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Unnatural born killers

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Mapping state lines

A network of filamentary conducting paths is behind the transition between insulating and conducting states in complex oxides

When water freezes or boils, its atomic structure undergoes a phase transition in response to temperature change. Phase transitions are common in nature, and have been exploited to make devices such as digital memories. Complex oxides, which involve multiple cationic elements that enable fine tuning of properties, exhibit a particularly rich set of phase transitions because electrons in these materials are correlated with each other, leading to collective behavior and complex self-organized patterns. Some phase transitions in complex oxides, including one called 'colossal magnetoresistance', can lead to drastic changes in conductivity and magnetism, with potential application to computing devices. However, the mechanisms behind these transitions remain imperfectly understood. Now, Masashi Kawasaki of the RIKEN Advanced Science Institute, Wako, Zhi-Xun Shen of Stanford University, USA, and their colleagues have produced unprecedented images of an important phase transition in a thin film made from the complex oxide, manganite[1].

Colossal transition under the microscope

The transition in question is characterized by an increase in the manganite film conductivity by a factor of 10,000 on application of a magnetic field at low temperature, and is an example of colossal magnetoresistance. The resulting transition has been previously characterized in terms of local magnetization, atomic displacement and density of available electronic states. A microscopic and spatially resolved picture of the film conductivity during the transition, however, has proven elusive. This is partly due to the difficulty of measuring large resistivity changes under extreme temperatures and magnetic fields and to the requirement for high-quality films with atomically flat surfaces and distinct phase transition behavior.

Kawasaki, Shen and colleagues solved the first problem by constructing a microwave impedance microscope able to operate over a wide range of temperatures and magnetic fields, but with internal shielding to prevent these conditions from interfering with the measurement. Their microscope works by passing a fine tip over the surface of the manganite film while applying microwave-frequency electrical excitation. This allows it to distinguish between conducting and insulating portions of the film even if they are structurally identical. In addition, the researchers were able to grow high-quality, single-crystal, thin manganite films by using pulsed-laser deposition, allowing phase transitions to be clearly observed.

Networking is important

This combination of an advanced microscope and high-quality thin film allowed the researchers to map the conductivity across a manganite film as it underwent the transition from low to high conductivity. The onset of the high conductivity state was accompanied by the formation of highly conducting manganite filaments aligned along two crystal axes of the underlying substrate made from the strontium titanium oxide (STO). These filaments, which consisted of a highly conducting metallic-like phase of manganite, began to form at very low magnetic fields, below the strengths required for the phase transition to complete, and grew as the magnetic field increased. At very high fields, the filaments formed an interconnected network across which charges could travel, or 'percolate' (Fig. 1). Using a numerical model of the film as a network of random resistors, the team was able to reproduce the observed phase change behavior, confirming the network's importance.

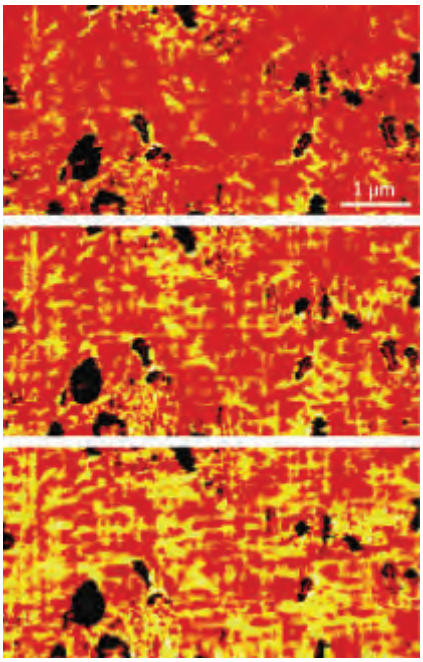

Figure 1: Magnetic impedance microscopy images at magnetic field strengths of 2.4 T (top), 6.6 T (middle) and 9.0 T (bottom) show the growth of self-organized conducting filaments.

When the manganite was switched to its insulating state, and then back to its high-conductivity state, the filaments reappeared in the same locations. According to Kawasaki, Shen and colleagues, this suggests that filament direction was not completely random, but was set by disorder and strain in the film, which result from the boundary between the film's metallic and insulating phases, as well as from strain between the film

Figure 2: A snowflake is the result of self-organized pattern formation over the course of a phase transition from water to ice, similar to the filament formation observed in manganite thin films during the metal-insulator transition.

and the underlying STO substrate. The ordered growth of filaments during the phase transition is reminiscent of the self-organized patterning of snowflakes that accompanies water's phase change from liquid to solid (Fig. 2).

Moving beyond silicon

The observed filament growth represents the first microscopic view of thin film conductivity during the colossal magnetoresistance phase transition, with direct implications for the science in this field. It may also be useful for future 'post-silicon' or 'post-CMOS' electronic devices. "Most proposed post-CMOS devices mimic existing silicon technologies like diodes and transistors," says Kawasaki. "The directional nature of the phase separation that we have observed may allow for a completely new method to process and transfer information." Such a technology would exploit the fact that insulating and metallic phases of the manganite thin film involve different electronic orbitals and can be controlled. Therefore, it may be possible to effectively store information in electron orbitals, rather than in charge quantity or electron spin as is done in other devices. The research team has dubbed this new approach 'orbitronics'.

In fact, Kawasaki notes that the potential to develop radically new electronics devices is what first sparked the RIKEN team's interest in manganite thin films. "We were thinking about using electronic phase separation for future electronics," he explains. "It was a fortuitous meeting with Zhi-Xun Shen at a workshop in Okinawa in 2009 that led to the present work." Shen had been developing a novel microwave impedance microscope at Stanford and was looking for interesting high-quality films to characterize with it. When the RIKEN team presented their manganite thin film and explained its phase separation properties, Shen had what he wanted.

While the new data may have an immediate impact on the colossal magnetoresistance community, Kawasaki says the RIKEN team's original focus on new devices has been well served: "This is a step forwards in a long-term basic research program directed towards creating an entirely new kind of electronics." ■

1. Lai, K., Nakamura, M., Kundhikanjana, W., Kawasaki, M., Tokura, Y., Kelly, M.A. & Shen, Z.-X. Mesoscopic percolating resistance network in a strained manganite thin film. *Science* **329**, 190–193 (2010).

About the researchers

Masashi Kawasaki was born in Osaka, Japan, in 1961. He graduated from the Department of Synthetic Chemistry of The University of Tokyo, in 1984, and obtained his PhD in 1989 from the same university. After two years as a postdoctoral researcher at the IBM Thomas J. Watson Research Center in New York, USA, he returned to Japan to join the Tokyo Institute of Technology as a research associate. He was promoted to associate professor in 1997 and in 2001 moved to the Institute for Materials Research at Tohoku University as a full professor. He was co-assigned as the leader of the Functional Superstructure Team, Cross-Correlated Materials Research Group at RIKEN in 2007. His field of research includes optics, electronics, magnetism and their mutual functionalities at correlated-electron oxide interfaces.

A trick of the light

Unusual properties predicted in superconducting thin films could deliver perfect lenses and other novel applications

All known natural materials have a positive refractive index so that light that crosses from one medium to another gets slightly bent in the direction of propagation. In some artificial 'metamaterial' structures, however, negative refraction occurs such that light gets bent backwards as it enters the structure (Fig. 1). Thin films of high-temperature superconducting materials may achieve a similar effect according to new findings from researchers from the RIKEN Advanced Science Institute in Wako, and colleagues at the Ukrainian and Russian Academies of Sciences and Harvard University[1,2].

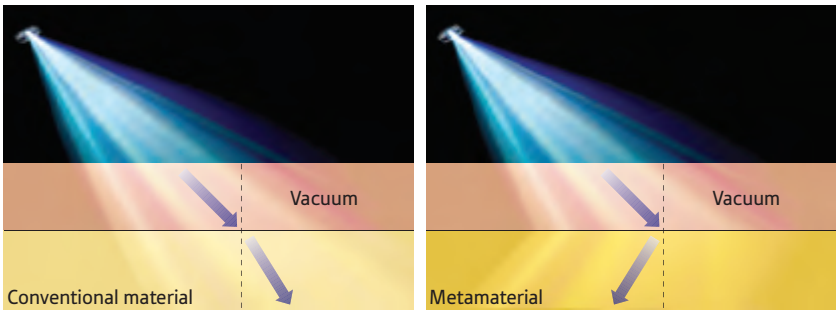

Figure 1: Schematic showing positive refraction (left) and negative refraction (right) of light in two types of materials (yellow). In conventional materials with a positive refractive index, light gets bent toward the normal axis. However, in negative refractive index materials, light gets bent the opposite way.

The realization of metamaterials and their unusual optical properties has enabled a number of novel devices, including 'invisibility cloaks' that can completely conceal an object, as well as perfect lenses that can generate images of an object with arbitrary precision. However, there is a drawback with metamaterials explains Franco Nori from RIKEN and the University of Michigan, USA, who led the research team. "Typically, these metamaterials consist of complex metallic wires and other structures that require sophisticated fabrication technology and are difficult to assemble."

In searching for alternative materials, Nori and his team turned to thin films of high-temperature superconducting materials. These materials crystallize in a pronounced layered structure, where superconductivity occurs only along specific atomic planes of the crystal. Beyond those planes these superconductors are insulating, so their electrical properties differ strongly between horizontal and vertical directions.

The researchers have now revealed how the layered structure of high-temperature superconductors affects the propagation of light. At certain wavelengths, electronic waves are known to be excited at the surface of the superconductor. While the existence of these surface waves is not unexpected, the researchers found that the surface waves cannot exist at some wavelengths in the far infrared (THz) part of the spectrum. "The particularities of the layered superconductor structure mean that, at these wavelengths, the structure shows a negative refractive index," explains Boris Ivanov from RIKEN and the Ukrainian Academy of Sciences.

Although the behavior of these layered superconductors that have a negative refractive index is slightly different to the refractive properties of conventional metamaterials, they do represent a promising alternative to the complex device designs of metamaterials, says Valery Yampol'skii from RIKEN and the Ukrainian Academy of Sciences. Eventually, we may see perfect lenses or even more complex structures such as invisibility cloaks made from natural superconductors rather than from complicated artificial metamaterials, adds Nori. ■

1. Rakhmanov, A.L., Yampol'skii, V.A., Fan, J.A., Capasso, F. & Nori, F. Layered superconductors as negative-refractive-index metamaterials. *Physical Review B* **81**, 075101 (2010).
2. Golick, V.A., Kadygrob, D.V., Yampol'skii, V.A., Rakhmanov, A.L., Ivanov, B.A. & Nori, F. Surface Josephson plasma waves in layered superconductors above the plasma frequency: evidence for a negative index of refraction. *Physical Review Letters* **104**, 187003 (2010).

Nuclear physics incorporates a 'strange' flavor

Calculating the binding energy between hyperon particles contributes to understanding a new type of neutron star

In 2009, physicists from Japan's KEK high-energy proton accelerator announced the sighting of a rare event: an unusually bulky beryllium nucleus that, in addition to four protons and five neutrons, contained two particles called 'hyperons'.

Now, Emiko Hiyama at the RIKEN Nishina Center for Accelerator-Based Science, Wako, and her colleagues from several Japanese universities have presented a calculation that provides the most precise description available of the interactions between nuclei and hyperons in the double-hyperon beryllium nucleus observed at KEK[1].

Hyperons—particles that contain at least one so-called 'strange' quark—exist for less than a billionth of a second before they decay. Scientists know relatively little about how hyperons interact with matter, but speculate that the hot, dense environment of a neutron star would allow these particles to exist in an almost stable state. If they are correct, a hyperon neutron star would be a new state of matter.

According to Hiyama, one of the main interests of hypernuclear physics is to understand interactions between baryons—particles such as protons and neutrons that consist of three quarks—and other particles. "Our study will contribute to understanding such interactions at the core of a neutron star."

Quarks come in six so-called 'flavors': up, down, strange, charm, bottom and top. Only the up and down quarks, which make up the protons and neutrons in atomic nuclei, are stable. High-energy collisions, such as those performed at KEK, are needed to produce the hyperons that contain the more massive strange quark.

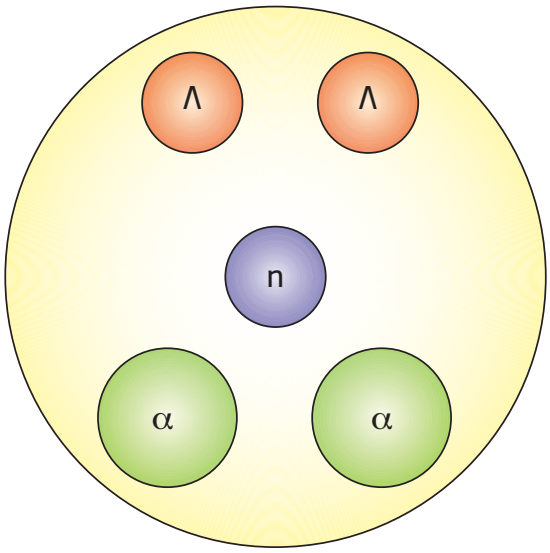

Figure 1: A schematic diagram of a double-hyperon beryllium nucleus. The usual 11 particles of this nucleus have been approximated to two helium nuclei (α), each with two protons and two neutrons, one neutron (n) and two hyperon particles (Λ) to simplify theoretical calculations of their interactions.

Finding the interactions between the eleven particles that constitute the double-hyperon beryllium nucleus is prohibitively difficult. To simplify the calculation of this 'many-body' problem, Hiyama and her colleagues approximated the double-hyperon nucleus as five particles: two helium nuclei, one neutron and the two hyperon particles (Fig. 1). This allowed them to predict the energy that binds the two hyperons together in the nucleus and compare their theoretical results with experimental data. Their calculations indicated that hyperons act to shrink the beryllium nucleus—an unusual effect, since nuclei are normally considered incompressible.

Hiyama's calculations will be an essential tool to understand the attractive forces between hyperons in a neutron star, and will help researchers to analyze experimental results at Japan's new proton accelerator complex, J-PARC, which is expected to produce multiple double-hyperon nuclei.

"At present, the only way to determine the energy of the hypernucleon is to perform these accurate many-body calculations," says Hiyama. ■

1. Hiyama, E., Kamimura, M., Yamamoto, Y. & Motoba, T. Five-body cluster structure of the double-Λ hypernucleus $^{11}_{\Lambda\Lambda}{}^{Be}$. *Physical Review Letters* **104**, 212502 (2010).

Welcome to the family

Modifying a familiar class of dye molecules with optically active carbon rings creates new possibilities for light-based medical therapies

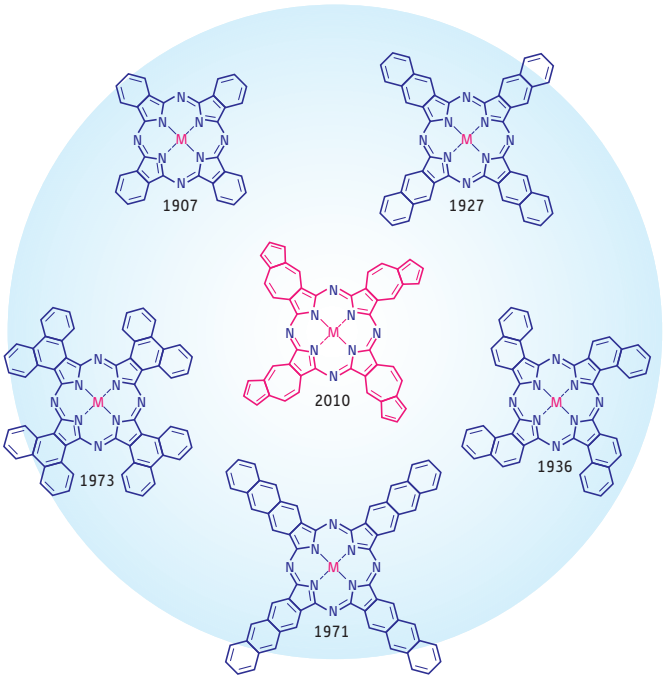

Figure 1: Azuleneocyanines (center) are new members of a historical class of cyclic organic dye molecules with unprecedented activity in the near-infrared spectral region.

A new family of molecules, termed 'azuleneocyanines', that can absorb large amounts of near-infrared light—a critical part of the electromagnetic spectrum—has been synthesized by Atsuya Muranaka, Mitsuhiro Yonehara and Masanobu Uchiyama from the RIKEN Advanced Science Institute in Wako[1]. The work has the potential to advance medical imaging and photodynamic cancer treatments because near-infrared light can penetrate deep into human tissue with little loss of intensity.

The key to the team's approach is a group of large, cyclic organic molecules known as porphyrins. The numerous carbon- and nitrogen-based double bonds found within these molecules make them extremely sensitive to light radiation and therefore intensely colored. Beginning in the early 20th century, chemists began to alter porphyrin structures to create the class of pigments called phthalocyanines (Fig. 1), which have emerged as important dyes owing to their stability under intense heat and light conditions.

Although many phthalocyanines can absorb near-infrared light with wavelengths between 700 and 800 nanometers, prospective medical applications require dye compounds with enhanced activity in the 700–1100 nanometer region—the so-called 'optical window'. To meet this challenge, Muranaka and colleagues synthesized a new dye that incorporates azulene—an aromatic molecule containing fused five- and seven-membered hydrocarbon rings—into the phthalocyanine framework. Azulene's unusual structure gives it unique electron-accepting characteristics that the researchers suspected would lead to an improved dye material.

In their synthesis, the researchers first added cyanide groups to the seven-membered ring of azulene, and then attached two butyl chains to its pentagonal component to improve the product's solubility. Finally, they linked four modified azulene units together to form the cyclic azuleneocyanine complex—a troublesome process, according to Muranaka, because several hard-to-distinguish structural isomers were produced during the cyclization reaction.

The effort required to produce azuleneocyanine paid off when the researchers observed this compound could absorb intense amounts of light in the optical window region—behavior distinct from other phthalocyanines and the azulene precursor. Theoretical calculations revealed that the seven-membered ring of azulene lowered the energy barrier for electron absorption in the complex, leading to the unprecedented near-infrared activity.

While the high stability and strong absorption capabilities of azuleneocyanine promise to be a boon for near-infrared applications, the researchers also take great pride in the discovery and christening of this molecular family. "Chemists have great enthusiasm for naming molecules," says Muranaka, "and it's really exciting for us to name a new class of compounds that we created." ■

1. Muranaka, A., Yonehara, M. & Uchiyama, M. Azuleneocyanine: A new family of phtalocyanines with intense near-IR absorption. *Journal of the American Chemical Society* **132**, 7844–7845 (2010).

Clogging up the plumbing

Vascular development in plants is controlled by a newly identified gene regulator that can block the formation of water-transporting vessels

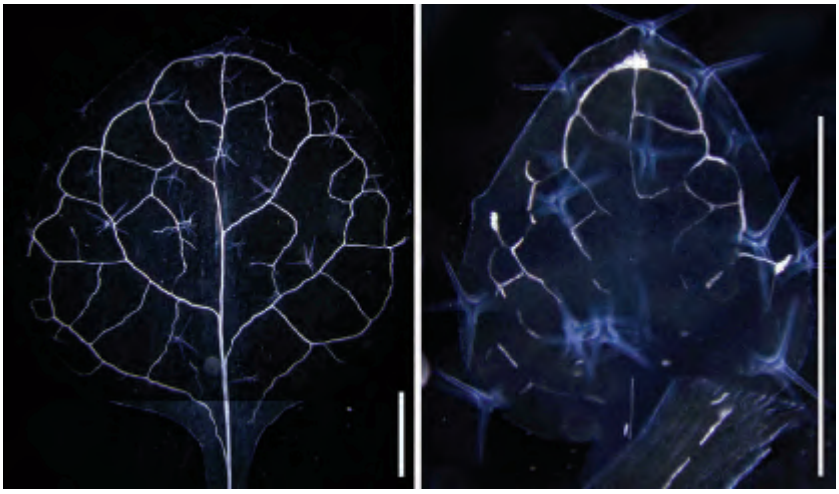

Figure 1: Inappropriately regulated expression of VNI2 causes defects in xylem vessel formation. In 14-day-old control plants, xylem vessel forms continuously (left). In contrast, when expression of VNI2 gene is extended to a later stage of xylem vessel differentiation, vessel formation is severely inhibited (right) (scale bars, 500 micrometers).

Every vascular plant contains an extensive network of xylem and phloem, specialized tissues that respectively transport water and nutrients throughout the plant body. Untangling the processes that determine how these two types of vasculature develop has proven challenging, but a team led by Taku Demura of the RIKEN Biomass Engineering Program in Wako has now uncovered an important novel regulator of xylem formation[1].

Several years ago, Demura and colleagues identified a family of seven VASCULAR-RELATED NAC-DOMAIN (VND) transcription factors; one of these, VND7, appears to activate a number of genes related to xylem development[2]. "The data suggest that VND7 likely functions as the principal regulator of vessel differentiation," Demura says. However, the activity of this factor appears to depend closely on the proteins with which it partners, and his team has subsequently focused on identifying these co-regulators.

In their most recent screen, the researchers identified VNI2, a novel transcriptional regulator that physically interacts with VND7 and whose expression appears to correlate closely with vascular development in both root and stem tissue. However, although both VND7 and VNI2 are categorized as 'NAC domain' proteins, VNI2 exhibited one surprising difference from other members of its family. "It is known that most of the NAC transcription factors are transcriptional activators," says Demura. "In contrast, VNI2 is a transcriptional repressor."

Indeed, VNI2 appears to act primarily as an inhibitor of vascular development (Fig. 1), and plants overexpressing this factor exhibited profound defects in xylem formation. These abnormalities were highly similar to those observed in plants overexpressing modified, inhibitory variants of VND7, further supporting a partnership between these two factors. In parallel, Demura and colleagues determined that VNI2 specifically represses several genes known to be induced by VND7 in the course of xylem differentiation.

These findings indicate that the VNI2–VND7 complex contributes directly to the timing and localization of vascular development, although this is most likely not the sole purpose of this repressor. "Our paper shows that VNI2 is expressed in various other cell types in addition to xylem vessels, and we want to know its other functions," says Demura. Accordingly, their initial protein–protein interaction data suggest that VNI2 might pair with other, non-xylem-specific NAC proteins, whose functional characteristics remain enigmatic.

"We still need to study the *VND* genes [more closely]," says Demura, "for a better understanding of xylem cell differentiation. Since xylem cells are a major source of lignocellulosic biomass, such knowledge could be applied to potential renewable materials and biofuels." ■

1. Yamaguchi, M., Ohtani, M., Mitsuda, N., Kubo, M., Ohme-Takagi, M., Fukuda, H. & Demura, T. VND-INTERACTING2, a NAC domain transcription factor, negatively regulates xylem vessel formation in *Arabidopsis*. *Plant Cell* **22**, 1249–1263 (2010).
2. Kubo, M., Udagawa, M., Nishikubo, N. Horiguchi, G., Yamaguchi, M., Ito, J., Mimura, T., Fukuda, H. & Demura, T. Transcription switches for protoxylem and metaxylem vessel formation. *Genes & Development* **19**, 1855–1860 (2005).

A turning point for young neurons

Inward flow of membrane material is critical for repulsive growth cone turning

During neural development, newborn neurons extend axons toward distant targets then form connections with other cells. This process depends on the growth cone, a dynamic structure at the growing axon tip of the neuron that detects attractive and repulsive guidance cues. Many axon guidance molecules have been identified, and their functions are well characterized, but exactly how they cause growth cone turning has been unclear.

Hiroyuki Kamiguchi of the RIKEN Brain Science Institute, Wako, and his colleagues have now shown that repulsive growth cone turning is driven by a process called endocytosis[1], whereby portions of the growth cone's membrane are removed and internalized.

Endocytosis occurs continuously in all neurons to remove receptors and other membrane proteins for recycling, and to take-up neurotransmitters after their release. It is mediated by a molecule called clathrin, which induces formation of spherical 'pits' in the membrane that are then pulled into the cell.

By tagging clathrin with a fluorescent marker and observing the cells under a microscope, Kamiguchi's group visualized the formation and movements of pits in the growth cones of dorsal root ganglion cells from embryonic chicks. They observed pits appearing at the edges of the growth cones that then migrated towards the center. Pit migration was significantly slowed by blebbistatin, a small molecule that inhibits the motor protein myosin II, which moves a structure called the cytoskeleton towards the growth cone center, suggesting that pits are coupled with cytoskeletal flow.

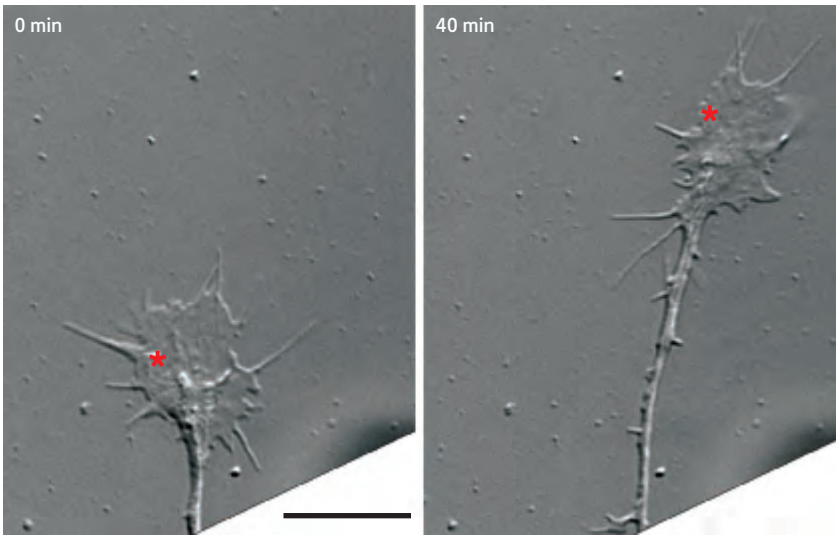

Figure 1: Time-lapse images show repulsive turning in a neuronal growth cone in response to increased calcium ion concentration (asterisk) (scale bar, 10 micrometers).

The researchers then induced localized increases of calcium ion concentrations in the growth cones, mimicking their response to repulsive guidance cues. On the side where calcium was elevated, asymmetrical endocytosis resulted and turned the growth cones the other way (Fig. 1).

When Kamiguchi and colleagues added compounds that inhibit endocytosis, however, they abolished repulsive turning in response to either increased calcium concentration or repulsive axon guidance molecules. In contrast, they showed that inducing asymmetric endocytosis in the absence of guidance cues and localized increases of calcium concentration was sufficient to cause growth cone turning.

They also calculated that endocytosis removes at least 2% of the growth cone membrane every minute, corresponding to 72% of the total surface area during the entire course of turning.

"We now know that repulsive turning depends on asymmetric endocytosis of adhesion molecules from the growth cone surface," says Kamiguchi, "but we think it also requires many other unidentified molecules to be internalized and recycled." The team is conducting large-scale analyses to find them. ■

1. Tojima, T., Itofusa, R. & Kamiguchi, H. Asymmetric clathrin-mediated endocytosis drives repulsive growth cone guidance. *Neuron* **66**, 370–377 (2010).

Gene theft by a parasitic plant

Plant genome evolution requires reassessment with the discovery that parasitic plants can 'steal' nuclear genes from their hosts

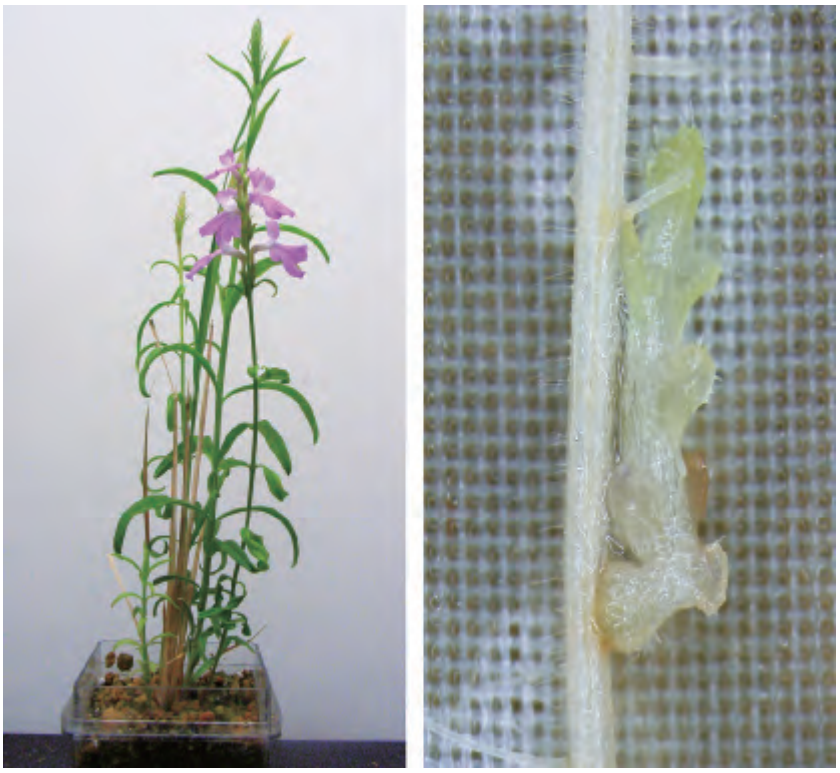

Figure 1: A photograph of flowering purple witchweed, *Striga hermonthica*, parasitizing rice (left), and a magnified photo of an *S. hermonthica* seedling invading a rice root (right).

The exchange of genes between non-mating species—a process known as horizontal gene transfer (HGT)—is common in bacteria but seemed confined to mitochondrial genes in plants. HGT between plants and microbes has also been documented.

Now, a team led by Ken Shirasu of the RIKEN Plant Science Center, Yokohama, has published evidence for nuclear gene transfer between host and parasite plant species[1]. Mitochondrial genes are those of cellular organ-like structures, whereas nuclear genes belong to the cell's nucleus and are therefore part of the plant's main genome.

The findings mean that, in principle, parasitic plants could adapt rapidly by acquiring useful genes from their hosts rather than having to evolve new functions *de novo*—just as today's plant breeders genetically modify crop plants by introducing into them genes for desirable traits, such as disease resistance, from other species.

As a model system, the researchers focused on the flowering plant known as purple witchweed (*Striga hermonthica*; Fig.1); it is a root parasite of sorghum (*Sorghum bicolor*), rice (*Oryza sativa*) and other cereals. The species is a major agricultural menace responsible for devastating crop infestations in subtropical Africa.

Sorghum and rice are members of the grass family. Like all other witchweed hosts, they are monocots, meaning that their seedlings have just one embryonic leaf, or cotyledon. In contrast, the seedlings of witchweed have two cotyledons, making it a dicot. "We reasoned that the discovery of monocot-specific genes in witchweed would provide compelling evidence for the existence of nuclear HGT between host and parasite plant species," says Shirasu.

By screening 17,000 witchweed genes, the researchers identified one gene, *ShContig9483*, similar to genes in sorghum and rice, but not present in parasitic or non-parasitic relatives (eudicots) of witchweed. An evolutionary 'gene tree' built by the researchers, using DNA sequences of *ShContig9483* and related protein-coding genes, revealed that the position of *ShContig9483* in the tree is not consonant with witchweed evolutionary relationships.

"Our analyses indicate that *S. hermonthica* most likely acquired *ShContig9483* from sorghum or a related grass species, and that the transfer event was relatively recent," Shirasu notes. "Although we do not, as yet, know the function of the protein encoded by *ShContig9483*, ours is the first clear evidence of nuclear HGT between host and parasite plant species," he adds.

The researchers believe that other similar cases of nuclear HGT await discovery and that HGT may be a powerful force in plant genome evolution, facilitating rapid adaption through the acquisition of new genes. ■

1. Yoshida, S., Maruyama, S., Nozaki, H. & Shirasu, K. Horizontal gene transfer by the parasitic plant *Striga hermonthica*. *Science* **328**, 1128 (2010).

The long and short of cell signaling

By bolstering a sophisticated computational model with quantitative experimental data, researchers begin to decipher the workings of a complex signaling network

Figure 1: Like dots and dashes from a Morse code transmission, brief and sustained cell signals can have different meanings for cell fate.

Like a telegraph transmission, the significance of a cellular signal can change greatly depending on whether it arrives as a brief 'dot' or a sustained 'dash' (Fig. 1). For example, transient activation of extracellular receptor kinase 1/2 (ERK) by epidermal growth factor (EGF) causes cells to divide, while prolonged ERK activation induced by heregulin (HRG) instructs these same cells to differentiate.

Cell biologists have struggled to untangle the relationship between this signaling network and cell fate, but a collaborative effort between Mariko Okada-Hatakeyama at the RIKEN Center for Allergy and Immunology in Yokohama and Boris Kholodenko at University College Dublin in Ireland has achieved an important breakthrough by pairing quantitative experiments with computational modeling[1].

Okada-Hatakeyama's team previously examined the expression of *c-fos*, a so-called 'immediate early gene' whose expression is induced shortly following ERK activation, and obtained somewhat contradictory findings[2]. "Early gene expression time-course profiles were the same regardless of whether the upstream ERK signal is transient or sustained," she says. "However, levels of c-Fos protein were 'all or none' for sustained and transient signals, respectively."

Based on an initial interpretation of their computational model of this pathway, Okada-Hatakeyama, Kholodenko and colleagues proposed that the effects of both HRG and EGF on *c-fos* expression were modulated purely by dual-specificity phosphatases (DUSPs), enzymes that inhibit ERK's capability to induce *c-fos*. However, experiments with a forced reduction of DUSP in cultured cells did not fully replicate these predictions. "There were long and serious discussions whether our experiment was working properly or the model was wrong," says Okada-Hatakeyama.

This reassessment led to experiments that enabled the researchers to demonstrate the existence of a second, previously unknown mechanism for repression of *c-fos* expression that is triggered only in response to HRG. Together, these two ERK-activated 'negative feedback' systems appropriately control *c-fos* transcription in the process of cellular differentiation.

In parallel, their model also revealed how the combination of ERK-induced *c-fos* expression and sustained signaling activity by ERK outside the nucleus lead to steady production of c-Fos protein. This system architecture results in a highly stable signaling arrangement that filters out extraneous background noise and induces all-or-none output, according to Okada-Hatakeyama. "We learned from this study that cells possess very simple but robust system structures that can fight against unwanted perturbations," she says. "This cellular signaling network is still a 'black box' and what we can do with computational modeling is very much limited… but we hope to untangle the cell decision program someday." ■

1. Nakakuki, T., Birtwistle, M.R., Saeki, Y., Yumoto, N., Ide, K., Nagashima, T., Brusch, L., Ogunnaike, B.A., Okada-Hatakeyama, M. & Kholodenko, B.N. Ligand-specific c-Fos expression emerges from the spatiotemporal control of ErbB network dynamics. *Cell* **141**, 884–896 (2010).

1. Nagashima, T., Shimodaira, H., Ide, K., Nakakuki, T., Tani, Y., Takahashi, K., Yumoto, N., & Hatakeyama, M. Quantitative transcriptional control of ErbB receptor signaling undergoes graded to biphasic response for cell differentiation. *The Journal of Biological Chemistry* **282**, 4045–4056 (2007).

Creating a life-saving killer

Cancer may be kept in check by a method for generating patient-specific immune cells with antitumor activity

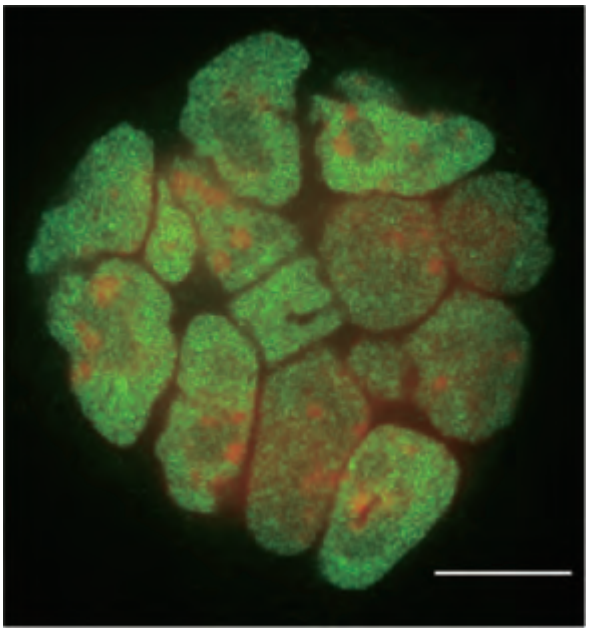

Figure 1: A cluster of undifferentiated iPSCs derived from reprogrammed NKTs with high expression levels of the Oct3/4 pluripotency factors (red fluorescence) (scale bar, 10 micrometers).

Upon receiving the appropriate activating signal, natural killer T (NKT) cells live up to their name, releasing a torrent of molecules that trigger the protective immune response necessary to eliminate pathogens or even thwart tumor growth.

These cells represent a promising clinical tool, as demonstrated in a recent clinical trial in which lung cancer patients received NKT-stimulating injections of dendritic cells that had been pretreated with α-galactosylceramide (α-GalCer)[1]. Some 60% of treated patients exhibited a striking seven-fold improvement in their median survival time relative to their untreated counterparts. "The effects are superior to other molecular-targeted cancer drugs," says Masaru Taniguchi of the RIKEN Research Center for Allergy and Immunology (RCAI), Yokohama, whose team participated in this study. "However, this therapy is not applicable to two-thirds of patients because of their limited number of NKT cells."

To solve this problem, Taniguchi teamed up with RCAI colleague Haruhiko Koseki to develop a method for generating transplantable NKTs[2]. They derived these from induced pluripotent stem cells (iPSCs), embryonic-like cells that are typically generated via virus-mediated delivery of 'reprogramming genes' into skin cells. However, NKT maturation involves a complex genomic rearrangement event, making them difficult to derive from conventional iPSCs. As such, Taniguchi and Koseki devised a novel approach for generating mouse iPSCs from existing NKTs (Fig. 1), which have already undergone this rearrangement. They used these iPSCs to generate large numbers of new NKTs *in vitro*.

Their method efficiently produced mature NKTs, which rapidly established a stable population within the liver upon transplantation into mice. To the researchers' pleasant surprise, these new NKTs displayed typical activation behavior in response to α-GalCer-treated dendritic cells and proved capable of coordinating an effective immune response. "In general, cells generated from *in vitro* culture die quickly *in vivo* or are killed by host immune cells … however, this was not the case here," says Taniguchi. "We detected iPSC-derived NKT cells with adjuvant activity and tumor-eradicating effects two weeks after cell transfer."

Taniguchi, Koseki and colleagues are now keen to begin working with human cells. This transition will involve many new challenges, but the researchers see great clinical potential in their approach—particularly in the US, where the Food and Drug Administration has approved development of cell-based therapies. "NKT cell-targeted adjuvant cell therapy is applicable [to] any type of cancer patient, because it can overcome [their] immunodeficient status and enhances antitumor responses," says Taniguchi. "At present, the delivery of patient dendritic cells is the main limiting factor." ■

1. Motohashi, S., Nagato, K., Kunii, N., Yamamoto, H., Yamasaki, K., Okita, K., Hanaoka, H., Shimizu, N., Suzuki, M., Yoshino, I., *et al.* A phase I-II study of alpha-galactosylceramide-pulsed IL-2/GM-CSF-cultured peripheral blood mononuclear cells in patients with advanced and recurrent non-small cell lung cancer. *Journal of Immunology* **182**, 2492–2501 (2009).
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Intercepting inflammation

Genetic data help scientists close in on the immunological malfunctions underlying a mysterious pediatric disorder

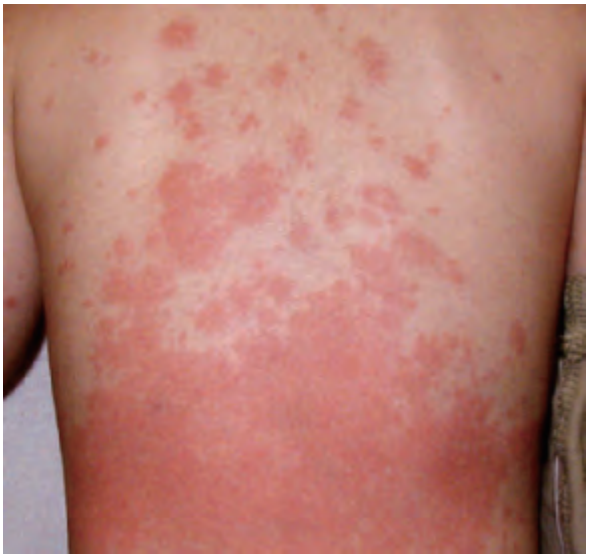

Figure 1: Skin rash is a typical symptom for children affected by Kawasaki disease, but this disorder is also associated with much more serious effects, including elevated risk of a potentially fatal coronary artery aneurysm.

Scientists and doctors continue to find themselves baffled by Kawasaki disease (KD), an inflammatory disorder that represents the leading cause of pediatric heart problems in the developed world (Fig. 1). "The cause of KD has remained unknown for more than 40 years since the first description of the disease by Dr. Kawasaki, and so there is no evidence-based therapeutic strategy," says Yoshihiro Onouchi of the RIKEN Center for Genomic Medicine in Yokohama.

Onouchi has partnered with other scientists in Japan and the United States to identify chromosomal regions containing genes potentially associated with this condition, uncovering strong evidence that KD arises in part from improper regulation of the immune system. Based on this hypothesis, he and his colleagues recently examined loci within chromosomal region 4q35, which contains a diverse array of genes relevant to this process[1].

The researchers were especially interested in the gene encoding caspase-3 (*CASP3*), an enzyme that participates in the initiation of programmed cell death and thereby helps to mitigate the extent of T cell-mediated immune responses. By comparing data from a cohort of Japanese individuals affected with KD relative to their unaffected counterparts, they were able to identify more than two dozen sequence variations near *CASP3* that appear to preferentially associate with disease onset.

Functional analysis of the gene revealed the presence of an 'enhancer', a stretch of DNA where regulatory proteins can bind to help ratchet up expression levels, surrounding one of the variants identified in this initial screen. The researchers determined that the genomic sequence alteration linked with KD appears to impair enhancer binding by the transcriptional regulator nuclear factor of activated T cells (NFAT), and this reduced NFAT binding in turn leads to significantly reduced *CASP3* expression. Importantly, this variant is also significantly associated with disease susceptibility in European populations.

Onouchi and colleagues have previously identified another KD-associated variation (or SNP) in the gene encoding inositol 1,4,5-trisphosphate 3 kinase-C (*ITPKC*), an enzyme that downregulates a T cell signaling cascade in which calcium ion (Ca^{2+}) flux is coupled with NFAT activation[2]. In combination, these findings suggest that NFAT may offer a promising drug target. "The calcineurin enzyme plays a key role in the Ca^{2+}/NFAT pathway, and we are now interested in the potential of calcineurin inhibitors like cyclosporin A as a therapeutic option," says Onouchi. "Our team is now collaborating with several medical institutes in Japan in an attempt to evaluate the effectiveness of cyclosporin A on refractory KD cases." ■

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Bright lights for live cells

Surface-selective fluorescent labeling enables cell tracking in the body while preserving initial cell function

Chemical reactions that create durable bonds between cells and fluorescent dyes are an attractive way to monitor biological functions in the body. However, they can also detrimentally modify key chemical groups on cell surfaces. Chemically binding fluorescent dyes to cells—with minimal impact on their original function—is now possible, thanks to a site-selective reaction developed by a team led by Yasuyoshi Watanabe and Tsuyoshi Tahara from the RIKEN Center for Molecular Imaging Science, Kobe[1].

Working closely with Katsunori Tanaka and Koichi Fukase from Osaka University, the researchers decided to use organic compounds called aldehydes as dye precursors as they readily react with nitrogen-containing functionalities, or amino groups, exposed at protein surfaces.

To assess the efficacy of their method, the team mixed the aldehydes with brain cancer cells *in vitro* for 10 minutes then compared them with typical amino reactive dye precursors known as succinimidyl esters (NHS) (Fig. 1). They discovered that the aldehyde precursors produced brighter fluorescence than the NHS dyes.

Confocal microscopy showed that the aldehydes reacted with amino groups of lysine amino acid residues on the cell surface and those of other cell membrane components, whereas the NHS dyes penetrated the cells. They confirmed this by treating the labeled cells with detergent: the aldehyde-derived labels washed off the cell surface, whereas their NHS counterparts remained in the cells. The aldehyde-derived labels also remained effective at exceptionally low concentrations, unlike the NHS-derived labels.

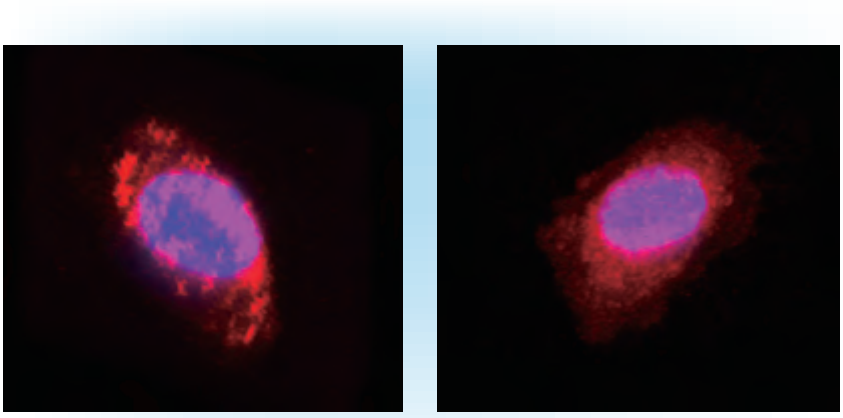

Figure 1: Confocal microscopy images of a brain cancer cell labeled using aldehydes (left) and succinimidyl esters (right) as fluorescent dye precursors. Nuclei are shown in blue.

"In contrast to pre-existing cell labeling protocols, this reaction tightly anchors the labels to the surface of living cells within 10 minutes at 10 nM [dye] concentrations and with a very simple 'kit-like' operation," say Watanabe and Tahara. The team also observed that the brain cells maintained their ability to undergo cell division after labeling because of the mild reaction conditions.

The researchers also labeled lymphocytes, extracted from mice, with the fluorescent dyes and injected them into live mice for *in vivo* monitoring. They found that the labels clearly highlighted the trafficking of the cells into the organs of the mouse immune system. In particular, they noted that the cells gradually accumulated in the spleen and intestinal lymph nodes in six hours before disappearing from the spleen.

In addition to investigating potential clinical applications, the team is currently planning to apply their method to the synthesis of metal binding labels to introduce radioactive and magnetic properties into cells for imaging techniques such as positron emission tomography and magnetic resonance imaging. ■

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Exploring the mysteries of atom nuclei at RIKEN's Radioactive Isotope Beam Factory

Tohru Motobayashi

Team Leader, SAMURAI Team
Coordinator, Research Instrument Group
RIBF Research Division
RIKEN Nishina Center for Accelerator-Based Science

Atomic nuclei come in various shapes, from the commonly imagined spheres to shapes more akin to rugby balls or mandarins. It is generally understood that the number of protons and neutrons determines whether a nucleus will be spherical or non-spherical. With the successful creation of short-lived unstable nuclei, however, scientists have found that certain nuclei predicted to be spherical by the conventional theory are often quite non-spherical. "Theoretically, there are about 10,000 different atomic nuclei, but less than one-third of these have been studied. There may be many interesting and strongly deformed atomic nuclei. Creating and investigating nuclei that have never been seen before will surely contribute to our understanding of the atomic nucleus," says Tohru Motobayashi from the RIKEN Nishina Center for Accelerator-Based Science in Wako, Japan. Motobayashi is using the center's Radioactive Isotope Beam Factory (RIBF) to elucidate the shapes and properties of atomic nuclei, obtaining remarkable insights into how elements are created. The RIBF, a next-generation heavy-ion accelerator research facility, is capable of creating an intense beam of any of about 4,000 unstable nuclei, making it one of the world's most useful tools for nuclear studies.

The RIBF, creating a thousand new radioisotopes

Motobayashi's work is predominantly with the RIBF, which went into full-scale operation in 2007. The RIBF includes linear accelerators, ring cyclotrons, radioisotope beam generation and separation facilities and other experimental instruments (Fig. 1). The superconducting ring cyclotron (SRC) at the heart of the RIBF is 18 meters in diameter and weighs 8,300 tons. "What we are studying in this large-scale facility is atomic nuclei with diameters of just several femtometers. With the RIBF, we are creating a lot of unstable nuclei and studying their shapes and properties, which allows us to elucidate how elements are synthesized," he says.

All matter consists of atoms, which in turn consist of an atomic nucleus and electrons, and the atomic nucleus itself is comprised of protons and neutrons. The element represented by an atom is determined by the number of protons, and there are about 90 naturally occurring elements, from hydrogen with one proton to uranium with 92. Each element, however, can have multiple 'isotopes'—atoms with the same number of protons but different numbers of neutrons. Including the isotopes, about 300 stable atoms are found in nature. Including unstable isotopes, however, there are about 10,000 in total. Most of the unstable isotopes are not found in nature because they quickly decay into one of the stable forms. "The difference between the numbers of protons and neutrons in stable nuclei is not very large. We are studying unstable nuclei, particularly those with many more neutrons than protons. The RIBF allows us to create and study unstable nuclei that differ considerably from stable nuclei."

In the RIBF, ions of various elements are accelerated in stages up to 70% of the speed of light and bombarded against target nuclei. The collisions strip off protons and neutrons to produce various unstable nuclei, which are then separated into a beam line and subject to analysis. With the help of numerous instruments installed on the beam lines, scientists can determine the shape, mass, lifetime and other properties of the nuclei. Although such experiments using radioisotope beams have been conducted since the 1980s,

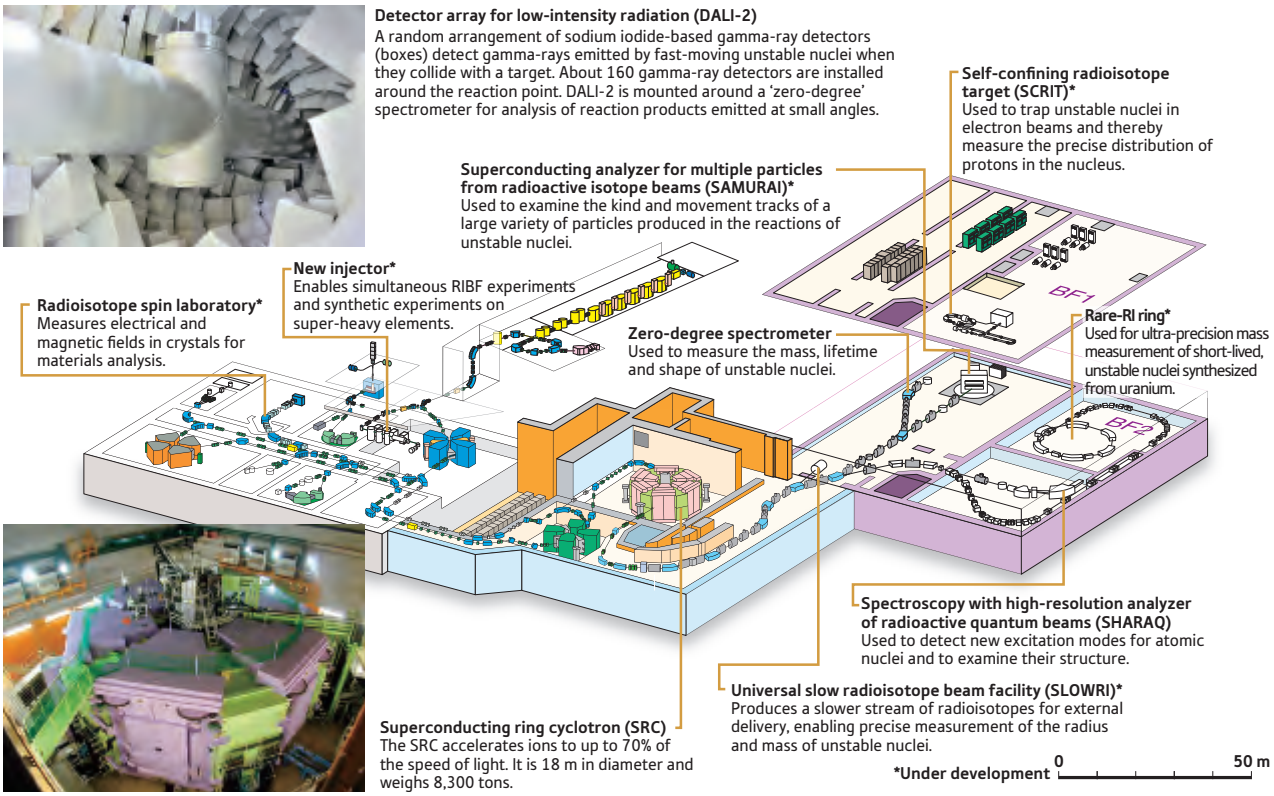


Figure 1: Experimental facilities and infrastructure of the RIBF.

previous facilities have only been able to create about 3,000 different atomic nuclei. The RIBF, which can accelerate a wider range of starting elements from hydrogen to uranium, is expected to make it possible to create 1,000 new types of unstable nuclei that have never been observed before (Fig. 2).

Disappearance of the magic number in neutron-rich nuclei

The interest in neutron-rich nuclei originates from a discovery in 1995 by a RIKEN team including Motobayashi that the nucleus of magnesium-32 (^{32}Mg) was significantly deformed from the expected spherical shape. Magnesium has 12 protons and normally 12 neutrons. The ^{32}Mg isotope with mass number of 32 (total number of protons and neutrons) has an extra eight neutrons, making it particularly neutron rich, and the discovery of deformation in such an isotope attracted a great deal of public attention. "Atomic nuclei were generally regarded as uniform mixtures of protons and neutrons. However, as scientists began to create neutron-rich nuclei in experiments, they discovered that certain unstable atomic nuclei can have characteristics remarkably different from those for stable nuclei. For example, in 'neutron halo' nuclei, the neutrons are localized around the rim of the nucleus. Even so, the deformation of ^{32}Mg was still quite unexpected," says Motobayashi.

Just as electrons orbit around the nucleus of an atom, neutrons and protons move around in orbits within the nucleus itself. There are multiple nuclear orbits, and each can hold up to a certain number of neutrons or protons. An atomic nucleus is spherical and particularly stable when one of its orbits is fully filled with neutrons or protons, and the number of neutrons or protons in a filled orbit is known as the 'magic number': 2, 8, 20, 28, 50, 82 and 126. "The atomic nucleus of ^{32}Mg was found to be deformed even though it has a magic neutron number of 20. This discovery was referred to as 'the disappearance of magic numbers' and was much discussed among scientists. The experiment with ^{32}Mg was our first neutron-rich nucleus experiment.

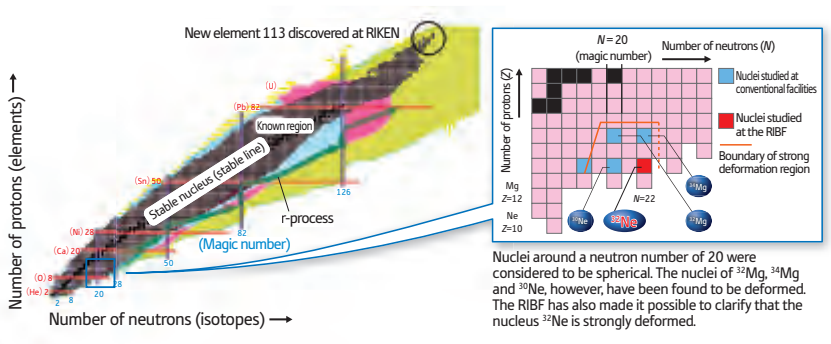


Figure 2: Nuclear chart and strong deformation region for atomic nuclei.
A nuclear chart showing atomic nuclei in terms of the numbers of protons and neutrons. Theoretically, there are about 10,000 different atomic nuclei. The RIBF is capable of creating about 4,000 different unstable nuclei, and allows the process of element synthesis to be verified through the artificial creation of unstable nuclei thought to have been produced by supernovae.

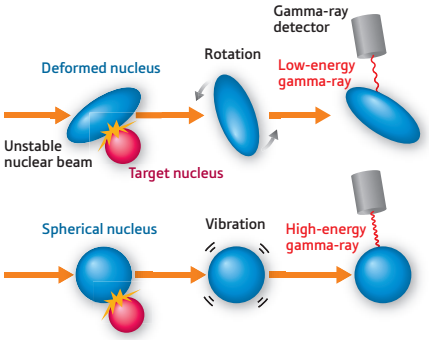


Figure 3: Experimental principle for determining the shape of a nucleus.
When a beam of unstable nuclei collides with a target nucleus, a nuclear reaction occurs that excites and rotates the unstable nuclei. The excited nuclei emit gamma-rays as they return to their original state. The more deformed a nucleus from spherical, the slower the rotational speed, and the lower the energy of the emitted gamma-rays.

Our findings could be attributed to beginner's luck, but it motivated me to delve into the study of neutron-rich nuclei, which I found very interesting," says Motobayashi.

Later, the atomic nuclei of neon-30 (^{30}Ne, 20 neutrons) and magnesium 34 (^{34}Mg, 22 neutrons), both with ten extra neutrons, were also found to be deformed, prompting scientists to start paying attention to atomic nuclei with mass numbers of around 30 and neutron numbers around 20, which appeared to be considerably deformed (Fig. 2). "Understanding why these nuclei are deformed requires investigation of other unstable nuclei in the high-deformation region. However, these nuclei are so unstable that they are extremely difficult to generate. Conventional accelerators failed to create adequate amounts of such unstable nuclei, forcing scientists to turn to the RIBF for this research."

The rugby ball-shaped atomic nucleus of ^{32}Ne

As soon as the RIBF went into operation in 2007, an experiment was conducted to create new unstable nuclei by accelerating and splitting the atomic nucleus of uranium. This experiment resulted in the successful creation of palladium-125 (^{125}Pd) and -126 (^{126}Pd) as the first fruits of the RIBF. Scientists also started experiments to investigate the properties of a range of unstable nuclei. The first target was the nucleus of neon-32 (^{32}Ne), which consists of ten protons and 22 neutrons. To produce ^{32}Ne, the scientists accelerated ions of calcium-48 (^{48}Ca) and bombarded them into a beryllium (Be) target to strip protons and neutrons from the ^{48}Ca nucleus, resulting in various unstable nuclei. The ^{32}Ne nuclei were then separated from the population of nuclei and collated into a beam, which was then used to investigate the shape of the atomic nucleus.

"We can estimate the shape of an atomic nucleus by rotating it," explains Motobayashi (Fig. 3). "When we bombard a carbon target with the ^{32}Ne beam, nuclear interactions can occur that excite and rotate the ^{32}Ne nuclei. The excited nuclei emit gamma-rays as they rotate back and return to their original unexcited state. The larger the deformation of the nuclei, the slower the rotational speed and the lower the energy of the emitted gamma-rays. In this way, we can study the shape of the nuclei by measuring the energy of the gamma-rays using a gamma-ray detector. We found that the energy of gamma-rays was significantly lower than expected for ^{32}Ne, proving that the nuclei are considerably deformed from spherical. A report on this finding was published in July 2009." The deformation of ^{32}Ne was the largest ever observed for neon isotopes (Fig. 4). It was also found that the larger the neutron number in this region, the greater the deformation.

The gamma-ray detector used to determine the shape of ^{32}Ne, called the detector array for low-intensity radiation or DALI-2, was developed under the leadership of Motobayashi. Determining the energy of gamma-rays accurately is not easy because the gamma-ray emission of fast-moving particles, such as the unstable nuclei generated by the RIBF, which move at about 60% of the speed of light, increases in energy if the particles are moving toward the detector, and decreases in energy when they are moving away from the detector. This is known as the Doppler effect, and to deal with it accurately, DALI-2 has about 160 detectors installed around the reaction point. "It seems like the detectors are arranged at random, and that's exactly what we intended," says Motobayashi with a smile. "If you do the calculations, you can arrange the detectors in strict pentagonal or hexagonal arrays. But once set, it is not possible to rearrange the detectors for a new experiment. With the random arrangement, we can easily change the location of each detector, making it a very flexible configuration. We can hold discussions on how to improve the measuring methods, and we can learn even from mistakes. This approaches help to yield new discoveries."

Using the RIBF, the ^{32}Ne experiment took only about eight hours, much faster than expected. "The RIBF successfully provided a thousand times the number of nuclei as anticipated. That's a good misjudgment, because we were prepared to spend at least half a year on the experiment," says Motobayashi.

One possible explanation for the severe deformation of ^{32}Ne is an effect known as 'orbital inversion', by which neutrons reverse their usual ordering from lower- to higher-energy orbits. This results in neutrons populating higher-energy orbits even when lower-energy orbitals are not fully filled. The region in the nuclear chart where this phenomenon is observed is also known as 'the island of inversion'. "The energy of gamma-rays observed through the ^{32}Ne experiment cannot be explained without the concept of orbital inversion or the assumption of two nuclear orbits that are extremely close to each other. We expect to be able to understand the causes of the strong deformation of atomic nuclei by taking advantage of the RIBF to investigate unstable nuclei in the island of inversion and adjacent regions."

Motobayashi points out that a future challenge is how to distinguish the roles of protons and neutrons. The energy of gamma-rays merely provides information related to the shape of the

atomic nucleus, which consists of both protons and neutrons. It is possible to determine the behavior of protons in an atomic nucleus by measuring the lifetime of the excited state, by bombarding it with electrons, or by using the 'Coulomb excitation' method, which was used in the discovery of ^{32}Mg nuclear deformation. However, there remains no effective method to clarify the distribution of neutrons. Motobayashi is now working on a method in which unstable nuclei are bombarded into a solid or liquid hydrogen target. "The hydrogen nucleus consists of a single proton. As protons can have a strong effect on neutrons in atomic nuclei, we should be able to clarify the behavior of neutrons by bombarding hydrogen with the unstable nuclei. We have started experiments using liquid hydrogen targets, and we are now producing results including the finding that ^{32}Mg is 'softly' deformed," says Motobayashi. The atomic nucleus of ^{32}Mg is now known to look like a rugby ball, but its shape is not fixed, and is in fact quite flexible. Studies are now being conducted to clarify the details.

Exploring the 'island of inversion' as one of the mysteries of elemental synthesis

"I want to find out whether there are other islands of inversion in the nuclear chart. I am particularly interested in the regions adjacent to magic numbers 28 and 50. This study is also related to element synthesis, another subject of research in our team."

Among the naturally occurring elements, hydrogen, helium and lithium were created immediately following the Big Bang, while other elements up to the atomic number of iron were created through nuclear reactions in stars. About half of the heavier elements, from iron to uranium, are considered to have been created in a period of just one second by supernovae at the end of the life of massive stars. A leading hypothesis that explains elemental synthesis is the theory of rapid neutron-capture, known as the 'r-process', by which atomic nuclei rapidly absorbed neutrons at a high temperature and pressure driving the continuous creation of unstable nuclei, which then decayed into stable nuclei. However, no solid evidence for this theory has been found as yet (Fig. 2). "We plan to create the world's first unstable nuclei that are considered to have been created through the r-process, and attempt to ascertain the facts by reproducing the elemental synthesis process. At present, the RIBF is the only available facility that can serve this purpose. In this study, the role of magic numbers is very important. I am interested in how the island of inversion affects the nucleosynthesis process." The team has already started conducting experiments to create some of the unstable nuclei that may been created through the r-process and to investigate their lifetimes.

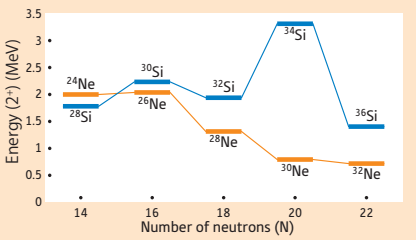


Figure 4: Nuclear deformation in neutron-rich neon isotopes.
The relationship between the number of neutrons and the energy of gamma-rays emitted as the excited nuclei return to their original state provides information on the shape of the nucleus. A neutron number of 20 is a magic number, and the energy emitted from nuclei with N = 20 should be as high as that for ^{34}Si, which is a known spherical nucleus. The low energy for ^{30}Ne shows that the nucleus is deformed from spherical. The nucleus of ^{32}Ne is even more deformed, as indicated by the lower energy compared to ^{30}Ne.

The RIBF evolves

Along with experiments, RIKEN is also promoting the design and development of new instrumentation (see Fig. 1). A typical example is the 'Rare-RI' ring, which is capable of measuring the mass of single short-lived unstable nuclei that may have been produced by the r-process. "Measuring the mass of each nucleus is based on RIKEN's unique idea that no unstable nuclei should be wasted because they are precious."

Motobayashi is leading the development of another instrument called SAMURAI, a superconductiing analyzer for multiple particles from radioisotope beams, which is due to be completed in 2011. "This instrument will enable accurate, simultaneous and wide-ranging measurements of multiple particles created by the reaction of unstable nuclei in terms of type, energy and movement tracks in all directions. SAMURAI will promote our understanding of the atomic nucleus and help elucidate the origins of elements. It will also contribute to the establishment of a new nuclear theory that could explain the behavior of both stable and unstable nuclei."

The RIBF is attracting the attention of nuclear researchers around the world, and the number of inquiries from researchers who want to use the RIBF for experiments is increasing rapidly. The team is planning to accept experimental ideas using SAMURAI on an international basis. Of course, Motobayashi also has his own ideas for using the instrument. "You won't want to miss it," he says with a smile. ■

Tohru Motobayashi

Tohru Motobayashi was born in Tokyo, Japan, in 1949. He graduated from the Faculty Sciences at The University of Tokyo in 1972, and obtained his PhD in 1977 from the same university. After one year of postdoctoral training at RIKEN, he moved to Osaka University as a research associate, where he started his career in experimental nuclear physics. In 1984, he returned to Tokyo as lecturer at Rikkyo University, where he was promoted to associate professor in 1986 and professor in 1994. In 2002, he was appointed as a chief scientist at RIKEN, where he led the Heavy Ion Nuclear Physics Laboratory until March 2010. He is currently RIBF Synergetic Use Coordinator and leader of the SAMURAI Team. His research is on the structure and reaction of nuclei far from the stability line and nuclear phenomena related to nuclear synthesis in the universe. He leads the research field by introducing new experiments using the radioisotope beams at RIKEN's accelerator facilities.

RIKEN at the 2010 EuroScience Open Forum

The EuroScience Open Forum (ESOF) is one of Europe's most important scientific gatherings. The 2010 forum was held in Torino, Italy, the third in the biennial ESOF series. RIKEN was one of 50 institutes across Europe, the USA and Asia to host a booth at the meeting, and additionally organized and chaired a 75-minute session on developmental perspectives in vertebrate evolution. RIKEN's participation at this year's ESOF has helped to raise the organization's international profile, promote collaboration with international research institutions, and attract young researchers to undertake studies at one of RIKEN's leading research institutes.

The ESOF features invited lectures and keynote speeches, workshops and forums, along with exhibitions with booths. Keynote speakers at this year's event included top-class scientists from around the world, among them three Nobel laureates. The event's main hall, a former factory of the car-maker Fiat, hosted a total of around 4,300 visitors. An associated "Science in the City" program of outdoor lectures and scientific experiments held in locations around the city drew a total of 75,000 visitors. The Science in the City events were supported by the efforts of dedicated volunteers and provided a diverse and engaging experience for ESOF's many participants from around the world.

Many of the visitors to the RIKEN booth were interested in the fields of environment and energy, reflecting a growing public awareness about these issues. Earthquake seismology also proved to be one of the most popular fields for those interested in RIKEN's work. The booth provided a valuable opportunity for RIKEN to raise its visibility in Europe beyond the academic sphere. Organizers plan to build on this year's success by hosting a single coordinated 'Japan booth' at the next forum in 2012 that will appeal even more effectively to a broader range of European participants.

Sharing information about recruitment opportunities at RIKEN was also a key success of the booth. The many interested visitors included groups of students from Australia and Europe. These interactions are vital in order to attract young researchers from around the world to join RIKEN in the future. Some of the students expressing interest at ESOF 2010 could one day be contributing to the advancement of science through participation in research at RIKEN.

Learn more about ESOF 2010 at http://www.esof2010.org/. ■

Three presenters at ESOF 2010. From left: Shigeru Kuratani from the RIKEN Center for Developmental Biology, Filippo Rijli from the Friedrich Miescher Institute for Biomedical Research in Switzerland, and Anne Burke from Wesleyan University in the USA.

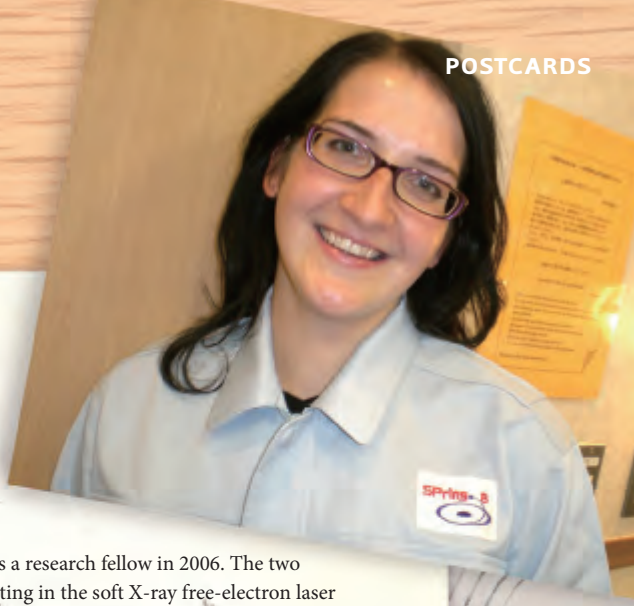
Developmental perspectives in vertebrate evolution

The presentations forming RIKEN's session at ESOF 2010 included a talk by Shigeru Kuratani from the RIKEN Center for Developmental Biology on the development of a turtle's shell.

"My talk followed a presentation by Annie Burke of Wesleyan University in the USA, who introduced the basic body architecture of the amniote, a group of tetrapod vertebrates. I myself spoke about the path by which the turtle obtains its shell, a unique anatomical feature, from features like ribs and vertebral bones. The way that these basic elements develop in early embryos is quite similar to how they develop in other amniotes, but at a late phase of development, a unique 'folding' of the body wall occurs. This folding encapsulates the shoulder blade and brings the ribs to the surface, thus forming the dorsal part of the shell.

"Following my explanation of this process to the audience at ESOF, I received many questions, many of which questions were of quite a high level of sophistication. It was very gratifying that the audience had truly grasped the depth and significance of the topic." ■

Shigeru Kuratani explains the process of turtle shell development at ESOF 2010.



Tsumoru Shintake
XFEL/SPring-8 Accelerator R&D Technical Director, Main Accelerator Construction Leader
SPring-8 Center, RIKEN, Hyogo, Japan

Dear Prof. Shintake,

This spring I visited Japan for the first time since my time with RIKEN as a research fellow in 2006. The two months I spent with your group as a doctoral exchange student participating in the soft X-ray free-electron laser project (SCSS) at the SPring-8 synchrotron research center in Hyogo was a memorable and enjoyable experience.

Apart from the visits to the facilities and participation in project meetings and simulation studies, I remember in particular the hospitality of everyone at SPring-8. It was a friendly workspace where I made friends and participated in many activities. The RIKEN staff were always friendly and helpful, and they offered a great variety of scientific and non-scientific activities.

What comes to my mind especially is the radiation safety course that I undertook when I first started my work at the lab. The course was in Japanese only, and our secretary, Takami Morishita, worked very hard to interpret the instructor's directions into English for me. But the best thing about the course was that I was able to make my own measurements of radiation dosage as a function of distance. It's a simple but impressive experiment, especially if it is done in a foreign language.

I also fondly remember my Japanese classes with Kitamura-sensei twice a week. The class has been a great aid in improving my Japanese and understanding customs and people in Japan. Kitamura-sensei's patience and friendliness were a great help.

Most of all, however, I remember the fun of our group trip to Ieshima island. It was one of my first weekend trips anywhere in Japan, and I enjoyed the time spent with my research group colleagues. I particularly remember the Japanese-style lunch we had and the many sightseeing spots that you described so well in English. Ieshima is a beautiful fishermen's island and you taught me much about country life in Japan.

After my stay at Spring-8, I returned to Germany to finish my PhD in physics. I then started a career in energy consulting, and I have been working for a Swiss company managing power plants for the past two-and-a-half years. I plan to switch to a new company soon, where I will lead a group consulting German municipalities in power plant optimization.

Despite my change from academia to industry, I continue to hear much from the accelerator community about the construction of the SCSS accelerator and the great success you have achieved with the free-electron laser. My congratulations to you and your team on the good work. The SCSS is a great project and I feel fortunate to have been able to participate.

My time at RIKEN was a wonderful experience and I am grateful to the many people who helped me find my way around and enjoy all aspects of life in Japan. I tell my friends about it often and will keep my time at RIKEN as some of my fondest memories.

Best regards,

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