


RIKEN

NATIONAL SCIENCE INSTITUTE of Japan

Extraordinary
people



Extraordinary science



RIKEN National Science Institute is Japan's most comprehensive institute for the natural sciences, conducting cutting-edge research in a wide range of scientific fields, including physics, chemistry, brain science, energy, medicine, nuclear physics, sustainable resources, computer science, plant science, genetics, nanoscience, developmental biology, electronics, artificial intelligence, and much more.

"History of nuclear physics"
by Yasuaki Yutani
RIKEN Image Competition

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MESSAGE FROM PRESIDENT HIROSHI MATSUMOTO

IN NORMAL times, I like to focus my message to our readers on the new and exciting research being done at RIKEN and to encourage young researchers to either collaborate with us or join us doing research in Japan. However, these are not normal times. As with other scientific institutes around the world, the coronavirus pandemic has had a huge impact on our ability to do research and continue our normal routines. We are still adjusting to the necessary changes and learning from our experiences.

The pandemic has reinforced my belief that collaboration between different institutes and scientists is crucial for overcoming the challenges that face humanity. Thankfully, we have seen an outpouring of cooperation in the face of the pandemic, and I am sure many of the partnerships being forged right now will continue after the current crisis has passed. Additionally, the pandemic has taught us that instead of limiting our thinking to scientific pursuits, we must also think about our lifestyles and how our society is organized. At RIKEN, we are planning to further emphasize the importance of philosophy in our work, as well as other fields outside the natural sciences.

This booklet describes some of our most important research achievements over the last few years, as well as some of the changes we have made. In particular, I am excited about a new company we have established to help put our discoveries into practical application. I hope that you find this booklet instructive, and as always, I would like to encourage talented young researchers to come work with us—though there may still be practical problems to overcome due to the aftereffects of the pandemic. I look forward to working with our partners around the world on the current challenges facing our civilization, as well as any that might occur in the future.



BRIEF HISTORY

KEY MOMENTS

RIKEN, THE Institute of Physical and Chemical Research, was founded in 1917 by prominent businessman and industrialist Eiichi Shibusawa along with leaders from various fields of research.

The initial years were rocky, but the third president, Masatoshi Okochi, strengthened the organization's foundation by creating a group of companies that commercialized RIKEN discoveries. In the prewar years, RIKEN contributed to scientific fields such as cosmic ray and cyclotron research, and also contributed to society through products such as vitamin A, piston rings, and a groundbreaking surface treatment for aluminum called alumite. However, the end of WWII marked a sudden end to an era of rapid expansion at RIKEN.

- 1917 - RIKEN is founded
- 1948 - RIKEN becomes KAKEN Scientific Research Institute Ltd.
- 1958 - RIKEN becomes a public corporation
- 2003 - RIKEN becomes an Independent Administrative Institution
- 2016 - RIKEN is designated as one of three National Research and Development Institutes in Japan
- 2017 - RIKEN celebrates its 100th anniversary.

The conglomerate created by Okochi was dissolved by the Occupation forces, and eventually reopened as a private company under the name KAKEN in 1948. Its leaders tried to make ends meet, but it was a difficult time. Things picked up in 1958 when it became a public corporation and changed its name back to RIKEN.

In 1967, just as it celebrated its 50th anniversary, RIKEN relocated to a large state-owned piece of land in the outskirts of Tokyo, and began to establish satellite institutions at other locations in Japan.

Modeled on the Max Planck Society in Germany, the satellite institutions were to be located across the country, each focusing on specific fields of research. Over the years, this vision has become reality, with the opening of multiple centers in Tsukuba, Sendai, Nagoya, Yokohama, and Kobe, and research expanding beyond physics and chemistry to numerous fields in the life sciences, computer sciences, and engineering.

NATIONAL RESEARCH AND DEVELOPMENT INSTITUTE

IN APRIL 2015, RIKEN became a National Research and Development Institute, and in 2016 was given new prestige as one of three Designated National Research and Development Institutes in Japan, just in time for the centennial celebration, which took place in 2017.

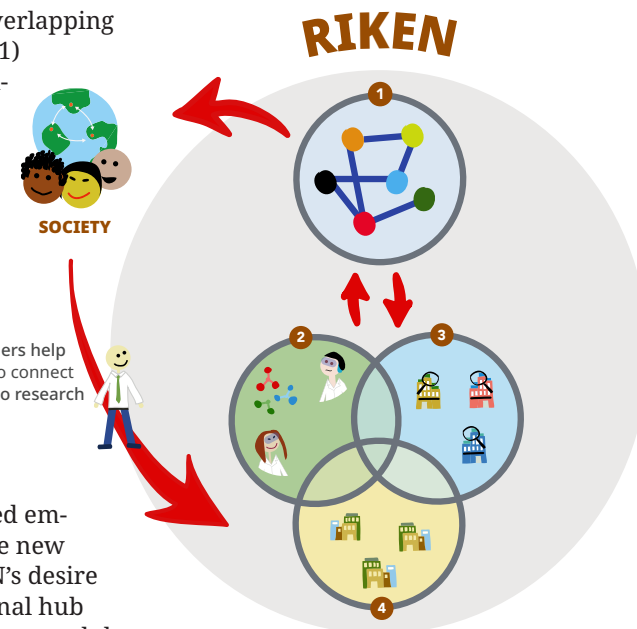
ORGANIZATION & FUTURE DIRECTIONS

ORGANIZATIONAL PHILOSOPHY

RIKEN HAS changed over the years, but its commitment to basic research remains the same. Now, under RIKEN's 4th mid- to long-term plan, research falls into four interactive and sometimes overlapping areas (see illustration): (1) Cluster for Science, Technology, and Innovation Hub (p. 51), (2) Cluster for Pioneering Research (p. 54), (3) Strategic Research Centers (p. 60), and (4) Research Infrastructure Centers (p. 63).

FUTURE DIRECTION

ALONG WITH a renewed emphasis on society, the new plan incorporates RIKEN's desire to become an international hub that links research from around the world to appropriate industries—all for society's benefit. To facilitate this, the new plan includes an Innovation Design Office with three innovation designers—appointees who specialize in identifying real-world problems and communicating those



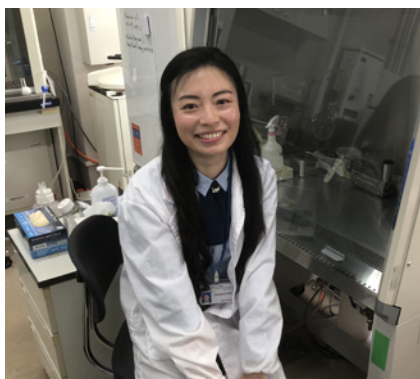
needs to researchers, not only from a scientific perspective but also from the viewpoints of the social sciences and humanities.



PROGRAMS FOR SCIENTISTS

SPECIAL POSTDOCTORAL RESEARCHERS PROGRAM

IN THE Special Postdoctoral Researchers (SPDR) program, young and creative scientists are given the opportunity to be involved in autonomous and independent research under the direction of their host laboratory's principal investigator.



Chao-Hui Feng, SPDR Fellow

The program helps promising young scientists to establish global careers with three years of funding. A generous remuneration package is supplemented with an annual research budget of 1 million yen (about US \$8,000) allocated to the host laboratory.

This program is open to researchers in mathematical sciences, physics, chemistry, biology, medical science or engineering who have a doctoral degree and fewer than five years of postdoctoral experience. This is one of RIKEN's initiatives aimed at opening our facilities and resources to the world and creating a stimulating research environment that places our organization at the forefront of global science and technology.

"The SPDR program has given me a wonderful stage for bringing my inspiration, curiosity and enthusiasm to my research work," says **Chao-Hui Feng**, from **China**, who is doing her postdoctoral research in the Terahertz Sensing and Imaging Research

Working at RIKEN

Team in Sendai. "This program has given me the opportunity to carry out research ideas in a unique, creative and original way; I've broadened my professional knowledge, strengthened my international research experience, and continued to accelerate my professional research career."

Qualified candidates of all nationalities are welcome to apply.

RIKEN's Joint Graduate School program are eligible to apply.

As of March 2020, IPAs from 32 universities in Asia and Europe were studying at RIKEN. They included students from Peking University in China, Seoul National University in South Korea, USM in Malaysia, Liverpool University in the United Kingdom, and ETH Zurich in Switzerland.



Marie-Therese Huebsch, IPA Fellow

INTERNATIONAL PROGRAM ASSOCIATES PROGRAM

RIKEN OFFERS non-Japanese PhD candidates at participating universities the chance to undertake their doctoral studies in Japan under the supervision of a senior RIKEN scientist. Each year RIKEN accepts about 100 students as International Program Associates (IPAs). Students enrolled, or about to enroll, in a PhD program at one of the Japanese or overseas universities participating in

Associates receive living expenses, a housing allowance and round-trip airfare, as well as the benefit of international collaboration in their research and the chance to experience a new culture.

"RIKEN has given me the perfect environment for fully immersing myself in my research on functional material design," says **Marie-Therese Huebsch** from **Germany**, "RIKEN has great computational infrastructure, and as a member of the IPA program I not only have liberal access to that infrastructure, but I also have ample opportunities to clarify my work through group discussions with experienced scientists. To me, the true heart of the IPA program is the support from an experienced team that always comes to my aid when I face challenges typical to life in a foreign country."

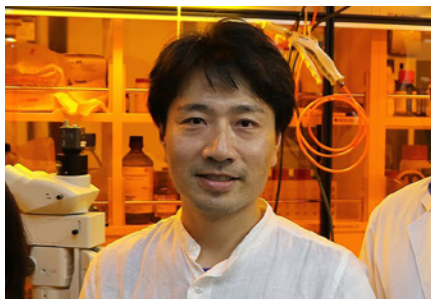
HAKUBI FELLOWS PROGRAM

THE RIKEN Hakubi Fellows Program offers junior laboratory-leader positions for research by

exceptional individuals. Fellows are given the opportunity to independently engage in creative and ambitious research in natural and mathematical sciences—including research areas bordering the humanities and social sciences—and are provided with a generous salary and research support. Laboratories established under the program can operate for up to seven years.

An important goal of the RIKEN Hakubi Fellows Program is to foster stimulating interactions among outstanding researchers with diverse backgrounds and to create an intellectual hub of scientists with different disciplines within and beyond RIKEN. The word *hakubi*, which literally means “white brow,” comes from the nickname of Ma Liang, an exceptional official featured in the *Three Kingdoms*, who was said to have white strands of hair in his eyebrows.

Hirofumi Shintaku, whose lab was established in April 2018, is studying new techniques for genetic



Hirofumi Shintaku, Hakubi Fellow

sequencing within cells. He says, “My research began from the study of fluid dynamics and transport phenomena in very small confined spaces, like those within cells. In my previous work, I developed a microfluidic system that enables high-throughput sequencing of cytoplasmic and nuclear RNA from single cells, and I am grateful for being accepted into the Hakubi program as it will allow me to use this system to look at the regulation of gene expression involving RNA localization and transport in single cells.”

In addition to our state-of-the-art research facilities and open research environment, we aim to provide a comfortable and congenial environment for researchers and their families from around the world. A wide range of programs, services, and welfare benefits are available to all RIKEN employees, regardless of gender or nationality.

OTHER PROGRAMS

SUMMER PROGRAMS

THE RIKEN Center for Brain Science (CBS) Summer Program is an opportunity for undergraduate and graduate students, as well as postdoctoral researchers, to study brain science in Japan in either a two-month laboratory internship at a CBS laboratory, or an intensive one-week lecture course given by distinguished international scientists.



CBS Summer School participants

The RIKEN Integrated Medical Sciences (IMS) International Summer Program (RISP) aims to provide PhD students and young postdoctoral researchers from around the world with the opportunity to learn about cutting-edge research in immunology and genomic medicine. It takes place over one week at the IMS facility in Yokohama and includes presentations from internationally distinguished scientists and each participant.

SCHOOLS

THE NISHINA School offers select students from Peking University, Seoul National University, The University of Hong Kong, and several Japanese universities, the

opportunity to acquire hands-on experience in theoretical and experimental nuclear physics in a two-week summer school at the RIKEN Nishina Center for Accelerator-Based Science (RNC).

WORKING ENVIRONMENT

ENGLISH IS OK!

MANY OF RIKEN’s laboratories are completely bilingual with Japanese and non-Japanese scientists and technical staff working side by side to achieve common goals, and many scientific seminars are given in English. RIKEN also offers a bilingual administrative environment that provides needed information in a timely fashion in both



Working at RIKEN

Japanese and English. RIKEN also provides introductory Japanese lessons for those who don't speak any Japanese. Rest assured, you will be able to succeed in your research and enjoy life in Japan even if you don't speak the language when you arrive.

In addition, all full-time RIKEN employees are members of the RIKEN Mutual Benefit Society, which sponsors a wide range of club activities and events, both cultural and sports-related, for employees.

HELP STAFF AND HOUSING

FRIENDLY BILINGUAL staff are on-hand at the major RIKEN campuses to provide information and support to help researchers deal with healthcare, housing, childcare and schooling, and the practical issues of daily life.

The main Wako campus has both single and family apartments, while other RIKEN campuses have a range of accommodation available, either

on or off campus. For long-term stays, we can provide introductions to local real estate agencies and, when necessary, assist with procedures.

FAMILY CARE AND SUPPORT

TO HELP researchers focus on their work without having to worry about taking their children off-campus, daycare programs are available for infants, toddlers and preschool-aged children at the Wako, Yokohama, and Kobe campuses.

RIKEN offers special leave, in addition to its regular paid leave, for caring for sick children or other family members.

RIKEN is a strong advocate of gender equality and has Personal Support Coordinators who provide individualized guidance on RIKEN's support programs and services related to pregnancy, childbirth, childcare, and the care of sick or elderly family members.



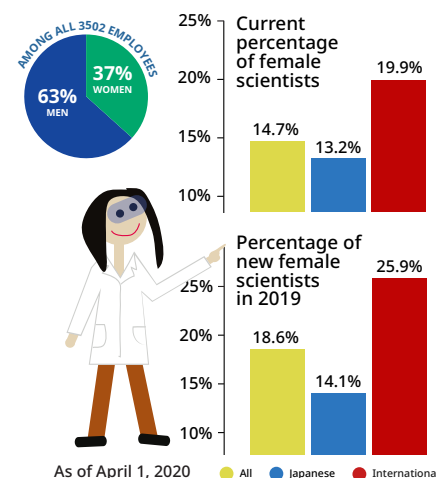
WORKFORCE AND DIVERSITY

INTERNATIONAL DIVERSITY ON THE RISE

RIKEN EMPLOYED 3,531 individuals in 2017, a figure that has remained relatively constant over recent years. Among the nearly 2,000 scientists employed by RIKEN, roughly 20% come from outside Japan.

GENDER DIVERSITY ON THE RISE

RIKEN is also making strong efforts to increase the number of women in research and management positions. In Japan, women are generally underrepresented in the world of science and technology, but RIKEN has shown leadership in this area by implementing a variety of programs to encourage the recruitment and retention of female scientists and staff.



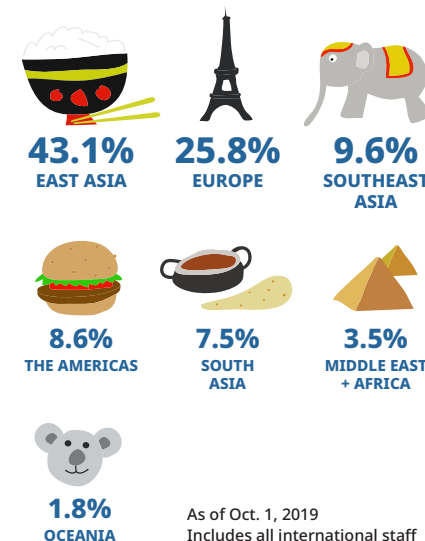
1888
SCIENTISTS

22%
INTERNATIONAL
(38% of new hires in 2019)



As of April 1, 2020.
Includes full-time researchers

822 INTERNATIONAL FACULTY AND STAFF



Medicine and disease

Life science research at RIKEN ranges from developmental biology and neuroscience to plant science and AI-assisted medical treatment. The common thread connecting these different disciplines is the desire to help society, whether it be by improving physical and mental health or by creating more durable crops and a more sustainable environment.

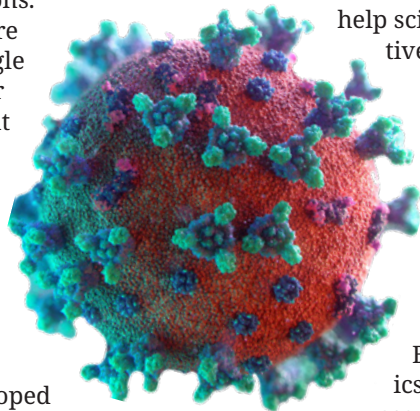
RESPONSE TO THE COVID-19 PANDEMIC

LIKE MANY other institutes around the world, RIKEN has rapidly launched a number of research projects and initiatives aimed at stemming the COVID-19 pandemic, some of which are opportunities for international collaborations.

RIKEN's initiatives are not focused on a single aspect of the virus or the current crisis, but are designed to attack the problems facing our society from as many angles as possible. Many of the new techniques, research methods, and findings being developed to fight SARS-CoV-2 (the virus that causes COVID-19) will be applicable to other infectious diseases that might break out in the future.

RIKEN is using its big-science infrastructure to combat the virus. Although still under development, the supercomputer Fugaku at the RIKEN Center for Computational

Science (**R-CCS**) has already been put to use on several projects related to the pandemic. One is simulating phenomena such as clustering and spread so that we can better predict when and where new clusters of infection might appear. Another is modeling how people get infected by SARS-CoV-2 viral droplets in indoor environments, which should help scientists devise effective countermeasures.



A third simulation project in conjunction with the RIKEN Center for Advanced Intelligence Project (**AIP**) and the RIKEN Center for Biosystems Dynamics Research (**BDR**) uses other supercomputers at RIKEN to simulate the molecular dynamics of the virus's protein structure. The artificial intelligence (AI) can then be used to make predictions about its structure that are not yet detectable. Researchers at **BDR** then use these predictions and the already known molecular structure of the viral proteins to efficiently

find compounds that can be used as drug treatments. A known or predicted protein structure allows efficient selection of drugs that can then be tested to determine whether or not they interfere with the proteins on the surface of the virus. Being able to block these surface proteins will prevent them from being able to attach to new cells, thus reducing the virus's ability to infect more cells once it has entered an organism.



Researchers are also working to improve COVID-19 diagnostic techniques. SmartAmp is a new technology developed by the RIKEN Preventive Medicine and Diagnosis Innovation Program (PMI) that can already detect the virus more than four times as fast as conventional PCR. Additionally, the RIKEN Cluster for Pioneering Research (**CPR**) is working on new methods for detecting the virus that do not require amplification of the viral DNA, thus saving even more time. In addition to detecting current infections, **IMS** is also advancing ways to detect past infection and studying how antibodies against SARS-CoV-2 increase during therapy.

Scientists at **AIP** are also using RIKEN's AI expertise to gain a better understanding of the indirect ways

Key centers: Medicine and Disease

- AIP:** RIKEN Center for Advanced Intelligence Project
- BDR:** RIKEN Center for Biosystems Dynamics Research
- CPR:** RIKEN Cluster for Pioneering Research
- IMS:** RIKEN Center for Integrative Medical Sciences

in which the pandemic has affected society and to provide solutions. Projects include a communication system that helps preserve the cognitive and physical health of older adults who must stay at home, and an analysis of hate speech and disinformation related to the pandemic on the Internet. In other research, machine learning is being used to find factors that help determine whether people will suffer from mild or severe cases of the disease. Further, **AIP** is researching the negative effects of extended teleworking, both physical and psychological, which will yield ways in which telework systems and online work tools can be improved. Even after the pandemic has passed, the findings might be used to improve the way that people work.

STEM CELLS, ORGANOGENESIS, AND TRANSPLANTS

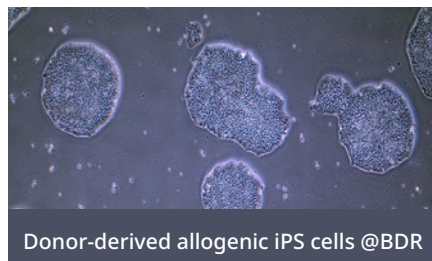
INDUCED PLURIPOTENT stem cells (iPS cells) are created from matured, differentiated cells, such as those found in the skin. Once they become stem cells, they can be directed to change into a desired cell type. Hoping to use iPS cells to repair or replace damaged tissues and organs, RIKEN scientists have been shaping this field of research since its infancy.

Regenerating the retina



RIKEN scientists at **BDR** are studying ways to use iPS cells for replacing damaged retinas and halting the progression of visual impairment. Since 2014, when they performed the first transplant of iPS cell-derived laboratory-grown tissue into a human patient with age-related macular degeneration, **BDR** researchers have moved beyond the use of autogenic iPS cells—cells derived from the same person who receives the transplant—and are now pursuing a more flexible allogenic system in which the donor is not the recipient. The goal is to be able to use a limited set of donor types to provide ready-made iPS cell-derived retinal tissue for anyone, without fear of rejection.

As a first step, the **BDR** team partnered with Kobe City Eye Hospital to launch a clinical research project using allogenic iPS cells. To date, they have performed the transplantation



surgery in five patients with macular degeneration and a one-year follow-up in 2018 confirmed the safety of the intervention.

Another issue is whether lab-grown tissue can function properly once transplanted. In a recent study, the team implanted lab-grown retinas derived from human embryonic stem cells into monkeys with retinitis pigmentosa, a disease that affects photoreceptors in the retina. Two years after transplant, they observed many new photoreceptors at the transplantation site, and importantly, evidence that these new receptors made connections to the host nervous system.

These results have directly led to a new clinical study at Kobe City Eye Hospital in Japan. In collaboration with **BDR** and other Japanese institutes, beginning in 2020, they plan to generate retinal tissue from iPS cells and transplant them into patients suffering from retinitis pigmentosa.

Skin/hair/gland regeneration

Other RIKEN laboratories are working on growing different types of

human tissue and organs. **BDR** scientists have reprogrammed iPS cells and successfully grown complex skin tissue in the laboratory—complete with hair follicles and sebaceous glands. Since the initial experiments, the researchers have developed a new method for mass producing regenerated hair follicles, and in 2018, animal testing of hair follicle regeneration began in conjunction with the RIKEN Program for Drug Discovery and Medical Technology Platforms. As of 2020, planning for a clinical study in humans is underway.



In 2019, the same laboratory succeeded in growing a three-dimensional salivary gland organoid from iPS cells. Once grown, they implanted it into mice that lacked salivary glands. The implanted tissues connected properly to the nerve tissue and produced a substance similar to real saliva when the mice were given citric acid.

Studying diseases with iPS cells

iPS cells can also be used to study diseases. **BDR** scientists used iPS cells derived from patients with spinocerebellar ataxia to grow three-dimensional mature Purkinje cells, whose degeneration in the cerebellum is a primary symptom of this

genetic disease. They found that patient-derived cells became vulnerable when deprived of thyroid hormone, indicating a potential treatment for the disease.

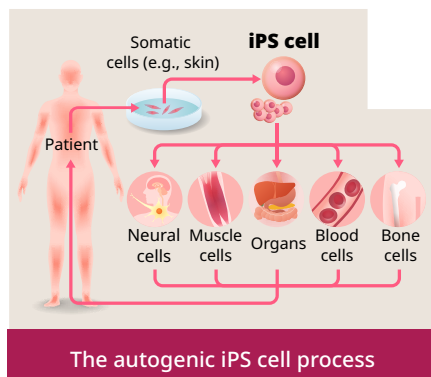


In another example, researchers at the **CBS** hypothesized that genetic factors in schizophrenia affect neuron function. They grew neurons from iPS cells that came from patients with schizophrenia and were lacking a region on chromosome 22. They found that one of the missing genes in that region was related to abnormal differentiation of neurons and an imbalance between the number of neurons and astrocytes in brains of people with schizophrenia.

In 2020 a group effort between the RIKEN BioResource Research Center (**BRC**) and other Japanese institutions generated two human iPS cell lines from patients with juvenile nephrophtosis, the most common cause of kidney failure in children. Both cell lines include a deletion in the *NPHP1* gene and will be useful for establishing disease models and developing effective drug therapies and other treatments.

CANCER RESEARCH

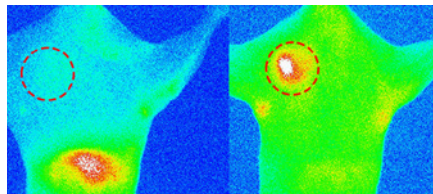
RIKEN researchers are attacking cancer from all sides, working to improve diagnostics and developing new treatments. Cancer treatments often comes down to location.



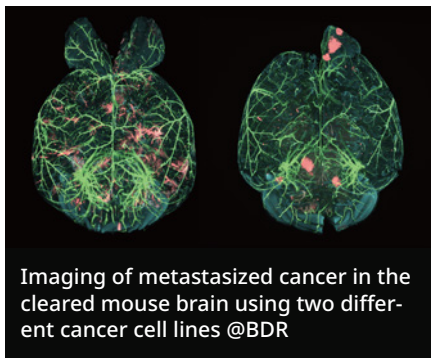
Identifying tumor locations

A key to treating cancer and avoiding relapses is making sure that all cancer cells are removed. Researchers at **BDR** have developed a cocktail of chemicals called CUBIC that clears tissue and visualizes postmortem cancer metastasis of whole organs in 3D. The technique is extremely sensitive and can be used to detect individual cancer cells, particularly those that are dormant or drug-resistant. This technique can make it easier to judge the effectiveness of anti-cancer drugs when they are first tested in animals, which in the long run will help reduce cancer relapse.

When doctors need to identify tumor locations in living organisms, tissue clearing is not an option. A laboratory at **BDR** recently developed a way to attach extremely bright near-infrared fluorescent probes—called quantum dots—to antibodies. Because the near-infrared light can easily penetrate animal skin and tissue, tumor cells with known biomarkers can



Near-infrared fluorescence images of breast tumors in mice (red circles). (left) Quantum dot injection. (right) Antibody-conjugated quantum dots specific for breast tumor cells correctly localized to tumor area. @BDR



Imaging of metastasized cancer in the cleared mouse brain using two different cancer cell lines @BDR

thus be imaged non-invasively by choosing the appropriate antibody that matches the biomarker.

Locating tumor cells during surgery is also critical. In 2018, a miscommunication between a Japanese researcher and a Russian student at **CPR** led to a mistaken experiment. By recognizing the importance of the results, the team was eventually able to develop a fluorescent probe that detects acrolein, a tiny molecule that can act as a marker for oxidative stress in breast cancer cells. The result is a 5-minute test that surgeons can use to determine which regions can be removed during breast cancer surgery.

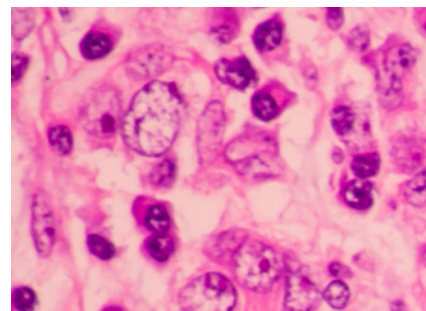
Targeted treatments

Surgery, radiation therapy, and chemotherapy all have a common problem: they are imprecise and can destroy healthy tissue as well as tumors. Researchers at RIKEN are therefore trying to develop treatments that can selectively destroy only cancer cells.



For example, in 2019, researchers at **CPR**, **BDR**, and **RNC** worked together to develop tumor-targeted therapy by attaching astatine-211 to antibodies. Because astatine-211 is a radioisotope that emits low level radiation in the form of alpha particles, it can selectively kill tumors when attached to antibodies that recognize antigens on the surface of cancerous cells.

Other researchers from the same **CPR** laboratory have developed a different targeting technique. In 2019, they created an artificial metalloenzyme using the element ruthenium. Ruthenium catalyzes a molecule into umbelliprenin, a plant-derived compound known to act against cancer cells. By tagging the surface of the artificial metalloenzyme with a particular chain of sugars, the researchers were able to target it specifically to cancer cells where the drug was needed.



Artificial intelligence was able to predict recurrence of carcinoma based on images like this. @AIP

Predicting recurrence

Recently, scientists at **AIP** used artificial intelligence to help predict the likelihood of prostate cancer recurrence. The AI learned from images of cancer pathology and was able to detect features that doctors have missed. The best predictions combined the AI with human-established criteria.

IMMUNOLOGY

UNDERSTANDING HOW the immune system functions can help in developing ways to fight off infection as well as combat hyperactive immune systems that are characteristic of autoimmune diseases and some types of viral infections. The key players in the immune system are white blood cells and antibodies. White blood cells come in many varieties, each with separate functions. Researchers at RIKEN are trying to understand these functions and what goes wrong in pathological conditions.

Innate immune cells, obesity, and allergies

The gut is where the immune system meets bacteria, both good and bad. A research group at **IMS** is studying innate immune cells in the gut—immune cells that occur naturally and are not acquired in response to any invader. In 2019, the group discovered that obesity is related to ILC2 cells, a subtype of innate immune cells. Unlike normal mice, mice lacking these ILC2 cells stayed lean, even

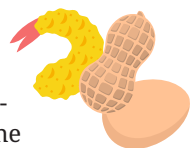
after eating a high-fat diet for several weeks. These cells are thus an attractive target for drug therapies that decrease obesity.



ILC2 cells are also found in tissues lining the stomach, esophagus, and lungs, where they seek out pathogens and alert white blood cells. Hay fever and asthma result when ILC2 cells confuse something like pollen or dust for a pathogen.

ILC2s do not get tired even when continuously activated, and the result is unabated allergic reactions. Researchers at **IMS** have recently discovered the protein responsible for this phenomenon, and were able to create exhausted ILC2s by interfering with the protein's ability to function. This protein, called Cbf β , represents a potential new target for direct immune therapy against asthmatic responses, which might be more effective than current therapies.

Most allergic reactions to food result from the release of abnormally high levels of histamine in the gut. While a bad reaction can be treated with a quick and powerful shot of adrenaline, a team at **IMS** has been working on alternative treatment options using a mouse model of food allergies. In 2017, they found that the release of abnormally high levels of histamine



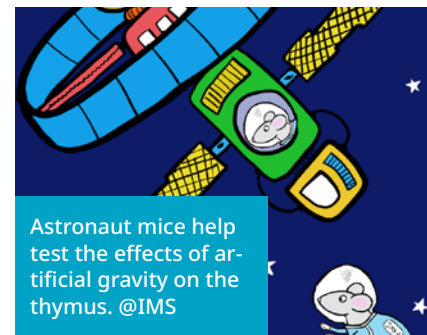
Livers. High-fat diets led to obesity in wild-type mice (bottom-left), while mice lacking ILC2s stayed lean (bottom-right). @IMS

was due to excessive activation of the protein HRF. When they pretreated model mice with an HRF inhibitor, they were able to reduce the allergic response.

T-cells (mice in space)

T-cells are critical for the immune system's response to foreign invaders. The majority are produced in the thymus, a part of the lymphatic system that can be impaired by spending time in outer space. In 2019, researchers at **IMS** reported that artificial gravity helped protect the immune systems of astronaut mice who spent over a month on the International Space Station.

Mouse cages were sent to the ISS and centrifuged in the Multiple Artificial-gravity Research System that was



developed by the Japanese Aerospace Exploration Agency. While mice that experienced space without artificial gravity lost 50% of their thymus, thymus deterioration was only 20% in those that experienced 1 g of artificial gravity, indicating that artificial gravity might help protect the immune systems of future astronauts.

GERONTOLOGY

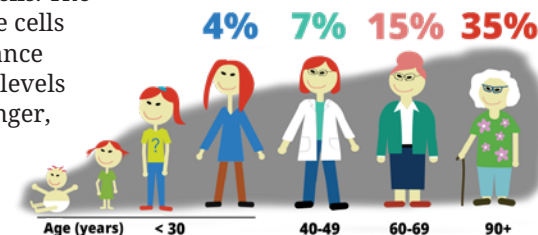
AS AGING populations increase, **RIKEN** has begun to place special emphasis on research into the aging process and conditions linked to older age. In 2019, an **IMS** study showed that supercentenarians—people over the age of 110—had excess amounts of cytotoxic CD4 T-cells. The researchers believe that these cells function in immune-surveillance and tumor elimination. High levels of these cells could lead to longer, disease-free lives.

In 2020, another group at **IMS** showed that age, especially advanced age over 90, is associated with increased

risk of clonal mutations in stem cells that give rise to white blood cells. European and Japanese populations differed in which types of leukemias were most prevalent and in which clonal mutations survived; mutations in T-cells were more likely in Japanese people, while those in B-cells occurred more often in Europeans. Now a simple blood test can check for both these mutations and the genetic risk factors, allowing earlier diagnosis and better treatment options.



At **BDR**, researchers are studying aging in the brain. A 2020 study showed that as we age the ventricles in the brain enlarge and outgoing blood circulation begins to lag. Because these two phenomena turn out to be correlated, the degree to which circulation lags makes it a good biomarker for aging brains and the risk of ventriculomegaly. Early detection using fMRI followed by simply draining the accumulated fluid can prevent excessive enlargement, which can affect cognition and cause dementia if left unchecked.



Chance of clonal mutations in blood stem cells increased with age. @IMS

STROKE

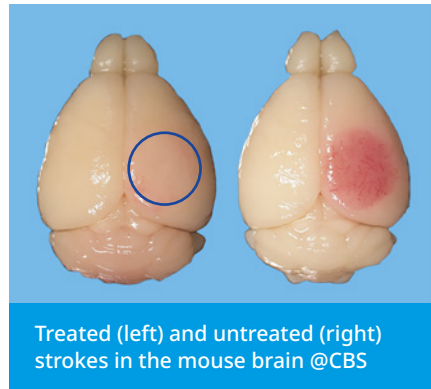
IN 2019, researchers at **CBS** tested a way to reduce damage from stroke in mice by targeting swelling and ion imbalances in the fluid surrounding the brain. By using a cocktail of drugs that block the activity of adrenaline in the brain, they were able to re-balance the fluid, particularly the elevated potassium levels. Even when administered two hours post-stroke, the adrenaline receptor blockers were effective in stopping the spread of infarcts. Overall, the treatment aided motor recovery and reduced cell death in the mouse brain.

MENTAL AND DEVELOPMENTAL DISORDERS

DEPRESSION, ALZHEIMER'S disease, schizophrenia, and autism spectrum disorders are just a few brain-related mental disorders that RIKEN scientists are tackling with animal models, genetic analysis, and electrophysiology.



Mitochondrial dysfunction (left) linked to excessive serotonergic activity (right) in a mouse model of bipolar disorder. @CBS.



Treated (left) and untreated (right) strokes in the mouse brain @CBS

Depression and bipolar disorder

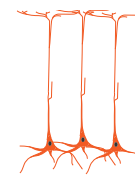
Researchers at **CBS** used *in vivo* calcium imaging and transgenic mice to determine that the benefits of transcranial direct stimulation of the brain in treating depression are due to calcium surges from astrocytes, a type of glial cell. This discovery could place astrocytes as a major therapeutic target for depression and other neuropsychiatric diseases.

In 2018, **CBS** scientists discovered a link between serotonin, mitochondria, and bipolar disorder. In mouse models of bipolar disorder that have the ANT1 mutation, they found that mitochondrial dysfunction led to hyperexcitable serotonergic neurons in the dorsal raphe region of the brain. Knowing this connection provides new targets for further research and treatment development.

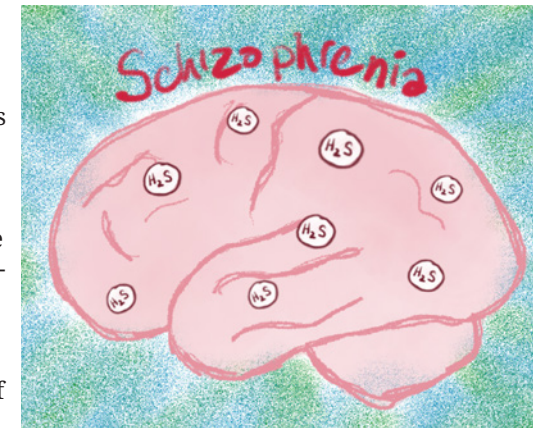
Schizophrenia

CBS researchers have also made several recent discoveries related to schizophrenia that could help in the search for new and improved treatments. Currently, all clinically effective drug treatments for schizophrenia block dopamine receptors on the surface of neurons. Unfortunately, these drugs are ineffective in over 30 percent of people with schizophrenia.

In 2019, a **CBS** group investigated betaine—a molecule that gets its name from the French word for "beet." The researchers found that levels of betaine were low in the postmortem brains of people with schizophrenia and that mice who could not make their own betaine showed schizophrenic-like symptoms that disappeared after eating supplements that included betaine.



Using a mouse model, that same year, the researchers found another potential target for drug therapy. Mice that exhibit a specific symptom of schizophrenia—a situation-based reduced startle response—had high levels of an enzyme that helps make hydrogen sulfide. They found similarly high levels of the enzyme in the postmortem brains of people with schizophrenia. Testing hair follicles of people with schizophrenia showed that high levels of this enzyme could

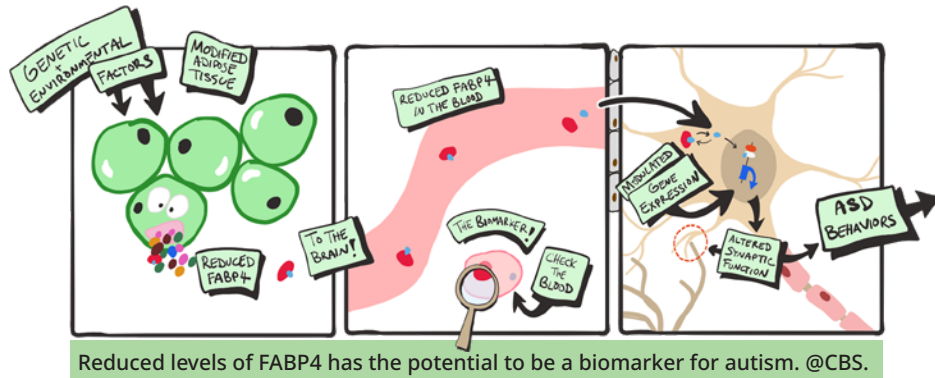


High levels of hydrogen sulfide (H_2S) found in schizophrenia. @CBS

be a biomarker for schizophrenia before other symptoms appear. In 2020, the team found a third candidate for drug development, this time related to lower amounts of white matter in the brain, a common symptom of schizophrenia. Analysis of postmortem brains showed degradation of a sphingolipid called SP1, which is necessary for making the myelin that wraps around neuronal axons. Drug therapy that activates the SP1 receptor could prevent white matter degradation and the accompanying disruptions in thought processes.

Autism spectrum disorders (ASD)

Early detection is particularly important in cases of autism because of the difficulties children face if their situation is not recognized. Researchers at **CBS** are addressing this need,



and in 2020 discovered a protein that can act as a biomarker for autism in preschool-aged children. Experiments showed that levels of the protein FABP4 were much lower in four- to six-year-old children with ASD than they were in typically developing children. Experiments in mice that lacked FABP4 revealed changes in neurons that resemble those found in the postmortem brains of people with ASD.

In 2019, another **CBS** team examined the relationship between two ASD characteristics that are related to mental inflexibility, which is a primary symptom of ASD. One is cognitive rigidity, which is typified by repetitive behaviors, and the other is overly stable visual perception, which can be seen in the lack of front/back perceptual switching when viewing a line drawing of a cube. The researchers found that the region of the brain called the posterior superior or parietal lobule was

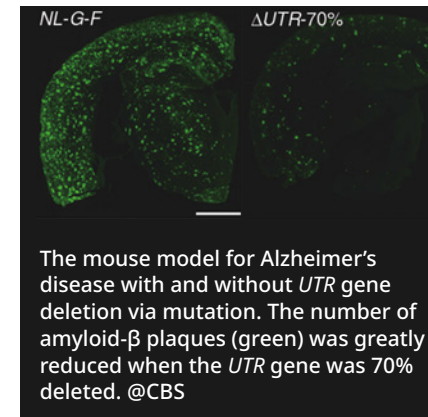
associated with the severity of both of these symptoms.

Alzheimer's disease

In 2014, following 12 years of work, scientists at **CBS** developed an innovative model mouse that closely resembles the human form of AD. Using these mice, a group of RIKEN researchers has found a mutation in the *UTR* gene that reduces amyloid- β plaque formation, one of the major physiological hallmarks of the disease.

In addition to amyloid- β plaques, the other primary pathology of AD is called tau pathology, or neurofibrillary tangles. In 2019, **CBS** researchers found that the protein CAPON may facilitate the connection between amyloid- β and tau, whose interactions cause brain cell death and symptoms of dementia. When extra CAPON DNA was inserted into AD model mice with high amyloid- β , the mice exhibited significant neurodegeneration, elevated levels of tau, and hippocampal shrinkage. On

the other hand, when CAPON was knocked out in an AD model with high levels of tau, the mice had less tau, less amyloid- β , less neurodegeneration, and less brain atrophy. Thus, using drugs to break the link between CAPON, amyloid- β , and tau is a promising avenue for treating AD.



LEARNING AND MEMORY

SEVERAL LABORATORIES at **CBS** study memory formation and the learning process in animals. In particular, they are interested in the circuits that make up memories and the molecular events that allow their storage and retrieval.

Memory engrams

In a series of studies using optogenetics, **CBS** researchers in collaboration with MIT have been studying memory engrams represented by neural circuits in the brain. Over the years, the group has been able to

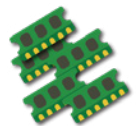
retrieve “lost” memories in amnesiac mice and in mouse models of Alzheimer’s disease, identify a brain circuit devoted to memories of social encounters, and find long-term memory engram cells in the frontal cortex.

More recently, another team at **CBS** found that memories of experience are not stored in hippocampal “place” cells as previously thought. These cells are critical for spatial memory, but the new study revealed the existence of “episodic” cells in the hippocampus that code for memories of events and experiences.

Fear learning

Another **CBS** research team is studying emotional learning, often related to how animals learn to avoid or fear unpleasant situations. They found that flexible fear learning—being able to “unlearn” a learned behavior—involves two separate pathways, both originating in the same brain region and using the neurotransmitter norepinephrine.

In 2018, they found another set of paired neuronal circuits that facilitated/blocked fear extinction, this time both using the neurotransmitter dopamine. Fear extinction is critical when danger is no longer associated with a situation. Phobias or post-traumatic stress can occur when fear extinction is prevented through this brain pathway. These neuronal



circuits are therefore potential targets for drug therapies for excess fear and anxiety.

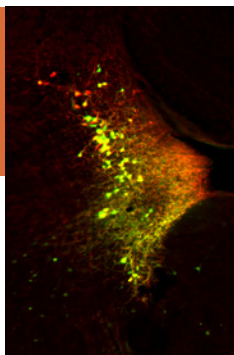
Memory consolidation

Neurons are not the only type of brain cells needed for memory formation and consolidation. When animals learn to associate a sound or odor with an unpleasant experience, they enter a state of vigilance or anticipation when they hear the sound or smell the odor. In 2020, **CBS** researchers found that during this time, norepinephrine is released by neurons, followed by a quick rise and fall of calcium in the surrounding astrocytes and a gradual rise in levels of the molecule cAMP. The calcium elevation in astrocytes appears to promote synaptic plasticity and cAMP elevation is thought to mobilize energy metabolism for memory consolidation.

Memory consolidation is thought to involve signals from frontal cortex to other regions. **CBS** researchers have used optogenetics in mice to show that some forms of tactile memory require “top-down” feedback circuits from motor to sensory cortex. In a related study, the same group showed that im-

Tactile memory tested in mice. @CBS

Norepinephrine release from the locus coeruleus (yellow) during vigilance @CBS



paired memory consolidation resulting from sleep deprivation could be alleviated by stimulating a specific “top-down” circuit during non-REM sleep.

In 2020, a **CBS** team developed an algorithm that could predict the age of memories, which can be thought of as the degree of consolidation. First they measured brain activity in the anterior cingulate cortex and the hippocampus as mice recalled memories. They found that synchrony in brain activity between the two regions was higher when mice recalled older memories than when they recalled newer ones. The team is now focused on understanding how impairments in long-term memory that often accompany aging and disease impact activity in these brain circuits.

NEW METHODS IN BRAIN SCIENCE RESEARCH

DISCOVERIES ARE often preceded by advances in technology and innovative new methodologies. In the last few years, RIKEN scientists

have made several breakthroughs that could improve how scientists study the brain and what we can learn.

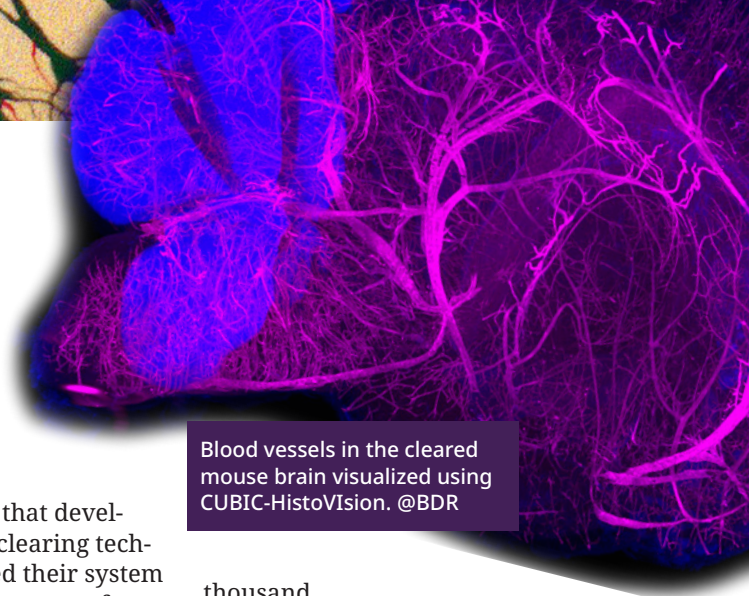
Staining cleared tissue

In 2020, the **BDR** team that developed the CUBIC tissue clearing technology (p. 16) optimized their system for visualizing different types of anatomy. They analyzed the staining and antibody labeling of artificial gels that resemble numerous types of tissue, including those in the brain. The new technique, called CUBIC-HistoVision, can create 3D images of neurons that use different neurotransmitters and can also differentially label glial cells. Using the new technique they found that glial cell distribution in the brain’s cerebellum differed between humans, mice, and marmosets, which could help explain the well-known structural differences in the cerebellum among these species. This technique has many applications beyond brain science.

Bioluminescence

In 2018, a laboratory at **CBS** developed a new non-invasive brain-imaging technology. By successfully mutating the enzyme luciferase, this team took bioluminescent molecules such as those found in fireflies and modified them to make bioluminescent signals that are a

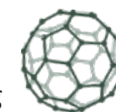
Blood vessels in the cleared mouse brain visualized using CUBIC-HistoVision. @BDR



thousand times brighter. When these molecules were introduced into the brains of mice or marmosets, individual neurons could be monitored from outside the head, simply based on the strong luminescence signal. No fancy wires, surgeries, additional attachments to the head or body, or external light sources are necessary.

Deep optogenetics

In 2018, a **CBS** team succeeded in combining optogenetics and nanotechnology to make optogenetics less invasive. By injecting the brain with nanoparticles that convert near-infrared light to blue light, they were able to activate optogenetically tagged cells by applying near-infrared light from outside the head. This opens the door for the development of noninvasive optogenetic technologies that can be used to study functional brain circuitry in people as they learn or perform normal everyday tasks.



ENVIRONMENTAL STRESS ON PLANTS

SCIENTISTS AT the RIKEN Center for Sustainable Resource Science (CSRS) are studying plants and working to develop crops that can withstand different kinds of environmental stress.

Drought stress

Drought has always been a problem for farmers, but increasing populations and unpredictable climate change have made it a much bigger concern in recent years. While RIKEN researchers cannot change the weather, they are developing ways to help plants survive periods without water.

In 2017, CSRS scientists collaborated with the International Center for Tropical Agriculture in Colombia and the Japanese International Research Center for Agricultural Sciences to develop a transgenic rice plant that yielded more seeds and had more biomass than wild-type rice when grown in real drought field conditions in Colombia. The higher yield



Field performance of unmodified Curinga rice (left) and a promising transgenic strain (right) that yielded more rice under drought stress @CSRS

SUSTAINABLE DEVELOPMENT GOALS

RIKEN, particularly CSRS, is committed to research that helps achieve the Sustainable Development Goals adopted by the United Nations in 2015.



was related to their greater water content, greater amount of chlorophyll in the leaves, and greater use of light for photosynthesis.

Also in 2017, a CSRS group found a completely different way to assist plants during drought. The team studied mutant *Arabidopsis* plants that were strongly resistant to drought. They found that the resistance was related to greater production of acetic acid, the main ingredient of vinegar. Tests showed that treating wild-type *Arabidopsis*, rice, wheat, and maize with acetic acid protected the plants from drought. In a 2018 follow-up study, the team



Treatment with acetic acid (vinegar) protects plants from drought. @CSRS

was able to make a drought-resistant transgenic plant that produces its own extra acetic acid only when water is scarce.

Other laboratories at CSRS are focused on understanding how plants regulate water retention. One research team studied a receptor that recognizes a chemical compound called karrikin that is found in smoke. Without the receptor, plants leak water through the damaged protective layer covering the leaf surface, and through larger-than-normal pores.



In 2018, another CSRS research team discovered that peptide hormone CLE25 is produced in response to overly dry soil and then travels to the leaves where it helps to close pores and keep water inside the plant. Researchers in the same laboratory have

also discovered that ABA—a plant hormone that also acts to close pores in leaves during drought—is regulated by the transcription factor NGA1. Mutant plants lacking NGA1 could not make any ABA when deprived of water, and thus could not survive. These findings provide several targets for further research aimed at improving water retention during drought.



Indeed, concrete results born from these kinds of basic research were evident in 2019 when CSRS researchers collaborated with other Japanese institutes and universities to develop a drought-resistant variety of wheat called TaPYLx. These plants have extra ABA receptors, which allow leaf pores to be closed even more effectively during drought. When tested, photosynthesis in TaPYLx plants was highly efficient and seed production was the same as normal wheat, even though the plants consumed very little water.

Temperature stress

Similar to drought, extreme temperatures also threaten plants and our ability to produce agricultural crops. A 2018 study at CSRS





hil1 mutants fared poorly after heat shock. @CSRS

identified a previously unknown gene that is activated by extreme heat. Without the *HIL1* gene, excessive heat destabilizes chloroplast membranes, which proves fatal over time. This gene could be a target for boosting protective responses in crops in response to global warming.

Salt stress

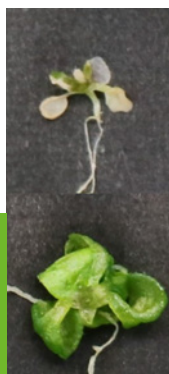
Another major problem facing crops is salt stress. When soil is too salty, it dehydrates plants by drawing their water out and poisons them with excess sodium.

In 2018, **CSRS** researchers found a gene for a plant peptide that naturally protects plants from salt stress, probably by combating the accumulation of excess sodium. The team was able to make synthetic pieces of the peptide that could confer the same protection, indicating the

potential for treating different plant species with supplements made from synthetic peptide fragments.

The same group also found that ethanol can increase tolerance to salt stress in *Arabidopsis* and rice by reducing toxic elements called reactive oxygen species—the same types of harmful molecules we try to eliminate when we eat foods like blueberries and acai that contain antioxidants. Like the drought protection afforded by acetic acid, this could be a simpler, safer, and more universal approach to salt-stress protection than making many different genetically modified plants.

In 2020, the team discovered that reactive oxygen species can also be reduced by inhibiting mitochondria and activating an alternative respiratory pathway. The researchers showed that blocking mitochondrial complex I with a novel compound called FSL0260 could improve salt tolerance in *Arabidopsis* and in rice. Importantly, FSL0260 does not block mitochondrial complex I in animals, making it a potentially safe treatment for plants in poor soil.



Plant treated with peptide fragment (bottom) is more tolerant to salt stress than control. @CSRS

Parasites



In addition to helping plants thrive in environmentally stressful conditions, researchers at **CSRS** are also studying parasites and how to help plants defend against them. *Striga* is a genus of parasitic plants that infect crops such as sorghum, maize, and sugarcane. *Striga* infestations worldwide cause an annual loss in productivity of almost 1 billion USD.

Researchers at **CSRS** have recently collaborated with other institutions to conduct a whole genome sequence analysis and transcriptome analysis of *Striga* strains that invaded the United States in the 1950s.

In 2020, the group showed that both parasitic and non-parasitic plants can detect and react to a class of organic compounds called quinones. While parasitic plants sensed quinones in their prey and used it to invade, quinones triggered defensive responses in non-parasitic plants that could protect them from bacteria and other microbes. Understanding the quinone signaling pathway will help in developing ways to protect plants from parasites and improve their immune systems.

COMBATING WATER POLLUTION

CONTAMINATED WATER is a global concern affecting developed and developing countries alike. Not

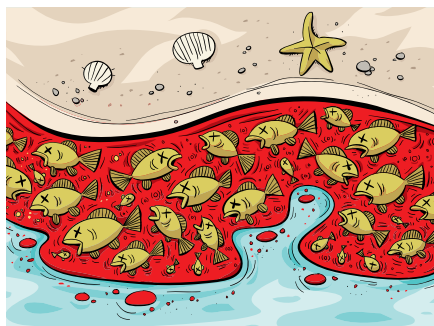


A maize field infested with witchweed (*Striga hermonthica*). Image courtesy the International Maize and Wheat Improvement Center (CIMMYT). Inset: closeup of *Striga hermonthica*

only is it dangerous if left untreated, decontaminating polluted water typically requires fossil fuels and a tremendous amount of energy. As an alternative to these typical processes, phytoremediation is a method that uses photosynthesizing organisms to clean up soil or water contamination.

Pollution from fertilizers

Nitrogen-based fertilizers are widely used in agriculture to ensure high levels of plant growth. However, fertilizers typically use inorganic nitrogen, which leaches through the soil into water, leading to contamination. In 2020, **BRC** researchers used a multiomics approach to successfully analyze the complex interactions between plants, microbes, and soil in an agricultural field. They discovered that organic nitrogen can also promote plant growth, which was a



Machine learning and time-series modeling can predict when and where toxic red tides will occur. @CSRS

surprise to everyone. Using organic nitrogen could decrease the use of chemical fertilizers in future crop production, and thus reduce water contamination.

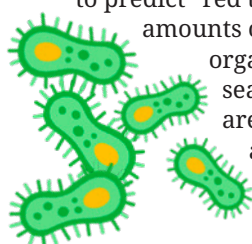


The major culprit in fertilizer contaminated water is nitrate. Normally, nitrate is converted to nitrite naturally by bacteria

and other microorganisms, and nitrite is ultimately converted to harmless dinitrogen. However, the large amounts of nitrogen-based fertilizers that are used in agriculture produce more nitrate than can be dealt with naturally. In 2020, CSRS researchers worked out a mechanism through which nitrate can be converted to nitrite using a catalyst that does not require high temperatures or high acidity, making the process environmentally friendly.

Predicting algal blooms

In addition to fertilizer-based pollution, rising seawater temperatures and excessive nutrients deposited from land runoff threaten to disrupt the balance of ocean microbial ecosystems. In 2018, CSRS researchers combined machine learning, factor mapping, and time-series modeling to visualize complex relationships between numerous elements in the seawater surrounding Tokyo Bay. Machine learning categorized the seawater based on inorganic ion concentrations. Factor mapping identified differences between water in the summer and other seasons. Vector auto-regressive modeling then revealed situations in which micro-algae bloom. Together, the three approaches can allow researchers to predict “red tides”, excessive



amounts of aquatic microorganisms that turn seawater red and are toxic for fish and other underwater life.



COUNCILS AND ADVISORS

As A Designated National Research and Development Institution, RIKEN works closely with the Ministry of Education, Culture, Sports, Science and Technology (MEXT) to ensure that while staying true to curiosity-based bottom-up science, it also conducts research in line with Japan’s science and technology goals.

RIKEN’s governance system ensures that it conducts healthy and efficient research. The highest management body is the Board of Executive Directors, which meets regularly to deal with important issues facing the organization’s management. The next level of management comprises the Center Directors who lead the individual centers.

Five councils provide essential input to Board of Executive Directors. The first is the Center Directors Meeting, which convenes bimonthly to discuss current issues. Equally important are the

RIKEN Science Council—a group of core researchers who make proposals regarding the direction of RIKEN’s research

and new areas to consider—and the Committee for Research Strategy—a body of outside experts who work with top leadership to make proposals that strengthen the organization’s management and who keep abreast of the latest research trends.

The fourth and fifth of RIKEN’s key governance structures are the Advisory Councils for Centers and the RIKEN Advisory Council (RAC), which provide regular advice to both individual centers and RIKEN as a whole. The RAC is composed of world-famous scientists, both Japanese and international, as well as individuals with experience in managing research institutes. The RAC meeting, held every two or three years, provides recommendations for both general research activities and the overall management of RIKEN, and provides guidance on future research strategies and improvement to management structures. This system, which was established in 1993, was a pioneering experiment in Japan, and has come to influence other research institutes across the country.

As a Designated National Research and Development Institution, RIKEN is annually evaluated by MEXT to ensure that it is maximizing research outcomes.



INTERVIEW WITH COLIN BLAKEMORE

As chair of the RIKEN Advisory Council (RAC), what achievements have impressed you most during the past few years?



As far as science is concerned, I would point to the techniques being developed for radioactive waste disposal, which could potentially be a huge public service in Japan. Another example is the clinical trial for adjuvant cell treatment, which shows great promise and is an indication of RIKEN's increased commitment to benefiting society.

Another welcome achievement is the establishment of the new RIKEN Innovation company. The members of RAC thought that the new company should focus on facilitating the establishment of start-up companies that can carry forward RIKEN intellectual property, rather than attempting to become a manufacturing company. We suggested that developing an intelligent evaluation system is extremely important. We also recommended that when making appointments, RIKEN should make more efforts to consider the international market, and should particularly search for able women researchers.

Which new research areas that RIKEN is pursuing do you think are particularly exciting?

The new developments in data science and artificial intelligence are clearly important. These are incredibly active fields with enormous potential and promise. RIKEN has made contributions in these areas in the past, but the recent move to establish new centers to cover these topics is very promising.

Colin Blakemore became chair of the RAC in 2016 (see page 31 for a description of the RAC).



We really applauded the establishment of the Hakubi program. The evidence that this program is needed and successful is there in the initial appointments. The demand for these posts is enormous, and that means that the quality of the people appointed is exceptionally high.

Do you have any thoughts about the Hakubi program for new team leaders?



We saw a real need for more Hakubi fellows. However, so far the program has been funded from the President's Discretionary Fund. I think it has proved its worth, so it is now time to persuade the government that this program should be independently funded as a program and should be enlarged. Getting a PhD is a big commitment in terms of time and money. People want to be assured that there are potential jobs at the end of that long relationship. So the provision of fixed-term appointments for young people to further their training after a PhD is really important and can help to address the problem of the declining interest in postgraduate training recently seen in Japan.

The UN's Sustainable Development Goals (SDGs) are becoming a big issue. Can you make any comments about how RIKEN is contributing to them?

RIKEN's commitment to the SDGs actually meshes very well with President Matsumoto's personal commitment to societal impact. Getting the right balance between top-down direction for research on specific SDGs and individual innovation—meaning curiosity-driven bottom-up research—is critical. RIKEN has done a very good job of this in the past, not meddling too much with the work of individual scientists but also having an over-arching plan for how the skills of scientists can be employed for greater benefit.

Why would you recommend RIKEN to young researchers who want to advance their careers?

RIKEN has been one of the world's finest research institutes for a long time, ranking with Max Planck, Fraunhofer, the Crick Institute, and the NIH. You can also judge it by metrics, for instance, by the proportion of very high-quality publications, where it stands near the top, something like ninth in the world. I think RIKEN offers fantastic opportunities for young people to gain the best training in a very high-quality environment, and to establish their reputations as scientists at a young age before moving on.



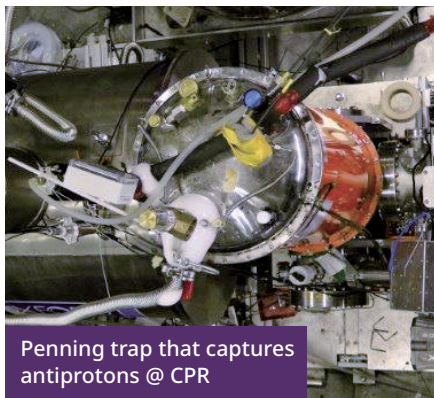
RIKEN scientists are leading efforts to understand how the universe is made, and how the things around us acquire the properties that they have. They are researching topics ranging from the smallest parts of the universe—fundamental particles—to the properties of materials and the large-scale structure of the universe.

PARTICLES

AT THE smallest scale, RIKEN researchers are looking at a variety of phenomena—including the mysteries of dark matter and antimatter—that will give us a better understanding of how the universe evolved and why it looks the way it does.

Antimatter

One of the key questions in physics today is why there is so little antimatter in our universe. Thanks to work done over the past decade by RIKEN and other scientists around



Penning trap that captures antiprotons @ CPR

the world, producing and almost indefinitely storing antiprotons and antihydrogen has become feasible, making it possible to do advanced research on antimatter. In 2017, an international collaboration led by **CPR** used sophisticated equipment to take the most precise measurements ever of the magnetic moment of the proton, and then subsequently the antiproton, finding that they seem to be equivalent.

Dark matter

RIKEN scientists are also part of the global effort to solve the great mystery of dark matter, a substance that is believed to make up about 27 percent of the universe's mass. In 2019, the same **CPR** group that had investigated antimatter began investigating the intriguing question of whether the mysteries of antimatter and dark matter might be linked, putting new limits on how much mass dark matter might have. Another group in **CPR** used a sky survey to look for a type of exotic particle called a nuclearite, which is one candidate for dark matter. They are continuing

the search using the Mini-EUSO, a cosmic ray observatory developed by a RIKEN-led international team that was put on board the International Space Station in 2019. Mini-EUSO is also observing exotic atmospheric phenomena such as sprites and ELVES.

ATOMS

Moving up to a larger scale, scientists at RIKEN are probing the mysteries of the atomic nucleus—mostly comprising protons and neutrons—using one of the world's most powerful cyclotron complexes, the Radioactive Isotope Beam Factory (**RIBF**). Through this research, they are helping to unravel mysteries such as how the universe came to be composed of the elements we see today, where the nuclear “magic numbers” lie, and where the “island of stability” will be found.

Atomic nuclei

One of the main missions of the **RNC** has been to create and study previously unknown nuclei. Scientists have hypothesized that 7,000 species could exist, but only a fraction have



Key centers/facilities:

Physics, Chemistry, and Engineering

- ⚙️ **CEMS:** RIKEN Center for Emergent Matter Science
- ⚙️ **CPR:** RIKEN Cluster for Pioneering Research
- ⚙️ **RAP:** RIKEN Center for Advanced Photonics
- ⚙️ **RNC:** RIKEN Nishina Center for Accelerator-Based Science
- ⚙️ **RIBF:** Radioactive Isotope Beam Factory (Facility)

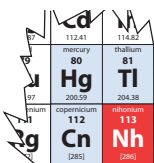
been studied. In 2017, researchers using the **RIBF** created 73 new exotic nuclei, adding to our body of knowledge. **RNC** scientists have also used the machine to study the nuclear dripline, which is important for understanding how elements heavier than iron were created by processes such as mergers of supernovae and neutron stars. In 2019, RIKEN scientists determined the nuclear dripline for two new elements, fluorine and neon.

The discovery of nihonium

Superheavy elements is another area of study in which RIKEN shines. In 2015, a group led by scientists from **RNC** gained official recognition as



Commemorating nihonium. Left: Nihonium Street sign post. Middle: Zinc, one of the 113 element plaques embedded on the Nihonium Street route. Right: The final plaque for nihonium at the entrance to the RIKEN campus in Wako.



the discoverers of nihonium—element 113—the first element to be discovered in Asia. Today, the group has upgraded its detector and is fast on the trail of element 119, the next undiscovered element on the periodic table. In 2017, they succeeded in producing and accelerating a vanadium beam, which will be crucial to the effort, and the new GARIS-II detector—a machine essential for the experiments—has been completed. The group also published a paper in 2020 providing better measurements of the repulsive forces between colliding nuclei and suggested a way to boost their chances of creating new elements.

MATTER

Particles come together to form atoms, and those atoms in turn behave in ways that lead to a variety of properties that affect matter. RIKEN scientists are studying these properties, discovering how interactions between particles and quantum effects can help humanity.

Spintronics

Current electronic devices are based on electron “charge,” which is the basis for electricity. Charge is easy to use, but is wasteful because it generates heat. Scientists at the Center for Emergent Matter Science (CEMS) have been instrumental in paving the way toward devices that



Young visitors at the Nishina Center learning about the elements on RIKEN Open Day @RNC

use an alternate property of electrons known as “spin”. Spin allows for much more efficient electronic devices that would not produce unwanted heat. In 2015, a CEMS research group demonstrated the existence of stable skyrmions—tiny spin-based magnetic vortexes in materials that could be manipulated to create low-power memory devices at room temperature.

In 2020, other CEMS scientists showed that they could manipulate these tiny magnetic vortexes with small currents of electricity. This could open the door to using skyrmions in new memory devices. In 2020, another group from the same center was able to create skyrmions in a magnetic field using sound waves.

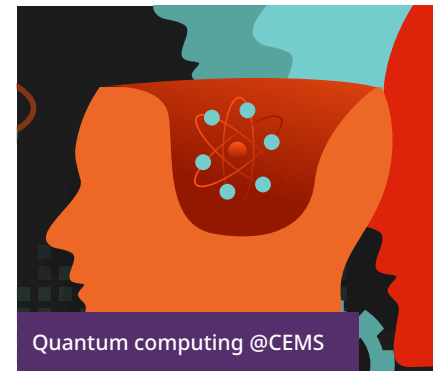
Quantum computing

Quantum computers promise to make certain classes of calculations

easier to perform, such as many-body problems, which are extremely difficult and time-consuming for conventional computers. In 2019, CEMS scientists used scanning tunneling microscopy to investigate the emergence of the “zero-energy vortex bound state,” phenomenon. This could be useful for creating quantum computers by allowing the control of Majorana quasiparticles. In 2020, other CEMS researchers succeeded in measuring the electron spin of a qubit without demolishing it. To do so, they used a type of “non-demolition” measurement that is important for creating quantum computers that are fault tolerant.

Superconductivity

Superconducting, a phenomenon discovered early in the 20th century, allows electricity to flow freely through a material when it is sufficiently cold. At RIKEN, scientists are searching for materials that can be superconducting closer to room temperature, which does not require energy to maintain. Although we have a good understanding of conventional superconductivity, some materials become superconductors through mechanisms that are not well understood. In 2019, researchers from CPR discovered that superconductivity in one type of unconventional organic conductor arises through a phenomenon called “geometric frustration.” That year, scientists from the same laboratory used calculations on the K computer to conclude that pulses

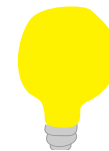


of light could theoretically be used to transform materials from conductors to superconductors, using a phenomenon known as “eta pairing.”

Photonics

In photonics—the study of light—RIKEN scientists are working to see things that were previously invisible. One avenue of research is to develop lasers and other light devices with ever more powerful and rapid pulses, with the aim to develop attosecond lasers that will be able to look at the positions of individual electrons within materials. In 2018, researchers at the RIKEN Center for Advanced Photonics (RAP) generated short, high-peak-intensity laser pulses with a wavelength of 3.3 micrometers, bringing science closer to the possibility of seeing the dance of individual electrons.

Scientists at RAP are also working on advanced lasers. In 2020, a group developed an incredibly powerful

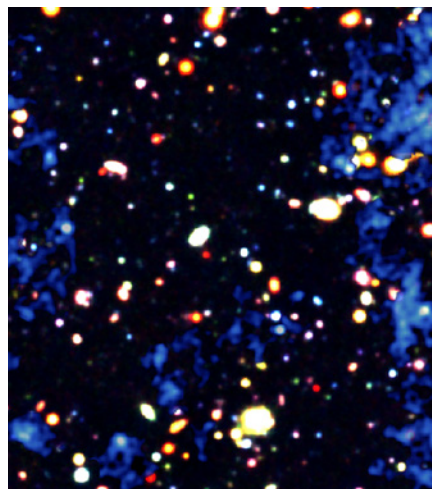


attosecond laser that will even allow scientists to see the interaction between photons—particles of light that move at a tremendous speed. They are also working to develop lasers that operate in the terahertz range—a long neglected portion of the electromagnetic spectrum that will allow explosives and illicit drugs to be imaged within luggage, making security checks more rigorous.

In 2017, another group from **RAP** developed a new way to control terahertz lasers, using backward optical parametric oscillation, and were able to create a device that is much smaller than typical terahertz sources. In 2018, RIKEN scientists developed nonlinear optical materials that can convert terahertz light to higher frequency infrared light, which can be detected more efficiently.

OUTER SPACE

RIKEN is also active in the fields of astronomy and astrophysics. In 2019, an international group of researchers from **CPR** and other institutes used several observatories to make detailed observations of the filaments of gas connecting galaxies in a large, distant proto-cluster in the early Universe. Based on direct observations, they found that in accordance with the predictions of the cold dark matter model of galaxy formation, the filaments are extensive, extending over more than 1 million parsecs—a parsec being



Filaments of gas connecting galaxies in ancient proto-clusters @CPR

just over three light years—and are providing the fuel for intense formation of stars and the growth of supermassive black holes within the proto-cluster.

One of the interesting attributes of RIKEN as a large-scale research institute working in a variety of fields is that scientists from different fields often come together to tackle some notable scientific problem.

One large group—a diverse gathering of chemists, astronomers, and physicists from **CPR**—is working together using powerful telescopes such as the Atacama Large Millimeter/submillimeter Array in Chile to work out how the universe evolved over different hierarchies, looking at how atomic nuclei, then atoms, and then molecules develop.

PHYSICAL CHEMISTRY

GOING BEYOND the atom, chemists at RIKEN are looking at how atoms in structures such as molecules and crystals interact in ways that give various forms of matter their unique properties. The research falls within numerous fields of chemistry, and in many cases provides a base for research collaborations inside and outside RIKEN in both physics and biology.

007s between atoms

Bonds—the way that atoms attach themselves to one another—are the basis of molecules and a fundamental topic in chemistry. Many things about bonds remain outside our understanding, but studies using high-speed, high-resolution tracking are giving us a better idea. In 2020, scientists from **CPR** used an advanced spectroscopy technique to look at the formation of bonds between gold atoms, watching the process at femtosecond temporal resolution—that's a quadrillionths of a second! By doing this, they were able to resolve a controversy over how bonds formed in a substance when exposed to laser light.

Metalloenzymes

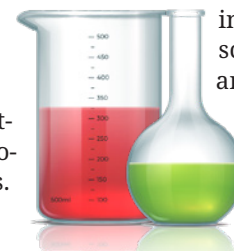
Other RIKEN scientists are using chemistry in innovative ways to create technologies that can help our lives. Scientists from **CPR** are

developing *in-vivo* synthesis technology, in which chemical reactions take place within the body itself. This can allow for more effective therapeutics and diagnostics. For example, recently they developed an artificial metalloenzyme—a type of molecule like albumin that allows an enzyme to act in a specific place—and used a sugar chain to transport it to cancer cells. This technology represents a new way of creating targeted therapies for cancer treatment (for more information, see *Cancer research: targeted treatments*, pp. 16-17). Further, by using metalloenzyme reactions within living plants, they succeeded in measuring ethylene gas, a plant hormone that is involved in processes such as fruit ripening.

The **CPR** group has also developed a way to make breast cancer surgery less burdensome by creating a compound that can accurately and rapidly show the surgical margin between tumor and non-tumor tissue (for details see *Cancer research: identifying tumor locations*, p. 16).

Surfaces

One key issue that RIKEN scientists are looking at is how matter behaves where different substances interface and interact. Using a scanning tunneling microscope, another group from **CPR** has looked at how aromatic molecules—an important type of molecule in biological and other systems—come





Organic Light Emitting Diodes (OLEDs)

together to form larger molecules. Their findings can help in the precise design of materials.

The group is already working on practical applications. As of 2019, an international collaboration with the laboratory used scanning tunneling microscopy and optical imaging to discover a way to make organic LEDs—a type of light device that promises to make computer displays less expensive, more flexible, and more efficient.

Better catalysts

Catalysts are substances that speed up chemical reactions without being consumed, allowing them to be used over and over again. They are extremely important for many industrial processes, and scientists are always looking for more environmentally friendly and inexpensive ones. RIKEN

Better cattle lists @CSRS



scientists are on the leading edge of efforts to both understand how catalysts work and to design better ones. Researchers at **CSRS** have found a catalyst that allows ammonia to be made from nitrate—an aquatic contaminant of global environmental concern (for details, see *Combating water pollution: pollution from fertilizers*, p. 30).

Scientists from **CSRS** are also researching ways to “split water,” a process that nature does as part of photosynthesis, but which industrially can only be done with expensive catalysts at high temperatures and pressure. The group developed a new catalyst that can operate at more normal temperature and pressure, thus reducing the burden on industries and some of the harm that the standard process does to the environment.

In more theoretical work, other researchers at **CSRS** have refined the design strategy of catalysts using a combination of mathematics and physical chemistry. They have identified the kind of interactions between the catalyst and the reactant that are necessary for increasing catalytic activity. This discovery could lead to better catalysts in the future.

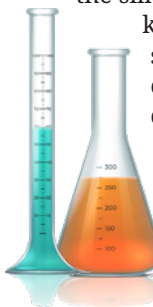
BIOCHEMISTRY

IN ADDITION to physical chemistry, scientists at RIKEN are researching the chemistry of living organisms, often in interdisciplinary collaborations. Studying chemistry can help us uncover—and recreate—some of the mysteries of life, such as how plants are able to take sunlight and use it to create sugar from water and carbon dioxide.

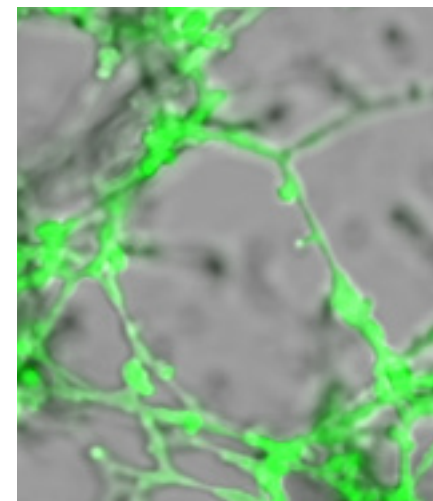
Making spider silk

In the case of a lab at **CSRS**, their research in biochemistry is helping us understand how spiders create their wonderful silk and threads. Spider silk is a striking material—tougher than steel by weight and yet extremely elastic. Even better, it is biodegradable, making it an environmentally friendly material.

In 2018, scientists from the group used nuclear magnetic resonance and other methods to examine spider silk from a golden orb-weaver spider—a type of spider that uses the silk to make webs for trapping insects. They found that the repeating domains in the silk's beta sheets, which are



known to be crucial for its strength, are composed of two patterns—random coils and a polyproline type-II helix. It turns out that the second type is crucial for the formation of strong silk.



Strands of spider silk @CSRS

The following year, they turned to the mystery of how spider silk changes from a liquid into an incredibly strong fiber. Their findings showed that a complex interplay among several ions—including sodium, chloride, phosphate, and sulfate—govern how it solidifies, with the different ions existing in a gradient within the spider's abdomen. Most recently, in 2020, they discovered that acidification is crucial for prompting the liquid to self-assemble into the powerful silk structure.

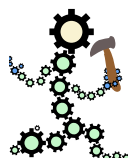
Work along these lines could be instrumental in creating spider silk analogues industrially. Indeed, in 2020 the group was able to induce bacteria to produce spider silk, without the need for spiders at all. This solves the issue of mass production, which is impossible using spiders themselves.

REVOLUTIONARY MACHINES

SINCE ITS foundation in 1917, RIKEN has been a leading institute in scientific research, but it has also been a leader in engineering—creating new devices that open up new areas of research and contribute to the development of society. In 2017, a new engineering network was created within RIKEN to create synergies among researchers working on engineering projects. Many of these projects are based on the leading-edge fundamental research being done by laboratories in physics, chemistry, and biology.

An atomic clock

A collaboration between **RAP**, **CPR**, and the University of Tokyo has built a pair of optical lattice clocks that can keep time with incredible precision. While a typical quartz watch can vary by about 15 seconds every month, these clocks will only go out of sync by a second in around 16 billion years—longer than the universe has existed so far. Using it, scientists plan to open the era of “relativistic geodesy,” where the shape of the earth can be precisely measured by clocks going faster or slower following Einstein’s theory of relativity. The group is currently working to develop a clock based on cadmium rather than strontium—which

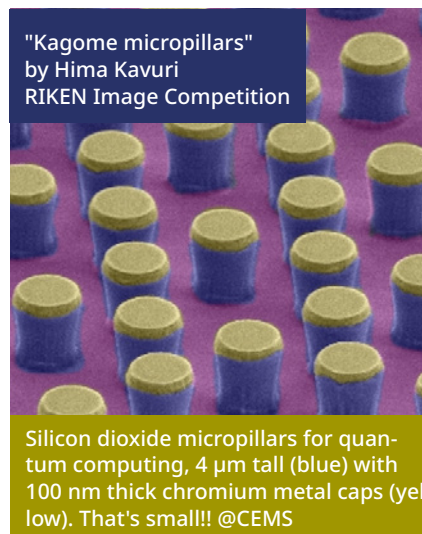


Tokyo SkyTree used to test Einstein's theory of relativity. Use QR code to watch video on YouTube!

would allow for smaller clocks—and recently used two transportable clocks to show that, in agreement with Einstein, time goes more slowly at the base of the tall Tokyo Skytree that at its observation deck 450 meters off the ground.

RANS: A compact neutron source

Researchers at **RAP** have been working for a decade to develop a compact neutron source. Since neutrons have no charge, they can travel deep into a material, and the scientists hope to create a transportable device that can be used to test bridges and



"Kagome micropillars" by Hima Kavuri
RIKEN Image Competition

Silicon dioxide micropillars for quantum computing, 4 μm tall (blue) with 100 nm thick chromium metal caps (yellow). That's small!!! @CEMS

other infrastructure for problems such as salt contamination. In 2016 and 2017, the team from **RAP** demonstrated that the device could detect internal damage and salt in concrete, and in 2019 announced the development of RANS-II, the most lightweight version of the device so far.

SACLA: Examining tiny objects

The SACLA x-ray free electron laser in Harima allows us to look at the world on the smallest scale. Despite being just 700 meters in length, it produces laser beams with a wavelength under 1 angstrom. These pulses are being used to see how bonds between atoms are formed to create molecules, and thus helping to answer fundamental questions about

how matter is put together. Using the instrument, scientists at the RIKEN SPring-8 Center (**RSC**) have shown how photons initiate a cascade that pushes protons out of a cell, creating an electric charge difference that is subsequently used to power the cell's activities.

A range of techniques are being developed by RIKEN scientists. For example, in 2018, researchers from **RSC**, which operates SACLA, analyzed car exhaust using a new technique called hard x-ray spectro-ptychography, which allows them to observe the oxidation process at the nanoscale. In 2019, another research group devised a way to generate x-ray beams with a sharp distribution of photon energies without sacrificing beam intensity. This finding can help speed up experiments at this high-demand facility.

RIBF: Mitigating nuclear waste and creating new plants

An interesting area being explored at **RNC** is the possibility of using the **RIBF** to “transmute” pesky nuclear waste products into other isotopes that are either stable or that decay very quickly. In 2019, the group published a blueprint of how this could be done in the accelerator.

The **RIBF** is also being used for plant breeding. A



research group has used ion beams from the accelerator facility to create sakura trees that blossom twice in a season, as well as rice that can grow in drought conditions. A number of plants bred in this way are already available on the market for users.

REVOLUTIONARY MATERIALS

ENGINEERS AT RIKEN are at the forefront of creating new materials with special properties, ranging from solar cells and hydrogels to computer monitors.

Wearable solar-cell tech

Scientists at **CEMS** have been on the leading edge of efforts to create environmentally friendly and efficient organic solar cells. In 2017, **CEMS** scientists created an ultra-thin, super-durable flexible solar cell that can be attached to a fabric and washed without losing its ability to generate electricity. Then in 2020, they announced the development of a new super-thin flexible material that degrades by less than 3 percent during 3,000 hours of exposure to atmospheric conditions, and with an energy conversion ratio of 13 percent, approaching the threshold of 15 percent that, it is believed, will lead to competitive organic solar cells.



Wearable, washable solar cells @ CEMS

This could lead to solar cells that are worn in clothes to power health monitors or other devices.

Hydrogels

RIKEN scientists are also actively working with hydrogels—a type of polymer that is made up mostly of water but which, due to its chemical structure, adopts interesting properties.

In 2017, a team from **CEMS** made a thin stretchable polymer that can be applied to human skin for long periods without triggering irritation, thanks to a structure that allows air to pass through it. They succeeded in monitoring muscle activity with a device attached to this material, highlighting the possibility of using this new material for medical monitoring.

More recently, in 2019, scientists from **CSRS** created a polymer that—even when immersed in water—can retain its shape and bind back together after being ripped apart. This could be useful for building more resilient LCD screens.

Shape-shifting colors

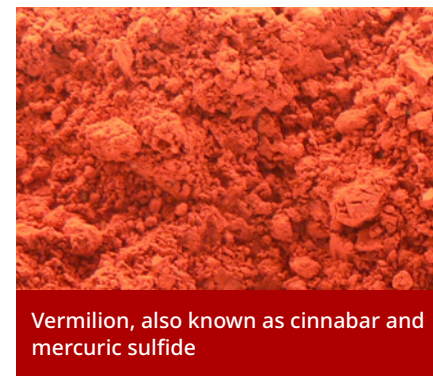
In research published in 2017 scientists from **CPR** and **RAP** used clues from nature—butterflies and peacocks—to make materials whose color can be fine-tuned by changing the shape of the material, rather than needing to be coated with a pigment.

Archeology with sulfur-free tape

Vermilion, sometimes called cinnabar or mercuric sulfide, is a bright red mineral that was used in paintings, figurines, statues, and ceramics dating back almost 9,000 years across Europe, Asia, and the Americas. In 2019, a group at **RNC** combined a highly sensitive sulfur analysis technique, which they had previously developed, with simple sulfur-free tape to test extremely small samples of vermillion from ancient artifacts.



Genetically engineered *E. coli* used to produce maleic acid for industrial use @CSRS



Vermilion, also known as cinnabar and mercuric sulfide

The analysis determines sulfur isotope ratios and only requires 1 microgram of vermillion—one millionth of a gram—which is about 500 times smaller than what other methods need. The researchers compared sulfur isotope ratios between samples from known locations and those from artifacts, confirming that trade likely existed between Japan's northern island of Hokkaido and the western part of Japan's mainland—a distance of over 1,000 miles—more than 3,000 years ago.

BIOENGINEERING

ENGINEERING IS more than just machines, however, as scientists are working actively on biological systems as well. In 2017, researchers from **CSRS** genetically reprogrammed a common microbe, *E. coli*, and used it to produce industrially important maleic acid from feedstock rather than from crude oil, which is the typical method used in industry.

Computational science and mathematics

RIKEN has been at the forefront of supercomputing for decades. More recently, we have opened two new strategic research centers, and scientists have begun to explore theoretical mathematical approaches and their application in scientific fields such as parallel computing and artificial intelligence. Together with a strength in modeling complex systems, RIKEN is already making breakthroughs in these new endeavors.

SUPERCOMPUTERS AND AI

RIKEN MADE a major splash in June 2020 when a new supercomputer, Fugaku, swept all the major supercomputer rankings—the first time that a Japanese computer has taken the first spot on the Top500 list since 2011—and repeated the feat in November. RIKEN also leads the world in the fields artificial intelligence, including theoretical mathematical approaches, as well as their application in scientific fields.



Next-generation supercomputing

In April 2020, it was announced that even before its formal opening to public use in 2021, the supercomputer Fugaku—which is currently being installed at the R-CCS in Kobe—would be put to use to help combat COVID-19 by helping to develop new diagnostics, therapies, and simulations related to the spread of the virus. Two months later, Fugaku set another milestone: though still in development, it took top place on four important high-performance computer benchmarks—Top500, HPCG, HPL-AI, and Graph

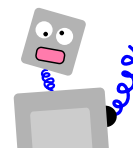


Supercomputer Fugaku
(富岳) @R-CCS

500. A year earlier, its prototype took the top spot on Green 500, a ranking of the most energy-efficient supercomputers. The new supercomputer will be put to use in research fields such as drug development, material analysis, and fundamental physics, as well as artificial intelligence and big data analysis.

Fugaku, like its predecessor, the K computer, is being used to perform simulations in a wide range of important fields. In 2020, R-CCS researchers gained attention for simulations of how the COVID-19 virus spreads in various situations such as crowded trains, with and without masks. Computer simulations are also being used as part of a system that predicts torrential rain in an area of western Japan, and which is gradually being extended to other regions.

Artificial intelligence



With the establishment of AIP in 2016, RIKEN entered the world of artificial intelligence research.

AIP was established as part of the government's plan to strengthen Japan's research in this crucial area. The center's research focuses on areas such as “deep learning,” in which machines go beyond performing simple operations and begin to recognize patterns, particularly when they only have limited information. Deep learning can also be applied to finding solutions to critical social problems such as infrastructure maintenance.

Scientists from AIP have made important advances in recent years. In one landmark project, researchers used an AI to help pathologists improve their predictions of cancer recurrence, and impressively, the AI was able to detect features that were not known to human pathologists. Another group developed a system that can help doctors screen fetuses for heart abnormalities, allowing them to prepare for needed surgery before the birth.

Other notable work includes: the development of a system that can make classifications without needing “negative data”; the

identification of a gene that exercises control over rice plant architecture; and the development of a system that can hunt for organic molecules based on desired excitation energies.

MATHEMATICS AND THEORY

SCIENTISTS AT the Interdisciplinary Theoretical and Mathematical Sciences Program (iTHEMS), are exploring the role of mathematics in science and going beyond disciplinary boundaries. Currently, most mathematics used in theoretical science were created more than 100 years ago. Scientists at iTHEMS are exploring newer abstract frameworks to see if they can be used to solve problems in natural science, or yield as yet unknown mathematical connections among phenomena in physics, biology, and other areas.

The center's work covers a remarkably broad range of areas. They have used mathematics to determine—for the first time—the strength of a magnetic field around a supergiant black hole, to gain an understanding of

how circadian rhythms are maintained in changing environments, to predict the existence of a new strange nucleus called a xi tetrabaryon, and to examine the genomes of 370 Japanese thoroughbred horses.



NATIONAL SHARED-USE LARGE-SCALE FACILITIES

SUPERCOMPUTING

THE R-CCS in Kobe is Japan's leading supercomputing center. In cooperation with Fujitsu Limited, it is currently developing a supercomputer called Fugaku, which has already made a mark on the global stage, capturing top awards on four major indices of supercomputer performance, including first place on the Top 500 list, for two successive periods. Following its opening for public use around 2021, it will be used to help resolve social challenges in areas such as health and longevity, disaster prevention, weather forecasting, energy conservation, clean energy, material design, and manufacturing processes, and will also be used in AI and data science research. Even before its completion, it has been put into use for research aimed at stemming the COVID-19 pandemic. In addition



to Fugaku, RIKEN has a number of more specialized supercomputers, including MDGRAPE-3, which is a machine dedicated to simulations of molecular dynamics for drug discovery and design, and RAIDEN, a system specializing in deep learning applications.

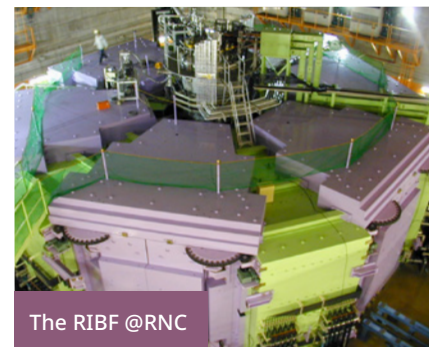
SPRING-8 AND SACLA

THE RSC in Harima is responsible for managing two large-scale facilities: SPRing-8 and SACLA.

SPRing-8 is a synchrotron radiation facility and SACLA is an x-ray free electron laser facility. SPRing-8 celebrated its twentieth anniversary of user operation in 2017.

These two powerful tools help researchers in both academia and industry to conduct advanced research in materials science, spectroscopic analysis, earth and planetary science, life science, environmental science, and industrial applications. SACLA produces laser beams of light with very short wavelengths that are a billion times brighter

and have a pulse width a thousand times shorter than the light available from SPring-8. This makes it an ideal instrument for observing ultrafast phenomena and small molecular structures.



RADIOACTIVE ISOTOPE BEAM FACTORY

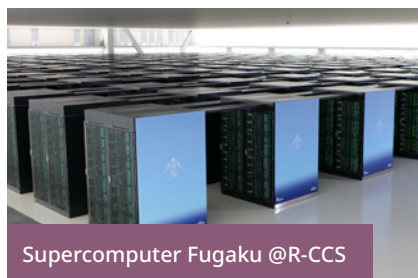
THE RADIOACTIVE Isotope Beam Factory (RIBF) at RNC in Wako is RIKEN's next-generation heavy-ion research facility. It provides researchers with the most intense ion beams in the world. At its heart lies a superconducting ring cyclotron—the world's largest—measuring 18 meters in diameter and weighing 8,300

tons, nearly as much as the Eiffel Tower. Recent upgrades to the facility allow for the generation of intense beams containing about 4,000 unstable nuclei, which range from hydrogen to uranium, making it possible to probe beyond the limits of the known nuclei. The facility is also used for heavy-ion breeding, allowing the efficient creation of new plant varieties (see p. 44).

OTHER FACILITIES

LIFE SCIENCE TECHNOLOGY PLATFORM

RIKEN HAS a rich set of advanced facilities used for research in medicine and other areas of life sciences. The NMR facility in Yokohama—one of the world's largest—operates 13 nuclear magnetic resonance spectrometers, which are used for three-dimensional structural analysis of proteins and other molecules. In addition to medicine, these tools are being used to promote technological innovation. The Genome



Supercomputer Fugaku @R-CCS



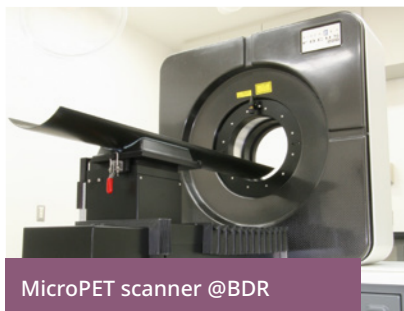
SACLA @RSC



Gene Sequencer @IMS



The NMR @RSC

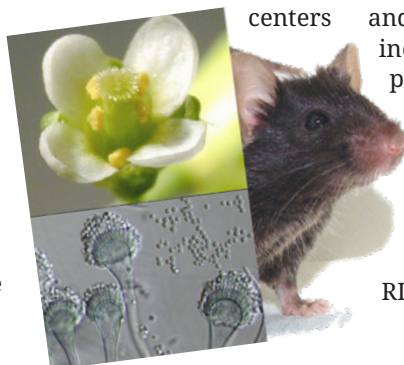


MicroPET scanner @BDR

Network Analysis Service, also in Yokohama, offers gene expression analysis and genomic sequencing using high-throughput next-generation sequencers. Further, the molecular imaging facility in Kobe, equipped with microPET scanners and cyclotrons for producing PET-scanner tracers, as well as MRI and CT facilities, provides a human resource development program for analyzing the dynamics of various molecules in the body.

BIORESOURCE RESEARCH CENTER

BIOLOGICAL RESOURCES, often referred to as bioresources, are essential experimental research materials for the life sciences and bioindustry. Under the three principles of Trust, Sustainability, and Leadership, **BRC** is committed to receiving the deposition/donation of bioresources from the research community,



confirming their authenticity by rigorously testing their quality, and preserving and distributing them back to the research community. In addition to these services, **BRC** conducts research and development to accelerate the active use and application of its bioresources.

HEAD OFFICE FOR INFORMATION SYSTEMS AND CYBERSECURITY

THE MISSION of this office is to provide IT support to the entire institute, and it is currently working on a strategy to develop IT systems that will encourage the maximization of research results by leveraging information systems to allow researchers to concentrate on what is most important—their research. In addition, it works closely with RIKEN researchers on research and development in informatics (incorporating information science, information processing, information systems, and computer science) and data science, which are essential for collaborations spanning all of RIKEN, as well as those between RIKEN centers and research groups, including interdisciplinary undertakings.

The Office manages a number of supercomputers that are used by researchers both inside and outside RIKEN.

Innovation & collaboration

THE CLUSTER FOR STI HUB

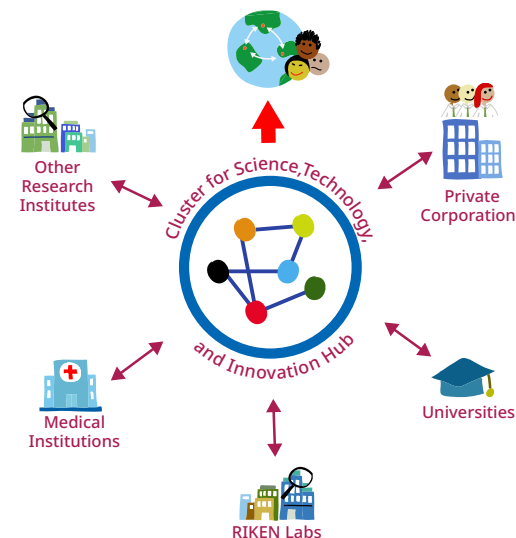
INNOVATION AT RIKEN

IT is very much in RIKEN's blood to transfer the products of its basic research into applications that can benefit society. Masatoshi Okochi, who took over a financially troubled RIKEN in 1922, set up a system where the fruits of research could be effectively returned to society, going as far as to create a group of companies—known as the RIKEN Konzern—that were dedicated to commercializing

the inventions made in RIKEN's laboratories. Under this system, RIKEN made major contributions to the development of Japanese industry.

In 2019, RIKEN launched RIKEN Innovation, a subsidiary that will help return the results of RIKEN's research to society. This is in addition to a dedicated organization within RIKEN—the Cluster for Science, Technology, and Innovation (STI) Hub—which focuses on creating collaborations with universities and private companies and on translating research breakthroughs into innovation. A number of programs within the Cluster look at specific areas of

science—drug discovery, preventive medicine and diagnosis, healthy living, and artificial intelligence and big data—and the labs work to translate discoveries at RIKEN into real-world technologies.



The Cluster for STI Hub is a group of programs through which RIKEN collaborates with other institutes, universities, local governments, and industries around the world to facilitate tech transfer and bring innovations to society.

RUNNING TOGETHER

THE INNOVATIVE “Baton Zone” is one of the key programs in which scientists and industry work together. The name, taken from the analogy of a relay runner passing the baton to the next runner, indicates how the program involves a handing on of knowledge from one partner to another. The program's goal is to transfer scientific

Programs in the Cluster for STI Hub

- Preventive Medicine and Diagnosis Innovation Program
- Medical Science Innovation Hub Program
- Drug Discovery and Medical Technology Platform Program
- Compass to Healthy Life Research-Complex Program
- Industrial Co-creation Program
- Baton-Zone Program

achievements into commercial products through partnerships with private companies.

Laboratories within the Baton Zone Program, which are staffed by a mixture of RIKEN and industry researchers to tackle specific challenges, focus on diverse areas including vaccines, plant breeding, organ preservation, and hydrogen energy storage.

Another important part of RIKEN's collaborations is the RIKEN Venture System. Under it, we contribute to industrial technology and people's everyday lives by using the new knowledge and new technologies that arise in the course of research at RIKEN in basic natural science. Some of the companies that have been established under the system are Photon-Labo, which is working in the field



of nondestructive measurement of infrastructure such as tunnels using a laser system, and Cykinso, which sells test kits that allow customers to gain an understanding of their intestinal flora. As of 2018, 47 companies have been certificated as RIKEN Venture and 16 RIKEN Venture companies are currently operating.

TARGETED PROGRAMS

WITHIN THE Cluster for Science, Technology, and Innovation Hub there are five research programs that are working to link basic research to innovation in key parts of society.

Drug discovery

The RIKEN Program for Drug Discovery and Medical Technology Platforms assists the identification of new treatments for cancer and other diseases by promoting collaboration within RIKEN on the development of innovative pharmaceuticals and medical technologies. The Program is involved in all phases of development from the discovery of promising drug targets to the identification of potential lead compounds such as small molecules and antibodies. It supports the acquisition of intellectual property rights to drugs and technologies that can then be brought to the development phase. The program also provides support for translational research and the transfer of potential drug candidates

to preclinical and clinical phases of drug development.

Personalized medicine



Personalized medicine is a new paradigm that represents a shift from statistical abstraction of patients toward the view that each patient is unique. This is a new scientific as well as social challenge. As a pillar of RIKEN's efforts to rise to this challenge, the Medical Sciences Innovation Hub Program (**MIH**) is developing a new biomedical science based on the pure description of diseases using multiomics data. Scientists at **MIH** have applied the Markov chain model, which is a well-known tool for modeling the temporal properties of numerous phenomena, to describe changes in individual conditions during the life course. Data is being gathered from patients with immune disorders, cancer and developmental disorders.

Preventative medicine

Disease prevention is more effective when signs or symptoms of disease are detected early. Research groups in the RIKEN Preventive Medicine and Diagnosis Innovation Program deploy a broad range of research resources in physics, chemistry, engineering, biology, and medical science to develop and establish more efficient detection technologies. They are working on the discovery

of new biomarkers, the development of detection technology for clinical practice, and the development of diagnostic kits. The Program interfaces between the scientific advances made at RIKEN and colleagues in medical institutions, companies, and research organizations, ensuring that scientific breakthroughs are effectively translated into clinical practice.

Healthy lives and communities

The Compass to Healthy Life Research Complex Program was established to create a platform that will bring together a range of research players to investigate diverse aspects of human health, in order to develop an integrated system for looking at individual health including novel methodologies to quantitatively measure the extent of health (precision health), and to develop best-matched solutions for the maximization of individual health. This program also supports the startup of new healthcare businesses based on the precision health model.



Using AI for better health

Diseases are typically tackled by identifying a cause and then targeting that cause. However, there are many disorders that have multiple factors associated with them, and the result is a combinatorial explosion. To overcome this, the **MIH** is

working to develop an information geometry based reasoning technology that consists of multidimensional descriptors for multi-omics data and dimensionality reduction technology. These technologies will be applied to the development of personalized prediction algorithms for multifactorial disorders. Developed technologies will be available to medical institutions and the medical industry.

Another new development in 2018 was the establishment of the Industrial Co-creation Program, which aims to solve challenges through large-scale collaborations between RIKEN and industrial partners. The first of these partnerships was between RIKEN and DAIKIN, an air conditioner manufacturer. Together, it is working to reduce the burden of fatigue by conducting research related to the indoors environment, where many people in advanced society spend much of their time.

TECH TRANSFER

IN ADDITION to these programs and laboratories, RIKEN is active in sharing its discoveries with the world through the licensing of technologies. In 2019, RIKEN had 512 domestic and 856 international patents in areas ranging from physics to medicine. A special section on our website allows potential partners to search for technologies that might fit their needs.

CLUSTER FOR PIONEERING RESEARCH

SMASHING BOUNDARIES



A UNIQUE ASPECT of RIKEN as an institute is the way in which scientists are encouraged to interact between disciplinary boundaries and organizational borders, and to take the lead in pioneering new areas of science.

One of the pillars of RIKEN's reorganization under our Fourth Mid-to Long-Term Plan was the establishment of a new organization—the **CPR**—which is dedicated to encouraging RIKEN researchers to work together across institutional boundaries and develop new fields of research. **CPR** is a large source of bottom-up, curiosity-driven basic research, and the Chief Scientist laboratories working in **CPR** are able to pursue their research from a long-term perspective while interacting with scientists from both within the cluster and at centers across RIKEN.

In fact, when President Hiroshi Matsumoto took the reins at RIKEN in April 2015, one of the things that he said surprised him was how low the barriers are between laboratories and disciplines compared to the situation in universities. Indeed, interdisciplinary collaboration—coupled

with a strategy to use such collaboration to pioneer new fields—has always been part of RIKEN's DNA (pp. 13, 16, 17, 34, 35, 37-39, 42, 45).

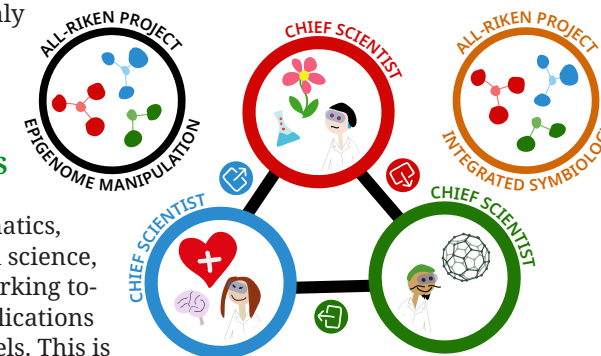
RESEARCH GROUPS

IN ADDITION to the interdisciplinary nature of the Chief Scientist laboratories, several of RIKEN's current strategic research centers have been deliberately organized with a multidisciplinary mission. **CSRS** brings together researchers in plant science, chemical biology, catalytic chemistry, and biomass engineering, and provides them with the latest technology in data science, artificial intelligence, and genomic analysis to contribute to achieving a number of the Sustainable Development Goals adopted by the United Nations. At **CEMS**, specialists in physics, chemistry, and electronics are collaborating to create a new generation of highly energy efficient devices and make quantum computing a reality.

Further, in the **iTHEMS** program, researchers in the fields of mathematics, physics, computational science, and life science are working together to find new applications for mathematical models. This is a milestone, as it has brought the study of mathematics back to RIKEN after a hiatus of about a hundred years, following the death

of RIKEN's first president, Dairoku Kikuchi—a mathematician.

Based on this multidisciplinary structure, a number of events are held each year in which scientists from different fields, nationalities, and positions can come together to share their results and discuss how they can collaborate to help answer the scientific questions and social needs in line with RIKEN's mission. These events include the Interdisciplinary Exchange Evening, held a few times each year, Discovery Evening, a venue for young scientists, the Summer School for junior scientists, and the reporting session for researchers working on grants awarded under RIKEN's competitive interdisciplinary program.



CPR forms the core of RIKEN's curiosity-driven cross disciplinary system. Chief Scientist Laboratories interact to pioneer emerging research fields and help plan future research strategies. CPR also manages two cross-organizational projects.

International partnerships

PARTNERSHIPS AND AGREEMENTS

RIKEN ACTIVELY supports research collaborations and the exchange of researchers, students, and staff with universities and institutions all across the globe. RIKEN has 15 overseas joint research centers and partners with over 40 countries around the world. Partnerships include General Collaborative Agreements and Memorandums of Understanding (MOUs).

Current projects

RIKEN researchers are working with partners around the globe on a slew of important research and societal issues. A major project is the FANTOM collaboration, which has been instrumental in clarifying the role of non-coding RNA, which was once known as “junk DNA,” in a number of important processes such as the regulation of RNA translation. The group is currently working hard to characterize non-coding RNAs called SINEUPs, which have only recently been discovered. SINEUPs present an attractive target as nucleic acid therapeutics as they help target messenger RNAs to produce proteins.

In 2019, RIKEN and two German organizations—the Max Planck Society and the National Metrology Institute of Germany—formed a new research collaborative to perform high-precision measurements that can answer

263 Research collaborations & MOUs (March 2020)



important scientific questions, such as why matter seems so much more abundant than antimatter, what are the microscopic properties of dark matter, and fundamental physical constants really constant over time. Another collaboration between RIKEN and the Max Planck Society—one of our oldest international partners—is conducting research in the field of chemical biology. The team is using libraries of compounds along with tools for understanding the relationships between ligands, including glycans, and proteins. The goal is to better understand how biological molecules interact, and ultimately, to help in the discovery of new pharmaceuticals.

Other important collaborations include a partnership with Tsinghua University in China that is focused on solid state physics. This partnership was set up to train a new generation of physicists. RIKEN also partners with Cincinnati Children’s Hospital in a project centered on the rapidly developing field of regenerative medicine. Together, we studying how organs develop and applying that knowledge towards the development of new organoids.

THE GLOBAL SUMMIT OF RESEARCH INSTITUTE LEADERS

IN 2011, RIKEN took the initiative in setting up what has become a highly awaited annual event for public research institutes around the world. The Global Summit of Research Institute Leaders is held every fall in Kyoto, in association with the Science and Technology in Society (STS) *forum*. The meeting is co-hosted by RIKEN and the National Institute of Advanced Industrial Science and Technology (AIST), two of Japan’s Designated National Research and Development Institutions. It was initially co-chaired by RIKEN and the French National Centre for Scientific Research (CNRS), and for the past few years has been co-chaired by RIKEN and the Leibniz Association in Germany.



At the summit, leaders from 20 or more institutes from around the

RIKEN Facility Office at RAL (UK: Rutherford Appleton Laboratory)

KFU-RIKEN (Russia: Kazan Federal University)

RIKEN-MPG (Germany: Max Planck Society)

RIKEN-Tsinghua (China: Tsinghua University)

RIKEN-XJTU (China: Xi’an Jiaotong University)

RIKEN-SJTU (China: Shanghai Jiao Tong University)

SIOM-RIKEN (China: Shanghai Institute of Optics and Fine Mechanics)

RIKEN-KRIBB (Korea Institute of Bioscience and Biotechnology)

NCTU-RIKEN (Taiwan: National Chiao Tung University)

RIKEN-BNL (USA: Brookhaven National Laboratory)

RIKEN-MIT (USA: Massachusetts Institute of Technology)

USM-RIKEN (Malaysia: Universiti Sains Malaysia)

NTU-RIKEN (Singapore: Nanyang Technological University)

RIKEN-NCBS (India: National Centre for Biological Sciences)

RIKEN-JNCASR-IISc (India: Jawaharlal Nehru Center for Advanced Scientific Research & the Indian Institute of Science)



world discuss critical issues for public research institutes, such as brain circulation and mobility, tackling the Sustainable Development Goals, and interacting with other sectors such as industry and academia. A major emphasis in the last few years has been how research institutes can collaborate multilaterally to tackle the major challenges facing humanity today.

public research institutes could work together to ensure that the world is better prepared for future pandemics.

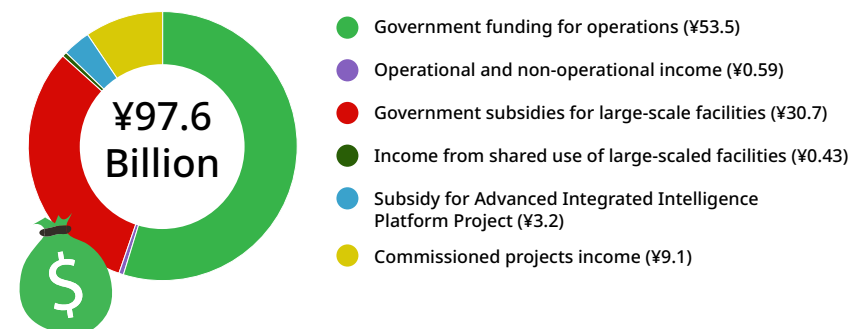
Yuko Harayama, RIKEN's executive director in charge of international affairs, said, "We feel that the annual summit has been an import event where we have been able to promote collaboration between public research institutes around the world. This helps us to better respond to the needs of the societies that we serve. In a world where we face many difficult challenges that cannot be tackled by any individual institute or country, this is an important initiative."



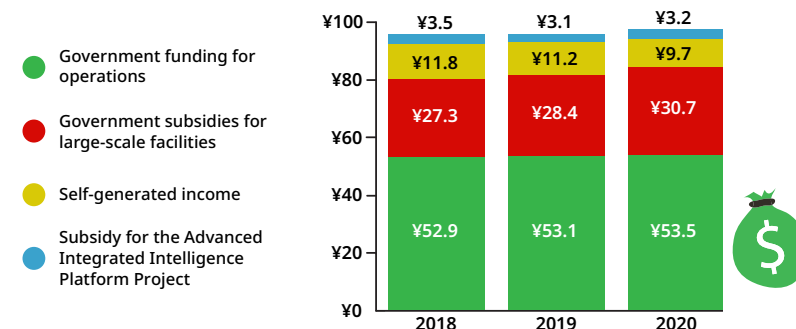
In 2020, under the exceptional circumstances of a global pandemic, the event was held online, and attracted 26 leaders from

Asia, Europe, North America, and the Pacific to discuss how

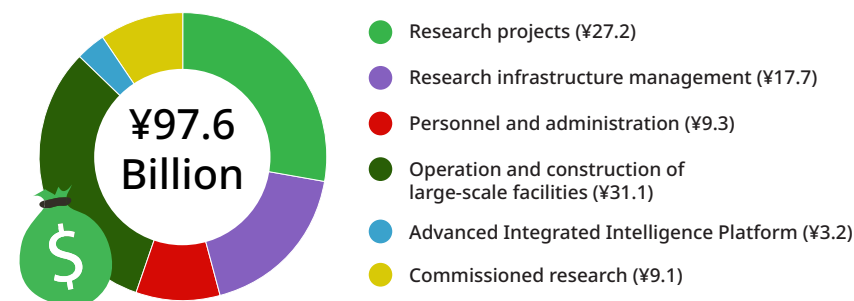
FY2018 YEAR-END REVENUE



YEAR-END REVENUE OVER TIME



FY2020 YEAR-END EXPENDITURES



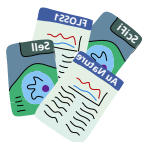
All values given in billion yen (1 billion yen is approximately 9.2 million US dollars)

*Inventors:
William S. Harley*

RESEARCH OUTPUT



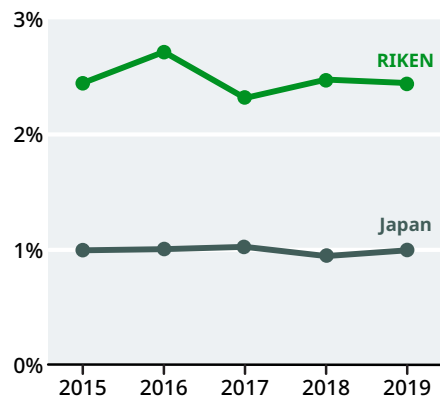
**RIKEN SCIENTISTS
PUBLISHED 2,664
PAPERS IN 2019**



**HIGH CITATION RANKINGS
BASED ON ALL PAPERS
PUBLISHED WORLDWIDE**

**65 papers ranked in
the top 1% in citation
number (2.4%)**

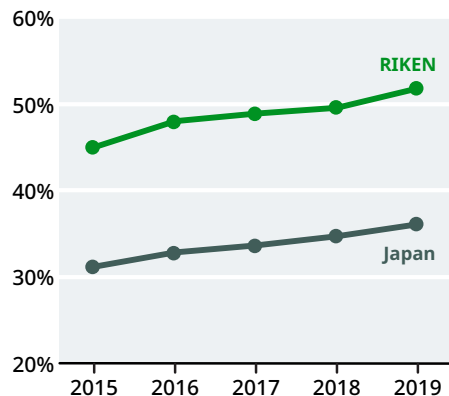
Percentage of papers with citation
number ranking in the top 1%



**CONTINUED INCREASES IN
INTERNATIONALLY
CO-AUTHORED PAPERS**

**1381 internationally
co-authored papers
(51.8%)**

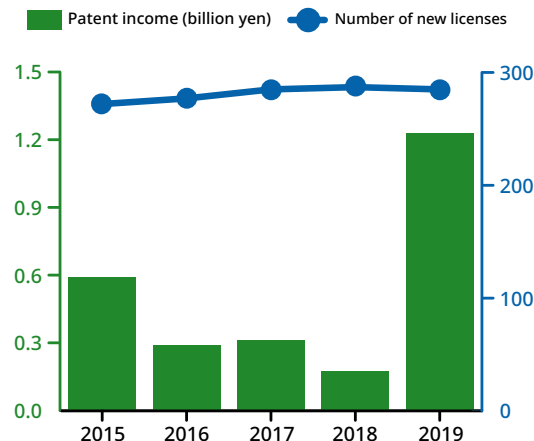
Percentage of internationally
co-authored papers



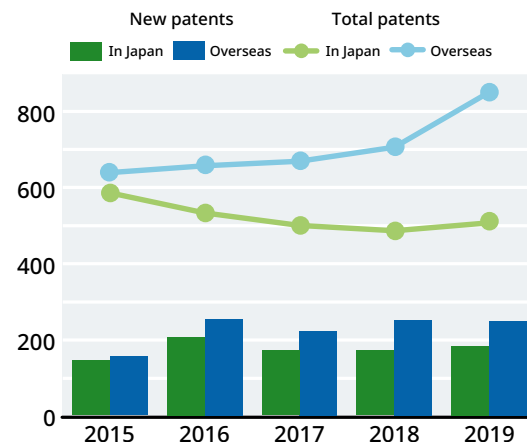
InCites dataset. Includes Web of Science content
indexed through Apr 30, 2020

PATENTS

**RIKEN EARNED 1.2 BILLION YEN
FROM PATENTS IN 2019**



**RIKEN FILED 430 NEW PATENTS IN
2019**



In addition to publishing research results in top-level journals, RIKEN also actively encourages scientists to patent their discoveries and protect RIKEN's intellectual property portfolio to ensure that industry can use it to improve people's lives. Some of our recently licensed technologies include a high-tech blood pressure monitor, new varieties of Japanese cherry blossom trees, and a safe and environmentally friendly line of pesticides.



Plants developed using heavy
ion beams to generate advantageous mutations @ RIBF @
RNC

STRATEGIC RESEARCH CENTERS

CENTER FOR ADVANCED INTELLIGENCE PROJECT (AIP)

AIP was launched in April 2016. We aim to achieve scientific breakthroughs and contribute to the welfare of society and humanity by developing innovative technologies. We also conduct research on ethical, legal, and social issues caused by the spread of AI technology, as well as develop human resources. (pp. 12, 13, 17, 47)



CENTER FOR ADVANCED PHOTONICS (RAP)

RAP is working to make the invisible visible by pushing the possibilities of light to the extreme. Attosecond (10⁻¹⁸ seconds) lasers



"Out on a date"
by Thomas Chater
RIKEN Image Competition



will make it possible to see the motion of electrons, super-resolution microscopes are making the nanoworld visible, metamaterials are allowing us to manipulate the spectrum, and terahertz light will open up new undreamt of technologies. At RAP, we focus not simply on making discoveries that are applauded by the research community, but also contribute to society through practical applications. (pp. 35, 37, 38, 42, 43, 45).

CENTER FOR BIOSYSTEMS DYNAMICS RESEARCH (BDR)

BDR AIMS to elucidate the biological functions that unfold within an organism during its life by viewing the life cycle from birth to death as a dynamic process involving the establishment, maintenance, and breakdown of a balanced and interlinked system of molecules, cells, and organs. BDR scientists carry out research to observe, manipulate, and model biological phenomena that take place on multiple scales—from molecular to whole-body—throughout the life cycle of multicellular organisms, including development, growth, maturation, aging, and regeneration stages. BDR also aims to apply its findings to regenerative medicine and the development of diagnostics, thereby contributing to the extension of healthy life expectancies. (pp. 12-17, 19, 25, 50)



"A swimming microworm"
by Ruiyuan Liu
RIKEN Image Competition

CENTER FOR BRAIN SCIENCE (CBS)

SCIENTISTS AT CBS are on a mission to advance basic research into the functions of the brain and the mind—from the levels of single-cells and whole bodies all the way to societal systems—and develop innovative technologies in the process. Research at CBS is multi-disciplinary and we focus on four themes: (1) High-level cognitive functions of the human brain: How do we reflect on ourselves, make inferences, and predict what others are thinking? (2) Universal biological principles: Hierarchical studies based on animal models to understand brain functions and brain-body interactions; (3) Data-driven research



led by theoretical and technological advances: Using big data to develop new theories and improved AI systems; (4) Tackling the global challenge of brain disease: Developing diagnostic and therapeutic methods for neuropsychiatric disorders. (pp. 8, 9, 15, 20-25)

CENTER FOR EMERGENT MATTER SCIENCE (CEMS)

SCIENTISTS AT CEMS are developing fundamental science and technology for reducing energy consumption and the environmental burden of energy production. We use condensed-matter physics, supramolecular chemistry, and quantum information electronics to generate novel materials and devices. New properties emerge in materials or molecular assemblies fabricated from interactions between large numbers of component electrons, atoms, or molecules at a nanoscale level. These new materials and properties can be used for technologies such as highly efficient energy-conversion devices and low-power-consumption electronics. (pp. 35, 36, 37, 43, 44, 55)



CENTER FOR INTEGRATIVE MEDICAL SCIENCES (IMS)

AT IMS, we study the pathogenesis of human diseases and establish new therapies through cutting-edge research on the human genome and



immune function. To that end, we have established four Divisions: (1) the Division of Genomic Medicine, (2) the Division of Human Immunology, (3) the Division of Disease Systems Biology, and (4) the Division of Cancer Immunology. IMS's research is based on the concept of disease as a dynamic body system interacting with environmental stresses. We maintain a research platform for clarifying the processes that maintain or disrupt body homeostasis and for transferring that knowledge into new therapies and medicines. (pp. 9, 13, 17-19, 49)

INTERDISCIPLINARY THEORETICAL AND MATHEMATICAL SCIENCES PROGRAM (iTHEMS)

THE GOAL of the iTHEMS program is to function as an international center that brings together researchers in theoretical, mathematical, and

computational science to use mathematical methods to unravel mysteries of the Universe, matter, and life, and solve key problems that affect modern society. Additionally, iTHEMS aims to develop an ideal environment for young researchers to make major breakthroughs by offering interdisciplinary and in-residence schools, workshops featuring leading-edge researchers in fundamental science, industry-academia partnership lectures for learning about how mathematics is being used by companies and society, and daily interactions among theoretical, mathematical, and computational scientists. (pp. 47, 55)

NISHINA CENTER FOR ACCELERATOR-BASED SCIENCE (RNC)

RNC on the Wako campus is a world-leading accelerator facility for theoretical and experimental nuclear physics research. It is named after Yoshio Nishina who constructed Japan's first (and the world's second) cyclotron at RIKEN in 1937. The Nishina Center was established in 2006 to promote research into the origin of matter by investigating the nature of nuclei and their constituents, elementary particles. That



"Ginkgo trees in the early morning" by Naohiko Yasui
RIKEN Image Competition



"Snow on cherry blossoms" by Ruiyuan Liu
RIKEN Image Competition



year, the Radioactive Isotope Beam Factory (RIBF), with its world's first superconducting ring cyclotron and superconducting radioactive isotope beam separator, started full-scale operation. The Nishina Center collaborates with researchers around the world. (pp. 9, 17, 35, 36, 43, 45, 49, 61)

CENTER FOR SUSTAINABLE RESOURCE SCIENCE (CSRS)

CSRS HAS been a leader in creating a sustainable society through transdisciplinary integration of plant science, chemical biology, and catalytic chemistry. Using the Sustainable Development Goals (SDGs) adopted by the United Nations in 2015 and the Paris agreement to achieve zero greenhouse gas emissions as guidelines, we have five major projects: (1) Innovative Plant Biotechnology, (2) Metabolic Genome Engineering, (3) Innovative Catalysts, (4) Leading-edge Polymers, and (5) Advanced Research and Technology Platforms. The goal of the CSRS is to help create a future world in which people can



live healthy and prosperous lives. (pp. 26-30, 40, 41, 44, 45, 55)

RESEARCH INFRASTRUCTURE CENTERS

BIORESOURCE RESEARCH CENTER (BRC)

THE BRC in Tsukuba was established in 2001 and has quickly developed into one of the world's most important repositories and distribution centers of biological resources for life-science research. The center's reputation derives from its capacity to handle a wide range of living strains of experimental animals and plants, cell lines of human and animal origins, genetic materials, microorganisms, and the associated bioinformatics. We are particularly notable for providing human induced pluripotent stem (iPS) cells to researchers. Please visit our website to find if there are resources that will be valuable in your research. (pp. 15, 29, 50)



RIKEN CENTER FOR COMPUTATIONAL SCIENCE (R-CCS)

THE R-CCS is the leading research center in high performance computing and computational science in



Japan, and home to the supercomputer Fugaku. Our objectives are to investigate “the Science of (high performance) computing, by computing, and for computing,” and promote the core competence of the research in a concrete fashion as open source software. Additionally, we collaborate with many other global leadership centers. Our previous supercomputer (the K computer) was open for public operation between the fall of 2012 and the summer of 2019, producing multitudes of world-leading scientific and engineering results, not only for academia, but also for industry. Following its success, we began developing the supercomputer Fugaku in April 2014, with which we aim to achieve orders of magnitude increases in our capabilities as well as better ease of use and synergy with other IT ecosystems such as big data and artificial intelligence. Fugaku is expected

to commence operations sometime around 2021 and serve as a keystone for solving some of the most important scientific and social problems facing the world. (pp. 12, 46, 48)

SPRING-8 CENTER (RSC)

THE PRIMARY mission of the RSC is to maintain stable and reliable operation of the large-scale research facilities—SPRING-8 and SACLA—by providing brilliant X-rays for researchers at universities, research institutes, and industries. We develop state-of-the-art technologies for the production and utilization of brilliant X-rays and create new science through the synergistic use of the two facilities. We also develop analysis tools for cryo-electron microscopy and high-performance NMR, which complements synchrotron radiation. (pp. 43, 48, 49)



THANK YOU FOR READING ABOUT RIKEN!

If you are interested in keeping up to date on current research throughout the year, or learning more about specific laboratories, please check out our website and follow us on social media.

<https://www.riken.jp/en/>
<https://itaintmagic.riken.jp>

