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Inside the expert brain

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Revealing how experts' minds tick

Neural activity representing intuitive responses in the brains of professional board game players shows what sets experts apart

Primates, particularly humans, are set apart from other vertebrates by more than a huge expansion of the cerebral cortex, the region of the brain used for thinking. The connection and coordination of the cerebral cortex with other, older parts of the brain also play a significant role, according to findings published recently in *Science* by a research team from the RIKEN Brain Science Institute (BSI) in Wako[1].

The researchers, led by Keiji Tanaka, found that professional players of the Japanese chess-like game of *shogi* (Fig. 1) can use part of brain associated with intuitive or habitual behaviors to establish a best next-move in a way that distinguishes them from amateurs. One result of experience and training seems to be the ability to shunt some immediate neural tasks from the cerebral cortex to the more intuitive basal ganglia, leaving the cortex free for planning higher-level strategy.

"Our findings may be regarded as showing that in amateur players problem-solving occurs mostly in the newly developed brain structure, but in professionals an important part of the process goes to the old brain structure," Tanaka says. "This shift makes the process quick and unconscious."

The work may have significant ramifications for training, particularly in understanding what constitutes an intuitive part of a job as opposed to the intellectual or educative part. It is also relevant to the development of computer expert systems. "The elucidation of such brain mechanisms may hint at a way to train engineers efficiently to become experts," Tanaka explains. "Trouble shooting of computer networks, for instance, is dependent on intuitive insights of experienced engineers. They often focus on specific points of the network, but cannot explain why they do so."

Figure 1: The Japanese board game called *shogi*, also known as Japanese chess, is a two-player board game that requires strategic thinking.

Using board games to understand the mind

Investigating mechanisms of higher brain functions of decision making has been one of the prime interests of Tanaka's laboratory at BSI. An important question in this field, which has long been a subject of inquiry, is how experts differ from the rest of us.

Board games, particularly chess, have been used extensively in these studies because specific questions can be asked within the boundaries of a set of well-defined rules. In complex games, such as chess or *shogi*, groups of players are clearly defined as either experts or amateurs.

Although psychologists have been studying the players of such games for more than a century, there has been almost no work on the underlying neural mechanisms. Consequently, differences in neural activity between the brains of amateur and expert players remain poorly understood. Tanaka and his team designed their study, in part, to provide much-needed data on brain function.

The psychological studies of board game players led researchers to propose that expert chess players perceive patterns more quickly than amateurs by matching them to a series of stereotyped arrangements known as 'chunks'. The theory is that these chunks are associated with best next-moves in the long-term memory of expert chess players, so they can use them as a rapidly

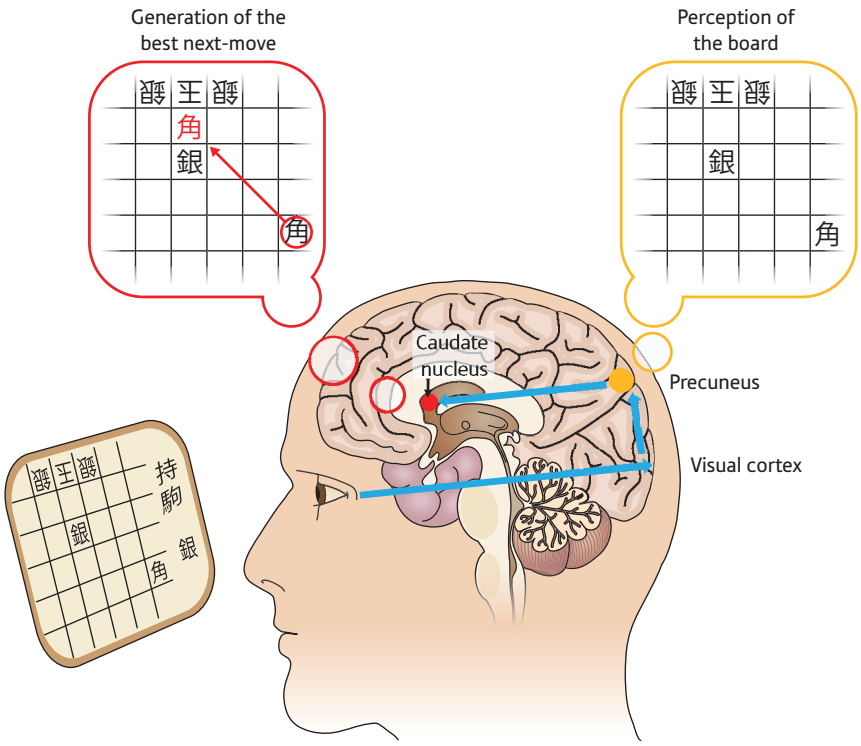


Figure 2: After seeing the state of play, professional *shogi* players respond intuitively to a game situation by recognizing the pattern in the precuneus area of the brain, which passes to the caudate nucleus for a response.

accessed starting point for responding to the problem.

To test this theory, Tanaka and his colleagues worked with groups of professional and high- and low-rank amateur players of *shogi*. They studied short and longer-term responses of players when asked to plot the best next-move in various *shogi* problems, akin to chess problems. *Shogi* problems can be more complex than those of chess because captured *shogi* pieces are allowed to re-enter play on the side of the player who has taken them.

Visualizing the minds of experts

Members of Tanaka's team with significant expertise in functional magnetic resonance imaging (fMRI) used this non-invasive technique to pinpoint which parts of the brain are active at a particular time. They initially presented *shogi* players with board game patterns of different types—opening *shogi* patterns, endgame *shogi* patterns, random *shogi* patterns, chess, Chinese chess—as well as other completely different stimuli such as scenes and faces. The board game patterns, but not the other scenes, stimulated activity in the posterior precuneus region of the cerebral cortex of all *shogi* players. Previous fMRI studies have shown that the precuneus is generally associated with tasks involving visuo-spatial imagery, the relationship of shapes to one another. In this study, activity was particularly strong in professional players presented with *shogi* opening and endgame patterns. The researchers suggest this is associated with pattern recognition specific to their area of expertise—in this case, *shogi*.

Tanaka and his colleagues then asked players to nominate the best next-move in a series of *shogi* problems under two sets of circumstances. In the first, they were allowed only one second to study the presented pattern; in the second, eight seconds. Reactions to the short-term problem would rely solely on intuition, the researchers reasoned, whereas the longer-term problem allowed time for conscious analysis. This contention was supported by interviews with the subjects afterwards.

Professional players presented with the short-term problem displayed activity in the caudate nucleus of the older, more primitive part of the brain, the basal ganglia (Fig. 2). The neural activity of amateurs in response to all problems and of professionals to the longer-term problem was confined to the cerebral cortex. The researchers propose, therefore, that development of an intuitive response is a result of the training and experience that marks experts.

"To further elucidate processes of intuitive problem-solving," says Tanaka, "we need to establish primate models, in which a wider range of experimental methods can be applied." ■

1. Wan, X., Nakatani, H., Ueno, K., Asamizuya, T., Cheng, K. & Tanaka, K. The neural basis of intuitive best next-move generation in board game experts. *Science* **331**, 341–346 (2011).

About the researcher

Keiji Tanaka graduated from the Department of Biophysical Engineering, Osaka University in 1973. He got his Ph. D. in 1983 from The University of Tokyo, Medical School by dissertation. He is now studying mechanisms of visual object recognition and those of goal-directed behavior by using single-cell recordings and lesion-behavioral methods on nonhuman primates. He has also pursued fMRI on the human cortex at sub-millimeter spatial resolution. He was one of the founding members of the brain science research group in RIKEN. He is now the deputy director of the RIKEN Brain Science Institute. He has also actively worked in the international neuroscience community; e.g. acting in the editorial boards of many important journals, including *Science*, *Neuron* and *The Journal of Neuroscience*, and serving as the deputy chair of the International Neuroinformatics Coordinating Facility.

Bacterial guests double as bodyguards

'Good citizens' in the human gut bacterial community produce protective compounds that help prevent onset of food poisoning

The bacterium *Escherichia coli* can be a scientist's best friend when it's being used as a tool for biological research, but some strains of it are better known for their nasty effects on humans as a causative agent in food poisoning.

Infection with the O157:H7 strain of *E. coli* usually occurs after consumption of meat that has been contaminated by exposure to fecal matter, and the symptoms can range from diarrhea to blood cell loss, encephelopathy and kidney failure. The causative factor is Shiga toxin (Stx), a bacterially secreted compound that makes its way from the intestine into the bloodstream, and ultimately binds to target receptors on cells in the kidney and brain.

According to Hiroshi Ohno of the RIKEN Research Center for Allergy and Immunology in Yokohama, the acquisition of protection against O157:H7 appears to be also related to diet. "In 1996, we experienced an outbreak of O157:H7 in Sakai, Japan," he says. "Epidemiologic research suggested that children with a history of breast-feeding were more resistant to O157:H7 infection than those with a formula-fed history."

In addition to nutrition, mother's milk helps to establish the community of gut bacteria that reside within every human being. These include the bifidobacteria, which have subsequently been associated with conferring O157:H7 resistance. A recent study from a team led by Ohno and Masahira Hattori at The University of Tokyo has revealed the defining characteristics of these defenders of human health[1].

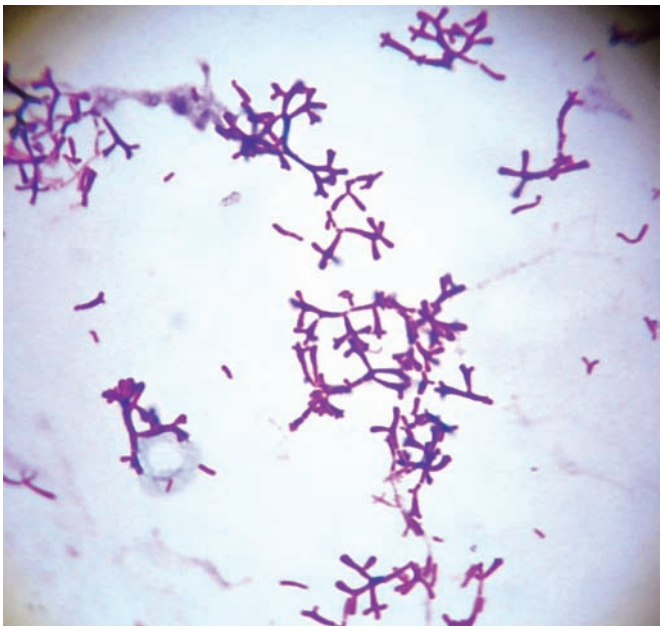


Figure 1: Certain strains of *Bifidobacterium longum* and other bifidobacterial species residing within the gut can help fight off the ill effects of *E. coli* food poisoning.

Knowing who your friends are

To characterize the protective properties of several different strains of bifidobacteria, the researchers used mice that lacked gut bacteria of their own. Completely 'germ-free' mice typically died within a week of exposure to O157:H7, but all animals pre-colonized with a protective strain of *Bifidobacterium longum* (Fig. 1), termed 'BL' survived. Mice carrying BL also showed considerably lower levels of Stx in their bloodstream, and the lining of their intestines appeared healthier. The *B. adolescentis* strain 'BA', however, bought germ-free mice only a few extra days of survival; the intestinal epithelia of these animals exhibited inflammation and evidence of increased levels of cell death following exposure to O157:H7.

In order to perform a more systematic analysis, Ohno, Hattori and their colleagues examined additional preventive and non-preventive bifidobacteria strains, and determined that these two groups were producing distinct metabolic signatures within the intestine. Gut bacteria in general play a prominent role in assisting in the digestion of carbohydrates, and the researchers learned that the preventive strains tended to generate higher levels of acetate as a byproduct of this process.

Acetate, in turn, switches on the activity of a group of anti-inflammatory genes. Experiments with human colon epithelial cells showed that acetate treatment was protective against the negative effects of Stx, which otherwise induced the formation of ruptures in layers of cultured cells. This suggests that acetate-producing bacteria prevent poisoning by actively preserving the integrity of the intestinal wall and keeping Stx out of the bloodstream.

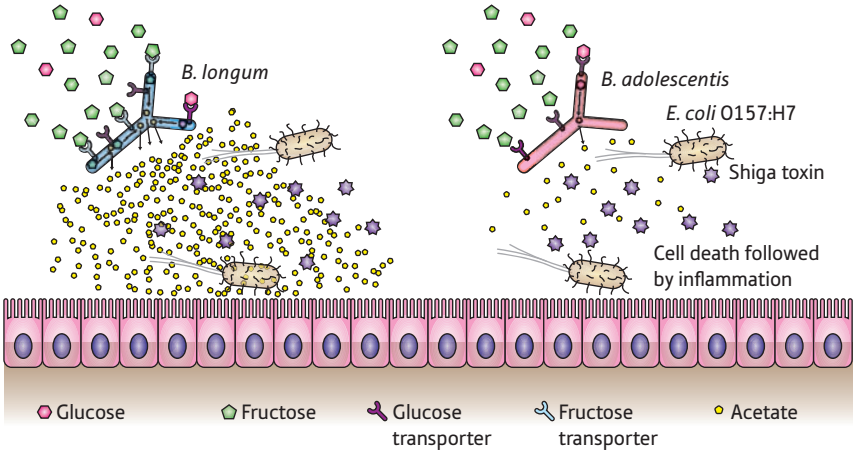


Figure 2: In the colon, bifidobacteria from a 'protective' strain of *B. longum* (left) metabolize fructose to produce high levels of acetate, preventing epithelial inflammation and cell death in the lower colon, thereby keeping Shiga toxin out of the bloodstream. Non-preventive bifidobacteria, such as *B. adolescentis* (right), lack this metabolic machinery and fail to prevent poisoning.

According to Ohno, these data help connect several important dots in understanding the protective benefits conferred by bifidobacteria in the human gut. "It was well known that acetate is produced by bifidobacteria and can be beneficial for the intestinal epithelium, and it is therefore rather reasonable that acetate is functioning in this role," he says. "However, I think it would have been difficult to predict from the beginning that acetate is the molecule responsible."

The secrets of their success

A comparison of the complete genomic sequences of five different bifidobacterial strains by the researchers revealed a subset of genes encoding proteins involved in uptake and metabolism of the sugar fructose that appear to be exclusively present in preventive strains. Accordingly, disabling these genes drastically undermined the protective qualities of such strains. They also determined that it was possible to cut out the bacterial 'middleman', and demonstrated that considerable protection against Stx lethality could be achieved by simply feeding mice a diet that was enriched in acetylated starch.

The team points out that all bifidobacteria strains produce acetate during the process of glucose metabolism, protecting the upper stretches of the colon. However, the selectively expressed fructose-metabolizing pathway is likely to provide important protection in the lower region of the colon, a portion of the digestive tract where glucose is likely to be largely depleted (Fig. 2).

Even when the ill effects of O157:H7 infection have been countered, these bacteria will continue to make themselves at home in the gut, although conventional antibiotics should be sufficient to kill them. "I doubt that antibiotics can totally exterminate O157:H7 from the intestine of germ-free mice, as small numbers of O157:H7 remaining in the gut could propagate quickly once antibiotic treatment is terminated," says Ohno. "But humans possess their own 'commensal' bacteria that greatly outnumber invading bacteria such as O157:H7, and these would not allow the pathogens to come back after antibiotic treatment."

Ohno and his colleagues see their bacterial detective work as a powerful proof of concept for understanding the health implications of the close relationship between microbes and their hosts, and for advancing the development of microorganism-mediated 'probiotic' therapeutic strategies in the future. "The beneficial effects of probiotics are diverse, and acetate alone could not explain everything; we would therefore like to elucidate the mechanisms underlying other probiotic effects," he explains, "and we would also like to apply the 'multi-omics' approach we took here for analyzing more complex gut ecosystems."

1. Fukuda, S., Toh, H., Hase, K., Oshima, K., Nakanishi, Y., Yoshimura, K., Tobe, T., Clarke, J.M., Topping, D.L., Suzuki, T. *et al.* Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature* **469**, 543–547 (2011).

About the researcher

Hiroshi Ohno was born in Tokyo, Japan, in 1958. He graduated from the School of Medicine, Chiba University, in 1983, and obtained his PhD in 1991 from the same university. He then became an assistant professor of the School of Medicine, and was promoted to associate professor in 1997. He spent three years from 1994 to 1997 as a visiting scientist at the National Institute of Child Health and Human Development, National Institutes of Health in the USA. In 1999, he became a full professor at the Cancer Research Institute of Kanazawa University. He joined the RIKEN Research Center for Allergy and Immunology as a team leader in 2002, where his research focuses on mucosal immunology, and in particular the role of epithelial cells in the development of the mucosal immune system, mucosal antigen uptake and initiation of mucosal immune responses. His team is also interested in the impact of host-commensal microbiota interaction on our health and disease conditions.

Vortices get organized

Exotic entities that arrange into a crystalline structure at near room-temperature could lead to a new approach to electronic memory

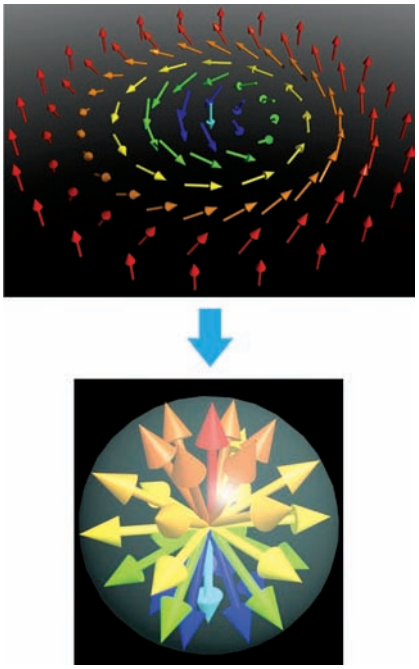


Figure 1: In a skyrmion (top) the electron spins, represented as arrows about which the electrons are rotating, are arranged such they map onto the surface of a sphere (bottom).

A crystal consisting not of atoms but exotic swirling magnetic entities, called skyrmions, has been identified at near room-temperature by Yoshinori Tokura of the RIKEN Advanced Science Institute, Wako, and his colleagues from several other institutes in Japan[1]. Previous observations of a skyrmion crystal state, in transition-metal–silicide materials, have been at cryogenic temperatures below 40 kelvin. The existence of skyrmions at room temperature improves the practicality of harnessing their potential for use in novel computer memories.

Skyrmions are formed on some surfaces when the spins of the electrons—think of an arrow about which each electron rotates—collectively arrange such that they wrap around the surface of a sphere (Fig. 1). This pattern spirals in such a way that the spins on the outside point up whereas those at the core point down. This collection of spins can display many properties associated with a single particle. "A skyrmion crystal is the periodic array of these particle-like entities," explains Tokura.

Earlier neutron-scattering experiments by other researchers identified this unusual effect in both iron–cobalt silicide and manganese silicide. Tokura and his team, however, investigated skyrmions in iron germanium. This alloy has the same cubic atomic crystal structure as iron–cobalt silicide and manganese silicide—the two materials in which skyrmions have been observed at low temperatures; but it remains in the necessary magnetic structure up to a much higher temperature.

Using a transmission electron microscope, the researchers probed the magnetization on the surface of polished layers of the iron–germanium alloy. They found tell-tale signs of skyrmions at temperatures up to 260 kelvin, particularly when they applied a small magnetic field perpendicularly to the surface.

This material also provides an excellent opportunity to investigate the stability of the skyrmion crystal, the team notes. Previous studies focused on very thin layers of material. Tokura and his team investigated the influence of film thickness and found that for thicknesses greater than the distance between skyrmions, about 75 nanometers in this case, the skyrmion crystal state is suppressed and a more conventional ferromagnetic phase starts to dominate.

Skyrmions could play an important role in the development of spintronics—using electron spin to carry information in the same way that electron charge is used in conventional electronics. "Skyrmion crystals could also be applied in memory and logic devices," says Tokura. The advantage over conventional systems is that control is achieved using electric, rather than magnetic fields, which is known to be more efficient. ■

1. Yu, X.Z., Kanazawa, N., Onose, Y., Kimoto, K., Zhang, W.Z., Ishiwata, S., Matsui, Y. & Tokura, Y. Near room-temperature formation of a skyrmion crystal in thin-films of the helimagnet FeGe. *Nature Materials* **10**, 106–109 (2011).

Predicting a chain of order

Calculations can now predict when and how spins of electrons and ions arrange in one-dimensional multiferroic materials

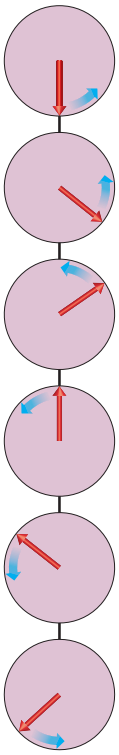


Figure 1: A one-dimensional chain of spins (red arrows), showing a chiral ordering (or spiral), which rotate (blue arrows) in response to incoming light radiation.

The properties of a material are greatly affected by the electrical and magnetic structure of its constituent ions and electrons. In a ferromagnet, for example, neighboring electron spins point in the same direction, producing a strong external magnetic field. In an antiferromagnet, however, neighboring spins point in opposite directions, negating its magnetism. This behavior can be exploited in devices ranging from switches to memory and computers.

Multiferroic materials exhibit an even richer physics—and an expanded set of applications—because their magnetic and electrical orderings are linked. However, the magnetic and electrical structuring of multiferroics is not yet completely understood. Now, Shunsuke Furukawa, Masahiro Sato and Shigeki Onoda of the RIKEN Advanced Science Institute, Wako, have successfully calculated how magnetic ordering arises in one-dimensional multiferroic materials—the simplest example of these materials[1].

This simplicity means that one-dimensional multiferroic materials are useful models for understanding multidimensional, or 'bulk', multiferroic materials. Their one-dimensional chain of spins can not only assume a variety of ferromagnetic and anti-ferromagnetic alignments, but they can also arrange into more complicated patterns, including spirals defined over long portions of the chain—referred to as 'long-range chiral order' (Fig. 1). Understanding these exotic patterns may lead to new foundational science, as well as new applications. In addition, a one-dimensional chain can also exhibit the electrical control of magnetic structure and the response to light that is characteristic of more complex multiferroics.

Onoda and colleagues focused on describing the magnetic structure in a one-dimensional chain in terms of how strongly neighboring spins were coupled to each other. They began by using a computational technique that uniquely allows for the accurate treatment of an infinitely large collection of spins to construct a phase diagram describing how spin ordering changed as the type of spin-to-spin coupling in the material changed. Most notably, the diagram indicated that ferromagnetic coupling between nearest neighbors was much more likely to cause a long-range chiral order than anti-ferromagnetic coupling.

This observation successfully explained the experimentally observed spin ordering of several one-dimensional multiferroic cuprates. In particular, the research team was able to correctly predict that the bulk multiferroic material $LiCu_2O_2$, whose unique physics has drawn the attention of physicists for over a decade, exhibits chiral order and has a unique response to light. "These results confirm that one-dimensional multiferroics are an ideal laboratory for studying spin dynamics", says Onoda, and he feels that the calculations will promote studies on new one-dimensional multiferroics and other novel states of matter. ■

1. Furukawa, S., Sato, M. & Onoda, S. Chiral order and electromagnetic dynamics in one-dimensional multiferroic cuprates. *Physical Review Letters* **105**, 257205 (2010).

Fridge magnet transformed

A common industrial magnet exhibits rare and potentially useful qualities when its composition is slightly altered

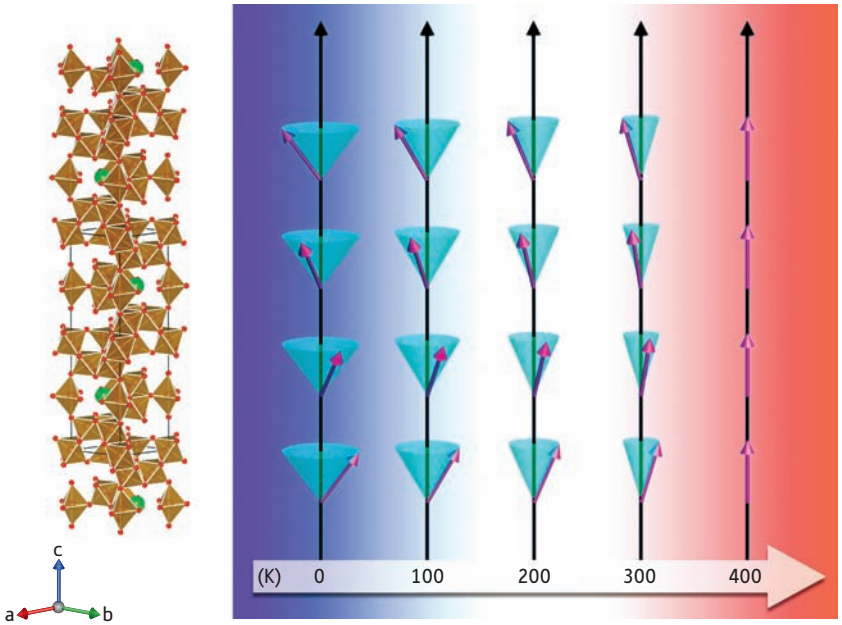


Figure 1: The crystal (left) and magnetic spin (right) structure of the magnet $BaFe_{12}O_{19}$ when some of its iron atoms are replaced by scandium and magnesium. In the crystal structure, green, red and bronze colors represent barium (Ba), oxygen (O) and the three elements iron (Fe), scandium (Sc) and magnesium (Mg), respectively. The spin structure persists to well above room temperature (~298 kelvin (K)).

The ubiquitous and unremarkable magnet, $BaFe_{12}O_{19}$, is manufactured in large volumes, has the simplest crystal structure in its class, and is often seen on refrigerator doors—but it is set for an interesting future. By substituting a few of its iron atoms with the elements scandium and magnesium, Yusuke Tokunaga and Yoshinori Tokura from the Japan Science and Technology Agency, along with Yasujiro Taguchi from the RIKEN Advanced Science Institute and their colleagues, have produced a very rare magnet[1]. The rarity of the magnet lies in three features that, taken together, endow it with a high degree of tunability.

Firstly, the new magnet is multiferroic: its magnetization and electric polarization are linked, and each can be potentially controlled by both electrical and magnetic fields. Multiferroic materials may allow for magnetic data storage devices that do not require magnetic fields, resulting in reduced cost, power requirements, and bulk. Other applications, such as sensors, may also be possible.

Another feature of this new magnet is that its electronic spins are arranged in a helix (Fig. 1). Therefore the handedness of the helix is a controllable material quantity, along with the material's magnetic strength and its electric polarization. By applying a magnetic field, the researchers were able to change the geometry of the helix, which in turn increased or decreased the strength of the electric polarization.

The third distinguishing feature is that the material's spin helix structure persists even above room temperature. This contrasts with many other known multiferroic materials, which require liquid nitrogen temperatures in order to form helical spin structures. In fact, the research team studied $BaFe_{12}O_{19}$ because a related but more complex magnet demonstrated a helical spin structure at low temperature[2]. It also proved relatively straightforward to fashion large crystals of $BaFe_{12}O_{19}$, making measurements and device manufacture easier.

The team concluded that the concentration of scandium, the temperature, and the applied magnetic field strength could all be used to control the strength and direction of the materials magnetic and electrical polarization, as well as the retention times of these polarizations. More generally, the new magnet uncovered by Tokunaga, Taguchi, Tokura and colleagues adds to the catalogue of room-temperature multiferroics, which material scientists have just begun to explore. A particularly alluring goal is the discovery of a material with magnetic and electrical ordering at room temperature and in the absence of magnetic field, says Tokunaga. ■

1. Tokunaga, Y., Kaneko, Y., Okuyama, D., Ishiwata, S., Arima, T., Wakimoto, S., Kakurai, K., Taguchi, Y. & Tokura, Y. Multiferroic *M*-type hexaferrites with a room-temperature conical state and magnetically controllable spin helicity. *Physical Review Letters* **105**, 257201 (2010).
2. Ishiwata, S., Taguchi, Y., Murakawa, H., Onose, Y. & Tokura, Y. Low-magnetic-field control of electric polarization vector in a helimagnet. *Science* **319**, 1643–1646 (2008).

The more the merrier

Computational search algorithms take the guesswork out of understanding complex, multi-molecule transformations

Multicomponent reactions (MCRs) that chemically combine three or more molecules into a brand new product are faster and generate less waste than traditional step-by-step synthetic procedures, making them invaluable in efforts to improve efficiency and sustainability. Since 1921, chemists have used an MCR called the Passerini reaction to produce bioactive, peptide-like chains made from three partners: carboxylic acids, carbonyl compounds, and cyanide-bearing molecules. However, a full understanding of this process has eluded researchers because its multipart workings are difficult to detect experimentally.

Now, Satoshi Maeda and Keiji Morokuma from Kyoto University and Shinsuke Komagawa and Masanobu Uchiyama from the RIKEN Advanced Science Institute in Wako have developed a computerized way to better identify the hidden mechanisms of one-pot, multi-step chemical transformations[1]. Their technique, the artificial force induced reaction (AFIR), systematically squeezes and joins model compounds together in order to rapidly detect signatures of real MCR energy barriers.

According to Maeda, detailed theoretical understandings of MCRs have been scarce because most calculations require excellent estimates of transition state structures—intermediate and often highly strained geometric arrangements between molecules that correspond to the energetic peak of a reaction barrier. "Consequently, a trial-and-error process based only on [chemistry-based] intuition is unavoidable," he says.

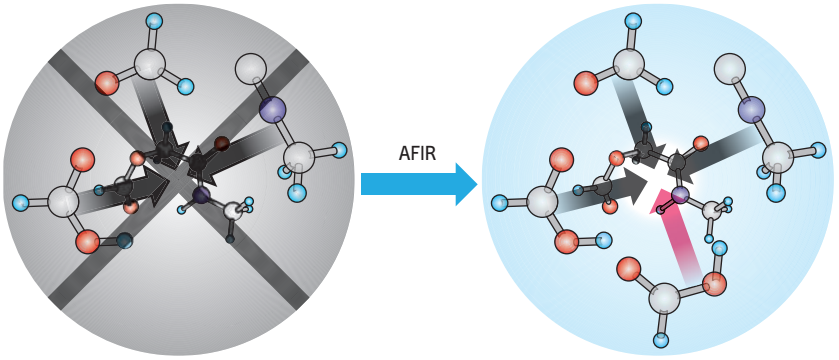


Figure 1: In contrast to a conventional three-component model (left), the artificial force induced reaction (AFIR) revealed that the Passerini reaction involves a fourth component (red arrow).

The AFIR method, on the other hand, requires no such presumptions. Maeda explains that when two molecules are pushed into each other with a weak force, they spontaneously relax into 'dents' in the potential barrier created by attractive electronic interactions between the reactants. By methodically pressing over all possible orientations, and inducing an artificial reaction from the relaxed positions, AFIR searches can identify every stable reaction pathway in a system.

To the team's surprise, applying AFIR calculations to the Passerini reaction revealed that four components, not the long-thought three, must be involved (Fig. 1). Since the reaction barriers were so high, the researchers realized that an additional carboxylic acid—a known proton transfer catalyst—had to participate in the transition states leading to the final product. This finding should enable design of Passerini reactions with improved structural selectivity, notes Maeda.

Once perfected, the researchers anticipate their technique will make MCRs even more widespread. "Unlike standard methods, giving only pathways that are easy to find, the AFIR method has a unique ability to find unknown pathways in MCRs systematically," says Maeda. "Information on reaction pathways is very important even for processes that do not normally occur, because chemists can initiate such reactions by controlling conditions, modifying substituents, and introducing new catalysts." ■

1. Maeda, S., Komagawa, S., Uchiyama, M. & Morokuma, K. Finding reaction pathways for multicomponent reactions: The Passerini reaction is a four-component reaction. *Angewandte Chemie International Edition* **50**, 644–649 (2011).

Nanotechnology points the way to greener pastures

Solar-powered 'nanoalloys' can convert polluting nitrates into ammonia fertilizer without releasing carbon dioxide

Nourishing crops with synthetic ammonia (NH_3) fertilizers has increasingly pushed agricultural yields higher, but such productivity comes at a price. Over-application of this chemical can build up nitrate ion (NO_3^-) concentrations in the soil—a potential groundwater poison and food source for harmful algal blooms. Furthermore, industrial manufacturing of ammonia is an energy-intensive process that contributes significantly to atmospheric greenhouse gases.

A research team led by Miho Yamauchi and Masaki Takata from the RIKEN SPring-8 Center in Harima has now discovered an almost ideal way to detoxify the effects of ammonia fertilizers[1]. By synthesizing photoactive bimetallic nanocatalysts that generate hydrogen gas from water using solar energy, the team can catalytically convert NO_3^- back into NH_3 through an efficient route free from carbon dioxide emissions.

Replacing the oxygen atoms of NO_3^- with hydrogen is a difficult chemical trick, but chemists can achieve this feat by using nanoparticles of copper–palladium (CuPd) alloys to immobilize nitrates at their surfaces and catalyzing a reduction reaction with dissolved hydrogen atoms. However, the atomic distribution at the 'nanoalloy' surface affects the outcome of this procedure: regions with large domains of Pd atoms tend to create nitrogen gas, while well-mixed alloys preferentially produce ammonia.

According to Yamauchi, the challenge in synthesizing homogenously mixed CuPd alloys is getting the timing right—the two metal ions transform into atomic states at different rates, causing phase separation. Yamauchi and her team used the powerful x-rays of the SPring-8 Center's synchrotron to characterize the atomic structure of CuPd synthesized with harsh or mild reagents. Their experiments revealed that a relatively strong reducing reagent called sodium borohydride gave alloys with near-perfect mixing down to nanoscale dimensions.

Most ammonia syntheses use hydrogen gas produced from fossil fuels, but the use of solar energy by the researchers avoids this. They found that depositing the nanoalloy onto photosensitive titanium dioxide (TiO_2) yielded a material able to convert ultraviolet radiation into energetic electrons; in turn, these electrons stimulated hydrogen gas generation from a simple water/methanol solution (Fig. 1). When they added nitrate ions to this mixture, the CuPd/TiO_2 catalyst converted nearly 80% into ammonia—a remarkable chemical selectivity that the researchers attribute to high concentrations of reactive hydrogen photocatalytically produced near the CuPd surface.

Yamauchi is confident that this approach can help reduce the ecological impact of many classical chemical hydrogenation reactions. "Considering the environmental problems we face, we have to switch from chemical synthesis using fossil-based hydrogen to other clean processes," she says. ■

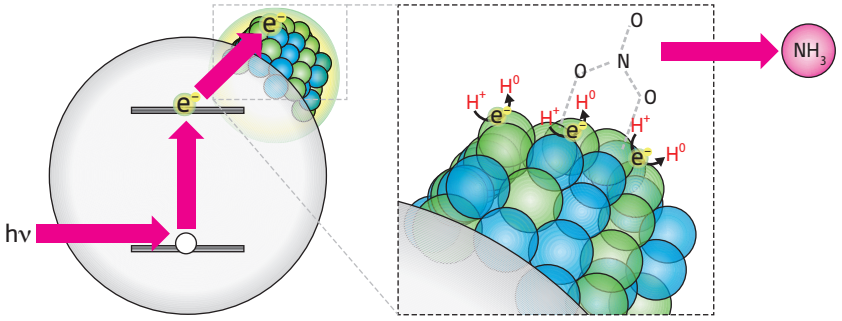


Figure 1: Using ultraviolet radiation (hν) to produce energetic electrons (e^-) enables a copper–palladium catalyst (green and blue spheres) to generate hydrogen (H^0) without using fossil fuels. This material can then transform nitrate ions (NO_3^-) into ammonia (NH_3).

1. Yamauchi, M., Abe, R., Tsukuda, T., Kato. K. & Takata, M. Highly selective ammonia synthesis from nitrate with photocatalytically generated hydrogen on CuPd/TiO_2. *Journal of the American Chemical Society* **133**, 1150–1152 (2011).

Encoding unchartered territory

Ensembles of neurons in the brain's hippocampus inform about future as well as past experiences

When a mammal explores an unfamiliar environment, ensembles of 'place' cells in the hippocampus fire individually, recording specific locations in a cognitive map that aid future spatial navigation of the area. Once the relationship between place cell activity and location has been established, the activity of the cells can be used to predict the animal's location within its environment. Activity patterns in the ensembles are later 'replayed' during rest and sleep, and neuroscientists believe this is important for consolidating the spatial memories of the new environment.

Neuroscientists also contend that the sequence of place cell firing corresponding to the new environment is established during the first exploration of that environment. Now George Dragoi and Susumu Tonegawa from the RIKEN-MIT Center for Neural Circuit Genetics at the Massachusetts Institute of Technology in Cambridge, Massachusetts, report that the activity of place cell circuits is also preconfigured to encode novel environments[1].

Dragoi and Tonegawa recorded the activity patterns of place cells in the CA1 region of the hippocampus while mice navigated a familiar environment. They also recorded from the same cells afterwards, while the mice rested or slept. As expected, some of the place cell activity patterns they observed corresponded to the familiar environment that the animals had explored, but they also recorded new patterns from place cells that were previously silent.

The researchers found that the novel activity patterns corresponded strongly to the sequences of place cell firing that were recorded when the mice subsequently explored an unfamiliar part of the environment (Fig. 1). This suggests that the activity patterns represent 'preplay' of the unexplored locations rather than replay of the familiar part of the environment. Thus, the activity of hippocampal place cells appears not only to consolidate spatial memories of newly experienced environments, but also to predict how novel, unexplored environments can be encoded when they are navigated in the future. The researchers also suggest that hippocampal preplay may accelerate spatial memory formation once the novel environment is eventually explored.

"Encoding of new information makes use of the pre-existing organization of the hippocampal network, and will stabilize faster compared to a case when the neuronal network has to re-organize to a new state that does not resemble the pre-existing one," says Dragoi. "In an immediate follow-up to this study, we will address the role of the intact hippocampal circuitry in the mechanisms and dynamics of the preplay phenomenon," he adds. ■

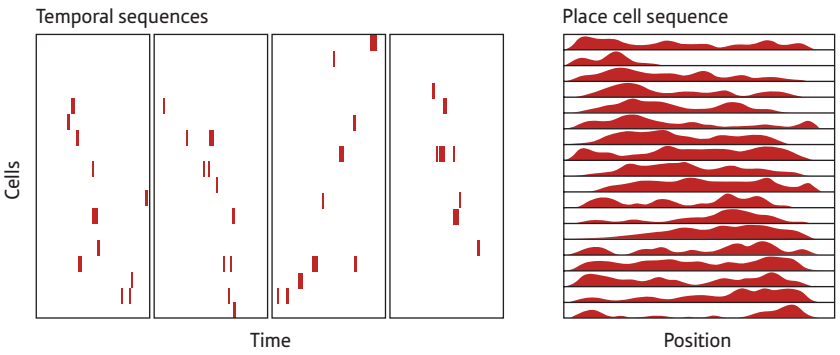


Figure 1: Novel place cell firing sequences recorded during rest and sleep (left) correspond closely to the activity observed when mice explore a new environment (right).

1. Dragoi, G. & Tonegawa, S. Preplay of future place cell sequences by hippocampal cellular assemblies. *Nature* **469**, 397–401 (2011).

Partners in inflammation

Two genes that affect Caucasians and a variant of the inflammatory gene *interleukin-6* affect the abundance of a marker of systemic inflammation in the Japanese

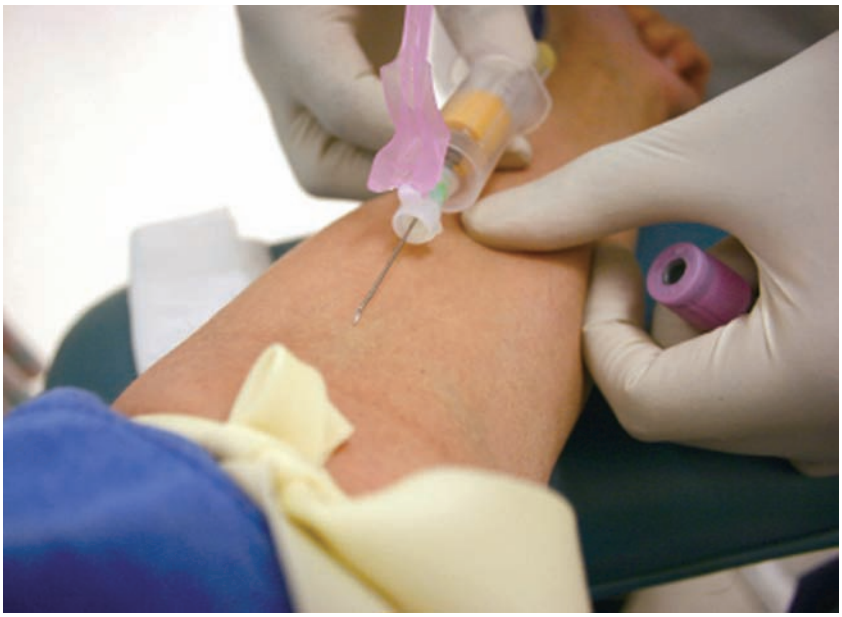


Figure 1: In the Japanese population, blood CRP levels are linked to three genes.

Individuals with increased levels of C-reactive protein (CRP) in the blood are at increased risk for various diseases linked to inflammation, such as colorectal cancer and cardiovascular diseases. Now, a research team in Japan including Yukinori Okada and colleagues at the RIKEN Center for Genomic Medicine in Yokohama, reports that single-nucleotide changes in three genes can affect the blood levels of CRP in Japanese individuals[1]. Two of these genes, *CRP* and *HNF1A*, had already been found to affect Caucasians, but it was unclear if those same genes would also play a role in Japanese people.

Doctors often measure blood CRP levels in the clinic to determine a patient's risk for inflammation-associated diseases. CRP is synthesized in the liver in response to inflammation in the body so elevated levels signal a problem, such as infectious and autoimmune diseases.

Okada and his colleagues found the three genes that were correlated with changes in blood CRP levels in a genome-wide association study (GWAS) of some 13,000 Japanese individuals (Fig. 1). Their discovery of a single-nucleotide change in the *interleukin*-6 (*IL-6*) gene in the Japanese population, however, was not detected in the GWAS of Caucasians.

The *IL-6* gene encodes a pro-inflammatory cytokine, IL-6, which has been linked to a variety of immune reactions, and plays a key role in inducing fever in response to infection. Blockers of IL-6 receptor are used successfully in the clinic to reduce the severity of rheumatoid arthritis, a disease long linked to joint inflammation. "The identified variation in *IL-6* could therefore be a promising target in the pharmacogenomics [matching drugs to an individual's specific genetic variants] of IL-6 blocking therapy," explains Okada.

The researchers also examined the blood of over 30,000 Japanese patients to determine whether or not the single-nucleotide change in *IL-6* that leads to increases in blood CRP levels could affect any other hematological or biochemical markers used in medical practice. They found an increase in: white blood cells, which are involved in inflammation; platelets, which are involved in blood clotting; and serum protein levels, all of which are associated with the *IL-6* gene variant that increases CRP levels. They also found a decrease in anemia-related markers.

The link between IL-6, CRP, and these blood parameters could explain why patients with elevated CRP have an increased risk for inflammation-related diseases, and, according to Okada, could provide a clue for how to move forward with personalized medicine. Okada next plans on extending the study to Africans and Caucasians. ■

1. Okada, Y., Takahashi, A., Ohmiya, H., Kumasaka, N., Kamatani, Y., Hosono, M., Tsunoda, T., Matsuda, K., Tanaka, T., Kubo, M., *et al.* Genome-wide association study for C-reactive protein levels identified pleiotropic associations in the *IL6* locus. *Human Molecular Genetics* advance online publication, 31 December 2010 (doi: 10.1093/hmg/ddq551).

Keeping to time counter-intuitively

Experimental work proves the theory that a circadian body clock requires a delay to function properly

Figure 1: Delay in the activation of the gene *Cry1* ensures that the circadian clock of mammals properly functions and adjusts to daily and seasonal changes in the environment.

For more than 20 years, theoretical mathematical models have predicted that a delay built into a negative feedback system is at the heart of the molecular mechanism that governs circadian clocks in mammalian cells. Now, the first experimental proof of this theory has been provided by an international research team led by molecular biologists and information scientists from the RIKEN Center for Developmental Biology in Kobe[1]. The demonstration of the feedback delay should lead to a better understanding of how cellular clocks function, and therefore how mammals adjust to the regular daily and seasonal changes in their environment. The work could also open the way to the development of treatments for circadian disorders, such as seasonal affective disorder, jet lag and even bipolar disorder.

Mammals not only show daily rhythms of waking and sleeping, but also body temperature, hormone secretion, and many other biological activities. The master cellular clocks that act as timers for these patterns are found in the suprachiasmatic nucleus of the brain. The molecular mechanism is built around a negative feedback system involving *cryptochrome* (Cry) genes, which code for proteins that repress their own activation by binding with the products of two other genes *Bmal1* and *Clock*. The whole clock system is orchestrated by the interaction of these proteins with a complex array of promoters and enhancers, genetic sequences that regulate gene activity.

Within these clock-gene regulators are short sequences often known as clock-controlled elements. Different clock-controlled elements bind with the different proteins likely to be prevalent at different times of the day or night. The researchers carefully modified these sequences, and observed the impact on circadian rhythms of cells. They focused their studies in particular on the gene *Cry1*, and observed how the rhythm of its activity was affected by the modifications of clock-controlled elements within promoters and enhancers.

In addition to revealing a previously unknown clock-controlled element in the *Cry1* promoter, the researchers also found that different combinations of clock-controlled elements led to different lengths of delay in the activation of *Cry1*. They demonstrated that this delay of *Cry1* was required for the circadian clock to function (Fig. 1).

Based on these findings, they proposed a simple model of the mammalian circadian clock and now want to construct it using artificial components. "We think further experimental and theoretical analyses of this minimal circuit will lead to a deeper understanding of the mammalian circadian clock," say team members Rikuhiro Yamada and Maki Ukai-Tadenuma.

1. Ukai-Tadenuma, M., Yamada, R.G., Xu, H., Ripperger, J.A., Liu, A.C. & Ueda, H.R. Delay in feedback repression by *Cryptochrome 1* is required for circadian clock function. *Cell* **144**, 268–281(2011).

Exposing the potential of sugar chains for the diagnosis and treatment of disease

Naoyuki Taniguchi

Team Leader, Disease Glycomics Team
Group Director, Systems Glycobiology Research Group
Chemical Biology Department
RIKEN Advanced Science Institute

Protruding from the surface of cells in the body like whiskers are sugar chains, a biological structure often bound to lipids and proteins embedded in the cell membrane. Recent studies have shown that sugar chains exhibit a broad range of functions, including signal transduction between cells and across the cell membrane, as well as functional regulation of immunity and hormones. "From among the diverse functions of sugar chains, we focus on their association with disease," says Naoyuki Taniguchi, group director of the Systems Glycobiology Research Group at the RIKEN Advanced Science Institute and a world-renowned researcher in sugar chains. "The ultimate goal of our research is to clarify the mechanisms of the onset of disease in terms of sugar chains, and to diagnose and treat disease using those mechanisms." Taniguchi's research is probing the frontiers of sugar chain research in the diagnosis and treatment of disease.

"The human body consists of about 60 trillion cells, and nearly all of them have sugar chains protruding from their surfaces, rather like whiskers," says Taniguchi. The sugar chain is literally a chain of monosaccharide sugars. "Traditionally, it has been thought that the primary functions of sugar chains are to store energy and build biological structures. However, it has recently been shown that most sugar chains occur in the form of glycoproteins or glycolipids, in which they are bound to lipids or proteins embedded in the cell membrane." About 50% of proteins bear sugar chains, and those sugar chains have diverse functions (Fig. 1).

The sugar chains bound to proteins or lipids comprise a sequence of several and occasionally up to several thousands of units of several kinds of sugars, which join together and branch in complex ways. The sugar chains exposed to cell surfaces are structurally distinct from each other depending on the type of cell, and even within the same kind of cell their structure changes under different conditions.

"The sugar chain is like the face of the cell," says Taniguchi. "When we communicate with other people, we look at their face to identify them. Likewise, cells, as well as proteins and many other biological molecules, recognize sugar chains exposed to cell surfaces and bind to them to achieve mutual communication. Viruses, bacteria and pathogenic toxins also recognize sugar chains, bind to them, and invade cells. When cells become cancerous, the sugar chains change and adopt a structure specific to cancer cells. Hence, the sugar chain comes to be the 'face' of the cancer cell."

Although sugar chains are involved in all biological phenomena, including development, differentiation and immunity, they have only been studied actively in the last 15 years or so. "The sugar chain is also called 'the third chain of life'. However, it is much more difficult to study than the first and second chains of life—DNA and proteins," says Taniguchi. DNA comprises a chain of bases, and protein comprises a chain of amino acids. There are four different bases constituting the DNA, and 20 amino acids make up protein. There are about ten monosaccharides that constitute sugar chains in humans, which link to each other in complicated ways and sometimes branch. As a result, there is no practical apparatus for amplifying or synthesizing sugar chains in the same way as exists for DNA and proteins.

Nevertheless, our understanding of sugar chains has grown thanks to the discovery of genes for glycosyltransferases, which elongate sugar chains by attaching sugars one by one, as well as improvements in mass analyzers and other

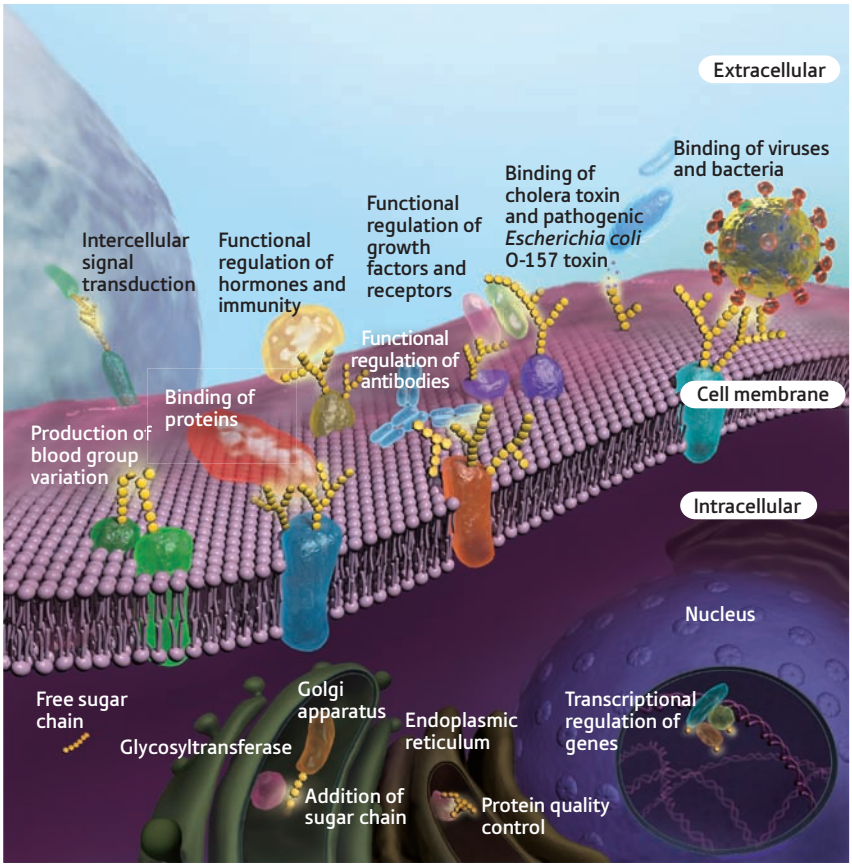


Figure 1: Various functions of sugar chains

instruments for examining the structures of sugar chains. "It has been found that sugar chains are important for biological activities and are closely associated with disease. We are working to understand the mechanisms of the onset of disease by studying sugar chains with the aim of linking them to the diagnosis and treatment of disease with sugar chains."

Sugar chains as biomarkers

Blood tests now routinely screen for γ-GTP (gamma glutamyl transpeptidase), PSA (prostate specific antigen) and other parameters. These are called biomarkers, and they are used for the early detection of diseases such as impaired liver function or liver cancer (γ-GTP) and prostate cancer (PSA). Biomarkers are molecules that change in abundance and composition with the onset and progression of disease, and can serve as effective diagnostic indicators.

"Most currently available biomarkers are glycoproteins or glycolipids. For example, an antibody that binds specifically to the protein moiety of a glycoprotein is created, and the protein is quantified. However, this does not provide an accurate diagnosis because there is no difference between the proteins of glycoproteins produced by normal cells and those produced by cancer cells," says Taniguchi. In fact, many people have elevated PSA levels but do not have prostate cancer, whereas others have normal PSA levels even though they have prostate cancer.

More than 20 years ago, Taniguchi proposed for the first time in the world that sugar chains, rather than the proteins in glycoproteins, could be used as biomarkers. "The structures of sugar chains are known to change due to the attachment or removal of their sugars upon onset of disease," he explains.

In 1983, Taniguchi demonstrated that the γ-GTP sugar chain in normal cells is bifurcated, and that the γ-GTP sugar chain of cancer cells assumes a 'bisect' structure with one molecule of the *N*-acetylglucosamine sugar bound to the base of the branch (Fig. 2). He later discovered the gene for the glycosyltransferase GnT-III, which catalyzes the formation of the structure. "By utilizing structural changes in sugar chains, it is possible to examine the cancerization of cells earlier and more accurately. When cancer starts, up to several molecules of fucose sugar attach to the structures of alpha-fetoprotein, which is a biomarker for liver cancer, and haptoglobin, which is a biomarker for pancreatic cancer. A technology for detecting alpha-fetoprotein with one fucose attached to it is already available for practical use, and we are now working to develop biomarkers for a variety of cancers based on structural changes in sugar chains to detect various cancer cells."

A role in chronic obstructive pulmonary disease

Another research theme for the Disease Glycomics Team is to clarify the role of sugar chains in chronic obstructive pulmonary disease (COPD), such as lung edema and bronchitis, and to develop therapeutic drugs for the disease. In Japan, it is estimated that 200,000 patients are being treated for COPD, but the potential patient population may be up to 5.3 million. Primary causal factors are smoking, including passive smoking, and air pollution. COPD is becoming more prevalent worldwide, and the World Health Organization predicts that the disease will become the fourth leading cause of death by 2020.

The Disease Glycomics Team did not target COPD at the beginning, but took

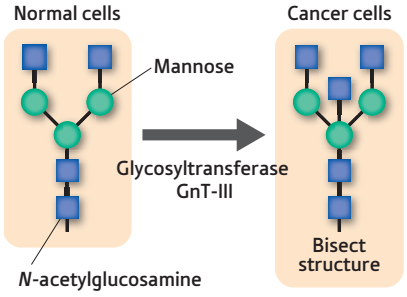


Figure 2: Change in γ-GTP sugar chain. The γ-GTP sugar chain in normal cells is bifurcated. If a cell becomes cancerous, the glycosyltransferase GnT-III acts to bind a sugar called *N*-acetylglucosamine to the branching base to form a bisect structure.

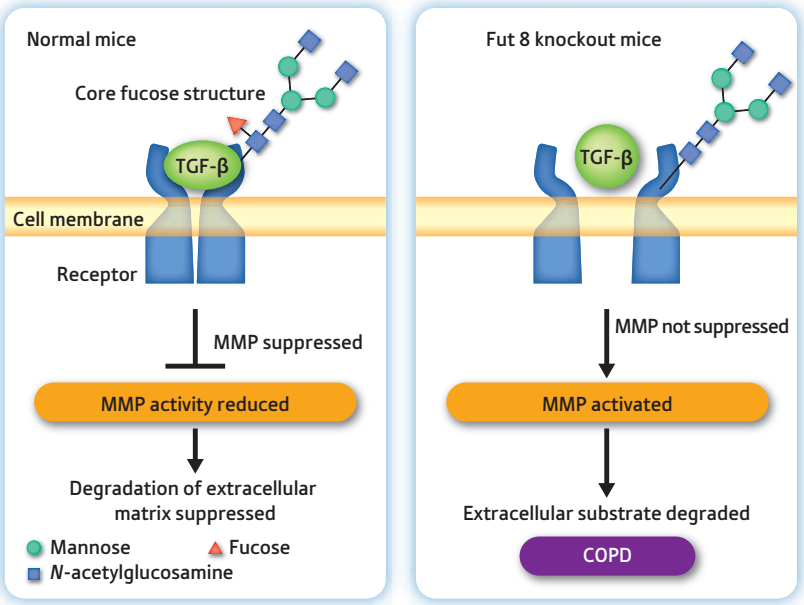


Figure 3: Mechanism of onset of chronic obstructive pulmonary disease (COPD). Left: In the pulmonary cells of a normal mouse, a core fucose structure is present in the sugar chain of the TGF-β receptor. TGF-β binds to the receptor, producing a signal for suppressing the expression of matrix metalloprotease (MMP). Right: In the pulmonary cells of a Fut 8 knockout mouse, no core fucose structure is present in the sugar chain of the TGF-β receptor. Therefore, TGF-β is unable to bind to the receptor and no signal is produced for suppressing the expression of MMP. As a result, the alveolar wall collapses and alveoli swelling, resulting in the onset of COPD.

up the case when Taniguchi discovered Fut 8, a core fucose structure formed when glycosyltransferase attaches fucose to the base of a sugar chain. Taniguchi and his colleagues generated a knockout mouse lacking the gene for Fut 8 to examine the function of the core fucose structure. "Seventy percent of our Fut 8 knockout mice died within three days of birth. The mice that survived suffered symptoms of COPD, such as alveolar swelling, around three weeks after birth. Human COPD patients were found to have lower blood Fut 8 concentrations in accordance with the severity of their condition. This finding strongly suggests that Fut 8 is involved in the onset of COPD, and it motivated us to investigate the relationship between sugar chains and the onset of COPD."

The swelling of alveoli—the tiny air sacs in the lungs—occurs due to excess activation of matrix metalloprotease (MMP), a protein-degrading enzyme, which causes the alveolar wall to collapse. In normal mice, the TGF-β molecule binds to its receptor in the cell membrane to generate a signal for suppressing the expression of MMP, thus preventing the collapse of the alveolar wall (Fig. 3). "When we examined the sugar chain attached to the TGF-β receptor, we found that the core fucose structure was present in normal mice but absent in Fut 8 knockout mice. Because the Fut 8 knockout mice lack the core fucose structure, TGF-β cannot bind to the receptor in their body. As a result, the signal for suppressing the expression of MMP is not functioning, so the alveolar wall is destroyed by the activated MMP. This proved to be the mechanism of the onset of COPD."

No radical therapies are available for COPD, which is currently treated merely by symptomatic approaches, such as with steroids or bronchodilators. Patients with COPD can suffer rapid, sometimes fatal, exacerbation of their symptoms upon viral or bacterial infection. "Since we demonstrated the association of sugar chains in the onset of COPD, we have been working on creating a new therapeutic drug that targets sugar chains," says Taniguchi. Although sugar-chain-targeting therapeutics may sound strange, in fact influenza remedies target sugar chains, while many other currently available therapeutic drugs target proteins.

Enhancing antibody pharmaceutical activity

"Research into Fut 8, which we discovered, is also expected to lead to improvements in antibody pharmaceuticals," says Taniguchi. Many cancer therapeutics, including Herceptin for breast cancer, are categorized as antibody pharmaceuticals—antibodies that recognizes a specific antigen on cancer cell surfaces and when administered to a patient binds not only to cancer cells, but also to immune cells, such as macrophages and 'natural killer' cells. These immune cells are thus activated by the antibody and attack and kill the cancer cells (Fig. 4). "Ordinary antibody pharmaceuticals have an attached sugar chain with a core fucose structure produced by Fut 8. Recently, two pharmaceutical companies, one in Japan and the other in the US, independently demonstrated that merely removing the fucose from the sugar chain enhances its activity against cancer cells by 50 to 100 times. This approach is applicable to antibody pharmaceuticals for a broad range of cancers, so there are great expectations for it."

Sugar chains are also closely related to cancer metastases. The glycosyltransferase GnT-V, which was discovered around the same time independently by Taniguchi and a US research group, attaches *N*-acetylglucosamine to the end of a sugar chain to bifurcate it. Cancer cells having a sugar chain with this structure are highly metastatic, whereas those having a sugar chain with a bisect structure produced by the glycosyltransferase GnT-III are non-metastatic. "It has been confirmed that cancer metastases decrease with the transfer of GnT-III to cancer cells. We are now working on this glycosyltransferase in the hope of developing new cancer therapeutics."

An era of systems glycobiology

As sugar chains are involved in all biological phenomena and diseases, the scope of research at the Disease Glycomics Team is broad. In addition to

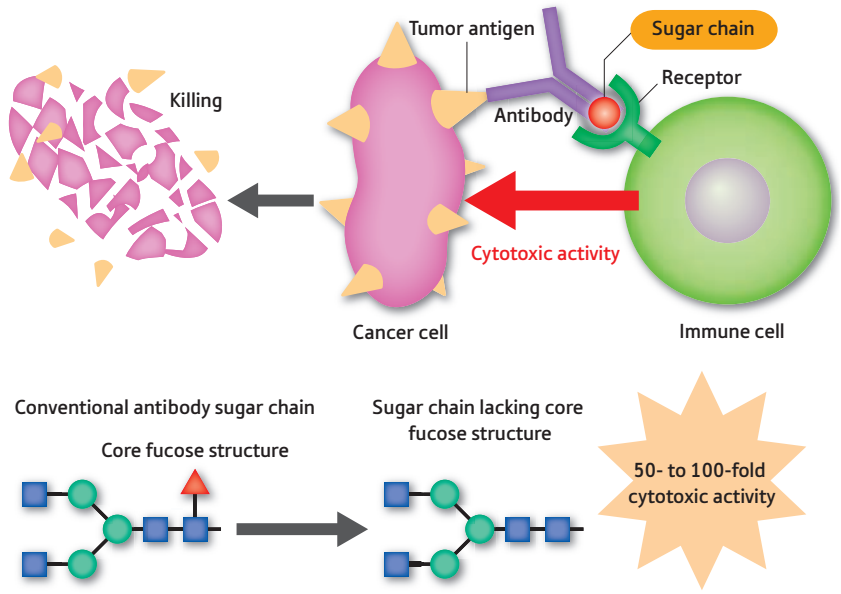


Figure 4: Action mechanism of antibody pharmaceuticals.
While binding to cancer cell-specific antigens, antibodies also bind to immune cells such as macrophages and natural killer cells. Activated immune cells attack and kill cancer cells (upper panel). The activity for cancer cell attack is increased 50- to 100-fold by removing one fucose from the sugar chain on the antibody to make the antibody free of the core fucose structure (lower panel).

the work described above, diverse studies are being conducted under the leadership of Shinobu Kitazume, deputy head of the laboratory, including the development of an early diagnostic for Alzheimer's disease using sugar chains attached to a β-amyloid precursor protein, and the development of a new type of neovascularization inhibitor that targets sugar chains.

Taniguchi's Systems Glycobiology Research Group is comprised of three teams: Disease Glycomics (headed by Naoyuki Taniguchi), Glycometabolome (headed by Tadashi Suzuki) and Structural Glycobiology (headed by Yoshiki Yamaguchi). "I think we're the first in the world to announce that we're a laboratory for systems glycobiology," says Taniguchi. "Traditionally in glycoprotein research, researchers have specialized in sugar chains, proteins or compounds, and there has been almost no overlap. However, the functions of glycoproteins cannot be fully understood unless not only sugar chains, but also proteins and compounds, are investigated from a broad perspective. I have therefore proposed the concept of systems glycobiology."

The Systems Glycobiology Research Group belongs to the Chemical Biology Department (directed by Hiroyuki Osada) in the RIKEN Advanced Science Institute. Chemical biology is the discipline for investigating the mechanisms behind biological phenomena using compounds. In RIKEN, a compound bank, the Natural Products Depository (NPDepo), systematically collects, preserves and supplies natural compounds of microbial origin. "We have begun screening the collection of the NPDepo in search of compounds that act on sugar chains to suppress the onset of Alzheimer's disease, COPD and the growth or metastasis of cancer cells."

A joint project undertaken by the Chemical Biology Department and the Max Planck Institute in Germany is also about to start. "Researchers at Max Planck became aware of the research into chemical biology and sugar chains being done at RIKEN and asked if they could work with us. Japan has a long history of sugar chain research and has been leading the world with outstanding achievements, including the discovery of 60% of the genes for glycosyltransferases. The Max Planck Institute also has a world-renowned sugar chain researcher and runs a large compound bank. By working with them, we want to drive systems glycobiology more powerfully."

Sugar chain imaging is the ultimate goal of Taniguchi's work on sugar chains. "I want to watch movie images of sugar chains to find out which sugar chains are present in what amounts at which locations in the body in real time. Researchers into sugar chains have long dreamed of this. We are determined to achieve it within a few years, to help understand the functions of sugar chains and link the findings to the diagnosis and treatment of disease." ■

Naoyuki Taniguchi

Naoyuki Taniguchi was born in Tokyo, Japan, in 1942 and grew up in Sapporo. He graduated from the Faculty of Medicine at Hokkaido University and obtained his MD degree in 1967 and then PhD degree in 1972 from the same university. He became assistant professor of the Department of Preventive Medicine at Hokkaido University, and later visiting associate professor at the Connell University Medical School in New York, USA, in 1976. After returning to Japan, he became associate professor of the Cancer Institute of Hokkaido University Medical School, where he started his career in glycobiology. In 1986, he became professor and chair of the Department of Biochemistry at Osaka University Medical School. In 2006, after retirement from the medical school, he became an endowed chair professor of Osaka University. He launched the Systems Glycobiology Research Group at the RIKEN Advanced Science Institute in 2007, and has been leading his group as group director. He is focusing on the structure and function of glycans, especially the role of N-linked glycoproteins in relation to the mechanism of disease, biomarker discovery and therapeutics.

Nobel Laureate Yuan T. Lee inaugurated as RIKEN Honorary Fellow

On 4 March 2011, Yuan T. Lee, winner of the 1986 Nobel Prize in Chemistry, was inaugurated as a RIKEN Honorary Fellow at an award ceremony at Suzuki Umetaro Hall on RIKEN's Wako Campus. Lee achieved worldwide recognition for his work on elucidating the collision dynamics of elementary chemical reactions. With his new title of Honorary Fellow, Lee joins a group of eminent figures including the former prime minister of Malaysia, Mahathir bin Mohamad, and Leo Esaki, winner of the 1973 Nobel Prize in Physics.

Following the award ceremony, Lee gave a special lecture on 'Science, Society and Sustainability', in which he discussed both his own scientific research as well as the state of global security. Starting with the path that led him from his studies in Taiwan to research in the United States, and extending to the research that would garner him worldwide acclaim, Lee turned to the connections between science and society. He stressed that in order to avoid a global environmental catastrophe, the world must follow a new path of development, different from the one that Americans and Europeans forged with the industrial revolution.

"We must learn to work together as one community," said Lee, emphasizing the importance of global institutions such as RIKEN in forging this new path. "There isn't much time to waste."

A member of RIKEN's Advisory Council, Lee has strong connections to RIKEN and has made great contributions toward its success. In conferring on him the title of Honorary Fellow, RIKEN both honors Lee for his illustrious career in science and expresses its heartfelt gratitude for these great contributions.

RIKEN Honorary Fellow and Nobel Laureate Yuan T. Lee and the award certificate

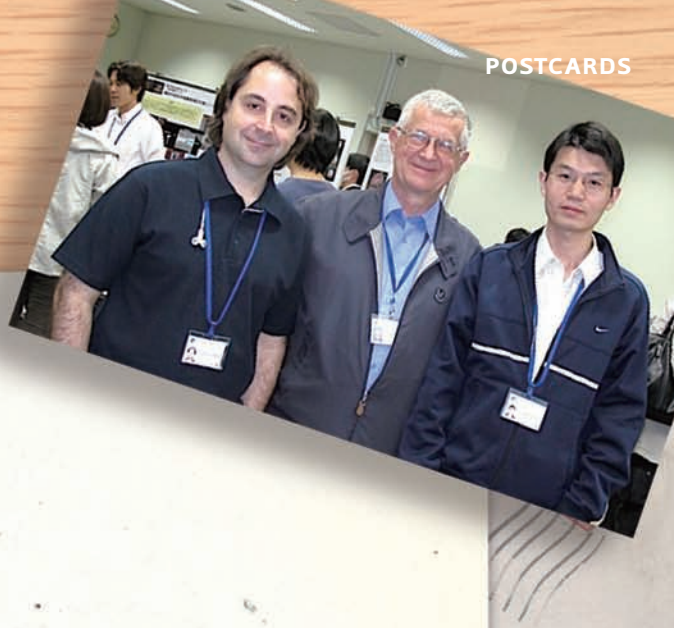
Special Lecture by visiting Nobel Laureate Ada Yonath

On 7 March 2011, the RIKEN Advanced Science Institute (ASI) welcomed Ada Yonath from the Weizmann Institute of Science in Israel to present a special lecture at RIKEN's Wako Campus. Yonath is winner of the 2009 Nobel Prize in Chemistry for studies on the structure and function of the ribosome, and her trip to Japan and lecture were made possible by a Japan Society for the Promotion of Science Award for Eminent Scientists.

Yonath also presented a lecture last year at the RIKEN Yokohama Institute, but this was her first visit to the Wako Institute. During her visit, she had informal talks with RIKEN President and Nobel Laureate Ryoji Noyori, Wako Institute Director Tomoya Ogawa, and ASI Director Kohei Tamao.

Organized by Antibiotics Laboratory Chief Scientist Hiroyuki Osada, the lecture provided a unique opportunity for participants to interact directly with a Nobel prizewinner. Researchers from a variety of fields packed the lecture hall to listen to Yonath's lecture. Entitled 'From Basic Science to Advanced Antibiotics', the lecture drew interest from researchers both inside and outside the field, and the question and answer session that followed exceeded its allotted time with active discussion.

Visiting Nobel Laureate Ada Yonath



Dr Andrzej Cichocki
Laboratory for Advanced Brain Signal Processing
RIKEN Brain Science Institute
Wako, Saitama, Japan

Dear Dr Cichocki,
Today I realized that almost three months have passed since I left RIKEN to return to my home country Argentina. Every day I have good memories of my days working at your lab. After I completed my PhD at the University of Buenos Aires, Argentina, I visited the Laboratory for Advanced Brain Signal Processing at RIKEN in May 2008 for a three-month stay. I remember that I was really impressed by the RIKEN facilities, the resources assigned to science and the high quality of the research conducted at RIKEN. Motivated by the fruitful collaboration achieved during my short visit, I decided to apply for a researcher position at the lab to work on multiway blind source separation, tensor decompositions and related problems. I know now that it was the right decision. During my two years' experience in your lab, I learnt many things about how to conduct research, and I had the opportunity to meet very interesting people and interact with researchers from all parts of the world in a very pleasant environment.

I am really satisfied with the quality of the results we have obtained together, which include two publications in prestigious journals on neural computation and mathematics besides many other short communications presented at important international conferences. I am grateful to you for introducing me in the world of tensor decompositions and multiway analysis, which opened my mind and allowed me to approach new mathematical theories with direct application to signal processing and data analysis.

In late 2009 I was selected for a permanent position as researcher at CONICET, the national research council in Argentina, so I had to organize to return to my country. Currently, I work at the Argentinean Radioastronomy Institute where I continue developing theory and algorithms for signal processing. I also hold a position as assistant professor in the Engineering Faculty of the University of Buenos Aires. My experience at RIKEN proved to be very useful for my current activities as researcher and professor.
Living in Japan was an exciting experience in my life. Now, I love Japanese food and Japanese culture in general. I miss the hanami, viewing the beautiful sakura blossoms and visiting the green open spaces in the Tokyo area. I think I was lucky to have this opportunity.

I am proud to continue the scientific collaboration with you and other members of your lab. I hope I can visit you in the near future and produce interesting and useful results together.

Sincerely,

Cesar Caiafa
Instituto Argentino de Radioastronomía, CONICET, Buenos Aires, Argentina
Engineering Faculty, University of Buenos Aires, Argentina

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RIKEN, Japan's flagship research institute, conducts basic and applied experimental research in a wide range of science and technology fields including physics, chemistry, medical science, biology and engineering. Initially established as a private research foundation in Tokyo in 1917, RIKEN became an independent administrative institution in 2003.

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