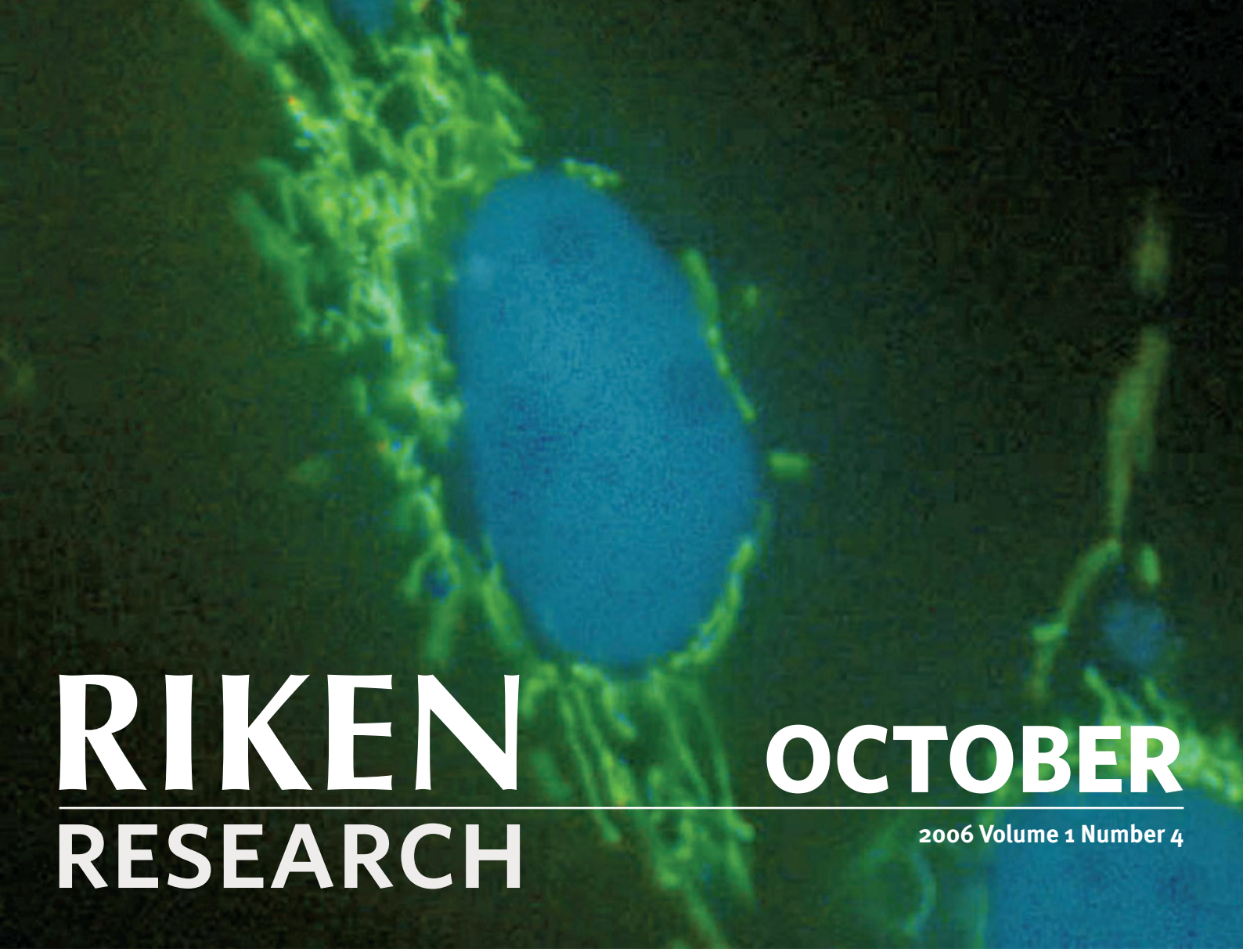

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Mitochondrial mutations linked to longevity

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A helping hand for proline

Potential clue discovered on 'left-handed' amino acids

Like most biological molecules, amino acids can take one of two different mirror-image forms. Now scientists think they may have found a clue to solve one of the biggest puzzles in science: why only the 'left-handed' form of amino acid is found in living systems.

Amino acids are the building blocks of every protein in our bodies, and just like your hands they are chiral—you cannot superimpose an amino acid on its mirror image (Fig. 1). These left- and right-handed forms are called enantiomers. But scientists are still unsure why left-handed amino acids should be preferred over right-handed, or how this situation first arose on the prebiotic Earth—the so-called 'origin of homochirality'.

Hiroyuki Koshino at RIKEN's Discovery Research Institute, Wako, and Yujiro Hayashi at the Tokyo University of Science, have now discovered how a left-handed amino acid might have got its first foothold as the preferred enantiomer. They have found that a mixture of the solid amino acid proline containing only a slight excess of the left-handed enantiomer can generate a solution that contains almost exclusively left-handed proline[1].

Creating such a large excess of one enantiomer can often pose a serious challenge for synthetic chemists, but Koshino and Hayashi's team say that the procedure is so simple that something similar could conceivably have happened by accident on the early Earth.

They found that in crystals of proline that contained an equal mixture of the two enantiomers—called racemic crystals—the molecules can fit together in a way that allows more chemical bonds to form than in crystals containing just one enantiomer (Fig. 2). These bonds are called hydrogen bonds, and rely on the attraction between partially charged positive and negative areas of the proline molecule. Although not as strong as the bonds that normally tie atoms together into molecules, they are tough enough to make the racemic crystals more insoluble in a mixture of chloroform and ethanol and therefore more likely to precipitate from the liquid.

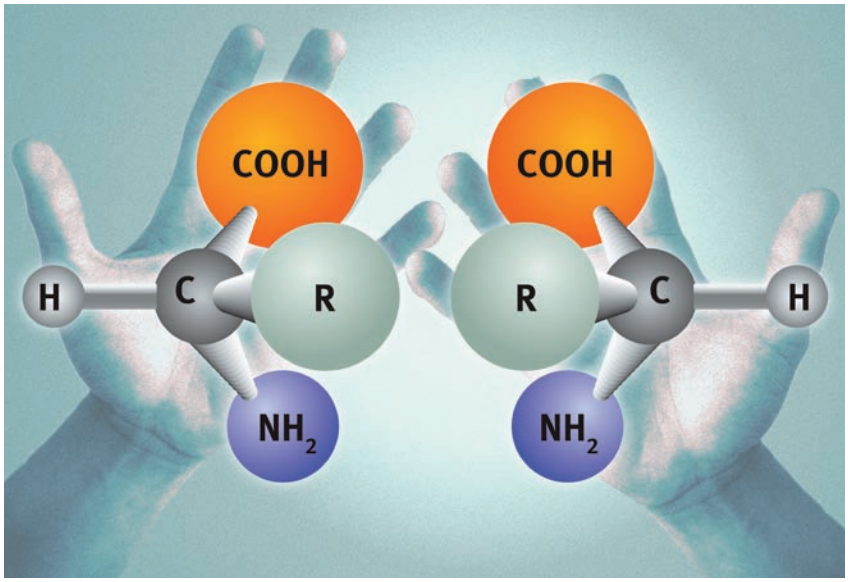


Figure 1: Amino acids, just like your hands, come in two mirror-image forms.

By carefully controlling the proportions of ethanol and chloroform, the team could exploit this to transform a 55:45 mixture of left- and right-handed solid proline into an almost pure solution of the left-handed enantiomer. This is the first time that a single enatiomer has been dramatically enriched by this mechanism, the team says.

"Many cases of the difference in solubility between some enantiopure and racemic crystals are well known, and most of them are focused on the enantiomeric excess of solid and crystals," says Koshino. "But we focus on the enantiomeric excess of solution—that is the unique difference."

The left-handed proline can act as a catalyst in the formation of other biological molecules, and other scientists have suggested that once left-handed amino acids were established on Earth, they could act as a template to determine the handedness of many other biological compounds, such as sugar molecules. To demonstrate the activity of their enantiomerically enriched proline solution, the scientists used it to catalyse a reaction between propanal and nitrosobenzene. These two molecules can stick together in two different ways, and would normally produce a racemic mixture of enantiomers. But with the enriched solution of proline added to the mix, only one enantiomer of the propanal-nitrosobenzene product forms.

The scientists speculate that similar processes could have been at work before life began on Earth. A very slight imbalance in the handedness of amino acids could be amplified into a biological

preference for left-handed enantiomers by the same mechanism, they suggest. For example, solid crystals of mixed left-right proline could be filtered out as a liquid dripped through rock strata, leaving an enriched solution of left-handed amino acid behind, primed to influence the subsequent reactions that kick-started life.

However, the solvent system they investigated—ethanol and chloroform—would not have existed on the early Earth. Nevertheless, the team is optimistic that they could find a water-based system able to purify proline in the same way. "I hope that there is some possibility for water under some special condition," says Koshino.

But even if this method for amplifying the relative amounts of left-handed proline does replicate what happened on Earth before life began, the system still needs a slight imbalance of the two amino acid enantiomers to begin with.

The team points out that one potential source for that initial excess could be meteorites. Some chunks of space rock are loaded with carbon-based organic materials that have been exposed to harsh conditions on their journey through space. Previous experiments on artificial mixtures of such compounds have shown that ultraviolet light can trigger the formation of proline.

Meanwhile, various astronomers have suggested that circularly polarised starlight—light whose electric field twists like a corkscrew as it travels—can preferentially destroy one amino acid enantiomer in preference to its twin. This would mean that when the meteorite arrived on Earth there would be a slight excess of one enantiomer of its proline cargo. In Earth's case, sheer chance brought us a little extra of a left-handed amino acid that subsequently set a four-billion-year precedent.

This part of the theory is far from being proved. However, key evidence for the meteorite delivery theory could come from the European Space Agency's Rosetta spacecraft, which is due to land on the comet Churyumov-Gerasimenko in 2014. Once there, it will search for amino acids on the surface, and will also be able to detect their handedness. ■

1. Hayashi, Y., Matsuzawa, M., Yamaguchi, J., Yonehara, S., Matsumoto, Y., Shoji, M., Hashizume, D. & Koshino, H. Large nonlinear effect observed in the enantiomeric excess of proline in solution and that in the solid state. *Angewandte Chemie International Edition* **45**, 4593–4597 (2006).

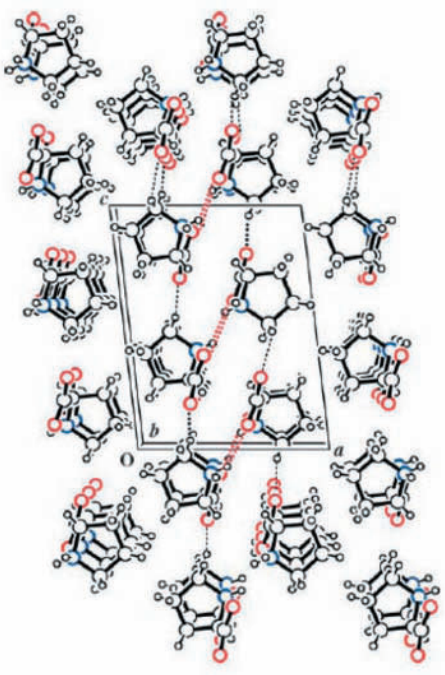
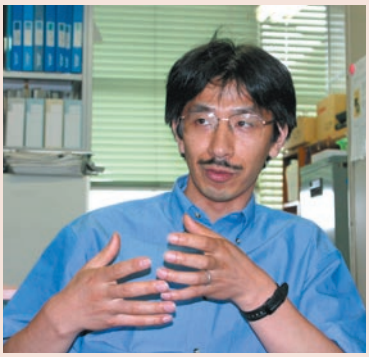


Figure 2: The crystal structure of racemic proline makes it less soluble than a crystal of a single enantiomer. Oxygen = red, Nitrogen = blue, Carbon = black (large), Hydrogen = black (small).
Reproduced with permission from *Angew. Chem. Int. Ed.* from Wiley-VCH, 2006, 45, 4595.

About the researcher

Hiroyuki Koshino was born in Hokkaido in 1963. He graduated from the Faculty of Agriculture, Hokkaido University in 1985 and received his doctorate in agriculture from the same university in 1990. In the same year, he joined RIKEN's Antibiotics Laboratory as a postdoctoral fellow. In 1992, he moved to the Molecular Characterization Division of the RIKEN Discovery Research Institute, and was appointed as the leader of the Molecular Characterization Team in 2003.



A PHENOMEnal plant collection

Observable traits of 4,000 *Arabidopsis* mutants could lead to an international effort to identify the function of a complete plant genome

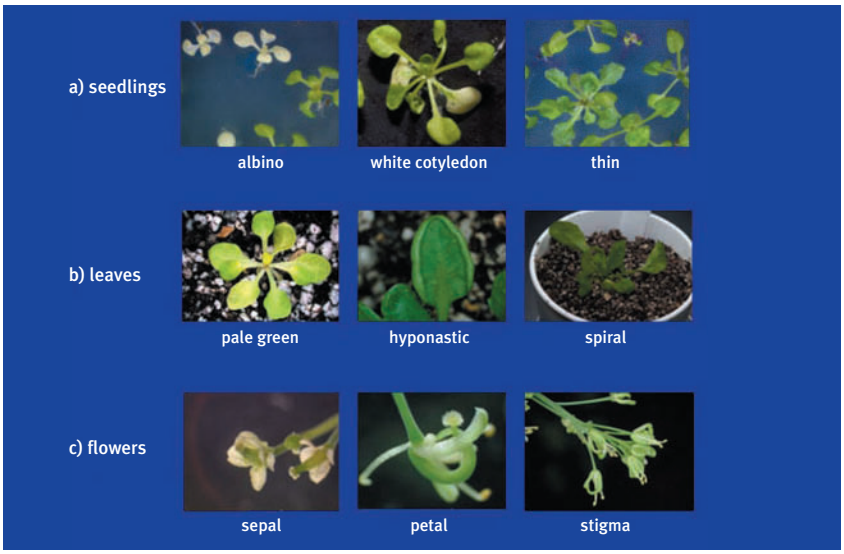


Figure 1: Kuromori and colleagues studied changes in eight morphological traits that set apart single-gene *Arabidopsis* mutants from the wild type. Variations in traits shown are a) seedlings, b) leaves and c) flowers.

Even in the era of molecular biology, much can still be learned about an organism just by looking at visible changes in its form and structure—or its phenotype. Based on this simple reality, plant biologist Takashi Kuromori and colleagues at the RIKEN Genomic Sciences Center and the RIKEN Plant Science Center, in Yokohama, have combined molecular approaches and visual observation to initiate the characterization of the 'phenome'. This is the complete collection of morphological traits associated with every single gene in the model plant *Arabidopsis thaliana*.

In previous efforts, Kuromori and colleagues, as well as other groups, generated 18,000 so-called 'transposon-insertional mutant *Arabidopsis* lines' [1,2,3]. These are *Arabidopsis* plants in which particular genes—or stretches of DNA encoding for particular functions—have been disrupted, one at a time, through the insertion of a small DNA element. The researchers can determine the exact location of the insertion through sequencing.

In their current paper in *The Plant Journal*[4], Kuromori and colleagues take the first step in characterizing the functions of 4,000 of these disrupted, or mutant, genes. The team looked closely at eight different plant traits including the color and shape of the seedlings, stems, leaves, fruits, flower structure, branching patterns, timing of flowering and growth, and seed yield (Fig. 1).

Through the systematic recording of the 4,000 mutant lines throughout their different growth stages, from germination to flowering and fruit production, Kuromori and colleagues compiled a large collection of images. The collection documents the development of the mutant lines chosen for this initial study. This information is available to the research community through a publicly accessible database hosted by RIKEN as part of a larger project called the RIKEN Arabidopsis Genome Encyclopedia (RARGE)[5].

"These data represent but the first step toward the more ambitious goal of characterizing the phenotypes associated with the tens of thousands of genes encoded by the *Arabidopsis* genome," says Kuromori. He also notes that the path from expression of a particular gene to an observable phenotype, that is, a morphological effect, is most probably a complex one rather than a direct cause-effect relationship. "Therefore, the thorough characterization and classification of morphological variations in *Arabidopsis* provides a solid foundation upon which to build further research on the network and relationship of genes in this model plant," he says. ■

1. Ito, T., Motohashi, R., Kuromori, T., Noutoshi, Y., Seki, M., Kamiya, A., Mizukado, S., Sakurai, T. & Shinozaki, K. A resource of 5,814 dissociation transposon-tagged and sequence-indexed lines of *Arabidopsis* transposed from start loci on chromosome 5. *Plant and Cell Physiology* **46**, 1149–1153 (2005).
2. Kuromori, T., Hirayama, T., Kiyosue, Y., Takabe, H., Mizukado, S., Sakurai, T., Akiyama, K., Kamiya, A., Ito, T. & Shinozaki, K. A collection of 11 800 single-copy Ds transposon insertion lines in *Arabidopsis*. *The Plant Journal* **37**, 897–905 (2004).
3. Ito, T., Motohashi, R., Kuromori, T., Mizukado, S., Sakurai, T., Kanahara, H., Seki, M. & Shinozaki, K. A new resource of locally transposed *Dissociation* elements for screening gene-knockout lines *in silico* on the *Arabidopsis* genome. *Plant Physiology* **129**, 1695–1699 (2002).
4. Kuromori, T., Wada, T., Kamiya, A., Yuguchi, M., Yokouchi, T., Imura, Y., Takabe, H., Sakurai, T., Akiyama, K., Hirayama, T., *et al*. A trial of phenome analysis using 4000 *Ds*-insertional mutants in gene-coding regions of Arabidopsis. *The Plant Journal* **47**, 640–651 (2006).
5. Sakurai, T., Satou, M., Akiyama, K., Iida, K., Seki, M., Kuromori, T., Ito, T., Konagaya, A., Toyoda, T. & Shinozaki, K. RARGE: a large-scale database of RIKEN *Arabidopsis* resources ranging from transcriptome to phenome. *Nucleic Acids Research* **33**, D647–D650 (2005).

Variability in mitochondrial DNA linked to longevity

Direct mechanism found connecting complex diseases with changes in mitochondrial DNA

A Japanese team led by RIKEN researchers has accumulated evidence of how genetic variability in the mitochondria—the energy production centres of the cell—can affect longevity.

The mitochondria, which are distributed in the body of the cell outside the nucleus, have their own DNA. It codes for parts of the enzymes involved in energy production as well as their protein manufacture system.

Mitochondrial DNA tends to have a relatively high degree of variability. Some of the mutations, or polymorphisms, are associated directly with muscle and nervous disorders; others appear to increase the risk of complex diseases, such as diabetes, Alzheimer's disease, Parkinson's disease, bipolar disorder and cancer. It is also reported that mitochondrial polymorphisms are related to individual variability in cognition, personality, athletic performance and longevity. Until now, however, there has been no direct biochemical and physiological mechanism to link these outcomes with changes in DNA.

In work reported online in *PLoS Genetics*[1], the research team used specially constructed cell lines to discover that two closely linked polymorphisms that code for respiratory chain proteins can affect the acidity and the levels of calcium inside the mitochondria. The finding opens the possibility of preventing any associated medical conditions with drugs that reverse these changes.

"We are now interested in the impact of this genetic variability on nerve and brain function," says research project leader, Tadafumi Kato of RIKEN's Brain Science Institute in Wako. "But it will be very challenging."

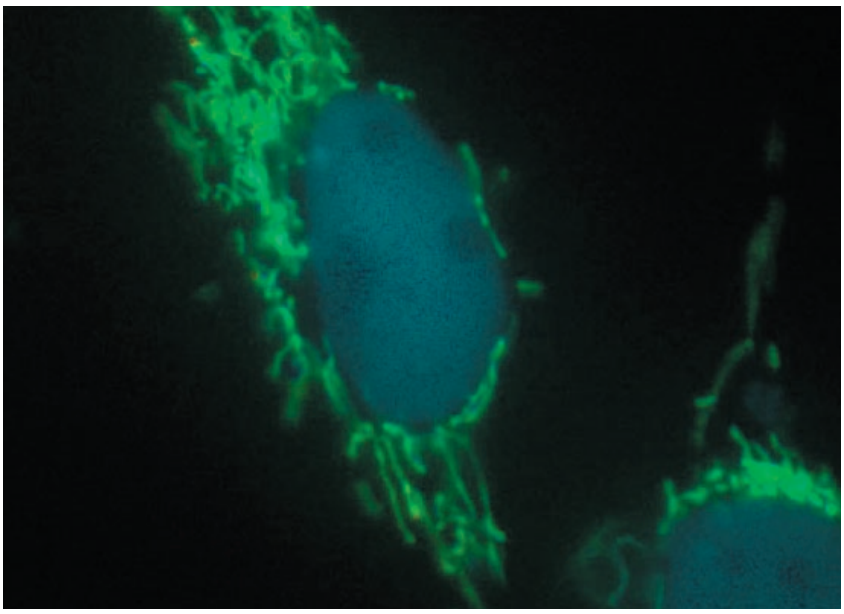


Figure 1: A pseudocolor image of a cybrid with fluorescent indicators targeted to mitochondria (green) and nucleus (blue).

In the course of its work, the research team created a series of cybrid cell lines. A cybrid is a hybrid cell formed by fusing cells treated to remove their mitochondrial DNA with cell fragments containing mitochondria, in this case platelets from the blood of 35 volunteers. The researchers incorporated fluorescent tags for calcium measurement into their cybrid cells (Fig. 1) and, using the fluorescence, were able to measure calcium levels within mitochondria.

By sequencing the mitochondrial DNA of these cell lines, the researchers identified two polymorphisms associated with changed calcium levels. These polymorphisms also affected the pH in mitochondria. These factors, calcium levels and pH, are linked to fundamental activities of the mitochondria.

One of the polymorphisms the researchers identified is known to be a risk factor for the disease conditions mentioned above. Previous studies have shown that individuals aged 100 years old or more tend not to possess this polymorphism. ■

1. Kazuno, A., Munakata, K., Nagai, T., Shimozono, S., Tanaka, M., Yoneda, M., Kato, N., Miyawaki, A. & Kato, T. Identification of mitochondrial DNA polymorphisms that alter mitochondrial matrix pH and intracellular calcium dynamics. *PLoS Genetics* **2**, Issue 8: e128 (2006); published online 11 August 2006 (doi: 10.1371/journal.pgen.0020128).

Connecting genes with proteins

New understanding of genes and the proteins for which they code could lead to identification of therapeutic drug targets

A team led by researchers from RIKEN has cloned the DNA sequences responsible for all the nearly 5,000 proteins produced in the cells of a particular strain of yeast.

The work provides a direct link between the complete set of genes—the genome—and the proteins for which it contains the plans—the proteome. Already, the team has been able to trace where about 90% of the proteins are utilized in the cell.

Genetic material consists of long chains of four different compounds, known as nucleotide bases. Parts of these sequences of bases code for the order of the amino acids which make up the proteins used to construct and operate living organisms. The genetic sequence is decoded by reading the bases in groups of three. But a correct outcome demands knowledge of exactly where each sequence starts and stops, and in which direction it is read. This is known as an open reading frame (ORF).

Led by Minoru Yoshida at the RIKEN Discovery Research Institute in Wako, the team employed a commercially available technique called recombination-based cloning to chop out, amplify and transfer all the predicted ORFs of the fission yeast, *Schizosccharomyces pombe*, to expression vectors used to stimulate the production of their matching proteins in target cells. *S. pombe* has the smallest genome of all higher organisms and shares many traits with human cells.

After eliminating duplicate, partial and false genes, the team had close to 5,000 cloned yeast ORFs. They then sequenced each ORF to check there were no serious errors.

As reported in *Nature Biotechnology*[1], by attaching a yellow fluorescent tag, the team tracked the protein produced from each ORF to where it was utilized (Fig. 1). Not only does this provide clues as to the protein's role, but in many cases its function could also be compared with similar proteins in closely related yeasts and in other organisms. They also studied the function of a gene product which helps guide some of the proteins into position by pushing them out of the nucleus. Such transport factors often play an important role in disease, and can become useful targets for therapeutic drugs.

In the immediate future, the research team will continue the analysis of its yeast results, says Yoshida. "But we will also utilize our clones to produce drug sensitivity data and to identify drug targets. Based on our results, we have already started a new project developing a screening system for therapeutic drugs." ■

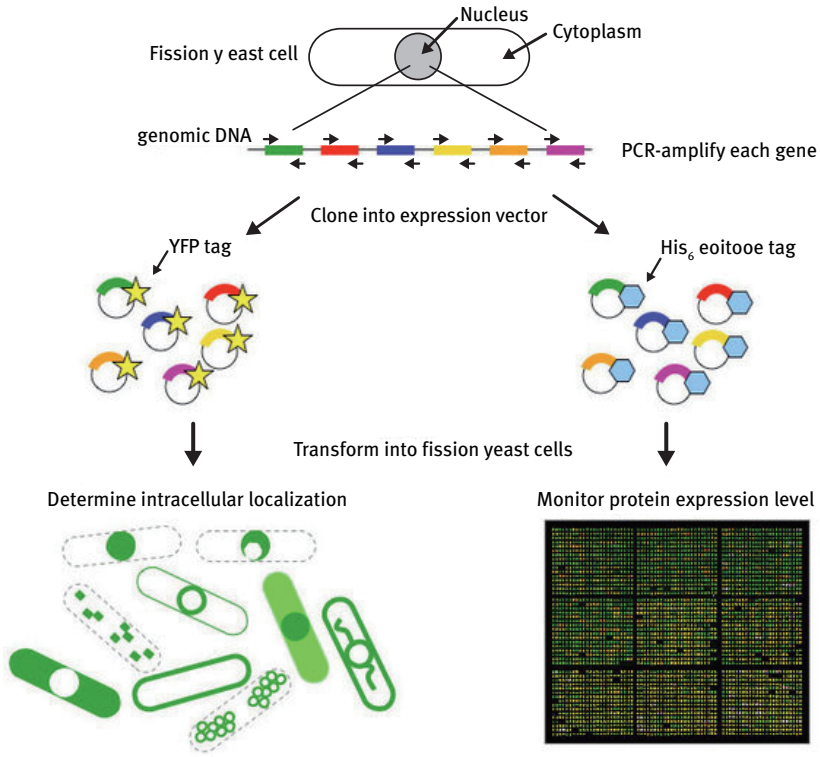


Figure 1: A schematic diagram of how the team analyzed the connection between genes and proteins in fission yeast.

1. Matsuyama, A., Arai, R., Yashiroda, Y., Shirai, A., Kamata, A., Sekido, S., Kobayashi, Y., Hashimoto, A., Hamamoto, M., Hiraoka, Y., Horinouchi, S. & Yoshida, M. ORFeome cloning and global analysis of protein localization in the fission yeast *Schizosaccharomyces pombe*. *Nature Biotechnology* **24**, 841–847 (2006).

Building proteins on a stable base

RIKEN researchers are probing how proteins keep in shape under extremely high temperatures with an eye to designing biologically active compounds for the future

A team from several Japanese institutes led by RIKEN researchers has found that the exceptional stability of a protein, from an archaebacterium that lives at temperatures close to the boiling point of water, is due to its ability to generate pairs of positive and negative charges along its surface that interact to bind it together.

The protein CutA1 from the archaebacterium *Pyrococcus horikoshii* can maintain its structure at temperatures of nearly 150 °C, the researchers report in *FEBS Letters*[1]. This is about 30°C higher than any other protein so far measured. The work could help bioengineers design and build proteins for therapeutic and bioengineering purposes.

"We are trying to understand the mechanism of stabilisation of proteins to allow us to design more stable proteins ourselves," says the research program leader, Katsuhide Yutani of the RIKEN SPring-8 Center in Harima.

The CutA1 protein is widely distributed in bacteria, plants and animals. In humans it is found in the brain, and thought to play a role in anchoring a key enzyme in the membranes of nerve cells.

The team measured and compared the characteristics of CutA1 proteins from archaea and bacteria that live and function optimally in three different temperature environments—*Escherichia coli* at 37 °C, *Thermus thermophilus* at 75 °C and *P. horikoshii* at 98 °C. The protein in each case is a trimer, consisting of three identical subunits bonded together. In each species, however, the subunits or monomers differ in the number and composition of amino acids.

Using a technique known as differential scanning calorimetry, the researchers could determine the temperature at which each of the three proteins denatures or begins to break down. Under neutral conditions, pH 7.0, this temperature for *T. thermophilus* was 113 °C and for *P. horikoshii* 149 °C, between 40 and 50 °C above the typical conditions encountered in each bacterium's environment.

The team then studied characteristics of the crystal structures of the three proteins that could contribute to this stability. They included such factors as the numbers of hydrogen bonds and ion pairs, the size of the internal cavity, and the lack of interaction with water. The most significant difference between CutA1 in the three species was the relative number of ion pairs that formed within each monomer. The surface of *P. horikoshii* was studded with them, *T. thermophilus* less so and *E. coli* had even few (Fig. 1). All the other characteristics were similar between the species. ■

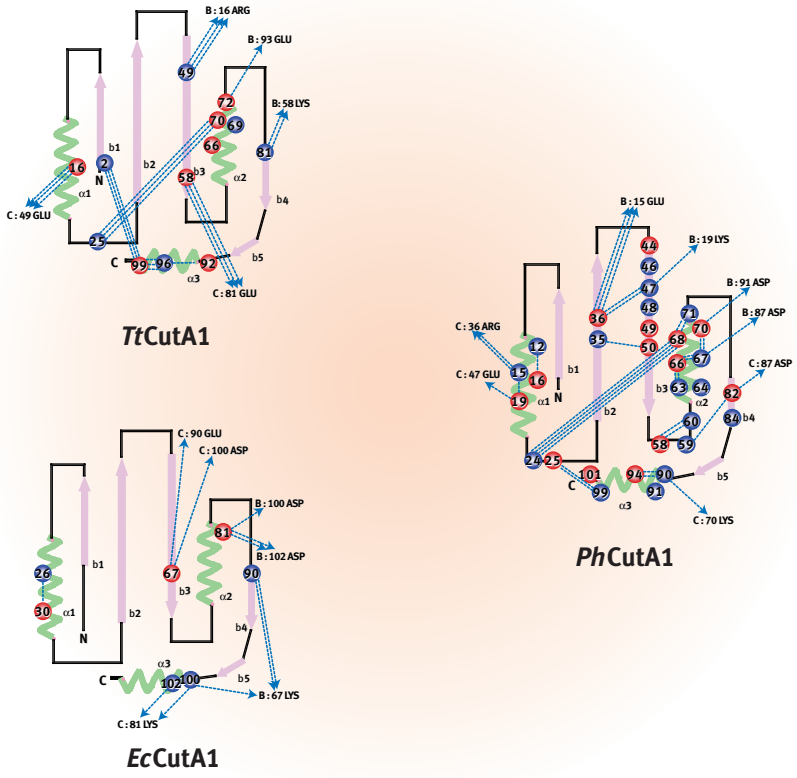


Figure 1: Schematic views of ion pairs of the three bacterial CutA1 proteins (*Ph*CutA1 from *P. horikoshii*, *Tt*CutA1 from *T. thermophilus* and *Ec*CutA1 from *E. coli*).

1. Tanaka, T., Sawano, M., Ogasahara, K., Sakaguchi, Y., Bagautdinov, B., Katoh, E., Kuroishi, C., Shinkai, A., Yokoyama, S. & Yutani, K. Hyper-thermostability of CutA1 protein, with a denaturation temperature of nearly 150 ˚C. *FEBS Letters* **580**, 4224–4230 (2006).

How young daughters establish their potential

New research suggests that when it comes to the proper development of individual cells, location is just as important identity

Asymmetric cell division, in which a 'parent' cell divides to generate different types of 'daughter' cells, is a fundamental process for the proper development of a complex organism, even in one as simple as the worm *Caenorhabditis elegans*. "About 80% of cell division during the development of *C. elegans* is asymmetric cell division," explains Yukinobu Arata, a member of Hitoshi Sawa's team at the RIKEN Center for Developmental Biology in Kobe.

Surprisingly, most of these divisions are regulated by the transcription factor POP-1/TCF, which is differentially localized in the resulting daughter cells. However, since individual daughter cells achieve different developmental fates depending on their position in the worm, other determining factors are clearly involved.

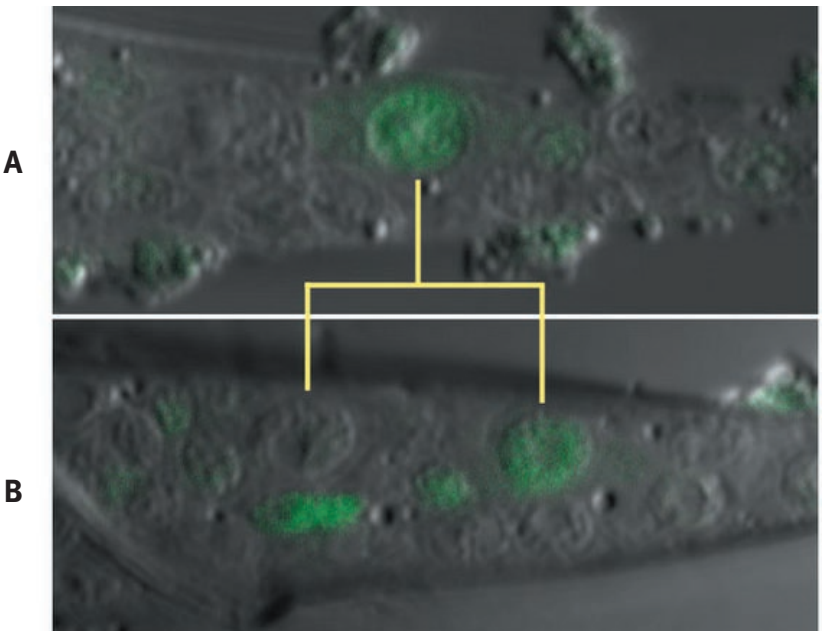


Figure 1: Asymmetric PSA-3 expression, indicated by green fluorescence, after the division of a hypodermal cell in the tail region of the worm *C. elegans*. The left side is anterior and the upper side is dorsal. A = parent cell, B = daughter cells.

As reported in *Development Cell*[1], Arata, Sawa and colleagues in Japan and the US generated large numbers of *C. elegans* mutants, which show the defective asymmetric division of a hypodermal cell, the T cell, in the tail region of the worm. Normally, this cell divides to generate an anterior cell (T.a), which yields hypodermal cells, and a posterior cell (T.p), which yields neural cells. In mutants, however, division produces only hypodermal cells. Their screen led to the identification of a novel gene, *psa-3*. They also identified mutations in genes encoding NOB-1, a *C. elegans* Hox protein that plays a role in establishing proper formation of the posterior region, and CEH-20, a Pbx protein that acts as a cofactor for NOB-1.

Arata and colleagues analyzed *psa-3* expression patterns. They found elevated levels of PSA-3 protein in cells derived from the T.p cells but not T.a cells (Fig. 1). This pattern matches the distribution of POP-1/TCF activity. Subsequent analysis confirmed that POP-1/TCF activity is necessary for *psa-3* expression, but not sufficient by itself—expression also requires position-specific co-activation by NOB-1 and CEH-20. Expression of *psa-3*, in turn, seems to play an important role in developmental events downstream of asymmetric T cell division.

According to Arata, these data could provide important insights into the genetic determinants of proper development. "The most interesting finding," he says, "is that cooperation between the mechanisms for asymmetric cell division and positional identity specifies a unique daughter's fate." The researchers further postulate[1] that this type of combinatorial signaling may be a relatively standard developmental process, even in higher organisms. "Our concept … may shed light on mechanisms for cell fate specification through asymmetric division in vertebrates," concludes Arata. ■

1. Arata, Y., Kouike, H., Zhang, Y. Herman, M.A., Okano, H. & Sawa, H. Wnt signaling and a Hox protein cooperatively regulate PSA-3/Meis to determine daughter cell fate after asymmetric cell division in *C. elegans*. *Developmental Cell* **11**, 105–115 (2006).

Uncovering a secret messenger

Scientists reveal first evidence that zinc plays an active role in immune response and, possibly, cellular signaling

It is well-established that zinc is vital to cellular function, although it has long been assumed that this is primarily due to its role as a cofactor for a variety of essential proteins, including metabolic enzymes and transcription factors. However, recent research by a team from the RIKEN Research Center for Allergy and Immunology, in Yokohama, and Osaka University suggests that zinc may be far more than just a passive biological bystander.

In 2004, the team, led by Toshio Hirano, found that proper cell migration during zebrafish development is mediated in part by increased expression of a zinc transporter protein in response to cytokine signaling[1]. This surprising finding led the investigators to explore whether zinc regulation might also play a role in the maturation of dendritic cells (DCs). This is the process by which these cells present foreign antigens to T cells to trigger a cellular immune response. This process is also a major focus of Hirano's team.

Initial experiments showed that exposure of isolated mouse DCs to the bacterial endotoxin lipopolysaccharide (LPS), a stimulant of immune response, led to a decrease in intracellular zinc concentration; by the same token, artificial depletion of intracellular zinc triggered DC maturation[2] (Fig. 1). Artificial elevation of zinc levels, on the other hand, suppressed the ability of DCs to respond to LPS. Hirano and colleagues found that LPS affects the expression of a number of zinc import and export proteins, with the net effect of increased zinc transport out of the cell. The group observed similar effects in live animals, where injection of LPS or zinc-depleting agents led to increased DC maturation.

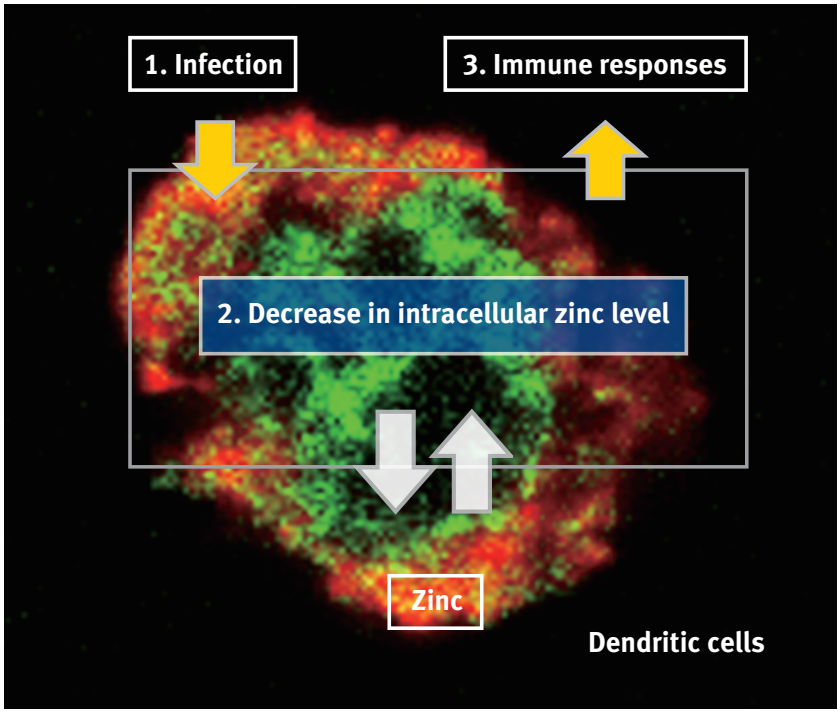


Figure 1: A schematic of zinc's role in mediating immune response in dendritic cells (red = a fluorescent indicator of dendritic cell maturation; green = a fluorescent indicator of zinc).

According to Hirano, this work offers important progress in understanding zinc's role in the immune system. "It is known that zinc deficiency causes immunodeficiency, but these observations are all phenotypic ones—no precise mechanisms are known," says Hirano. "This is the first evidence that zinc plays an active role in immune response."

However, the implications could go well beyond the immune system, and these data may offer evidence of a previously unrecognized mode of cellular signaling. "Our findings indicate that the level of intracellular free zinc changes in response to extracellular stimuli, such as cytokines and growth factors. This strongly suggests that zinc acts as a signaling molecule like calcium," he says. "If this process can be generalized to other cell types, this would be one of the most exciting findings in the field of signaling pathways." ■

1. Yamashita, S., Miyagi, C., Fukada, T., Kagara, N., Che, Y.S. & Hirano, T. Zinc transporter LIVI controls epithelial-mesenchymal transition in zebrafish gastrula organizer. *Nature* **429**, 298–302 (2004).
2. Kitamura, H., Morikawa, H., Kamon, H., Iguchi, M., Hojyo, S., Fukada, T., Yamashita, S., Kaisho, T., Akira, S., Murakami, M. & Hirano, T. Toll-like receptore-mediated regulation of zinc homeostasis influences dendritic cell function. *Nature Immunology* **7**, 971–977 (2006).

Promoting brain science research through Japan–US collaboration

RIKEN Brain Science Institute (BSI) was established in 1997 to serve as a core center for brain science research in Japan. In 1998, BSI established RIKEN–MIT Neuroscience Research Center (RMNRC) at the Massachusetts Institute of Technology (MIT) in the United States. The aim was to develop a leading, world-class research system, and to promote collaboration with domestic and international research institutes.

This July, we interviewed Susumu Tonegawa, Nobel laureate, director of RMNRC and working scientist in charge of the six research teams in the center. We asked him how he evaluated the research activities conducted so far, and the future prospects of the Institute.

Reducing research barriers in Japan by promoting exchange among researchers

How would you evaluate the research activities promoted by RMNRC?

Tonegawa: One of the main objectives in establishing RMNRC was to promote the globalization of BSI by inviting outstanding overseas researchers who are currently serving as laboratory heads, and providing them with a place to conduct research. BSI intends to increase the percentage of overseas researchers to 25–30% of all research staff. This target has not yet been achieved; however, I'm sure that the percentage will soon increase. I say this because for the past eight years since the establishment of RMNRC, researchers of MIT have visited BSI and participated in symposia, summer schools, retreats and short-term seminars sponsored by BSI laboratories. Through these experiences they have developed closer ties with BSI and have become less resistant to doing research in Japan.

If the living environment for overseas researchers continues to improve, more and more researchers would choose to do research in BSI, as it is a leading Japanese research institute comparable to the top-level European and American institutes.

Fostering creativeness in the open research environment

The Japanese researchers from BSI who visited RMNRC—could you tell us how they were influenced by these visits?

Tonegawa: Well, the research environment of MIT is very open. For example, regardless of rank or position, the MIT staff relate



on a first-name basis. Beyond the confines of the laboratories, the researchers know what others are doing and develop strong friendships at the individual level. The researchers from Japan were very impressed, and observing the friendly relations among the researchers at MIT was a real eye-opener for them.

Japanese researchers have the ability to maintain their concentration and conduct elaborately planned research. However, they tend to communicate less with each other and devote themselves only to their own research activities. To be a full-fledged researcher, one should be more interested in colleagues' research activities and also in other research fields. A full-fledged researcher should be able to accept and understand other researchers' ideas. One should make more efforts to develop informal personal relationships with their colleagues and expand their interpersonal relations.

I am proud that MIT, including RMNRC, has an outstanding open atmosphere compared with other research institutes in the US. I would go as far as to say that MIT provides the ideal environment for research. Because the laboratories are on cooperative terms with one another, they frequently conduct joint research projects.

If we take an interdisciplinary approach, we can generate a remarkably synergistic effect. In this case, we can expect one plus one to make, not two, but three or four. My research team often carries out joint research projects with the research team led by Matthew Wilson (See pages 11–12). Wilson originally specialized in electrical engineering. By taking a collaborative approach, the two teams have effectively promoted joint research projects and published important results.

One of the factors that enabled the realization of such an ideal research environment is the fact that RMNRC brings together outstanding researchers who respect each other. 'Outstanding researchers' does not necessarily mean those who can produce many articles. Outstanding researchers are co-workers who are interesting to work with, who influence one another positively in the research process. A narrow-minded researcher who shows a winning-is-everything attitude cannot perform good research.

Another factor is that all the laboratory heads of RMNRC make efforts to foster an open and creative research environment, and manage their laboratories with this same enthusiasm. Whether the research environment is good or not depends not on overall institute policy but largely on the laboratory head's work philosophy.

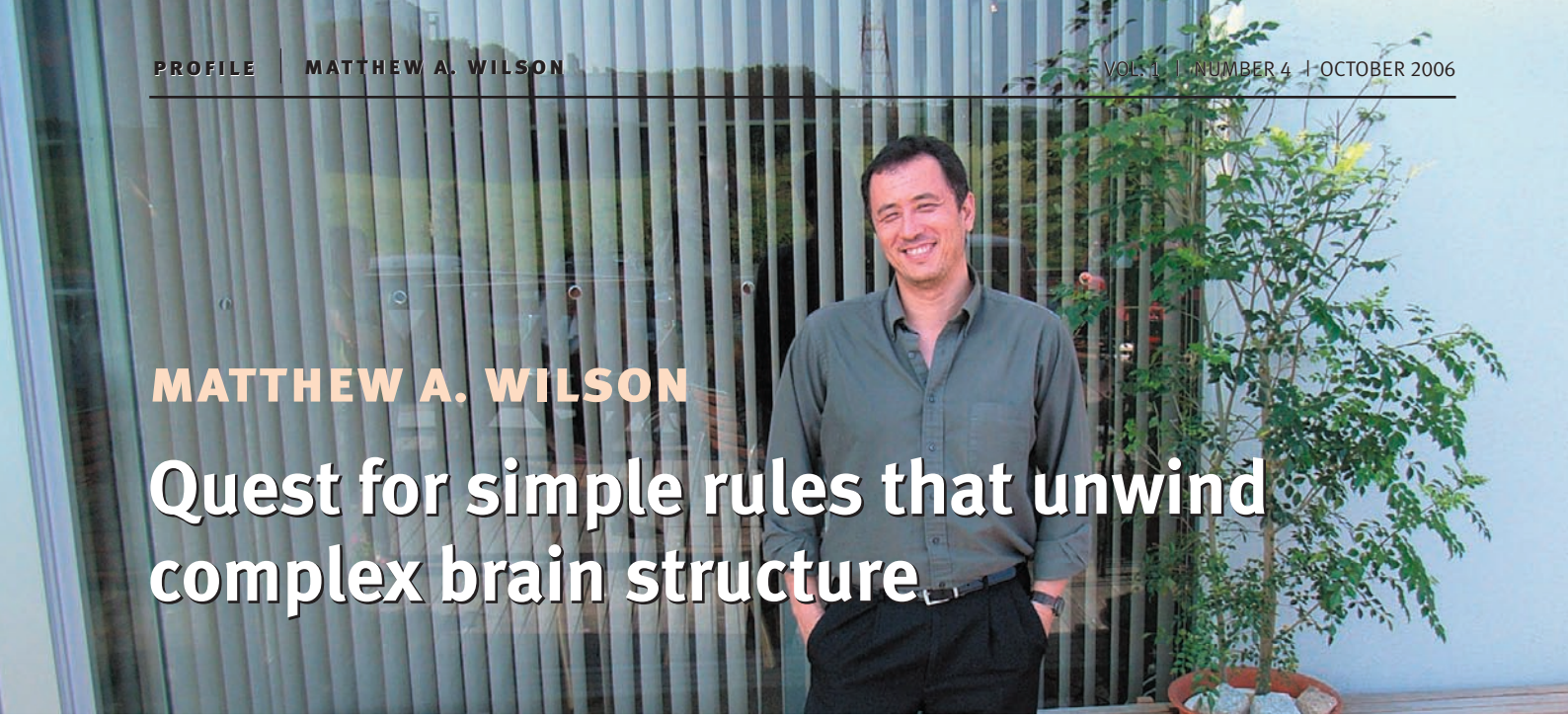
Having a long-term view and promoting brain science research in Japan

Could you explain the future development of RMNRC, and what you expect from brain science research in Japan?

Tonegawa: In the field of brain research, the technology of mouse gene manipulation is very important. In our laboratory, we have established world-class cutting-edge technology using laboratory mice. In order to further advance this technology, we are now planning a research project in collaboration not only with BSI but also with another research center of RIKEN. I believe that if this joint research project is realized, it will play a hugely important role in determining the direction of future neuroscience .

Regarding brain science research in Japan, I would like to emphasize strongly that we need to raise awareness that BSI is a very unique and important research institute, and to promote its further development. I have great admiration for Masao Ito, the founder and special advisor of BSI, because he is a person of tremendous foresight who fully understands the importance of having a flexible and open research system. I would like to keep further development of BSI.

I earnestly request that the government officials who determine key policy regarding science and technology promote the continuation of brain science research from a broad perspective. Once Americans decide to implement a new project, they push ahead with it relentlessly. This brain science research has been promoted as a 100-year scheme, and it has only just begun. I hope that the officials concerned will promote brain science research in Japan from a long-term viewpoint. ■



MATTHEW A. WILSON

Quest for simple rules that unwind complex brain structure

An American engineer-turned-neuroscientist at RIKEN-MIT is bringing fresh approaches to the study of how the brain works

On a sunny day in August, more than 50 students were listening avidly to an energetic lecture entitled "The hippocampal memory for spatial experience" being given by Matthew A. Wilson, a neuroscientist from the RIKEN-MIT center in the US. "Feel free to challenge any ideas," he said, and then the class became livelier as enthusiastic students plied him with questions.

"One of the nicest things about giving talks is that you get opportunities to think about the same materials in different ways," Wilson says, showing no trace of fatigue after his three-hour lecture. The lecture was one of the programs of a summer school at the RIKEN Brain Science Institute (BSI), which offers internships and classes for top students selected from around the world at its laboratories in Wako, near Tokyo. "Thinking is the most enjoyable and important part of doing science."

This deep interest in 'thinking' led Wilson to switch careers from electrical engineering to looking into how the brain gains cognition based upon experiences. As the leader of the Reinforcement and Emotion in Ensemble Memory Formation Laboratory at the RIKEN-MIT Neuroscience Research Center in Cambridge, US, the 44-year-old neuroscientist takes advantage of his expertise in optimising the use of technologies to bring fresh perspectives to the field. With a fine-tuned microelectrode device that he created to measure brain activities, his team has generated some surprising results—such as the formation of memory during sleep in rats.

Good with his hands

As a child, Wilson liked to construct things and play with computers. At around 11, the child of a Korean mother and American father, he was struck by a computer program about artificial life that "created complex structures using simple rules," he says. Naturally, Wilson chose electrical engineering as his undergraduate course. At the same time, he always cherished another interest: 'the inner world'. "The complexity of behavior, how we learn, how we interact with the environment … I was drawn into these as an engineer."

In early days of his new career, however, it wasn't easy to find how best to tackle the brain. Initially, Wilson tried to create models of creating large-scale neural ensembles, and completed his PhD work at the California Institute of Technology. But he soon found modelling was insufficient to understand the brain's actual functions and problems in behaving animals.

Wilson then shifted his focus from building synthetic networks to measuring brain activities, and developed a multiple electrode recording device during his postdoctoral fellowship at the University of Arizona. Wilson says some of the inspiration for the device came from the design of flexible offshore oil drilling rigs, which deal with similar issues of stability in the face of movement and distribute control of multiple independent probes. After trials and errors to create an optimal tool, he realized too much technology could be a problem, and kept the basic specifications as simple as possible.

The recording device is shaped like a pincushion, and implanted on the head of a rat (Fig. 1). This involves digging an ultra-tiny hole in a skull and inserting 72 fine wires—each as thin as a hair—distributed over 18 sites of brain cells in the hippocampus, a brain region responsible for learning and maintaining records of experiences. The rat doesn't feel any pain. Researchers then spend several days lowering the wires until they reach the right cell layer, and monitor the electrical activity of many brain cells.

A place where disciplines meet

After finishing postdoctoral work in 1994, Wilson applied for a position at the Fairchild Center for Learning Memory, newly established at the Massachusetts Institute of Technology and headed by Susumu Tonegawa. (It later became the Picower Institute for Learning and Memory, which also joined with the BSI to create the RIKEN-MIT Neuroscience Research Center. See pages 9–10). Wilson was the first scientist taken on by the center. He found the place attractive because it was open to scientists with different disciplines who shared a common interest in learning and memory.

In particular, Wilson says he was grateful to have Tonegawa as a mentor. "When I talk, I think about things. Susumu doesn't accept answers that don't make sense. He's very sophisticated in that way and that turned out to be very valuable."

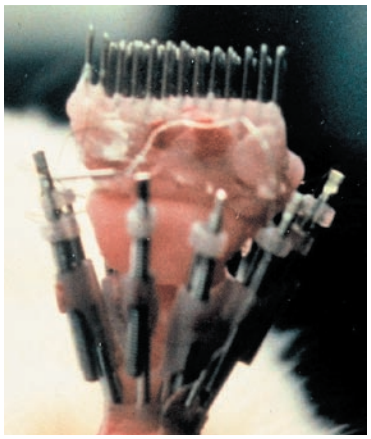


Figure 1: **Wilson got some of the inspiration for the recording device from offshore oil drilling rigs.**

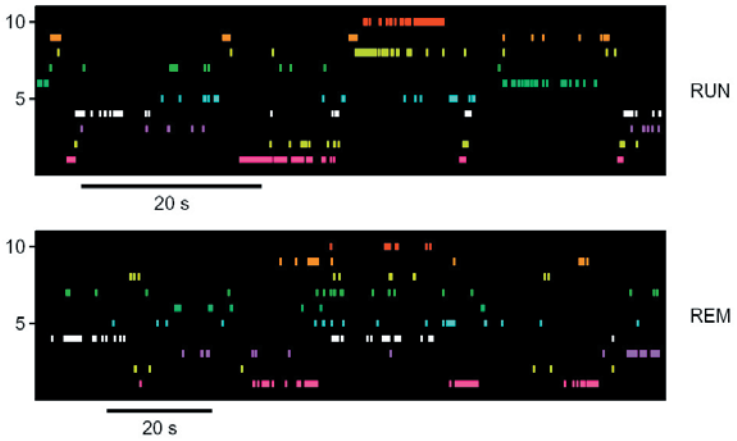


Figure 2: **The data show the pattern of activity of 10 hippocampal neurons recorded while a rat ran around a simple circular maze over a period of approximately 2 minutes (top panel), and the activity of the same neurons during a single REM episode in which that pattern is replayed over a similar timeframe (bottom panel).**

Tonegawa says Wilson is one of the most creative scientists and one of the most lovable people he has ever met, and has an excellent instinct for recognizing scientific directions. "I thought if we combined his recording technology with our conditional genetic engineering technology for mice, we could raise the sophistication of memory research to a new height," Tonegawa says. He adds he respects Wilson's attitudes in setting a very high ethical standard to himself while being tolerant of others.

Rats may think, even think back

Even today, Wilson uses simple techniques he invented during his postdoctoral era at his laboratory. But he requires everyone in his 16-member laboratory to learn all the techniques related to the science, from understanding devices and analysing algorithms to conducting surgery on rats. It seems demanding, but he says anyone with the right motivation can acquire these skills.

But Wilson notes that the devices he developed are merely the starting point for an understanding of what patterns brain activities. He says careful observation, deep commitment to the work and respect for nature are the keys to success. As a research focus, he assumes sleep may be a critical period in which the process of memory takes place. "Sleep is a unique period during which animals may be able to take past experiences and bring them together, which cannot be done at any other time. We think about this process as contributing to some aspects of cognition in a unique way," Wilson says.

Wilson's most surprising result so far was published in 2001[1]. His team trained rats to run along a circular track and detected patterns of electrical firing triggered by hippocampal cells over tens of seconds to minutes—much longer periods than similar experiments conducted in the past. They also examined these patterns during rapid-eye-movement (REM) sleep, a sleep state in which people dream and their neurons are active as much as in the awake state. As a result, researchers detected a long timescale of episodic memory being replayed in the brain during REM sleep, as if it were a short movie (Fig. 2). "To me, it was astonishing. Animals had recorded and stored minutes of their experiences," Wilson says. The result suggests rats may have a similar depth of experiences to humans, although the complexity of understanding is different.

More recently, Wilson's team found an intriguing result—a reverse replay of experiences when rats are awake, not sleeping[2]. A postdoctoral researcher recorded the electrical activity of hippocampal cells in rats and let them do what they naturally do, instead of forcing them to run. They walked one into the other, stopped, and sat there for minutes doing nothing. Then the same brain cells that he observed during active moments replayed the sequence of electrical firing repeatedly, but surprisingly in a temporally reversed order. It implies that, while sitting quietly, the rats were thinking back and replaying experiences they had just had.

Cherish an engineering spirit

Despite some exciting results, Wilson says neuroscientists, including himself, are just seeing pieces of the brain system. For now, he's trying to find a fundamental structure of how the brain learns to memorize, and ultimately wants to demonstrate the ability to control and manipulate it. Further down the road, Wilson could be building devices that would allow humans to extend their ability to understand the world by processing experience-based information in a wiser way. "As an engineer, I want to understand how the brain works," he says. ■

1. Louie, K. & Wilson, M. A. Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. *Neuron* **29**, 145–156 (2001).

2. Foster, D. & Wilson, M. A. Reverse replay of behavioural sequences in hippocampal place cells during the awake state. *Nature* **440**, 680–683 (2006).

About the researcher

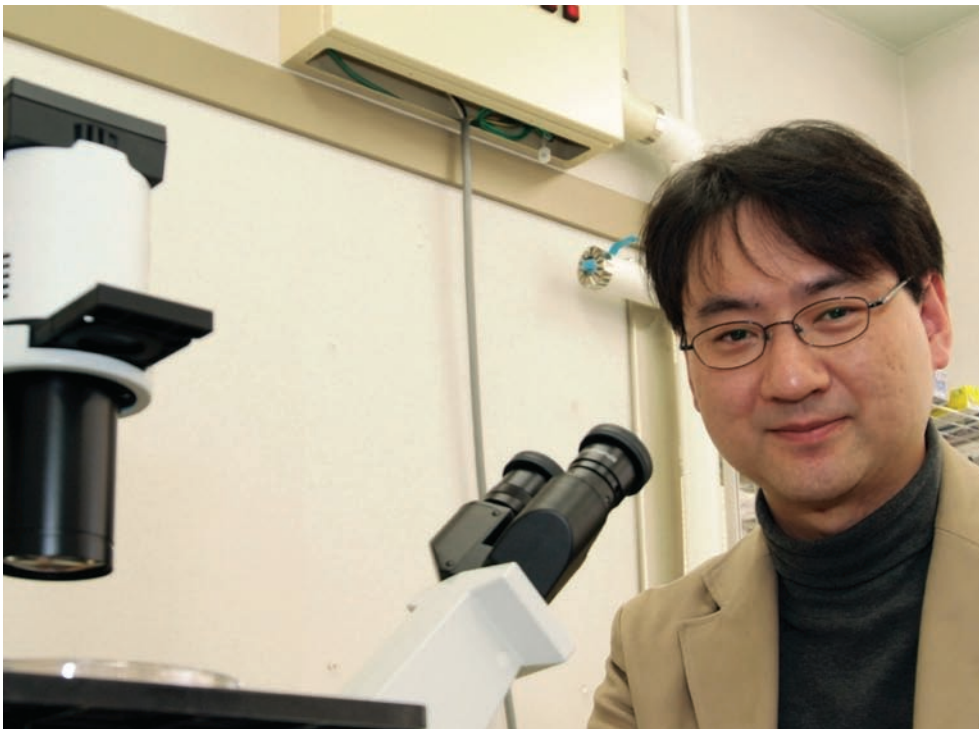
Matthew A. Wilson was born in 1961 in Seoul, and moved to the US in 1969. In 1990, he received a PhD in Computational and Neural Systems from the California Institute of Technology, and completed his postdoctoral training at the University of Arizona. In 1994, he joined the faculty of the Department of Brain and Cognitive Sciences and the current Picower Institute for Learning and Memory at MIT. In addition to being the head of the Reinforcement and Emotion in Ensemble Memory Formation Laboratory at RIKEN-MIT Neuroscience Research Center, Wilson serves as a scholar and professor at the same departments at MIT.

His laboratory's website: http://web.mit.edu/wilsonlab

Solving the mystery of biodiversity and creating antibody drugs

Kunihiro Ohta

Associate Chief Scientist
Genetic System Regulation Laboratory
RIKEN Discovery Research Institute



According to a UN report, there is a new type of influenza, which, if it were to spread across the world, could result in the loss of as many as 150 million lives in a worst-case scenario. To treat and diagnose emerging infectious diseases, RIKEN researchers are developing a new system that can produce antibody drugs in approximately one week. The system is called the 'ADLib (Autonomously Diversifying Library) system', and it is being developed under the leadership of Kunihiro Ohta, Associate Chief Scientist of the Genetic System Regulation Laboratory, the RIKEN Discovery Research Institute. Recently, research into antibody drugs has been advancing rapidly with their use as anticancer drugs spreading increasingly. Antibody drugs have a significant therapeutic effect while having almost no side-effects. However, the conventional methods that employ animal bodies to produce antibodies have some major problems: more than a few months are needed to produce a new antibody, and some antibodies cannot be produced. Ohta and members of his laboratory are focusing on overcoming these difficulties. The team is also expanding the potential of antibody drugs by developing the ADLib system—so that antibodies can be produced in a test tube.

Accelerating DNA recombination

Ohta has been interested in living organisms since he was a child. "What is a living organism? One of the main features is its diversity. There are a great variety of species living on the earth, and some differences exist even in the same species. We want to probe the mystery of what the significance of diversity is for living organisms and how they produce this diversity," he says.

One of the processes that produce the diversity of living organisms is DNA recombination (genetic recombination), which occurs when sperm and eggs are formed during meiosis. In the meiotic process, the DNA, which is inherited from the parents, is cut into fragments, which are then modified or blended into new combinations of DNA that form individual sperm or eggs. This is one of the reasons why facial features and personalities are different between siblings. Children are born with different combinations of DNA allowing them to adapt differently to environmental variations. Successful variations can then be passed on to their offspring.

DNA usually has a structure like beads on a string, known as a chromatin structure, with proteins called histones being wrapped with the DNA chain (Fig. 1). This structure repels the enzymes that are capable of cutting the DNA chain, so it effectively prevents recombination, a process during which the DNA is cut and modified. Ohta's team clarified that DNA recombination starts when a rise in the acetylation level of the histones exposes part of the DNA, and that this reaction is accelerated when living organisms are stressed. "Living organisms fulfill their potential when they are in trouble. For example, plants start DNA recombination in winter,

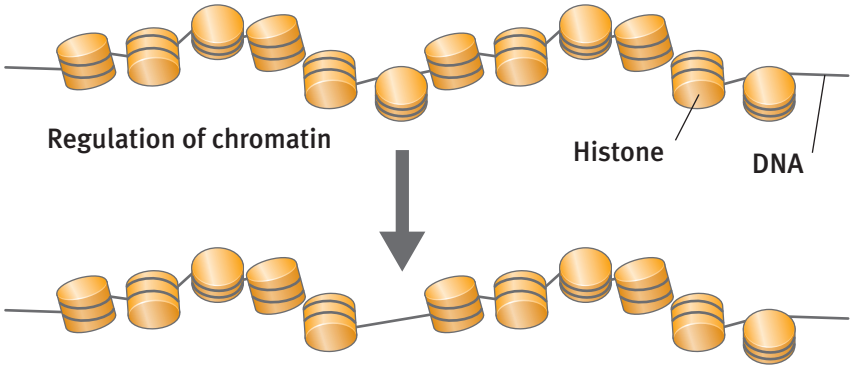


Figure 1: Regulation of chromatin and DNA recombination
DNA recombination starts when the DNA wrapped around histones is exposed, and a chain-breaking enzyme acts on the DNA.

when they are stressed because of the shorter sunlight hours and deficiency in nutrition," says Ohta. "Thus they prepare to produce flowers and leave offspring. For example, in the history of life's diversity, about 550 million years ago there was an event called the 'Cambrian Explosion,' when species of organisms drastically increased in diversity and complexity. Some sort of environmental variations before or during the period may have placed a stress on organisms, promoting DNA recombination and diversification."

Ohta's team is promoting the analysis of DNA recombination mechanisms and technological developments, including how to cause DNA recombination at a designated position in the DNA chain, and how to activate and accelerate the DNA recombination to produce useful crops or yeasts.

Creating various antibodies in a test tube

The mechanism to produce antibodies by the immune system is based on forms evolved through genetic recombination. Antibodies are Y-shaped proteins, parts of which are slightly different from each other, forming 100 billion different kinds. The immune system provides a number of antibodies that can bind exactly to specific foreign bodies (antigens), thus protecting the organism.

A human has 22,000 genes, the blueprints for proteins. What makes it possible to produce 100 billion kinds of antibodies from 22,000 genes? Susumu Tonegawa, the current Director of RIKEN-MIT Neuroscience Research Center, and 1987 Nobel Laureate in Physiology or Medicine, cleared up this mystery. He revealed the fact that the formation of B cells, which serve as a manufacturing plant to produce antibodies, causes DNA recombination to start, thus leading to the production of a variety of antibody genes.

Recently, antibody drugs have been attracting much attention. The purpose is to produce artificial antibodies available for diagnosis and medical treatment. "Herceptin, an antibody drug for breast cancer is well-known. Conventional anticancer drugs have serious side effects and unsatisfactory survival benefit. However, scientists have started developing anticancer-antibody drugs that have a significant therapeutic effect but have little side effects," Ohta explains.

However, conventional antibody-producing methods have serious drawbacks. In the conventional method, antibodies are produced *in vivo* by injecting antigens into mice or rats, but it normally takes four to six months to produce good antibodies. Further,

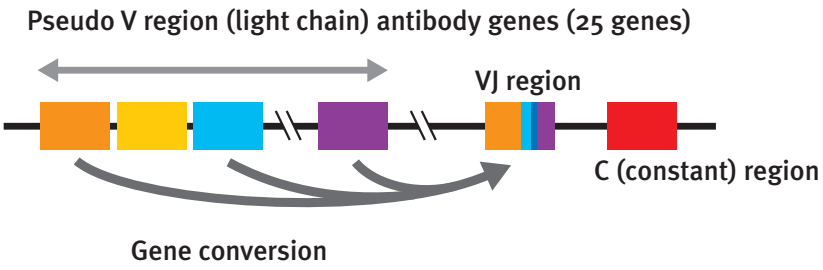


Figure 2: Gene conversion
Various antibody genes are formed when the information of 25 antibody genes is randomly transcribed from the pseudo V region, and the information in the VJ region, which serves as the information in the variable portion of the antibody, is overwritten with the transcribed information.

antibodies for the antigens similar to the biological molecules that are originally in their bodies, are not obtained because they are unrecognized as foreign bodies. This is due to the 'immune tolerance' mechanism, which eliminates B cells that produce antibodies to attack the original organism. Injection of highly toxic antigens can possibly lead to the death of test animals.

"We can solve these difficulties by creating a mechanism to produce a variety of antibodies in a test tube. Thus we looked at the cultured cell, DT40, derived from B cells of chickens. These cells can cause a type of DNA recombination called 'gene conversion' even in a test-tube (Fig. 2), although the frequency of occurrence is very low. If we can activate the gene conversion, we are sure to produce various antibodies," Ohta says.

To activate the DNA recombination of DT40, Hidetaka Seo, a member of Ohta's laboratory, conducted an experiment to increase the acetylation level of the histones by using a drug called trichostatin A. "However, no effect was observed even after a week of treatment," explains Ohta. "Most scientists may give up the experiment at this stage, but Seo did not give up culturing the DT40 cells, and several weeks later, the DNA recombination was finally activated."

This experiment triggered the development of a new antibody-producing system called the 'ADLib system' (Fig. 3). First, the DT40 cells are treated with trichostatin A, and are cultured for several weeks. Then the DNA recombination is accelerated, which leads to the formation of a cell population with a variety of antibody genes called a 'library.' Next, specific antigens are stuck to granular magnets (magnetic beads), and the magnets are put into this library consisting of slightly less than 100 million cells. Individual cells in the library can bind to specific cells because they have antibodies protruding from their surfaces. Thus the researchers can obtain the cells that produce target antibodies by lifting the magnetic beads with a magnet. Those cells are cultured for a week, and the researchers can finally obtain the target antibodies.

New medical and life science development through antibodies

Biological molecules that are more important to vital activities possess common attributes, and are similar in shape. In conventional antibody-producing methods, most of the important human biological molecules are unrecognized as foreign bodies, even in animal bodies. Thus the immune tolerance mechanism eliminates the cells that should produce the antibodies. However the ADLib system can offer a way to produce the antibodies against any human biological molecules. This feature of the ADLib system is also expected to open up applications to diagnostic products for 'personalized medical treatment,' in which patients can select the medical treatment that is most suitable for their constitution. "We have a lung cancer drug, 'Iressa,'" says Ohta. "This drug is quite effective for some patients, but not for others because it has serious side effects. The difference is decided depending on the fine difference among individuals, found in specific biological molecules. Then, the antibodies that are produced by the ADLib system can be used to distinguish the difference, and we can decide whether or not to administer Iressa."

In conventional antibody-producing methods, more than a few hundred micrograms of antigen are required, but in the ADLib system, less than one microgram of antigen is enough in principle to produce antibodies. The ADLib system can also be used to produce antibodies with small molecular mass. The ADLib system will also make it possible to produce antibodies against polysaccharide chains, which have been considered impossible to reproduce well. Sugar chains are the biological molecules that transmit information between cells, and have been important target molecules in the medical and life sciences fields. However, their structures and functions have been too complex to analyze. Thus the antibodies that can distinguish the difference between various sugars will significantly contribute to research achievements.

"It used to take more than a half year for us to produce a new antibody. However, the ADLib system will allow us to continuously produce antibodies that have been impossible to produce, thus facilitating experiments," Ohta says. "The ADLib system will become the research infrastructure technology for clinical medicine, basic medicine, and all kinds of bioscience. We have

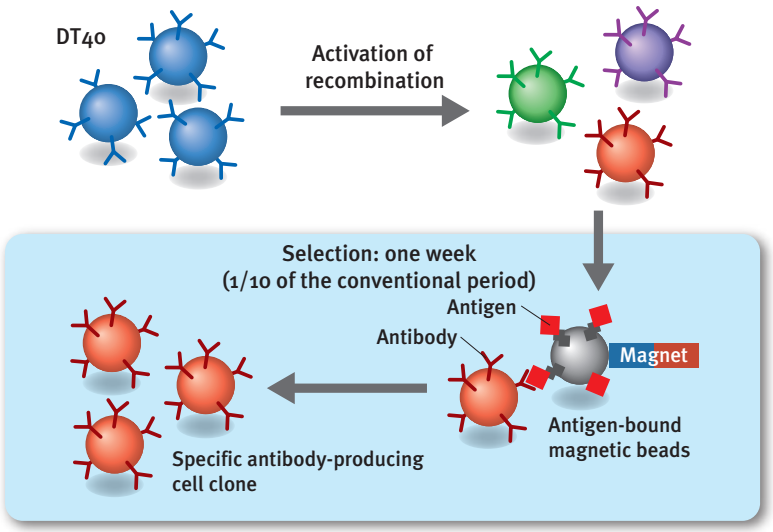


Figure 3: **Principle of the ADLib system**

many bio-related laboratories at RIKEN. We will cooperate with other laboratories to produce various antibodies, thus exploring a new branch of knowledge."

The ADLib system could save mankind from a crisis

"Interestingly, antibodies that are produced for research and diagnostic purposes are often available as therapeutic agents with a slight modification," Ohta comments. Thus the ADLib system that is capable of producing new drugs will contribute to the development of new therapeutic agents for malignant diseases such as cancer. Furthermore, because new antibodies can be produced within a week, the system is expected to contribute to curbing the expansion of biological terrorism, new types of influenza and emerging infectious diseases including SARS.

Even if pathogens that can cause emerging infectious diseases or be used in acts of biological terrorism can be determined, they can still develop into epidemics because of the time it takes for conventional technologies to develop vaccines, diagnostic products, and therapeutic agents. However, the ADLib system is expected to be able to swiftly produce those diagnostic products and therapeutic agents. At present, the government is calling for stockpiling a medicine called 'Tamiflu' for fear of new types of influenza occurring in an epidemic. Patients need to take this medicine within 48 hours of infection, because it is a drug to prevent the proliferation of the virus. In contrast, antibody drugs can directly attack viruses. Thus, unlike Tamiflu, they have no temporal restriction, and therapeutic effects continue for about a month.

Greatly expanding the potential of antibody drugs

Today, companies mainly in the United States have been actively developing antibody drugs, and conducting clinical investigations with many of those drugs. The market for antibody drugs is rapidly growing, and according to predictions, the antibody drug market in the US will grow to about 5 trillion yen in 2010. However this market prediction is based on antibodies that are produced using conventional methods. Thus the ADLib system will further expand the antibody market because the system can produce any kind of antibody.

Ohta established a RIKEN venture company, Chiome Bioscience Inc. in February 2005 to put the ADLib system into practical use. An increasing number of excellent staff are now working there.

At present, the ADLib system is capable of producing Type Ig (Immune globulin) M, an antibody for chickens. However it should be modified so that we can develop Type IgG, which is a more stable, easy-to-produce antibody available for humans. "It is now time to act, because we know the principle behind developing the antibody. I am sure we can develop the antibody in the near future. Furthermore, we are aiming to develop a 'Super ADLib system' that can produce an antibody-producing mechanism for humans in a test tube. Thus we need to steadily advance basic research into DNA recombination," Ohta explains.

Ohta has a clear policy to advance both basic research and applications. Many scientists are now sure that the future will see new possibilities in medical science and life science. ■

Background information

Japanese patent application No.2004-524174 and No. 2002-376555.

About the researcher

Kunihiro Ohta was born in 1962 and graduated from the Department of Biophysics & Biochemistry, the Faculty of Science at the University of Tokyo in 1985. He completed his PhD work in 1990 and then worked as a postdoctoral fellow until 1991 at the University of Tokyo. From 1991 to 1999, he was a research scientist at the Cellular & Molecular Biology Laboratory at RIKEN. In 2003, he was appointed as the leader of the Genetic Dynamic Research Unit of the RIKEN Discovery Research Institute, and named as the Associate Chief Scientist at the Genetic System Regulation Laboratory at the same institute in 2006. Since 2004, he has been concurrently serving as the Chief Scientific Officer of Chiome Bioscience Inc.

Next-Generation Supercomputing Symposium 2006

Which came first, the chicken or the egg? As dramatic increases in computing speeds continue to spur science on to even more impressive achievements, scientists eagerly await new supercomputers that will be able to do more precise calculations even faster. In view of this demand from scientists, in April the Ministry of Education, Culture, Sports, Science and Technology (MEXT) started a national project to build a Next-Generation Supercomputer. This supercomputer will be the fastest in the world, with a processing speed of ten petaflops.

RIKEN is the headquarters for the project, and will play a leading role in the development and management of the new supercomputer, and especially joint use of it. On September 19 and 20, RIKEN held the Next-Generation Supercomputing Symposium 2006, to launch the project and discuss the breakthroughs in science that the supercomputer will make possible. This event was held in Tokyo and attended by scientists and engineers from a wide variety of fields.

The symposium opened with a lecture. Next there were panel discussions on how the Next-Generation Supercomputer will be used for research projects in the life sciences, engineering, nanotechnology, the environment and disaster prevention, physics and astronomy, and user environments on computers. Each of the panels included prominent scientists from the relevant fields. The audience numbered more than 200.

One of the panelists for the life sciences discussion was Ryutaro Himeno, director of the Development Group at RIKEN's Next-Generation Supercomputer R&D Center. Himeno is also an active researcher who works on bioengineering simulations. The discussion ranged from basic biology to medical treatment. The panel talked about some of the problems that the supercomputer will be used to solve—for example, improving efficiency in drug design, and refining medical treatment by improving simulations at levels ranging from the cell to the whole body. Panelists even expressed the bold view that the supercomputer could revolutionize life science by changing it from a merely descriptive field into a predictive field. ■

The Century of the Brain

Nearly 400 people gathered in downtown Tokyo on September 13 for a day of lectures that was one of the events marking the 'Century of the Brain'. The audience came to learn about the brain from four neuroscientists from various neuroscience institutes in Japan, and hear how one engineer's curiosity about the brain contributes to biological investigations. Each of the four lectures covered one of the four research areas of the brain: understanding the brain, creating the brain, protecting the brain, and nurturing the brain.

The morning started with a simple greeting by Masao Ito, former director of the RIKEN Brain Science Institute and the current president of the parent organization for the event, Society and the Human Brain. "The brain is the core of who we are," he said to emphasize why it is so important to understand how it works. Ito also highlighted how technological developments in recent years put that understanding within our grasp.

After a keynote address by Jun-ichi Nishizawa, the president of Tokyo Metropolitan University, that reflected on the relationship between humanity and science, the next two lectures explained how a synapse functions. Tomoyuki Takahashi of the University of Tokyo's Department of Neurophysiology first introduced the biological mechanisms of the synapse, and then Shinya Kuroda, of the same university's Department of Biophysics and Biochemistry, showed how computation models can be used to reproduce synaptic behaviors and help refine our understanding of those behaviors.

The final two lecturers looked at healthy brain development and the adverse effects of stress on that development. With a focus on bipolar disorder, Hiroshima University Medical School's Shigeto Yamawaki showed how the molecular mechanisms that respond to stress also affect the onset of and periodicity of mood cycles in bipolar disorder. Tadafumi Kato, a Group Director of RIKEN Brain Science Institute, closed the day by explaining the work of one of his researchers, Kumi Kuroda. Kuroda has identified the molecular events that regulate paternal care, namely an interruption of ERK-FosB-SPRY-1 signalling that impairs the quality of parenting given to off-spring.

The annual Century of the Brain Symposium seeks to strengthen ties between scientists and the public through lectures that explain current understanding of the human brain and place it within larger social contexts. This year's event was the 14th public symposium. ■

RCAI International Summer Program 2006

For one week in September, RIKEN's Research Center for Allergy and Immunology (RCAI) in Yokohama held its first International Summer Program, for selected graduate students and young postdoctoral students from around the world. To support the participation from many countries, travel and accommodation expenses were paid in full by RCAI.

This new program aims to teach young scientists about recent research in immunology, and to make Japan and RCAI better known, with the idea that some participants might come to work there in the future. The participants all brought posters about their research, and there were lectures by eminent immunologists including Paul W. Kincade of Oklahoma Medical Research Foudation, and Ralph M. Steinmanis of Rockfeller University.

The program was attended by forty scientists from 21 countries. Ten of them stayed on at RCAI for another week as summer interns to experience research at the Center.

The program ended with great success and the participants said that they would definitely recommend this program to their colleagues when they go back. "This was my first time to participate in the Summer Program, but it totally widened my view," an attendant commented. ■

The road to modern biology

Expertise accumulated from RIKEN's former quest to develop much-needed pesticides has advanced biology

About 90 years ago, RIKEN started as a private foundation to research chemistry and physics. Life science was later added as another core discipline. Development of agricultural chemicals until 1987 was one of the key factors that beefed up RIKEN's biological research.

In 1959, the Science Council of Japan, an advisory panel to the government, recommended that Japan establish a large-scale body to research and develop effective low-toxicity agro-chemicals to improve the yield of major crops. That reflected the rapid economic and population growth in the postwar era, which caused a serious shortage of food. Instead of creating a new institute, the government asked RIKEN to help improve agricultural productivity in a country where food self-sufficiency is poor. RIKEN had a history of agro-chemical research dating back to 1921, when it began producing a pesticide to control brown rice pests. Thus, in 1962, RIKEN became the sole public research institute to develop new types of pesticides in Japan.

In the same year, RIKEN compiled a plan to create an agro-chemical division independent of other research groups, and opened the first laboratory in 1962. By 1970, a total of nine laboratories were created, and RIKEN completed establishing the organizational framework for its agro-chemical research.

Some existing laboratories in other divisions were moved to the newly established agro-chemical division. An animal physiology laboratory, for example, was re-designed in 1970 to study animal pharmacology. It was headed by Tomotari Mitsuoka, a scientist renowned for research into lactobacillus in the intestine. While tackling its new assignment to test the acute toxicity of pesticides, Mitsuoka's team continued their original research. Mitsuoka had garnered much attention from internal and external researchers wishing to learn his methods on culturing and detecting gut bacteria—such that it was dubbed the 'Mitsuoka School'. Mitsuoka's laboratory stemmed from the prominent laboratory of Umetaro Suzuki, who discovered vitamins for the first time in the world in 1910.

In 1964, researchers at RIKEN also discovered a natural fungicide derived from microbes, which was effective in controlling fungi that causes sheath blight disease on paddy rice, purple blotch on pears and other plant diseases. The environmentally friendly fungicide, known as polyoxin, is still in use today as one of the major pesticides (Fig. 1).

Fig. 1: RIKEN's fungicide 'polyoxin' is highly effective in preventing frogeye disease in plants.
LEFT: Leaves not sprayed with polyoxin RIGHT: Leaves sprayed with polyoxin

Initially, RIKEN concentrated on basic research into agro-chemicals, but its role changed when a new law requiring tougher safety tests was enacted in 1973. Private companies began giving up on low-margin pesticides, and many registered pesticides were withdrawn from the market. To meet increasing demand for pesticides to prevent plant epidemics, RIKEN split its agro-chemical division into two in 1979: one to continue basic research, and the other to develop new pesticides that were too difficult and expensive for private companies to produce.

As Japan's economy grew, social demands also changed. At the end of 1986, the government advised RIKEN to overhaul its agro-chemical division because the level of pesticide development had been boosted sufficiently. Following the recommendation, RIKEN dissolved the agro-chemical division in 1987, and its laboratories were restructured or integrated with others.

During the 25 years between 1962 and 1987, RIKEN's contribution to buoy Japan's agro-chemical research was immeasurable. But the accumulated know-how has been retained and well applied to advance life science research. For example, a former laboratory studying insect pharmacology became involved in the study of molecular mechanisms that control specific biological events in insect behavior. A researcher from that laboratory determined how hornets are capable of flying long distance and his finding has been applied to a sports drink that is sold commercially.

www.rikenresearch.riken.jp

RIKEN Public Relations Office
2-1, Hirosawa, Wako, Saitama, 351-0198, Japan
TEL: +81 48 467 4094
FAX: +81 48 462 4715
E-Mail: rikenresearch@riken.jp