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Dr Anindya Datta (Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai, India)

Japanese genomes inform on gut inflammation culprits

Revealing genes linked to the inflammatory bowel disease ulcerative colitis may speed the development of treatments

Ulcerative colitis is an inflammatory disease of the colon characterized by ulcers in that organ as well as by severe abdominal pain and chronic diarrhea during the active phase of the disease. Anti-inflammatory or immunosuppressive drugs are often used to treat ulcerative colitis, but in severe cases, the only known cure is surgical removal of the colon.

The cause of ulcerative colitis thus far remains a mystery. Studies aiming to determine genetic variations that are more frequently found in individuals with the disease are a first step in determining what may go wrong in the gut of affected individuals to cause the onset of ulcerative colitis. Developing drugs against the proteins that are encoded by these genes may represent future avenues for therapeutic discovery.

Now, as reported in the journal *Nature Genetics*¹, Japanese scientists have uncovered five discrete areas of the genome that are linked to ulcerative colitis in the Japanese population. The study was led by Michiaki Kubo from the RIKEN Center for Genomic Medicine in Yokohama, Japan.

Genome-wide hunt extends to Japan

The approach that the researchers took was called a 'genome-wide association study' (GWAS). Instead of searching for differences within only one gene of interest that may explain disease susceptibility, Kubo and colleagues looked for genetic variation across the entire genomes of the individuals in the study. This allows for an unbiased approach to gene discovery, which may uncover novel mechanisms by which the disease is initiated.

Previous GWAS studies, focused on individuals of European ancestry, have



Figure 1: Genes associated with susceptibility to ulcerative colitis in Europeans may not be linked to susceptibility to this disease in the Japanese population or in other ethnic groups.

identified genes linked to ulcerative colitis. But because different ethnic groups may harbor different susceptibility genes for the same disease, the genes linked to ulcerative colitis in Europeans may not relate to this disease in the Japanese population or in other ethnic groups (Fig. 1). In fact, the researchers found that although the European and Japanese populations share a few of these susceptibility genes, they don't share some of the other genes identified in the European study.

Also, Kubo and colleagues identified some genes linked to ulcerative colitis in the Japanese that were not identified in the European studies. Knowing these genetic differences—and similarities—is important when trying to create a drug that will work in as many ethnic groups as possible.

Common culprits

Major histocompatibility (MHC) molecules, which are expressed on the surface of cells, are involved in presenting antigens to the immune system to initiate—or to halt—an immune reaction. The region of the genome containing the MHC genes, found on chromosome 6 in humans, has been linked to many inflammatory diseases, and has been associated with ulcerative colitis in Europeans. The researchers also found a strong link between the MHC region and ulcerative colitis in the Japanese population.

Crohn's disease is another type of inflammatory bowel disease that affects a larger portion of the gastrointestinal tract than ulcerative colitis (Fig. 2), and lesions of the gut lining from this disease appear quite different to those caused by

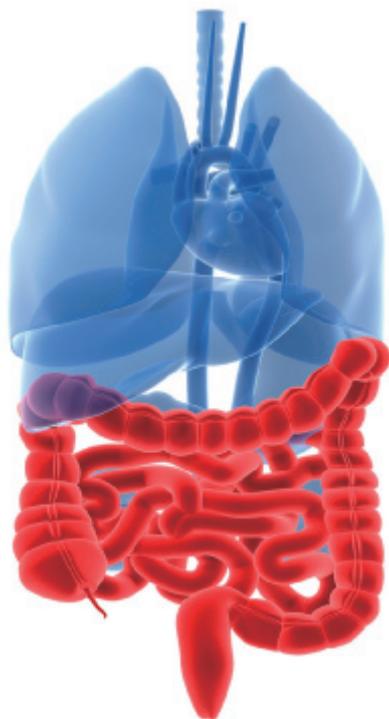


Figure 2: Crohn's disease and ulcerative colitis are two types of inflammatory bowel disease that affect the gastrointestinal tract (red) differently.

ulcerative colitis. Because the two diseases look so dissimilar, separate genes could be expected to play a role in their induction. However, Kubo and colleagues found a genomic region linked to ulcerative colitis in the Japanese population that had previously been reported to play a role in Crohn's disease. This locus had also been identified in the European ulcerative colitis GWAS. Future experiments are needed to determine why one genomic locus could enhance disease susceptibility for two different types of inflammatory bowel disease.

The guilty parties

In the five areas linked to ulcerative colitis in the Japanese, Kubo and colleagues identified three areas that had not been previously associated with this disease. One area, on chromosome 13, did not contain any known genes. The researchers suggest that this region could control the expression of nearby genes. Additional

studies are necessary to understand how this control could occur.

The other two areas contain the genes *FCGR2A* and *SLC26A3*. *FCGR2A* encodes a receptor protein found at the cell surface of immune cells. When this receptor binds to antibodies, it can cause secretion of cytokine molecules from the immune cells, which may then trigger inflammation. Since the *FCGR2A* gene variant associated with ulcerative colitis would bind more tightly to antibodies, it may enhance the activation of immune cells, leading to the inflammation that is observed in ulcerative colitis. Surprisingly, previous findings indicated that an opposing change in the *FCGR2A* gene, which would instead reduce antibody affinity to the receptor, was linked to three autoimmune diseases: lupus, multiple sclerosis and type 1 diabetes. Why altering the affinity of this receptor for its antibody ligand would induce so many different types of disease is a key question for future work.

SLC26A3 encodes a transporter of chloride and bicarbonate ions that is expressed on gut epithelial cells. The expression of this transporter is reduced in humans with ulcerative colitis. Because the change in this area of the genome, which the researchers report as linked to ulcerative colitis, was outside of the protein coding region of the *SLC26A3* gene, it is likely that this change in the DNA would regulate the expression of *SLC26A3*.

Kubo and his colleagues now plan to examine exactly how the observed variation in *FCGR2A* and *SLC26A3* affect susceptibility to ulcerative colitis. Because the link between these genes and ulcerative colitis had not been made before, these

findings “will open the door to further understanding of the mechanism of ulcerative colitis,” says Kubo. ■

1. Asano, K., Matsuhita, T., Umeno, J., Hosono, N., Takahashi, A., Kawaguchi, T., Matsumoto, T., Matsui, T., Kakuta, Y., Kinouchi, Y., *et al.* A genome-wide association study identifies three new susceptibility loci for ulcerative colitis in the Japanese population. *Nature Genetics* **41**, 1325–1329 (2009).

About the researcher

Michiaki Kubo was born in Miyazaki, Japan, in 1963. He graduated from the Faculty of Medicine, Kyushu University in 1988, and then began work as a medical doctor at the Second department of Internal Medicine, Kyushu University. In 1995, he joined the Hisayama study, a prospective population-based study of cardiovascular disease, as a research fellow of clinical epidemiology. In 2003, he joined the Professor Yusuke Nakamura Lab as a visiting fellow of the Institute of Medical Science, the University of Tokyo. He discovered two susceptibility genes for brain infarction in 2007. He joined the RIKEN Center for Genomic Medicine in 2006 as group director of the Research Group of Genotyping. His work at RIKEN focuses on finding susceptibility genes for common diseases by genome-wide association study.



Strong and free electrons

Long-predicted physical effects confirmed for the first time by a model system of strongly interacting electrons

From the study of an unusual two-dimensional electron system that is generated on the surface of low-temperature liquid helium, a RIKEN-led international research team has revealed that electrons free of atoms interact more strongly with each other than their counterparts in a semiconductor¹.

The work provides valuable insights into both electron interactions and thin films of so-called ‘two-dimensional free electron gases’, which have useful applications. Low-noise amplifiers in mobile phone base stations, for example, use the electrical characteristics of weakly interacting two-dimensional electron gases in thin-film semiconductor devices.

The strong electron interaction observed by the researchers was evident once the free electrons were excited into a higher energetic state by microwave radiation (Fig. 1). “As soon as the first electrons are in the higher state, the strong interaction between electrons in both states means that the energy difference between these two states changes as a result,” comments Denis Konstantinov from the research team.

This energy shift has been long predicted theoretically, although the weak electron interactions in semiconductors meant that it was too small to be observed. It is the strong electron interactions in the liquid helium system that enabled its detection for the first time. “It is due to its simplicity and extreme cleanness of our system that many theoretically predicted phenomena can be observed,” says Konstantinov.

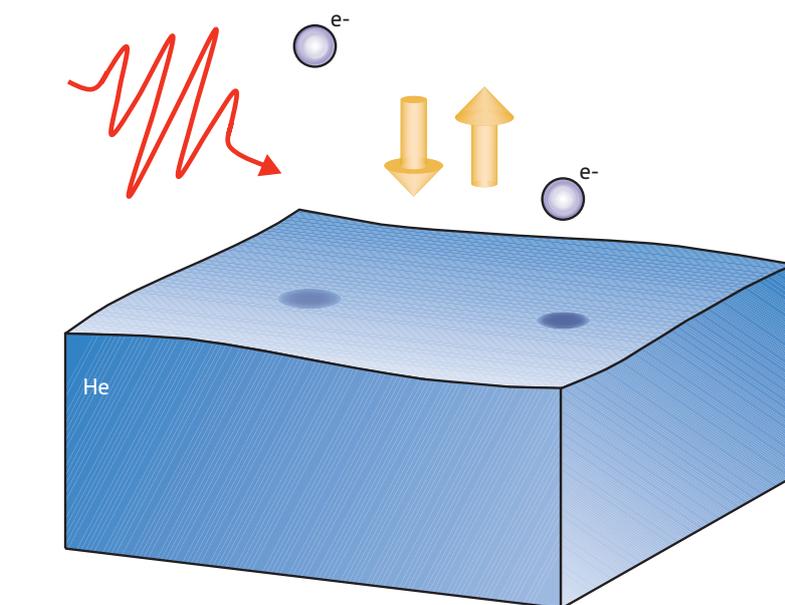


Figure 1: A two-dimensional electron gas on the surface of helium (blue). Microwave radiation (red arrow) can be used to excite electrons into higher states, where their interaction leads to novel effects.

The researchers then ventured to more complex experiments and applied a strong magnetic field perpendicular to the electron gas. This forced the electrons into a number of quantum states. As they increased the magnetic field, the energies of these quantum states shifted towards higher values. Successively, each quantum state changed to match the fixed energy of the higher energy surface state, again induced by the microwave radiation. At the matching condition, the electrical resistance of the quantum states increased owing to the interaction with the surface state. This resulted in characteristic oscillations in the electrical resistance with increasing magnetic field.

Konstantinov and colleagues also observed that in this configuration the strong interactions between the electrons can lead to a destruction of

the quantum states and therefore to the complete disappearance of the resistance oscillations².

At a more general level, however, the implications of these experiments are profound, and open a new arena for the study of such systems. Citing just one example, Konstantinov says that, “this is a model system to emulate quantum physical effects such as those explored for quantum computing.” ■

1. Konstantinov, D., Dykman, M. I., Lea, M. J., Monarkha, Y. & Kono, K. Resonant correlation-induced optical bistability in an electron system on liquid helium. *Physical Review Letters* **103**, 096801 (2009).
2. Konstantinov, D. & Kono, K. Novel radiation-induced magnetoresistance oscillations in a nondegenerate two-dimensional electron system on liquid helium. *Physical Review Letters* **103**, 266808 (2009).

Unexpected partners

Palladium catalysts containing unique molecular ligands couple aromatic rings together in surprising ways

Sometimes, molecules need help making the right connections. When multiple ways exist to join organic fragments together, metal catalysts can direct the assembly process so that only certain structures form. Now, Shunpei Ishikawa and Kei Manabe from the RIKEN Advanced Science Institute in Wako and the University of Shizuoka, Japan, have developed a palladium-catalyzed procedure that couples aromatic rings in completely unexpected ways, thanks to a new molecular ligand with specially designed spatial attributes¹.

Ishikawa and Manabe studied how to attach a benzene-based molecule to another aromatic ring containing an alcohol (–OH) group and two bromine (Br) atoms, located either beside (*ortho*) or far across from the –OH. Reactions that can link the rings at one of the Br sites, while leaving the other untouched, are extremely valuable to synthetic chemists for creating drug compounds and materials like liquid crystals. Because the *ortho*-Br is the geometrically and electronically least favored addition site, it is particularly difficult to establish couplings there.

The researchers designed a new series of molecular ligands, called dihydroxy-terphenylphosphines (DHTP), to enable *ortho*-selective aromatic couplings. DHTP consists of three benzene rings, linked end-to-end through rotationally flexible carbon–carbon (C–C) bonds; the first benzene contains a phosphorus group, while the third has dual –OH units. According to Manabe, DHTP ligands had the right geometric balance needed for this reaction.

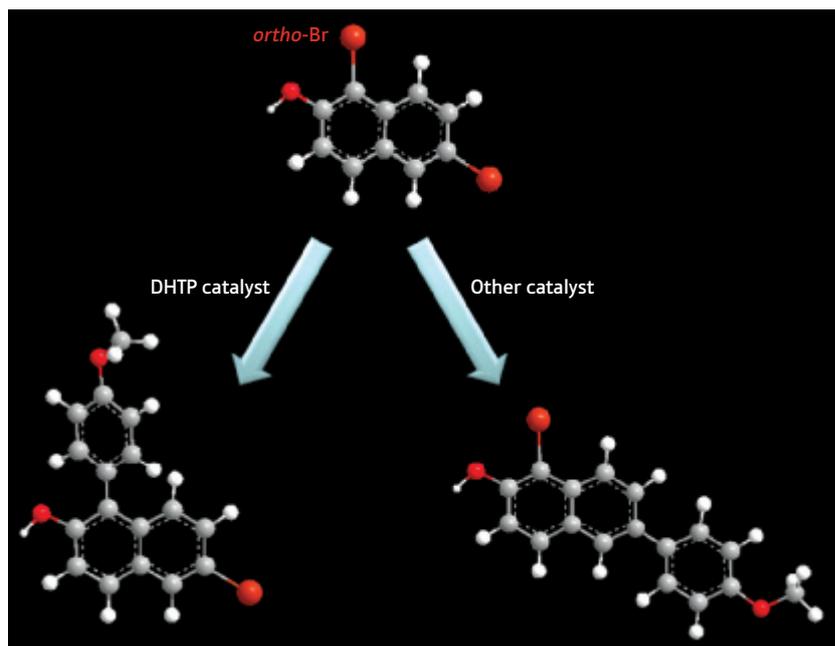


Figure 1: A new molecular ligand, called DHTP, helps selectively generate *ortho*-coupled aromatic rings (left) instead of the usual coupled product (right).

“Catalysts should not be too flexible, and not too rigid,” says Manabe. “Our DHTP catalyst can rotate about the C–C bonds, making it flexible enough to fit its structure to the catalytic transition state.”

The researchers attached the DHTP ligand to the bromine-containing aromatic ring via a magnesium atom that bridges the molecules together through their respective –OH functionalities. Then, they added a palladium catalyst to the reaction, which they assumed would bind to DHTP through the phosphorus unit. In this geometric configuration, the palladium atom can only interact efficiently with the *ortho*-Br atom to initiate a catalytic cycle that yields *ortho*-coupled aromatic rings with 80–90% selectivity and few by-products (Fig. 1)—a complete reversal of the usual aromatic coupling.

The DHTP-based catalytic system

improved upon the authors’ previous work² by having two –OH groups on the ligand, instead of one; this way, there is always a magnesium atom located close to the palladium catalyst, even if a C–C bond rotation occurs. “For me, it is very interesting that introducing only one –OH group improves selectivity and reactivity to a great extent,” says Manabe. ■

1. Ishikawa, S. & Manabe, K. DHTP ligands for the highly *ortho*-selective, palladium-catalyzed cross-coupling of dihaloarenes with Grignard reagents: A conformational approach for catalyst improvement. *Angewandte Chemie International Edition* **49**, 772–775 (2010).
2. Ishikawa, S. & Manabe, K. Oligoarene strategy for catalyst development: Hydroxylated oligoarene-type phosphines for palladium-catalyzed cross coupling. *Chemistry Letters* **36**, 1302–1303 (2007).

Plants on steroids

The identification of a gene involved in steroid hormone signaling in plants could benefit agriculture and reduce atmospheric carbon dioxide

Working with *Arabidopsis*, a member of the cabbage family, a team led by Takeshi Nakano of the RIKEN Advanced Science Institute in Wako has identified a gene¹, *BPG2*, that encodes a previously uncharacterized protein expressed by chloroplasts, the power houses of plant cells where energy from sunlight is harvested by the green pigment chlorophyll and used to build sugars for growth.

The researchers found that *BPG2* is involved in signaling mediated by brassinosteroids, plant hormones related to steroid hormones of animals. In plants, these hormones have specific roles in growth and development of stems, leaves and roots. They are also involved in pollen tube growth required for sexual reproduction, and in senescence.

“Our identification of a chloroplast gene controlled by brassinosteroids demonstrates that these steroid hormones are also important for chloroplast regulation,” says Nakano.

Nakano and colleagues genetically screened some 10,000 *Arabidopsis* lines using a new chemical biology method and identified a pale green mutant (Fig. 1) that was insensitive to the acceleration of greening normally caused by Brz (brassinazole), a chemical that specifically inhibits the biosynthesis of brassinosteroids. This suggested the disruption of brassinosteroid-chloroplast signaling in the mutant plants and led to the identification of *BPG2*.

Further investigation revealed that chloroplast proteins normally induced by Brz failed to accumulate in the mutant plants. Electron microscope studies also showed that the structure of chloroplasts

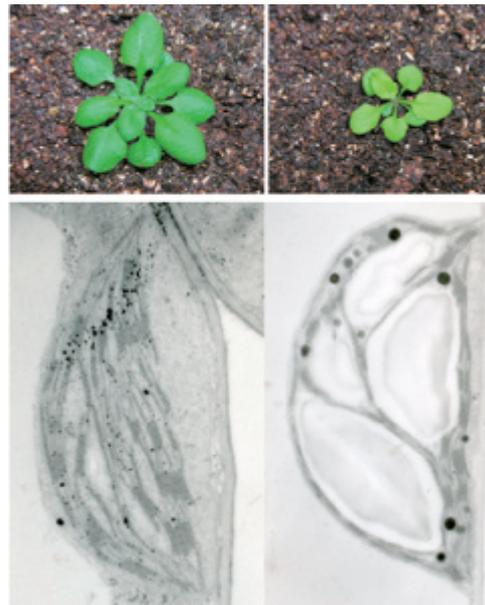


Figure 1: Photographs of a three-week old wild-type *Arabidopsis* plant (top left) and the pale green mutant (top right), *bpg2*, at the same age. Electron micrographs of normal (bottom left) and mutant (bottom right) chloroplasts isolated from these plants. The electron micrographs were taken by Chieko Saito of the Molecular Membrane Biology Laboratory, RIKEN Advanced Science Institute.

was abnormal in these plants.

The researchers then found that *BPG2* expression is induced by light and Brz. The *BPG2* protein is not directly involved in transcribing DNA to messenger RNA, the genetic template of protein. Instead, it regulates the splicing in chloroplasts of molecular precursors of ribosomal RNA, the core component of the machinery called the ribosome that manufactures proteins.

A computer search of DNA sequence databases revealed that *BPG2*-related genes occur in the genomes of other plants, including green algae, mosses and rice, and also in the common soil bacterium *Bacillus subtilis*.

Plants arose from a union of two organisms, including the bacterial ancestor of chloroplasts, which explains why chloroplasts have their own genomes.

“The fact that *BPG2*-related genes are conserved in bacteria suggests that the *BPG2* gene family arose early in the evolution of life on Earth,” explains Nakano. “We hope to genetically engineer plants to increase the expression of *BPG2* so as to promote chloroplast and photosynthesis activity, which in future could potentially increase the productivity of agricultural crops and reduce the amount of carbon dioxide in Earth’s atmosphere.” ■

1. Komatsu, T., Kawaide, H., Saito, C., Yamagami, A., Shimada, S., Nakazawa, M., Matsui, M., Nakano, A., Tsujimoto, M., Natsume, M., Abe, H., Asami, T. & Nakano, T. The chloroplast protein BPG2 functions in brassinosteroid-mediated post-transcriptional accumulation of chloroplast rRNA. *The Plant Journal* **61**, 409–422 (2009).

Finding the right combination

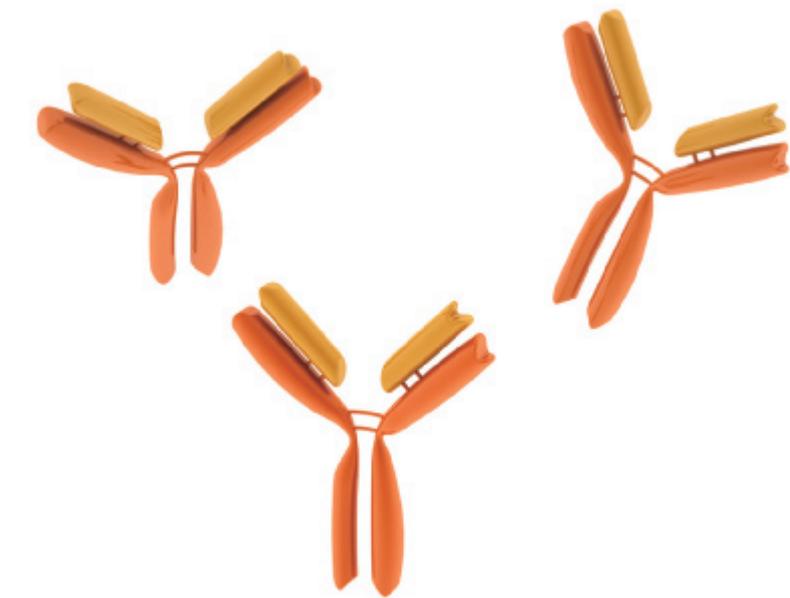
A combination of positive and negative regulation narrowly restricts a genome-shuffling enzyme's activity

Diversity may be the spice of life, but it's also the key to an effective immune system, as B lymphocytes rely on extensive recombination to shuffle their antibody-coding genes to produce molecules that can recognize a diverse array of potential threats.

Antibodies with established targets can also undergo further alterations to modulate the immune response that they trigger upon antigen binding. Known as 'class switch recombination' (CSR), this process relies on activation-induced cytidine deaminase (AID), an enzyme that induces major rearrangements in antibody-coding loci.

Unregulated, AID can generate cancer-causing genomic rearrangements, and a team led by Tasuku Honjo and Hitoshi Nagaoka at the University of Kyoto, with Sidonia Fagarasan's group at the RIKEN Research Center for Allergy and Immunology in Yokohama, recently set about exploring the mechanisms that help constrain expression of the *Aicda* gene.

"AID is tightly regulated in activated B cells and speculated to be a B cell-specific factor—however, the *Aicda* promoter is not lymphocyte specific," says Think Huy Tran, lead author of the team's recent article in *Nature Immunology*¹. Comparison of the mouse and human versions of this promoter revealed four discrete segments that had been closely conserved throughout evolution. To assess their contributions to gene specificity, the researchers generated artificial promoters consisting of various subsets of these conserved regions, which they used to regulate a bioluminescence-producing 'reporter' gene in cultured lymphocytes.



istockphoto.com/taramol

Figure 1: An artistic representation of antibodies. Even after the gene rearrangement event that locks in an antibody's designated target antigen, further genetic alterations can modify the nature of the immune response that it triggers.

They found that two of these four segments directly contribute to specificity. 'Region 2' contains binding sites for transcription factors known to guide B lymphocyte development, but also contains sequences that strongly inhibit *Aicda* expression. The other promoter segment, 'region 4,' appears to participate in the strong induction of this gene in response to signaling factors that trigger CSR *in vivo*.

"Our results demonstrate for the first time that two separate regions contribute together to regulating *Aicda* expression, in which silencers are derepressed by B lineage-specific and stimulation-responsive enhancers," says Tran. "The negative factors that restrict *Aicda* expression might contribute to retaining genomic stability, while region 4 is essential for *Aicda*

response in B cells to environmental stimulation ... and is critical to generate antibody diversification."

The investigators are now examining the individual importance of these various putative *Aicda* regulators, but also intend to further explore the bigger picture of the effects of AID dysregulation. "We plan to investigate the correlation between *Aicda* expression levels with mutation frequency in non-immune genes ... and the role of AID in tumor development," says Tran. ■

1. Tran, T.H., Nakata, M., Suzuki, K., Begum, N.A., Shinkura, R., Fagarasan, S., Honjo, T. & Nagaoka, H. B cell-specific and stimulation-responsive enhancers derepress *Aicda* by overcoming the effects of silencers. *Nature Immunology* **11** 148-154 (2010).

Decoding the soybean genome

The newly sequenced genome of the soybean could allow for the development of hardier plants

Scientists have sequenced the genome of the soybean plant, *Glycine max*, an important agricultural crop (Fig. 1). As reported in the journal *Nature*¹, the sequencing was accomplished through collaborative work between scientists in the United States and at the RIKEN Plant Science Center in Yokohama.

Soybeans are an important food source for humans, since they are used to produce foods such as soy sauce and tofu, as well as to make vegetable oil for cooking. But soybeans also are an important component of animal feed throughout the world, and play a key ecological role in taking nitrogen from the air and putting it back into the soil.

From their analysis of the 20 chromosomes of the soybean plant, the researchers predict that there are over 46,000 genes, more than double the number of genes in humans. Consistent with the known genome duplication of the soybean at two different points in its evolution, the geneticists identified many blocks of genes, corresponding to three-quarters of the soybean's 46,000 genes. These blocks were found more than once across the genome, including across different chromosomes.

The existence of multiple copies of a gene within a genome may allow for genetic diversity if some of those copies mutate in such a way that they take on novel functions, or so that their expression can be controlled separately under different environmental conditions. As an example of this, the researchers found double the number of fatty acid synthesis genes in the soybean genome than in *Arabidopsis*, a



Figure 1: Soybeans growing in the field.

flowering plant that has not undergone genome expansions. This may explain why soybeans are such a good source of cooking oil, while *Arabidopsis* is not.

As soybean plants are sensitive to disease, such as Asian soybean rust, which lead to losses in agricultural yield that adversely affect the world food supply, farmers need disease-resistant varieties of this important crop. Soybean varieties that have high nutritional content, hardier seeds and plants, and easier reproduction would also be agriculturally attractive.

“The genome sequence opens the door to crop improvements that are needed for sustainable human and animal food production, energy production and environmental balance in agriculture worldwide,” write the authors. ■

1. Schmutz, J., Cannon, S.B., Schlueter, J., Ma, J. Mitros, T., Nelson, W., Hyten, D.L. Song, Q., Thelen, J.J. Cheng, J. *et al.* Genome sequence of the palaeopolyploid soybean. *Nature* **463**, 178–183 (2010).

When siblings grow apart

Characterization of changes acquired by gene pairs over time reveals principles underlying evolution of gene function

The genomes of higher organisms generally contain numerous genes originating from duplication events. In many cases, the resulting gene pairs maintain essentially parallel functions over the course of evolution, as demonstrated recently by Kousuke Hanada and colleagues from the RIKEN Plant Science Center in Yokohama. Working with thale cress (*Arabidopsis thaliana*), the investigators found that evolution often tends to select for duplications that build redundancy into the genome, shielding organisms from potentially disastrous effects of function-altering mutations¹. However, this doesn't tell the full story about gene duplication.

“Knocking out either of two duplicate genes sometimes induces totally different phenotypes, indicating that the two copies have different functions,” says Hanada. This speaks to a process of ‘functionalization’, in which the two duplicate genes either evolve distinct functional profiles or else divide up the functions of the original, pre-duplication gene. Hanada and colleagues have now subjected *A. thaliana* to further analysis in order to better understand the molecular and evolutionary basis of this ‘morphological diversification’².

Gene function can be altered either through changes to the encoded protein sequence or modifications to their expression behavior (Fig. 1). The researchers began by assessing these characteristics in 398 gene pairs that had undergone functionalization relative to 94 pairs that had not, using sequence and expression data from the published literature and publicly available gene

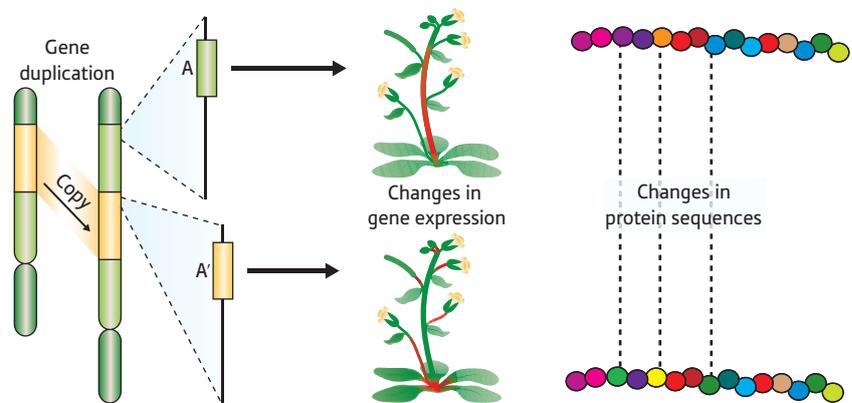


Figure 1: Modes of evolution for gene functionalization. Genes resulting from duplication events (left) can acquire changes that result in modified expression patterns (middle) or that introduce alterations into the amino acid sequence of the encoded protein (right).

expression databases.

As expected, sequence and expression variability were both found to be significantly higher within gene pairs that had undergone some degree of functionalization. However, there was also a striking difference in the relative contribution of these factors to morphological diversification. “Our analysis suggested that changes [in] expression pattern play the minor role—between 33 and 41%—and that changes [in] protein sequence play the major role—between 59 and 67%,” says Hanada. “This result is most surprising; most people believed that changes in expression pattern play the major role because such changes are essential for development.”

The investigators are now keen to apply their classification strategy to other organisms, including the fruit fly and mouse, in an effort to determine whether

similar evolutionary patterns exist. “I expect that changes of expression pattern are more important in complex organisms than simple organisms, but I do not know the real answer yet,” says Hanada. Collectively, the resulting data could inform development of tools that enable scientists to better understand the evolution of gene function based on observed sequence and expression changes. ■

1. Hanada, K., Kuromori, T., Myouga, F., Toyoda, T., Li, W.-H. & Shinozaki, K. Evolutionary persistence of functional compensation by duplicate genes in *Arabidopsis*. *Genome Biology and Evolution* **409**, 409–414 (2009).
2. Hanada, K., Kuromori, T., Myouga, F., Toyoda, T. & Shinozaki, K. Increased expression and protein divergence in duplicate genes is associated with morphological diversification. *PLoS Genetics* **5**, e1000781 (2009).

Kousuke Hanada

Tackling the genetic onset of Down syndrome

Researchers at the RIKEN Brain Science Institute are developing a highly efficient system to create mouse model lines that could dramatically advance genetic research on the most common mental retardation.

Chromosome 21 is the smallest of the 23 pairs of chromosomes in humans, yet it is responsible for Down syndrome—the most common genetic mental retardation. Down syndrome (DS) is caused by the erroneous replication of human chromosome 21 (HC21), which results in three copies of the chromosome instead of the normal pair of two. The most common cause of this ‘trisomy’ on HC21 is the failure of the chromosome pair to divide in an egg cell—often linked to advanced maternal age. Such an egg cell has two copies of HC21, and when fertilized, accepts another copy of HC21 from the sperm cell, resulting in a total of three, instead of the normal two, copies of the chromosome.

Unlocking the molecular pathology of trisomy 21 is greatly anticipated. Worldwide, it is estimated that up to one in every 700 babies is born with DS, and there are no specific therapeutic treatments. Yet little is known as to what determines the various phenotypes associated with the disorder. Patients typically suffer from neurological and behavioral difficulties, including language delays and attention difficulties, and some also face immunological, digestive and cardiac problems. The severity of mental retardation differs by patient and age—sometimes the symptoms are alleviated with age, while for others the symptoms become worse, developing into conditions such as Alzheimer’s disease. “We’d like to understand the molecular pathways responsible for the disease so that we can contribute to the development of effective therapies in the future,” says Kazuhiro Yamakawa, head of the Neurogenetics Laboratory at the RIKEN Brain Science Institute in Wako, Saitama.

In fiscal 2008, Yamakawa’s team secured a grant from the President’s Fund under the category of ‘challenging research’



Figure 1: Laboratory Head Kazuhiro Yamakawa (middle) and members of the Neurogenetics Laboratory including four members participating in the Down syndrome project. Other members of the laboratory are involved in epilepsy research.

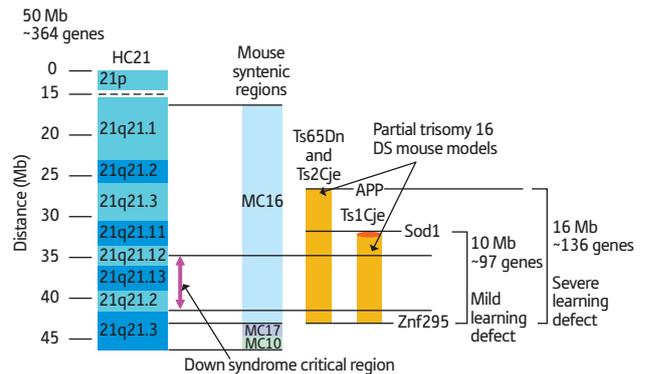


Figure 2: Mouse models with partial trisomy 16, such as Ts2Cje and Ts1Cje, are widely studied to identify the genes responsible for Down syndrome.

for a two-year project aimed at developing a highly efficient system to generate transgenic mouse lines for DS research. Their goal is to establish a high-throughput system to generate partial-trisomic DS mouse models and to identify the gene or genes responsible for DS features. In the 14-member laboratory, which also studies epilepsy, Yamakawa and four young researchers participate in this exciting project (Fig. 1).

Down syndrome mouse models and lines of research

HC21 carries approximately 360 genes and contains the Down syndrome critical region (DSCR) that many researchers believe is key to the occurrence of DS (Fig. 2). HC21 is orthologous (similar by shared ancestry) to part of mouse chromosome 16 (MC16), and several fortuitously generated DS mouse models with partial MC16 have been reported, including Ts1Cje, which has approximately 100 genes and is responsible for milder learning defects; and Ts2Cje, which has approximately 140 genes, partially shared with Ts1Cje, and is responsible for learning defects. Both Ts1Cje and Ts2Cje trisomic segments contain DSCR.

Some researchers believe that the imbalance in chromosomal number for HC21 induces DS by affecting the expressions of genes on the overall genome. Yamakawa and several other groups, however, support a different idea that the initial switch for the disorder is the dosage-dependent overexpression of genes located only on HC21. In 2004, Yamakawa’s team found that the expression levels of genes in the trisomic region of MC16 in Ts1Cje mice were increased by 50%, whereas the levels of other genes on other chromosomes or the normal euploid region of MC16 were almost the same as in normal

mice¹. Yamakawa adds that many of these overexpressed genes may not result in substantive damage, so identification of a few 'master' genes is critical. Some of those genes might also work collectively to contribute to the disorder.

In attempts to identify such master genes, several transgenic mouse models overexpressing individual candidate genes in distinct systems have been developed in other laboratories. However, even though some of the mice models displayed DS-like phenotypes, such as learning disability, the expressions of HC21 or MC16 genes in those models were too excessive (much more than 1.5-fold), ectopic (out of place) or occurred in the wrong developmental timings, making it difficult to compare the results. To improve on this, Yamakawa and his colleagues established a common platform in which heterozygous knockout mice for the HC21-orthologous MC16 candidate gene were mated with partial trisomy MC16 mice such as Ts1Cje. This procedure ensures that the number of copies of the candidate gene is returned to two, while other genes on the trisomic segment retain three copies. Using this system, it is possible to investigate whether any of the DS-like abnormal phenotypes are improved, allowing the contribution of each gene to the biochemical, biophysical or behavioral DS abnormal parameters to be compared impartially. The team has already identified and reported a large number of parameter abnormalities, including decreases in mitochondrial membrane potential and adenosine triphosphate production, increases in reactive oxygen species and kinase activities in Ts1Cje, and enlarged brain ventricles, impaired developmental and adult neurogenesis in Ts1Cje and Ts2Cje. These DS mouse models also display behavioral abnormalities indicative of learning defects. Knockout mice for more than ten HC21-orthologous MC16 genes have been generated, including a model for *Dscam*—a neural cell adhesion molecule that Yamakawa's team has long been investigating as a promising candidate for DS mental retardation². The team is now characterizing mice obtained by mating these model mice with Ts1Cje or Ts2Cje, and evaluating the role of each gene in the DS-like abnormal phenotypes.

A highly efficient system for generating Down syndrome mouse models

Although Yamakawa's strategy is promising, the generation of many knockout mice is still a daunting task. To implement large-scale analysis more effectively, Yamakawa's group is now establishing a new system that will allow mice to be generated with high efficiency and with free design of partial trisomic segments harboring gene knockouts as desired (Fig. 3). In their approach, a selection marker is introduced into MC16 in a mouse primary fibroblast, which is then processed into

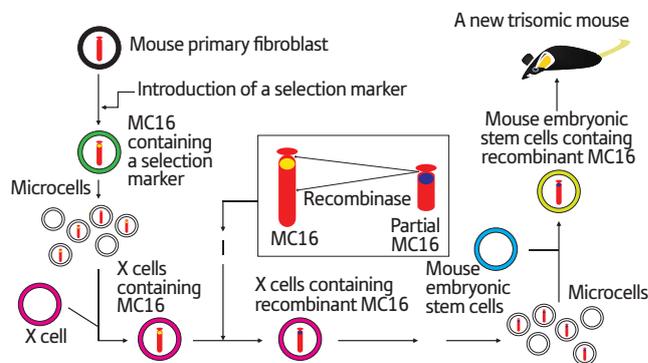


Figure 3: Flow for the generation of ideal DS model mice having freely designed segments of MC16 as partial trisomic segments.

'microcells', each of which contains, on average, a single chromosome string fused to a special 'X' cell. In the cells containing MC16, which are separated out, MC16 can be manipulated to achieve the desired chromosomal segments and gene knockouts with high efficiency. The designed cell containing recombinant MC16 is once again processed into microcells, and then fused into a mouse embryonic stem cell to generate a partial trisomic MC16 mouse. "This system will enable us to not only accelerate our research but also implement experiments that have been impossible, such as the inactivation of multiple genes simultaneously," Yamakawa says.

Atsushi Shimohata, a member of the technical staff at Yamakawa's laboratory, and Kenji Amano, a research associate, are currently devoting much of their endeavors to establishing this new system and to removing unnecessary segments from MC16 within the fused cell. Ei-ichi Takaki and Sachie Asada, both research scientists in Yamakawa's laboratory, are concurrently attempting to establish backup systems, including another type of mouse generating system and a high-efficiency *in vitro* screening system.

Within 3–5 years, Yamakawa hopes to establish these systems and identify several critical DS genes to elevate DS research to the next level. "We hope that our great passion for this project will eventually lead to alleviating patients' conditions," Yamakawa says. ■

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Creating the ultimate nuclear theory to help solve resource and energy problems

Through close collaboration between theoreticians and experimentalists, RIKEN's Radioactive Isotope Beam Factory is poised to deliver breakthroughs in our understanding of the origin of matter and nuclear theory.

Takashi Nakatsukasa

Associate Chief Scientist
Theoretical Nuclear Physics Laboratory
RIKEN Nishina Center for Accelerator-Based Science

Takashi Nakatsukasa, Associate Chief Scientist at the Theoretical Nuclear Physics Laboratory of the RIKEN Nishina Center for Accelerator-Based Science, has a vision for the future. "Theoretical calculations will make it possible to analyze all atomic nuclei and elucidate the origins of matter and elements. Energy will be generated from unused atomic nuclei, and high-level radioactive waste will be converted into stable nuclei that do not emit radiation. The nuclei of rare-earth elements will also be created. Nuclear theory could lead to us to achieve these dream technologies in as little as ten years."

Calculations for atomic nuclei up to a mass number of ten

"It was in 1935 that Dr Yukawa unveiled the original idea for his 'meson theory'. In his theory, the positively charged protons and uncharged neutrons that constitute an atomic nucleus are held together by strong 'nuclear forces' produced when 'mesons' are exchanged between the protons and neutrons. The basic theory that explains what constitutes a nucleus or what kinds of forces exist in the nucleus has been known for more than 70 years. However, no-one has been successful in deriving an equation that can accurately calculate all the characteristics of nuclei on the basis of the basic theory of nuclear forces," says Nakatsukasa.



The basic theory of nuclear forces is still based on the Yukawa model (Fig. 1). The complexity of calculations based on the basic theory, however, increases rapidly with increasing mass number — the total number of protons and neutrons constituting a nucleus. For example, a deuterium nucleus, which has a mass number of two (one proton and one neutron), can be simulated using basic theory for the nuclear forces with parameters such as lifetime, mass, shape, hardness and how the nucleus splits or fuses. "The calculation becomes extremely difficult, however, when the number increases to three, because the amount of calculation increases dramatically every time the number increases," says Nakatsukasa.

Why is simulation of the nucleus so complex? "There are three main reasons. Firstly, the atomic nucleus must be modeled on the basis of the quantum mechanics used to describe the microscopic world. Secondly, the

calculations involve 'anti-symmetrization' of the wave function, because protons and neutrons belong to the group of particles known as 'Fermi' particles. Thirdly, the long-range Coulomb force acts only on positively charged protons, and the nuclear forces act as an attractive force when atomic particles come within a distance of 10–15 m and a repulsive force when they get closer. In other words, the forces in the nucleus are a complex mixture of long-range, short-range, attractive and repulsive forces, so the calculation of forces in the nucleus becomes very complex."

A research group from the US recently succeeded in deriving the characteristics of dozens of atomic nuclei up to a mass number of ten, using a supercomputer to compute the basic theory of nuclear forces. "Theory predicts the existence of about 10,000 kinds of nucleus. The calculation based on the conventional theory, however, is available for only 1% or less of these nuclei." RIKEN's next-

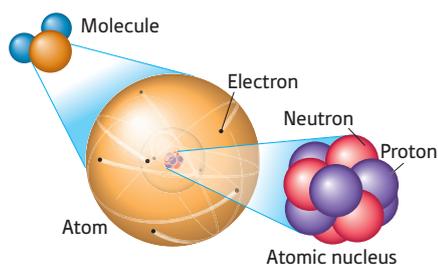


Figure 1: The atomic nucleus.

An atom is about 10⁻⁹ m in diameter, with a tiny atomic nucleus of about 10⁻¹³ m in diameter surrounded by electrons. In the nucleus, protons and neutrons are held together by a strong nuclear force. About 10,000 different nuclei are predicted to exist because of the possible combinations of protons and neutrons.

generation supercomputer scheduled for completion by 2012 and capable of an incredible 10¹⁶ calculations per second could greatly assist these calculations. “Even using the next-generation supercomputer, however, only a relatively few new nuclei can be calculated.”

In search of the equation that explains all atomic nuclei

There is another obstacle to Nakatsukasa’s goal: the current equations based on the basic theory of nuclear forces are unable to explain the characteristics of all nuclei. “To make this possible, we need another calculation approach. Thus, we started developing a calculation method based on the ‘density functional equation.’ We can accurately calculate all the characteristics of nuclei using a functional equation that describes the distribution of protons and neutrons (Fig. 2). The density functional equation has been proved mathematically, but has yet to be established with high accuracy. Thus, many researchers working on the theory of the atomic nucleus around the world are working hard to find a rigorous functional equation.”

The current equation is still useful, however, and can be used to derive at least some of the characteristics of nuclei. “The equation can predict the mass of a nucleus with an accuracy of 0.1%. But to predict the structure and reaction accurately, the accuracy of the

mass prediction must be refined by an order of magnitude.”

Nakatsukasa and the members of his laboratory are endeavoring to derive an equation with this level of prediction accuracy. “In addition to an experimental approach, we can use a purely theoretical approach. We can use an equation based on the basic theory of nuclear forces to calculate the characteristics of the nuclei up to a mass number of about ten. We can create a virtual nucleus using a supercomputer and deform the nucleus by applying an external force to create various nuclei with various density distributions and then calculate their characteristics. Thus, we are striving to derive a density functional equation that can completely describe the relationship between the density distribution of nuclei and their characteristics.”

Predicted by theory and verified using RIKEN’s Radioactive Isotope Beam Factory

“The substances around us are composed of atoms with basically stable nuclei. A stable nucleus consists of almost the same number of protons and neutrons. About 300 stable nuclei are known to us, and conventional nuclear theory has been established mainly on the basis of experimental data on these stable nuclei. Yet about 10,000 atomic nuclei are predicted to exist theoretically. Most, however, are unstable, consisting of different numbers of protons and neutrons, and

they decay, emitting radiation.”

In the 1980s, scientists successfully created beams of unstable nuclei using particle accelerators, allowing experiments to be conducted to examine the characteristics of unstable nuclei. Over time, scientists discovered various phenomena that could not be explained by the conventional theory. For example, the atomic nucleus, which had been accepted as being spherical by conventional theory, is in fact shaped more like a rugby ball. Scientists also found nuclei consisting of protons and neutrons with different density distributions, and discovered a new type of radiation involving the emission of multiple kinds of particle.

So far, about 3,000 nuclei have been created using accelerators. In 2007, RIKEN started operating its Radioactive Isotope Beam Factory (RIBF), which is capable of creating the world’s most intense beam of any of about 4,000 unstable nuclei ranging from hydrogen to uranium. Most conventional facilities are able to create only a limited range of nuclear beams and therefore do not provide sufficient information to derive general characteristics. The RIBF, however, is capable of creating a beam of any nucleus, and thus provides detailed information (Fig. 3). Although scientists in Europe and the US are planning to develop a new generation of accelerators, it will be at least seven or eight years before they can conduct experiments similar to those being performed today at the RIBF.

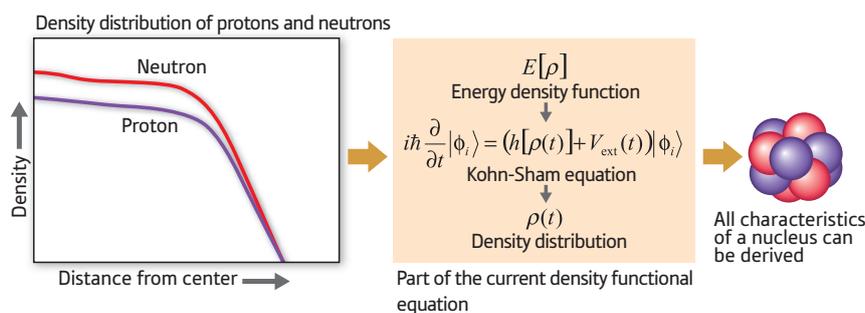


Figure 2: Density functional theory.

It has been proved mathematically that the density functional equation for protons and neutrons can be used to derive all the characteristics of a nucleus very accurately. However, the full expression for the density functional equation has yet to be derived.

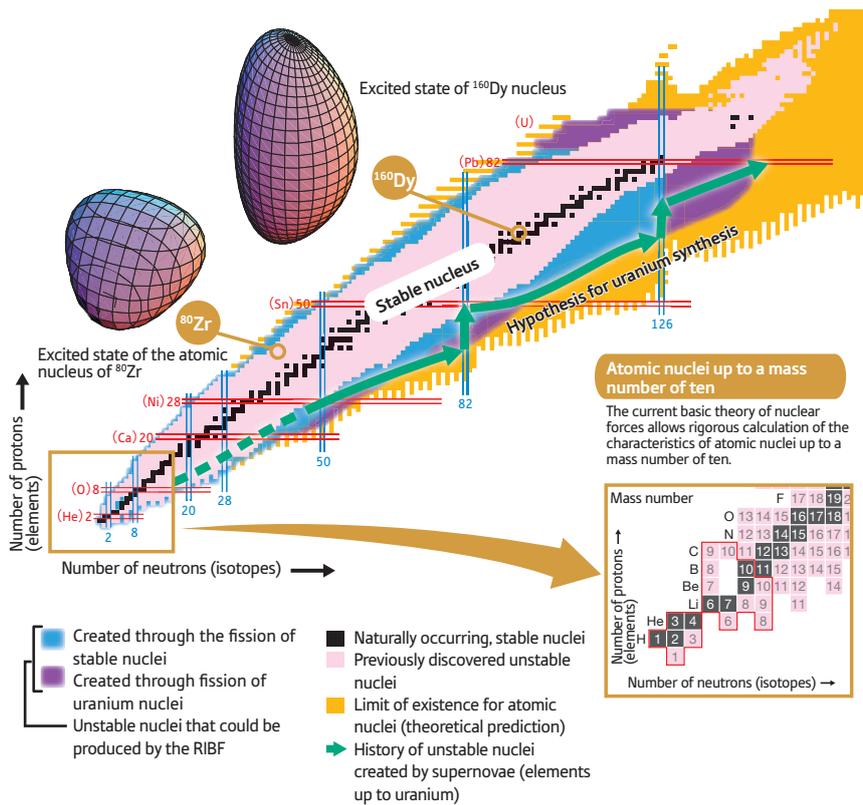


Figure 3: Atomic nuclei that could be created using the RIBF and the shapes of nuclei predicted by theory. The RIBF can be used to improve the prediction accuracy of the density functional equation by experimentally verifying theoretical predictions such as the mango-shaped (^{160}Dy) and rice-ball-shaped (^{80}Zr) nuclei predicted by the density functional equation. Red and blue numbers denote the numbers of protons and neutrons that conventional theory considers to be stable (magic number).

“Conducting research in collaboration with the experimental group at the RIBF has many advantages. We obtain the latest experimental data, which can be used for theoretical research; conversely, we can propose experiments based on theoretical approaches. I want to use the density functional equation to predict in advance the characteristics of the thousand or so unknown atomic nuclei that could be created by the RIBF in the future. I would like to make suggestions to the experimental groups, such as ‘This nucleus seems to have these interesting characteristics.’”

Using the density functional equation, Nakatsukasa predicts that the dysprosium-160 nucleus, consisting of 66 protons and 94 neutrons, and similar nuclei become mango-shaped when revolving at high speed. Another theoretical group in Japan predicts that

zirconium-80, consisting of 40 protons and 40 neutrons, will become rice-ball-shaped in a quasi-stable state. These theoretical predictions have not yet been verified experimentally, but the RIBF provides the means to do so.

Pursuing supernova explosions and the origin of elements

A major goal for research using the RIBF is to probe the origins of matter and elements. Most elements, from iron (atomic number 26) to uranium (atomic number 92), are considered to have been created when a supernova, the final explosive stage of a star, expels huge amounts of unstable heavy elements, which then decay into lighter and lighter elements (Fig. 4).

Scientists are planning to use the RIBF to create such heavy unstable elements for the first time to examine

their characteristics. “In collaboration with researchers in astrophysics, we are planning to theoretically predict the characteristics of nuclei with high accuracy, thereby reproducing the processes in a supernova and the creation of elements.”

Although the mechanism of supernovae has yet to be properly clarified, the mechanism of creation and the origin of elements appear to be well understood through experiments in astronomy and at the RIBF, and through theoretical studies on the nucleus and astrophysics. Studies in these fields will lead to the verification of new theories using experimental and astronomical observation data, and to improvements in the accuracy of the density functional equation.

“Our ultimate goal is to predict the characteristics of all atomic nuclei; that is, to find a way to calculate all of their characteristics based on the numbers of protons and neutrons that constitute the nucleus.”

Generating energy from unused atomic nuclei

“Within ten years, I think we will discover a density functional equation that allows us to predict the characteristics of all atomic nuclei with accuracy ten times higher than that of the conventional equation. I think a more accurate prediction of the mechanism of how an atomic nucleus splits into fragments will greatly contribute to solving energy and resource problems,” says Nakatsukasa.

Current atomic power plants use uranium-235 (^{235}U) as a fuel source because it is readily fissile. However, ^{235}U is a limited resource, accounting for only 0.7% of all naturally occurring uranium. The remainder is primarily uranium-238 (^{238}U), which contains three more neutrons than ^{235}U . “The nuclei of ^{238}U and other heavy elements around it in the periodic table are fissile, but we do not yet know how to use them effectively as a fuel source.”

In modern nuclear power plants, low-

energy neutrons are forced to collide with ^{235}U nuclei to cause nuclear fission. Other heavy elements, such as ^{238}U , have not yet been used as a fuel source in this way. Yet these heavy nuclei can also undergo nuclear fission when bombarded with high-energy neutrons. For example, some scientists are proposing a new type of nuclear power plant in which fission is induced by bombardment of high-energy neutrons produced by an accelerator. There are great hopes for this new type of nuclear power plant because it has several advantages, including the ability to use previously unused heavy elements as a fuel source, and its high safety because nuclear fission ceases when the accelerator is stopped. Unfortunately, these proposals have yet to be put into practice.

“Various experiments have been conducted with ^{238}U to examine the conditions required for the fuel to be used and the energy level of the bombarding neutrons required to cause the nuclei of the fuel atoms to split effectively. A mere theoretical approach seems unable to provide new data. However, we may be able to propose a new type of nuclear fission reactor by taking advantage of nuclear theory to

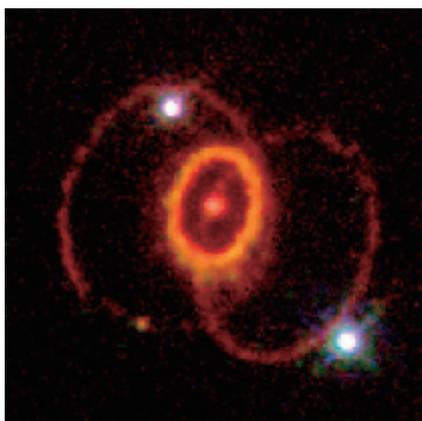


Figure 4: Supernova 1987A.

Supernova 1987A, discovered in 1987, is in the Large Magellanic Cloud about 160,000 lightyears from Earth. Supernovae are thought to create heavy unstable nuclei, which in turn disintegrate into major heavy elements ranging from iron to uranium. Researchers are now predicting theoretically the rate at which elements are synthesized by supernovae, and comparing the results with actual observation data to verify their predictions.

accurately predict the mechanism of the nuclear fission in atomic nuclei produced in nuclear reactors, such as neptunium, americium and curium, which have so far been disregarded.”

Is it feasible to convert high-level radioactive waste to stable nuclei to produce rare-earth elements?

Some of the nuclei produced by the nuclear fission of ^{235}U in nuclear reactors have very long half-lives—the period over which half of a sample undergoes radioactive decay. As a result, the inclusion of such nuclei in high-level radioactive waste poses a major problem for disposal. “If these unstable, long-life radioactive nuclei are bombarded by protons or neutrons, or even light (photons) of a specific energy, they may split into smaller nuclei that have a shorter half-life, or into stable nuclei that do not emit radiation.”

Even now, some reactions are known to be able to convert long-life radioactive nuclei into short half-life species. “However, the probability of the occurrence of the reactions is so small that disposing of all high-level radioactive waste in this way is too costly and time-consuming to be practical. Furthermore, experimental attempts to find a reaction with a higher probability of occurrence are also costly and time-intensive. I think nuclear theory will help to find a reaction with a higher probability in the near future. We may be able to find a reaction that creates rare-earth elements as well as convert high-level radioactive nuclei into stable species.” Rare-earth elements are essential materials for light-emitting diodes, fuel cells and high-tech equipment. Thus, the creation of rare-earth elements in this way could be good news not only for resource-poor Japan, but also for the entire world.

Advancing nuclear physics by leaps and bounds using the RIBF

Nakatsukasa believes that a new nuclear theory with high accuracy will be established within ten years, and that the theory will contribute to technological development in

various areas, but he is also excited about a completely different scenario.

“Experiments based on the RIBF might provide experimental data that could be completely different from the results predicted by the latest nuclear theory. This could be of great benefit even to theoreticians, because theories are refined and reformulated whenever new phenomena that existing theories fail to explain are found. Thus, physics has developed by leaps and bounds. I think the theoretician’s main work is to refine and reformulate conventional theories. Quantum dynamics, the basics of nuclear theory, was established in the 1920s. In the more than 80 years since then, no data has been found that suggests some error in the theory. If the RIBF contributes to finding such data, it will bring about a great innovation in physics.”

In either event, RIKEN with its RIBF is very well positioned to achieve major breakthroughs in nuclear physics and become a world research base in the field over the coming years. ■

About the researcher

Takashi Nakatsukasa was born in Tokyo, Japan, in 1967. He graduated from the Faculty of Science, Kyoto University, in 1989, and obtained his PhD in 1994 from the same university. He spent more than 4 years as a postdoctoral researcher at Atomic Energy of Canada Limited in Chalk River, Canada, and at the University of Manchester Institute of Science and Technology in Manchester, UK. He returned to Japan as a special postdoctoral researcher at RIKEN in 1999, then became an assistant professor at Tohoku University in 2001 and a lecturer at the University of Tsukuba in 2003. Since 2007, he has acted as associate chief scientist at the RIKEN Nishina Center for Accelerator-Based Science. His current research focuses on computational nuclear physics using density functional theory.



The RIKEN Science Lectures

The most recent round of RIKEN's annual public lecture series focused on the diagnosis and treatment of infectious diseases at a time of renewed concern about global pandemics.

The RIKEN Science Lectures are a series of annual events bringing together pioneering researchers at RIKEN and leading scientists in related fields to share their findings with the public. The latest set of lectures took place on December 5th 2009 at the Marunouchi Building Hall in central Tokyo, in what was the 31st year of the event. The program was dominated by the theme of infectious diseases and was the second in a four-year series focusing on the role of RIKEN, as Japan's largest research institute devoted to the natural sciences, in tackling problems of health, environment and energy. The 2009 lecture series occurred against a backdrop of fear about a global H1N1 influenza pandemic, further emphasizing the importance of research on treatments for infectious diseases.

RIKEN's efforts in the area of infectious diseases are concentrated on a powerful research network connecting

ten universities and research institutions in Japan to twelve collaborative research centers spread across eight countries in Asia and Africa. Organized through the Program of Founding Research Centers for Emerging and Reemerging Infectious Diseases, an initiative of the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT), the network answers a pressing need for on-site research toward advances in diagnosis and treatment. RIKEN's contribution is coordinated by the RIKEN Center of Research Network for Infectious Diseases (CRNID), which oversees activities of the research centers and offers support through the hosting of symposia and sharing of information.

In the opening lecture of the series, Yoshiyuki Nagai, director of the CRNID and a world-leading specialist in virology, emphasized that Japan cannot tackle the challenge of infectious diseases in isolation. "We can't talk about

the security of Japan without talking about the security of Asia, and of the world," he said, pointing out that while infectious diseases heed no national borders, borders do exist in research on infectious diseases.

Taking his cue from this observation, Akira Suzuki of the Tohoku University School of Medicine introduced one of the key international collaborations in the CRNID-supported network. Connecting researchers in Japan to on-site facilities and hospitals in the Philippines, the TOHOKU-RITM Collaborating Research Center on Emerging and Reemerging Diseases has played a pivotal role in clarifying the nature of many diseases afflicting the region (see box).

Along with international collaboration, development of technology for diagnosis is also essential in responding to today's global pandemics. In his lecture, RIKEN Omics Science Center (OSC) Director

Yoshihide Hayashizaki explained how his center's trademark SmartAmp (Smart Amplification Process) technology contributes to this response. SmartAmp reduces single nucleotide polymorphism (SNP) analysis time to just half an hour, enabling fast, affordable on-site care testing for a range of different diseases, including the new influenza (H1N1) virus.

In the final lecture, Takehiko Sasazuki,

president emeritus of the International Medical Center of Japan, discussed the link between infectious diseases and cancer, one which underlies 10% to 30% of all cancer cases worldwide. "DNA is remarkably stable, but if it was perfectly stable there would be no evolution, and we would not be here today," he said, noting that this same instability is also what gives rise to cancer. As the link connecting infectious diseases and cancer, he pointed

to extremely complex genetic pathways, whose cancer-causing mechanisms science has yet to fully clarify.

Although many questions regarding the treatment of infectious disease worldwide remain unanswered, the 2009 RIKEN Science Lectures provided a broad overview of this field, showcasing the research that will ensure our society remains safe and secure in the years to come. ■

Chasing the Forgotten Killer

UNICEF and the WHO describe pneumonia as the "forgotten killer of children", because while this disease kills more children than any other, little attention is paid to it. At the TOHOKU-RITM Collaborating Research Center on Emerging and Reemerging Diseases, a joint collaboration between the Tohoku University Graduate School of Medicine in Japan and the Research Institute of Tropical Medicine (RITM) in the Philippines, we are focusing significant efforts toward understanding this disease. In May, 2008, in cooperation with local hospitals, we initiated a study to determine the causes of death among children with severe pneumonia on the island of Leyte.

The conditions in hospitals in Tacloban, the city where we are stationed for this study, are very different from those in Japan. In emergency rooms, there is none of the equipment one would expect to find. Most patients require mechanical ventilation for respiratory support, but ventilators are not available, and equipment that is available is left unused for lack of maintenance funds.

Our study set out to investigate conditions in this region, while also training local staff and establishing a system for on-site diagnosis and treatment. Of the total 800 cases we enrolled, 8% of patients died during hospitalization, a mortality rate higher than in other regions of the country. In our study, we identified rhinoviruses and respiratory syncytial virus (RSV) as the pathogens responsible for most severe cases of pneumonia in children. While we did not detect any sign of the new influenza virus (H1N1), we are currently working with local health authorities to monitor for and respond to this strain if and when it arrives.

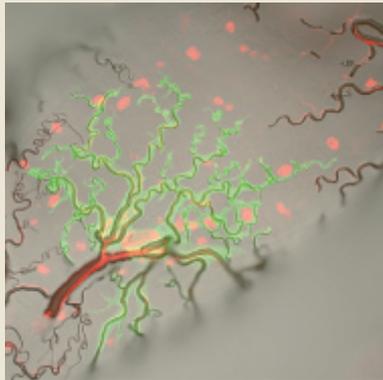
Given the global nature of today's health problems, we are confident that our research in the Philippines will bring much-needed improvements not only to the lives of local people, but also to the people of Japan, and of the world. ■

Akira Suzuki is an Assistant Professor at the Tohoku University School of Medicine.



RIKEN Researchers win top prizes in Leica Japan Photo Contest

Two researchers from the RIKEN Center for Developmental Biology (CDB) have been awarded top prizes for photographs they submitted to the 2009 Leica Japan Photo Contest. "The Breathing Cell", a photograph submitted by Shigeo Hayashi of the CDB's Laboratory for Morphogenetic Signaling depicting the branching of a tracheal fruit-fly cell, won



the prestigious grand prize in the contest. Tada Motoki of the CDB's Laboratory for Evolutionary Morphology was awarded one of three Outstanding Performance awards for a photograph, titled "Mm-e10.5", of neurofilament antibodies in a five-day-old mouse embryo. Organizer Leica Microsystems Japan received 54 entries from a range of individuals, institutions and companies throughout the country.

Hayashi's grand-prize-winning photograph symbolizes the focus of research at his laboratory, where his group studies developmental mechanisms of the trachea using the fruit fly as a model. "The Breathing Cell" depicts the complex tree-like branching of a single tracheal cell into tubes that transport air to the body. One of two members of the jury, photographer Herbie Yamaguchi, noted that the photograph "really conveys the mystery of life." The other jury member, University of Tokyo Associate Professor

Kei Ito, remarked on the beautiful contrast between the fluorescence green labeling and the three-dimensionality produced by differential interference contrast optics.

Reflecting on the prize, Hayashi described how he jumped at the chance to enter the contest. "There are photo contests like this in Europe and America, but this was the first such contest in Japan," he explained. "It's a very special contest, because it goes beyond the science and also evaluates more general artistic aspects of the work. I am overjoyed that the image has been awarded the prestigious top prize, and that it has succeeded in conveying to its audience the wonder of science."

The winning photographs are currently viewable on the Leica Microsystems Japan website and will also be featured in the February issue of the journal *Cell Technology*, published by Gakken Medical Shujunsha Co. ■

RIKEN co-hosts symposium on molecular imaging

In January this year, RIKEN and the National Institute of Radiological Sciences (NIRS) co-hosted Molecular Imaging 2010, a two-day symposium reviewing five years of research conducted under the Molecular Imaging Research Program with funding from the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT).

Two research centers figured prominently at the symposium: the RIKEN Center for Molecular Imaging Science (CMIS) in Kobe, and the Molecular Imaging Center (MIC) of the NIRS in Chiba. CMIS Director Yasuyoshi Watanabe introduced his center's work on molecular imaging probes for positron emission tomography (PET), which are used to study the distribution of target molecules quantitatively in animals and humans. "Nowhere else in the world can you find these," he said, referring to more than 70 original probes developed at the CMIS. These probes are expected to bring dramatic advancements in essential therapeutics and early diagnosis for diseases such as cancer, Alzheimer's disease and diabetes.

One area where molecular imaging is having a significant impact is neuroimaging. MIC researcher Tetsuya Suhara cited nicotine addiction as an example. "We know from animal experiments that nicotine triggers the release of dopamine leading to addiction," he noted. "But to understand what is happening in humans, we need a non-invasive approach. Molecular imaging does this, enabling us to study the underlying molecular processes directly." The same technology can also be used to monitor serotonin in the brain, opening new doors for treating depression.

Further expanding on these applications, Shuichi Enomoto and his group at the CMIS are

developing the world's first camera for real-time imaging using multiple molecular probes, called gamma-ray emission imaging (GREI). "Using multiple probes, we can produce a thorough diagnosis with only a single, non-invasive test," he explained. "This technology is very effective in tumor imaging and regenerative medicine."

With the world's leading research on display, Molecular Imaging 2010 highlighted Japan's unparalleled strength in molecular imaging science. It also gave a taste of the upcoming revolution in diagnosis and drug discovery, one which promises to transform the whole of medical science. ■

2010 RIKEN Conference on Soft Materials and Interfaces

Initiated with the goal of spotlighting leading advancements in a given field, the RIKEN Conference series provides a unique opportunity for scientists to build and expand international networks for cutting-edge research. Focusing on the field of soft materials and interfaces, this year's conference featured presentations by 20 researchers from overseas and 20 from Japan, who were all invited to the RIKEN Harima Institute to introduce their research.

One topic that attracted a great deal of attention this year was environmentally friendly materials. Tadahisa Iwata of the University of Tokyo demonstrated how radiation from SPring-8, the Harima Institute's world-class synchrotron radiation facility, could be used to develop biodegradable bio-based polymers. Controlling the biodegradation rate of such polymers, Hideki Abe of the RIKEN Advanced Science Institute (ASI) explained, is key to their use as functional materials, a goal that his research team is striving to achieve.

A wide variety of other novel materials

were also discussed. Jonathan S. Dordick of the Rensselaer Polytechnic Institute described enzyme-nanomaterial composites that endow surfaces with self-cleaning properties, and highlighted their potential use in places such as hospitals. David C. Martin of the University of Delaware conveyed the challenges of developing materials that could act as the interface between biomedical devices and living tissue, and Yoshihito Osada of the RIKEN ASI demonstrated how novel hydrogel materials with high stress and friction properties could substitute for certain living tissues entirely.

Asked about his impressions of the event, RIKEN ASI researcher Yoshihiro Ito referred to a comment by Kevin Healy of the University of Berkeley. "Healy reminded us that back in 1931, when Ernest O. Lawrence built the first cyclotron, it was only 4.5 inches in size," Ito said. "Look how far we have come. We now have, thanks to Lawrence's early guidance, a synchrotron the size of SPring-8, used by researchers across all fields of science, including soft materials."

"Conferences like this one provide a crucial opportunity for scientists to forge new directions in research," Ito said. Needless to say, these opportunities also lay the seeds for long-lasting friendships, which are also a vital part of the research enterprise. ■





Dr Tahei Tahara
Chief Scientist
Molecular Spectroscopy Laboratory
RIKEN Advanced Science Institute
Wako, Saitama, Japan

Dear Tahara-san,

You might be surprised to receive this postcard after so long, but I thought I should let some time pass since returning from RIKEN before writing, so as to gain some perspective.

As you know, my visit to your group last summer was my first trip to Japan. Even though I knew several Japanese scientists and had heard of the unique work culture from friends who had been there, the first-hand experience was still amazing and beyond any expectation. I returned with a tremendous amount of respect for Japan in general, and for RIKEN and the Molecular Spectroscopy Laboratory in particular. Wherever we went, we felt a warm glow of friendship and acceptance that made us long to go back again and again.

During my stay in RIKEN, I was most impressed by the work culture there. All the researchers are highly zealous about their work and would go all the way to get to the bottom of the problems they are addressing. The intensity and enthusiasm of discussion in the group meetings were infectious. What I liked most was that very fundamental issues of physical chemistry were being addressed using novel state-of-the-art techniques. Seeing your group at work, I was constantly reminded of some famous lines composed by Rabindranath Tagore, a celebrated poet of India: "where the mind is without fear and the head is held high, where knowledge is free,...where words come from the depths of truth, where tireless striving stretches its arms towards perfection..." On a different note, it felt great to be involved in experiments with Wei and Takeuchi-san. While doing so, I felt as if I had grown younger. Of course, the social gatherings were awesome too.

Thank you for having arranged the visits to other laboratories as well. The attosecond lab, the microscopy lab and the novel materials fabrication lab were particularly impressive. I feel that my exposure has increased manifold during the couple of months that I spent in RIKEN and I have come back rejuvenated and more motivated, with goals set much higher than before.

Let me thank you once again for having invited me to visit last summer. It was really a wonderful experience. I am really happy that our institute and RIKEN have signed an agreement on an international joint graduate school and that the first student under this program, Achintya, is now working in your group. I hope that the relationship between our institutes and our laboratories will get stronger and stronger with the passage of time.

Best regards,

Anindya Datta
Associate Professor
Department of Chemistry
Indian Institute of Technology Bombay
Powai, Mumbai 400 076, India



Dear Anindya,

Thank you very much for your wonderful postcard. I am not sure whether we deserve your nice words, but I am very happy to hear that you enjoyed your stay with us.

As I said to you before, I hope that our personal relationship could be a seed for a future broader relationship between your institute and RIKEN, and more generally, between India and Japan. I believe that good international relationships are based on mutual trust between individuals. Let's keep in touch!

Best wishes,

Tahei



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