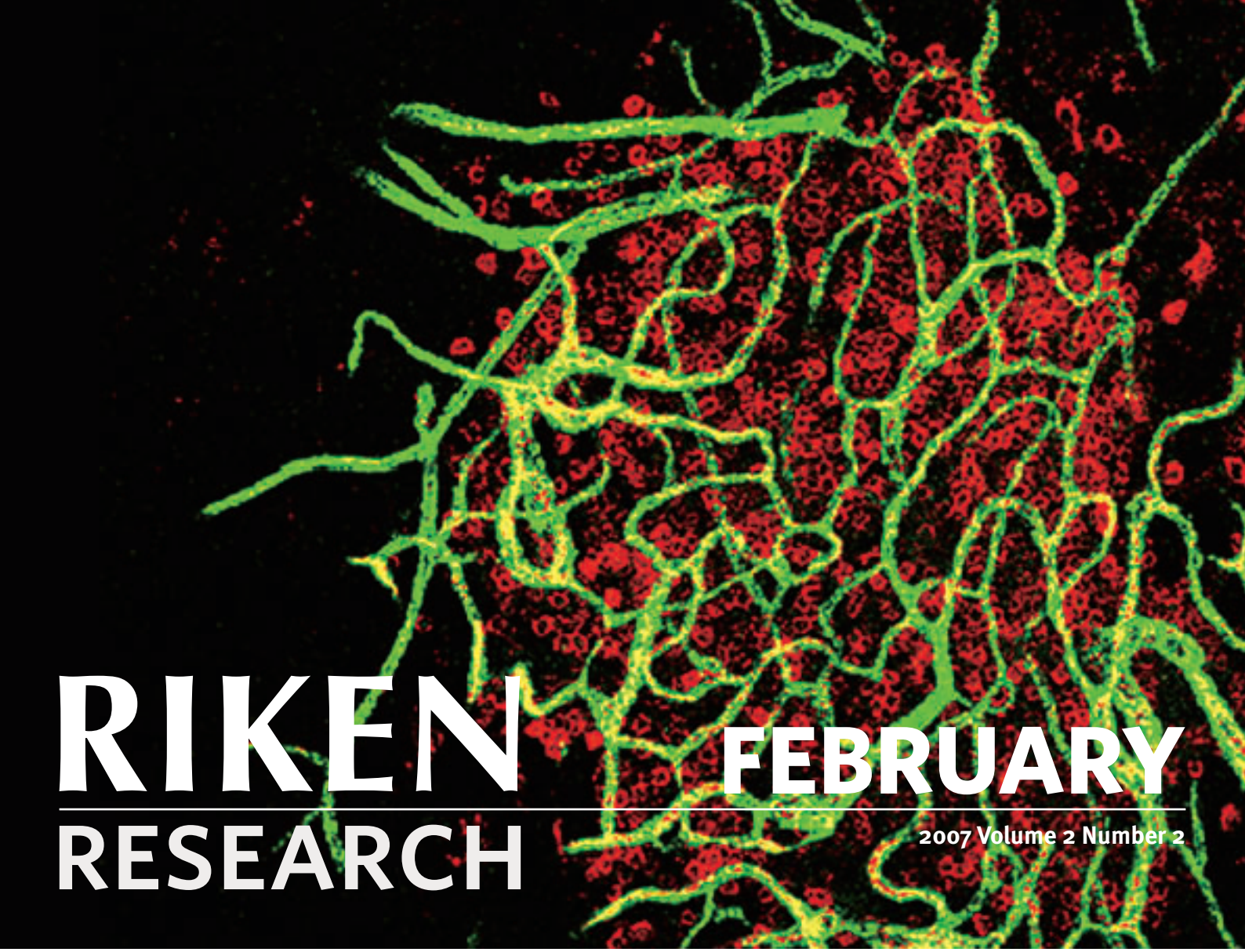

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A force reveals its magic

The inclusion of the long-neglected tensor force into theoretical models revises our understanding of 'magic numbers' in the atomic nucleus

The world of nuclear physics is a relatively ordered one. Atoms are made up of a nucleus, surrounded by electrons. The nucleus itself is composed of nucleons, the protons and neutrons, where the number of positively charged protons determines the chemical element and the number of neutrons its isotope.

For radioactive elements, certain isotopes live longer than others before they decay, depending on particular combinations of neutron and proton numbers. Whenever the number of either neutrons or protons adds up to a certain 'magic number', the nuclei are particularly stable (Fig. 1). In the rare case where both the number of protons and neutrons are identical to a magic number, the isotope is very stable and called 'doubly magic'. An example is lead-208, which consists of the magic numbers of 82 protons and 126 neutrons.

This empirical finding is explained by a theoretical model where the nucleus is structured into different shells that are filled with neutrons and protons. When a magic number of protons and neutrons is reached, the shells are completely filled and therefore very stable. This concept is very similar to an atom's electronic states, where the electrons are also arranged in shells surrounding the nucleus. Whenever all shells are completely filled, the atomic element is very stable and chemically inert—it is a noble gas.

The nuclear shell pattern is described in detail by a successful class of theories, the mean-field models. Mean-field theory allows the precise calculation of the shell structure and the energy required to add or remove a proton or neutron from the nucleus. This allows the direct determination of the magic numbers, and is of importance to improving our fundamental understanding of the stability of isotopes more generally.

Enter the tensor force

A research team from RIKEN's Nishina Center for Accelerator-Based Science and the University of Tokyo has now shown these traditional models to be incomplete. Writing in the journal *Physical Review Letters*, the researchers demonstrate that a force occurring in the nucleus, rooted in a prediction by Hideki Yukawa, does indeed play an important role[1].

In 1935, Yukawa, Japan's first Nobel laureate, postulated the existence of a new type of particle, the meson. And it is by the exchange of a particular meson, the pi meson, that the tensor force manifests itself (Fig. 2). The pi meson acts as a mediator between the nucleons (proton or neutron). This exchange

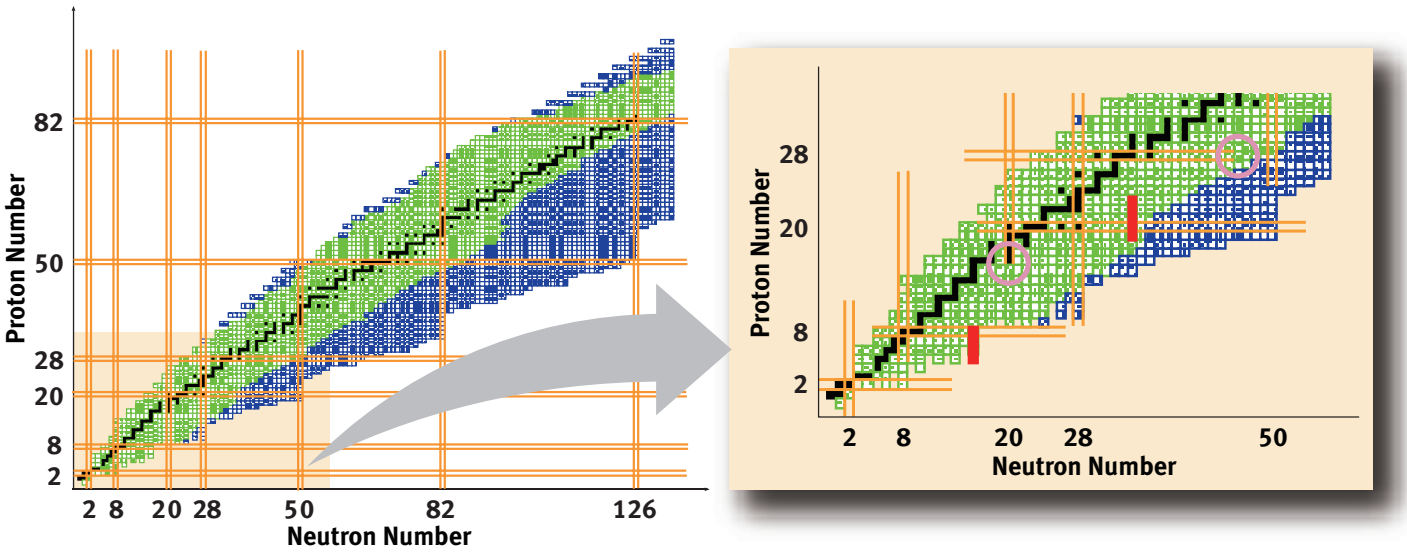


Figure 1: A plot of the nuclear isotopes of different elements, which are determined by the composition of protons and neutrons in the nucleus. Stable isotopes are plotted in black and unstable (radioactive) isotopes are given in green (experimentally produced) and blue (predicted). Intersecting lines of the orange grid depict the original magic numbers, as numbered along the axes. Inset: In the revised shell model, magic numbers are not constants (for instance, vanished in pink circles). Instead, for more unstable isotopes, new magic numbers appear (red bars as examples).

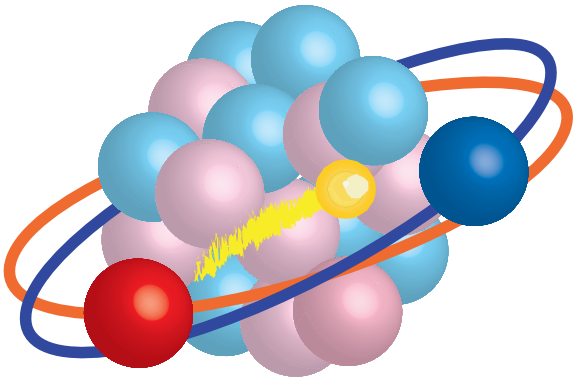


Figure 2: Schematic depiction of the atomic nucleus. Protons and neutrons moving in the nucleus (pink and blue spheres), interact with each other through the nuclear forces, among which the tensor force, mediated by a pi meson (yellow), influences the shells and thus changes the magic numbers.

depends strongly on their relative position as well as the spinning motion of these nucleons, so that the tensor force can be either attractive or repulsive.

Such broad variation in the effects of the tensor force means that the force has quite an influence on the arrangement of particles in the nucleus and the structure of the nuclear shells. "Although the tensor force has been known to exist, it has never been studied in connection with magic numbers," explains Takaharu Otsuka from the RIKEN team. As the force is rather complicated and previously thought to have negligible influence on the magic numbers, it was long-ignored in conventional theories describing the nuclear shells. When included explicitly in the mean-field model, the results differ significantly compared to conventional expectation.

A new magic

The most significant discrepancies to previous results occur away from the region of stability for nuclear isotopes and where the number of neutrons and protons are unbalanced and isotopes are highly radioactive. For those isotopes, the influence of the tensor force is expected to be significant. Consequently, the shape of the nucleus can be different from conventional expectation and the calculated energy it takes to remove a nucleon from the nucleus differs. These findings might therefore lead to the disappearance of conventional magic numbers and the appearance of new ones for exotic isotopes (inset of Fig. 1). For instance, nickel-78, comprised of 28 protons and 50 neutrons, is a classical example of a doubly magic nucleus, but may now turn out not to be so.

This finding is surprising, as magic numbers were expected to remain stable. "What we have shown is that magic numbers are not constants and that for some rare isotopes, conventional magic numbers may disappear, and new ones may arise," Otsuka says.

Importantly, estimates for the production and decay rates of certain radioactive isotopes need to be revised, which is relevant for example to understand supernova explosions.

Towards an experimental verification

The aim now is to verify the theoretical predictions. This will be one of the key experiments scheduled for the new RIKEN Radioactive Ion Beam Factory (RIBF) facility that is currently being completed at Wako[2].

At RIBF, beams of various heavy ions will be generated so that their properties such as nuclear structure and radioactive decay times can be studied. For some of the more exotic isotopes, where significant differences between the existing mean-field models and the new model are expected, RIBF will be ideally suited to study those isotopes in detail.

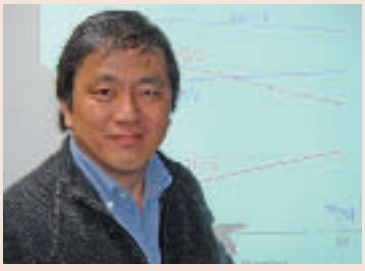
Although the tensor force has a long history in nuclear physics, in retrospect it seems surprising that its implications for the nuclear shell structure were considered to be only of minor relevance. Indeed, the exciting discovery by the RIKEN researchers fundamentally revises our understanding of the nuclear shells and may lead to a better knowledge of radioactive processes. More generally, these findings are a continuing testament to the influence of the tensor force, reaching far beyond the atomic nucleus. ■

1. Otsuka, T., Matsuo, T. & Abe, D. Mean field with tensor force and shell structure of exotic nuclei. *Physical Review Letters* **97,** 162501 (2006).

2. RI beam facility is now ready for heavy-ion acceleration, Roundup, *RIKEN RESEARCH* **2**(1), 17 (2007).

About the researcher

Takaharu Otsuka was born in Yokohama, Japan, in 1952, and graduated from the University of Tokyo in 1974. He earned his masters degree in 1976 and his Doctor of Science in 1979 from the same university. From 1979 to 1986, he worked as a researcher at the Division of Physics, the Japan Atomic Energy Research Institute. During that time, he did a two-year stint as a postdoctoral researcher at the Los Alamos National Laboratory in the US, from 1983 to 1985. In 1987, he became an associate professor in the Department of Physics, University of Tokyo, and in 1997 he was appointed professor in the same department. He has been concurrently serving as a senior guest researcher at RIKEN since 1994 and as the Director of the Center for Nuclear Study at the University of Tokyo since 2005.



Fast enough to fly against the stream

Argon ions flying through a crystal get excited by its periodic structure

When done in the right way, high-energy ions shot into a single crystal can show intricate effects that enable us to learn more about the fundamental physics governing crystals and their interactions with ions. As single crystals such as silicon have extremely periodic structures, the electric fields of the crystal atoms under the right conditions are able to resonantly excite the internal electronic states of the ions traveling through the crystal. This process is called resonant coherent excitation (RCE).

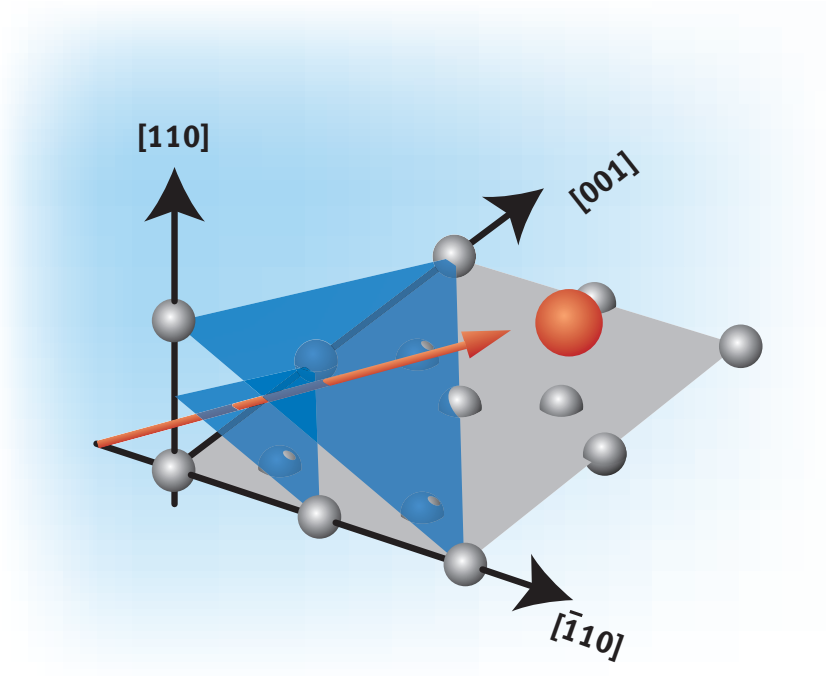
Traditionally, RCE has only been possible if the incident beam path of the ions towards the crystal was chosen such that the ions fly exactly along a 'channel' parallel to the atomic array. This avoids collisions that would throw the ions in the beam off track and disturb the coherent excitation process.

Now, a team from RIKEN's Discovery Research Institute, the University of Tokyo, Tokyo Metropolitan University, and the National Institute of Radiological Science, has shown in experiments using equipment known as the Heavy Ion Medical Accelerator in Chiba (HIMAC) that this restriction is not necessary. In fact, RCE can be observed under more general conditions if sufficiently heavy, high-energy ions such as argon are used. Their results were published recently in *Physical Review Letters*[1].

"Everybody had believed that the observation of RCE required channeling," explains Chikara Kondo from the RIKEN team. "Our work avoids this complicated process and made the study of this phenomenon easier and more fascinating."

The channeling ions along the atomic arrays of crystal tend to be influenced by the static electric fields of the channel wall, which affects the experimental results. Non-channeling ions—that cut through atomic planes of the crystal planes instead of flying along regular channels (Fig. 1)—are free from such influence, so exhibit a clear resonance profile. This allows the high-precision study of RCE and could be used to study the electronic states of the high-energy ions themselves.

The team is already working on the next generation of experiments. Kondo says he is hopeful that: "In the near future, highly accelerated ion beams will become available that would allow us to access a higher energy region". Intriguingly, such high energies might allow the researchers to look beyond the electron states of the ion and directly into the atomic nucleus. And this could open a completely new avenue for studying nuclear physics, particularly in the case of unstable nuclei. ■



PRL/American Physical Society

Figure 1: Argon ions (red) that cut through the atomic planes of silicon crystals (grey and blue) yield more information than those traveling between the planes.

1. Kondo, C., Masugi, S., Nakano, Y., Hatakeyama, A., Azuma, T., Komaki, K., Yamazaki, Y., Murakami, T. & Takada, E. Three-dimensional resonant coherent excitation of nonchanneling ions in a crystal. *Physical Review Letters* **97,** 135503 (2006).

Cosmic rays track Milky Way's rotation

Elusive sources of high-energy particles come into focus

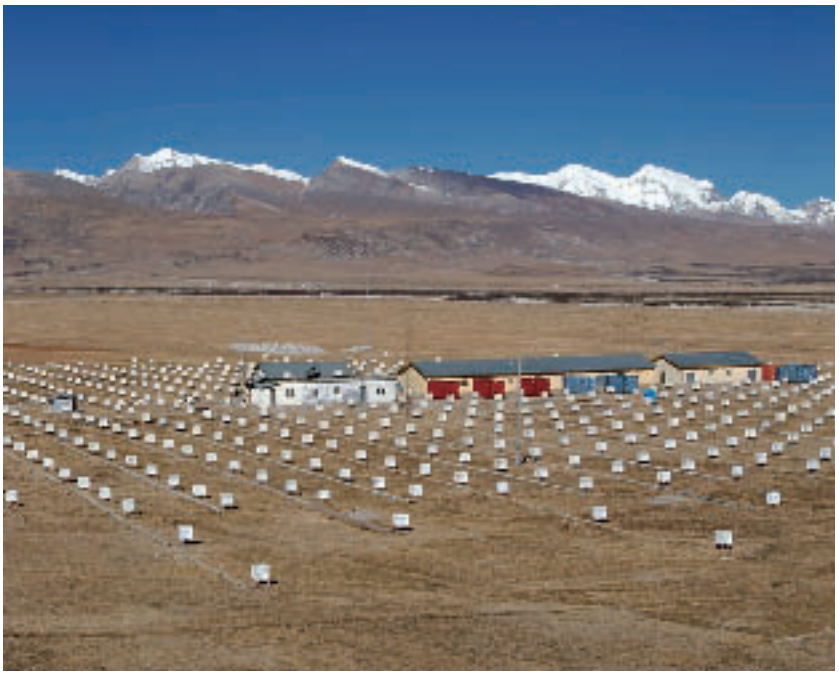
Earth is bombarded constantly by cosmic rays, high-energy particles that travel close to the speed of light. The source of the most energetic cosmic rays has long been a mystery, but now astrophysicists have made a breakthrough that may help to identify their origins[1].

Each of the high-energy cosmic rays—mostly protons—hit Earth's atmosphere. These cosmic rays shatter air molecules into fragments that cascade to the ground in a shower, and can be spotted by detectors such as the Tibet Air Shower Array (known as Tibet ASγ) (Fig. 1).

Low energy cosmic rays are more abundant, but are easily deflected by local magnetic fields, so any sense of where they originated is lost. High energy rays are less likely to be deflected, hence more easily sourced—but they are exceedingly rare.

Still, over the past few years, Tibet ASγ has observed tens of billions of cosmic ray events in the high-energy range, measured in trillions of electron volts. These events are distributed unevenly around the sky, because high-energy cosmic rays are likely to be generated in very specific conditions found only in certain parts of the Milky Way.

Earth's motion also plays a part. Experiments show that there are more high energy cosmic ray impacts on the 'leading face' of Earth as it rotates around the sun, just as the front windshield of a moving car will have more bugs splattered on it. However, scientists have long been unsure whether the rotation of our Solar System around the galactic center also plays a similar part in concentrating the rays in certain areas.



Tibet ASγ Collaboration

Figure 1: The Tibet Air Shower Array that was built to observe high-energy cosmic rays.

Now, results from Tibet ASγ show that it does not. Instead, the sources of high-energy cosmic rays appear to rotate at the same rate as the galactic magnetic field itself, ruling out any contribution from Earth's journey around the Milky Way.

Understanding precisely how these cosmic rays move through space should help to pin down their origins, says Harufumi Tsuchiya from RIKEN's Discovery Research Institute and part of the Tibet ASγ collaboration. It should also reveal details of the magnetic fields around the sun and between the stars that affect the cosmic rays' trajectories, he adds.

One place to start looking is the Cygnus region of our Galaxy. The team found elevated levels of high-energy cosmic rays streaming from that part of space. They hope to investigate the source further in the quest to find the origin of cosmic rays . ■

1. Amenomori, M., Ayabe, S., Bi X.J., Chen, D., Cui, S.W., Danzengluobu, Ding L.K., Ding, X.H., Feng C.F., Zhaoyang Feng, *et al.* Anisotropy and corotation of Galactic cosmic rays. *Science* **314,** 439–443 (2006).

Surfing electrons make a splash

Electron arrays floating on superfluid helium provide access to the fundamental properties of the liquid below

One of the most well-known fundamental physical effects is superconductivity: the flow of electrons without electrical resistance in certain materials that occurs when the electrons form pairs at very low temperatures.

A related effect occurs in the rare helium isotope helium-3 (^{3}He) at extremely low temperatures of only a thousandth of a degree above absolute zero, where ^{3}He is a liquid. In a similar fashion to electrons in superconductors, the ^{3}He atoms form pairs and create a new physical state—superfluidity. One of the characteristics of superfluids is the free flow of the liquid without any viscosity or resistance. Superfluid liquids can creep up on surfaces and leak through the tiniest of cracks.

The superfluid state of ^{3}He is complex and shows a variety of different effects. In particular, the texture of ^{3}He pairs at the surface of the liquid reveals fundamental properties that are difficult to obtain experimentally.

Using an ingenious method, Hiroki Ikegami and Kimitoshi Kono, who are physicists at RIKEN's Discovery Research Institute at Wako, now report on the first complete mapping of the ^{3}He superfluid properties[1]. Their method is based on electrons that are deposited and trapped on the surface of the ^{3}He superfluid. Owing to the low temperature, the electrons arrange themselves in a regular two-dimensional array, known as a Wigner solid (Fig. 1). The properties of the liquid strongly influence the electrical resistance of the electrons. When remaining unpaired ^{3}He particles travel towards the surface, they hit periodic deformations and thus slow down the flow of electrons. Therefore, measurements yielded from mapping this electrical resistance can be used to determine the texture of the superfluid.

In fact, Ikegami and Kono are now able to map electrical resistance at an unprecedented range of temperatures and magnetic fields—external parameters that affect superfluids. Magnetic field data is particularly valuable, because the field modifies the pairing state of ^{3}He atoms. "Previously, similar low-temperature measurements have been performed, but without a magnetic field," says Ikegami. Determining the superfluid texture under different experimental conditions is a key achievement as it allows the verification of theoretical models.

"The aim is now to go to even lower temperatures of below a tenth thousandth of a degree above zero, where further delicate scattering effects at the surface are expected to occur," says Ikegami. If successful, those experiments will advance our fundamental understanding of superfluidity and provide invaluable information on related effects such as high-temperature superconductivity. ■

1. Ikegami, H. & Kono, K. Texture of superfluid ^{3}He probed by a Wigner solid. *Physical Review Letters* **97,** 165303 (2006).

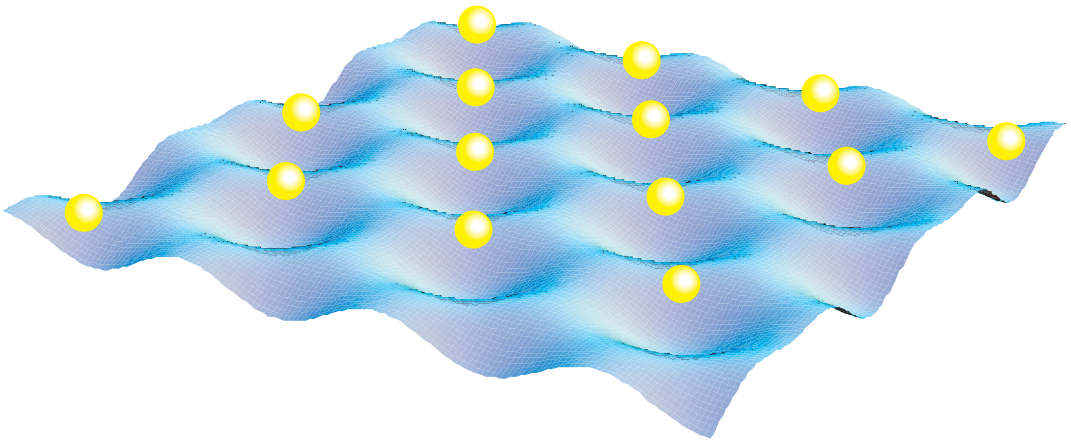


Figure 1: Schematic of the regular array of electrons (yellow)—the Wigner solid—that floats on top the superfluid ^{3}He (blue), leading to periodic deformations.

A step away is a step ahead

A reduced coupling between quantum bits and read-out circuit provides the basis for valuable information on the lifetime of quantum bits

Quantum computers are a promising concept for future computers, as they are able to perform certain mathematical operations much faster than conventional computers. However, the coherence of the quantum states of qubits, which are at the heart of quantum computers, degrades very quickly due to tiny fluctuations, or 'noise' from external sources. In order to reduce this noise, its origins need to be understood. But gaining this knowledge has been difficult since even the measurement apparatus itself influences the delicate qubits, thus distorting the results.

Now a team from RIKEN's Frontier Research System in Wako, with researchers from two other institutes in Japan and one in Finland, is able to provide key information on the processes affecting the lifetime of qubits.

The qubit studied by the team, known as a 'flux qubit', is a small superconducting loop intersected by four Josephson junctions (Fig. 1). The quantum state of this qubit is set by the magnetic field, or flux, through the loop, and is read by a superconducting device, the SQUID. The SQUID is coupled to the flux qubit. This coupling plays a crucial role for qubit degradation, because coupling that is too strong reduces the coherence of the flux qubit, explains Fumiki Yoshihara, a condensed-matter physicist from the RIKEN team.

In a study published recently in the journal Physical Review Letters1, the researchers use an electronic circuit optimized to reduce the coupling (Fig. 1). This enables high-quality measurements that provide unprecedented details on the origins of noise and make it possible to rule out a number of possible candidates for sources of noise that influence the device, such as thermal fluctuations. In fact, the researchers are able to prove for the first time that random variations in the magnetic flux are the key contributors to qubit decoherence. They are also able to quantify its behavior.

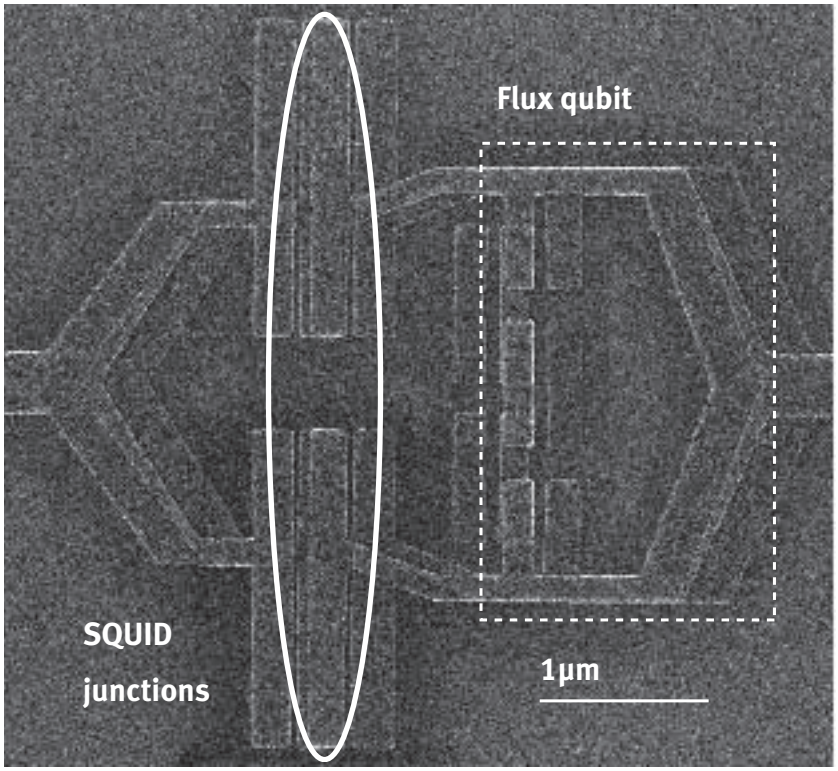


Figure 1: The SQUID for read-out with two large Josephson junctions (ellipse) is coupled with a flux qubit (rectangle with dashed lines).

Surprisingly, the team's experiments reveal that, under the right conditions, the flux noise can be decoupled entirely from the qubit such that the only remaining contribution to the decoherence is its intrinsic energy relaxation. This finding could have important practical implications for the optimization of the device properties. However, according to Yoshihara, "the fundamentals of the intrinsic relaxation are unknown". So the team is now planning to study its origins. Based on these very promising results, the dream of a quantum computer with a Josephson junction flux qubit may be a step closer to reality. ■

1. Yoshihara, F., Harrabi, K., Niskanen, A. O., Nakamura, Y. & Tsai, J. S. Decoherence of flux qubits due to 1/f flux noise. *Physical Review Letters* **97,** 167001 (2006).

Insights into brain architecture

Cross talk between neurons helps generate the cerebellum

Interactions between cells in the cerebellum—or 'little brain'—are essential for normal function. A collaboration of Japanese researchers has now found that the proper development of the tree-like morphology of Purkinje cells in the cerebellum requires signals from other cerebellar cells called granule cells.

The cerebellum is a region of the brain (Fig. 1) that coordinates sensory information. Lesions in the cerebellum cause subtle defects in movement and balance, and some evidence suggests conditions such as schizophrenia are caused by cerebellar dysfunction.

Unique to the cerebellum are the specialized Purkinje cells (Fig. 2)—named for the Czech anatomist Jan Purkyně. Development of the great numbers of Purkinje cell 'branches' or dendrites, which project into the outer layer of the cerebellum where they interact with other neurons such as parallel fibers, is essential for cerebellar function.

Remarkably, although the cerebellum represents only about 10% of total brain size, the number of cerebellar neurons constitutes some 50% of total brain neurons. Upwards of 60 billion granule cells occupy the inner region of the cerebellum.

The collaboration of neuroscientists led by Katsuhiko Mikoshiba and Chihiro Hisatsune of the RIKEN Brain Science Institute, Wako, found that signals produced by granule cells are required for proper growth of the complex Purkinje cells[1]. The team evaluated mice that lack inositol 1,4,5-triphosphate receptor type 1 (IP_3R1), a signaling protein found throughout the brain.

By studying isolated Purkinje cells and granule cells from normal mice and mice lacking IP_3R1, the team showed that granules cells, not Purkinje cells, need IP_3R1 in order to produce brain-derived neurotrophic factor (BDNF), a growth factor that Purkinje cells need for development of their tree-like dendrites.

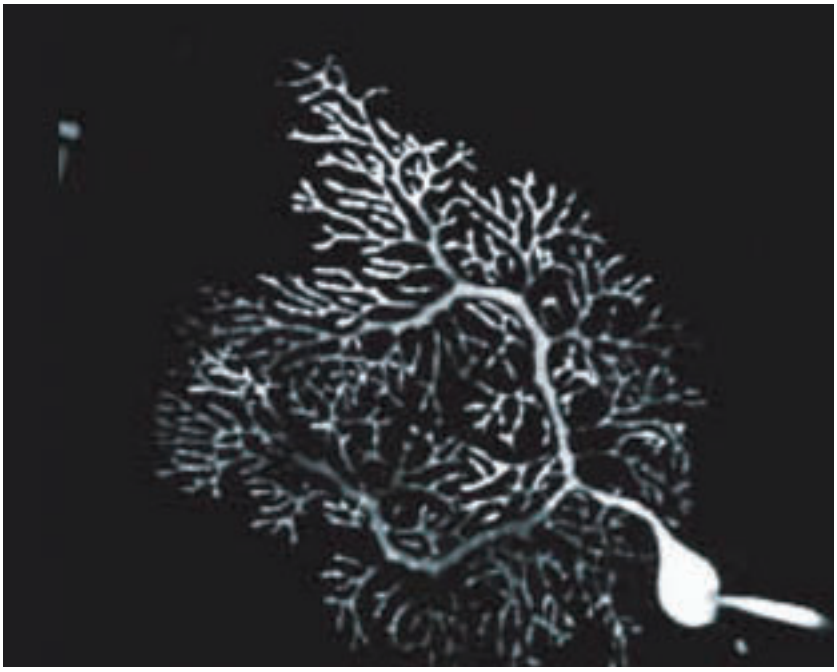


Figure 2: A Purkinje cell.

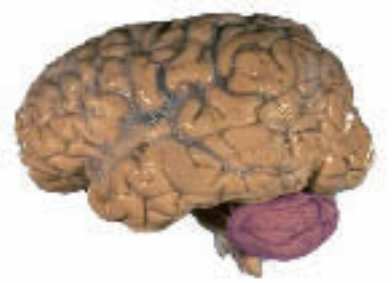


Figure 1: The human brain, with the large cerebrum and smaller cerebellum (purple).

The team also visualized dendrite branches of Purkinje cells in brains of mice that lack IP_3R1. Compared to normal mice, the IP_3R1-deficient brains showed reduced connections between Purkinje cells and parallel fibers in the outer layer of the cerebellum, clearly implicating IP_3R1 in regulating normal cerebellar development.

"We now want to know the molecular mechanism by which IP_3R1 regulates BDNF expression from granule cells," says Mikoshiba. "And because IP_3R1 is found in many regions of the brain, future work will hopefully reveal the physiological roles of IP_3R1 in cells forming these other regions as well."

Understanding the architecture of the brain requires understanding how individual neurons interact with one another. Mikoshiba and colleagues' work highlights the complex interactions between cerebellar Purkinje cells and granule cells that are required for forming correct connections between them. ■

1. Hisatsune, C., Kuroda, Y., Akagi, T., Torashima, T., Hirai, H., Hashikawa, T., Inoue, T. & Mikoshiba, K. Inositol 1,4,5-triphosphate receptor type 1 in granule cells, not in Purkinje cells, regulates the dendritic morphology of Purkinje cells through brain-derived neurotrophic factor production. *The Journal of Neuroscience* **26,** 10916–10924 (2006).

How cats produce their distinctive smell

Biochemists unlock the molecular secret to cat odor

Researchers have uncovered the molecular pathway whereby cats produce the species-, sex- and age-specific compounds with which they mark their territories (Fig. 1). Cats may also use the same substances to identify each other and attract mates.

The work provides significant new information on chemical communication in mammals, and may lead to a practical way of neutralizing the odor of cat urine in domestic environments.

Previous studies showed that felinine, an odorless compound thought to be the precursor of cat pheromones, is present in cat urine. It was believed that felinine was produced from the 3-methylbutanol-glutathione (3-MBG) present in cat's blood, but the reaction pathway was unknown.

Reporting in *Chemistry and Biology*[1], biochemists from the RIKEN Frontier Research System in Wako, in collaboration with colleagues from several other institutions, discovered that as well as felinine, there were also high concentrations of a protein component called cauxin in the urine of normal male cats. Cauxin, a member of a group of enzymes that breaks chemical bonds in a variety of organic compounds, is produced only in the kidney of the domestic cat and closely-related species of the cat family.

In the laboratory, the team found that cauxin split 3-methylbutanol-cysteinylglycine (3-MBCG), converted from 3-MBG by an enzyme, into felinine and glycine. The researchers then monitored the levels of cauxin and felinine in the urine of male and female cats over time, and discovered that the two compounds tended to increase in step with each other in cats older than three months. Neither was present in cats younger than two and a half months.

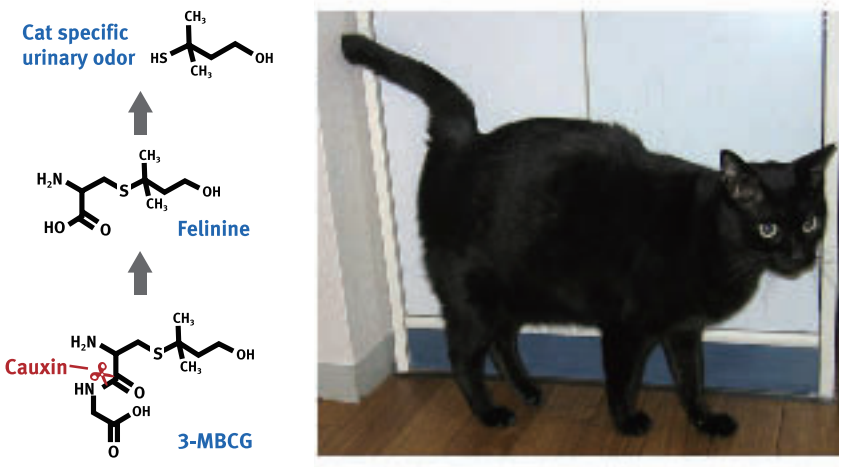


Figure 1: A cat spraying a vertical surface with a fine stream of urine to mark its territory (right), and the biochemical pathway involved (left).

Although felinine is odorless, it develops a smell similar to cat urine when stored at room temperature. When the researchers analyzed volatile compounds from the air above cat urine, they found natural breakdown products of felinine which produced the characteristic odor. These volatile compounds, which vary according to age and sex, may well be the active ingredients in cat chemical communication, the researchers speculate.

Based on this work, the team has suggested ways of eliminating cat odor. One possibility is to block felinine production by adding a cauxin inhibitor to cat food. This would be difficult, says team member Masao Miyazaki. An easier alternative, he says, may be to use compounds containing metal ions, such as gold, silver and copper, which bind to and neutralize felinine derivatives carrying the pungent thiol group.

Miyazaki now wants to investigate the impacts of felinine and its derivatives on cat behavior. "We are looking for pheromonal activity in cats." ■

1. Miyazaki, M., Yamashita, T., Suzuki, Y., Saito, Y., Soeta, S., Taira, H. & Suzuki, A. A major urinary protein of the domestic cat regulates the production of felinine, a putative pheromone precursor. *Chemistry and Biology* **13,** 1071–1079 (2006).

How a protein regulates cell structure

Japanese researchers unveil details of a key molecular interaction

A RIKEN research team has combined electron microscopy with sophisticated image analysis to reveal details of a molecular interaction that regulates the activity of actin filaments, a key element in cellular structure and function.

Actin filaments are double-stranded helical chains or polymers of which the protomer, or basic unit, is the globular protein actin. These filaments form a contractile cellular skeleton which plays an important role in cell division, enables cells to move and assists the migration of protein complexes and organelles within cells. Controlling the activity of the filaments themselves is fundamental to cellular function.

Much of the activity of the filaments depends on their ability to lengthen and shorten by gaining or losing actin protomers. They do this preferentially at the end known as the barbed-end, as opposed to the pointed-end. This capability is inhibited by means of a capping protein that binds to the barbed-end, and locks in place. In a recent paper in *EMBO*[1], the research team proposes a convincing model of how this molecular interaction occurs.

The team took high resolution electron micrographs of the barbed-ends of filaments with the capping proteins literally frozen in place. Subsequent image analysis using a novel procedure developed by the team revealed the orientation of the capping protein when bound to the filament.

The structure of the capping protein has been published previously—a globular body from which two tentacles, labeled α and β, protrude. In the orientation shown in the team's electron micrographs, the α-tentacle lies across the two exposed actin protomers at the barbed-end of the filament. A region of basic, positively charged amino acids on the tentacle, sits next to negatively charged areas of acidic amino acids on each of the actin protomers.

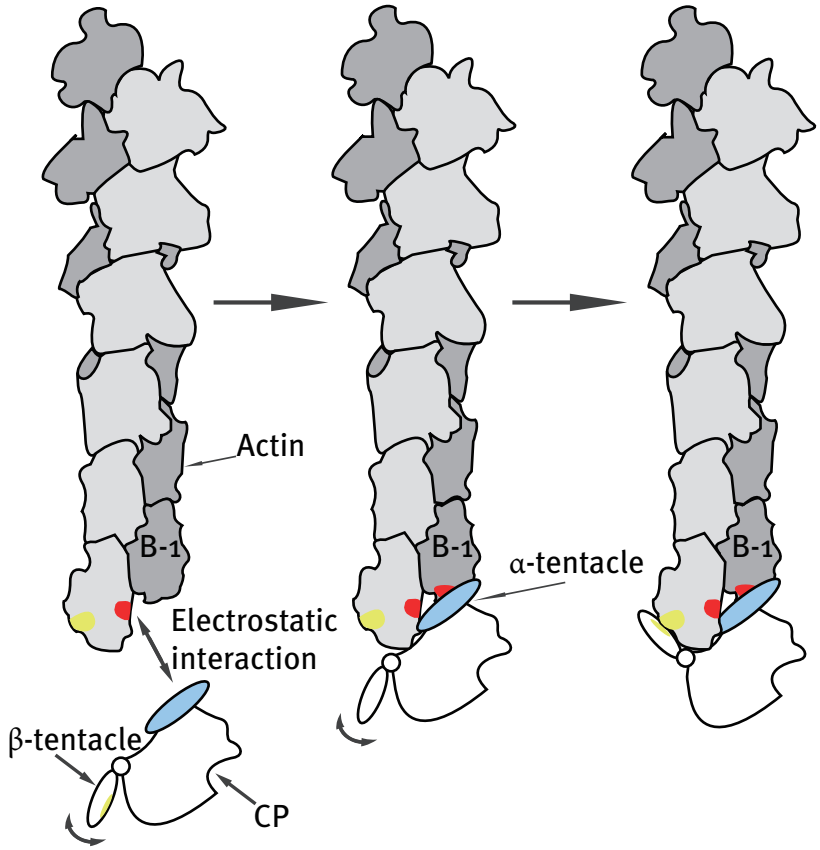


Figure 1: A model of the interaction of the capping protein (CP) with the barbed-end of an actin filament as proposed by the research team.

The research team proposes that the electrostatic attraction between these areas draws the capping protein into position (Fig. 1). Once there, the freely swinging β-tentacle locks the capping protein into place as it is repelled by water into a position along the outer side of one of the actin protomers. This model fits with previous observations that while deletion of the α-tentacle severely weakens the interaction between capping protein and filament, deletion of the β-tentacle has a much milder effect.

The research team is now working on elucidating the structure of the pointed-end, says research team member Akihiro Narita of the RIKEN SPring-8 Center in Harima. "The difference between the two ends is one of the basic features of actin filaments."

1. Narita, A., Takeda, S., Yamashita, A. & Maéda, Y. Structural basis of actin filament capping at the barbed-end: a cryo-electron microscopy study. *The EMBO Journal* **25,** 5626–5633 (2006)

Mobilizing front-line immune defenses

New data highlight ways in which immune cells are quickly pulled into the fight against microbial intruders

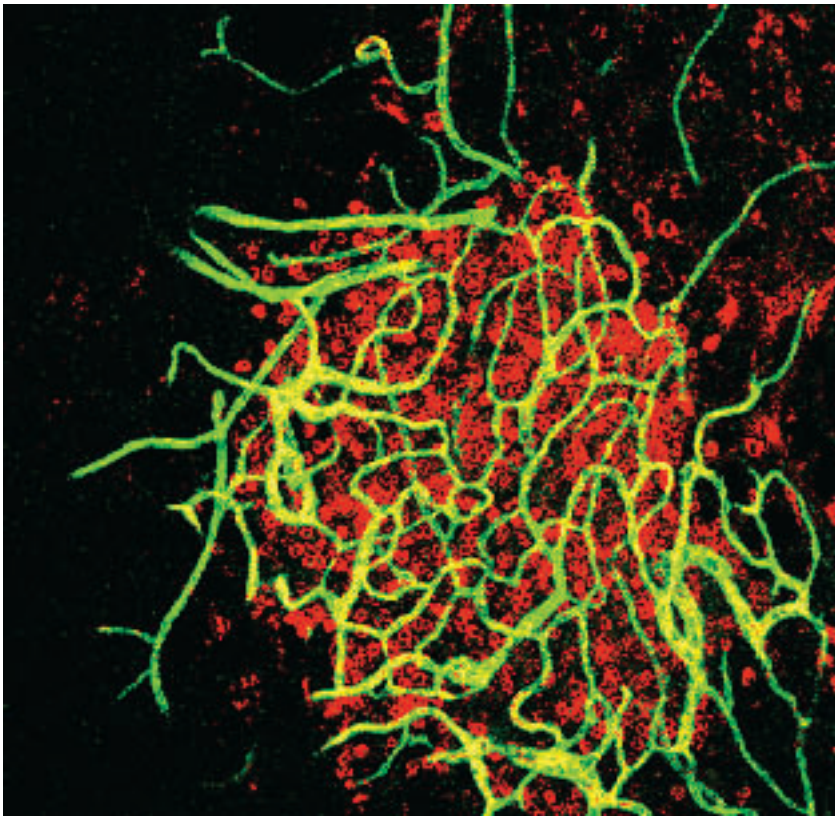


Figure 1: An image of omentum, the exit route from the peritoneal cavity, with B1 cells (red) and blood vessels (green).

Researchers report fresh insight into the events required for rapid recruitment of immune cells, called B1 lymphocytes, to lymphoid organs. In quiescent conditions, B1 lymphocytes reside between the membranes lining the abdominal cavity—the peritoneum. Post-infection, these immune cells are among the first to arrive in lymphoid organs, where later phases of the immune response develop. Due to their exquisite sensitivity to the presence of immune 'danger signals', B1 lymphocytes constitute ideal first responders.

Now a research team led by Sidonia Fagarasan, a scientist at RIKEN's Research Center for Allergy and Immunology in Yokohama, has determined precisely how B1 cells sitting within the peritoneum quickly traffic towards immune responses developing at distant locales throughout the body[1].

To simulate conditions of an infection, the team injected mice with a drug that injures the gut epithelium, thereby allowing microbes normally present within the small intestine to penetrate tissues close to the peritoneum. Dramatically, within six hours of drug injection, a substantial portion of B1 cells proceeded from the peritoneum to the spleen and gut-associated lymphoid organs (Fig.1).

The researchers hypothesized that proteins decorating the surface of bacteria might somehow provoke B1 cells to leave the peritoneum. Indeed, B1 cells departed the peritoneum after injection of lipid A, a component of many types of bacteria. In contrast, B1 cells lacking the sensor required for recognition of lipid A, known as Toll-like receptor 4, remained in the peritoneum even after lipid A injection.

The team also revealed the underlying mechanism. B1 lymphocytes express high amounts of proteins that allow cells to adhere or stick to tissues. However, exposure to lipid A triggered a drop in the expression of two such adhesion proteins known as integrins and CD9. Blockade of these adhesion proteins, even in the absence of bacterial components, allowed B1 cells to 'disengage' and leave the peritoneum.

However, B1 cell egress from the peritoneum was not the result of passive drift alone. After injection of bacterial components, cells lining the B1 cell departure route ramped up production of soluble proteins called chemokines, which actively attract B1 cells. Accordingly, B1 cells unable to receive chemokine signals remained within the peritoneum.

Unraveling the complexity of the series of events required to disengage B1 cells from the peritoneum presents multiple opportunities for therapeutic intervention. "These findings will open a new phase in immunology and hopefully in cancer research, because adhesion proteins on tumor cells may be regulated by similar mechanisms," says Fagarasan. ■

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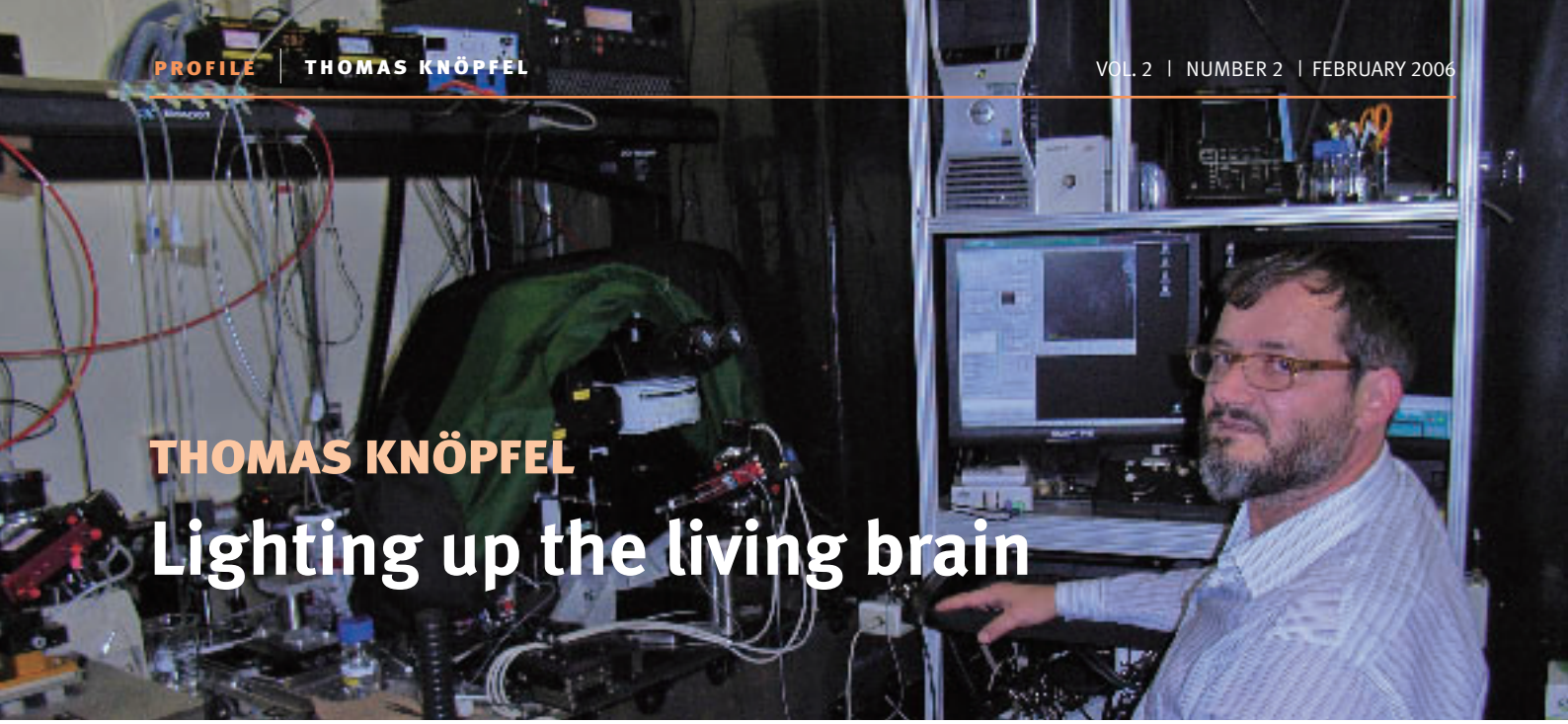


THOMAS KNÖPFEL

Lighting up the living brain

A brain scientist at RIKEN is devising next-generation optical imaging techniques to visualize the dynamics of neural circuits

Seeing is believing. The amazing performance of the human brain results from the interaction of huge numbers of nerve cells that communicate with each other simultaneously. But how can we capture and analyze this spatially distributed information processing? Increasingly, attention is turning to the technique of neuroimaging—literally, seeing brain cells.

"What we are doing in optical neuroimaging is like having a camera above the brain to film the activities of brain cells at many sites simultaneously," says Thomas Knöpfel, a neuroscientist at the RIKEN Brain Science Institute (BSI). "It's like making a movie. We place molecular light bulbs inside the brain. Each time a nerve cell is active, it lights up."

The German neuroscientist has been developing cutting-edge imaging technology during the past decade. His trick is to use genetically encoded fluorescent proteins that are sensitive to the electrical signals of nerve cells. With ultra high-end cameras and illumination techniques, his team observes living brain cells as they 'flicker' like little light bulbs whenever they produce electrical signals.

Road to brain science

Knöpfel's interest in neuroscience began when he was a student at the University of Ulm—Albert Einstein's home town—in southern Germany. He double-majored in medicine and physics, and found that brain science was his favorite subject. After graduating he moved to the University of Zurich, Switzerland, earning his doctorate in physiology in 1985.

Then, he joined the Brain Science Institute at the University of Zurich, becoming an assistant professor at the institute in 1989. Three years later he earned his privatdozent (PD) status—a qualification for a professorship in some European countries—from the University of Zurich. After working at a pharmaceutical company and as a visiting professor at University College London, UK, Knöpfel came to RIKEN in 1997 to head the Laboratory for Neuronal Circuit Dynamics at the newly established BSI.

From the beginning of his career, Knöpfel had been interested in imaging systems, such as high-speed cameras. His first main research theme at school was to look into a reflex in frogs: how linear movement of a head can keep the eye seeing the same target. "We knew the signals that go in and come out, but we still didn't know how these signals were processed in the brain," Knöpfel says. "I wanted to see inside the 'black box.'"

So Knöpfel shifted his focus towards observing directly how individual nerve cells in the brain interact and exchange signals. First he focused on the cerebellum, a part of the brain that involves in the organization of movements, and about five years ago, Knöpfel added the olfactory bulb as another area of his research.

An optical view of brain activity

In the early 1990s, Knöpfel and others were hunting for voltage-sensitive dyes to stain the plasma membrane of nerve cells so that they could record neuronal signals optically at multiple sites. But when they tried to stain a particular population of nerve cells, the dyes often diffused and painted the entire environment. To solve the problem, the idea emerged of developing a fluorescent protein sensor that could be genetically targeted to the cells of interest.

The first successful fluorescent protein sensors were calcium-sensitive ones. Calcium concentrations change during electrical activities in nerve cells, so calcium measurements provide an indirect indicator of membrane voltage.

These sensors worked in laboratory cell cultures, but the technique would be useless unless it could work in living brain cells. To this end, the researchers decided to create a transgenic mouse carrying an artificial protein as a sensor. The sensor would light up fluorescently in response to signals from neurons.

Knöpfel and his coworkers created the mice,[1] but they had a more ambitious goal: a voltage-sensitive fluorescent protein that could measure neural activity directly and in real time.

To make such a sensor protein (Fig. 1), two kinds of genes are inserted into a mouse genome. One, from a jellyfish, induces the production of a fluorescent protein. Another, from a rat or other animals, encodes a portion of a voltage-gated ion channel, a protein that allows the flow of ions in response to membrane voltage. Expressed together as a fusion protein in a mouse, these two proteins then act as a fluorescent voltage sensor. In addition

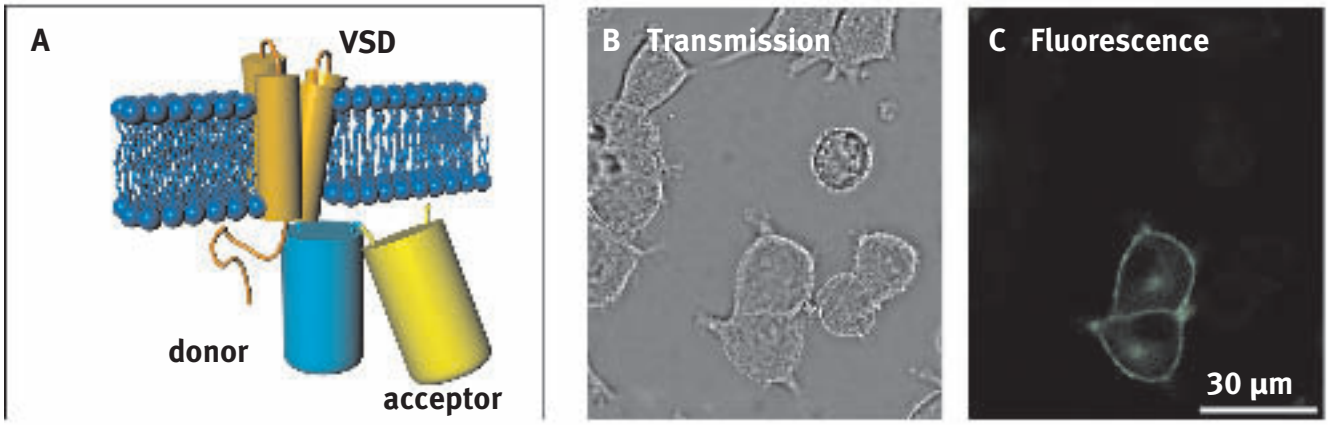


Figure 1:
A light bulb for brain cells—design and cellular expression of the voltage-sensitive fluorescent protein VSFP. A: A pair of cyan (donor) and yellow (acceptor) fluorescent proteins is attached to a 4 transmembrane voltage sensing domain (VSD). B, C: Confocal transmission (B) and fluorescence images (C) of cultured cells transfected with VSFP. Note labeling of the plasma membrane of selective cells.

to these two genes, Knöpfel also puts in a third gene containing regulatory sequences that determine in which specific cell types the sensor is synthesized, so that only these cells light up.

Two suitcases and one risky concept

In 1997, the lab of Ehud Isacoff at the University of California, Berkeley, published the first voltage-sensitive fluorescent protein sensor, named FlaSh, based on a protein from the fruitfly Drosophila[2]. At that time, Knöpfel was on a sabbatical in Italy, and was looking for a place to develop his ideas. He chose RIKEN because of its excellent working environment and ample resources, including an outstanding facility for transgenic mice and high-speed imaging equipment that can capture sensor signals at up to 10,000 pictures a second. Knöpfel says RIKEN was brave, in a good sense, to support the new, risky research at a time when no one was sure if the protein sensor concept would work.

So one day in 1998, Knöpfel arrived in Japan with two suitcases—but the main building of the BSI was still incomplete, and he had to work in another office temporarily for a year. In April 1999, however, Knöpfel was the first researcher to enter the brand-new BSI central building, where he set up the Laboratory for Neuronal Circuit Dynamics.

Competitors team up

In 2001, Knöpfel developed the world's second voltage-sensitive fluorescent protein sensor, VSFP-1,[3] followed one year later by Vincent Pieribone's lab at Yale University demonstrating the sensor SPARC.

The three fluorescent sensors were all first-generation, and their expression in the membranes of mammalian nerve cells was limited. "It is this problem that we are working together to solve," says Lawrence Cohen, another neuroscientist at Yale. In 2003, five of the top neuroscientists in this field—Knöpfel, Cohen, Isacoff, Pieribone and Thomas Hughes at Montana State University—started to cooperate. Last year, they jointly published a paper[4] in which they concluded that the first-generation sensors were not good enough for studying brain function.

Meanwhile, they continued their efforts to improve the sensor prototypes. An upgraded version of Knöpfel's sensor, VSFP-2.1, has superior targeting to the cell membrane, and they will soon start observing the sensor's performance in transgenic mice.

Knöpfel says this kind of friendly collaboration between competitors is unusual in brain science, but its synergy is highly valuable partly because the collaborators can mutually check the quality of their work, instead of competing to publish a paper before rivals.

But the successful collaboration couldn't have worked without Knöpfel. "Thomas is an unusually imaginative and determined scientist. It's been a pleasure to collaborate with his laboratory," Cohen says.

Knöpfel's unconventional approach and warm personality attract not only competitors but also young, able scientists like Dimitar Dimitrov. The 29-year-old Bulgarian joined the lab two years ago, and has been working on sensors that could signal voltage changes on the basis of different design principles. Knöpfel is good at guiding him to organize his thoughts, Dimitrov says. "We are trying different strategies now, and have got some very exciting results."

1. Diez-Garcia, J., Akemann, W. & Knöpfel, T. In vivo calcium imaging from genetically specified target cells in mouse cerebellum. *Neuroimage* **34(3),** 859–69 (2007).
2. Siegel, M.S. & Isacoff, E.Y. A genetically encoded optical probe of membrane voltage. *Neuron* **19(4),** 735–41 (1997).
3. Sakai, R., Repunte-Canonigo, V., Raj, C.D. & Knöpfel, T. Design and characterization of a DNA encoded voltage sensitive fluorescent protein. *European Journal of Neuroscience* **13,** 2314–18 (2001).
4. Baker, B.J., Lee H., Pieribone, V.A., Cohen, L.B., Isacoff, E.Y., Knöpfel, T. & Kosmidis, E.K. Three fluorescent protein voltage sensors exhibit low plasma membrane expression in mammalian cells. *Journal of Neuroscience Methods* [Epub ahead of print] PMID: 17126911, Nov 24 2006.

About the researcher

Thomas Knöpfel was born in 1959 in Germany. He earned his MD in 1984 and Master of Science in 1985, both from the University of Ulm. He then obtained his doctorate in physiology in 1985 and privatdozent (PD) in 1992, both from the University of Zurich, Switzerland. In 1985, he became an assistant at the Brain Science Institute at the University of Zurich, and was appointed as an assistant professor in 1989. In 1992, he became a team leader and project leader at Ciba-Geigy Pharmaceuticals (now Novartis). After serving as a guest scientist at University College London in 1996, he joined the RIKEN Brain Science Institute as head of the Laboratory for Neuronal Circuit Dynamics in 1998.

Mouse resource opens a new era of life science

Atsushi Yoshiki

Senior Scientist
Experimental Animal Division
Department of Biological Systems
BioResource Center (BRC)
RIKEN Tsukuba Institute

The human genome project was completed in April 2003. Since then, about 22,000 genes have been identified, but the functions of the majority of these genes remain unclear. Large-scale experimental projects to elucidate the functions of all genes and explore the relationships between genes and disease using mice have been launched in Europe and the US. The RIKEN BioResource Center (BRC) is Japan's only comprehensive institution dedicated to the collection, preservation, development and supply of bio-resources (genetic resources from living organisms). The Experimental Animal Division is responsible for the RIKEN mouse resource. It has a huge collection from over 2,000 strains of mice—including disease-model mice developed by Japanese researchers—and supplies researchers all over the world on request. Other activities of the Division include an international cooperative for preserving and supplying mouse resources. These resources are expected to bring about an explosive increase in the development of technologies for digitizing mouse morphological information and correlating data with genes, as well as investigating mutant mice discovered while breeding the colony.

Large-scale knockout mouse projects

To date, gene functions have been determined individually by exploring genes related to biological phenomena and disease, investigated by individual researchers. Research into human genes largely depends on mouse models. This is because there is a 99% homology between human and mouse genes, and also because a great deal of knowledge on mouse genetics and diseases has been accumulated during the history of their use as laboratory animals over more than 100 years. In addition, various experimental techniques, including gene manipulation, have been established in mice. For example, we can know how a particular gene functions in the body using knockout mice that have been manipulated to suppress that gene's function. As such, knockout-mouse technology has produced mouse models of human disease that have contributed significantly to the elucidation of the mechanisms of pathogenesis and drug-discovery research. However, it takes a great deal of money and labor to create such knockout mice, and, in addition, a major hurdle against the distribution of the knockout mice has arisen. The knockout mice that have been created to date worldwide include many prepared in duplicate by more than one researcher, with the same target gene. In extreme cases, more than 700 genes have been knocked out in triplicate or more, and one particular gene was knocked out 11 times. This situation represents a major loss to the research community as a whole.

In the past 10 years, the human and mouse genome projects were completed, and the locations of all the genes on the respective genomes were determined. Hence, it has become possible to knock out all genes, and to extensively investigate the functions of all genes and their relationships with disease. Large-scale projects for creating knockout mice were instigated in Europe in October 2005 (the European Conditional Mouse Mutagenesis Program: EUCOMM) and in the US in June 2006 (the NIH (National Institutes

of Health) Knockout Mouse Project: KOMP). These projects aim to target all genes using their own approaches. A similar project is ongoing in Canada.

Genetic information is written in the form of arrangements of the four kinds of bases: adenine (A), thymine (T), guanine (G) and cytosine (C). Recent research has gradually shown that susceptibility to disease, efficacy of drugs, adverse drug reactions, and the like are all affected by a single-nucleotide polymorphism (SNP)—a type of genetic polymorphism in which only one kind of base at a particular position differs among individuals. An international project is being planned for completion in the coming 5 to 10 years, in which all genes will be manipulated with 10 kinds of SNP to create about 300,000 strains of mice, and their functional differences and relations to disease will be explained.

To preserve the rapidly increasing quantities of mouse strains generated by these projects, and to supply them to researchers, the Federation of International Mouse Resources (FIMRe, http://www.fimre.org) was established with a coalition of 17 major mouse-resource centers around the world, including BRC, in 2005. Atsushi Yoshiki, head of the Experimental Animal Division, responsible for the mouse-resource project in BRC, explains the background to the foundation of FIMRe:

"Actually, more than 70% of the knockout mice that have been created to date are unavailable to researchers because the companies and researchers who developed them are reluctant to supply them to outside sectors," says Yoshiki. He adds that for this reason, many genes for which knockout mice already exist remain to be fully analyzed for functions. Hence, many of the resources created, through great efforts, have not been effectively distributed or utilized. "The currently ongoing knockout-mouse project takes this fact into consideration," he says. "To allow researchers throughout the world to smoothly conduct functional analysis of genes using quantities of mouse strains that will increase explosively, an international distribution system has been established with international cooperation."

FIMRe opens to the public mouse strains available from individual resource centers in the integrated database International Mouse Strain Resource (IMSR; http://www.informatics.jax.org/imsr/index.jsp) as a one-stop shop. The mice deposited and preserved at BRC are also registered in this database and are supplied worldwide.

"In Japan, there is no knockout-mouse project covering all genes," Yoshiki says. Nevertheless, he points out that BRC and the Center for Animal Resources and Development (CARD) at Kumamoto University participate in FIMRe, an outlet for the international distribution of mice. "This reflects the fact that Japan's capability for developing and investigating knockout mice is highly valued internationally," he adds. According to Yoshiki, knockout mice developed at leading research institutions, including RIKEN, attract the world's researchers. Depositing mice strains with BRC increases their availability to more researchers. "I hope," says Yoshiki, "That many more researchers will take advantage of BRC to make significant international contributions with their own mice."

Assuring the reliability of animal experimentation

When the function of a given gene is manipulated and examined, the results must be compared with those of control mice, which are subject to the same genetic and environmental factors except for the investigated gene. This is because a difference in any other factors can affect the experimental results. "The first step we take is to examine the deposited mice for pathogen contamination," says Yoshiki. "Then, we remove any contamination using caesarian section, embryo transplantation and other techniques to obtain clean mice." Genes are also examined to determine genetic

characteristics. According to Yoshiki, there are cases where deposited mice are contaminated with pathogenic microorganisms that adversely affect the health of the mice, including those where the mice are incorrect genotypes. In the case of knockout mice, it is examined whether they are from a genetically pure line with a uniform genome as a whole. Most knockout mice are used as genetically mixed hybrids. However, the validity of experimental results is assured by their reproducibility and it is difficult to obtain reproducible results by using mice with a mixed genetic background. "It is highly recommended to use a genetically pure line to obtain valid results," says Yoshiki. "This is true not only in Japan, but also worldwide. Our mission is to provide highly reliable animal-experimentation systems that enable researchers to focus only on knockout genes in mice reared to have a uniform genetic background by eliminating mixed-genetic components." This is laborious and time-consuming and could not be achieved by individual researchers, but Yoshiki adds, "Improving the quality of mice and providing them to researchers for sophisticated animal experimentation is also an important role for resource centers like ours."

While large-scale experimental projects to examine the functions of all genes using mice are ongoing, BRC and other resource centers should play a major role in assuring the quality of mice created in those projects.

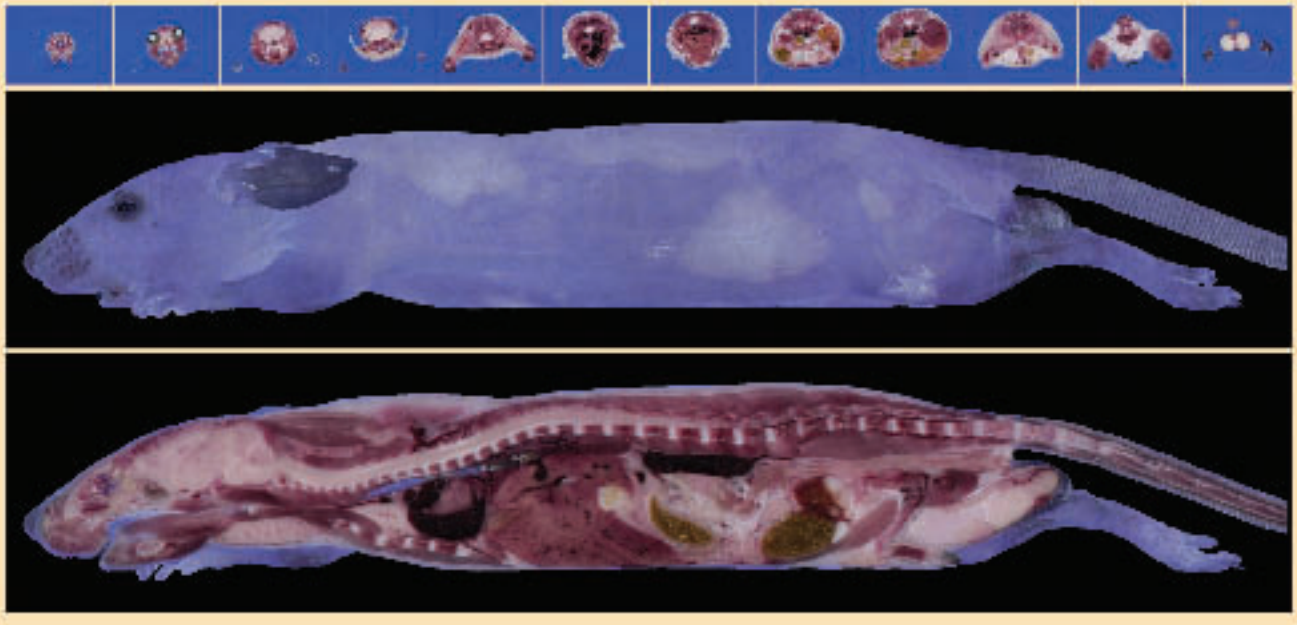
Digital anatomy of mice

Yoshiki and others are working to digitize the morphological information on the mice preserved in BRC to help research into the relationships between genes and morphology and between genes and disease. Morphological data, represented by image data, is enormous in volume and difficult to handle. Yoshiki and others are conducting joint research with Hideo Yokota, an expert in information technology and Laboratory Head of the Bio-research Infrastructure Construction Team at the VCAD System Research Program at the RIKEN Center for Intellectual Property Strategies (Computational Biomechanics Unit at Discovery Research Institute), and other experts. The three-dimensional internal structure microscope developed by Yokota and others is capable of taking and digitizing cross-sectional images of the whole mouse body with a cellular-size resolution of 0.02 mm within three hours (Fig. 1).

"It should be noted, however," points out Yoshiki, "That even if live tissue or cells are examined, as they require a high resolution, we cannot know the types or structures of the cells." He adds that they can be visualized only by special staining or labeling techniques etc. "We must develop techniques for visualizing the structures of different tissues and cells."

In the future, it will be possible to make computer-based comparisons of morphological characteristics of tissues and cells throughout the whole body of healthy mice versus disease model mice, to elucidate the mechanisms of the onset of disease, and to evaluate its systemic effects. "Getting sick can result in morphological changes in tissues and cells," says Yoshiki. He says that if possible, a morphological comparison of tissues and cells in the whole body between healthy and disease model mice would provide a strong tool for determining the mechanisms of disease and the functions of genes. "For example, an expert on the brain usually uses a mouse [for investigations] and

Figure 1: **Cross-sectional view of a mouse taken by three-dimensional internal-structure microscopy**



examines only its brain, but cannot afford to analyze other organs. It takes enormous amounts of time and labor and is hence quite unrealistic for a researcher to extensively examine the whole body." Yokota's technology is groundbreaking because of its capability for generating images of the internal structure of the whole body in real colors at micrometer resolution in a short time. According to Yoshiki, computer-based comparisons of the whole body would provide a new approach to explaining the mechanisms of pathogenesis.

Yoshiki says that digitalization of morphological information is also important from the viewpoint of animal welfare. The Law for the Humane Treatment and Management of Animals as amended came into force in June 2006. "The older law was amended to include new provisions in view of research methods that can be used as substitutes for animal experimentation and reductions in the number of laboratory animals used," he says. In animal experiments, anatomical knowledge of the animals used is essential. He adds, "If an atlas of standard mouse anatomy were available on a computer before the start of experiments, the number of animals used would be reduced significantly."

Yoshiki believes that digitized morphological information should also serve as educational material. "In the near future, we would like to make our data of whole-body three-dimensional cross-sectional images of standard mouse strains accessible on our website," he says. "We want to post an anatomical atlas associated with characteristic information on various mouse strains on our website. Through this a broad range of people, from children to adults and experts, would know more about the laboratory mouse as a model animal for studying humans and other animals."

Discovery of Hague mice

In the Experimental Animal Division, many mice are reared and crossed to maintain a collection of strains. In this process, animal-care technicians sometimes find novel phenotypes, which in turn often lead to the discovery of new genes and mutations. Described below is an example of such a case.

"A mutant mouse with curled fur was found," Yoshiki begins. "If this mutation occurs in one of the maternal and paternal genomes, their offspring will have curled fur, that is, this character is dominant. The homozygous individual, which has a pair of genes that both have this mutation, is bald (Fig. 2). Hence, we called this mouse 'Hague' (pronounced 'ha-gue', meaning 'bald-headed' in Japanese). We continued to rear Hague mice and crossed them with ordinary mice. Surprisingly, the young were born not with curled fur, but with ordinary fur. A dramatic change occurred from dominant to recessive."

Yoshiki and his colleagues have shown that the Hague gene is quite a unique mutation, which essentially represents a change in the base-sequence length. "In gene manipulation, the target gene is modified on the basis of a combination of existing pieces of knowledge," he says. "In the Hague mouse, however, an unknown mutation occurred. It is probable that organisms may undergo mutations through yet unknown mechanisms, and these mutations may cause disease and evolution."

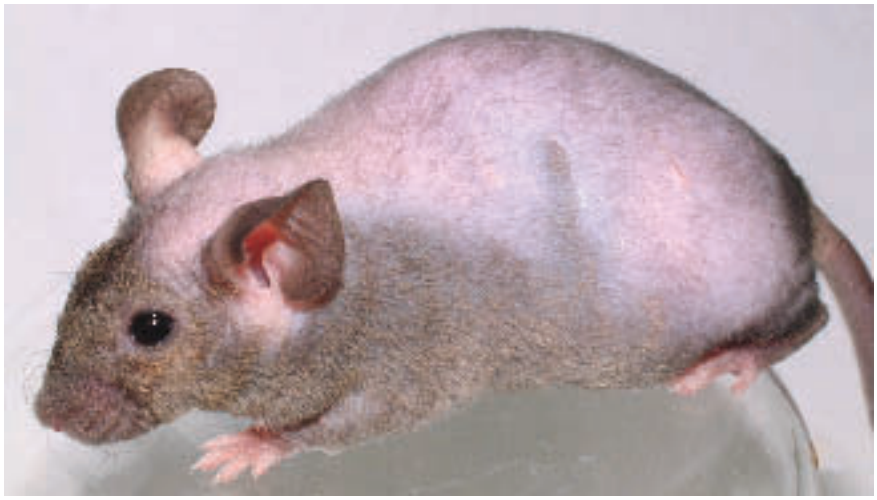


Figure 2: **A Hague mouse**

The Experimental Animal Division will support fundamental research in medicine and the life sciences in the 21st century to aid the achievement of groundbreaking discoveries.

Insight into mice and increased analytical capabilities throw light on as yet unchartered territory in genetic engineering and can lead to the discovery of as yet undocumented mutant mice. ■

Background information:

Japanese Patent, No. 3796623

About the researcher

Atsushi Yoshiki was born in 1961 in Aichi, Japan, and graduated from the School of Agriculture, Nagoya University, in 1985. In 1987, he obtained his masters degree in agricultural science from the same university. Before earning his doctoral degree, he worked from 1991 to 1993 as an instructor in the Department of Dynamic Pathology, at the Research Institute for Neurological Diseases and Geriatrics, Kyoto Prefectural University of Medicine. In 1993, after earning his PhD in agricultural science from Nagoya University, he joined the Life Science Tsukuba Research Center at the RIKEN Tsukuba Institute as a research scientist. In 2001, he became a senior research scientist at the Experimental Animal Division at the RIKEN BioResource Center, and in 2004 he was appointed head of the same division.

Two summer programs are now calling for participants

The RIKEN Brain Science Institute (RIKEN BSI) and the RIKEN Research Center for Allergy and Immunology (RCAI) are now both accepting applicants for a summer program.

RIKEN BSI offers a summer program to train advanced students interested in brain function. Applicants may choose either a two-month laboratory internship in a RIKEN BSI laboratory, or participate in an intensive 11-day lecture course featuring a distinguished international faculty. Those participating in the internship may also enroll in the lecture course.

Typically, around 45 international students are accepted to the Summer Program each year. Attendees have wide-ranging academic backgrounds and are usually enrolled in graduate courses, or have recently embarked on postdoctoral research. However, candidates holding other positions are encouraged to apply.

Attendee accommodation is usually provided on the RIKEN Wako campus, where there is ample opportunity to interact with invited lecturers, other attendees and RIKEN BSI researchers. Students unable to provide their own financial support will be considered for travel and accommodation bursaries provided by RIKEN BSI.

The RCAI International Summer Program aims to provide young scientists with the opportunity to learn about cutting-edge immunology research. The program consists of lectures from internationally distinguished immunologists and poster presentations from each participant. It is open to both talented graduate students and young postdoctoral researchers with lodging and travel expenses fully covered.

Up to 40 participants will be invited to spend a week (from July 20 to July 27) at the RCAI facilities in Yokohama, during which all members will attend the RCAI–BSI International Symposium on Immunology 2007. This lecture course was developed to present both basic concepts as well as state-of-the-art research to promote a better understanding of allergies and immunology.

From the participants, up to ten scientists will remain for an additional week as Summer Interns. During this Summer Internship (from July 30 to August 3), participants will carry out research activities at a specific RCAI laboratory following the summer lecture course.

The deadline for applications for both programs is February 28. For more information, please refer to http://www.brain.riken.go.jp/summer.html or http://web.rcai.riken.jp/risp/.

RIKEN and the Government of India agree to promote a collaboration in science and technology

On December 8, RIKEN and India's Department of Science and Technology (DST) entered into a Memorandum of Understanding, to increase their collaboration in scientific research, especially on genome-related research, including systems biology, and computational science, such as the development of bioinformatic tools. And on December 15, Prime Ministers Manmohan Singh and Shinzo Abe emphasized the research cooperation between RIKEN and DST in a joint statement on Prime Minister Singh's visit to Japan.

RIKEN has laboratories at the Rutherford Appleton Laboratory in the United Kingdom and at both the Brookhaven National Laboratory and the Massachusetts Institute of Technology in the US. Recently RIKEN also set up offices in Singapore and China as part of its active international strategy.

RIKEN research on accelerator science with Raja Ramanna Centre for Advanced Technology, from 1996 to 2001, was the first full-scale collaboration with India. RIKEN has also been collaborating on neuroscience with the National Brain Research Institute since 1999 and with the Indian Institute of Technology since 2002. It has just commenced exchange activities in bioinformatics and computational science with the Indian Institute of Science and the Institute of Genomics and Integrative Biology.

RIKEN hopes that the agreement with DST and the joint statement by the two countries' Prime Ministers will lead to further organized development of research collaboration, and accelerate the pace of progress of this collaboration.

Tsung-Dao Lee won the Gold and Silver Star of the Order of the Rising Sun

On January 15, the Japanese government awarded the Gold and Silver Star of the Order of the Rising Sun to Tsung-Dao Lee, University Professor at Columbia University, Nobel Prize laureate and Director Emeritus of the RIKEN Brookhaven National Laboratory Research Center (RBRC). The government acknowledged his work for years of fostering Japanese researchers and promoting academic exchange between Japan and the US in the field of physics. On receiving the award, Lee noted, "The symbol of this great award resonates deeply with the very existence of my discipline. It was the planetary motion of Mars, Jupiter and other planets around the Sun that guided Galileo and Newton to create the foundation of physics. Thus, for a physicist, it is a true privilege and a double pleasure for me to accept the Order of the Rising Sun, Gold and Silver Star."

The following day, he held a memorial lecture at the Koshiba Hall, the University of Tokyo. He gave a speech on symmetry and asymmetry from a physical point of view, referring to his research on the laws of parity, for which he earned the Nobel Prize. He also talked about the proposed International Linear Collider and noted, "I believe this accelerator would be an indispensable tool to clarify symmetry in particle physics."

At the banquet after the lecture, he first of all expressed his thanks for the award of the order and said, "This order was given to all the people who have contributed to the construction and development of RBRC." He held the RBRC in high esteem saying, "RBRC is an outstanding international research institute that has allowed young researchers the opportunity to develop their skills. It owns QCDSP, a supercomputer constructed for studying quantum chromodynamics and winner of the Gordon Bell Prize, and QCDOC, an advanced version of QCDSP. The researchers at RBRC also have access to the Relativistic Heavy Ion Collider, developed by Brookhaven National Laboratory (BNL). Blessed with these excellent facilities, RBRC research activities can maintain an internationally first-class standard." He closed his speech wishing that Japan and China could establish a prime international research institution similar to RBRC in the near future.

On the same day, RIKEN and BNL decided to extend the research collaboration agreement, including RBRC research activities, for another five years, and RIKEN President Ryoji Noyori and Samuel Aronson, BNL laboratory director, signed a statement of mutual agreement.

President Noyori (left) and T. D. Lee (right)

Getting ahead in neuroscience

The Brain Science Institute leads the way with a competitive research environment and a diversity of talent

In the 1970s, the exciting and challenging field of brain science drew scientists from various backgrounds to pioneer new cross-disciplinary research. In Japan, the focus of brain research is largely at RIKEN's Brain Science Institute (BSI), which has grown into one of the world's largest and most competitive neuroscience bodies just 10 years after it was established in 1997.

In the US and Europe, government support for neuroscience research expanded throughout the 1980s and 1990s. Around that time, Japanese policymakers also recognized the importance of brain science, but neuroscientists were exasperated at their slowness to take action—even after the US embarked on the 'Decade of the Brain' in 1990 to provide generous support for neuroscience. In 1993, some of these researchers voluntarily organized an annual symposium called 'the Century of the Brain' to educate the public and solicit their understanding.

In April 1996, Masao Ito, a neuroscientist at RIKEN submitted to the government a recommendation on the promotion of neuroscience. Four months later, Ito and members of a government study group compiled a report and proposed Japan inject as much as 2 trillion yen into neuroscience over the next 20 years. The group recommended setting long-term goals, and called for the establishment of a large brain research institute with three main research themes—understanding the brain, protecting the brain and creating the brain. A fourth theme, nurturing the brain, was added in 2003.

Neuroscience research at RIKEN actually started as special projects back in 1977. In 1986, RIKEN founded the Frontier Research System, in which three research teams—dedicated to neuroscience—were first established two years later. In the early 1990s, brain science research gathered momentum within RIKEN such that 10 brain research teams had formed by 1996. Then, following Ito's lead, RIKEN submitted a budget request to create the BSI. In 1997, the BSI was founded to realize 20-year strategic goals (Fig. 1).

The BSI took a new approach to make it internationally competitive. First, it employed all researchers on a contract basis, not lifetime employment, and only those who passed strict evaluation had their contracts renewed. This system was effective to garner young, capable researchers from around the world. The BSI also aimed to employ 30% of its researchers from abroad. Currently, the number is slightly below target, but the nationality base of researchers is diversifying and about one-fifth of the team leaders are non-Japanese. Moreover, international collaboration has been notable. For example, the BSI and the group led by Susumu Tonegawa at the Massachusetts Institute of Technology set up a joint research center in 1998[1].

Figure 1: The BSI has been contributing to boosting Japan's brain science research effort over the past 10 years.

To make the institute progressive and improve management skills, group directors at the BSI have held discussions to decide internal protocols and implemented recommendations of the advisory council. The BSI also initiated stimulating and valuable activities: it holds an annual retreat, hears seminars given by guest lecturers almost weekly, and organizes a summer school for students from around the world to introduce the appeal of cutting-edge neuroscience.

The BSI has developed rapidly to become a large institute with more than 50 laboratories and units and more than 500 staffers. Its researchers publish more than 300 original papers related to neuroscience every year. Meanwhile, since its establishment, the BSI has obtained more than 350 patents, including one for the development of fluorescent proteins that are useful to mark targeted genes and cells.

Researchers at the BSI are aiming to maintain their innovative research approach and continue to differentiate their institute from rival institutes in the US and Europe. ■

1. Promoting brain science research through Japan–US collaboration. *RIKEN RESEARCH*, **1** (4), 9–10 (2006).

For more details, please refer to http://www.brain.riken.go.jp/index.

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