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Probing medicinal properties in plants

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Materials, Chemistry

Organic electronics edge closer

A self-assembled organic superstructure formed on a gold electrode displays rare, and potentially useful, semiconducting properties

Rays of sunshine bathe our planet in reliable and free renewable energy; yet, harnessing this energy remains a costly process because today's solar cells depend upon expensive materials to capture light. An emerging solar technology based on cheap organic materials could one day offer an attractive alternative, and potentially make solar cells affordable enough to install on every rooftop. Such low-cost solar cells are just one example of the organic electronic devices that could result from the joint research of Yousoo Kim at the RIKEN Advanced Science Institute (ASI) in Wako and Maki Kawai at the University of Tokyo.

Kim and Kawai's team is exploring the electronic properties of thin films of organic molecules derived from soccer-ball-shaped structures of carbon atoms, called fullerenes. These molecules are covered with delocalized electrons, giving them potentially useful electronic properties that can be fine-tuned by modifying the fullerene's structure. Attaching fluorine atoms to the fullerene is a particularly attractive method for tuning these attributes, as the resulting fluorinated fullerenes should show a useful semiconducting behavior, known as 'n-type behavior', which is rare in organic materials. However, to date, the resulting materials have proved difficult to study, owing to their structural complexity, and tendency to form as mixtures.

By coating gold electrode surfaces with an ultra-thin layer of fluorinated fullerenes in the form of a powder, Kim, Kawai and their colleagues studied the properties of fluorinated fullerenes in detail using scanning tunneling microscopy (STM)[1]. They found that when they deposited the powder onto the gold at room temperature, fluorinated fullerene islands—just a single molecule thick—formed in patches across the gold surface. However, the orientation of molecules in these patches was jumbled, and the electronic properties of each island were inhomogeneous.

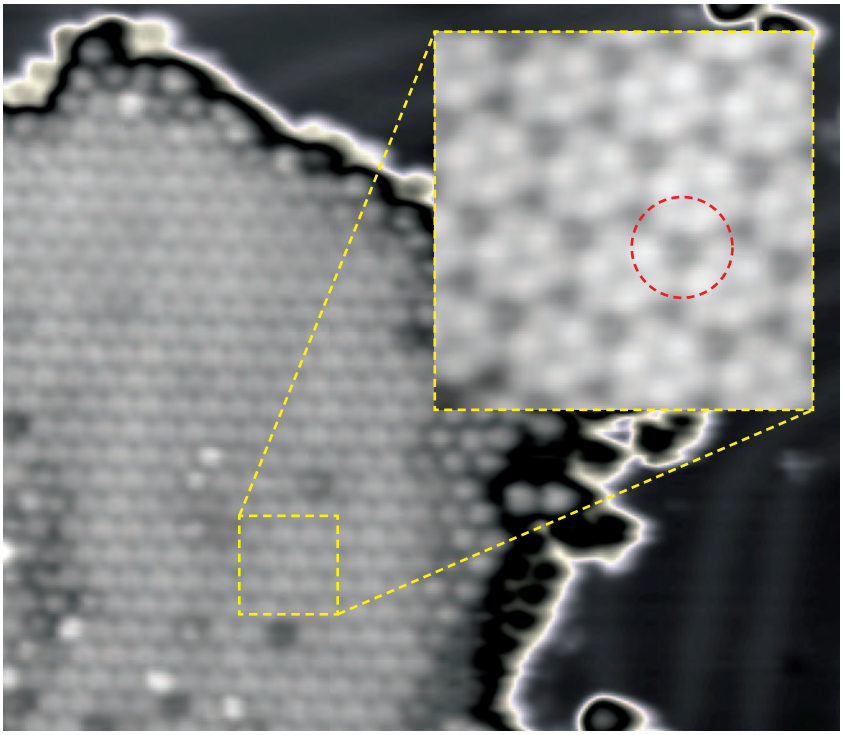

Figure 1: A scanning tunneling microscopy image reveals the homogeneous pattern of fluorinated fullerene molecules (one molecule is circled) that form on the surface of a gold electrode.

When they gently warmed the gold surface, however, a very different picture emerged from the STM images: the islands had assembled into uniform films in which all molecules oriented in the same manner, with homogeneous electric behavior.

Mastering the monolayer

"We were very surprised by the well-ordered monolayer that formed on the gold surface," says Tomoko Shimizu, a member of the team based at RIKEN ASI.

To investigate how the homogeneous fluorinated fullerene film formed, she and her colleagues first determined its exact molecular composition—a process complicated by the impurity of the fluorinated fullerene powder. Although each fluorinated fullerene was coated with precisely 36 fluorine atoms, these atoms could be distributed in different patterns across the fullerene surface. This formed three different fluorine distributions, or isomers: C_3, C_1 and T.

"When I first saw the well-ordered structure in the STM images, I thought it was a mixture of the three isomers," Shimizu says. However, subsequent computer modeling studies revealed otherwise. Through the scanning

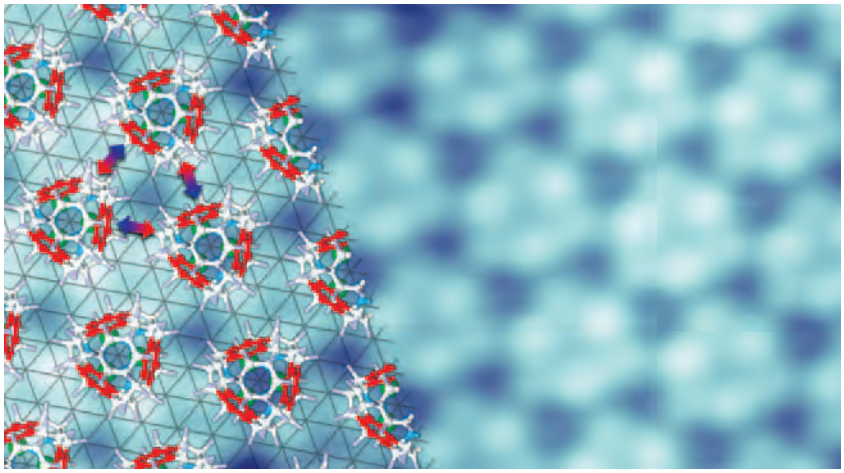

Figure 2: Computational calculations show that intermolecular interactions (arrows) drive the fluorinated fullerenes to self-assemble precisely on a gold surface (underlying grid).

tunneling microscope, each molecule in the homogenous region had an identical appearance—a dark spot surrounded by six bright lobes, arranged in a roughly hexagonal shape (Fig. 1).

Kim, Kawai and colleagues used density functional theory (DFT) calculations to predict how each isomer would orient on the gold surface, and therefore appear under a scanning tunneling microscope. The calculations predicted that each isomer should look quite different; however, each molecule in the STM images of the homogenous regions looked identical. By comparing these images with the structures predicted by DFT, the researchers concluded that the monolayer consisted exclusively of the C_3 isomer—the only isomer predicted to align itself directionally on the gold. "Nature is great; the molecules have filtered themselves though a self-assembling process," says Shimizu.

Further calculations revealed that attractive forces between neighboring fluorinated fullerene molecules drove the selective self-assembly process. When a fullerene is decorated with fluorine atoms, the molecular surface consists of an electron-rich and an electron-poor region because of the strong electron-withdrawing property of fluorine atoms. As the researchers heated the gold, the fluorinated fullerenes reoriented in a way that maximized the attractive forces between the fluorine atoms on one molecule and the delocalized electrons on part of the next molecule (Fig. 2).

Applications beckon

The self-assembling fluorinated fullerene monolayer showed electronic properties that are particularly promising for future applications in organic electronic devices ranging from computers to television screens to solar cells. The fluorinated fullerene–gold superstructure exhibits semiconductor behavior, a property that underpins such devices. The semiconductor industry is currently dominated by expensive semiconducting silicon wafers. Organic alternatives would not only be cheaper, they would also be ultra-thin, light-weight and flexible.

Most electronic devices need pairs of semiconductor materials in order to function: n-type semiconductors, which are rich in electrons; and p-type, which are electron poor. Thus far, this need for pairing has limited the uptake of organic semiconductors. Despite the availability of p-type organic semiconductors, n-type organic materials are rare. "Our fluorinated fullerene monolayer has a perfectly homogeneous structure and electronic properties all over the well-ordered superstructure area, and indeed n-type behavior on a chemically stable gold electrode, making it potentially useful for organic devices," says Shimizu.

Inexpensive solar cells are undoubtedly one area that could benefit from the researchers' novel material. Most solar cells use a 'p–n junction' to funnel electrons, which have been knocked free by incoming light, out of the cell and around an electrical circuit. This is one of the potential applications that the researchers plan to investigate first. "There are a few possibilities for our next step in this area," says Shimizu. "One is to study structure and energy level alignment of organic p–n junctions with and without light irradiation for solar cell applications."

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ABOUT THE RESEARCHER

Tomoko Shimizu was born in Saitama, Japan, in 1979. She graduated from the Faculty of Science and Technology, Keio University in 2002, and obtained her PhD in 2007 from the Department of Materials Science and Engineering at the University of California, Berkeley, USA. At Berkeley, Shimizu worked on the instrumentation of scanning probe microscopy and performed research in the field of surface science for catalysis and the environmental sciences. She returned to Japan as a research associate in 2007 and became a special postdoctoral researcher in 2009 in the Surface Chemistry Laboratory at RIKEN. Shimizu then transferred to the Surface and Interface Science Laboratory at RIKEN in 2010, and was promoted to scientist at the Advanced Science Institute in 2012. Her research focuses on the structure and electronic properties of atoms and molecules as well as the defects of various types of surfaces using scanning tunneling microscopy and atomic force microscopy.

Odd lipid out

Spectroscopic evidence for the unusual handedness of a mammalian lipid may advance our understanding of evolution

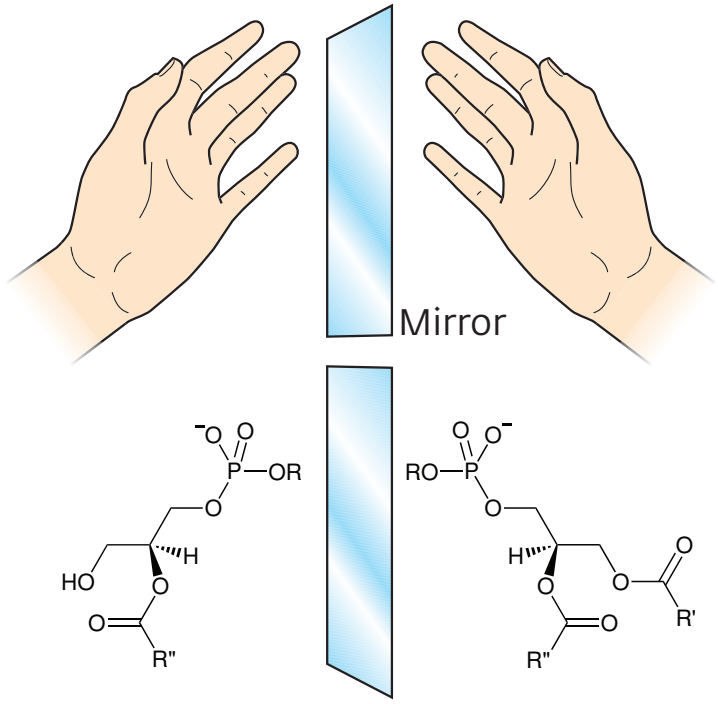

Figure 1: The backbone of the chemical structure of phospholipids in archaea is left-handed; in more complex organisms, it is right-handed.

Phospholipids are the main constituents of the cellular membranes in all organisms, ranging from single-celled archaea to highly complex plants and mammals. According to conventional wisdom, the chemical backbone of phospholipids in archaea is 'left-handed', but right-handed in all other organisms (Fig. 1). The little-understood mammalian phospholipid bis(monoacylglycero) phosphate (BMP), however, is a possible exception to this rule. Peter Greimel, HuiHui Tan and their colleagues at the RIKEN Advanced Science Institute, Wako, have now obtained the first proof that BMP is indeed left-handed[1].

BMP is found only in mammals, and is a common—but minor—constituent of all animal tissues. The internal membranes of the waste treatment and recycling centers of cells—so-called late endosomes and lysosomes—have a higher proportion of BMP than any other animal membranes. This raised an intriguing question, explains Greimel: "How does BMP escape degradation inside these organelles, unlike all the other lipids and proteins?" This led to the [hypothesis] that BMP might actually be left-handed, allowing it to avoid attack by the organelle's digestive enzymes that are only capable of recognizing, and therefore destroying, right-handed lipids. All previous attempts to confirm the suspected unusual handedness—or chirality—of BMP had hit problems.

The research team first synthesized all the possible variations of BMP. They then reacted these variations with the chiral reagent D-camphor. "The D-camphor induced a change in the spectroscopic behavior of each synthetic BMP analogue," explains Greimel. This meant that the nuclear magnetic resonance (NMR)—a common spectroscopic technique—spectra of the BMP analogues were different enough to be distinguished from each other.

Next, the researchers isolated natural BMP from baby hamster kidney cells using standard techniques, then reacted it with D-camphor under very gentle conditions and analyzed it spectroscopically. They then compared the NMR spectra of the natural BMP derivative and the synthetic molecules. "Analysis of the spectroscopic data revealed that natural BMP is exclusively left-handed," Greimel says.

"Since BMP is left-handed, it means it most likely originated from the same common ancestor as archaea," he explains. The research team now plans to identify the enzymes involved in the biosynthesis of BMP, with the hope that detailed knowledge of this biosynthetic pathway will eventually lead to a better understanding of how life evolved on Earth.

Additionally, Greimel says that "now we know the [chirality] of the molecule, we can think about synthesizing analogues in order to develop novel drugs, in this case to treat lysosomal storage diseases." ■

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Algal proteins light the way

Recently published insight into the structure of a light-powered protein may lead to more effective tools for probing brain function

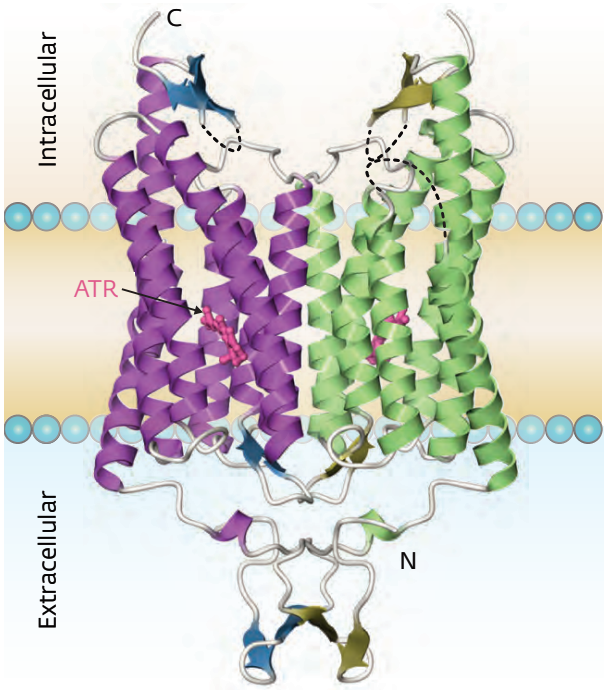

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Figure 1: The structure of a chimeric channelrhodopsin protein (C1C2), a combination of elements of ChR1 and ChR2 from *C. reinhardtii*. The small pink structure represents all-*trans* retinal (ATR), a light-reactive molecule bound to C1C2 that plays an essential role in this protein's activation.

Channelrhodopsins (ChRs) are remarkable proteins that respond to specific wavelengths of light by allowing ions to cross the cell membrane, a mechanism that makes them useful for manipulating ion-driven processes in the brain. Akin to cellular-scale power switches, ChRs allow scientists to selectively switch on individual neurons or neural circuits with a flash of laser light, even in live and alert animals. These valuable tools could soon become even more useful thanks to an international collaboration at the RIKEN SPring-8 Center in Harima that has unveiled the fundamental structure of these proteins[1].

"Researchers have engineered ChR variants with improved properties, including ion selectivity, kinetics and absorption spectrum, but these approaches were limited by the lack of the structural information about ChR," explains lead author Hideaki Kato, a researcher in senior author Osamu Nureki's laboratory at the University of Tokyo. X-ray crystallography is a powerful tool for mapping the three-dimensional structure of proteins, but ChRs had proved a tricky target. Since they are difficult to produce in useful quantities and hard to crystallize, Kato and colleagues engineered a more stable hybrid chimera protein composed of parts from the closely related ChR1 and ChR2 proteins from the alga *Chlamydomonas reinhardtii*.

The researchers used the powerful x-ray source at the RIKEN SPring-8 Center to generate a high-quality structure of the entire light-responsive segment of ChR (Fig. 1). "The RIKEN beamline, which started operation in May 2010, is highly effective for structure determination from tiny protein crystals," says SPring-8 scientist and co-author Kunio Hirata. "The manuscript [on our results] is the evidence."

The resulting structure revealed the path through which positively charged ions are transferred across the cell membrane, resolving an ongoing debate among molecular biologists. A large outer 'vestibule' structure at the cellular exterior gives way to a pore lined with negatively charged surfaces, which favor the entry of positively charged ions. This pore is blocked when ChR is inactive, but illumination at the proper wavelength triggers a series of proton transfer events within the protein that eliminate these obstructions, enabling ions to pass. A series of mutation experiments provided additional support for this mechanism.

"[Further] detailed structural information around this pathway should provide useful insights for the precise and principled design of ChR variants with altered ion selectivity and absorption spectra," says Kato. He and his colleagues now plan to pursue such targeted protein engineering efforts, while also working to obtain additional ChR structures that provide further confirmation for their functional model. ■

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Revealing a pollutant's Achilles' heel

Recent elucidation of the structural architecture of a bacterial enzyme involved in microbial denitrification could help to reduce its harmful effects

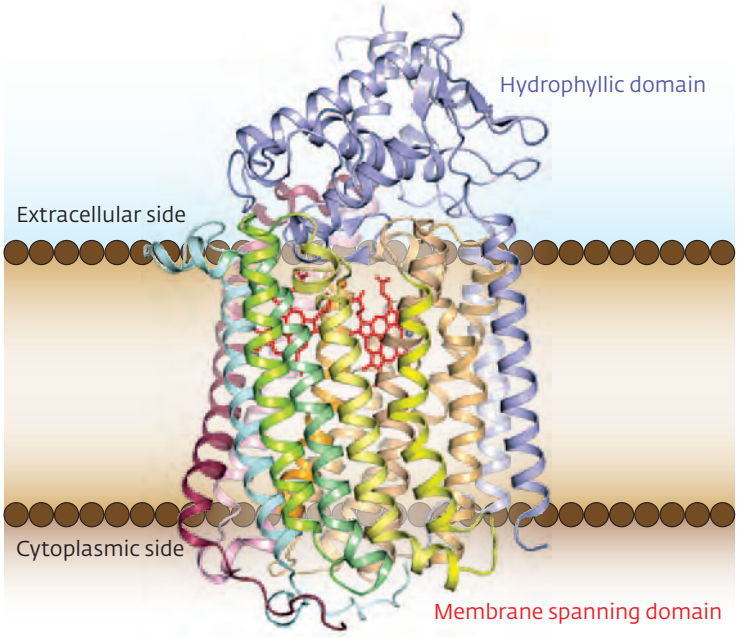

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Figure 1: The structure of *G. stearothermophilus* qNOR, with the transmembrane portion visible between the brown lines.

Nitric oxide (NO) is a versatile free radical that plays central roles in the environment as well as living organisms. At low concentration in the human body, for example, NO protects organs against pathogens by acting as a chemical weapon. Bacteria counter this response with respiratory enzymes called nitric oxide reductases (NORs) that effectively neutralize NO. By solving the crystal structure of the quinol-dependent reductase (qNOR) from the bacterium *Geobacillus stearothermophilus* (Fig. 1), a research team in Japan led by Yoshitsugu Shiro from the RIKEN SPring-8 Center, Harima, has provided insight into this microbial denitrification process[1].

In previous investigations of reductases, biologists had limited their focus to the enzyme called cytochrome *c*-dependent NOR (cNOR), despite the greater abundance of qNOR in macro-organisms. This is because cNOR exhibits similar amino acid sequences and metal ligands to other respiratory enzymes known as cytochrome oxidases.

To elucidate the molecular evolution of these respiratory enzymes, and to understand how this evolution affects enzymatic function, Shiro and his team compared the newly determined three-dimensional structure of qNOR to those of cNOR and the cytochrome oxidases. They discovered that the overall structures of the reductases were identical and the portions of qNOR and cNOR that span cell membranes matched those of the oxidases. However, qNOR lacked the iron-containing functional group, heme *c*, which provides electrons to the activation site of cNOR. Unexpectedly, this domain maintained an analogous folding pattern to that of cNOR, thanks to bulky residues that compensate for the void created by the absence of heme *c*.

By identifying key structural components of qNOR, Shiro and colleagues revealed the mechanism of this enzyme: the electron-donating quinol molecule interacts with the transmembrane portion of qNOR through hydrogen bonds, facilitating electron transfer to it. In addition, the crystallographic data showed that this transmembrane domain enclosed water molecules that formed a hydrophilic channel extending to the cytoplasm. Computer-aided simulations indicated that this channel could transport catalytic protons to the reaction center where NO reduction takes place. "The water channel of qNOR is located in the same region as the proton channel of oxidases—[this helps explain] how respiratory enzymes acquired their proton-pumping ability," adds Shiro.

The researchers are currently investigating compounds that can interact with qNOR and cNOR. "In the near future, we plan to characterize the structure and function of bacterial NOR–inhibitor complexes," says Shiro. These inhibitors could be harnessed to reduce global nitrous oxide emissions or used in antibacterial drug design. ■

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Measuring attention to detail

Human attention to a particular portion of an image alters the way the brain processes visual cortex responses to that image

Our ability to ignore some, but not other stimuli, allows us to focus our attention and improve our performance on a specific task. The ability to respond to visual stimuli during a visual task hinges on altered brain processing of responses within the visual cortex at the back of the brain, where visual information is first received from the eyes. How this occurs was recently demonstrated by an international team of researchers led by Justin Gardner at the RIKEN Brain Science Institute in Wako[1].

In a contrast discrimination task, the researchers showed three observers a stimulus of a group of four circles, each containing grey and white bars that created stripes of different contrasts (Fig. 1). After a short pause, the researchers showed the circles again, but the contrast within one of the circles was different. The observers were instructed to choose which group of circles contained the higher contrast.

In 'focal cue trials', an arrow directed the observers' attention to a particular circle. In 'distributed cue trials', four arrows directed their attention diffusely, across all four circles. Gardner and colleagues found that the observers' performance was better in the focal cue trials.

Using a magnetic resonance imaging (MRI) scanner, the research team was able to map the precise location within the visual cortex that was activated by the visual information within each of the four circles. During the contrast discrimination task, Gardner and colleagues could therefore measure the observers' visual cortex activity elicited by the stimuli. In this way, they could correlate brain activity in the visual cortex with the observers' attention and their choice of contrasting circles.

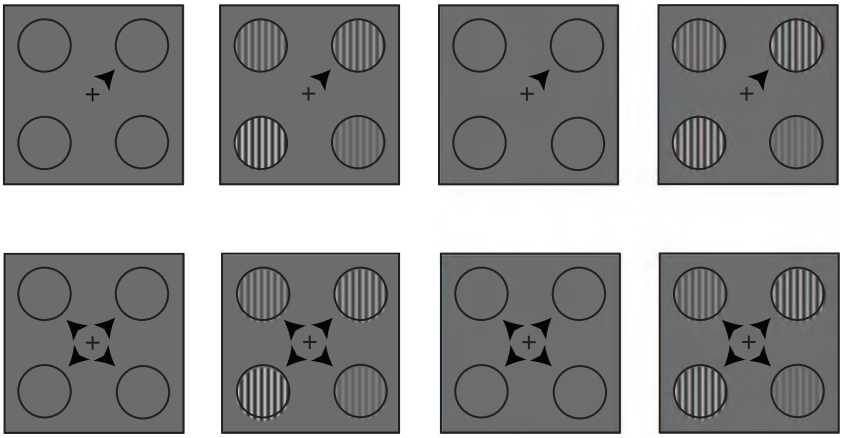

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Figure 1: A schematic diagram of the contrast discrimination task, showing the focal cue trial (top row) and the distributed cue trial (bottom row). The contrast within the top right circle increases from the first interval (second column) to the second interval (fourth column). The third column is the interstimulus interval.

Visual cortex responses tended to be largest when the observers were paying attention to a particular target circle, and smallest when they were ignoring a circle. The researchers determined that the largest visual cortex responses to the stimuli guided the eventual choice of each observer, leading to enhanced performance on the visual task.

"We used computational modeling to test various hypotheses about how attention affects brain processing of visual information to improve behavioral performance," explains Gardner. "We concluded that the observers' attention causes their brains to select the largest cortical response to guide contrast choice, since we found that an 'efficient selection' model best explained the behavioral and fMRI data," he says.

If the findings extend to other senses, such as hearing, researchers may begin to understand how humans make sense of a perceptually cluttered world. ■

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Balancing connections for proper brain function

Identification of a protein that can lead to brain disorders through impaired development sets the trajectory of future studies

Neuropsychiatric conditions such as autism, schizophrenia and epilepsy involve an imbalance between two types of synapses in the brain: excitatory synapses that release the neurotransmitter glutamate, and inhibitory synapses that release the neurotransmitter GABA. Little is known about the molecular mechanisms underlying development of inhibitory synapses, but a research team from Japan and Canada has reported that a molecular signal between adjacent neurons is required for the development of inhibitory synapses[1].

In earlier work, the researchers—led by Jun Aruga of the RIKEN Brain Science Institute, Wako, and Ann Marie Craig of the University of British Colombia, Vancouver—showed that a membrane protein called Slitrk2 organizes signaling molecules at synapses[2]. They therefore tested whether five related proteins are involved in inhibitory synapse development. They cultured immature hippocampal neurons with non-neural cells expressing each of the six Slitrk proteins. They found that Slitrk3, but not other Slitrk proteins, induced clustering of VGAT, a GABA transporter protein found only at inhibitory synapses.

The researchers also examined the localization of Slitrk3 by tagging it with yellow fluorescent protein and introducing it into cultured hippocampal cells. This revealed that Slitrk3 co-localizes in the dendrites of neurons with gephyrin, a scaffold protein found only in inhibitory synapses. They then blocked Slitrk3 synthesis, and found that it led to a significant reduction in the number of inhibitory synapses.

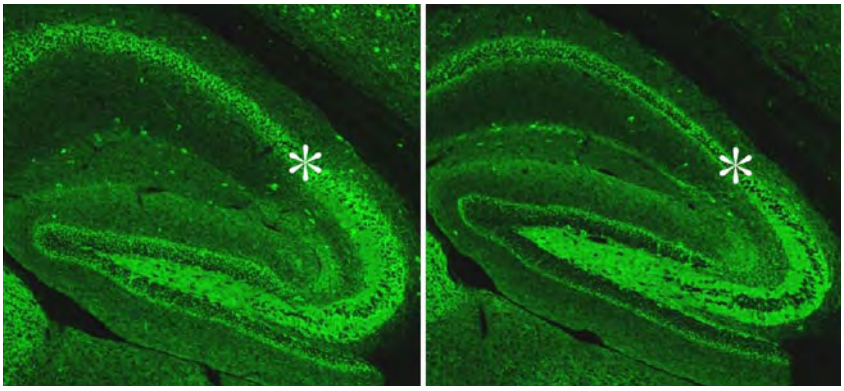

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Figure 1: Compared with the brains of normal animals (left), mice lacking the *Slitrk3* gene (right) have a reduced density of inhibitory synapses in the hippocampus.

To confirm these findings, the researchers generated a strain of genetically engineered mice lacking the *Slitrk3* gene. These animals had significantly fewer inhibitory synapses than normal animals (Fig. 1), and therefore impaired neurotransmission of GABA. They were also susceptible to epileptic seizures. From a screen for proteins that bind to Slitrk3, Aruga, Craig and colleagues identified the protein PTPδ as its only binding partner. Introduction of PTPδ fused to yellow fluorescent protein to cultured hippocampal neurons showed that it is expressed in neuronal dendrites and cell bodies, but not in axons. Blocking PTPδ synthesis prevented the induction of inhibitory synapses by the Slitrk3 protein.

These results demonstrated that the interaction between Slitrk3 on dendrites and PTPδ on axons of adjacent cells is required for the proper development of inhibitory synapses and for inhibitory neurotransmission in the brain.

"We are now examining whether the balance of excitatory and inhibitory synapses is affected by other members of the Slitrk protein family," says Aruga. "It is possible that Slitrk3 and other Slitrk proteins are acting synergistically or antagonistically. We are also clarifying whether Slitrk3 is involved in any neurological disorders." ■

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Inside a plant's pharma factory

A newly discovered enzyme brings scientists one step closer to understanding how plants manufacture a chemical with potent medicinal properties

Photo by Kiminori Toyooka, RIKEN Plant Science Center © 2011 American Society of Plant Biologists

Figure 1: Licorice root is incorporated into a number of traditional medicines.

Plants of the genus *Glycyrrhiza* are best known as key ingredients in the popular treat licorice, but they also have a valuable place in the medicine cabinet (Fig. 1). These plants employ a complex assembly line of enzymes to produce a chemical called glycyrrhizin, a potent sweetener that also acts as a highly effective anti-inflammatory and antiviral agent.

The process of glycyrrhizin biosynthesis is incompletely understood, but research from a team led by Kazuki Saito and Toshiya Muranaka at the RIKEN Plant Science Center in Yokohama helps to fill some of the gaps[1]. According to Saito, these efforts depended on close collaboration between multiple research teams. Members of the 'All-Japan Licorice Research Consortium', pooled their research resources, which was the strong basis for the success of this project, according to Saito.

The researchers were particularly interested in enzymes known as cytochrome P450 mono-oxygenases. For a previous study, they prepared a large library of gene sequences expressed by *Glycyrrhiza* to identify previously uncharacterized P450s[2]. This time around, Saito and Muranaka performed a functional assay in which they expressed several of these putative P450s in cultured cells so they could identify enzymes that act on specific intermediates in glycyrrhizin manufacture.

They identified one protein, CYP72A154, which recognized the early glycyrrhizin intermediate 11-oxo-β-amyrin as a substrate. Remarkably, this enzyme appears to perform multiple sequential oxidation reactions on this compound, effectively moving the synthetic process forward three steps. To confirm these findings, they tested the function of CYP72A154 by co-expressing it alongside other enzymes known to participate in this biological process. "We achieved biotechnological production of glycyrrhetinic acid, an intermediate of glycyrrhizin, by means of synthetic biology in yeast," says Muranaka.

This demonstration of partial glycyrrhizin biosynthesis represents an important step in the right direction: even though this valuable chemical is easily purified from licorice plants, scientists may ultimately find themselves forced to resort to laboratory production methods. "There is a potential risk of a shortage of natural resources in the near future," says Saito. "Another problem is that China, the dominant supplier of licorice, is setting restrictions on licorice exports as a governmental policy."

Several pieces are still missing from the puzzle, but Saito and Muranaka are excited to learn what remains to be found, both from a biotechnology perspective and in terms of understanding aspects of plant evolutionary history. "We still don't know why and how higher plants have evolved the production systems for such interesting compounds," says Muranaka. ■

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Maintaining restraint in the face of danger

A central regulator of the inflammatory response shows signs as an appealing target for therapies against autoimmune disease

Some bacterial infections trigger the formation of structures known as granulomas, which essentially quarantine compromised cells. "Infected macrophages get surrounded by other immune cells, such as T cells and neutrophils," explains Takashi Tanaka of the RIKEN Research Center for Allergy and Immunology in Yokohama. "This serves to wall off pathogens that resist destruction and limits their infection within a restricted area."

This response is generally beneficial but can lead to a harmful overreaction, especially in patients with autoimmune conditions, where the inflammatory response is not properly regulated. In collaboration with Tadashi Matsuda of Hokkaido University, Tanaka's group has now revealed a key regulatory checkpoint in the granuloma formation process, which might ultimately inform the development of more effective immunomodulatory drugs[1].

Historically, a subset of the immune system's helper T cells, called T_H1 cells, has been associated with autoimmunity. Previous research by Tanaka demonstrated that a protein called PDLIM2 helps restrict production of these cells[2]. More recently, other researchers identified a population of helper T cells called T_H17 cells that also contribute to this process, although their role was unclear, so Tanaka sought to determine whether PDLIM2 regulates these cells as well.

His team found that mice lacking the gene encoding PDLIM2 formed many more granulomas in response to infection with *Propionibacterium acnes* bacteria (Fig. 1), and that this process was dependent on the action of T_H17 cells. In fact, the researchers showed that PDLIM2 directly inhibits the differentiation of $CD4^+$ T cells into T_H17 cells, as was previously demonstrated with T_H1 development. This protein works by marking other proteins for rapid degradation. Tanaka and colleagues learned that PDLIM2 specifically promotes the destruction of STAT3, a signaling protein that switches on genes responsible for T_H17 development. Without PDLIM2 constraining the formation of these pro-inflammatory cells, the immune response has the potential to spiral out of control.

This protein therefore appears to be a key safeguard against autoimmunity. "Recent studies suggest that T_H1 and T_H17 cell subsets are not mutually exclusive, but cooperatively induce inflammatory responses," says Tanaka. "Our work demonstrates that PDLIM2 can negatively regulate the development of both cells, and thus represents a useful new target for the treatment of human autoimmune and inflammatory diseases." Tanaka and colleagues now hope to better understand this protein's function by clarifying the regulatory factors that act upstream and downstream of PDLIM2, and by clarifying how this system influences other inflammatory processes, such as those observed in cases of asthma or during wound healing. ■

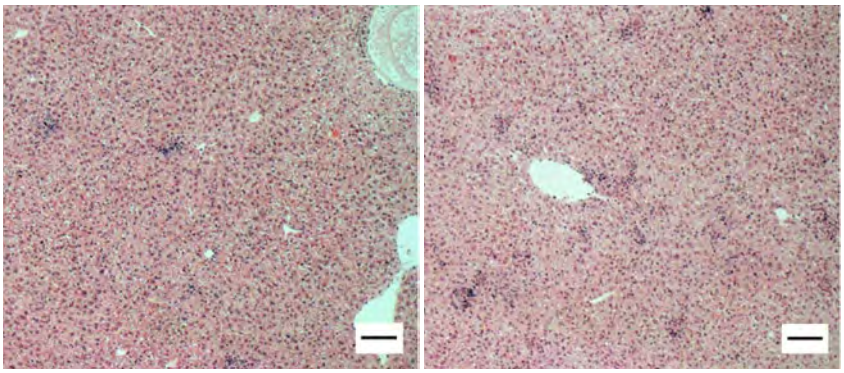

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Figure 1: Relative to wild-type animals (left), the livers of PDLIM2-deficient animals (right) show considerably higher levels of granuloma formation. Granulomas are indicated by dark spots formed following staining with hematoxylin and eosin (scale bars, 100 µm).

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Fast and sensitive flu tracking

A field test for the deadly H1N1 pandemic strain of flu is an effective tool for monitoring disease spread

A practical means of tracking pandemic flu in the field—using an assay known as RT-SmartAmp—was developed recently by a research team in Japan led by Toshihisa Ishikawa at the RIKEN Omics Science Center, Yokohama[1]. In trials in Japanese hospitals and clinics, the researchers demonstrated that their rapid assay was at least as sensitive as currently available tests, easier to manage, and could provide results within 40 minutes.

The new test can be used to plot the spread of the pandemic flu A(H1N1) virus (Fig. 1) and to detect any changes in transmission mode. Similar assays, the researchers say, could be developed for monitoring other strains of influenza, such as H5N1 avian flu.

In the year after it was first reported in May 2009, the pandemic flu A(H1N1) virus was responsible for more than 200 deaths in Japan. Epidemiologists are still worried that this virus might follow the course of the 1918 Spanish flu pandemic virus, which first appeared in a relatively mild form but later returned as a more virulent strain. Widespread use of the anti-influenza drug oseltamivir may have also encouraged the increase of resistant strains of pandemic H1N1. Ishikawa and his colleagues recognized that a rapid and highly sensitive test for pandemic flu could be hugely beneficial in detecting either of these occurrences.

The RT-SmartAmp assay combines a reverse transcriptase—an enzyme which generates DNA sequences from viral RNA—with an isothermal DNA amplification reaction. The test works by detecting HA, one of the eight segments of RNA that comprise the 2009 pandemic flu virus, and the one most resistant to mutation. Since the assay requires no expensive laboratory equipment, it works in any typical medical environment.

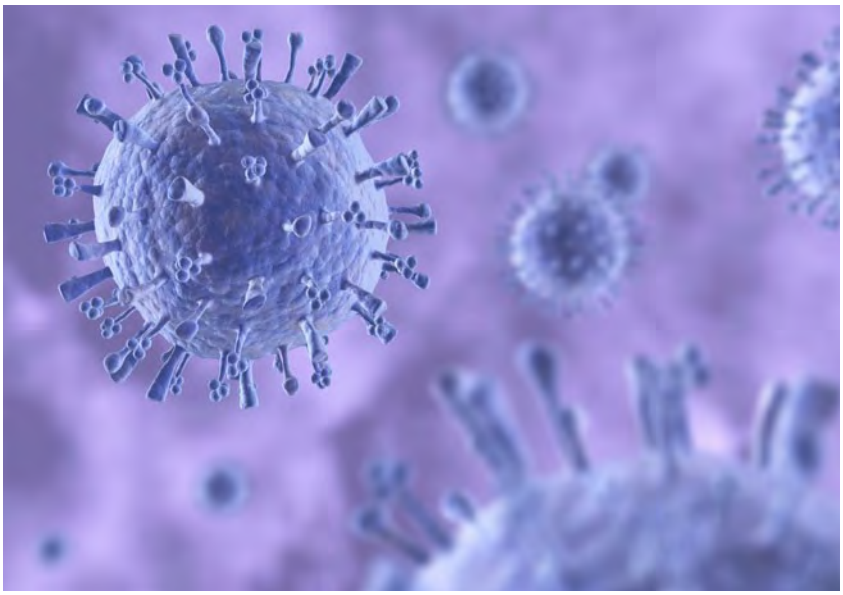

Figure 1: The 2009 pandemic flu A(H1N1) virus.

The researchers evaluated RT-SmartAmp during the height of the 2009 pandemic flu using swab samples taken from 255 patients at three hospitals and 11 clinics in Japan. They compared the results against the best and fastest tests then available, using viral genome sequence analysis to determine whether virus was present in cases where there was a discrepancy. RT-SmartAmp was sensitive enough to detect the 2009 pandemic A(H1N1) flu virus within 24 hours of infection.

Ishikawa and colleagues hope to develop their assay further. At present, the potential of the deadly H5N1 avian flu virus to develop a capacity for human-to-human transmission is of enormous concern. "Simple, cost-effective and highly sensitive methods to detect [H5N1] could be developed along the lines of the RT-SmartAmp assay," Ishikawa says. ■

1. Kawai, Y., Kimura, Y., Lezhava, A., Kanamori, H., Usui, K., Hanami, T., Soma, T., Morlighem, J.-E., Saga, S., Ishizu, Y., *et al*. One-step detection of the 2009 pandemic influenza A(H1N1) virus by the RT-SmartAmp assay and its clinical validation. *PLoS ONE* **7**, e30236 (2012).

Treading a common path to metabolic maintenance

Mammals and fruit flies share an evolutionarily conserved mechanism to regulate the production of key metabolic hormones

Fruit flies and humans both rely on hormones secreted by insulin-producing cells (IPCs) for metabolic maintenance and the regulation of numerous other physiological processes. In some ways, fly IPCs differ considerably from their mammalian counterparts; they emerge from different embryonic precursor cells, and reside within the brain rather than the pancreas. Yet, they also show striking functional similarities. Now, new findings from Takashi Nishimura and colleagues at the RIKEN Center for Developmental Biology in Kobe have demonstrated that these cells employ highly similar molecular mechanisms to manage hormone production[1].

Fly IPCs secrete various *Drosophila* insulin-like peptides (Dilps), which contribute to diverse functions including regulation of growth and metabolic activity, and Nishimura's team was interested in understanding regulation of Dilp production. Via gene expression analysis, they learned that numerous proteins involved in eye development also contribute to IPC differentiation and the expression of Dilp-encoding genes.

Among these, they identified a prominent role for a protein called Dachshund, which is continuously expressed in IPCs (Fig. 1) and promotes production of Dilp5 at both early and intermediate stages of fly development. A second protein called Eyeless was known to bind to the gene encoding Dilp5. Nishimura and colleagues learned that Eyeless acts in a similar fashion to Dachshund. In fact, they demonstrated that the two act cooperatively, forming a complex that binds to and activates the *dilp5* gene.

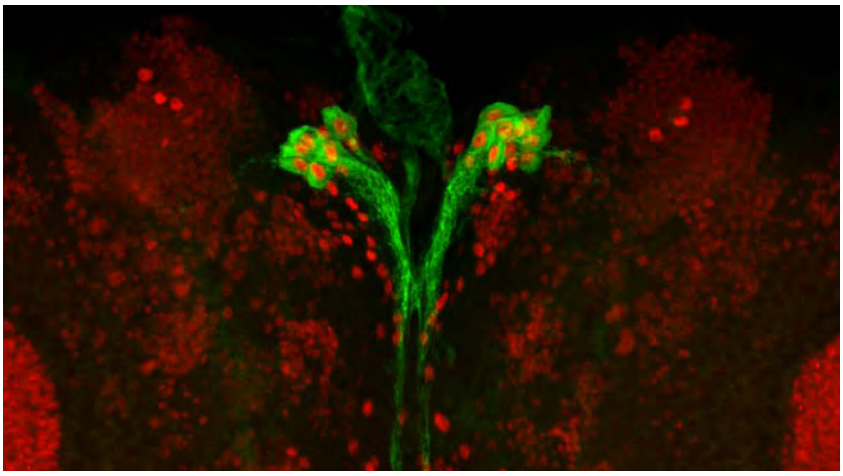

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Figure 1: A cluster of IPCs within the fruit fly brain (green), with red fluorescent labeling indicating expression of the nuclear protein Dachshund.

Both Dachshund and Eyeless have several mammalian counterparts that, remarkably, appear to act in a similar fashion in mammalian IPCs. The researchers determined that the mammalian homologues of these fly proteins assemble into a complex and work synergistically to switch on the production of insulin in cultured human cells. Likewise, experiments reducing expression of any of these proteins in rat pancreatic cells consistently resulted in reduced insulin production. "Although analogies between *Drosophila* IPCs and mammalian pancreatic islet cells have been described previously," says Nishimura, "we show here for the first time that the molecular mechanism for the regulation of insulin expression is conserved."

Many complexities regarding the regulation of Dilp5, however, remain to be untangled. For example, new experiments from Nishimura and colleagues have shown that nutrient deprivation leads to reduced expression of Dilp5, even though both Dachshund and Eyeless levels appear to remain normal. "It is possible that IPCs receive nutritional signals, and this signal modulates Dachshund and Eyeless activity to regulate Dilp5 expression," says Nishimura. Future experiments should help clarify how diet-induced signals modulate production of this and other key metabolic hormones. ■

1. Okamoto, N., Nishimori, Y. & Nishimura, T. Conserved role for the Dachshund protein with *Drosophila* Pax6 homolog Eyeless in insulin expression. *Proceedings of the National Academy of Sciences USA* **109**, 2406–2411 (2012).

Stopping gout in its tracks

Detecting imminent attacks of gout is now possible using a new modification to an established medical imaging technique

Agonizing and debilitating attacks of gout, an inflammatory disease affecting the joints, could soon be consigned to history, thanks to a non-invasive test that can detect the disease before the first painful symptoms strike. Keiji Yashio and Yasuyoshi Watanabe at the RIKEN Center for Molecular Imaging Science at Kobe and their colleagues developed the test that, as well as being useful for diagnosis, could finally reveal exactly what triggers bouts of the disease[1].

Gout attacks can occur when uric acid levels rise to abnormally high levels in the blood, and then begin to accumulate and crystallize in the lubricating, or synovial, fluid within joints. Patients tend to experience the disease as a series of attacks, and currently there is no way to detect when an attack is about to begin.

To provide a test for the disease, Yashio and Watanabe developed a way to synthesize uric acid labeled with carbon-11, a positron-emitting form of carbon that can be detected by the medical imaging technique called positron emission tomography (PET). Using this tool, medical investigators could scan the body and follow the flows of uric acid around it. If uric acid is beginning to accumulate in the joints, an attack of gout could be imminent, and so preventive medicine can be given.

Yashio and Watanabe successfully tested this idea in rats, showing that the uric acid probe accumulates in the limbs of diseased rats at levels 2.6-fold higher than healthy specimens (Fig. 1). The next step is to test it in people. "Of course, we will test it in gout patients, in remission and in attack," says Watanabe. The team hopes that their whole-body approach will also allow other uric acid related diseases to be detected in this way. "The PET study could reveal the accumulation of uric acid in the other tissues, such as the kidneys," he adds. Uric acid build up in the kidney can lead to conditions as serious as renal failure.

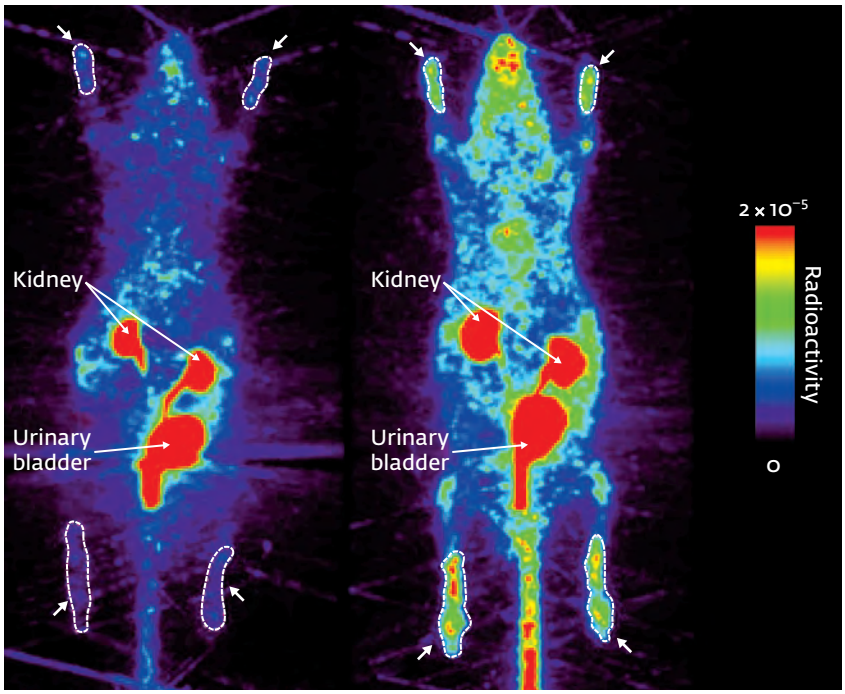


Figure 1: PET imaging reveals that compared to a healthy rat (left), a rat model with gout (right) accumulates much higher levels of radiolabeled uric acid in it limbs.

Despite decades of study, the relationship between uric acid levels in the blood and the onset of disease symptoms remains unclear. The team's whole-body snapshots of uric acid distribution may provide the answer. "The PET analysis could clarify whether clearance of uric acid from the kidney in patients is the problem, or whether the problem might be in the circulation of synovial fluid in the cavity of the affected joint," explains Watanabe. ■

1. Yashio, K., Katayama, Y., Takashima, T., Ishiguro, N., Doi, H., Suzuki, M., Wada, Y., Tamai, I. & Watanabe, Y. Synthesis of [^{11}C] uric acid, using [^{11}C]phosgene, as a possible biomarker in PET imaging for diagnosis of gout. *Bioorganic & Medicinal Chemistry Letters* **22**, 115–119 (2012).

TOSHIYUKI AZUMA

Chief Scientist
Atomic, Molecular & Optical Physics Laboratory
RIKEN Advanced Science Institute

Recreating interstellar molecular synthesis on Earth

Amino acids and nucleic acids are the building blocks of life. After the Big Bang, various astronomical objects and interstellar materials were formed in the universe during the gradual evolution of materials, which eventually led to the beginning of life on Earth. Scientists have already begun astronomical observations in a search for evidence of this remarkable process. Replicating the cryogenic formation of these molecules on Earth is also a significant challenge. Toshiyuki Azuma, chief scientist of the Atomic, Molecular & Optical Physics Laboratory at the RIKEN Advanced Science Institute, is currently heading an experimental program aimed at achieving just that.

The secret of dark nebulae

The stars of our galaxy make up the billions of points of light we call the Milky Way. Among the stars, however, are molecular clouds known as dark nebulae (Fig. 1). These interstellar clouds of dust and ice can be dense enough to appear dark and obscure our view of distant stellar objects, and it was not until radio astronomy was used in their observation that they were found to consist of a surprising range of complex molecules.

"The density of molecules in an interstellar molecular cloud is comparatively low. They essentially consist of molecules sparsely distributed in a vacuum," says Azuma. "Most of the molecules in these clouds are electrically neutral or positively charged, and the speed of intermolecular collisions is low, allowing chemical reactions that produce new molecules. I want to study these chemical reactions, although it has proved to be very difficult to achieve a sufficiently low collision energy to allow such reactions to be recreated experimentally on Earth."

Manipulating molecules using electric fields

Experiments involving the collision of ions or molecules are not new. However, it has so far been impossible to achieve the level of control needed to recreate the slow collisions that occur in interstellar molecular clouds. The Radioisotope Beam Factory (RIBF) at RIKEN, which has been operating since 2006, is an accelerator facility that can collide any naturally occurring nucleus, ranging from hydrogen to uranium, and produce the most intense ion (or radioisotope) beam in the world. The facility is used to study how heavy elements are created, and to examine the nature and structure of atomic nuclei.

"In experiments with accelerators like the RIBF, the trajectory of a beam of nuclei is controlled by a powerful magnetic field," says Azuma. "However, even the RIBF is unable to control the trajectory of a beam of large molecules consisting of many atoms because they are too heavy. Controlling the trajectory of such a beam of large molecules requires an impractically huge magnet. Conventional magnetic facilities have enabled us to control a beam of molecules consisting of up to three atoms, such as water molecules."

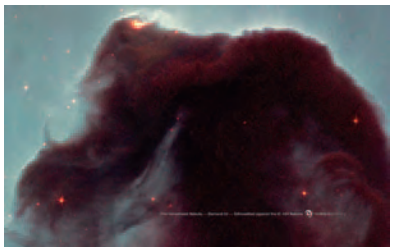
In 1997, S. P. Møller of Aarhus University in Denmark developed an electrostatic ion storage ring in which a beam of large molecules is made to bend around a continuous circular path using an electric field generated by electrical poles. "We

NASA, NOAO, ESA and the Hubble Heritage Team (STScI/AURA)

took it for granted that our molecular experiments would involve using a magnetic field, like in the RIBF. However, we could have used an electric field. When we recognized this possibility, it was a revelation, like Columbus's egg."

There are good reasons, however, why electric fields are not used in facilities like the RIBF. "An electric field cannot be used to control the trajectory of a high-speed beam. In experiments using a beam of nuclei like at the RIBF, the nuclei are accelerated almost to the speed of light, and controlling the trajectory of the high-speed beam requires a magnetic field. However, in experiments with a beam of atoms or molecules larger than nuclei, the beam is not accelerated to such high speeds. We believe Dr Møller recognized this when he used an electric field to control the trajectory of a low-speed beam of large molecules."

The use of an electric field for controlling the trajectory of molecules also requires the molecules to have a positive or negative charge, or in other words, to be ionized. "A wonderful technique has already been developed for ionizing macromolecules such as proteins without damaging them by irradiating the macromolecules with laser light, a method known as matrix-assisted laser desorption. This technique was developed for mass spectrometers by Dr Koichi Tanaka of Shimadzu Corporation. The American chemist Dr J. B. Fenn also discovered that molecules can be ionized when a solution of the molecules is turned into a fine spray, a technique called the electrospray method. Drs Tanaka and Fenn were awarded the 2002 Nobel Prize in Chemistry for their inventions."



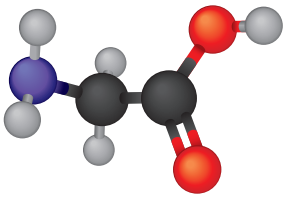


Photo courtesy of NASA, NOAO, ESA and the Hubble Heritage Team (STScI/AURA)

Figure 1: The Horsehead Nebula, a dark nebula in the Orion Constellation and the molecular model of glycine, an amino acid.

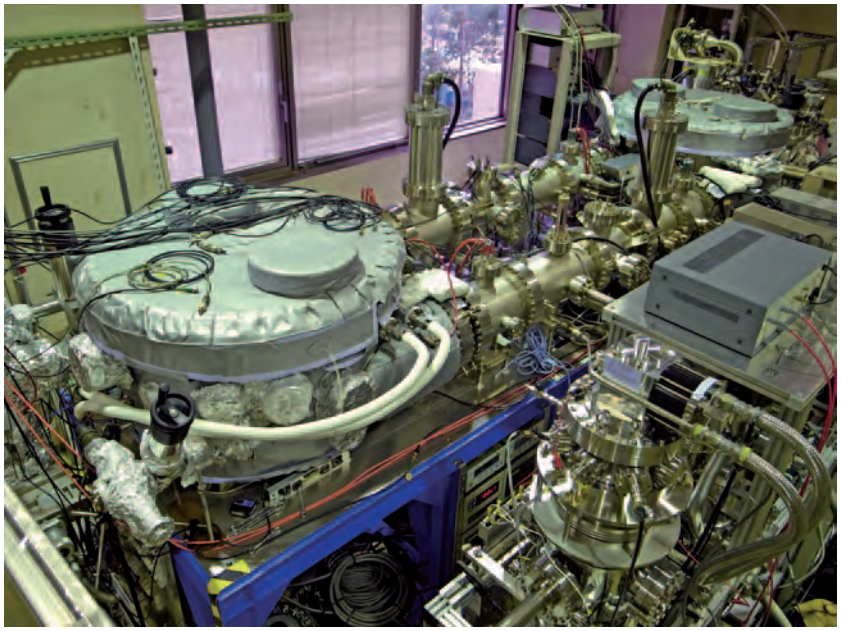


Photo courtesy of Tokyo Metropolitan University

Figure 2: The TMU E-ring ion storage ring at Tokyo Metropolitan University. Experiments are performed using a ring of about 7.7 meters in circumference and a vacuum vessel cooled with liquid nitrogen to 77 K.

Japan's High Energy Accelerator Research Organization constructed their own electrostatic ion storage ring in 2002. "I was working for Tokyo Metropolitan University at the time and decided to construct a third electrostatic ion storage ring which has an advantage over the previous two electrostatic rings. The entire unit is designed to be cooled in order to keep the stored molecular ions in the vibrationally cooled states."

In 2003, Azuma and his laboratory team completed the world's first cooled electrostatic ion storage ring, called the TMU E-ring, which can be cooled with liquid nitrogen to temperatures of 77 kelvin (K), or −196 °C (Fig. 2).

Recreating interstellar chemical synthesis

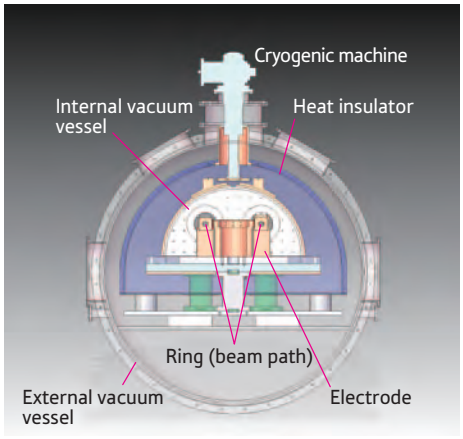
Recent astronomical observations have revealed the existence of negatively charged molecules in interstellar molecular clouds, a result that is inconsistent with prevailing theory. "Negative molecular ions can be easily produced in water solution because they are stabilized by water molecules, but they are extremely unstable in a vacuum because there are no similar effects there."

The negative molecular ions observed to date include C_4H^-, consisting of a single hydrogen (H) atom and four carbon atoms (C) with a net negative charge, as well as C_6H^-. "We have used the TMU E-ring to measure the stability of these molecular ions in a vacuum," says Azuma. "We confirmed that both molecules were stable for periods of up to a few seconds while moving through the vacuum."

In 2010, observations using the US Spitzer space telescope revealed the existence of C_{60} fullerene — a soccer-ball-shaped structure consisting of 60 carbon atoms — in interstellar space. The possibility of C_{60} as a product of interstellar molecular synthesis was discovered in 1985 by the UK chemist H. W. Kroto, who was awarded the 1996 Nobel Prize in Chemistry for his work. "Surprisingly, it was found to be possible for C_{60} to be created in space," says Azuma. "It is considered that the soccer-ball-like structure of C_{60} forms through the cryogenic cooling of molecules produced at much higher temperatures of tens of thousands of degrees. We are studying the cooling process of C_{60} using the TMU E-ring by irradiating the ions with laser light to heat them to high temperatures then letting them cool in the cryogenic storage ring. These experiments enable us to reproduce part of the C_{60} formation process in space."

Exploring the mystery of the origin of life in space

Japan, the US, and some European countries are jointly constructing a huge telescope in Chile called the Atacama Large Millimeter/submillimeter Array (ALMA).



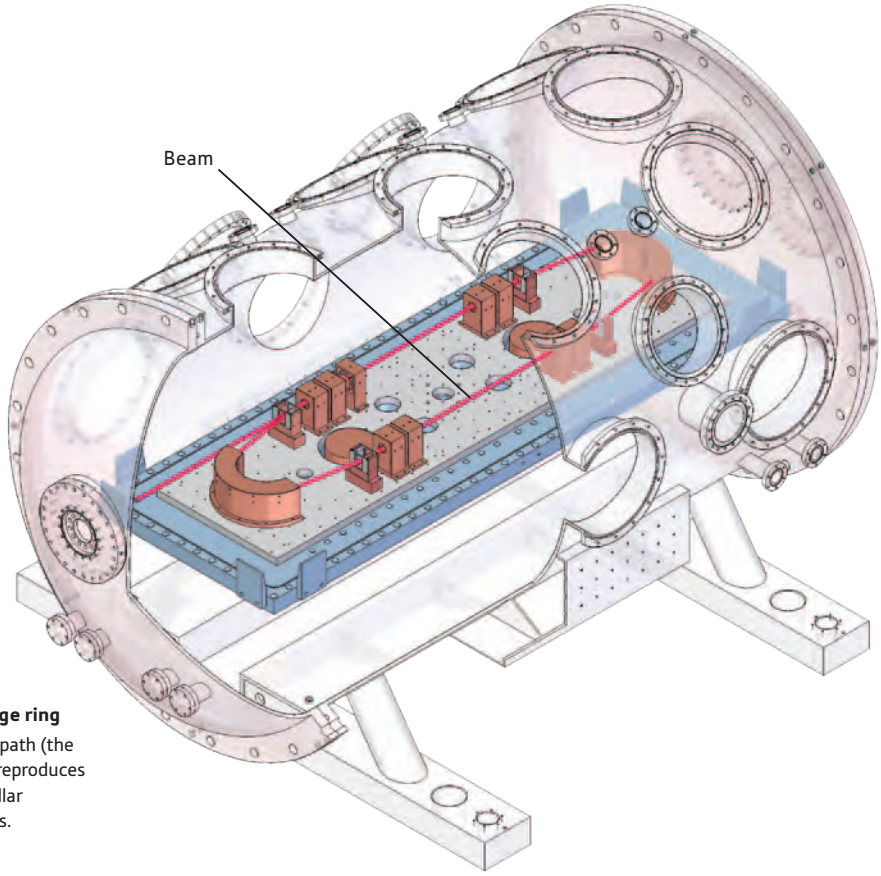


Figure 3: The cryogenic vacuum electrostatic ion storage ring
A molecular beam is produced and passed around a circular path (the storage ring) in a vacuum vessel cooled to 10 K. The system reproduces the conditions of molecular synthesis that occurs in interstellar molecular clouds. The ring has a perimeter of about 3 meters.

The first observations using ALMA were made in 2011 and full-scale observations will begin in 2013 once the facility is completed. One of the main purposes of ALMA is to find complex biotic molecules — the building blocks of life — in space. Amino and nucleic acids have been found in meteorites on Earth. To date however, it is unknown whether such molecules originate from molecular clouds in interstellar space or some other source.

"Amino or nucleic acids might have been produced in molecular clouds, but how? I want to reproduce the chemical syntheses that are occurring in cryogenic space at temperatures as low as 10 K in a laboratory here on Earth. I moved to RIKEN in 2009 to achieve this goal."

Azuma and his laboratory team aimed to develop an electrostatic ion storage ring capable of cooling the entire vacuum vessel to just 4 K, or −269 °C — the temperature of liquid helium. "At first, I thought that the only difference between the TMU E-ring and the new storage ring would be a change from liquid nitrogen cooling to liquid helium. However, we began to understand that cooling the vacuum vessel to 4 K would be quite difficult compared with cooling to 77 K."

Liquid helium has been used successfully in other research facilities where superconducting coils or small vacuum vessels have been cooled to cryogenic temperatures. "The vacuum vessel we are constructing has a circumference of about 3 meters. Such a large vessel has never been cooled using liquid helium, so instead we decided to use a cryogenic freezing machine to cool the vessel, which will allow us to get down to 10 K. We also had difficulty finding materials that could maintain a vacuum under such extreme conditions. However, after much testing we managed recently to identify appropriate materials." The new electrostatic ion storage ring (Fig. 3) is due to be completed in 2012.

Now, research groups in Germany and Sweden are also constructing electrostatic ion storage rings that can be cooled to liquid helium temperatures, with completion soon to be finalized, and US and French researchers are planning to construct similar facilities. "Rival research will expand, and we will face increased competition in this field. However, at RIKEN we are surrounded by experts in the areas of superconductivity at liquid helium temperatures, mass spectroscopy for large ionized molecules, laser spectroscopic technology, low-temperature

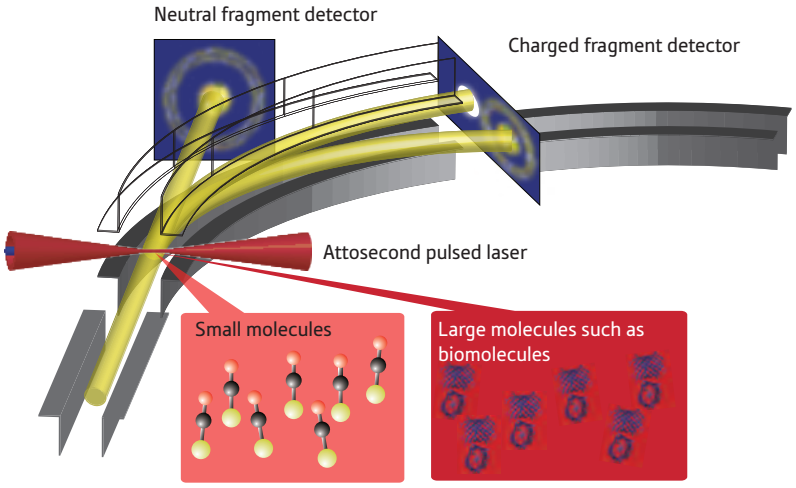


Figure 4: Experiments using the electrostatic ion storage ring currently under development at RIKEN.
A beam of molecules is repeatedly passed around a circular path, and the beam is broken by attosecond laser light. The fragments are detected and the shapes of the molecules are examined.

science, and accelerators — we expect to be able to use the support of these world-leading researchers to our advantage in the fields critical to our experiments. For example, we have introduced a cutting-edge laser technique capable of attosecond pulses of laser light developed by the Laser Technology Laboratory at the RIKEN Advanced Science Institute." Azuma intends to use the technique to conduct molecular synthesis experiments that cannot be performed without it (Fig. 4).

Azuma and his laboratory team plan to use the new facility to collide neutral molecules with positive ions at relatively low speed in a vacuum at temperatures near 10 K in an attempt to reproduce the conditions of interstellar molecular synthesis of amino and nucleic acids. "At cryogenic temperatures, we can also conduct extremely precise measurements of radio signal emissions from the amino and nucleic acids. With these data, astronomers at ALMA might have a better chance to discover amino and nucleic acids in molecular clouds. To start this discussion we have hosted symposiums to deepen our exchange with astronomers."

In interstellar molecular clouds, chemical synthesis is considered to occur not only under vacuum conditions but also on the surface of floating ice particles. Naoki Watanabe of the Institute of Low Temperature Science at Hokkaido University and his laboratory team are conducting experiments aimed at reproducing such chemical reactions here on Earth. "Professor Watanabe is a graduate of Tokyo Metropolitan University, and we communicate with each other on a daily basis to advance our respective research activities."

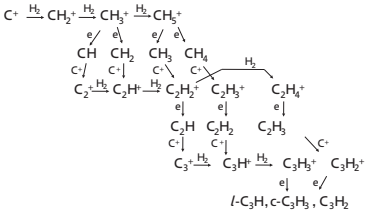


Figure 5: Hydrocarbon synthesis in an interstellar molecular cloud.
Azuma and his laboratory members are attempting to reproduce the synthesis of carbon–carbon-linked hydrocarbon molecules in interstellar space using the cryogenic vacuum electrostatic ion storage ring currently under development at RIKEN.
Reference: S. Yamamoto. How Molecules Were Born. *Encouragement for Chemistry* 1997 (Chikumashobo Ltd, Japan)

This research aims to clarify how a variety of molecules are being synthesized in space. "That will offer an important insight into how life might be created in space."

The effect of a cryogenic vacuum on atoms and molecules

"I am interested in the primordial properties of atoms and molecules. We really do not know much about either. For example, we do not know how the first hydrogen molecule was created in space; the mechanism and speed of synthesis remain a mystery," says Azuma.

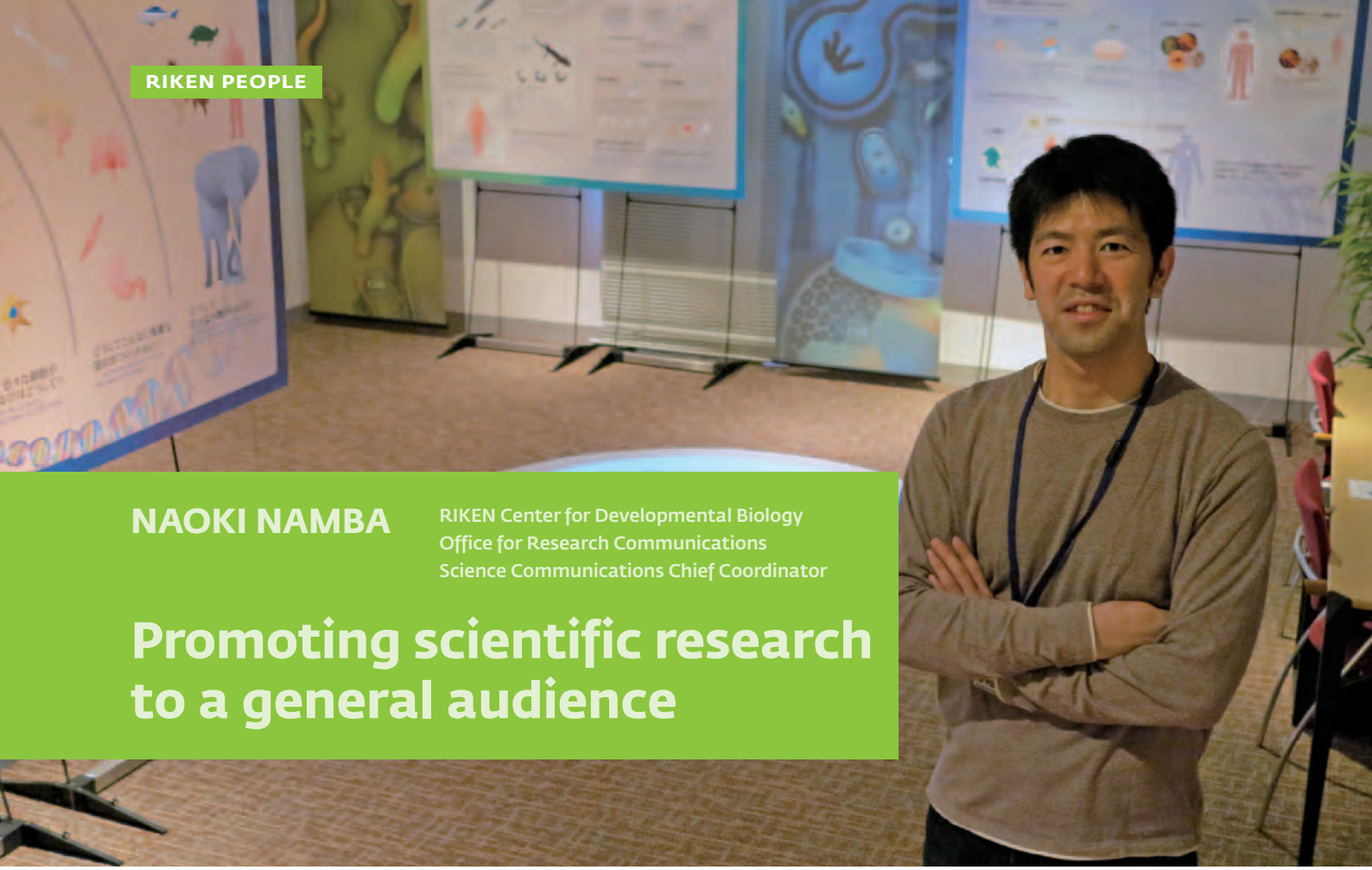
Electrons and protons are thought to have been created in the Big Bang, and to have combined some 380,000 years later to form hydrogen atoms. "Assuming that these hydrogen atoms collided with each other to form a pair of hydrogen atoms, the standard hydrogen molecule, and that the first star was made of hydrogen molecules, the hydrogen atoms would have released part of their initial energy as light. However, this release of light energy is known to be difficult, so how were hydrogen atoms synthesized into hydrogen molecules in a cryogenic environment? What was the speed of that synthesis? These facts are not yet completely understood. We do not know much about primordial reactions involving large molecules such as amino acids or C_{60}, or even those involving small molecules such as hydrogen molecules. I am planning to use the new facility to combine individual carbon atoms to form hydrocarbon molecules, each consisting of five to six carbon atoms (Fig. 5). Hydrocarbon molecules have been identified in astronomical observations, but we do not know how fast the hydrogen molecules are being synthesized in a cryogenic vacuum environment."

Conventionally, the properties of atoms and molecules have been studied in solutions or on substrates. "Even if the temperature of a solution is set exactly, the collisions among molecules that lead to chemical reactions can occur over a range of speeds and can also be affected by surrounding water molecules," says Azuma. "In experiments using a substrate, the influence of the substrate cannot be eliminated. However, using an electrostatic ion storage ring, we can study reactions at a specific speed in a vacuum; by causing molecules to collide with each other at a specific energy level or by bombarding them with laser light or electrons at a specific energy level. In this way, we can measure the properties of atoms or molecules rigorously without the influence of extraneous factors. I think precise measurements of this kind could lead to the discovery of phenomena that have not been explainable by conventional theories."

Azuma predicts that electrostatic ion storage rings will be made even more compact in the future. "In principle, they can be downsized to a compact facility that can be placed on a benchtop. At present, there are only a few groups in the world that have conducted experiments using electrostatic ion storage rings. If such compact facilities become available commercially, many researchers will be able to use the facility to conduct a variety of experiments. There are so many atoms, molecules, and chemical reactions for us to study."

ABOUT THE RESEARCHER

Toshiyuki Azuma was born in Kobe, Japan, in 1960. He graduated from the Department of Nuclear Engineering at the University of Tokyo in 1983, and obtained a DEng degree in liquid-phase muon spin resonance in 1988 from the same university. After two years postdoctoral training at Zurich University and ETH Zurich, in Switzerland, he returned to Japan as a research associate at the Institute of Physics of the University of Tokyo, where he started his career in experimental atomic physics using high-energy heavy ions. He subsequently moved to the University of Tsukuba as an associate professor in 1998, and later to Tokyo Metropolitan University where he became full professor in 2005. He has since acted as director of his own research group, and been involved in research on low-energy ion collisions and the development of ion storage ring technology for large molecular ions. He joined RIKEN in 2009 as chief scientist of the Atomic, Molecular, and Optics Laboratory. His present research covers a wide range of fields from high-energy heavy-ion collisions with crystals to laser-induced reactions of large molecular ions.



NAOKI NAMBA

RIKEN Center for Developmental Biology
Office for Research Communications
Science Communications Chief Coordinator

Promoting scientific research to a general audience

What do you do at RIKEN?

I work as the Science Communications Chief Coordinator in the Office for Research Communications in the RIKEN Center for Developmental Biology (CDB) at the RIKEN Kobe campus.

How and when did you join RIKEN?

Before entering RIKEN I had just started working for a medical publishing company after completing my master's degree in the life sciences, and I was looking to develop my skills to share with the public my interest in science and show the importance of the role that science plays in society. These days, this field is known as "science communication," but when I started in my current job the term was almost unheard of. The RIKEN CDB was ahead of its time in creating this type of position and when I read the recruitment ad it fit my goals so perfectly I was extremely excited and applied straight away.

How was the transition to life at RIKEN?

I joined the CDB just after the Office for Research Communications had opened and we had to start everything from scratch, so it was a bit of a bumpy ride at first. However, together with the head of the office, I worked to fulfill the ideas our scientists had, which was very enjoyable. In addition, our scientists were happy that the CDB was getting its own science communications office and were very supportive of our work. Moreover we were given some freedom to try out our own ideas in the office which made my work extremely gratifying.

Please tell us about your work at RIKEN.

My work is really varied – basically our division handles anything and everything to do with public relations. This can involve arranging tours for local residents and elementary school groups or official visits for VIPs, to updating the CDB website with summaries of our latest published papers in order to inform students and scientists about our research activities. We also proactively work with local high schools running classes and workshops for the students and teachers with the aim of fostering the next generation of researchers. In addition, our division produces a range of promotional materials such as educational books, science-themed games and goods which we use in our outreach work.

What is the best thing about working at RIKEN?

The thing I like most is that at RIKEN, whether you are a scientist or an administrative officer you are given your own discretion to experiment your ideas, which would be often hard to find in another organization. I enjoy the freedom that I have to use my imagination and individual initiative. I also like the environment at RIKEN where I am constantly in contact with cutting-edge research taking place at the center and I am responsible for communicating this to the general audience. RIKEN covers a diverse range of fields – from investigating individual cells to entire universe – so I get to encounter all sorts of science, which is also exciting.

What would you say to other people considering joining RIKEN?

I would say that what you get out of RIKEN depends on what you put into it. If you have a clear vision of what you want to achieve, and have ideas of your own and the desire to see them through, at RIKEN the sky's the limit.

CONTACT INFORMATION

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RIKEN delegation tours Russian research institutions

A delegation from RIKEN led by its president, Ryoji Noyori, visited several top institutes and universities in the Russian Federation from 2–7 May 2012 in order to further strengthen RIKEN's connections with leading figures in the Russian science community. Commencing in Kazan, the capital city of the south western republic of Tatarstan, the visit celebrated the opening of the RIKEN-Kazan Federal University Joint Research Laboratory. Noyori was accompanied by Kohei Tamao, director of the RIKEN Advanced Science Institute (ASI) and Kimitoshi Kono, chief scientist at the RIKEN ASI Low Temperature Physics Laboratory, which already maintains a program of joint research with the Kazan Federal University. The opening was followed by the conferring of an Honorary Doctorate from the university on the RIKEN president. A plenary lecture held to commemorate the award focussed on asymmetric catalysis–an area in which Noyori's discoveries earned him the 2001 Nobel Prize in Chemistry–and the role played in this field by the rare metal ruthenium which was first isolated by Karl Klaus of the Kazan Federal University in 1844.

Following this, the RIKEN president met with Rustam Minnikhanov, the president of Tatarstan and later in the day the delegation visited the Institute for Organic and Physical Chemistry to discuss future arrangements for greater cooperation.

On the third day of the tour, the delegation visited the Moscow State University and met with its rector Victor Antonovich Sadovnichy. In addition to discussing ways to foster mutual scientific ties, the delegates also visited the university's supercomputer, named "Lomonosov" after Mikhail Lomonosov the 18th century Russian polymath. This was of particular interest to the visitors from RIKEN which is home to the K computer, the first supercomputer to achieve 10 petaflops.

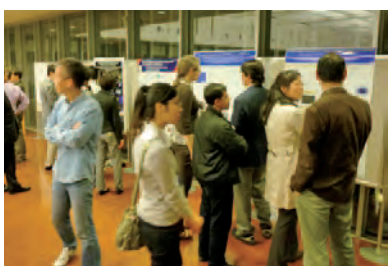
Moving to Saint Petersburg in the north, the RIKEN delegation met with Vadim Kukushkin, professor at Saint Petersburg State University and president of the Chemical Society of Saint Petersburg and Sergey Tunik, vice rector of Saint Petersburg State University on 6 May. The week-long tour was concluded with a meeting between RIKEN and representatives of the Institute of Silicate Chemistry of the Russian Academy of Science (RAS) including RAS academician professor Mikhail Vorononkov, a longstanding associate of Tamao. During this meeting the attendees pledged to maintain close dialogue in an effort to further stimulate Japan-Russia relations. ■

RIKEN President Ryoji Noyori (left) is presented with an honorary doctorate from the Kazan Federal University by the rector Ilshat Gafurov (right).

The Second RIKEN–McGill University Scientific Workshop

The 2012 RIKEN–McGill University Scientific Workshop, the second of the series, was held in the Okochi Hall at the RIKEN Wako Campus in Saitama from 25–26 April 2012 and saw 14 visitors from McGill University—one of the top research institutes in Canada—make the journey to Japan for an intensive two-day program of academic exchange. The current meeting follows the workshop held in Montreal in September 2010 under the auspices of a comprehensive cooperative agreement concluded between RIKEN and McGill University in 2009 following a visit to the Canadian institution by RIKEN President Ryoji Noyori in the same year.

The 2012 workshop opened with welcoming remarks from RIKEN Executive Director Maki Kawai and the associate vice-principal of McGill University, Rima Rozen. Following these, the more than 50 delegates embarked upon a program of 17 lectures covering a diverse array of topics including green chemistry, materials science and nanotechnology given by leading researchers from RIKEN and their Canadian counterparts. The academic program also included a poster session on the afternoon of the first day which was attended by in excess of 60 participants who engaged in lively exchange and discussions. In response to an expressed desire on both sides for a further development of the relationship to include the life sciences, the workshop was also accompanied by visits by Rozen and senior McGill colleagues to other RIKEN campuses in Kobe and Yokohama. ■



Part of the RIKEN-McGill University Scientific Workshop poster session.

RIKEN and Universiti Sains Malaysia sign memorandum of agreement

As part of its ongoing program to develop scientific links with leading regional and international research centers, RIKEN put in place a Memorandum of Agreement (MoA) with Universiti Sains Malaysia (USM) at a signing ceremony in Japan on 6 April 2012. The agreement, concluded by RIKEN President Ryoji Noyori, who holds an honorary Doctor of Science from USM, and the university's vice-chancellor Dato' Omar Osman, will further strengthen the ongoing collaboration between the two institutions.

RIKEN's association with USM—one of the largest universities in Malaysia and a leading research institution in Southeast Asia—began in 1993 with the first academic exchange between RIKEN and USM. Since then a number of USM students and researchers have been sent to RIKEN to pursue research in a wide range of fields including biomass, chemical biology and immunology. Future research collaboration will be overseen at USM by microbiologist K. Sudesh Kumar who earned his PhD at RIKEN between 1995 and 1999 and then subsequently carried out research there until 2001.

The memorandum will help to expand the number of fields covered under the collaborative umbrella, an example of which is the launching of the USM-RIKEN joint Laboratory for Bioprobe Discovery in September 2011, where researchers make use of the rich natural resources of Southeast Asia in order to produce drugs for dengue fever and malaria. ■

RIKEN President Ryoji Noyori and Universiti Sains Malaysia vice-chancellor Dato' Omar Osman commemorate the signing of an MoA in Japan with RIKEN and USM colleagues.

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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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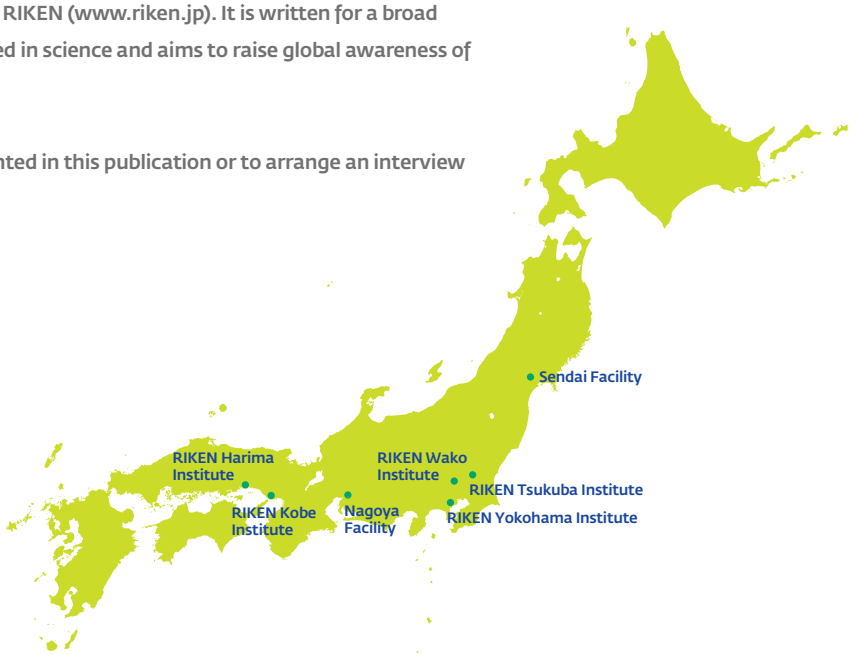

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