed information is presented on pages 30–32.)

Activities to generate public understanding

Numbers of visitors to RIKEN Open Days

	2004			2003
Wako Institute	April 17		5,843	5,667
Tsukuba Institute	Open to the public	April 14	655	662
	Special opening	April 17	395	293
	Total		1,050	955
Harima Institute	April 24		3,391	2,866
Yokohama Institute	June 26		1,589	941
Kobe Institute	April 17		1,626	1,150
Photodynamics Research Center	April 14		90	125
Bio-Mimetic Control Research Center	July 24		255	614

Public lecture

" Starting from the molecule, the birth of new science "October 20, 2004

Audience: 504

Lecture titles: Photocatalyst are active in various fields
(Akira Fujishima, President, the Kanagawa Academy of Science and Technology)

Searching into chemical reactions
(Toshinori Suzuki, Chief Scientist, Chemical Dynamics Laboratory, Discovery Research Institute)

Watching molecules inside the humans
(Masaaki Suzuki, Professor, Gifu University, Graduate School of Medicine)

Toward competent chemical synthesis
(Ryoji Noyori, President, RIKEN)

Research Ethics Committee Hearings

As progress between bioscience advances and the ties between society and science deepen, it has become necessary to think about how research should be conducted. Research activity involving human subjects requires both the understanding and cooperation of those subjects before samples can be donated or tests can be done. RIKEN has assembled six ethics committees on four campuses that are charged with approving research proposals, ensuring that potential participants or donors fully understand and give informed consent for their participation, and ensuring that scientific and human ethical considerations are taken into consideration before approving any procedure.

Wako Institute

The 1st Research Ethics Committee: Research on the human genome and gene analysis

- Number of committee meetings during fiscal 2004: 4
- Number of examinations (grand total): 16
- Results of examinations: 11 approvals and 5 conditional approvals

The 2nd Research Ethics Committee: Research on human subjects using fMRI (functional Magnetic Resonance Imaging) in high magnetic fields

- Number of committee meetings during fiscal 2004: 2
- Number of examinations (grand total): 2
- Results of examinations: 2 approvals

The 3rd Research Ethics Committee: Research on human subjects and research using samples of human origin

- Number of committee meetings during fiscal 2004: 15
- Number of examinations (grand total): 65
- Results of examinations: 44 approvals, 20 conditional approvals and 1 other

Tsukuba Institute
Research Ethics Committee

- Number of committee meetings during fiscal 2004: 5
- Number of examinations (grand total): 16
- Results of examinations: 15 approvals and 1 other

Yokohama Institute
Research Ethics Committee

- Number of committee meetings during fiscal 2004: 6
- Number of examinations (grand total): 60
- Results of examinations: 47 approvals, 12 conditional approvals and 1 other

Kobe Institute
Research Ethics Committee

- Number of committee meetings during fiscal 2004: 4
- Number of examinations (grand total): 7
- Results of examinations: 4 approvals, 2 conditional approvals and 1 other

Technology transfer and research cooperation

Cooperation with industry for efficient transfer of technology

To provide the widest possible social benefit from its activities, RIKEN actively seeks to put its intellectual property, and patents, into practical use within and beyond its own research uses. To this end, the Center for Intellectual Property Strategies was established in April 2005.

(1) Patent acquisitions

- RIKEN provides a system to find out the patent potential through reviews by experts, and offers consultations on inventions. In addition, it holds patent seminars based on contents and methods which suit the current situation of each project undertaken at RIKEN, in order to educate researchers on finding invention potential by paying meticulous attention to researchers' needs and to their understanding of intellectual property. This has increased researchers' interest in patent application and intellectual property. Consequently, all RIKEN's institutes have increased their number of patent application.
- For foreign patent application, RIKEN investigates the possibility of commercialization for all patent applications, and applies for foreign patents in accordance with a specified policy.
- RIKEN periodically assesses the commercial viability of all its current patents, to determine whether to sustain or release patent protection rights, according to its regulations. This process allows RIKEN to deal effectively with its patent interests.
- 570 patent applications and one trademark application were filed in 2004 (449 patent applications and one trademark application were filed in 2003).

Table/ Fig. 1 Patent applications and registrations

Fiscal year

	2000	2001	2002	2003	2004
Newiy registered patents (domestic)	41	38	38	80	102
New registered patents (overseas)	48	58	64	108	140

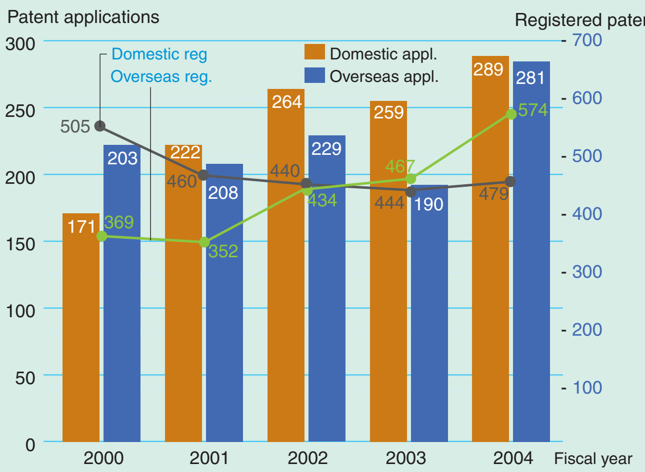
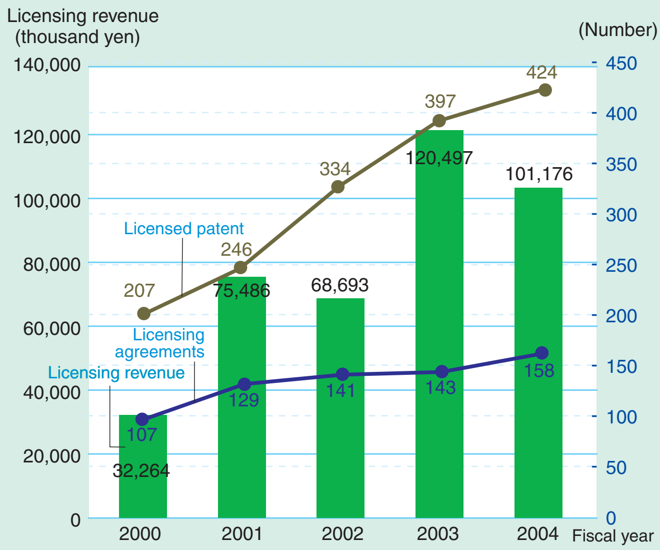


Fig. 2 Patent licensing trends



(2) Technology transfer and enabling practical adoption of applications

- RIKEN has implemented several programs to encourage increased technology transfer, including industrial collaboration programs and a partnership program for proteomics research. RIKEN also uses business experts and supports RIKEN Ventures. Furthermore, RIKEN actively disseminates relevant information through information magazines, its web site and networking events for technology transfer.
- The Integrated Collaborative Research Program with Industry started recently. This program enables companies and RIKEN laboratories to develop joint research activities that merge human resources and knowhow from RIKEN

with the R&D potential of companies with Japan-based production operations. This program uses a new framework for research collaborations which hopes to start new technological infrastructures and commercialize the results rapidly.

- As a measure for improving licensing activity, RIKEN has contracted a trading company to search for interested parties and collaborators to improve the rate and process for licensing patented RIKEN inventions. Furthermore, RIKEN will also review its public patents, categorise them by industry and research field, and develop an on-line, searchable database that will be published in fiscal year 2005.
- To support the RIKEN Venture, RIKEN held seminars relating to venture financing, inviting external consultant companies, and business report meetings, inviting venture capitalists; this gave practical support such as offering RIKEN Ventures, opportunities to inform the venture capitalists about their businesses.
- These measures helped RIKEN attain a 12.5% patent license ratio, exceeding its target of 10%, in fiscal year 2004. In order to define the role of technology transfer and promote this trend, RIKEN established the Center for Intellectual Property Strategies at the start of fiscal year 2005. This center will facilitate business development by acquiring external funding sources, seeking to create and to use RIKEN's intellectual property assets, supporting venture generation, and fostering outside business collaborations. The center will also synthesize ideas from its three research programs to develop an effective and efficient model for technology transfer.

(3) Supplying bioresources

Bioresources are collected and maintained at various facilities throughout RIKEN, especially the BioResource Center (BRC). Information about these resources will be stored on a database to facilitate external distribution.

Table 3 ● Bioresources at BRC

As of Mar 31, 2005

Laboratory Animals	1,668	Strains
Laboratory Plant Seeds	47,208	Strains
(Arabidopsis) Genes	217,409	Lines
Cultured Cell Lines	34	Cell Lines
Cell Bank	2,521	Cell Lines
DNA Samples	764,968	Clones
Microorganism	11,919	Strains

(4) Research collaboration

RIKEN established institutional collaborative agreements with several Japanese and international organizations. These include Saitama Prefecture, the University of Tokyo, and Karolina Institutet in Sweden. The SNP Research Center also made an agreement with the National Research Institute of Police Science. RIKEN will continue to seek beneficial collaborations between industries, institutes, and governments around the world.

Joint Graduate School Programs (Domestic)

Closer relationships within Japan between RIKEN and universities are being created through research collaboration and student research training at RIKEN. In 1989, Japan's first joint graduate school emerged from the efforts of Saitama University and RIKEN. Since then, more than 21 universities have established similar programs with RIKEN. They are listed below, ordered by the year the collaboration started.

List of joint graduate schools (starting year of the collaboration)

Saitama University (1989)
University of Tsukuba (1992)
Tokyo University of Science (1995)
Toyo University (1997)
Tokyo Institute of Technology (1997)
Tohoku University (1997)
Rikkyo University (1998)
Chiba University (1998)
University of Hyogo (1999)
Tokyo Denki University (2000)
University of Tokyo (2000)
Yokohama City University (2001)
Kyushu Institute of Technology (2001)
Kobe University (2002)
Kyoto University (2002)
Nara Institute of Science and Technology (2003)
Toho University (2003)
Kwansei Gakuin University (2004)
Niigata University (2004)
Tokyo Medical and Dental University (2004)
Nagaoka University of Technology (2004)

Joint Graduate School Program (Asia)

To foster young Asian Ph.D. course researchers and build a strong Asian research network that will push Asian science forward, RIKEN established a graduate school program in 2001 with various universities throughout Asia. Through this program, Asian Ph.D. candidates are invited to train at RIKEN. Cooperative relationships have been established with seven universities, listed below in the order in which agreements were finalized.

Pusan National University (Korea)
Universiti Sains Malaysia (Malaysia)
Kasetsart University (Thailand)
Beijing University (China)
Hanoi University of Science (Vietnam)
National Chiao Tung University (China)

Other activities in 2004

Internal Joint Forums

Three of RIKEN's research establishments held RIKEN's first Joint Seminar on September 13–14, 2004, on the Wako Campus, to encourage greater interaction between the laboratories of Discovery Research Institute, Brain Science Institute, and Center for Developmental Biology.

New on-site day-care service

RIKEN Kids, RIKEN's first on-site day-care service, began providing care to children of RIKEN staff on April 1, 2004. Not only will this service make RIKEN more attractive to exceptional researchers and administrators who seek a better way to balance work and life choices without compromising RIKEN's standard of research output; it will also create an emvironment on campus that encourages more interaction between all of RIKEN' s staff and their families.

Prizes

IN 2004,122 RIKEN researchers received awards acknowledging for their contributions to science. Most notable was the award conferred on Hiromichi Kamitsubo, the supervisor of RIKEN Accelerator Research Facility. He received one of Japan's highest awards, the Order of the Sacred Treasure (Gold Rays with Neck Ribbon) for his contributions to Japan's accelerator research, in particular in developing the RIKEN Ring Cyclotron and SPring-8.

Visitors

RIKEN welcomed many visitors from Japan and around the world in 2004. We were especially honored by visits to the Wako campus from Dr. Phillipe Kourilsky, the Director of Institut Pasteur, in April 2004, and Mr. Phillip Yeo, Singapore's Chairman of the Agency for Science, Technology and Research, in November. Japan's Minister of Education, Culture, Sports, Science and Technology (MEXT) paid a visit to the Yokohama Institute in February 2005.

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