



# RIKEN RESEARCH

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## The butterfly effect

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#### Working in concert

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# Working in concert

RIKEN biochemists decipher how the precisely choreographed activity of a pair of enzymes helps protein synthesis move forward

As cells go about the process of building new proteins, each amino acid gets delivered individually to the protein-synthesizing machinery of the ribosome by a specialized transfer RNA (tRNA) molecule. This process is generally facilitated by a variety of RNA synthetase enzymes, with each type of amino acid-attached tRNA formed as the product of a distinct synthetase.

However, archaea and most bacteria lack the capacity to directly synthesize every necessary tRNA-amino acid conjugate. For example, the glutamine-linked tRNA (Gln-tRNA<sup>Gln</sup>) in such species is instead produced via a two-step process, a synthetic pathway that is initiated by glutamyl-tRNA synthetase (GluRS), the enzyme normally responsible for producing the glutamate-bearing tRNA (Glu-tRNA<sup>Glu</sup>).

In this case, however, GluRS needs to make a ‘wrong move’ in order to produce an unusual hybrid tRNA, Glu-tRNA<sup>Gln</sup>, which serves as an essential intermediate in the Gln-tRNA<sup>Gln</sup> production process. This pathway has proven baffling to biochemists such as Shigeyuki Yokoyama, director of the RIKEN Systems and Structural Biology Center (SSBC) in Yokohama. “This mechanism has the possibility of forming harmful byproducts, including Gln-tRNA<sup>Glu</sup> and Glu-tRNA<sup>Gln</sup>, which can cause serious errors in protein synthesis,” he says. “We wanted to know how such a risky system functions efficiently.”

To further add to the mysteries surrounding Gln-tRNA<sup>Gln</sup> production, the complex responsible for the second step in this process, GatCAB, has been proposed to interact with the same region of Glu-tRNA<sup>Gln</sup> as GluRS. This has left it unclear how these two enzymes are able

to effectively partner with their common substrate in a manner that enables the two stages of synthesis to flow seamlessly without interfering with one another or potentially releasing toxic intermediates into the cellular environment.

## Taking turns

Yokoyama recently teamed up with SSBC colleague Takuhiro Ito in an effort to tackle these various mysteries, collecting high-resolution structural data from the bacterial species *Thermotoga maritima* for both the GluRS-tRNA<sup>Gln</sup> complex as

well as the ‘glutamine transamidosome’—the ternary complex containing tRNA<sup>Gln</sup>, GluRS and GatCAB. They confirmed that the latter is indeed a stable complex (Fig. 1), indicating that some mechanism must exist that prevents the two enzymes from simultaneously occupying the same space and disrupting each other’s function. Yokoyama and Ito have published their findings in the science journal *Nature*<sup>1</sup>.

Comparison of the two structures revealed that tRNA<sup>Gln</sup> undergoes structural changes when assembled within the glutamine transamidosome, interacting

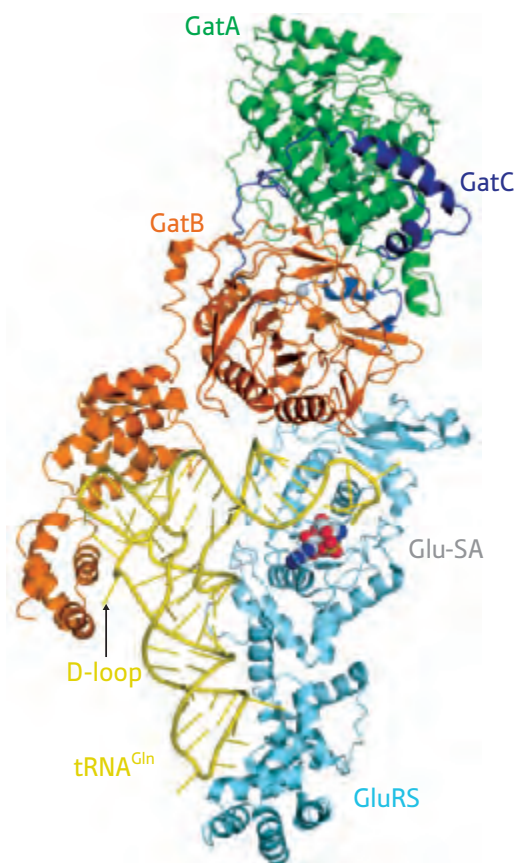


Figure 1: A high-resolution crystal structure of the *T. maritima* glutamine transamidosome, which incorporates the GatCAB enzyme (components labeled blue, green and orange) the GluRS enzyme (labeled light blue) and the tRNA<sup>Gln</sup> molecule (labeled yellow).

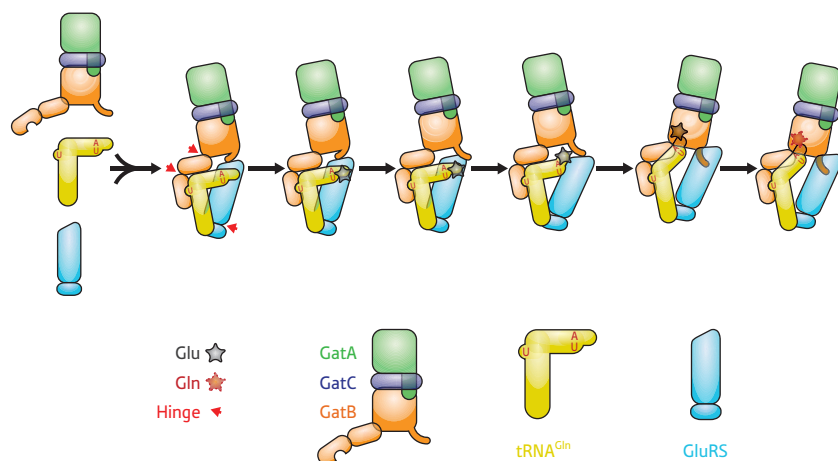


Figure 2: Schematic of the process of Gln-tRNA<sup>Gln</sup> synthesis. Glutamine transamidosome formation (top left) is mediated by the GatCAB complex (green/purple/orange) which recognizes tRNA<sup>Gln</sup> (yellow) based on sequences in the D-loop, while GluRS (light blue) modifies the acceptor arm to incorporate a glutamate residue (black star). Subsequent rearrangements, utilizing the identified hinges (red arrow heads), put the acceptor arm in proximity to the GatCAB catalytic site, which mediates the second step of transforming this glutamate to a glutamine molecule (red star).

with GatCAB via structural elements that are absent in tRNA<sup>Glu</sup>. In order to confirm this mechanism, Yokoyama and Ito constructed a series of hybrid tRNA<sup>Glu</sup> molecules that contain various elements from tRNA<sup>Gln</sup> and examined the extent to which they could successfully be processed to yield Gln-tRNA<sup>Glu</sup>. Based on these experiments, they were able to confirm that the region in question—also known as the D loop—is an essential structural feature in this process, revealing the mechanism by which this complex avoids introducing inappropriate modifications to Glu-tRNA<sup>Glu</sup>. “Our structure clearly shows how GatCAB recognizes tRNA<sup>Gln</sup> without inhibiting the reaction by GluRS,” says Yokoyama.

Their analysis also revealed a number of flexible ‘hinge’ segments in both GatCAB and GluRS that appear to contribute to their capacity to perform modifications in a stepwise manner (Fig. 2). Each of these factors initially binds to a different segment of tRNA<sup>Gln</sup>, with the GatCAB interaction contributing the discrimination mechanism revealed by Yokoyama and Ito. GluRS subsequently transfers a glutamate amino acid to the tRNA and undergoes a structural rearrangement that frees the newly modified ‘acceptor arm’ domain of the tRNA<sup>Gln</sup> molecule. GatCAB then executes a pivoting motion that brings its own catalytic domain in contact with

the glutamate-bound acceptor arm, at which point it initiates the amidation chemical reaction necessary to transform this amino acid into a glutamine residue. “This structure itself is very unique and interesting,” says Yokoyama. “One substrate tRNA is bound by two different enzymes working consecutively.”

### Protein evolution—past and future

Based on the unusual mechanism that they identified, the researchers hypothesize that this process of tRNA modification may have emerged relatively recently in the evolution of protein synthesis. As such, glutamine and asparagine—another amino acid whose synthesis is also the result of a two-step synthesis in a number of bacterial and archaeal species—could represent late additions to the genetic code.

In other work, Yokoyama and colleagues have explored methods for producing proteins whose characteristics have been selectively modified through the inclusion of atypical or synthetic amino acids, typically by inducing cells to express altered versions of tRNA synthetase enzymes that exclusively work with these alternative amino acids. However, the pathway described here could provide a useful model for future engineering efforts. “It might be possible to incorporate a new unnatural amino acid into the genetic code via this mechanism—modifying amino

acids after tRNA formation, but before they are transferred to the ribosome,” explains Yokoyama.

However, all of the data presented in their study of Gln-tRNA<sup>Gln</sup> represent deductions drawn from only a relatively small number of structural ‘snapshots’, based on a transamidosome complex that was essentially trapped in the first stage of Gln-tRNA<sup>Gln</sup> synthesis. In order to further understand the detailed operation of this cellular machine, Yokoyama now intends to collect additional structural data that will help fill in the gaps and provide additional confirmation for the model that he and Ito have developed. “We have not succeeded yet, but we would like to continue our trials to crystallize the amidation form of the transamidosome,” he says. ■

1. Ito, T. & Yokoyama, S. Two enzymes bound to one transfer RNA assume alternative conformations for consecutive reactions. *Nature* **467**, 612–616 (2010).

### About the researcher

Shigeyuki Yokoyama was born in Tokyo, Japan, in 1953. He received his BS and PhD degrees from The University of Tokyo in 1975 and 1981, and following completion of five years of postdoctoral work, became an associate professor in 1986 and a professor in 1991 in the Department of Biophysics and Biochemistry, The University of Tokyo. In 1993, he was appointed chief scientist of the RIKEN Cellular Signaling Laboratory, and later project director of the Protein Research Group in the Genomic Sciences Center. He played a pivotal role as science director of the RIKEN Structural Genomics / Proteomics Initiative (RSGI). Since 2008, he has acted as director of the Systems and Structural Biology Center (SSBC) at the RIKEN Yokohama Institute.



# Catching a chemical butterfly

Bulky molecules help trap boron compounds into a never-before-seen structural arrangement

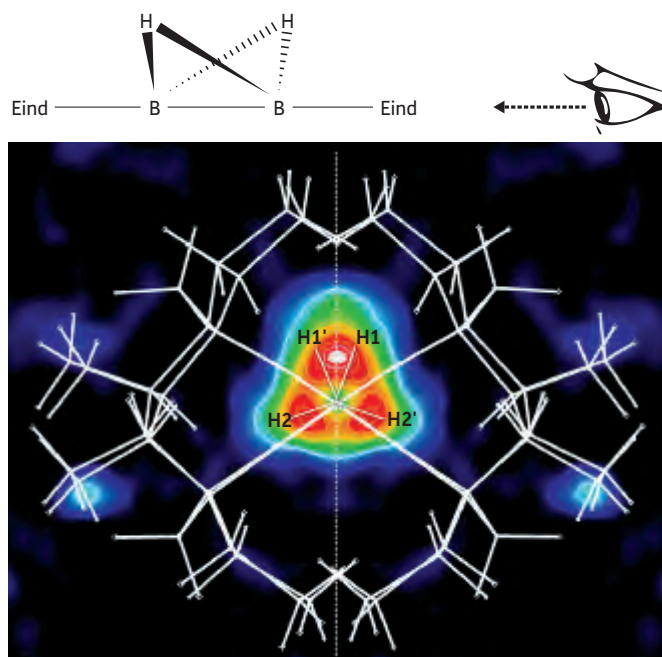


Figure 1: X-ray measurements (bottom) reveal that a butterfly-shaped boron compound (top left) has an intense electron distribution in its  $B_2H_2$  core (red areas) that is stabilized by exterior bulky ligands (white lines). The human eye (top right) shows the direction from which you look at the electron density map.

When it comes to chemical bonding, boron has a reputation for being unconventional. While covalent bonds are usually formed by sharing two electrons between two atoms, some compounds—including diboranes ( $B_2H_6$ )—contain B–H–B bonds in which an electron pair is distributed over three sites. The electron-deficient nature of these ‘3-center, 2-electron’ bonds can generate a variety of distinct chemical structures, some of which—such as triple-bonded diborane derivatives—have only been seen theoretically.

Kohei Tamao and colleagues from the RIKEN Advanced Science Institute in Wako and Kyoto University have now isolated the first stable diborane molecule with butterfly-shaped B–H–B bonds and a boron–boron link with triple bond characteristics<sup>1</sup>. This discovery unlocks new insights into the workings of 3-center, 2-electron boron interactions and puts scientists one step closer to synthesizing the elusive boron–boron triple bond.

The key to this approach is a bulky molecule known as ‘Eind’ that contains a rigid core of fused hydrocarbon rings covered with ethyl side chains. Previously, the researchers used Eind ligands to stabilize heavy elements into multiply bonded species<sup>2</sup>. This time, the team hoped to generate a neutral boron–boron double bond by substituting Eind groups for hydrogen atoms in diborane.

However, after characterizing the structure of the diborane–Eind compound—a difficult task requiring synchrotron x-rays to detect hydrogen atom positions—the researchers saw a previously unidentified arrangement at

the  $B_2H_2$  core: a central boron–boron connection nearly as short as a theoretical triple bond, flanked by two symmetric B–H–B ‘wings’ (Fig. 1). “We did not expect this butterfly-shaped structure at first, and finding it was a kind of serendipity,” says co-author Yoshiaki Shoji.

Quantum computations revealed that the Eind ligands enforced a linear bonding geometry upon the boron atoms, creating molecular energy levels closely related to the triple-bond species. Furthermore, the bridging hydrogen atoms enhanced the multiple bonding characteristics. “Based on this analysis, it is possible to consider triple bonding interactions between the two boron atoms,” says team-member Tsukasa Matsuo.

Matsuo notes that the butterfly-shaped molecule already displays unique chemical reactivity, and the insights gained from

this new structure could lead to additional multiply-bonded diboranes. “We may be able to synthesize a more triply bonded species in the near future by replacing the bridging hydrogen atoms with alkali metals,” he says. “At the moment, this compound is just a dream but I think we have a chance to obtain it.” ■

1. Shoji, Y., Matsuo, T., Hashizume, D., Fueno, H., Tanaka, K. & Tamao, K. A stable doubly hydrogen-bridged butterfly-shaped diborane(4) compound. *Journal of the American Chemical Society* **132**, 8258–8260 (2010).
2. Li, B., Matsuo, T., Hashizume, D., Fueno, H., Tanaka, K. & Tamao, K.  $\pi$ -Conjugated phosphasilenes stabilized by fused-ring bulky groups. *Journal of the American Chemical Society* **131**, 13222–13223 (2009).

# Searching for purpose in proteins

## A small-molecule screening method helps scientists probe mysteries of protein function

As scientists continue to acquire immense amounts of genomic and biochemical data from various organisms, they routinely find themselves confronted by proteins of known structure but enigmatic function—and resolving those mysteries may require a chemical-based ‘fishing expedition’.

“The discovery of small molecules that bind to and disrupt the function of a specific target is an important step in chemical biology, especially for poorly characterized proteins,” explains Isao Miyazaki, a researcher with Hiroyuki Osada’s team at the RIKEN Advanced Science Institute in Wako. “We call these small molecules ‘bioprobes.’”

Recent work from Miyazaki and Osada has demonstrated a highly effective strategy for identifying such bioprobes, which they have used to identify inhibitors of the human pirin protein<sup>1</sup>. Pirin is conserved across a diverse array of organisms, and has been tentatively linked to cancer malignancy in humans; however, little is known about how this protein might govern tumor progression.

The investigators produced glass slides containing a large array of small molecules, which they then treated with cellular extracts containing pirin protein fused to DsRed, a fluorescent tag. By identifying the spots selectively highlighted by the labeled protein, they were able to zoom in on a candidate molecule with apparently high specificity and binding affinity for pirin, which they named triphenyl compound A (TPh A).

High-resolution structural analysis demonstrated that TPh A inserts itself deeply within the pirin protein (Fig. 1),

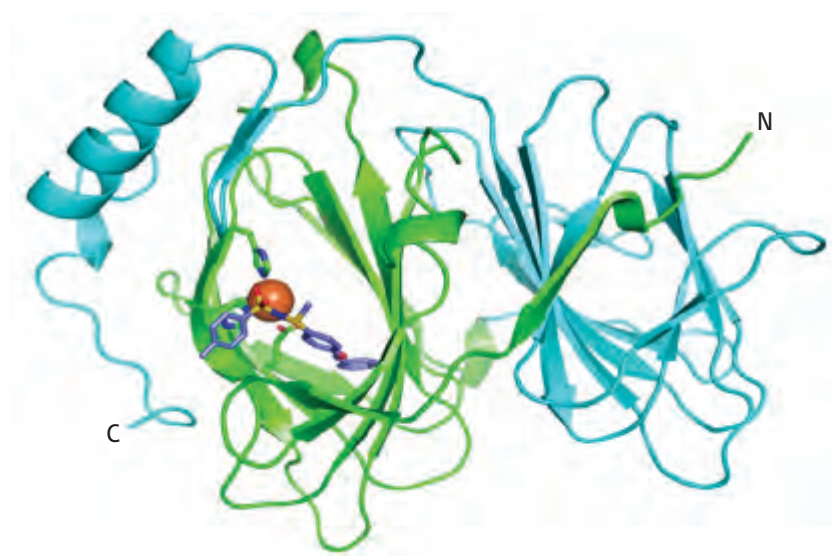


Figure 1: A structural diagram of the TPh A-pirin complex showing the small molecule (purple and red) stably lodged within a pocket of the protein (green and light blue).

and Miyazaki sees this as proof of the utility of their screening strategy. “There has been a question of whether ligands identified using chemical array approaches typically bind at shallow surfaces,” he says. “Our study confirms that chemical array methods can identify molecules that bind to buried pockets in proteins.”

Accordingly, TPh A appears to act as an effective functional inhibitor. Melanoma cells treated with this compound showed a marked reduction in cell migration, and this effect appears to arise from TPh A-mediated disruption of the interaction between pirin and the cancer-related protein Bcl3. By analyzing cellular gene expression profiles, the researchers subsequently uncovered evidence that pirin and Bcl3 collaborate to switch

on the *SNAI2* gene, which is known to contribute to tumor progression and metastatic growth.

These findings demonstrate the potential of bioprobe screening as a strategy for uncovering hidden protein functions. Miyazaki and Osada anticipate that TPh A will provide a valuable tool for future investigations of the role of pirin in other cancers and may even prove useful for studying related proteins from other organisms. ■

1. Miyazaki, I., Simizu, S., Okumura, H., Takagi, S. & Osada, H. A small-molecule inhibitor shows that pirin regulates migration of melanoma cells. *Nature Chemical Biology* 6, 667–673 (2010).

# Revealing a missing link

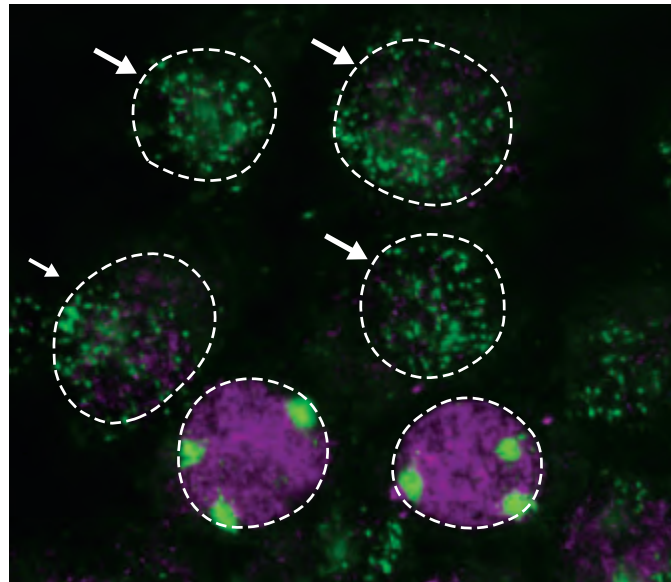
Scientists discover that a protein with an essential role in controlling gene dosage in female cells has been hiding in plain sight

When it comes to genes, it's definitely possible to have too much of a good thing. Accordingly, mammalian females have a mechanism that randomly inactivates one of the two X sex chromosomes within each somatic cell nucleus, ensuring that X-linked genes are represented to the same extent as in their single-X-bearing male counterparts.

This process is executed by the product of the *Xist* gene. Although messenger RNAs typically get exported to the cytoplasm to produce protein, *Xist* RNA remains in the nucleus and accumulates along the surface of the X chromosome that is to be inactivated, and new findings from a team led by Shinichi Nakagawa at the RIKEN Advanced Science Institute in Wako have provided valuable insights into the mechanism behind this unusual localization<sup>1</sup>.

Their screen of RNA-binding factors revealed a central role for heterogeneous ribonuclear protein U (hnRNP U) in regulating *Xist* distribution, and this RNA was scattered diffusely throughout the nuclei of cells in which hnRNP U levels were artificially reduced (Fig. 1). Closer analysis indicated that hnRNP U acts as an intermediary that binds directly to both RNA and chromosomal DNA and tethers the two together. This physical association appears to be essential to X inactivation; although mouse embryonic stem cells lacking hnRNP U successfully initiated the maturation process, they were significantly more likely to exhibit gene activity from both X chromosomes.

Previous investigations have identified a structural role for hnRNP U within the nucleus, and at least one group has



**Figure 1:** Fluorescence experiments in mouse cells demonstrate that hnRNP U expression is essential to the proper localization of *Xist* RNA. Arrowheads indicate cells with reduced expression of hnRNP U (purple), resulting in diffuse distribution of *Xist* (green) rather than the tight X chromosome-associated clusters seen in cells expressing hnRNP U (purple).

demonstrated that this protein tends to cluster near X chromosomes, although this potential aspect of its function remained unaddressed for the better part of decade. Indeed, Nakagawa was taken aback by its involvement in X inactivation. “I was surprised that we came across a factor that has been well-studied in the field of molecular biology rather than a ‘novel’ gene,” he says.

Although *Xist* is unique in its capacity to engineer the shutdown of an entire chromosome, there are numerous other non-protein-coding RNAs that contribute to the regulation of gene activity at a far smaller scale. Nakagawa hopes that this

study will offer a window onto those mechanisms as well. “In most cases these non-coding RNAs control neighboring genes on the same chromosome, in a similar manner to *Xist*,” he says, “and it is possible that these non-coding RNAs are, in general, also retained around the site of transcription by hnRNP U.” ■

1. Hasegawa, Y., Brockdorff, M., Kawano, S., Tsutui, K., Tsutui, K. & Nakagawa, S. The matrix protein hnRNP U is required for chromosomal localization of *Xist* RNA. *Developmental Cell* **19**, 469–476 (2010).

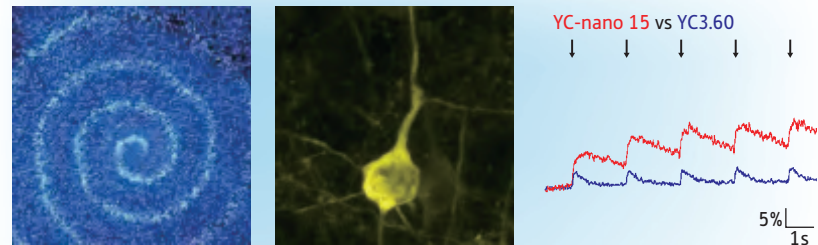
# Follow that thought

Refinements to a fluorescent calcium ion indicator give scientists a powerful tool for tracking neuronal activity in the living brain

As electrical signals travel along chains of neurons, each cell undergoes a dramatic shift in its internal calcium ion ( $\text{Ca}^{2+}$ ) concentration because specialized channels allow ions to flood into the cytoplasm. This shift provides a valuable indicator for tracking neural activity in real time, so scientists have developed several fluorescent protein-based  $\text{Ca}^{2+}$  indicators that are genetically encoded and can therefore be expressed directly in cells of interest.

Generally these indicators do not perform as well in live animals as *in vitro*. Takeharu Nagai of Hokkaido University and Katsuhiko Mikoshiba of the RIKEN Brain Science Institute in Wako suspected that indicators with higher affinity for  $\text{Ca}^{2+}$  might work better. However, their approach was risky. “It was generally believed that extremely high-affinity  $\text{Ca}^{2+}$  indicators would result in low cell viability due to disturbed  $\text{Ca}^{2+}$  homeostasis, and show no signal changes due to saturation by resting  $\text{Ca}^{2+}$ ,” say Nagai and Mikoshiba. “From this point of view, our attempt was totally against common sense.”

Nevertheless, the indicators, dubbed YC-Nano, developed by Nagai and his colleagues proved to be a remarkable success<sup>1</sup>. The indicators were derived from yellowameleon (YC), a genetically encoded indicator consisting of two fluorescent proteins, a ‘donor’ and an ‘acceptor’, connected by a  $\text{Ca}^{2+}$ -binding domain. In the presence of  $\text{Ca}^{2+}$ , the structure of YC rearranges such that the two come close together in a manner that allows energy from the excited donor to induce a readily detectable signal from the acceptor; in the absence of  $\text{Ca}^{2+}$ , only



**Figure 1:** The fluorescent indicator YC-Nano reveals waves of calcium flux (left) corresponding to signals generated by *Dictyostelium* cells as they undergo aggregation and action potentials in mouse cortical pyramidal cells (center) with a better signal to noise ratio (right).

a minimal signal is produced.

The researchers introduced various modifications that lengthened the  $\text{Ca}^{2+}$ -binding segment between the two fluorescent domains, introducing additional flexibility that considerably improved indicator sensitivity. The best-performing versions exhibited five-fold greater  $\text{Ca}^{2+}$  affinity than YC and a high dynamic range. “We were quite surprised that we managed to systematically produce a series of indicator variants with different affinity by a very simple protein engineering trick,” says Nagai.

YC-Nano accurately tracked the complex patterns of  $\text{Ca}^{2+}$  activation seen in the aggregating process of social amoeba *Dictyostelium*, revealing propagating waves throughout the aggregates in a rotating spiral (Fig. 1). These indicators also performed well

in monitoring neuronal activity in the brains of mice, and Mikoshiba foresees numerous experimental applications in the near future. “Since YC-Nano can be stably expressed in specific types of neurons for a long range of time,” he says, “we expect to perform chronic *in vivo* imaging and analyze the modifications of neuronal network activities underlying learning, development or diseases of the brain.” ■

1. Horikawa, K., Yamada, Y., Matsuda, T., Kobayashi, K., Hashimoto, M., Matsu-ura, T., Miyawaki, A., Michikawa, T., Mikoshiba, K. & Nagai, T. Spontaneous network activity visualized by ultrasensitive  $\text{Ca}^{2+}$  indicators, yellow Cameleon-Nano. *Nature Methods* 7, 729–732 (2010).

# Getting a round gene loss

A naturally occurring back-up system in plants to produce metabolites compensates for experimentally induced gene loss

Genes 'knocked out' experimentally in metabolic networks of the model plant species, *Arabidopsis thaliana* (Fig. 1), are compensated for by duplicate genes or alternative synthetic pathways, according to research led by Kousuke Hanada of the RIKEN Plant Science Center, Yokohama<sup>1</sup>.

Gene knockouts often have no obvious effects on an organism's biological characteristics or 'phenotype', because their function is compensated for by duplicate genes or alternative pathways allow the effects of gene loss to be circumvented.

For metabolic products, studies on these mechanisms have been limited to yeast. Hanada's team therefore assessed the relative importance of these mechanisms in *Arabidopsis*. "*Arabidopsis* suited our purposes beautifully because many gene knockout mutants have been generated and many of its metabolic networks are known," explains Hanada.

To study the robustness of *Arabidopsis* metabolic networks to gene loss the researchers knocked out individually some 2,000 highly expressed genes and then quantified 35 metabolic products in the seeds of the mutant plants by high-throughput analysis.

They compared what happened to production of metabolites when genes with and without duplicates were knocked out. The metabolites assessed included 17 essential amino acids (primary metabolites) found in all organisms, and 18 secondary metabolites called glucosinolates produced specifically by *Arabidopsis* and its relatives.

Knocking out either single-copy genes or genes with only distantly related 'duplicates' tended to have larger metabolic effects than those caused by knocking out genes



Figure 1: In the plant, *Arabidopsis thaliana* which is commonly used as an experimental model, duplicate genes or alternative synthetic pathways make the plant robust against the deletion of highly expressed genes.

having closer copies resulting from more recent gene duplication events. "Only recently duplicated genes appear to play a significant role in functional compensation of metabolites in *Arabidopsis*," says Hanada.

By analyzing the structure of the *Arabidopsis* metabolic network, the researchers found that primary metabolites are more often synthesized by alternative biochemical pathways than are secondary metabolites.

Primary metabolites are more likely than secondary metabolites to be essential for plant survival. Surprisingly, however, the researchers found that duplicate genes more often compensated functionally for experimentally induced gene loss in the synthesis of secondary metabolites than in that of primary metabolites. This contrasted with their previous work that showed that, in general, more severe phenotypic effects in *Arabidopsis* tend to be better compensated for by gene duplication than less severe effects<sup>2</sup>.

Hanada suggests that the existence of multiple alternative pathways for synthesizing primary metabolites makes these particular *Arabidopsis* networks highly robust to the loss of individual genes.

"Our findings shed valuable new light on the gene-phenotype relationship, laying the groundwork for new theoretical models in systems biology," says Hanada. ■

1. Hanada, K., Sawada, Y., Kuromori, T., Klausnitzer, R., Saito, K., Toyoda, T., Shinozaki, K., Li, W.-H. & Hirai, M.Y. Functional compensation of primary and secondary metabolites by duplicate genes in *Arabidopsis thaliana*. *Molecular Biology and Evolution Advance Access*, published 24 August 2010 (doi:10.1093/molbev/msq204).
2. Hanada, K., Kuromori, T., Myoga, F., Toyoda, T., Li, W.-H. & Shinozaki, K. Evolutionary persistence of functional compensation by duplicate genes in *Arabidopsis*. *Genome Biology and Evolution* **1**, 409-414 (2009).



# Copycat protein finds a perfect match

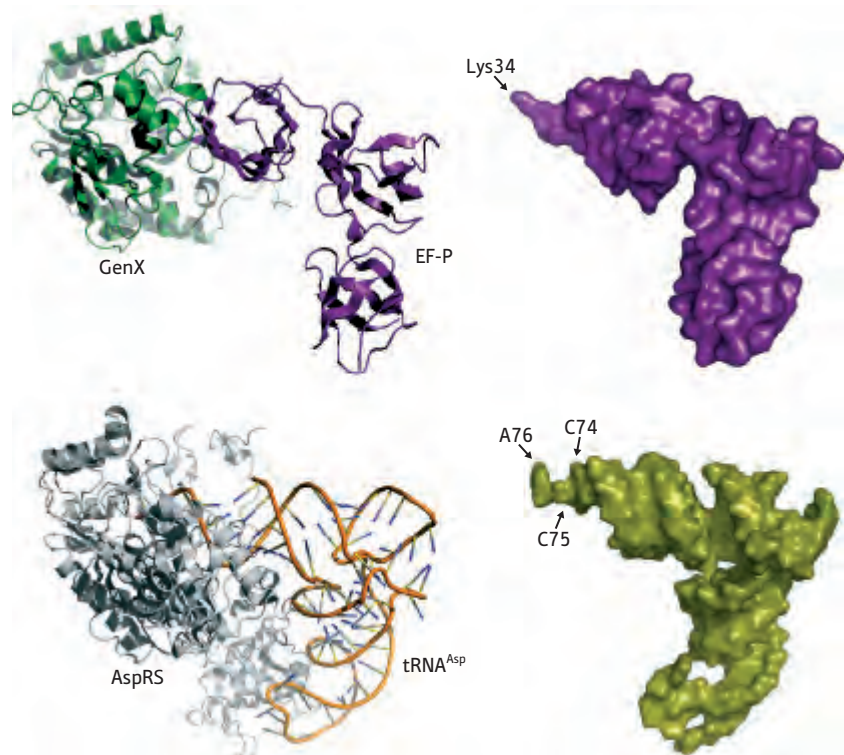
Evolution has left a protein and nucleic acid molecule with remarkably similar structures, allowing them to undergo modification by closely related enzymes

As proteins are synthesized during messenger RNA translation, fresh amino acids are delivered to the ribosome of the cell by nucleic acid molecules known as transfer RNAs (tRNAs). Each amino acid has a cognate tRNA, and the two are joined by specialized enzymes known as aminoacyl-tRNA synthetases (aaRS).

Scientists have also identified a number of bacterial aaRS paralogs, counterparts that resemble these enzymes but lack key functional domains. The role of these proteins is mostly a mystery, but a team led by Shigeyuki Yokoyama at the RIKEN Systems and Structural Biology Center in Yokohama has now revealed an unexpected function for the *Escherichia coli* aaRS paralog GenX<sup>1</sup>.

“I thought that elucidation of the structure and function of aaRS paralogs would lead to an understanding of not only mechanisms of genetic code translation but also the evolution of living organisms,” explains Yokoyama. In fact, GenX is closely related to the aaRS that transfers the amino acid lysine; although it can no longer bind lysine’s tRNA, it still associates strongly with lysine, and on the whole these two proteins are highly similar in structure.

This similarity suggested to the team that GenX transfers lysine to a different molecular target, subsequently identified as elongation factor P (EF-P): a translation-associated protein whose structure closely resembles the distinctive L-shape of tRNA molecules. “This is the first discovery of such striking similarities in structure and function between a nucleic acid and a protein, although they are completely different molecules,” says



**Figure 1:** The EF-P-GenX complex (top left) exhibits strong structural similarities to the well-characterized tRNA-aaRS complex (bottom left). This is because the EF-P protein (top right) has evolved with a structure that resembles the L-shape of nucleic acid-based tRNA molecules (bottom right), and both molecules interact with their partner enzyme at a similar point on their structure (Lys34 for EF-P, A76 for the tRNA).

Yokoyama. He proposes that these two molecules may have come to resemble each other by a process of ‘convergent evolution’, which favored the ability to productively interact with such closely related enzymes (Fig. 1).

Although it is extremely common for one protein to modulate the activity of another by attaching one of a selection of chemical groups, this represents the first known example of a protein being modified by the enzymatic addition of an entire amino acid. Nevertheless, the researchers demonstrated that this activity plays a vital role in protein production by *E. coli* cells, and is therefore essential to their survival.

Yokoyama now hopes to more closely explore the details of this process, but he also sees the potential for short-term applications as well. “GenX exists only in bacterial species, such as *E. coli* and *Salmonella*, and not in eukaryotic organisms, such as humans,” he says. “Therefore, GenX is a promising target for developing new antimicrobial agents for pathogenic bacteria ... without adverse side effects.” ■

1. Yanagisawa, T., Sumida, T., Ishii, R., Takemoto, C. & Yokoyama, S. A paralog of lysyl-tRNA synthetase aminoacylates a conserved lysine residue in translation elongation factor P. *Nature Structural & Molecular Biology* **17**, 1136–1143 (2010).

# Holding fire on the ‘good guys’

Tolerating the foreign materials in food that mice and humans need hinges on the presence of B7 proteins

An international team of molecular biologists led by RIKEN researchers has unraveled key details of the molecular mechanism whereby the body’s immune system determines what to attack among the organisms and food taken into the mouth, and what to leave alone or tolerate. The researchers have shown the pivotal role of two proteins found on the surface of cells that stimulate the immune system into action, the dendritic antigen-presenting cells (APCs). The work may lead to new therapies for immune disorders, and to ways of boosting the effectiveness of oral vaccines.

Animals could not survive without the nutrients and beneficial microorganisms they ingest when feeding. But the foreign material taken in through the mouth and passing through the gut also contains harmful substances and organisms (Fig. 1). So the immune system must balance active protection against pathogens and toxins with a non-responsiveness to food and commensal bacteria known as oral tolerance. In the past, researchers have proposed two mechanisms for oral tolerance—reducing the numbers of effector T cells, the immune-system foot soldiers that move against foreign material and suppress their action by means of specialized regulatory T cells.

The triggering of effector T cells depends on interaction with two distinct types of proteins on the surface of the APCs, antigens that are markers of foreign material and co-stimulatory proteins of the B7 family, which regulate the response. Both must be present, however, to initiate any action.



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Figure 1: In addition to nourishment, food can deliver harmful materials and microorganisms to our bodies, which the immune system must distinguish between.

Using mice deficient in B7 co-stimulatory proteins Katsuaki Sato and colleagues from the RIKEN Research Center for Allergy and Immunology in Yokohama, together with researchers from other laboratories in Japan, and in the US and France, found that oral tolerance demanded the presence of B7-H1 and B7-DC proteins<sup>1</sup>. In fact, without these proteins the immune response was enhanced. Of the APCs, the dendritic cells of the mesenteric lymph nodes, in the membranes surrounding the digestive system, display higher levels of these proteins.

When the researchers investigated the role of the two B7 proteins, again using B7-deficient mice, they discovered the proteins induced the generation of regulatory T cells rather than normal

effector cells. These regulatory T cells then damp down the immune response promoting tolerance. During inflammation, however, their action is swamped.

The research group wants to continue analyzing the role of different groups of dendritic cells in live mice, Sato says. “In particular, we wish to identify the molecular basis of the regulation of the function of these cells.” ■

1. Fukaya, T., Takagi, H., Sato, Y., Sato, K., Eizumi, K., Taya, H., Shin, T., Chen, L., Dong, C., Azuma, M., Yagita, H., Malissen, B. & Sato, K. Crucial roles of B7-H1 and B7-DC expressed on mesenteric lymph node dendritic cells in the generation of antigen-specific CD4<sup>+</sup>Foxp3<sup>+</sup> regulatory T cells in the establishment of oral tolerance. *Blood* **116**, 2266–2276 (2010).

# X marks the spot

Cloning efficiency is undermined by widespread disruption of genomic regulation resulting largely from defective expression of a single gene

Despite their name, not all clones are created equal. This is especially true for the products of somatic cell nuclear transfer (SCNT), which entails the transplantation of the nucleus from a mature somatic cell, or non-reproductive cell, into an oocyte, or immature female ovum, whose nucleus has been removed. The result is a genomically reprogrammed cell that has been ‘tricked’ into acting like a fertilized egg, and subsequently develops into a clone of the nucleus-donor organism; however, the success rate for this procedure is remarkably low and many of the resulting clones exhibit a spectrum of developmental problems.

“We wanted to know if there were any clone-specific gene expression patterns in these embryos that might be related to their phenotypic abnormalities,” says Atsuo Ogura of the RIKEN BioResource Center in Tsukuba. To solve this mystery, Ogura and colleagues performed an extensive analysis of gene expression activity, comparing the profiles of SCNT-derived mouse embryos versus healthy embryos obtained from *in vitro* fertilization (IVF)<sup>1</sup>.

They observed a striking pattern of clone-specific reduced expression of genes situated on the X sex chromosome. This suggested that there may be a malfunction in the activity of the *Xist* locus, which ensures that gene expression levels in female cells mirror those of their single X chromosome-bearing male counterparts. “In female somatic cells, one of the X chromosomes is inactivated by RNA transcripts from the *Xist* gene on the same X chromosome,” explains Ogura. “Both male and female embryos



Figure 1: The success rate of producing mice using SCNT cloning improves considerably after disrupting the *Xist* gene on the activated X chromosome of the donor nucleus.

have an X chromosome inherited from the mother (oocyte). This oocyte-derived X chromosome is always active, while the sperm-derived X chromosome in females is inactive.”

This memory appeared to be lost or disrupted in SCNT embryos, with many embryos showing evidence of widespread gene inactivation on both X chromosomes as early as the four-cell stage. However, the researchers found that this effect could be mitigated considerably by deriving SCNT embryos from donor nuclei in which the active X chromosome contains a defective copy of *Xist*. Strikingly, this also helped to normalize the expression of many non-X-linked genes that were abnormally regulated in SCNT but not IVF embryos, indicating that the effects of this X

chromosome inactivation were more far-reaching than expected.

This strategy yielded eight- to nine-fold improvement in their SCNT success rate in mice (Fig. 1). Ogura and colleagues now hope to confirm that the same mechanism is specifically impeding cloning in other animal species as a prelude to the development of methods that might broadly bolster the efficacy of SCNT for both research and therapeutic applications. ■

1. Inoue, K., Kohda, T., Sugimoto, M., Sado, T., Ogonuki, N., Matoba, S., Shiura, H., Ikeda, R., Mochida, K., Fujii, T. *et al.* Impeding *Xist* expression from the active X chromosome improves mouse somatic cell nuclear transfer. *Science* **330**, 496–499 (2010).

# Replacing faulty neurons

An effective method for generating cerebellar neurons could lead to new treatments for movement disorders

Researchers from the RIKEN Center for Developmental Biology, Kobe, have shown that neurons called Purkinje cells can not only be generated from embryonic stem (ES) cells, but can also become fully integrated into existing neuronal circuits when transplanted into the brains of mouse fetuses<sup>1</sup>.

Purkinje cells are the largest neuronal subtype in the mammalian brain, and their output in the brain region called the cerebellum controls balance, co-ordination and movement.

Yoshiki Sasai and his colleagues cultured ES cells and then treated them at different times with the hormone insulin, the naturally occurring chemical cyclopamine, and a protein called fibroblast growth factor 2, which normally induces the differentiation of Purkinje cells at a specific location in the developing hindbrain.

This treatment caused the ES cells to express genes that are specific for Purkinje cells, and then to differentiate into mature neurons with the extensive, two-dimensional dendritic tree and electrical properties that are characteristic of Purkinje cells. They found that the differentiation of the cells recapitulate the events that take place during neural development. The Purkinje cell-specific genes were expressed in the same sequence as in the embryo, and the immature cells exited the cell cycle, or stopped dividing, on a timescale comparable to that of the neurons in the developing cerebellum.

Sasai and colleagues then separated immature Purkinje cells from the ES cell cultures, and transplanted them into

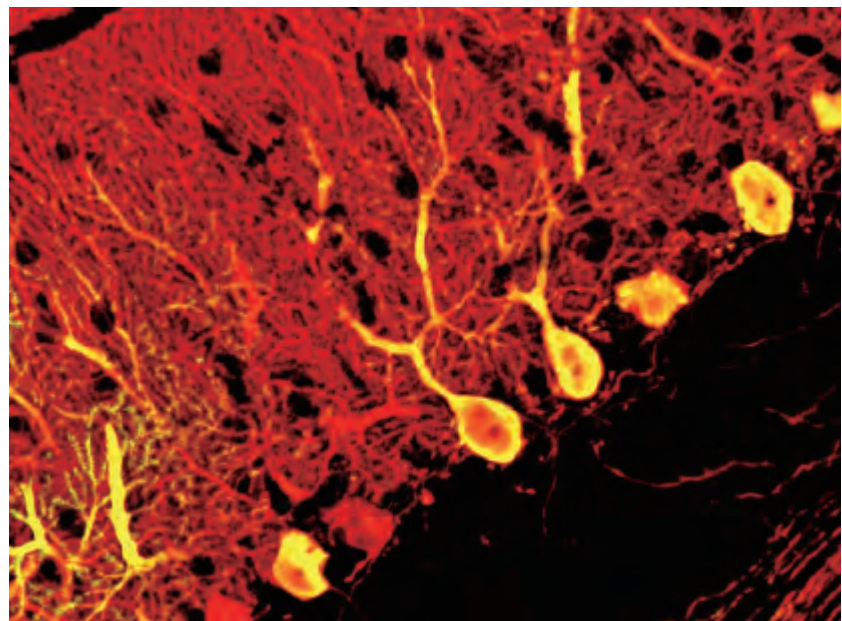


Figure 1: Purkinje neurons (yellow) generated from embryonic stem cells integrate into the cerebellum (red) when transplanted into the fetal mouse brain.

the brains of embryonic mice, injecting approximately 10,000 cells into each animal. They found that the transplanted cells integrated effectively into their proper location within the circuitry of the cerebellum (Fig. 1). The majority began to express Purkinje cell genes between 1 to 4 weeks after transplantation, and then differentiated into mature neurons, each with a long axon projecting down into the deep cerebellar nuclei.

The methods of Sasai and his team significantly improve on earlier methods for generating Purkinje cells from ES cell cultures. By successfully reproducing the microenvironment of the developing cerebellum, they generated up to 30-fold more Purkinje cells than previous methods.

These results therefore raise the possibility of developing cell

transplantation therapies the cerebellar ataxias, a group of movement disorders characterized by severe motor in-coordination, which occur because of Purkinje cell degeneration.

“As a next step, we are attempting to generate Purkinje cells from human ES cells,” says Sasai. “This technology would be useful in establishing an *in vitro* disease model for spinocerebellar ataxia, to investigate its pathogenesis and to explore the possibility of gene therapy for this genetic disease.” ■

1. Muguruma, K., Nishiyama, A., Ono, Y., Miyawaki, H., Mizuhara, E., Hori, S., Kakizuka, A., Obata, K., Yanagawa, Y., Hirano, T. & Sasai, Y. Ontogeny-recapitulating generation and tissue integration of ES cell-derived Purkinje cells. *Nature Neuroscience* **13**, 1171–1180 (2010).

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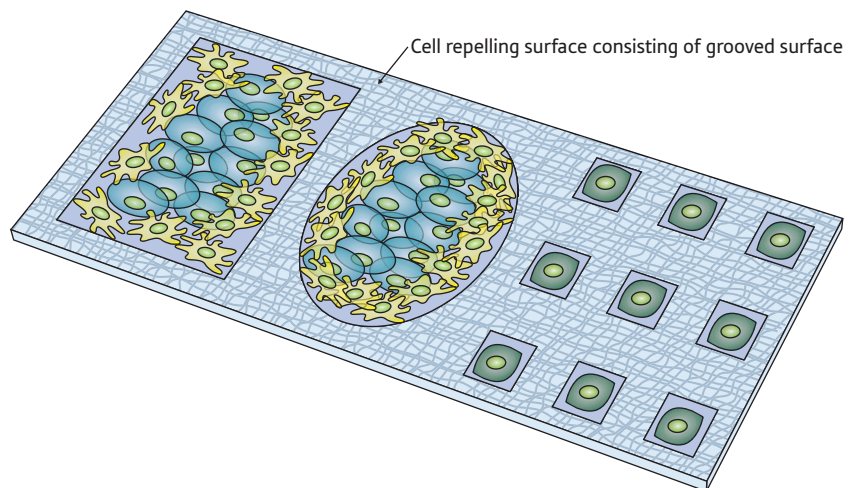
# Guided by the groove

Cells can be cultured and sorted on specifically patterned surfaces of biomaterials

Patterns of grooves etched into the surface of a silicon chip can guide, trap and filter migrating cells, biomaterials scientists from Japan and Korea have discovered<sup>1</sup>. The results open the way to engineering surfaces to study the movement of particular cell types during development and cancer, or to confine cells in tissue culture and protect against interference by cellular invaders. As the technique is biologically non-invasive, it should be ready for use in biomedical applications without years of safety testing.

The research team is led by Taiji Adachi of the RIKEN Innovation Center in Wako and includes colleagues from that institute and Pusan National University in Korea. Using time-lapse photography the researchers observed the behavior of the epidermal cells associated with fish scales known as keratocytes. These cells migrate rapidly and are often used in studies of cell movement.

Hiromi Miyoshi, a researcher of Adachi's team and her colleagues engineered grooves of different dimensions in the silicon dioxide coating of a silicon chip. The grooves were all 20 micrometers deep but of three different widths—1.5, 4 and 20 micrometers. Initially, the researchers observed what happened when moving cells encountered a single groove of these dimensions. They then etched a rectangular crisscross pattern of intersecting grooves 1.5 and 4 micrometers wide and the same depth. The widths were carefully selected with respect to the dimensions of the cells. Four micrometers is about the size of the cell nucleus and 20 micrometers the reach of the moving front of the cell, Miyoshi explains.



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**Figure 1:** Cells can be corralled on a chip in different ways by etching grooves into its surface. Depending on the area and shape of non-etched areas, cells can be separated and cultured either singly or in clumps of different forms.

When the migrating cells encountered a single groove, they responded in one of three different ways. Some simply crossed the groove, some turned back, and some moved into and along the groove since they were constrained by it. As the width of the groove decreased, the proportion of cells turning back increased to the point where, at 1.5 micrometers, there were no cells crossing and more than 90% turned back.

The intersecting grooves four micrometers wide tended to slow movement of the cells considerably, and in some cases stop or trap the cells. As it is known from previous work that

different cell types respond differently to the topography of the surface over which they travel, the researchers suggest that different etched patterns could be used to filter or exclude individual cell types (Fig. 1).

“We are now planning a more detailed study of cell migration in a three-dimensional environment,” says Miyoshi. ■

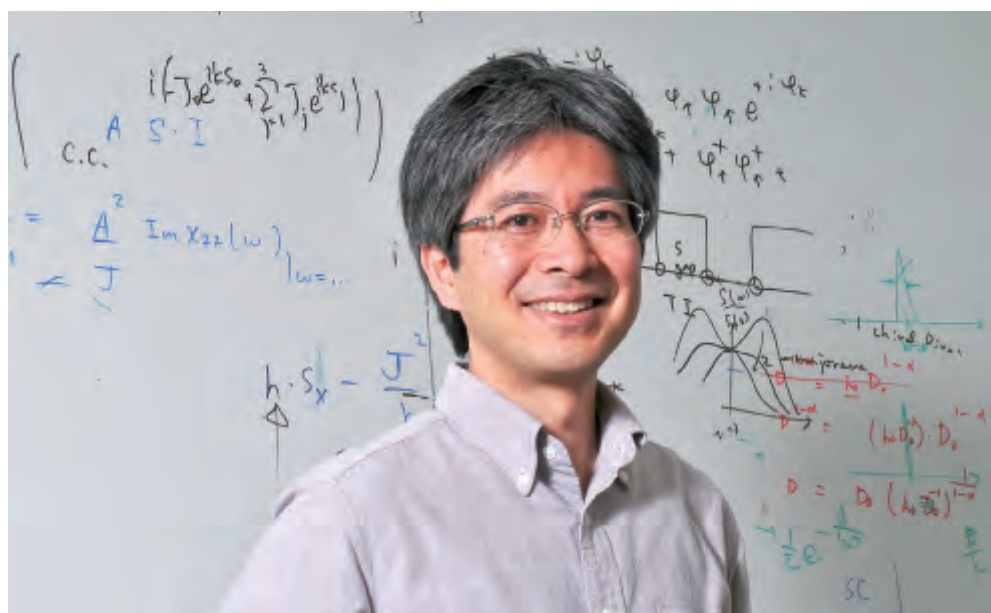
1. Miyoshi, H., Ju, J., Lee, S.M., Cho, D.J., Ko, J.S., Yamagata, Y. & Adachi, T. Control of highly migratory cells by microstructured surface based on transient change in cell behavior. *Biomaterials* 31, 8539–8545 (2010).

# Opening the door to new forms of matter at the Condensed Matter Theory Laboratory

## Akira Furusaki

Chief scientist  
Condensed Matter Theory Laboratory  
RIKEN Advanced Science Institute

Matter can show a wide variety of states and forms, including liquids, solids and gases, and metals, semiconductors, insulators and superconductors. Research in the past few years has revealed a new class of materials known as topological insulators and topological superconductors, which have attracted much attention in the field of condensed matter physics. A key feature of topological insulators/superconductors is their ‘massless’ particle behavior. Akira Furusaki, chief scientist in the Condensed Matter Theory Laboratory at the RIKEN Advanced Science Institute (ASI), and colleagues have created a classification table to explain the kinds of topological insulators/superconductors that can exist theoretically, leading to the discovery that Majorana particles, first predicted more than 70 years ago, are present in certain topological superconductors.



### New states of matter

The discipline of geometry dealing with properties that remain constant even under continuous deformation is known as topology. In this field, all objects that can be transformed from one to another by continuous deformation are considered identical. For example, continuously deforming a coffee cup can produce a toroidal form, and conversely, a toroid can be deformed into the shape of a coffee cup (Fig. 1). Coffee cups and toroids are therefore regarded as being ‘topologically identical’. However, to transform a coffee cup into a figure with two openings requires the additional step of making another opening, and so cannot be reached by simple continuous deformation of the coffee cup. Coffee cups are therefore ‘topologically different’ from a figure-of-eight shape.

“Topology has not been widely employed in physics to date,” says Furusaki. “However, research over the past few years has shown that, unlike in known insulators and superconductors, electron states—or ‘wavefunctions’—in certain substances

that are now called topological insulators and topological superconductors possess topological ‘numbers’. In quantum physics, an assembly of electron states in a substance can be mathematically regarded as a ‘space’. The number characterizing the shape of the space is the topological number.”

“The first topological insulator was actually discovered in 1980, although it wasn’t recognized as such at the time. It was a material exhibiting an integer quantum Hall effect.” The classical Hall effect is the production of an electric potential at right angles to an injected current and an applied magnetic field in conducting materials. The integer quantum Hall effect is an analogous phenomenon in quantum physics, usually manifesting itself only on the scale of atoms and electrons. At ultralow temperatures, however, certain quantum phenomena, such as the quantum Hall effect, can manifest at the macroscopic level. Superconductivity, the disappearance of electrical resistivity at low temperature, is another example of low-temperature quantum-based phenomena.



$$\nu[q] = \int \frac{d^3 k}{24 \pi^2} \epsilon^{\mu\nu\rho} \text{tr}[(q^{-1} \partial_\mu q) (q^{-1} \partial_\nu q) (q^{-1} \partial_\rho q)],$$

**Figure 1: Topologically identical figures and the equation defining topological numbers of three-dimensional topological superconductors.**

Continuous deformation of a coffee cup by stretching and shrinking can result in a toroid. Any property that remains constant despite such continuous deformation is known as a topological property. In topology, figures that permit continuous deformation are considered identical.

“To observe the integer quantum Hall effect, we apply an intense magnetic field perpendicular to the plane of an electron system confined to a two-dimensional planar interface between two semiconductors at ultralow temperature. The ratio of the resulting electric current to the voltage produced at right angles with respect to the current and magnetic field is an integer multiple of a number made of fundamental constants in quantum physics. This is a manifestation of quantum physics on a macroscopic scale. Any electron system in this state is a topological insulator, with an integer value for the topological number.”

The importance of this discovery of the integer quantum Hall effect is reflected by the fact that its discoverer received the Nobel Prize in Physics in 1985, just five years after the groundbreaking discovery. “However, it was another major discovery—the quantum spin Hall effect—that has led to recent advances in research into topological insulators.”

Spin refers to a property possessed by electrons and other particles, analogous to clockwise and counter-clockwise rotations and referred to as up-spin and down-spin. “These spins

are involved in spin-orbit interaction, by which certain two-dimensional substances exhibit the integer quantum Hall effect on ‘spin flows,’ even without application of a magnetic field. American researchers predicted in 2005 that this state would be a ‘ $Z_2$  topological insulator’ with a binary topological number (0 and 1). This is a manifestation of the quantum spin Hall effect.”

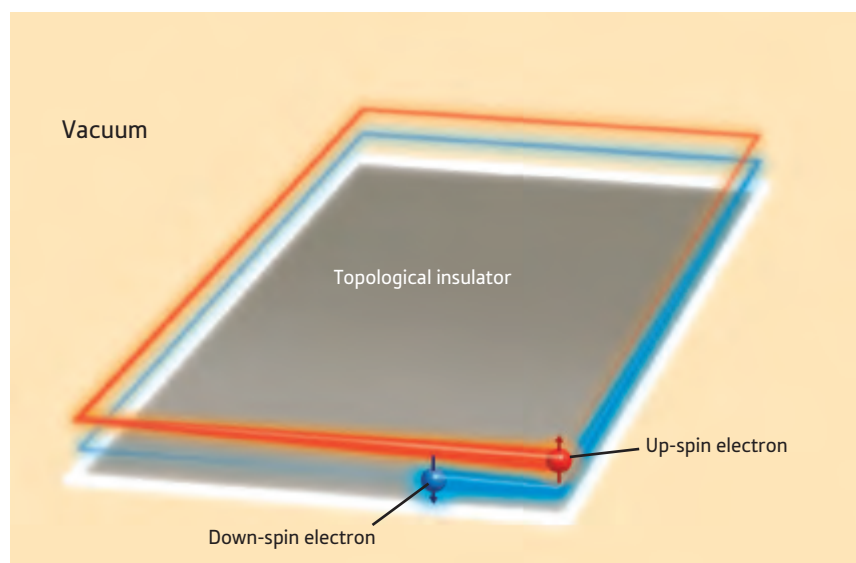
This phenomenon was verified experimentally in 2007, and the suggestion that the  $Z_2$  topological insulator also occurs in three-dimensional substances was verified experimentally in 2008.

“Subsequent research has shown theoretically that an insulator exhibiting an integer quantum Hall effect or quantum spin Hall effect can be understood to represent a novel state of matter called a topological insulator, and that certain superconductors can also become topological superconductors characterized by topological numbers.”

### Massless particles

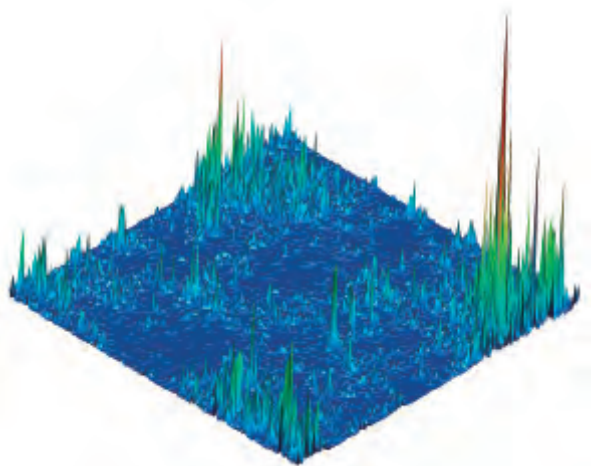
“One fascinating feature of topological insulators/superconductors is their ‘massless’ particle behavior,” says Furusaki. Massless particles move around freely at the edges of a two-dimensional topological insulator/superconductor, or over the entire surface of a three-dimensional topological insulator/superconductor.

“A topological insulator and the insulating vacuum surrounding it have different topological numbers. Massless particles emerge at the interfaces of



**Figure 2: Topological insulator exhibiting the quantum spin Hall effect.**

At the boundaries of a two-dimensional substance exhibiting the quantum spin Hall effect, up-spin and down-spin electrons move in mutually opposite directions. Although the electron essentially has a mass one-1836th that of the proton, the moving up-spin and down-spin electrons behave as massless particles.



**Figure 3: An example of Anderson localization.**  
 In the Condensed Matter Theory Laboratory, theoretical research into Anderson localization has also been proceeding. This numerical simulation demonstrates the localization of electrons (wavefunction amplitudes) at the phase transition from a metal to an insulator due to Anderson localization. Electrons are localized at higher crests. Furusaki and his colleagues discovered that the amplitude contours assume fractal properties.

regions of differing topological numbers, such as at the edges and surfaces of a substance. At the edges of a two-dimensional material exhibiting the quantum spin Hall effect, for example, up-spin and down-spin electrons are moving in mutually opposite directions (Fig. 2). Although electrons have a mass equivalent to 1/1,836th of a proton, the up-spin and down-spin electrons moving at the margins behave as massless particles, moving according to the Dirac equation of motion for electrons in a vacuum but assuming a zero electron mass, and so can be deemed massless particles.”

The presence of electrons that behave as massless particles was first verified experimentally in 2005 in graphene, a substance distinct from topological insulators/superconductors. Graphene is carbon in the form of a flat, honeycomb lattice just a single atom thick. The electrons in graphene behave as massless particles, moving at a speed close to 1/300th of the speed of light. This is several times faster than the speed of electrons in silicon, such as in modern electronics. For this reason, graphene is also expected to serve as a material for ultra-high-speed computers in the future.

In 2009, senior research scientist Naoya Tajima and others in the ASI’s

Condensed Molecular Materials Laboratory led by Chief Scientist Reizo Kato verified the presence of electrons behaving as massless particles in the organic semiconductor known as  $\alpha$ -(BEDT-TTF)<sub>2</sub>I<sub>3</sub>, attracting a great deal of attention. “Massless particles are an exciting subject of research for condensed matter physicists such as myself,” says Furusaki.

**Classifying topological insulators/superconductors**

“The research into topological insulators/superconductors that I have described has principally been conducted by researchers in the US. We worked together with collaborators in the USA to clarify the kinds of topological insulators and superconductors that can exist theoretically.

“Electrons move freely around the surfaces of topological insulators and superconductors. In an ordinary material, an impurity or defect in the crystal lattice causes the electrons to become localized and immobilized at that site due to interference between electron waves, resulting in what is known as an Anderson localization, where electric currents no longer flow,” says Furusaki (Fig. 3). “In a topological insulator or superconductor, however, the surface allows the electrons to move on freely,

	Complex space		Real number space							
	A	AIII	AI	BDI	D	DIII	AII	CII	C	CI
Two-dimensional substances	Z	0	0	0	Z	Z <sub>2</sub>	Z <sub>2</sub>	0	Z	0
Three-dimensional substances	0	Z	0	0	0	Z	Z <sub>2</sub>	Z <sub>2</sub>	0	Z

**Figure 4: Table of classification of topological insulators/superconductors (superfluids).**  
 Classes A, BDI etc. in the upper row indicate categories of electron systems classified according to symmetry. Zero (0) in the table indicates that no topological insulators/superconductors can exist; Z and Z<sub>2</sub> indicate the existence of a topological insulator/superconductor (superfluid) having an integer and a binary topological number, respectively. Substances exhibiting the integer quantum Hall effect or quantum spin Hall effect are two-dimensional topological insulators of class A or AII, respectively.

even if they encounter impurities. We applied the theory of Anderson localization, and determined the conditions under which electrons would flow freely without being localized. Figuring out when these conditions can be met, we made our classification table.”

**Discovery of particles predicted by a genius more than 70 years ago**

The classification of these conditions (Fig. 4) has led to some interesting findings. “We know that when helium-3 is cooled to an ultralow temperature, a state known as ‘superfluid B phase’, or <sup>3</sup>He-B, emerges. This was found to be classifiable as a ‘topological superfluid’ under category DIII.”

When cooled to a temperature near absolute zero, <sup>3</sup>He liquefies, and becomes a superfluid with further cooling. As a superfluid, all viscosity is lost; when superfluid helium is placed in a cylindrical vessel and caused to flow in some way, the flow continues without slowing. As such, superfluidity is another manifestation of quantum physics at the macroscopic level.

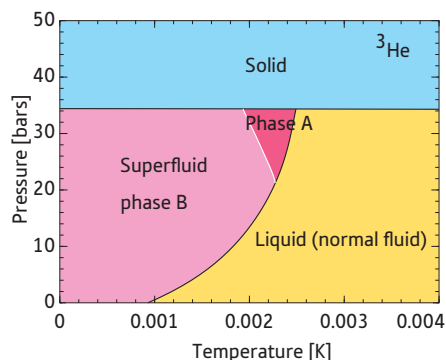
“On the surface of superfluid <sup>3</sup>He-B, which is a topological superfluid, excited <sup>3</sup>He atoms move around freely as massless particles. To our surprise, we demonstrated that these particles theoretically represent Majorana particles.”



The existence of Majorana particles was predicted by the Italian physicist Ettore Majorana more than 70 years ago. “Majorana was a physicist and genius,” explains Furusaki, “but he became a legend when he went missing the year after he made the prediction, when he was still in his early 30s.”

In 1929, before Majorana went missing, the British physicist Paul Dirac predicted the existence of ‘antiparticles’ with a charge and other properties opposite from the ordinary particles that form a material. “For example, he deduced theoretically that negatively charged electrons should have a counterpart, positively charged positrons, and that positively charged protons should be partnered by negatively charged antiprotons.” In 1932, positrons were discovered in cosmic rays, confirming the presence of antiparticles.

“Majorana predicted in 1937 the existence of particles that are electrically neutral and do not permit any distinction between particles and antiparticles, that is, particles that are their own antiparticle. Those are now called Majorana particles. Although the existence of such particles has not been confirmed experimentally, the neutrino, an elementary particle, has been hypothesized to be one kind of Majorana particle.”



**Figure 5: Phase diagram for helium-3.**

The Helium 3 ( $^3\text{He}$ ) nucleus consists of two protons and one neutron. As absolute zero is approached (under a pressure below 34 bar),  $^3\text{He}$  turns into the superfluid B phase, on the surface of which Majorana particles emerge.

These suggestions by Furusaki and others have made Majorana particles the focus of research in the field of topological insulators/superconductors and superfluids. “Majorana particles should exist not only in the superfluid B phase of  $^3\text{He}$ , but also at the boundaries of certain topological superconductors. We recently published a paper proposing an experimental method for demonstrating the existence of Majorana particles.”

At the ASI, the Low Temperature Physics Laboratory headed by Chief Scientist Kimitoshi Kono ranks foremost in the world in physical experiments of low-temperature phenomena such as  $^3\text{He}$  superfluidity. “I want to cooperate with Kono and others in contributing to the experiments aimed at confirming the existence of Majorana particles.”

Other research groups are proposing applications of Majorana particles to quantum computers, a concept for a futuristic computer capable of rapidly calculating solutions to problems that would take thousands of years to resolve with currently available supercomputers due to the vast numbers of computations required. However, in developing the quantum computer, the ‘coherent’ state for quantum physical phenomena quickly collapses under outside influences, posing a major problem. According to Furusaki, “Majorana particles formed on the surfaces or at the edges of topological superconductors are predicted to be unlikely to be affected by any external influence and should therefore be capable of retaining their coherence for a long time. For this reason, researchers are considering ways to apply Majorana particles to quantum computers.”

### Exploring the properties of matter

Before starting research on topological insulators and superconductors, Furusaki’s primary research theme was strongly correlated electron systems that achieve high-temperature super-

conductivity and the like. “Although strongly correlated electron systems remain one of my major research themes, for several years now I have been focusing my efforts on the study of topological insulators and superconductors. Any number of unimagined and fascinating phenomena may be awaiting discovery here. In several years time, I could be engaged in investigating unknown quantum phenomena in materials quite distinct from topological insulators and superconductors—after all, curiosity is central to being a researcher.” The buds of the truly innovative sciences and technologies needed to support the societies of the future will no doubt sprout from basic research based on such unconfined curiosity. ■

### Akira Furusaki

Akira Furusaki was born in Hatogaya in Saitama, Japan, in 1966. Graduating from the Faculty of Science at The University of Tokyo in 1988, he obtained his PhD in physics in 1993 from the same university. After becoming a research associate in the Department of Applied Physics at The University of Tokyo in 1991, he worked as a postdoctoral associate from 1993 to 1995 in the Department of Physics at the Massachusetts Institute of Technology, USA. Soon after returning to Japan, he was appointed as an associate professor at the Yukawa Institute for Theoretical Physics, Kyoto University in 1996. Since October 2002, he has been chief scientist in the Condensed Matter Theory Laboratory at RIKEN. His research focuses on the search for new states of matter and the development of quantum theory for electronic transport, superconductivity and magnetism.

# A meeting of minds at the second Noyori Summer School

On September 17–18, the RIKEN Harima Institute hosted the second Noyori Summer School, a retreat for PhD students in the International Program Associate (IPA) and Junior Research Associate (JRA) programs conducting research at RIKEN. With

the aim of training young researchers for a future in science, the summer school provides a cross-disciplinary, international setting and opportunities for young researchers to present their work to a broad audience. This year’s program included lectures and

presentations as well as tours of local facilities: the SPring-8 synchrotron radiation facility and soon-to-be-opened X-ray Free Electron Laser (XFEL), which be made available for shared use. ■



Achintya Kundu of the Molecular Spectroscopy Laboratory at the RIKEN Advanced Science Institute, one of the researchers who participated in this year’s summer school, received a ‘Best Poster’ award for his work on a surface active molecule at the air/water interface. Kundu recounts how listening to lectures and meeting students from many different countries provided renewed motivation for his own research.

For an aspiring scientist, having the chance to meet Nobel laureates in person and attend their lectures is tremendously inspiring. As a graduate student at RIKEN, I was provided this opportunity at this year’s Noyori Summer School, and it was one of the most memorable experiences of my life. The event also provided a unique chance to make new friends in different research fields and of different nationalities.

Presentations at the summer school included inspirational lectures by RIKEN President Ryoji Noyori, Executive Director Maki Kawai and SPring-8 Center Deputy Director Masaki Takata. I came away from these lectures with a deeper knowledge of RIKEN’s history and its position in the world as a research institute. Hearing about the scientific careers and early research efforts of President Noyori and Executive Director Kawai was extremely inspiring, and a powerful motivation for my own scientific career.

Beside lectures, other events included a tour of SPring-8 and the X-ray Free Electron Laser (XFEL), as well as poster sessions and a banquet. RIKEN’s XFEL, a new light source with a wavelength roughly the size of an atom, is among only a handful of such cutting-edge facilities in the world. Seeing the XFEL’s electron gun and accelerator, and

learning about its applications, was very exciting for me. The poster sessions were also fascinating, not only those in my own field of chemistry but also those presented by students in other fields.

One of my fondest memories from the summer school was of our late-night talks in which each of us shared our own cultural perspectives on various topics such as the Japanese way of life. The poster session awards ceremony was also very exciting, with awards handed out to top presenters in the fields of chemistry and materials science, biology and medical science, and

physics and engineering. But my real moment of excitement came with the announcement of two additional prizes, the Noyori Prize (best poster award) and the ballot box prize. To my great surprise, my name was announced as the winner of the Noyori Prize.

Before attending the summer school I never dreamt that I would have the chance to present my work to President Noyori, yet this dream came true. I returned from the Noyori Summer School this year with a fresh outlook and new enthusiasm about my research, and many new avenues for future collaboration.



Achintya Kundu speaks with RIKEN president and Nobel Laureate Ryoji Noyori.



Teruhiko Wakayama  
 Team Leader  
 Laboratory for Genomic Reprogramming  
 RIKEN Center for Developmental Biology, Kobe, Hyogo, RIKEN

Dear Prof. Wakayama,

It has been more than nine years since I first met you at the RIKEN Center for Developmental Biology, how time flies! I am currently an assistant professor in the Department of Animal Biotechnology at Konkuk University in Seoul, Korea. In my lectures to students, I often speak of my time as a research scientist in your laboratory from 2002 to 2007.

I was pleased to see your recent success in cloning a mouse from tissue that had been frozen for 16 years. This news even made it onto Korean television. I and my family were very happy to see it, and it reminded me of my time working with you at the RIKEN CDB. Remembering back to September 2002, I learnt a lot from you about how to set up a laboratory for studying reproduction and animal cloning. That experience proved to be very useful when setting up my own lab at Konkuk University. I learnt many things from you during my five years at your Lab.

The research environment at the RIKEN CDB and in your laboratory was great, the best I have seen anywhere. You are also a great advisor and team leader, and now four of the eight research scientists who have graduated from your lab have become professors at high-level universities in Japan and abroad. Through your activities in science and education, I can say that the RIKEN CDB system is really an incubator for young scientists.

Now, whenever my students are frustrated in their experiments and research efforts, I tell them your story about how you succeeded in the produced the world's first cloned mouse at the University of Hawaii in 1997, and how that work was published in Nature in 1998. After that story, my students have a better understanding of scientific discovery and the scientific 'road'. You continue to inspire, through not only your scientific activities but also your efforts in rescuing young scientists in developing Asian countries, which has been so important to the success of the Asian Reproductive Biotechnology Society.

I had a wonderful time in your laboratory at the RIKEN CDB, and regard it as one of the defining periods of my life. Thank you for the memorable experience. I wish you and your family happiness and health, and that you will continue to succeed in your research.

Best regards,

Nguyen Van Thuan  
 Department of Animal Biotechnology  
 Konkuk University,  
 Seoul, Korea





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For further information on the research presented in this publication or to arrange an interview with a researcher, please contact

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