



## Deciphering the human genome

### HIGHLIGHT OF THE MONTH

## Searching for the social brain

### RESEARCH HIGHLIGHTS

There's more to Higgs than bosons  
A perfect couple  
Heavy oxygen holds it together  
All together now  
Mapping genes onto brain structures  
My mistake or yours? How the brain decides  
Finding elements of regional risk  
Staking out unknown genomic territory  
Gut shortcut for migrating cells  
How molecular transports change gear

### FRONTLINE

Exploring the chemistry of iron and organisms

### RIKEN PEOPLE

Chieko Yamada, Experimental Animal Division

### NEWS ROUNDUP

The RIKEN Quantitative Biology Center Inaugural Symposium 2012  
RIKEN Nishina Center and Universiti Sains Malaysia sign Memorandum of Agreement  
The Nishina School program in 2012

## Medicine

# Searching for the social brain

Imaging of marmoset brains provides an insight into the brain regions involved in regulating social behavior

Humans exhibit complex social behavior. Understanding the brain function underlying this behavior would help to explain how it goes wrong in social disorders. Evidence shows that the neurotransmitter serotonin is involved in regulating emotional and social behaviors in humans and other primates, particularly negative traits such as anxiety and aggression. It has also been implicated in the formation of social behavioral traits such as social affiliation, dominance and openness.

Despite this, no direct link has been made between such behaviors and the action of serotonin in specific brain regions. Most work has focused on the primitive regions of the brain, such as the amygdala, which is involved in negative emotions. But there is also some evidence for involvement of the cerebral cortex, the outer layer of the brain responsible for higher cognitive function.

A team led by Hiroataka Onoe at the RIKEN Center for Molecular Imaging Science, Japan, has studied the brain and behaviors of common marmosets to show that specific regions of the midline cortex, close to the center-line of the brain, are indeed crucial in the formation and regulation of social behavior traits<sup>1</sup>. Onoe says it is the first study of non-invasive brain functional imaging in conscious marmosets that has been analyzed in combination with measurements of the animals' social behavior.

## The social brain

The researchers started by observing and classifying behavioral traits displayed by

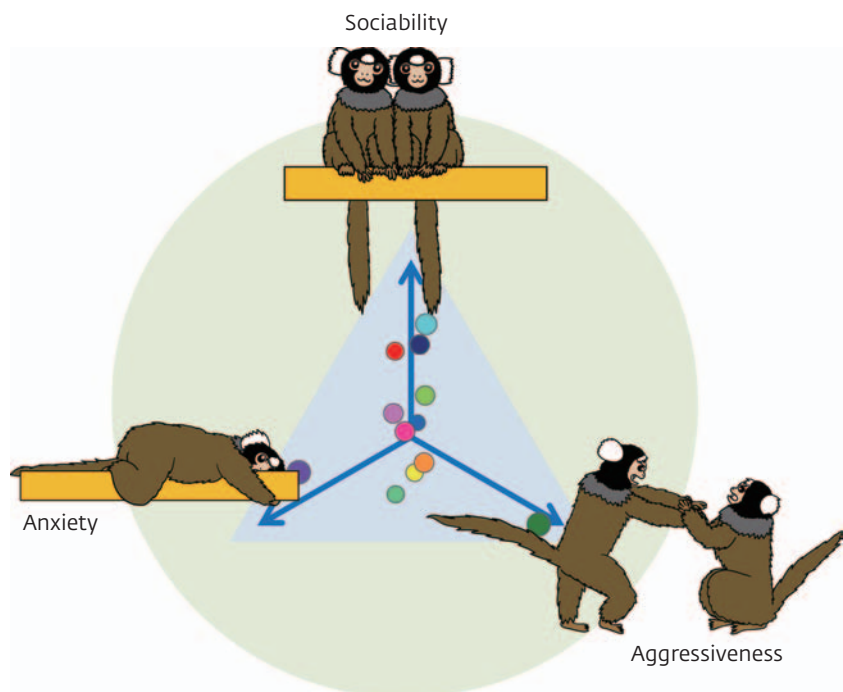


Figure 1: Behavioral traits of common marmosets were identified by their actions during encounters with an unfamiliar animal. Circles represent individual marmosets characterized with three traits.

the male marmosets when they encountered an unfamiliar male. They identified three traits: aggressiveness, anxiety and sociability (Fig. 1). The combination of these traits expressed in an individual can be considered equivalent to 'personality' in humans. The team then moved on to see how serotonin function in the brain related to these traits.

To do this, they measured levels of the serotonin transporter protein (SERT) in the brains of the same marmosets. This protein transports serotonin back into cells after it has been released

from neurons. High levels of SERT correspond to high levels of serotonergic nerve terminals in the same region. Measurements were made by injecting a radioactive compound that binds to SERT into the marmosets and detecting the radioactivity in their brains by positron emission tomography (PET). Higher levels of SERT in specific regions were revealed by higher levels of radioactivity.

The researchers found that SERT levels in specific regions correlated with the social traits seen in the marmosets



(Fig. 2). Low levels of SERT correlated with lower unfriendliness and higher aggression in the posterior cingulate cortex (PCC). In the anterior cingulate cortex (ACC) and the lateral prefrontal cortex (LPFC), low levels of SERT correlated with higher anxiety. These results indicate that the cognitive basis of these traits is localized to these specific subregions of the midline cortex.

The researchers also measured activity in these regions in different social situations. To do this, they again used PET, but this time they used a radioactive compound to measure the level of metabolism across the brain, corresponding to the amount of neural activity. They found that activity in the PCC, but not the ACC, varied according to whether a marmoset remained alone or was put with an unfamiliar male. Using the same approach, they also showed that functional connections of the PCC and ACC with other regions of the brain were altered by different social situations. The differences in activity show that these regions are central to the cognitive basis of social traits.

### A model of human personality

The insights add to the evidence that areas of the midline cortex are involved in the regulation of social behavior by serotonin. What's more, the differences seen between specific areas demonstrate that different aspects of social behavior are localized to these subregions. Common marmosets are known to have complex social behaviors similar to humans, such as a high level of social learning. By conducting these studies in marmosets, the results are therefore directly relevant to our understanding of human social cognition.

"Our approach uses a reliable model of social traits underlying 'personality' in humans," says the lead author, Chihiro Yokoyama. "Our findings confirm the previous knowledge of the relationship between serotonin and social behaviors and further highlight the role of the medial part of the cerebral cortex as the site of action." The study could lead to a better understanding of complex social disabilities such as depression, anxiety disorders and autism. Using the same approach, Onoe's team now want to gain

a deeper understanding of the action of serotonin in specific brain regions.

"In the next step of this research we would like to elucidate a pivotal role of the serotonergic system in the medial part of the cortex in expressing social behaviors," Onoe says. "Our method of live imaging provides not only visualization of the neural processes in the living and functioning brain, but can also shed light on the relationship between genes and social behavior." ■

1. Yokoyama, C., Kawasaki, A., Hayashi, T. & Onoe, H. Linkage between the midline cortical serotonergic system and social behavior traits: positron emission tomography studies of common marmosets. *Cerebral Cortex* advance online publication, 12 July 2012 (doi:10.1093/cercor/bhs196).

### ABOUT THE RESEARCHER



Hirotaka Onoe was born in Tokyo in 1960. He graduated from the Tokyo University of Pharmacy and Life Sciences in 1983, and in 1993 obtained his PhD in Pharmacology from Osaka University. After working at the Osaka Bioscience Institute as a research scientist for nearly ten years, Onoe held the position of senior researcher at the Tokyo Metropolitan Institute for Neuroscience for nine years from 1998. He joined the RIKEN Molecular Imaging Research Program as Laboratory Head of the Functional Probe Research Laboratory in 2007, and the laboratory was incorporated into the RIKEN Center for Molecular Imaging Science in 2008. His research focuses on the development of molecular imaging probes for positron emission tomography (PET) and neuroscience.

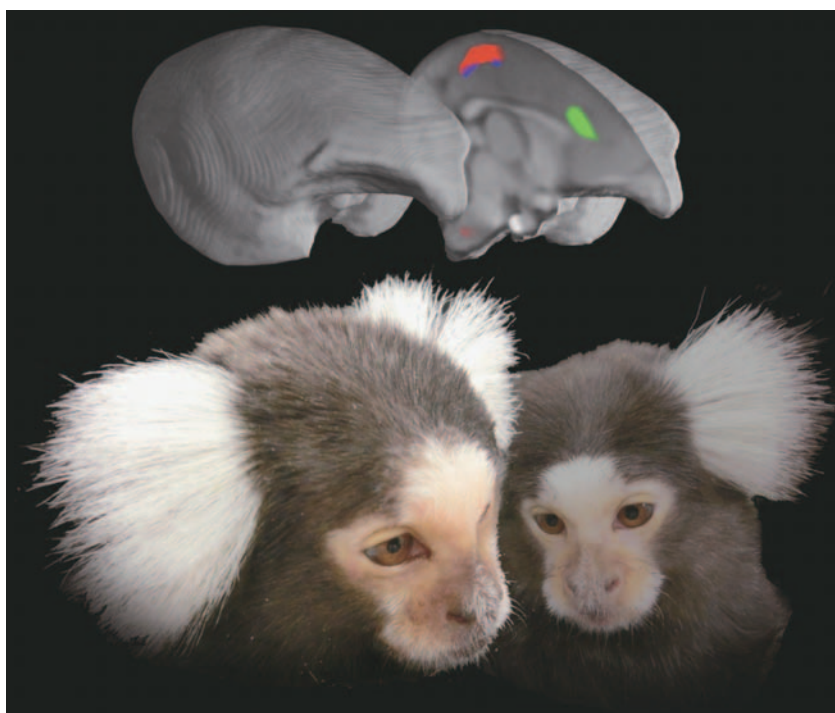


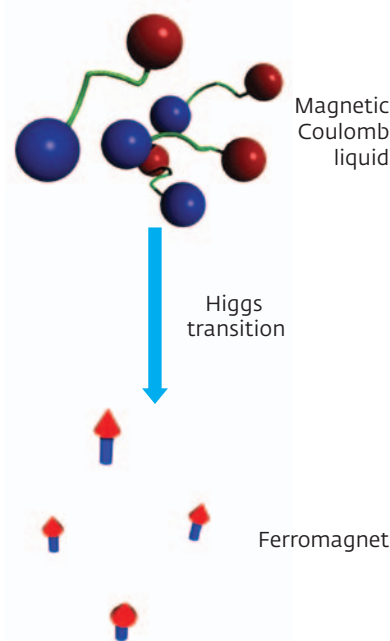
Figure 2: Specific brain regions represent the link of the social traits with serotonin transporter binding revealed by PET imaging. Aggressiveness (red), sociability (blue) and anxiety (green) traits are localized in the medial part of the cerebral cortex.

# There's more to Higgs than bosons

The observation of novel behavior in a magnetic material suggests a fresh approach to studying fundamental quantum phenomena

The name Higgs has been the talk of the town this year, since the elusive 'Higgs boson'—an elementary particle that, among other things, endows other particles with mass—was discovered in the CERN research facility. Now, an international research team including Shigeki Onoda of RIKEN Advanced Science Institute, Wako, has provided strong evidence that the same basic mechanism—the so-called Higgs mechanism—that endows particles with mass is also at play in an entirely different system, namely a magnet<sup>1</sup>. Their finding establishes a solid-state material as a versatile platform for studying the Higgs mechanism and related phenomena and may lead to important technological advances in the field of spintronics.

The team of scientists from Japan, Taiwan, Germany and the United Kingdom has studied the material  $\text{Yb}_2\text{Ti}_2\text{O}_7$ . This compound is of particular interest as it is a variant of a material known as 'spin ice', where the two poles of the magnetic subunits within the crystal become almost detached from each other (Fig. 1, top). Such magnetic 'monopoles' are unknown in conventional magnets—in a bar magnet, for instance, the attractive and repulsive ends can never exist separately. In materials like  $\text{Yb}_2\text{Ti}_2\text{O}_7$ , however, magnetic monopoles can occur. Moreover, previous work has suggested that at temperatures very close to absolute zero,  $\text{Yb}_2\text{Ti}_2\text{O}_7$  undergoes a transition from the monopole state to a so-called ferromagnetic state (Fig. 1, bottom), which corresponds to the magnetic order found, for example, in iron.



**Figure 1: An international research team has found clear evidence for a Higgs transition in a magnetic material, in which a so-called magnetic Coulomb liquid, consisting of magnetic monopoles, assumes ferromagnetic order upon cooling.**

The transition to the ferromagnetic state was possibly linked to the Higgs mechanism but without definite evidence. "There was a controversy over the earlier findings and the problem turned out to be related to the sample quality," explains Onoda. "So we had to show more convincing evidence for the ferromagnetic order and emergent magnetic monopoles below and slightly above the transition temperature, respectively." This evidence has come from a detailed neutron-scattering study, in which the researchers looked at the magnetic structure of  $\text{Yb}_2\text{Ti}_2\text{O}_7$ . The new findings confirm the previous results, while also supporting the

researchers' theoretical picture and providing a key observation required as a minimum for the interpretation of the transition in terms of a Higgs transition.

These results suggest that  $\text{Yb}_2\text{Ti}_2\text{O}_7$  and related spin-ice systems can serve as a platform to explore aspects of quantum physics. They also provide important new insights into the behavior of magnetic monopoles, indicating a route to novel designs for spintronics devices. ■

1. Chang, L.-J., Onoda, S., Su, Y., Kao, Y.-J., Tsuei, K.-D., Yasui, Y., Kakurai, K. & Lees, M.R. Higgs transition from a magnetic Coulomb liquid to a ferromagnet in  $\text{Yb}_2\text{Ti}_2\text{O}_7$ . *Nature Communications* **3**, 992 (2012).

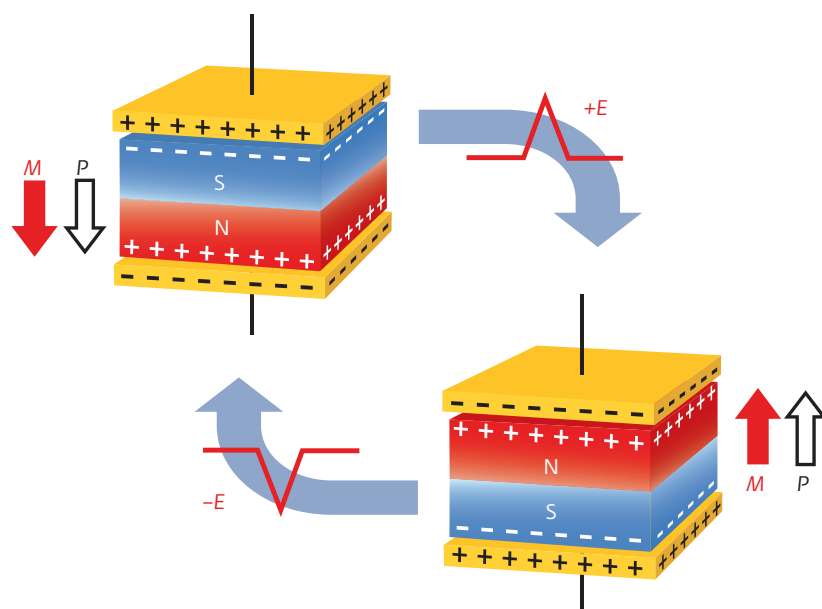
# A perfect couple

Reversal of a magnetic moment by an electrical voltage in a single material could lead to new low-power electronic devices

Researchers at the RIKEN Advanced Science Institute at Wako have discovered a material whose magnetic orientation can be fully switched by electric voltages<sup>1</sup>. Such switchable materials have applications for magnetic data storage or novel electronic devices that use the electron's magnetic properties. As Yusuke Tokunaga from the research team explains, "Reversal of magnetization by a voltage enables ultra-low power consumption electronic devices because applying a voltage and not an electrical current means that such devices are free from Joule heating loss."

Many materials show magnetism and many also show electric polarization, where permanent electric dipole moments persist even when the external electrical voltage is turned off. However, only a few materials—known as multiferroics—show both these so-called ferroic properties simultaneously. In many multiferroics, these two properties are coupled so that the electric polarization can be changed around by switching the magnetic field. But from a practical perspective, for example in data storage, the opposite scenario of switching magnetism with an electrical voltage is more interesting (Fig. 1). Until now, this type of coupling had not been observed in a material.

The first type of coupling occurs, for example, in  $\text{GdFeO}_3$ . This material has been shown previously to be multiferroic by the same research group, but changes in the electric field had only minor influences on magnetism. The related compound  $\text{DyFeO}_3$ , on the other hand, is known to have a strong



**Figure 1: Switching magnetism.** In the material studied the magnetic moment ( $M$ ) and the electrical polarization ( $P$ ) are coupled, so that negative electrical charges ( $-$ ) accumulate near the magnetic southpole ( $S$ ), and positive ones near the northpole ( $N$ ). By applying an electric voltage ( $E$ ), the direction of  $M$  and  $P$  can be reversed.

coupling between magnetism and electric polarization in principle, but it is not a multiferroic as it requires external magnetic fields to show this coupling. The researchers' aim was to try and unify these properties by synthesizing crystals of  $(\text{Dy,Gd})\text{FeO}_3$ , and indeed some of the resulting compounds—including compounds where  $\text{Tb}$  was used instead of  $\text{Gd}$ —show the desired properties. Not only are they multiferroic, but for the first time they also show a complete reversal of magnetization by an electric field.

So far, the effect is limited to temperatures barely a few degrees above

absolute zero. Extending the work to compounds that show this behavior at higher temperatures is an important next step, says Tokunaga. "For the practical application toward ultra-low power consumption devices we need to find new multiferroics that can operate at higher temperatures." With the insights gained on how to achieve magnetic switching, he believes this is highly possible. ■

1. Tokunaga, Y., Taguchi, Y., Arima, T.-H. & Tokura, Y. Electric-field-induced generation and reversal of ferromagnetic moment in ferrites. *Nature Physics* **8**, 838–844 (2012).

# Heavy oxygen holds it together

An oxygen nucleus with twice as many neutrons as normal is shown to be surprisingly stable

The nucleus at the heart of an atom is held together by a subtle balance between the nuclear force that binds protons and neutrons and the electric repulsion that tries to fling the positively charged protons apart. Understanding how the number of nucleons—the collective term for protons and neutrons—affects this balance is crucial for predicting nuclear processes such as radioactive decay. RIKEN researchers, working as part of an international team, have now shown that ‘heavy’ oxygen nuclei with 16 neutrons form into a solid ball, which makes them unexpectedly stable<sup>1</sup>.

More than 99% of the oxygen in the Earth’s atmosphere is in its most stable form with eight protons and eight neutrons at the center. However, scientists can create neutron-heavy versions, or isotopes, in the laboratory to help them better understand what happens in a nucleus. Tohru Motobayashi from the RIKEN Nishina Center for Accelerator-Based Science, collaborating with Yoshinori Satou from the Seoul National University, Korea, Takashi Nakamura from the Tokyo Institute of Technology, Japan, and co-workers from France, Hungary and China have now performed the first spectroscopic study of oxygen nuclei with 16 neutrons using a technique known as proton inelastic scattering. They fired a beam of these oxygen-24 atoms at a liquid-hydrogen target (Fig. 1), and then extracted the properties of the neutron-rich nuclei by tracking the direction and speed of the particles after the collision.

A nucleus has either a spherical or elliptical shape depending on the



**Figure 1: The RIKEN Projectile fragment Separator (RIPS) (pictured) produces high-intensity beams of radioactive ions, which help scientists in the study of nuclear processes.**

number of neutrons and protons. “The nucleus is more stable and solid when it is spherical,” explains Motobayashi. “In our experiments we can hear the sound associated with this solidity, just as you can when you strike an everyday solid object.”

An intriguing aspect of this result is that it runs contrary to the now well-established observation that nuclei are usually stable when the number of neutrons and protons corresponds to a so-called magic number: 2, 8, 20, 28, 50, 82 or 126. “We can now confirm that a neutron number of 16 is magic when proton and neutron numbers are largely unbalanced,” says Motobayashi. “This

supports other recent experiments on different nuclei.”

This cutting-edge experiment is another example of the importance of the steadily growing research collaboration between RIKEN, the Tokyo Institute of Technology and a number of Korean universities. “We next hope to explore more neutron-rich oxygen isotopes with 17, 18 or more neutrons to see if another stable oxygen nucleus exists,” says Motobayashi. ■

1. Tshoo, K., Satou, Y., Bhang, H., Choi, S., Nakamura, T., Kondo, Y., Deguchi, S., Kawada, Y., Kobayashi, N., Nakayama Y. *et al.* *N = 16 spherical shell closure in <sup>24</sup>O*. *Physical Review Letters* **109**, 022501 (2012).



# All together now

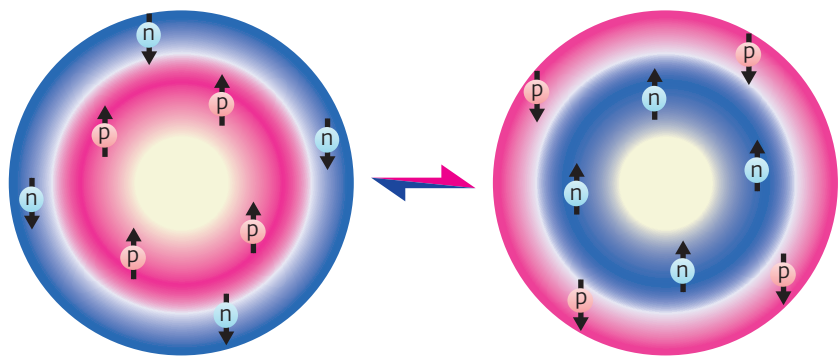
An experimental demonstration that the protons and neutrons in an atomic nucleus move in unison could set a benchmark test for theoretical models of nuclei

The interactions between the protons and neutrons at the heart of an atom play an important role in processes that occur when a star explodes. Understanding these dynamics can thus lead to a better understanding of the origin of planets, including Earth.

Researchers from institutes in Japan, including the RIKEN Nishina Center for Accelerator-Based Science, the United States and China have worked together to experimentally show that the 208 subatomic particles in the middle of a lead atom can vibrate in unison<sup>1</sup>. This observation will provide a crucial test of the accuracy of theoretical quantum models of the many-body interactions that take place in atomic nuclei.

If just the right amount of energy is supplied to a nucleus, by a collision for example, it can cause all the protons and neutrons to oscillate at a high frequency. This many-body effect is known as giant resonance. RIKEN researcher Kenjiro Miki and his co-workers (the SHARQA collaboration) have observed a tell-tale signature of a giant resonance in lead-208 in which the protons oscillate away and then toward the nucleus center while the neutrons move in the opposite direction (Fig. 1). This is known as the isovector spin monopole resonance. “Isovector spin excitations are caused by particles known as pi mesons, which are also responsible for a large part of nuclear interactions,” Miki explains. “The study of the isovector spin monopole resonance can therefore tell us a great deal about these important nuclear interactions.”

The researchers produced a high-energy beam of particles known as tritons, made



**Figure 1: The isovector spin monopole resonance involves the protons (p) radially expanding and compressing inside the nucleus while the neutrons (n) oscillate in reverse. The arrows indicate the axis about which each subatomic particle is rotating—this movement is known as the spin.**

up of one proton and two neutrons, and fired them at a lead target. “RIKEN’s RI Beam Factory can provide a high intensity triton beam at an energy best suited for generating isovector spin excitations,” says Miki. The triton triggers the giant resonance through an interchange of a pi meson with the target and turns into helium-3 nucleus (two protons and a neutron). The team could therefore determine the reaction rate by counting the number of helium-3 produced.

To distinguish the isovector spin monopole resonance from other possible excitations, the team compared the reaction rates for tritons with those for

neutrons as measured in previous experiments. “It has been theoretically predicted that the isovector spin monopole resonance will be more efficiently excited by tritons than neutrons,” says Miki. “The significant rate enhancement in the triton experiment we observed is therefore clear evidence for the isovector spin monopole resonance.” ■

1. Miki, K., Sakai, H., Uesaka, T., Baba, H., Bai, C.L., Berg, G.P.A., Fukuda, N., Kameda, D., Kawabata, T., Kawase, S. *et al.* Identification of the  $\beta^+$  isovector spin monopole resonance via the  $^{208}\text{Pb}$  and  $^{90}\text{Zr}(t, ^3\text{He})$  reactions at 300 MeV/u. *Physical Review Letters* **108**, 262503 (2012).

# Mapping genes onto brain structures

A new technique comprehensively generates three-dimensional maps of gene expression in the brain

A research team led by Yuko Okamura-Oho and Hideo Yokota of the RIKEN Advanced Science Institute, Wako, has developed a novel technique for three-dimensional (3D) mapping of gene expression patterns onto brain structures<sup>1</sup>. The technique, known as transcriptome tomography, combines tissue sectioning with microarray technology and produces comprehensive maps of the density and location of gene expression, which have a higher resolution than the maps produced by existing methods.

To produce their first dataset, the researchers sliced six mouse brains into five micrometer sections, in each of three anatomical planes. They collected the sections in batches of 200 to produce ‘fractions’ of 1-millimeter thickness that were used for microarray analysis. They then treated 61 such fractions with more than 36,000 RNA probes and reconstructed the data to produce 3D maps of

gene expression throughout the whole mouse brain (Fig. 1).

Transcriptome tomography is semi-automated, making it more cost-effective and faster than existing manual approaches—it took the researchers just one month to generate the first dataset. The technique can also be used to map the tissue distribution of any type of biological molecule, such as proteins, lipids, sugars and microRNAs.

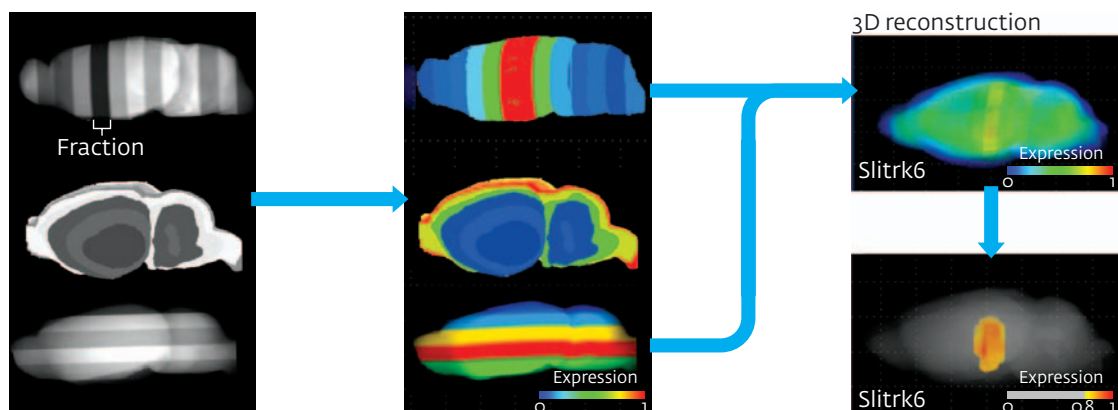
Okamura-Oho and her colleagues validated the technique by comparing their first dataset to pre-existing ones generated by other methods. They also analyzed the expression patterns of the *Huntingtin* gene, which when mutated causes Huntington’s disease, a progressive neurodegenerative condition characterized by the death of neurons in the basal ganglia, followed by cell death in the cerebral cortex.

The analysis revealed that *Huntingtin* was expressed at high levels in brain

regions known to be severely affected by the condition, such as the basal ganglia, but at significantly lower levels in areas that are less vulnerable, such as the midbrain and cerebellum. “We could make expression maps in 20-times higher resolution comparable to MRI. Such maps have the potential to reveal more detailed disease-related abnormalities with continuous technical advancing,” says Okamura-Oho.

Transcriptome tomography datasets can be uploaded to Waxholm Space, a coordinate-based space for open resources. The space facilitates the creation of researchers’ own datasets that can then be shared and analyzed in the space. ■

1. Okamura-Oho, Y., Shimokawa, K., Takemoto, S., Hirakiyama, A., Nakamura, S., Tsujimura, Y., Nishimura, M., Kasukawa, T., Masumoto, K., Nikaido, I. *et al.* Transcriptome tomography for brain analysis in the web-accessible anatomical space. *PLoS ONE* 7, e45373 (2012).



**Figure 1: Transcriptome tomography.** Tissue sections in each of three orthogonal planes are fractionated, and 36,558 gene expression densities in them are measured with microarrays and then reconstructed to generate 3D maps (an example map is shown).



# My mistake or yours? How the brain decides

A study of brain activity in monkeys shows how the brain processes mistakes made by others

Humans and other animals learn by making mistakes. They can also learn from observing the mistakes of others. The brain processes self-generated errors in a region called the medial frontal cortex (MFC) but little is known about how it processes the observed errors of others. A Japanese research team led by Masaki Isoda and Atsushi Iriki of the RIKEN Brain Science Institute has now demonstrated that the MFC is also involved in processing observed errors<sup>1</sup>.

The team studied the brains of monkeys while the animals performed the same task. Two monkeys sat opposite each other and took turns to choose between a yellow and green button, one of which resulted in a liquid reward for both. Each monkey's turn consisted of two choices.

After blocks of between 5 and 17 choices, the button that resulted in reward was switched unpredictably, usually causing an error on the next choice. The choices made by each monkey immediately after such errors, or errors that were random, showed that they used both their own errors and their partner's to guide their subsequent choices. While the monkeys performed this task, the researchers recorded activity of single neurons in their brains (Fig. 1).

In this way they were able to determine which behavioral aspect was most closely associated with each neuron's activity, explains Isoda. "We found that many neurons in the medial frontal cortex were not activated when the monkey made an error itself, but they became active when their partner made



**Figure 1: Activity of individual neurons in the medial frontal cortex of monkeys was recorded while they observed their partner making errors.**

an error." This brain activity shows that it is the MFC that processes observations of another's error, and the corresponding behavior shows that observing and processing such errors guides subsequent actions.

"Such error identification and subsequent error correction are of crucial importance for developing and maintaining successful social communities," says Isoda. "Humans are tuned into other people's mistakes not only for competitive success, but also for cooperative group living. If non-invasive techniques become available in humans, then we

should be able to identify medial frontal neurons that behave similarly."

Having identified the MFC as being involved, Isoda now wants to delve deeper into the process. "The next steps will be to clarify whether the inactivation of medial frontal cortex neurons reduces the ability to identify others' errors, and to determine whether other brain regions are also involved in the processing of others' errors." ■

1. Yoshida, K., Saito, N., Iriki, A. & Isoda, M. Social error monitoring in macaque frontal cortex. *Nature Neuroscience* **15**, 1307–1312 (2012).

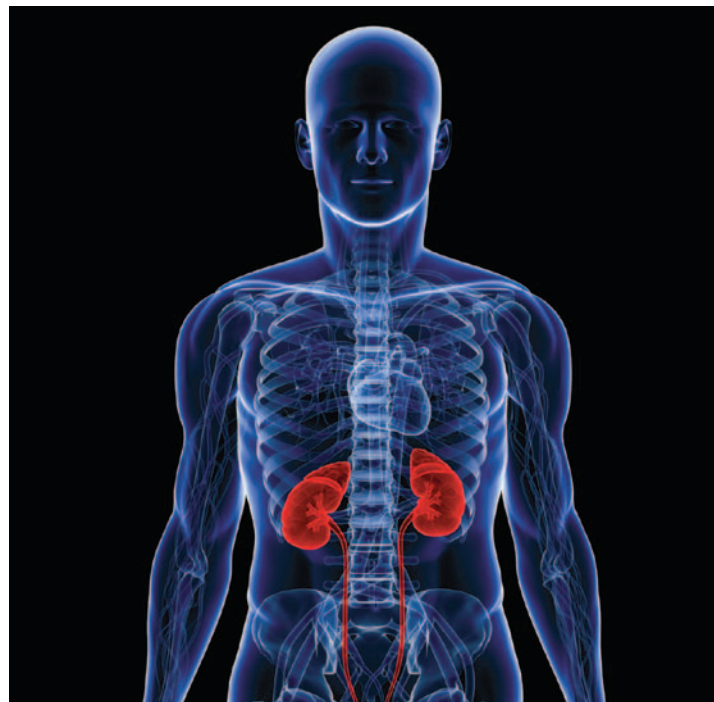
# Finding elements of regional risk

A consortium of geneticists has uncovered a trail of variants associated with kidney dysfunction specifically among East Asian populations

The past decade has seen a steady torrent of data linking human genetic variants associated with disease risk, and yet many important gaps remain. For example, many of these studies have focused primarily on Caucasian populations in North America and Europe. The resulting data may be less relevant to other ethnic groups that may have accumulated distinct subsets of risk factors over the millennia since our ancestors first parted ways in Africa.

The Asian Genetic Epidemiology Network (AGEN) was formed to address this issue by identifying disease risk loci specific to Asian populations. A new study from AGEN-affiliated scientists has now identified 17 genomic sites that potentially predispose East Asian individuals to chronic kidney disease (CKD)<sup>1</sup>. CKD, which puts patients at risk of kidney failure and cardiovascular disease, encompasses a host of potential metabolic symptoms. Accordingly, project leaders Yukinori Okada and Toshihiro Tanaka of the RIKEN Center for Genomic Medicine designed their study to identify potential genetic variants linked with four different physiological manifestations of CKD.

They performed what is known as a meta-analysis, conducting a broad examination of genomic data obtained from 11 previously studied cohorts comprising over 70,000 East Asian individuals. In particular, they were interested in identifying tiny genomic sequence variations known as single-nucleotide polymorphisms (SNPs) that appear to be associated with CKD symptoms. This yielded 25 candidate loci, which the AGEN team



**Figure 1: Chronic kidney disease (CKD) can be associated with a wide range of symptoms and physiological abnormalities, with potentially severe consequences for patients.**

then double-checked against another dataset obtained from nearly 20,000 more East Asian subjects.

Alongside several previously identified potential risk factors, their analysis uncovered 17 loci that appear to be meaningfully linked with CKD. Importantly, only a subset of these showed equally strong association with CKD symptoms in datasets obtained from large numbers of Caucasians. They were also able to identify individual variants linked to multiple CKD manifestations, including SNPs within three genes that were significantly associated with all four symptoms selected for this study.

Several of the SNPs identified here were linked to genes involved in immunity and embryonic development, including

one gene with an established role in the formation of the kidney. At least three others have been tied to kidney function in previous studies. For many of the other genes identified, however, the connection to kidney or metabolic disease remains unclear. Further study will be required to assemble these diverse data into a coherent map of CKD etiology and to understand which factors are particularly important 'red flags' for health risk in East Asian patients. ■

1. Okada, Y., Sim, X., Go, M.J., Wu, J.-Y., Gu, D., Takeuchi, F., Takahashi, A., Maeda, S., Tsunoda, T., Chen, P. *et al.* Meta-analysis identifies multiple loci associated with kidney function-related traits in east Asian populations. *Nature Genetics* **44**, 904–909 (2012).

# Staking out unknown genomic territory

A data treasure-trove from a multinational genome-charting effort enables powerful insights into cellular function and the roots of human disease

Scientists have long known that the human genome is incredibly complex. However, after almost 10 years of hard work, a team of more than 400 scientists at 32 research institutions worldwide has finally made serious headway in beginning to understand the structure, function and internal logic of the approximately 3.2 billion bases found within every cell of our body (Fig. 1).

The Encyclopedia of DNA Elements (ENCODE) Consortium is coordinated by the US National Human Genome Research Institute and draws upon intellectual firepower from the world's leading geneticists—including Piero Carninci and colleagues at the RIKEN Omics Science Center (OSC) in Yokohama, Japan. In early September 2012, ENCODE finally shared the initial fruits of its labors with the world<sup>1</sup>.

The results revealed some surprises. For example, ENCODE's most inclusive model suggests that up to 80% of the genome serves some biochemical function in at least one of the cell lines studied. ENCODE scientists also found that considerably more of the genome is dedicated to regulating gene function than to genes themselves. They have mapped many previously identified disease-associated genomic variants to such regulatory regions.

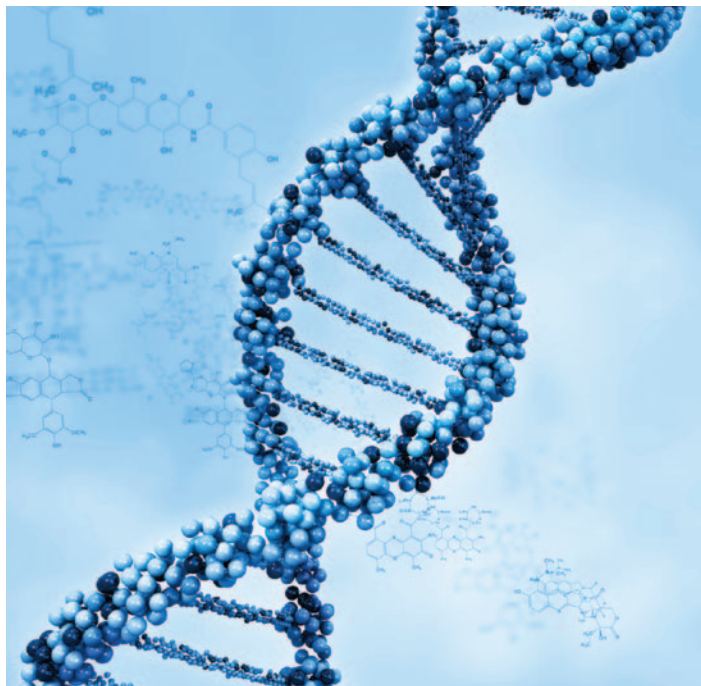
The RIKEN team was well-versed in the complexities of international collaboration through their experiences with FANTOM, a major genomics consortium headquartered at OSC, but Carninci says the guidance of lead analysis coordinator Ewan Birney was essential to the success of such an ambitious effort as ENCODE.

Standardization was also a challenge, as different cells can have highly divergent patterns of gene expression. ENCODE selected 147 human cell lines and prioritized them so that all groups focused their efforts on common sets of targets.

Every group had its own specialization, and Carninci and colleagues used techniques devised at RIKEN to map genome-wide sites where DNA gets transcribed into RNA<sup>2</sup>. Their team confirmed striking differences between cell lines, with no one cell type expressing more than 56.7% of the pool of RNA molecules identified in the total sample set. They also identified many cell-specific 'enhancers' of gene expression and characterized fundamental differences in expression behavior between genes that encode proteins and those that do not.

The ENCODE effort will continue but Carninci sees great value in the data already uncovered. "I believe this information will be generally used to broadly classify functional parts of the genome in many unrelated biomedical studies," he says. "We have better programs to identify regulatory elements and rules to define those elements, and can now expand this to examine, for instance, biological samples related to diseases." ■

1. The ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. *Nature* **489**, 57–74 (2012).
2. Djebali, S., Davis, C.A., Merkel, A., Dobin, A., Lassmann, T., Mortazavi, A., Tanzer, A., Lagarde, J., Lin, W., Schlesinger, F. *et al.* Landscape of transcription in human cells. *Nature* **489**, 101–108 (2012).



**Figure 1:** Through nearly a decade of effort, the ENCODE Consortium has started to construct a functional framework for the human genome.



# Gut shortcut for migrating cells

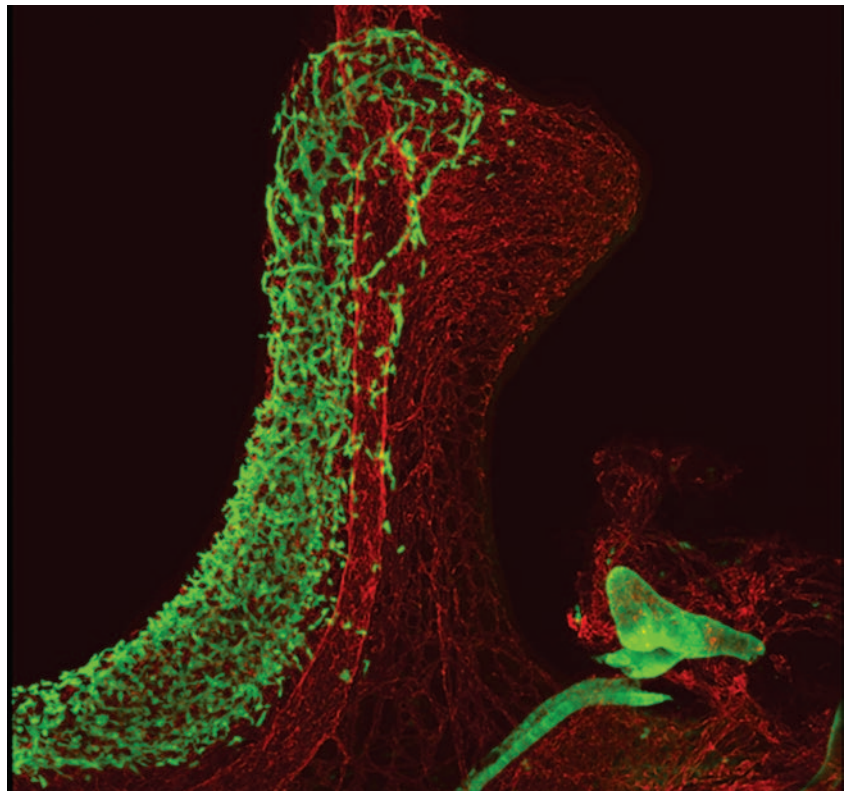
Insight into how neuronal precursor cells migrate in the gut may reveal the cause of an intestinal disease

During development, many cells migrate from their site of production to their final destination. This process is crucial to the development of organs and incorrect migration can cause many diseases.

Enteric neural crest cells (ENCCs) are one of these migrating cell types. ENCCs are precursors of neurons that make up the nervous system of the gut, called the enteric nervous system (ENS) (Fig. 1). If ENCC migration goes wrong, it can cause Hirschsprung's disease, a disorder characterized by the absence of the ENS in the colon that results in continuous contraction in this region, causing blockage of the digestive system.

At the same time as ENCC migration, the length and shape of the developing gut changes considerably. In particular, the tubular structure of the gut folds back on itself to form a hairpin bend, with the mid-gut and hind-gut briefly juxtaposed. This folding causes the mesentery, a wall that encases the developing gut, to be sandwiched in between. Until now, exactly how the migrating ENCCs find their way to the correct place at the same time as these changes occur was unknown.

An international research team led by Hideki Enomoto at the RIKEN Center for Developmental Biology, Kobe, has shown that a large part of the ENS in the hind-gut develops from ENCCs that migrate from the mid-gut to the hind-gut through a shortcut via the mesentery while it is sandwiched in between<sup>1</sup>. The team showed this by labeling ENCCs with a protein called humanized KikumeGR (hKikumeGR), which allows tracking of cell movements. "We



**Figure 1:** Staining of the mouse gut in a developing embryo showing ENCCs in green and blood vessels in red. At this stage, ENCCs fully colonize the small intestine and will next invade the large intestine.

expressed hKikumeGR in mice ENCCs," explains Enomoto. "Upon UV exposure, hKikumeGR changes its conformation and the green fluorescent color becomes red. This technique allows non-invasive cell tracing."

By using photo-conversion to change the color of cells that migrated via the mesentery (tmENCCs), but not cells that migrated along the gut (cfENCCs), the researchers showed that most cells in the ENS of the colon developed from the tmENCCs. Using the same method to follow ENCCs in a mouse model of Hirschsprung's disease, the team found that, while migration across the mesentery did occur, it was delayed and there

were fewer tmENCCs cells. "A decrease in the numbers of tmENCCs suggests that failure in trans-mesenteric migration is a major cause of the disease," explains Enomoto. "Further characterization of genetic and cellular features of tmENCCs will provide vital information toward developing a strategy to induce colonic enteric neurons from embryonic stem cells." ■

1. Nishiyama, C., Uesaka, T., Manabe, T., Yonekura, Y., Nagasawa, T., Newgreen, D.F., Young, H.M. & Enomoto, H. Trans-mesenteric neural crest cells are the principal source of the colonic enteric nervous system. *Nature Neuroscience* **15**, 1211–1218 (2012)

# How molecular transports change gear

Environment determines the motion of motor proteins

The motor protein myosin-V, which hauls molecular cargoes around cells by ratcheting along filaments of actin, switches between two different molecular mechanisms of movement depending on the environment. This finding by a research group led by Toshio Yanagida of the RIKEN Quantitative Biology Center, Osaka, and Osaka University, could form the basis for designing energy-saving artificial nano-motors<sup>1</sup>.

Previous work by other researchers showed that myosin-V typically uses the two mechanisms—lever-arm swing and Brownian search-and-catch—alternately to propel itself along a filament hand-over-hand. Myosin-V possesses two arm-like projections, the heads of which bind to actin. When myosin-V links to the energy storage molecule adenosine triphosphate (ATP), the rear head detaches from the actin filament. As ATP releases energy by losing a phosphate, the front head then goes through a lever-arm swing motion pulling forward on the filament like an oar through water, dragging the rear projection with it. The rear head then swings over and forward while buffeted by passing molecules in random Brownian motion. As it nears the filament in front, it catches onto it.

Yanagida and his colleagues, including Keisuke Fujita and Mitsuhiro Iwaki, were able to attach a fluorescent polystyrene bead to the rear projection of myosin-V with a strand of DNA. This allowed them to measure the motions of the motor molecule accurately by tracking the displacement of the bead. They could also measure the force each head exerted by trapping the bead and holding it steady

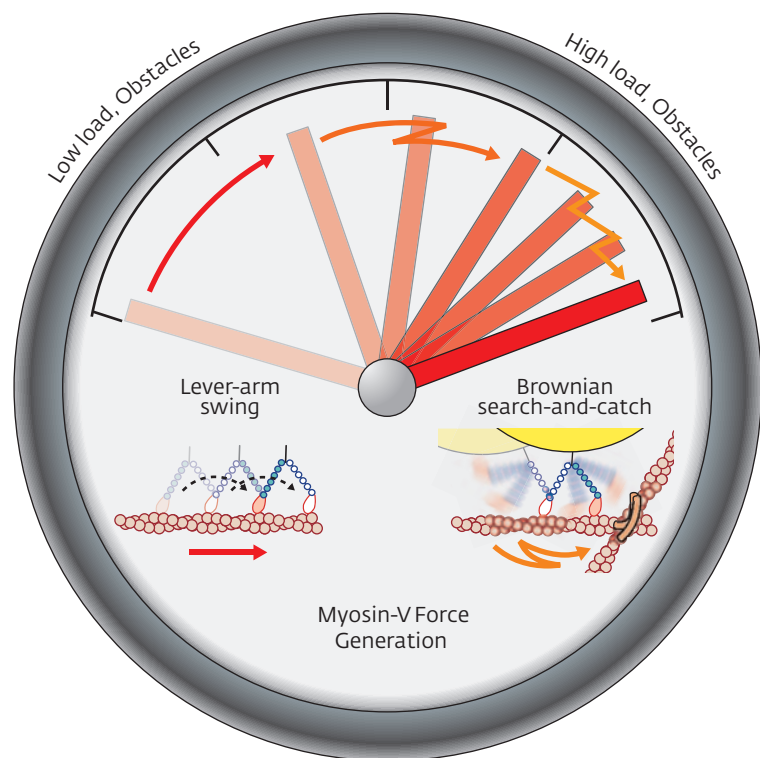
using the laser light mechanism known as optical tweezers under different loads and environmental conditions.

The results showed that for low loads along filaments where there are no obstacles, the bulk of the work of myosin-V's motion is executed by the lever-arm swing mechanism. But at higher loads, and in less predictable environments, the force capable of being exerted by lever-arm swing reaches a maximum and Brownian search-and-catch motion automatically takes over (Fig. 1). Cells contain a meshwork of crisscrossing actin filaments and there is always the possibility of colliding with moving molecules and vesicles to hinder the transport of

myosin-V's molecular cargoes. Under these circumstances the 'high-stepping' Brownian search-and-catch motion comes into its own.

"We are hopeful that the studies of other biological actuators or simulations will show that our theory for myosin-V movement is universal and therefore adds a much more concrete paradigm to the design of artificial nano-machines," says Yanagida. ■

1. Fujita, K., Iwaki, M., Iwane, A.H., Marcucci, L. & Yanagida, T. Switching of myosin-V motion between the lever-arm swing and Brownian search-and-catch. *Nature Communications* **3**, 956 (2012).



**Figure 1:** As the molecular load on myosin-V increases, lever-arm swing motion (left) switches to Brownian search-and-catch (right).



**YOSHITSUGU SHIRO**

Chief Scientist  
Biometal Science Laboratory  
Photon Science Research Division  
SPring-8 Center  
RIKEN Harima Institute

## Exploring the chemistry of iron and organisms

The human body contains approximately 100,000 kinds of protein, 30% of which contain at least one metal in the form of ions or complexes. “The inclusion of metal allows chemical reactions that cannot otherwise occur with proteins consisting essentially of amino acids,” says Yoshitsugu Shiro, chief scientist at the Biometal Science Laboratory in the SPring-8 Center, RIKEN Harima Institute. In his laboratory, he has been mainly analyzing the conformations of iron-containing enzymes and other proteins to clarify the mechanisms of their chemical reactions. His study of bacterial enzymes published in January 2012, which explored the evolution of organisms in terms of protein structures, has attracted much attention.

### Conformations stimulate the imagination

Many metal-containing proteins act as enzymes and catalyze various chemical reactions. The metal forms an “active site” in the enzyme, where it interacts with reactive substances to bind atoms together or, conversely, to break molecular bonds; the proteins around the active site control the metal-reactant interactions. “I am interested in how the metal in the enzyme binds atoms together and breaks their bonds to allow chemical reactions to proceed,” says Shiro. However, with current technology, chemical reactions that occur instantaneously on the atomic scale cannot be directly observed, and so the process of each chemical reaction remains a black box. At present,

the only available approach is to make estimations based on observations before and after the reaction.

Shiro joined RIKEN in 1987. “I had long been interested in the structural analysis of an iron-containing enzyme, so after joining RIKEN, I decided to conduct structural analysis.”

Essentially, a protein is a chain sequence of amino acids arranged according to genetic information and folded to form a three-dimensional structure. Analyzing the structure of a protein at a resolution of 2 to 3 ångströms or less, it is possible to identify atoms and amino acids and determine their arrangements. “Actually, structural analysis on the atomic scale does not alone clarify the processes of chemical reactions. However, if we know

what kinds of amino acids and atoms there are and how they are arranged, we chemists can use our powerful imaginations to estimate and discuss the chemical reaction processes.”

A typical approach to structural analysis of proteins uses x-ray crystallography. In this method, the subject protein is crystallized and the resultant crystal, which is composed of a large number of protein molecules orderly arranged, is exposed to x-rays. The subject protein’s steric structure, or conformation, can then be estimated on the atomic scale from the pattern of the x-rays’ diffraction. “When I joined RIKEN, however, few members were engaged in protein x-ray crystallography, so I began structural analysis with the help of an expert on crystallization.”



### Seeing is believing

Shiro chose as his first target of structural analysis the nitric oxide reductase (NOR) possessed by *Fusarium oxysprum*, a fungal species (Fig. 1). NORs are a class of enzymes that catalyze chemical reactions reducing nitric oxide (NO) into nitrous oxide ( $N_2O$ ) (Fig. 2). When two molecules of nitric oxide (NO) react with two protons and two electrons, two distinct phenomena occur simultaneously: the two N (nitrogen) atoms bind together, and oxygen (O) is cleaved from one of the NO molecules. This process produces  $N_2O$  and water ( $H_2O$ ). “This process is simple but is the essence of chemistry. I proceeded to study this enzyme not only by x-ray crystallography but also using spectroscopic and other methods, and proposed a hypothesis on the reaction process involved in its action.”

Shiro hypothesized that when the first NO approaches the iron at the active site and two electrons enter it at one time, the reaction is very likely to occur. He further proposed that next the second NO approaches the active site, and the two nitrogens (N and N) bind together while the O is cleaved simultaneously. “When I published this hypothesis, one stunned researcher told me I was making

rather bold claims. This was because a chemical reaction involving the entry of two electrons in a single molecule at one time is very rare in living organisms. Later in 1997, we succeeded in analyzing the conformation of a fungal NOR (Fig. 1, part A): the conformation we found supported my hypothesis, and my theory was accepted by many researchers. Seeing truly is believing!”

The fungal NOR is one of the proteins whose structures were first registered with the Protein Data Bank under the name of RIKEN. In October 1997, just after the publication of this achievement, the RIKEN Harima Institute opened and soon began operating the large synchrotron radiation facility, SPring-8—a powerful tool for x-ray crystallography. Shiro took this opportunity to move his research base from the Wako Institute to the Harima Institute.

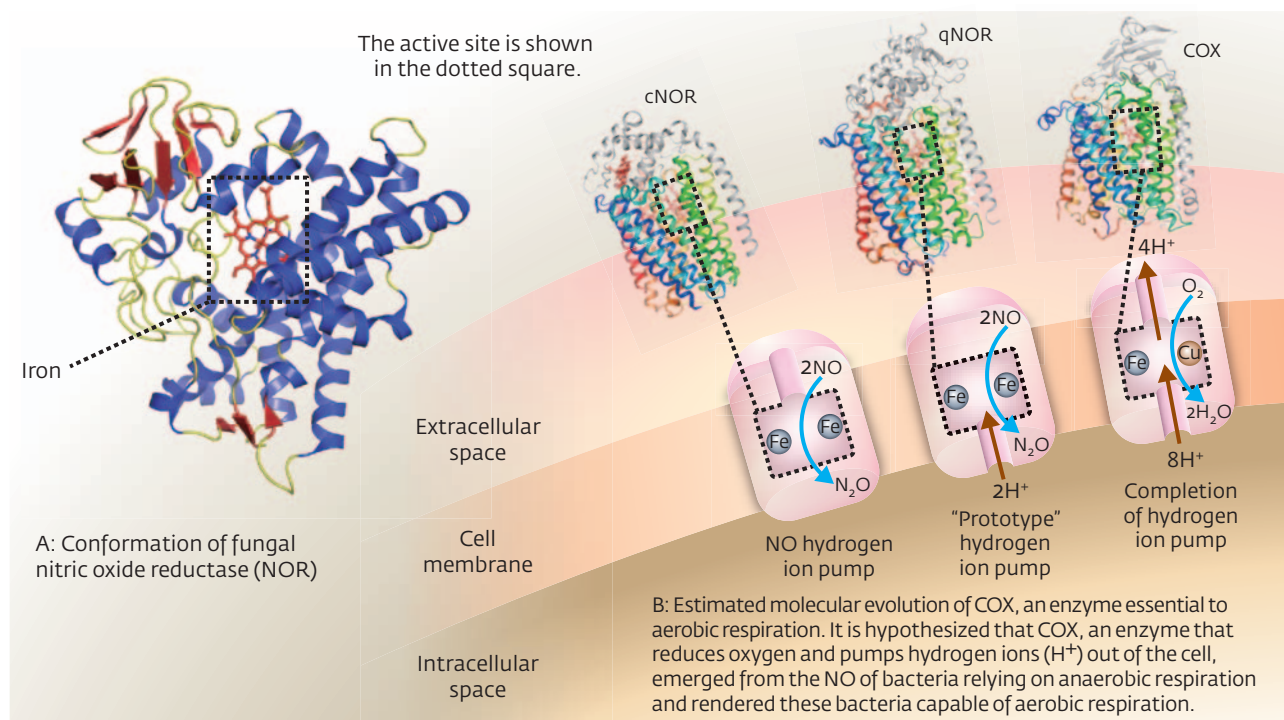
### The evolution of organisms in terms of protein conformations

Around 1990, gene analyses revealed structural similarities in the amino acid sequence of COX, a cytochrome oxidase indispensable to aerobic respiration using oxygen by organisms, and the NORs of bacteria that are capable of oxygen-free

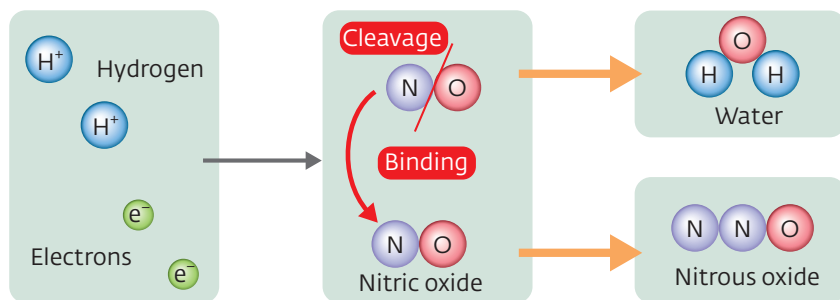
anaerobic respiration. The bacterial NORs were identified as enzymes having an amino acid sequence distinct from fungal NORs. To better understand the relationship between COX and the bacterial NORs, it is necessary to look back and consider the formation of Earth.

It is thought that there was no oxygen ( $O_2$ ) in the atmosphere and oceans of the primitive Earth when it formed about 4.6 billion years ago. Therefore, the first organisms that emerged on Earth about 3.8 billion years ago are believed to have relied on anaerobic respiration using oxides of nitrogen and sulfur, rather than oxygen. About 3.0 billion years ago, organisms that released oxygen by conducting photosynthesis emerged, and thus the abundance of oxygen in the atmosphere and oceans began to increase.

In those days, oxygen was highly toxic to organisms because it oxidizes and damages DNA and protein. However, organisms capable of aerobic respiration using the oxygen evolved. As aerobic respiration allows energy to be generated much more efficiently than anaerobic respiration, the evolution of these organisms progressed remarkably, leading to the birth of a eukaryotic organism that is the common ancestor of animals and plants.



**Figure 1: Nitric oxide reductase (NOR) and cytochrome oxidase (COX)**



**Figure 2: Reduction of nitric oxide to nitrous oxide**

When two molecules of nitric oxide (NO) react with two hydrogen ions ( $H^+$ ) and two electrons ( $e^-$ ), two phenomena occur simultaneously: the two N (nitrogen) atoms bind together, and oxygen (O) is cleaved from one of the NO molecules. Nitrous oxide ( $N_2O$ ) and water ( $H_2O$ ) are thus produced.

Acquisition of the ability to perform aerobic respiration is one of the defining moments in the history of biological evolution, and the protein that played the key role in enabling aerobic respiration is COX. Embedded in the cell membrane, COX reduces oxygen and works as a pump to move protons from the inside to the outside of the cell. This action produces a bias in proton concentration between the intra- and extracellular space, and based on this a biological energy source known as adenosine-5'-triphosphate (ATP) is produced.

“It was hypothesized that in the process of biological evolution, the COX of organisms capable of aerobic respiration evolved from the NORs of anaerobic bacteria. To verify this hypothesis, much research on the conformational analysis of NORs was undertaken worldwide in the 1990s. Bacterial NORs can be roughly divided into two classes: cNORs and qNORs. In 2003, we began a study to crystallize the cNOR of *Pseudomonas aeruginosa* and analyze its structure using SPring-8.”

Shiro and his colleagues then proceeded to analyze the structure of the qNOR of *Geobacillus stearothermophilus*, a thermophilic bacterium. “We first succeeded in

analyzing the conformation of the qNOR, and submitted an article on the analytical results to an academic journal. But we received from the referees a plethora of counterarguments because our results overturned the conventional theory.”

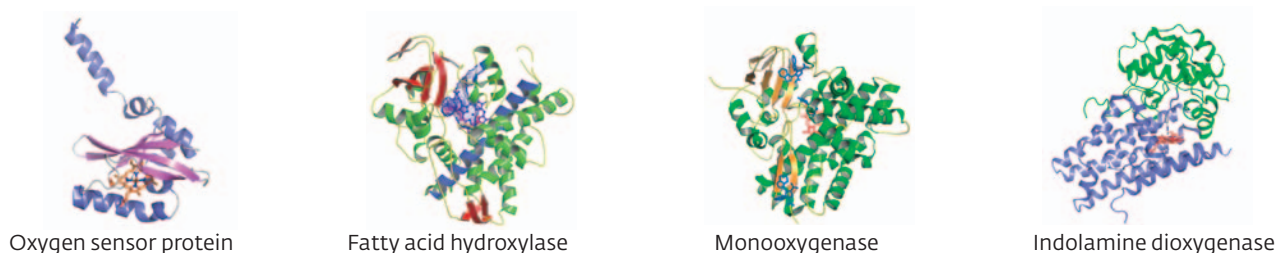
As an enzyme embedded in the cell membrane, the qNOR absorbs protons, which are needed for its reaction, into its active site. “It had been the established theory that a NOR absorbs protons into its active site from outside of the cell. We reached the opposite conclusion—that the qNOR absorbs protons from inside, not outside, of the cell,” explains Shiro (see Fig. 1, part B).

To obtain data to counter the referees' rebuttal, Shiro conducted various additional experiments, but his qNOR article remained unpublished for another 3 years. “Before long, we succeeded in determining the structure of the cNOR of *Pseudomonas aeruginosa*. Our paper reporting the results was published in 2010. Why was this paper accepted so quickly? I believe that was because our analytical results were consistent with the established theory that the cNOR absorbs protons from outside of the cell,” says Shiro (see Fig. 1, part B).

Meanwhile, their qNOR article was finally accepted for publication in January 2012. At present, Shiro and his colleagues are the only team in the world that has successfully analyzed the structure of a bacterial NOR. “As I expected, the structure of the bacterial NOR was found to be completely different from that of the fungal NOR. However, the conformations of the three enzymes cNOR, qNOR and COX look alike, so it is obvious that they are mutually related in an evolutionary context. The fact that cNORs and qNORs have different modes of proton uptake had not been revealed merely by determining their amino acid sequences by genetic analysis.”

While cNORs and qNORs have two iron atoms at their active sites, COX has one iron atom and one copper (Cu) atom. Although both qNORs and COX absorb protons from inside the cell, COX has an additional pathway, known as the proton pump, for driving out hydrogen ions to the extracellular space.

Hence, Shiro hypothesizes that qNORs are a prototype of the proton pump and that COX emerged as a finished product from the prototype. “My joint research partner Yuji Sugita, chief scientist at the Theoretical Molecular Science Laboratory in the RIKEN Advanced Science Institute, conducted computer simulations and predicted that a pathway for driving out protons from the inside to the outside of the cell is formed as a result of the substitution of some amino acids in NOR by other amino acids. We are now conducting experiments to confirm the amino acid substitution to determine whether the structure will change as expected from the simulation.”



**Figure 3: Proteins whose conformations were determined by the Biometal Science Laboratory**

These proteins are attracting the attention of pharmaceutical companies and the like. The fungal nitric oxide reductase (Fig. 1, part A), fatty acid hydroxylase and monooxygenase are very similar in conformation, but their reactivities and bioactivities are completely different.

“Traditionally, biological evolution has been investigated in terms of body morphology and at the gene level. It is a groundbreaking achievement that we are now able to explore biological evolution at the protein structure level,” says Shiro.

### Using the K computer and SACLA

“In bacterial NORs, how do the two iron atoms act to reduce NO? I am most interested in the process of this reaction. To elucidate the process, I am working to create a composite crystal by binding a NOR and a molecule consisting of two atoms, such as NO, and to analyze its conformation using SPring-8. I want to simulate the reaction process using the K computer—RIKEN’s supercomputer in Kobe—on the basis of the analytical results.”

The SPring-8 Angstrom Compact Free Electron Laser (SACLA), which was built as an annex to SPring-8, entered service in March 2011. There are high expectations that it will be possible to directly observe chemical reaction processes by using the SACLA, which produces an x-ray laser that is one billion times brighter than SPring-8 and which has a very short light-emitting time of one-100 trillionth of a second. “I would like to work on observing the reaction processes of NORs using the SACLA in the future, so we must develop techniques that enable us to do this.”

### Humans, iron and pathogenic microorganisms

NO is known to be a harmful substance with high chemical reactivity. It is produced in the process of anaerobic respiration in fungi and bacteria, which reduce the NO using a NOR into harmless N<sub>2</sub>O.

However, the greenhouse effect of N<sub>2</sub>O is 300 times that of carbon dioxide. N<sub>2</sub>O is also thought to be a major cause of ozone layer depletion. “With collaborators from the Advance Science Institute, I have already started searching for an inhibitor of the function of NOR as a way of preventing global warming and ozone layer depletion,” explains Shiro of his collaborative work with Hiroyuki Osada, chief scientist at the Antibiotics Laboratory; Minoru

Yoshida, chief scientist at the Chemical Genetics Laboratory, and other researchers at the RIKEN Advanced Science Institute.

Shiro and his colleagues at the Harima Institute have also been researching the chemical reactions of oxygen and a wide variety of iron-containing proteins other than the NORs mentioned here. Examples include: sensor proteins that sense oxygen concentrations; fatty acid hydroxylases, which are involved in the metabolism of fatty acids; monooxygenases, which catalyze the production of compounds expected to serve as anticancer agents from amino acids; and indolamine dioxygenase, an enzyme that plays a key role in the metabolism of tryptophan in humans (Fig. 3). Their structures and reaction mechanisms should provide insights for drug innovation and the production of a variety of useful substances at low cost.

“Next, we must analyze the conformations of proteins involved in the absorption and utilization of the essential element iron by organisms, and elucidate the mechanisms behind the chemical reactions. This is truly ‘biometal science.’”

Shiro points out that man and pathogenic microorganisms are competing with each other for iron. “Pathogenic microorganisms such as those causing malaria and diphtheria deprive oxygen-carrying blood hemoglobin of iron and utilize the metal for their survival. To fight against such pathogens, the human immunocyte, macrophage, releases toxic NO to attack them. The pathogenic microorganisms resist this attack by NORs, which contain iron, to make the NO harmless to themselves.”

While iron is critical to the survival of organisms as described above, it can be toxic when absorbed in excess. This is because the reaction of iron and oxygen produces reactive oxygen. Highly reactive oxygen reportedly damages DNA and protein, causes diseases and accelerates aging. “Microorganisms, including pathogenic ones, have their own sensor proteins belonging to a two-component regulatory system for sensing iron concentrations in their bodies; they close the iron inlet when the iron concentration

reaches a threshold. Humans lack such a type of iron sensor protein. Any inhibitor that suppresses the action of the two-component sensor protein is potentially effective against a wide variety of pathogenic microorganisms while being harmless to humans.”

### Of iron and organisms

The research on the chemistry of iron and organisms undertaken by Shiro and his colleagues should stimulate the imaginations of researchers in a broad range of fields, including engineering and drug discovery.

“Today’s high-performance electronic devices contain rare metals with excellent catalytic function, such as platinum and palladium. In contrast, living organisms utilize iron, zinc, copper and other common metals that are abundant on Earth instead of rare metals, to carry out a wide variety of chemical reactions that enable their complex biological activities. Based on the findings in conformational analysis, applied research is being conducted, including the search for candidate drug substances and altering the conformations of naturally-occurring enzymes to create new enzymes with excellent functions. Investigations into the mechanisms of chemical reactions in metal-containing proteins should help us learn the very essence of the chemical reactions that are cleverly carried out by organisms, which can then be applied to ourselves.” ■

#### ABOUT THE RESEARCHER

**Yoshitsugu Shiro was born in Nagoya, Japan, in 1956. He graduated from the Faculty of Engineering, Kyoto University, in 1980, and obtained his PhD in 1985 from the same university. After postdoctoral training at Kyoto University, Shiro moved to RIKEN in 1987 as a research scientist and in 2000 became chief scientist at the Harima Institute. Since then, Shiro has been director of his own research group and his current research focuses on the structures/functions of proteins in relationship to the dynamics of metal elements in biology.**





## CHIEKO YAMADA

Animal Technician  
Experimental Animal Division  
RIKEN BioResource Center

# Taking care of laboratory mouse strains

### What do you do at RIKEN?

I work as an animal technician from Tokyo Business Service at the animal facility of the Experimental Animal Division in the RIKEN BioResource Center (BRC) based in Tsukuba city. I am in charge of the care and breeding of laboratory mice as well as the maintenance of mouse strains.

### Please tell us about your work at RIKEN.

The BRC has over 700 live mouse strains and I am in charge of 80 strains of transgenic and knockout mice. Every time new mice are born, we check their genotype in order to maintain the genetic quality of the mouse strain. We manage the number of the mice we breed depending on the quantity of requests we receive from customers.

My usual morning task is to transfer mice to a new breeding cage and to give them food and water. If we need to distribute mice to our customers that day, I first assess the health condition of the mice and then I prepare the mice in containers for transportation to our customers.

In the afternoon, I wean baby mice and collect tissue samples for genetic testing. When the test results are ready,

I select those mice with specific genotypes and establish new breeding pairs to maintain the strain.

### How do you work as a team?

Under the supervision of one manager, there are 18 animal technicians working at the BRC and we are divided into two teams. Each team has a leader, who supervises individual tasks and manages the workflow of the team.

As team leader, I discuss the progress of our work, report any issues and share information with the other team leader as well as our manager in a fortnightly meeting. These meetings have helped us to smoothly manage the actual workflow of our teams.

At our weekly group meeting, the technicians in charge of each strain give a report on the progress of breeding. If there are any problems, we discuss how best to resolve them. At the weekly meetings, RIKEN researchers also give us technical advice on breeding and caring for mice.

We also organize workshops and use the materials provided by RIKEN researchers as reference materials. These meetings and workshops have provided us with great opportunities to share useful information and improve our skills in the field.

### What are the challenges of your work? How do you handle them?

The healthcare of mice is of the utmost importance in my daily work and requires the greatest attention to detail. I carefully observe and examine mice to ensure that they do not have any injuries, illness, or ruffled fur.

I also take care of social interactions between male mice living in group housing.

### What is the best thing about working at RIKEN?

I am very pleased and proud that the mice I have bred and cared for have made an important contribution to advancements in the biomedical sciences.

It has been a highly rewarding experience to be involved in breeding mice that play such a significant role in groundbreaking scientific research at research institutions around the world as well as RIKEN.

### CONTACT INFORMATION

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# The RIKEN Quantitative Biology Center Inaugural Symposium 2012

Established in 2011, the RIKEN Quantitative Biology Center (QBiC) held its inaugural symposium—"Toward whole-cell modeling"—on 5–7 November 2012 in Kobe. The event attracted over 300 people and featured 14 speakers from QBiC as well as 12 speakers from universities, research institutes, and research laboratories in Japan and overseas.

As this symposium provided QBiC's first formal opportunity to share its research with an international audience, both RIKEN President Ryoji Noyori and philanthropist and former president of Osaka University, Tadamitsu Kishimoto, officially opened the proceedings with a welcome address about the vision and future direction of the center. QBiC Director Toshio Yanagida went on to give a general introduction of the goals and research advances made by the center in his address, "QBiC challenges whole cell modeling."

On the first and second day of the symposium, keynote speeches were given by Michael Sheetz, Director of the Mechanobiology Institute in Singapore (MBI), and Adrian Elcock, Professor at the University of Iowa, respectively. Both Director Sheetz and Professor Elcock addressed the topic of intracellular decision-making, but from two different approaches—one from an experimental aspect and the other from a more mathematical approach.

Twenty-six speakers gave presentations on their research over the 3-day program, including 14 QBiC researchers who had the chance to present and discuss their findings to a broad audience. The program also afforded informal opportunities for young QBiC researchers to meet and share their research with some of the foremost scholars in the field.

QBiC's first symposium was organized by Director Yanagida, QBiC Group



Professor Adrian Elcock from the University of Iowa gives his keynote speech on the topic of intracellular decision-making.

Directors Masahiro Ueda, Makoto Taiji and Hiroki Ueda, and the organizers look forward to holding another symposium in 2014.



The first QBiC symposium attracted over 300 people and featured 26 presentations and two keynote lectures.

## RIKEN Nishina Center and Universiti Sains Malaysia sign Memorandum of Agreement

On 1 November 2012, Director Hideto En'yo of the RIKEN Nishina Center (RNC) signed a Memorandum of Agreement (MoA) between the RNC and Universiti Sains Malaysia (USM). The signing of the MoA, which took place at the USM, will further enhance ongoing collaborations between the RNC and USM in the rapidly developing field of muon science, which looks at research of the solid state in the areas of physics, chemistry and materials science.

This is the second MoA between RIKEN and the USM to be concluded in 2012; the first MoA was finalized in April 2012 for joint research in the fields of biomass, chemical biology and immunology.

The RNC and USM will work together utilizing muon spin relaxation ( $\mu$ SR) experiments at the RIKEN-RAL Muon Facility in the UK in tandem with USM's renowned expertise in muon-site calculation. Through these collaborations, RIKEN hopes to facilitate research activities that will have a high impact in muon science research.

## The Nishina School program in 2012

The Nishina School, initiated as part of an agreement between RIKEN and China's Peking University in 2008, offers undergraduate students and selected doctoral students from Peking University a unique opportunity to acquire hands-on experience in theoretical and experimental nuclear physics at the RIKEN Nishina Center for Accelerator-Based Science in Wako.

The fifth Nishina School was held over 2–12 October 2012, and included lectures and practical training for nine exceptional participants from Peking University. In addition, over the period 6–10 August 2012 the first Nishina School catering to participants from Seoul National University (SNU) was held as part of an agreement made between RIKEN and SNU in 2010. Professors from SNU, who conduct collaborative experiments at RIKEN's Radioactive Isotope Beam Factory, served as lecturers at the school. Their participation further enhanced RIKEN's broad practical educational program for Nishina School participants.

Through the Nishina School program, RIKEN aims to continue fostering an interest in physics research among undergraduate students, as well as strengthening educational ties with China and Korea.



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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.

RIKEN RESEARCH is a website ([www.rikenresearch.riken.jp](http://www.rikenresearch.riken.jp)) and print publication intended to highlight the best research being published by RIKEN ([www.riken.jp](http://www.riken.jp)). It is written for a broad scientific audience and policy makers interested in science and aims to raise global awareness of RIKEN and its research.

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

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