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In search of massless systems

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Mutual controllability of electricity and magnetism in a weak magnetic material points the way to low-power electronics

Conventional electronic devices use the flow of electrons to process and transmit information throughout the conducting and semiconducting circuits of a computer chip, which requires external power. Scientists are striving to decrease this demand by electrically controlling a property of the electron, called spin, which is the source of magnetization. Making so-called 'spintronic chips' from multiferroics, a new class of materials with strongly coupled ferroelectric and ferromagnetic properties, could enable electrical control of magnetization.

Yusuke Tokunaga from the RIKEN Advanced Science Institute, Wako, and his colleagues have now discovered that the well-known ferromagnet gadolinium iron oxide ($GdFeO_3$) is also ferroelectric and that its ferromagnetic and ferroelectric properties are strongly coupled[1]. This means that new multifunctional devices based on this material are now a possibility, and could operate with much less power than their conventional counterparts (Fig. 1).

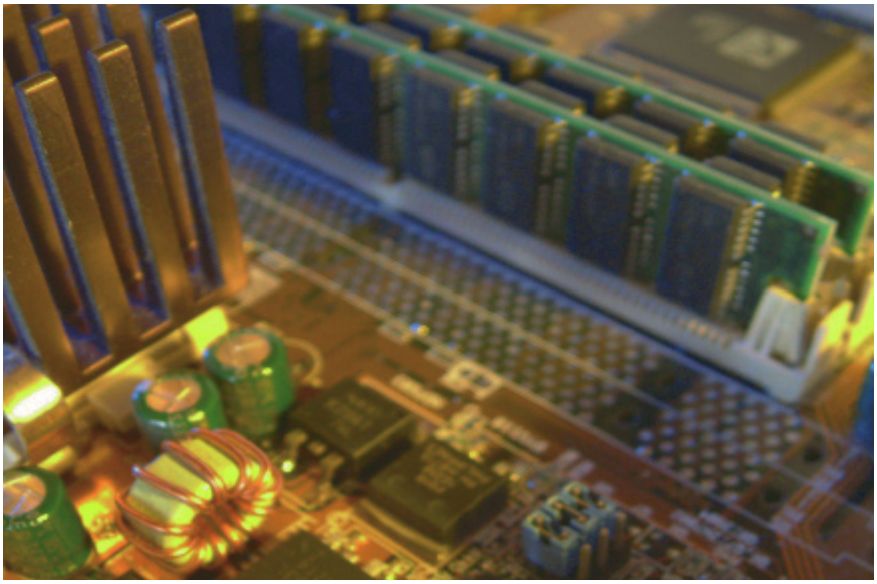

Figure 1: Conventional electronic devices may be consigned to history by novel devices built from multiferroic materials that are expected to process more information and use less power.

A tale of two properties

Ferromagnetism and ferroelectricity, which rarely occur in the same material, arise from different physical processes.

Ferromagnetism occurs in materials, such as iron, below a certain temperature (the Curie temperature), and the magnetic moments of regions of atoms, called ferromagnetic domains, align to point in the same direction when placed in a strong magnetic field (Fig. 2). This alignment remains once the field is removed. Most common magnetic materials are ferromagnetic, including those used to store information electronically.

Ferroelectricity, on the other hand, occurs in materials in which oppositely charged atoms form regions of locally aligned dipoles, and the net polarity can be aligned by a strong electric field (Fig. 3). As with ferromagnetism, this polarization remains once the field is removed.

If the ferromagnetic and ferroelectric properties of a multiferroic material are linked, or coupled, they can be manipulated simultaneously, which would allow the development of multifunctional components. Indeed, the discovery by Tokunaga and co-workers of the multiferroic properties of $GdFeO_3$ began with a series of materials that barely exhibited either property.

"We are always searching for new multiferroics," says Tokunaga. "We started our search with the perovskite ortho-aluminate, $DyAlO_3$. This material is known to be magnetoelectric, but in the absence of any applied field is neither ferromagnetic nor ferroelectric."

Powerful combination for low-power electronics

Magnetoelectric materials, such as $DyAlO_3$, are crystals in which charge polarization can be induced with a magnetic field as well as an electric field. In previous work, Tokunaga and co-workers tried substituting the aluminum (Al) atoms in this material with iron (Fe) atoms[2]. They found that it did become weakly ferromagnetic and ferroelectric, but only while it was held in a magnetic field—when the field was removed both characteristics disappeared.

"As a next step, we searched for a material with the same magnetic structure as $DyFeO_3$ in an applied field," explains Tokunaga. Since the researchers knew that the arrangement and orientation of the magnetic moments of $GdAlO_3$ are the same as those of $DyAlO_3$, they suspected that $GdFeO_3$ might be able to support a

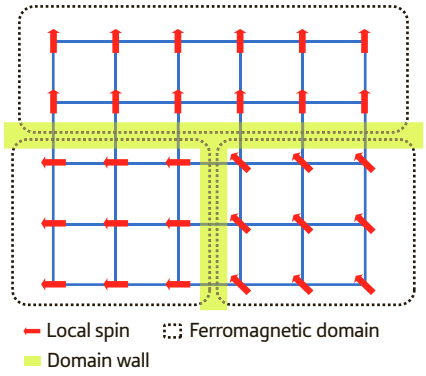

Figure 2: Schematic showing the possible arrangement of the individual spins of electrons in an unmagnetized ferromagnetic material. Regions, or domains, of the magnetic moments of atoms in ferromagnetic materials align when placed in a magnetic field.

similar magnetic structure to that of the magnetic field-induced multiferroic state of $DyFeO_3$, but without the need for a magnetic field.

When the researchers grew large crystals of $GdFeO_3$ and measured their properties, they found that this material was indeed both ferroelectric and ferromagnetic without any applied field. Moreover, they discovered that its ferroelectric and ferromagnetic properties were intrinsically linked and its polarization could be altered with a magnetic field. But more significantly,

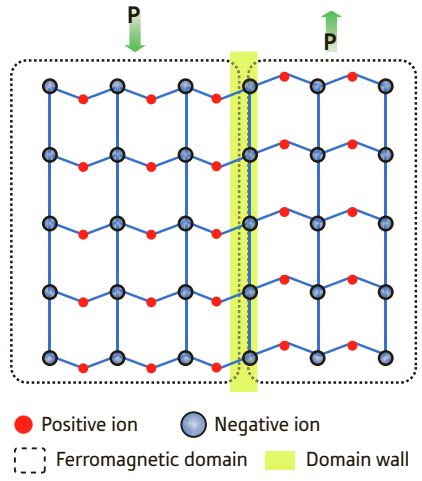

Figure 3: Schematic showing atomic displacement of a ferroelectric material in an unpolarized state. Regions, or domains, of the positively and negatively charged atoms of a ferroelectric material rearrange in a way that polarizes these charges when placed in a strong electric field (*P*, polarity).

they revealed that its magnetization could be changed with an electric field—a property that is particularly useful for making low-power electronics.

"Current-induced magnetization reversal is intensively studied as a means of making devices that use the spin of electrons, as well as their charge, for processing information," notes Tokunaga. However, the metallic and semiconducting materials used in these devices require the flow of current, which dissipates energy. "The great advantage of multiferroic insulators, such as $GdFeO_3$, is that their magnetization can be changed by an electric field with almost zero current and very little energy loss," he says.

Composite domain walls

Interactions between the so-called domain walls, or boundaries between regions of different magnetization and polarization in a material, cause the coupling the ferromagnetic and ferroelectric properties of $GdFeO_3$, according to the researchers.

When a strong magnetic field is applied to a ferromagnetic material, the changes in alignment of its magnetic moments occur gradually through the growth of smaller aligned regions, or domains. As they grow, the domain walls push through the material and, eventually, all the moments of the material align in the direction of the magnetic field. A similar process occurs to the electric dipoles of a ferroelectric when its polarization is switched in response to an electric field.

In a multiferroic material, ferromagnetic and ferroelectric domain walls can exist at different points of the material. A collision between these walls in $GdFeO_3$ can result in the formation of a composite multiferroic domain wall that switches both the magnetization and the polarization of the material as it moves. Moreover, when a composite wall hits a defect in the material, it can decouple to form separate ferromagnetic and ferroelectric walls once more. The merging, propagation and separation of the walls allows the material's magnetization to be switched with an electric field, and allows its polarization to be switched with a magnetic field.

The multiferroic behavior of $GdFeO_3$ occurs only at temperatures below 2.5 K (-270.65 °C), so the researchers plan to search for materials that behave similarly at much higher temperatures. If successful, their endeavor will bring novel practical electronic devices a step closer to realization.

1. Tokunaga, Y., Furukawa, N., Sakai, H., Taguchi, Y., Arima, T. & Tokura, Y. Composite domain walls in a multiferroic perovskite ferrite. *Nature Materials* **8,** 558–562 (2009).
2. Tokunaga, Y., Iguchi, S., Arima, T. & Tokura, Y. Magnetic-field-induced ferroelectric state in $DyFeO_3$. *Physical Review Letters* **101,** 087205 (2008).

About the researcher

Yusuke Tokunaga was born in Tokyo, Japan, in 1977. He graduated from Department of Applied Physics, the University of Tokyo, in 2000, and obtained his PhD in 2005 from the same university. Since then, he has been working as a postdoctoral researcher. After spending two years at ERATO Tokura Spin Superstructure Project, JST, he moved to ERATO Tokura Multiferroics Project, JST. His working place was changed from AIST, Tsukuba, Japan to RIKEN in 2008. He is now working as a visiting researcher at the RIKEN Advanced Science Institute. His current area of interest is in strongly correlated electron systems including multiferroics.

Magnetic sensors attract attention

Chemical-induced switching of polymer magnetism achieved at room temperature

When we smell an aroma or taste a flavor, we convert a chemical stimulus—adsorption of a particular molecule—into an information signal. Researchers are seeking to reproduce such interactions, in a simplified form, to develop new types of chemical sensors for practical and safety applications.

One approach is to use materials known as porous coordination polymers. Consisting of an ordered framework of inorganic metals linked together through carbon-based connectors, these polymers are extremely flexible, allowing large amounts of gas molecules to be adsorbed within the pores. Moreover, adsorption of guest molecules can alter the physical properties of the material.

Now, an international team of researchers has developed a route to detect adsorption through reversible chemo-switching of the magnetic properties of a porous coordination polymer[1]. According to lead author Masaaki Ohba, a guest researcher at the RIKEN SPring-8 Center and an associate professor at Kyoto University, because the chemo-switching occurs at room temperature, this polymer can be developed into new environmentally responsive materials.

In the team's polymer, iron and platinum atoms are joined into a regular cubic framework through a cyclic carbon–nitrogen molecule called pyrazine and cyanide connection units. The spin state of the iron atoms—the number of unpaired electrons that determine magnetism—is dependent upon their proximity to the organic connectors.

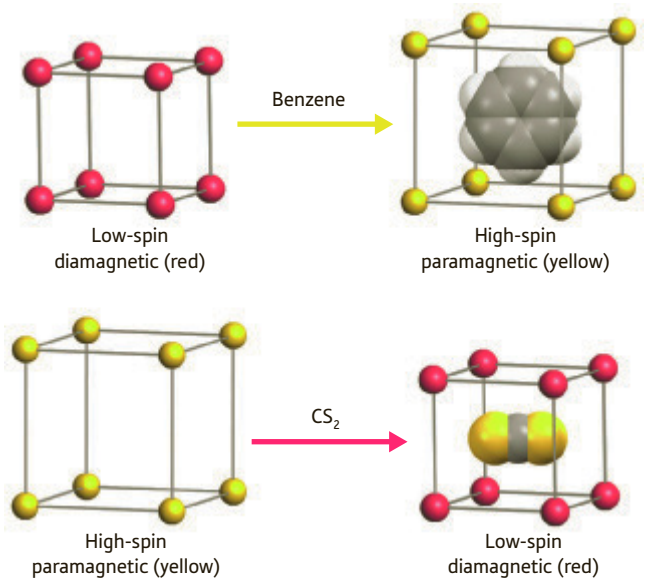

Figure 1: Schematic diagram of magnetic chemo-switching by guest molecules. When the diamagnetic low-spin porous polymer (top left, red) adsorbs benzene, the polymer expands to form the paramagnetic high-spin state (top right, yellow). Conversely, when the high-spin porous polymer (bottom left, yellow) adsorbs CS_2, the polymer shrinks to the low-spin state (bottom right, red).

"The spin state directly relates to the bond distance between iron and the organic connectors," explains Ohba. "A short bond distance stabilizes the low-spin state, while a long bond distance stabilizes the high-spin state."

Ohba and colleagues found that adsorption of certain molecules into the porous polymer altered the bond distances between iron and the organic connectors, setting off a switching of the magnetic spin state (Fig. 1). When the polymer is initially in the low-spin, or diamagnetic, state, adsorption of gases such as benzene, water, and alcohols causes expansion of the polymer framework—and a switch to the high-spin, or paramagnetic, state.

In contrast, adsorption of carbon disulfide (CS_2) gas by a polymer in the high-spin state shrinks the framework, and switches the magnetism to the low-spin state. Even after guest molecules are removed, the polymer retains its magnetic state—a form of non-volatile molecular memory.

"These porous coordination polymers combine properties such as gas adsorption and storage with the physical properties incorporated in their frameworks," says Ohba. "They can be processed into nanoscale particles or films for applications such as chemical sensors and molecular memories." ■

1. Ohba, M., Yoneda, K., Agusti, G., Muñoz, M.C., Gaspar, A.B., Real, J.A., Yamasaki, M., Ando, H., Nakao, Y., Sakaki, S. & Kitagawa, S. Bidirectional chemo-switching of spin state in a microporous framework. *Angewandte Chemie International Edition* **48,** 4767–4771 (2009).

Electrons narrow the gap

An organic compound provides a rare opportunity to study electrons that behave as if they have no mass

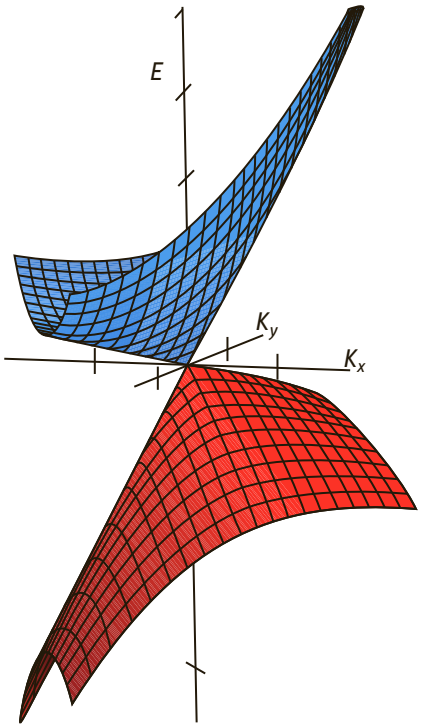

Figure 1: Two-dimensional plot of energy *E* versus momentum k of the electron states in α-(BEDT-TTF)$_2$I$_3$. The plot shows the lack of a gap between the upper (blue) and lower (red) energy states. In its diagonal cross-section, the plot also shows the linear dependence of energy on momentum. Note that the origins of the axes are taken at the position of the contact point.

Researchers from the RIKEN Advanced Science Institute in Wako, in collaboration with colleagues from Toho University, Japan, have discovered an organic compound, α-(BEDT-TTF)$_2$I$_3$, that exhibits a rare feature: the compound's electrons behave like particles without mass, so they do not obey Newton's second law of motion[1]. This is the first 3D material where all requirements for massless systems are confirmed.

In most materials, electrons do follow this law of motion, such that the energy of an electron is proportional to the square of its momentum. There are only a few known 2D systems, notably graphene, where electrons behave in a fundamentally different way. They appear to have no mass when propagating through the material, so the relationship between their energy and momentum is linear.

Some 3D materials also have massless electrons, but the electrons in these materials have a gap between their energy states that makes them behave more like semiconductors than metals. The zero gap is a prerequisite for fully massless systems. In α-(BEDT-TTF)$_2$I$_3$, not only do the electrons appear massless, there is also no gap in the energetic structure (Fig. 1). "This is the first known three-dimensional material with zero gap," says Naoya Tajima from the research team.

In some respects, α-(BEDT-TTF)$_2$I$_3$ resembles a 2D material, as it is composed of two different layers of conducting BEDT-TTF molecules and insulating I_3^- anions. The system remains metallic down to the low temperatures where electrons are massless, but only under the application of high pressure.

To produce watertight evidence for massless electrons in this system, the researchers applied strong magnetic fields. The linear dependence of energy on momentum became apparent from these experiments and, more importantly, the experiments provided direct evidence for the zero energy gap.

In the presence of a magnetic field applied perpendicularly to the layers, an electronic state forms at zero energy. This state is occupied by electrons only when the band gap is zero. The higher the magnetic field, the more electrons are in this state, thus an increasingly reduced electrical resistance is predicted. Accordingly, the researchers observed in their experiments that electrical resistance decreased with increasing magnetic field in the perpendicular direction.

Armed with this evidence, further intriguing effects are bound to arise from these systems. "We recently discovered [other] novel phenomena characteristic particular to these three-dimensional systems," notes Tajima. A large class of related organic molecules seems destined to provide further examples of massless systems and the discovery of related unusual electronic properties. ■

1. Tajima, N., Sugawara, S., Kato, R., Nishio, Y. & Kajita, K. Effect of the zero-mode Landau level on interlayer magnetoresistance in multilayer massless Dirac fermion systems. *Physical Review Letters* **102,** 176403 (2009).

Organic lighting offers a bright future

New phosphorescent complexes improve manufacturing of high-efficiency light sources

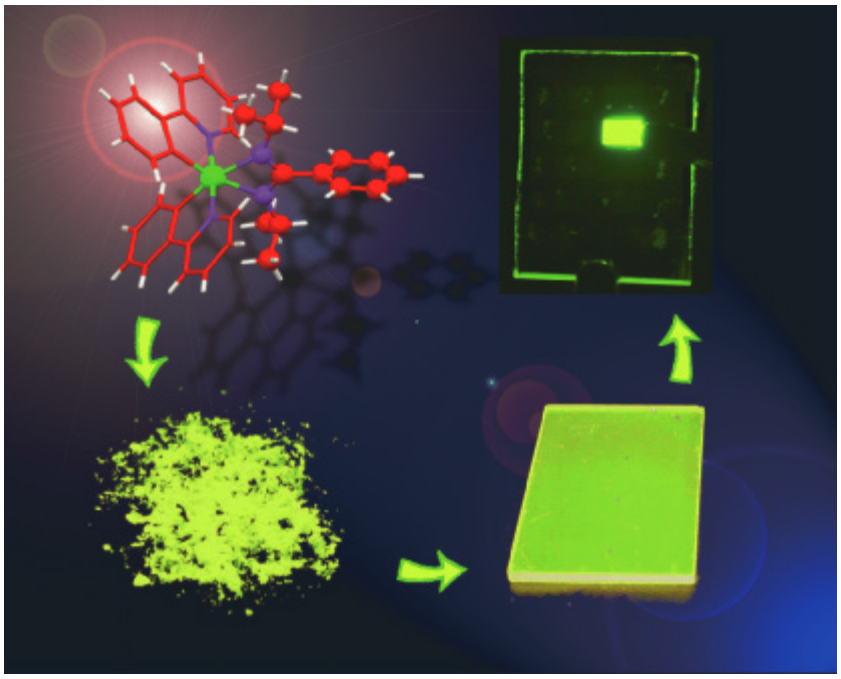

Figure 1: A phosphorescent iridium–amidinate complex (top left) serves as an excellent emitter (bottom), enabling the first successful fabrication of highly efficient non-doped phosphorescent OLEDs (top right).

Organic light-emitting diodes (OLEDs) are set to revolutionize lighting technology, ushering in an era of thin, flexible, and ultra-bright devices. At the heart of recent OLED devices are phosphorescent metal complexes that, when stimulated by an electric voltage, produce a sustained emission of light with higher efficiency than other sources. Furthermore, because OLEDs create their own light, they eliminate the need for backlights used in liquid crystal displays, and therefore consume low amounts of power.

Although the advantages of OLEDs are impressive, manufacturing these devices remains a challenging and expensive process. Phosphorescent OLEDs are normally fabricated by via a process known as 'doping' where metal complexes are added into a host matrix under strict concentration requirements. If the metal concentration is too high, the complexes interact and quench each other's phosphorescent abilities.

Now, a team of scientists led by Zhaomin Hou from the RIKEN Advanced Science Institute in Wako has developed a way to eliminate precise doping limits from the OLED manufacturing process[1]. By using a metal dopant containing molecular groups that block the self-quenching interactions, the scientists have, for the first time, fabricated high-efficiency OLEDs with a wide range of doping concentrations.

Hou and colleagues modified a phosphorescent iridium metal complex with a class of molecules known as amidinates. These molecules bind to iridium through a nitrogen atom that localizes electrons near the center of the metal complex. Bulky carbon groups on the edges of the complex are inert and prevent the materials from attaching and self-quenching their phosphorescence.

Prototype OLED devices made with the iridium–amidinate complex exhibited a bright yellow-green emission (Fig. 1) using very low driving voltages. The scientists found that a wide range of doping concentrations—from 7% to 100%—could be used to produce the OLED devices.

"One of the research projects in my group led to an efficient synthesis of various amidinates," says Hou. "We envisioned that a geometrically hindered amidinate group might overcome the problems encountered previously in phosphorescent metal complexes."

According to Hou, the iridium complex itself possesses charge-transport ability, removing the need for a host matrix. Moreover, because of the excellent performance and the ease of synthesis, the iridium–amidinate phosphorescent complexes should have high potential in practical applications such as flat-panel displays and organic lighting.

"We are now applying the amidinate molecules to phosphorescent metal complexes that emit light at different wavelengths," says Hou. "This will allow us to produce new high performance OLED devices with different colors." ■

1. Liu, Y., Ye, K., Fan, Y., Song, W., Wang, Y. & Hou, Z. Amidinate-ligated iridium(III) bis(2-pyridyl) phenyl complex as an excellent phosphorescent material for electroluminescence devices. *Chemical Communications* **25**, 3699–3701 (2009).

Cellular insights via barcoded yeast genes

A newly created yeast gene archive will enable efficient analysis of the function of bioactive compounds with potential pharmaceutical use

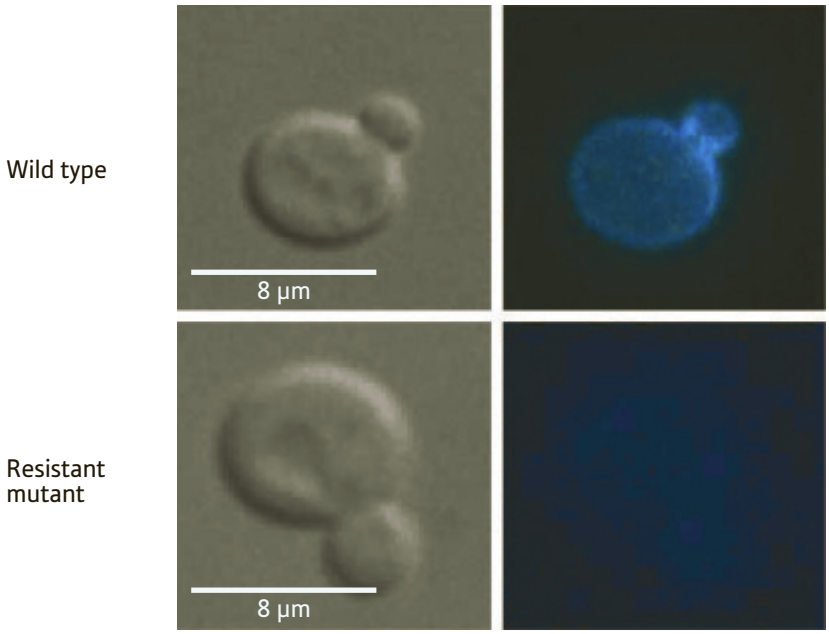

Figure 1: Localization of a novel antifungal compound (left) visualized by fluorescent microscopy (right). The upper panels show normal (wild type) cells and the lower panels show a cell containing a mutant gene resistant to the compound.

By establishing a library of individual yeast genes, each cleverly tagged with its own molecular barcode, an international team of molecular geneticists has designed a valuable resource for pharmaceutical research with advantages over previous approaches.

The research team, including Minoru Yoshida at the RIKEN Advanced Science Institute in Wako, and Charles Boone at the University of Toronto, Canada, developed the library in which each yeast gene is copied and attached to two unique single stranded DNA molecules that act as barcodes. This enables researchers to efficiently identify each gene.

The yeast-based chemical-genomics approach, presented recently in *Nature Biotechnology* by Yoshida and colleagues[1], is useful because many medicinally important drugs target fundamental biological processes that are conserved between yeast cells and higher organisms.

Using the team's approach, all the gene-carrying units, or plasmids, in the yeast are carefully constructed individually, as opposed to conventional genomic libraries that are created from random fragments of DNA. Each plasmid carries a single yeast gene as well as two 20-nucleotide barcodes that identify it. The library comprises plasmids for almost 5,000 genes and covers approximately 90% of the yeast genome.

Other approaches to examine the genetic influence of potential drugs have limitations such as needing high volumes of test compound, which can be of limited availability, or being labor intensive.

Most significantly, the newly created gene catalogue will enable researchers to identify at the genetic level the precise modes of action of specific compounds that are being screened as potential pharmaceuticals. The library can be used to efficiently identify mutant genes that confer resistance to a test drug by comparing cells that show resistance and susceptibility to the compound. Determination of the mutant genes leads to the identification of the functional impact of a potential drug.

In a demonstration of the usefulness of the library, Yoshida and colleagues identified the gene responsible for conferring resistance to a novel class of compounds with pharmaceutical potential (Fig. 1). Identifying this gene enabled the team to characterize the mechanism of action of these molecules and to determine that they are antifungal compounds, a property not detected by other techniques.

An essential but challenging step in the development of small molecules into therapeutic drugs is identification of their cellular target. "Using this library, our group intends systematically to study chemical–genetic interactions in which an altered gene dosage or gene mutation leads to a change in cellular response to a bioactive compound," says Yoshida. ■

1. Ho, C.H., Magtanong, L., Barker, S.L., Gresham, D., Nishimura, S., Natarajan, P., Koh, J.L.Y., Porter, J., Gray, C.A., Andersen, R.J. *et al.* A molecular barcoded yeast ORF library enables mode-of-action analysis of bioactive compounds. *Nature Biotechnology* **27,** 369–377 (2009).

A matter of taste

A combination of computational and experimental techniques helps researchers to identify a gene involved in taste bud development

A well-tuned sense of taste is about far more than being able to enjoy a fancy dinner—it represents a key survival mechanism, helping animals to rapidly identify potential food sources as tasty or toxic (Fig. 1).

The basic principles of how taste buds enable us to recognize the five primary flavor sensations—sweet, sour, salty, bitter and *umami*—are reasonably well understood. Remarkably little is known about the development and maintenance of the various sensory cell types that underlie this process, however, although evidence suggests there are many interesting discoveries waiting to be made. "Taste is an interesting system, as it is continuously renewed during the lifetime," explains Takashi Kondo of the RIKEN Brain Science Institute in Wako. "It suggests that there is a nice underlying stem cell system."

In a new study, Kondo and colleagues have combined computational and experimental techniques to analyze the development of type II taste cells, which detect sweetness, bitterness and *umami*[1]. This process is specifically mediated by numerous taste receptor calcium signaling molecules (TRCSMs), and Kondo's team started by searching for factors that might control production of these proteins during development of taste bud bundles known as circumvallate papillae (CVP).

Starting with five different TRCSMs that are all co-expressed by the same population of type II cells, they performed a computational analysis of the DNA sequences that govern the activity for each of these genes, searching for shared binding sites used by regulatory proteins.

Figure 1: The varied diet of humans requires a well-honed system for distinguishing between different flavors.

One notable candidate was HES1, a known regulator of neural development, and multiple HES1 binding sites were observed in the mouse, rat and human versions of all five genes.

After experimentally confirming that HES1 indeed binds these regulatory sequences, the researchers demonstrated that it was expressed many cells throughout the developing CVP. However, in cells expressing TRCSMs, HES1 was localized in the cytoplasm rather than the nucleus, sequestered away from the genes that it regulates, suggesting that it acts as a repressor for genes involved in type II taste cell development. This model was further supported by the observation that CVPs in mouse embryos lacking HES1 produce much greater numbers of TRCSM-expressing cells than those in normal embryos.

The authors conclude that HES1 may be involved in maintaining stem cell identity in taste cell precursors, with export of this protein from the nucleus representing an early step in type II taste cell differentiation, and Kondo says that his team is now looking deeper into this process. ■

1. Ota, M.S., Kaneko, Y., Kondo, K., Ogishima, S., Tanaka, H., Eto, K. & Kondo, T. Combined *in silico* and *in vivo* analyses reveal role of Hes1 in taste cell differentiation. *PLoS Genetics* **5,** e1000443 (2009).

Shaping the matrix

A mesh-like structure formed by two synaptic scaffolding proteins controls the shape and protein make-up of the synapse

An international team of researchers, including Mariko Kato Hayashi at the RIKEN Brain Science Institute in Wako, has found that the scaffolding proteins Shank and Homer polymerize to form a large matrix that regulates key features of the synapse[1]—namely its shape, protein composition, and function.

Chemical communication between neurons occurs at the synapse. Many synaptic proteins—such as neurotransmitter receptors, scaffolding proteins, and signaling proteins—are poised at the receiving end of the synapse, called the 'postsynaptic density' (PSD). Increasing the expression of the PSD scaffolding proteins Shank and Homer within neurons increases the size of dendritic spines, in which the PSD is located. These new findings explain why.

The researchers incubated pure Shank protein, pure Homer protein, and a mixture of both proteins to allow them to interact. When they observed these three different preparations under the electron microscope, the pure Shank protein looked like compact globs, while the pure Homer protein looked like longer threads.

Notably, incubation of both Shank and Homer together resulted in a large mesh-like structure, with Shank proteins forming 'hubs' which attached to the ends of Homer protein fibers. The formation of this large Homer–Shank matrix within neurons may explain why the dendritic spines of these neurons are abnormally large when these two proteins are artificially expressed at high levels.

Using a technique called x-ray crystallography, which allows scientists to determine the shape of proteins, the researchers were able to establish the structural basis by which Homer forms long filaments: four Homer protein monomers interact in a special crossing tail-to-tail tetrad structure (Fig. 1). Interference with the creation of this structure, by mutating key parts of the tetrad structure, blocks formation of the Homer–Shank matrix.

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Figure 1: When four Homer protein monomers interact, they form a long tail-to-tail tetramer. The crystal structure of the carboxy-terminal of Homer is shown; each of the four Homer monomers is represented by a different color.

The team found that expressing this mutant Homer in neurons resulted in abnormal synaptic development and the normal accumulation of Shank and other synaptic proteins was reduced at the synapse. Also, the dendritic spines of these neurons were long and thin, which is characteristic of immature spines. These changes seemed to affect neuronal function, because neurons expressing the mutant Homer protein, which could not form the tetrad structure, had reduced excitatory neurotransmission compared with neurons expressing the normal Homer protein.

"The Homer–Shank matrix could be the structural framework of the PSD," says Hayashi, "and could work as the platform for other important synaptic proteins. It would therefore be playing a role much like the circuit board of a computer." ■

1. Hayashi, M.K., Tang, C., Verpelli, C., Narayanan, R., Stearns, M.H., Xu, R.-M., Li, H., Sala, C. & Hayashi, Y., The postsynaptic density proteins Homer and Shank form a polymeric network structure. *Cell* **137,** 159–171 (2009).

The path to olfaction

Neurons conveying information about smell from the olfactory bulb communicate with multiple regions of the brain

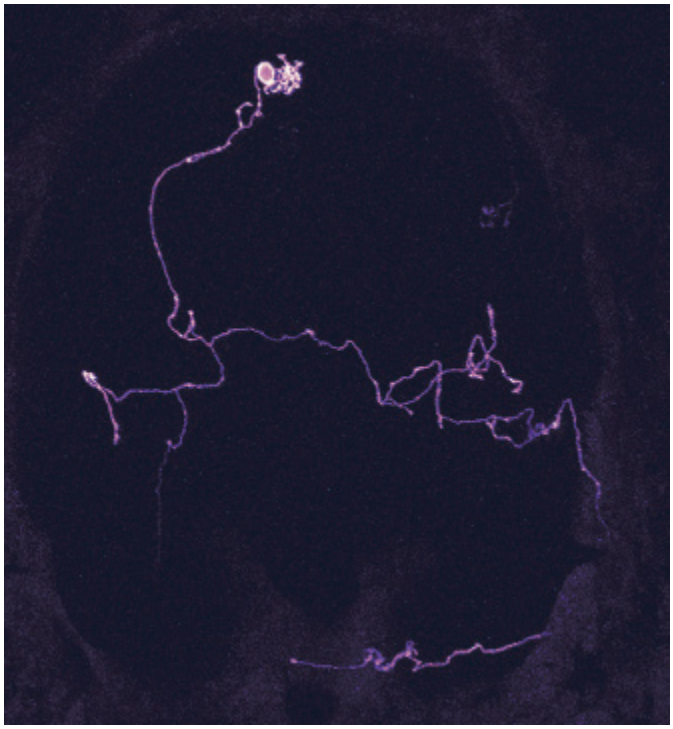

Figure 1: A fluorescently labeled mitral cell in a zebrafish. This mitral cell projects its axon to three different parts of the brain, with its axon finally terminating within the right habenula.

Olfactory signals are transmitted through the nose to the olfactory bulb, where information about distinct odors is spatially separated, leading to the formation of an 'odor map' in that structure. To determine how this information is sent to other parts of the brain, a team of researchers led by Yoshihiro Yoshihara and Nobuhiko Miyasaka at the RIKEN Brain Science Institute in Wako used genetic fluorescent labels to visualize the axon trajectories of mitral cells, the output neurons of the olfactory bulb, within small vertebrates called zebrafish.

They report in *The Journal of Neuroscience* that these neurons transmit information to several brain structures on both sides of the brain, but the odor map is not maintained intact in these higher brain structures[1].

The researchers found, for example, that information from one part of the odor map is sent in a divergent manner to many different higher brain structures. At the same time, information from many parts of the odor map can converge onto a single brain structure. This mixing of olfactory information in higher brain regions could serve to control the behavioral and hormonal responses of the zebrafish to multiple odors in their environment, according to the researchers.

Axons that project long distances within the central nervous system tend to cross the midline only once before reaching their targets. But, surprisingly, Yoshihara, Miyasaka and colleagues found that some of the mitral cells they labeled crossed the midline twice, sending information along the way to as many as three brain regions on both sides of the brain (Fig. 1). This suggests that multiple brain regions simultaneously respond to identical olfactory information from a single mitral cell.

Projection neurons on one side of the brain tend to send their axons—and therefore to control—bodily functions on the other side of the body. But the researchers found unexpectedly that one particular population of mitral cells in both the right and the left olfactory bulb project their axons directly and asymmetrically only to the right side of the brain—to a structure called the right habenula. Because the habenula controls emotional and social behaviors, this may mean that zebrafish could show a left/right preference for exhibiting olfactory behaviors, such as an innate escape response.

As the next step in this research, Yoshihara says "we now aim to dissect olfactory neural circuits mediating various odor-induced behaviors, such as attraction, escape, memory, and social behaviors." ■

1. Miyasaka, N., Morimoto, K., Tsubokawa, T., Higashijima, S., Okamoto, H. & Yoshihara, Y. From the olfactory bulb to higher brain centers: genetic visualization of secondary olfactory pathways in zebrafish. *The Journal of Neuroscience* **29,** 4756–4767 (2009).

Water-powered reactions

Water molecules at the heart of a key enzyme facilitate biosynthesis of an antitumor drug

An international team, led by Shingo Nagano from the RIKEN SPring-8 Center in Harima and Hiroyasu Onaka from Toyama Prefectural University, has uncovered the vital role of water in the generation of the antitumor drug staurosporine[1].

The researchers mainly focus on the enzyme P450 StaP, which belongs to the cytochrome P450 enzyme family. These enzymes are involved in metabolic and biosynthetic reactions, including the activation and degradation of drugs in humans, and the synthesis of medically relevant natural products.

P450 StaP's active site consists of a sulfur-bound iron atom enclosed in a large hydrocarbon ring called heme. It catalyzes the oxidation of a five-ring compound called chromopyrrolic acid (CPA) and facilitates the formation of an intramolecular carbon–carbon bond to generate a six-ring staurosporine precursor. This carbon–carbon bond formation is unusual for P450 enzymes, which typically insert an oxygen atom into bonds. The researchers demonstrated that water molecules mediate this carbon–carbon coupling.

Nagano and co-workers had previously revealed that strong interactions held CPA tightly in a binding pocket, modulating proton and electron transfer reactions between substrate and enzyme. However, they observed that those interactions kept the substrate away from the heme oxygen, impeding any direct contact, and thus proton transfer, between the two species.

In their latest work, they mutated the enzyme by replacing a residue positioned between the two water molecules with hydrocarbons, which significantly decreased its activity. They also substituted CPA with a chlorine-containing compound (CCA) and discovered that the chlorine atom prevented water molecules from approaching the heme (Fig. 1). Further, they observed decreased activity in presence of CCA, highlighting the importance of water in the mechanism.

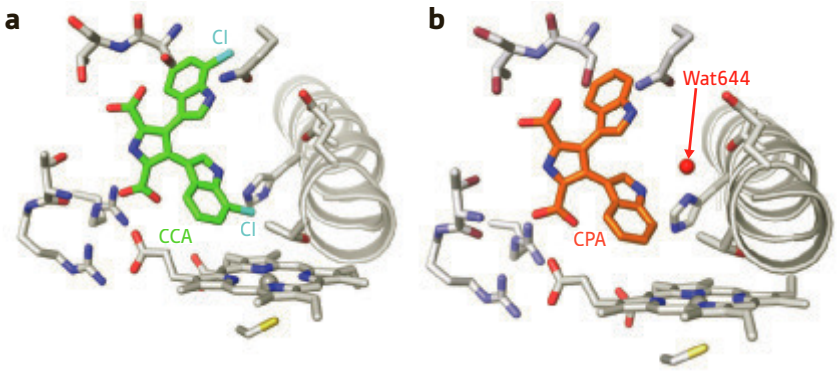

Figure 1: The crystal structures of the binding pockets in StaP containing (a) CCA in which water (Wat644) is absent, and (b) CPA.

"CCA is very poor substrate but we had no idea why this happens," says Nagano. Since his collaborator proposed that this water molecule was very likely to be a key player in this enzyme catalysis, they ran a detailed computational investigation. They found that two water molecules in the enzyme active site acted as a proton relay between CPA and the heme.

"Similar water-assisted proton transfer between heme and substrate is also found in horseradish peroxidase (HRP), another heme enzyme," explains Nagano. "The natural substrate-bound HRP has a water molecule close to the substrate and heme as we have observed in CPA-bound P450 StaP." The researchers' ultimate goal is to transpose this carbon–carbon coupling to other P450 enzymes and generate new staurosporine-like therapeutic agents. ■

1. Wang, Y., Chen, H., Makino, M., Shiro, Y., Nagano, S., Asamizu, S., Onaka, H. & Shaik, S. Theoretical and experimental studies of the conversion of chromopyrrolic acid to an antitumor derivative by cytochrome P450 StaP: the catalytic role of water molecules. *Journal of the American Chemical Society* **131**, 6748–6762 (2009).

All in the timing

Knocking out a clock gene in plant cells interrupts mitochondrial function and energy release

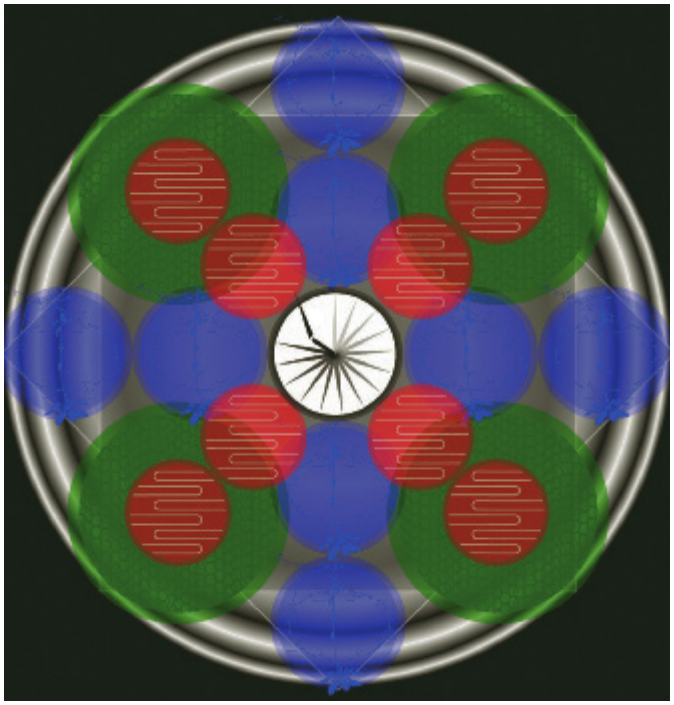

Image courtesy of Hiroyuki Hanamura

Figure 1: An artistic representation of the plant circadian clock as a mandala. This clock, previously known to regulate many developmental and physiological processes, including photosynthesis and stress response, has now been linked to mitochondrial function. (Blue and red circles represent the tricarboxylic acid cycle in *Arabidopsis* and mitochondria, respectively.)

A RIKEN-led group of molecular biologists has established the first direct link between the circadian clock mechanism in flowering plants and the functioning of the mitochondria, where energy is generated in the cells.

Daily rhythms in the biochemical or metabolic activity of cells have long been known across all biological kingdoms. They are governed by the oscillating activity of clock genes, the impairment of which has been shown in mice to be related lifestyle diseases such as obesity. In plants, production of plant biomass is likely to be linked with clock genes.

Recent studies in the genetic model plant *Arabidopsis* have revealed three key genes involved in the timing mechanism—*CCA1, LHY* and *TOC1*. These genes form the centerpiece of several interlocked feedback loops which establish and adjust the daily oscillation pattern.

Kazuki Saito and colleagues from the RIKEN Plant Science Center in Yokohama and Nagoya University studied the molecular impact of mutations in these key clock genes. They analyzed not only the direct changes in the nucleic acid and protein products generated by mutant genes, but they also looked at the differences in the downstream metabolic products formed. Details of their work were published recently in the *Proceedings of the National Academy of Sciences*[1].

TOC1 is one of five related proteins known as the pseudo-response regulator (PRR) family. Previous work has shown them to be important components in adjusting the circadian system to changes in temperature and light. The researchers focused on a triple mutant of *PRR9, 7* and *5* which leads to inability to establish a circadian rhythm under constant light. In previous work the research group demonstrated a strong link between this mutant and stress response in plants (Fig. 1).

The triple mutant leads to late-flowering plants with dark green leaves. They are similar in appearance to those generated when the *CCA1* gene becomes overactive. But the researchers found the metabolic details of two plant forms to be utterly different. In particular, they were surprised to find that the triple mutant led to a build-up of three key intermediate compounds of the tricarboxylic acid pathway, the standard energy release process which takes place in the mitochondria of all higher organisms. The impact of the mutant PRR clock genes on the mitochondria was direct and unequivocal.

"We now want to determine the molecular components involved in this link between the clock genes and metabolism," says Saito. ■

1. Fukushima, A., Kusano, M., Nakamichi, N., Kobayashi, M., Hayashi, N., Sakakibara, H., Mizuno, T. & Saito, K. Impact of clock-associated Arabidopsis pseudo-response regulators in metabolic coordination. *Proceedings of the National Academy of Sciences USA* **106,** 7251–7256 (2009).

Taking proteins for a ride

A recently discovered structure in plant cells functions to transport proteins and glycans around the cell

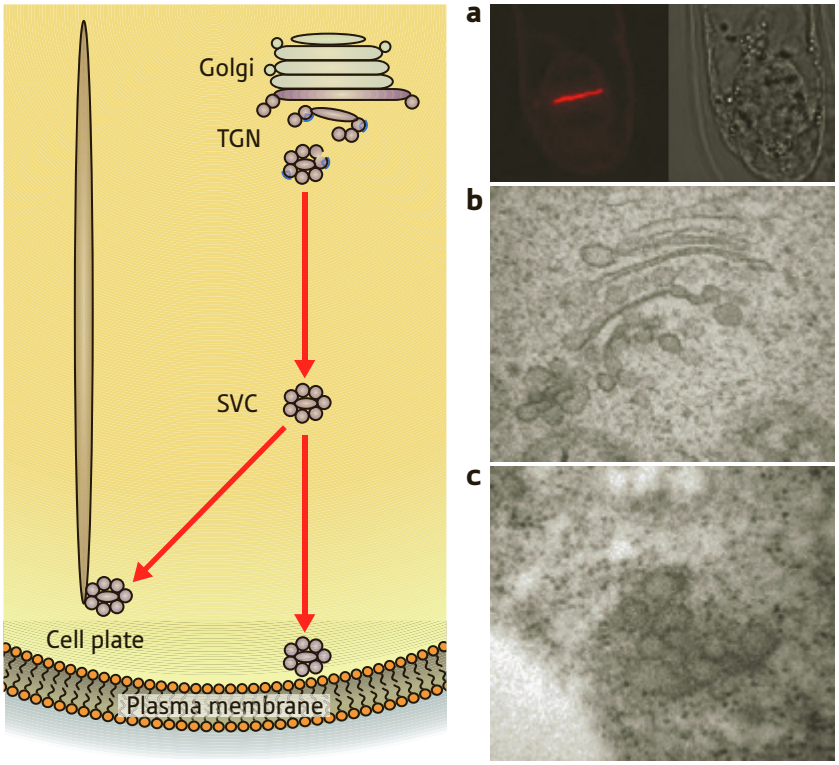

Figure 1: Secretory vesicle clusters (SVCs) emerge from the Golgi apparatus in plant cells. They move either to the plasma membrane to secrete proteins and glycans, or to the cell plate where they are involved in cell division. On the right are microscope images of (a) the cell plate, (b) the Golgi apparatus and (c) an SVC.

Cells produce thousands of proteins that are essential for life, but the proteins are of no use unless they can be delivered to the right places. Now, Ken Matsuoka and co-workers at the RIKEN Plant Science Center in Yokohama, Kyushu University in Fukuoka and Niigata University have discovered a subcellular structure in plants that carries proteins and glycans to the correct locations, especially outside of the cell[1].

The newly identified delivery structure arises from another substructure in the cell called the Golgi apparatus. If one imagines a cell as a factory producing proteins, the Golgi apparatus can be thought of as the sorting office, where proteins are organized and packaged into bundles ready for their journey around the body.

The protein bundles, packed together with lipids, are called transport vesicles. One of their functions is to travel to the cell membrane and secrete proteins from the cell—a process called exocytosis.

Plants, in particular, have complicated 'post-Golgi' compartments that influence vesicles during the last stages of exocytosis. "It is not yet clear whether these compartments are the sole elements in the late secretory pathway of plants, how they interact, or how they are involved in exocytosis," says Matsuoka.

Matsuoka and co-workers monitored the movement of vesicles in tobacco plant cells, by fluorescent tagging of a known vesicle protein called secretory carrier membrane protein 2 (SCAMP2). They found that SCAMP2 accumulates in the Golgi network, but not in known post-Golgi compartments. Instead, it appears in clusters of between 5 and 12 vesicles, each around 50 to 100 nanometers in diameter.

The researchers named these new structures 'secretory vesicle clusters', or SVCs. The SVCs can move separately from the Golgi network, and are often seen tethered to cell walls, where they are probably involved in secreting proteins and glycans from the cell.

Furthermore, the SVCs appear to play an important role in cell division. SVCs in dividing cells were targeted towards the cell plate—a thick wall of glycans and proteins that forms down the centre of a cell before the cell splits in two (Fig. 1).

The researchers found SVCs in *Arabidopsis* and rice plants as well as tobacco. Therefore the SVCs represent a standard delivery mechanism supplying cells with the necessary ingredients for maintaining life.

"We are now isolating the SVCs to analyze their constituents," says Matsuoka. "[Then] we will be able to analyze the molecular mechanisms of SVC transport and for tethering vesicles together in SVCs." ■

1. Toyooka, K., Goto, Y., Asatsuma, S., Koizumi, M., Mitsui, T. & Matsuoka, K. A mobile secretory vesicle cluster involved in mass transport from the Golgi to the plant cell exterior. *The Plant Cell* **21,** 1212–1229 (2009).

Combining organic molecules and metal elements to explore a new chemistry

Masanobu Uchiyama

Associate Chief Scientist
Advanced Elements Chemistry Laboratory
RIKEN Advanced Science Institute

Chemistry supports our modern society both directly and indirectly, from the materials used in devices such as light-emitting diodes and fuel cells to the foundation of skilled manufacturing. Many of these advanced and energy-saving technologies take advantage of rare and precious metals. Although these materials have amazing properties, Japan, which is poor in resources, should avoid importing such precious metals. "I started studies on base metals about 15 years ago, especially focusing on zinc. In those days, hardly any chemists paid attention to zinc," says Masanobu Uchiyama, Associate Chief Scientist. He has continued to pursue his studies by combining organic molecules and base metals, such as zinc, seeking to create hybrid molecules with properties equivalent to those of precious metals, or molecules that can cause completely new chemical reactions; in this way he is seeking to make a unique contribution to society (Fig. 1).

Studying things that nobody else studies

"Although my grandmother seemed fine, she came down with an illness in the winter when I was a third-year student in high school. We were told that she had only a week to live," says Uchiyama, reflecting on the incident that stimulated him to become a researcher. "The doctor said to us, 'I am sorry, but very few cases of this disease have been reported. At present, there are no curative drugs because pharmaceutical companies are reluctant to create new drugs for which there are few patients, it is not profitable.' I remember how upset I was. I thought I would become a researcher and try to study things that nobody else would attempt to study, and make a contribution to society in that way."

Uchiyama went on to join a faculty of pharmaceutical sciences, and later, a chemical laboratory. He initially wanted to study in a biological laboratory because he was interested in life phenomena, but changed his mind on realizing that chemistry is absolutely central to understanding such life processes. He decided to pursue computational and theoretical chemistry, which take advantage of spectroscopy and computers, as well as synthetic chemistry. At that time, few researchers in the faculty of pharmaceutical sciences took this approach. In those days, biological phenomena were observed from the perspective of proteins or at the genetic level. However, Uchiyama thought that the day would surely come when biological phenomena would be investigated at the atomic level from the perspective of hydrogen and carbon atoms and electrons.

Metal elements as cheap as vegetables

In 1995 Uchiyama took a position as an assistant professor in a chemical laboratory at Tohoku University. "We were running short of research funds

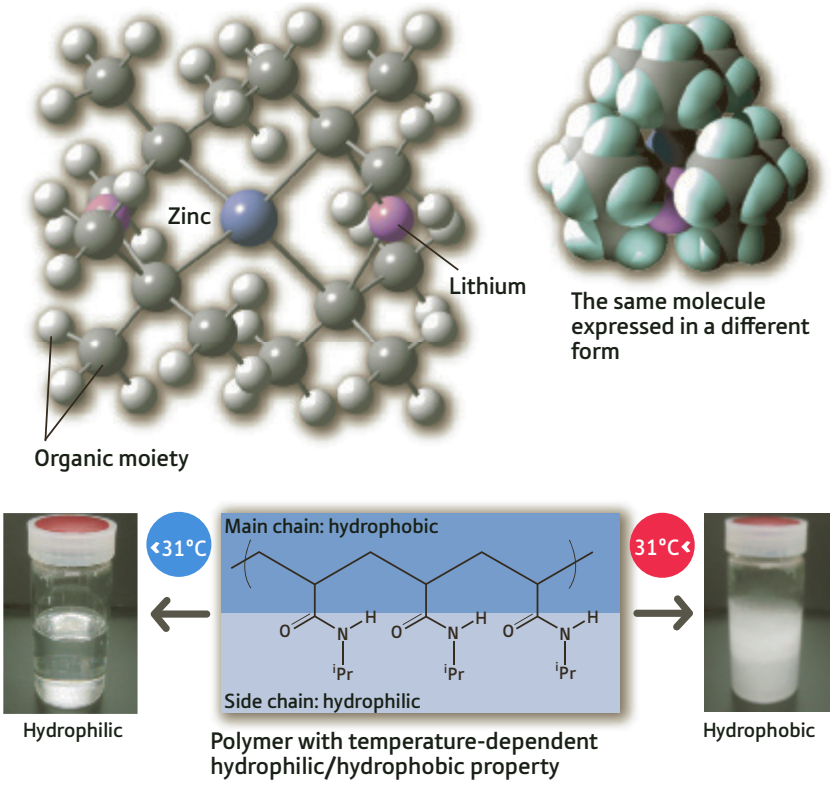

Figure 1: A new functional hybrid molecule combining metals and organic molecules.
Zinc and lithium elements are surrounded by four bulky organic molecules. This hybrid molecule was used as a catalyst to synthesize a polymer in water that changes from being hydrophilic to hydrophobic at 31 °C.

because the laboratory had just started when I joined it. We could not afford to buy expensive rare and precious metals. So I was asked to conduct research with inexpensive base metals such as zinc that are available anywhere. In those days, few chemists expected that base metals had the potential for new functions, and consequently little attention was being paid to zinc. I was fortunate, however, because I had learned in a class at the faculty of pharmaceutical sciences that zinc has various important roles in the body. I officially decided to study chemical reactions using zinc, and started my research life as an assistant professor, making efforts to answer the question, 'Why is this low-profile metal zinc necessary in the body?'"

Zinc is an essential metal in the body and is second only to iron in abundance there. For example, the body of a person weighing 70 kg contains on average about 2.3 g of zinc. Essential metals such as zinc can combine with proteins to fulfil important functions as enzymes, which promote chemical reactions in the body. "In the body, just seven metals—including iron, zinc and cobalt—cause the chemical reactions that support biological phenomena. These base metals are inexpensive, safe and available anywhere."

In contrast, many kinds of rare and precious metal are used in present high-technology products. For example, fuel cells, which are predicted to become one of the keys to saving energy, require platinum as the catalyst. "Per unit weight, the price of platinum is as expensive as a jet fighter, whereas many metal elements in the body are as cheap as vegetables." Rare and precious metals are expensive, and some people are concerned about their depletion. Thus, the 'element strategy' started as a national project, seeking to develop new molecules that can substitute for rare and precious metals.

"It is only recently that attention has focused on research into methods of deriving the same functions from base metals, which are cheap and available anywhere."

Combining organic molecules and metal elements

How do we derive these functions from base metals? "In the body, enzymes cause various chemical reactions by a 'hybrid method' that combines the functions of organic molecules such as proteins with those of metals."

On the basis of the mechanism of enzymes, Uchiyama and his team members have pursued their research by focusing on hybrid molecules (so-called 'ate' complexes), which are a combination of two different metals and organic molecules. Their research method involves mainly synthetic chemistry, spectroscopy and computational chemistry. "Whenever we try to observe chemical reactions in the body, we end up finding that they cannot be separated from the body. We depend on spectroscopy and computational chemistry to a large extent: spectroscopy uses light to explore the essence of substances, and computational chemistry, which is based on computer technology, helps us to make a precise estimate of the behavior of molecules and electrons (Fig. 2)."

Uchiyama and his team members used the advantages of computational chemistry to predict the possible emergence of a new function if zinc and lithium elements were surrounded by four bulky organic molecules (Fig. 1). "The molecule differs in shape from others because the metal at the center is completely surrounded by organic molecules. We attempted to synthesize the molecule, expecting something special to happen."

The hybrid molecule was used as a catalyst to synthesize a special polymer with new functions. A polymer is a long chain of connected units (monomers). The new functional polymer has a unique structure that consists of a hydrophobic organic component as its main chain and a hydrophilic organic component as its side chain. The polymer was found to change from hydrophilic to hydrophobic at 31 °C (Fig. 1). The polymer is now

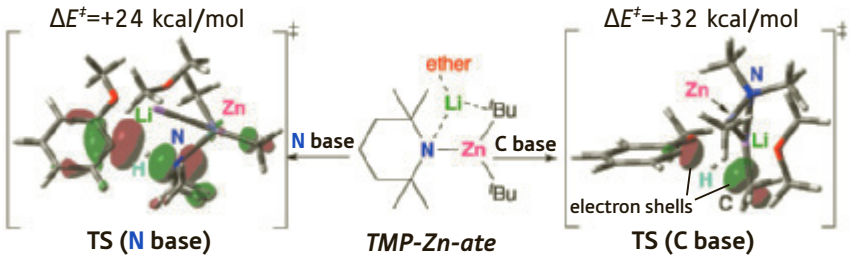

Figure 2: Visualization of chemical reactions by computational chemistry.
Reconstructing electron shells can serve to clarify the mechanism of chemical reactions.

attracting wide attention in various fields of science, including biotechnology.

"So far, no method has been reported that can synthesize these polymers in one step." The conventional catalysts used in polymer synthesis are so active that they can activate several portions of a monomer that should not be activated. The chemical reaction is therefore always accompanied by a step to introduce protecting groups that can block these portions, and by another step to remove them from the polymer when polymerization is complete. However, when thousands, or tens of thousands, of monomers are connected together, it is almost impossible to remove all the protecting groups from the polymer.

The new hybrid molecule that Uchiyama and his team members have developed by combining zinc and organic molecules is capable of activating specific parts of a monomer without the use of protecting groups. Furthermore, the molecule has allowed the synthetic reaction to be developed effectively even in water, whereas conventional reactions are always performed in an organic solvent. "Unlike in a test tube, there are many molecules of different kinds in the water of body cells. In addition, enzymes that can activate various molecules are considered dangerous for the body. What the body needs is enzymes that can activate specific portions of a specific molecule to create what is needed when certain conditions are satisfied. The molecule we have developed can serve as an enzyme that behaves in this way."

Conventional chemistry has sought to develop 'highly active' catalysts that can activate various kinds of molecules (functional groups). Such catalysts, however, can cause violent chemical reactions unless the temperature is properly controlled. Such reactions could lead to a fire or the generation of harmful by-products, and in some cases the reactions require large amounts of energy. "I believe that in the future, society will require 'highly selective' catalysts such as enzymes that can cause specific reactions only when certain conditions are satisfied."

Direct absorption of zinc by the affected part

Uchiyama and his team members are also advancing research into the use of zinc to create therapeutic agents. Lack of zinc in the body is known to be a cause of various diseases. For example, a zinc deficiency impairs the ability of the tongue to detect taste stimuli. "When you have a cold, you often lose your sense of taste. The lack of zinc in your body contributes to your loss of appetite."

Zinc is effective in treating hepatitis, glaucoma and skin cancers. "Nobody has yet conducted a study investigating how metals such as zinc could be absorbed directly by the affected part of a patient. Zinc is an inorganic, ionizable material, and it can be absorbed by the body only with difficulty because our cells are enclosed in lipophilic (fat-containing) membranes. By surrounding zinc ions with organic molecules, we think we will be able to develop an agent that will allow zinc to be absorbed effectively by the affected part in the form of eye drops or skin ointment."

Getting closer to the mystery of the blue color in flowers

Uchiyama and Atsuya Muranaka, a contract researcher, are also pursuing studies to chemically analyze the mechanism of highly functional molecules working in the body. "Recently we have seen the color blue used in various things from traffic lights to illumination devices. Producing a natural color blue, however, is still difficult. Why can flowers produce such

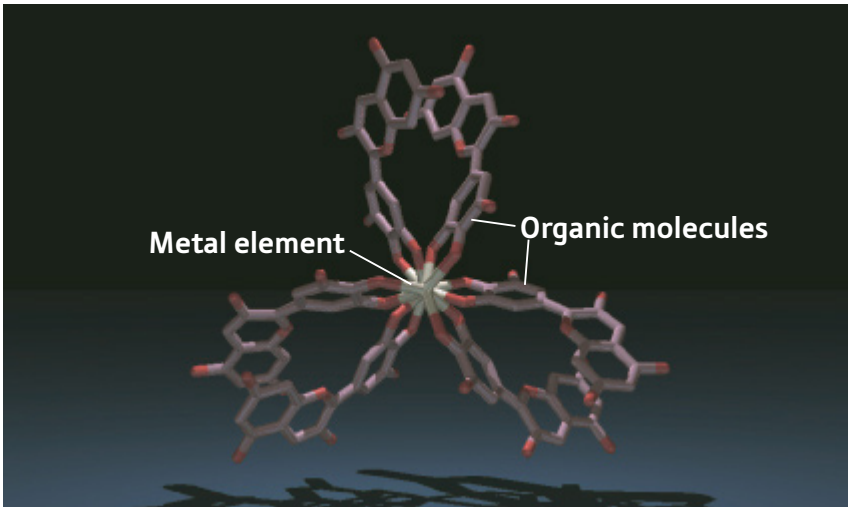

Figure 3: Molecules that create the blue coloration in flowers.
A metal element located at the center is surrounded by organic molecules. In flowers, it is known that the overlaps between the organic molecules contribute to absorbing the orange wavelengths from sunlight, thus producing the color blue.

Figure 4: Pigment molecules used in photosynthesis.
The overlaps between 18 flat molecules contribute to the absorption of sunlight at short to long wavelengths.

beautiful blues? We are exploring the mystery chemically."

Uchiyama and his team members focused on a certain molecule among the components extracted from a blue flower by an agricultural researcher (Fig. 3). Analysis by spectroscopy has shown that the molecule absorbs orange light. When orange light is removed from sunlight, what is left is a beautiful blue color. Thus, the molecule is producing the blue in the flower.

Now, how does the molecule absorb the color orange? "The molecule consists of two metals at the center and six organic molecules around the center. The six molecules are arranged with overlaps in the same way as a pinwheel. We separated these elements by computer simulation and attempted to investigate how individual elements absorb orange light; we found that they did not absorb light. This suggests that the six organic molecules can absorb orange light, leaving blue, only when they are all connected to a metal at the center and arranged around the metal like the six petals of a flower."

Chloroplasts, which are responsible for photosynthesis, include pigment molecules that absorb sunlight efficiently. The pigment molecule has 18 flat molecules with slight overlaps, forming a large circular molecule (Fig. 4). "Using chemical synthesis, we tried to connect similar flat molecules with a slight overlap and found that these molecules absorb light of a longer wavelength. This pigment molecule is known to be able to absorb light at short to long wavelengths efficiently because of the overlaps between the flat molecules. I believe that chemical analysis of the functional mechanism of these natural molecules will lead to a modification of the mechanism and the design of molecules with new functions."

Exploring functions from electrons

"In the days when I started my study of zinc, I had to present papers at conventions in rooms with few participants because almost no researchers showed any understanding of, or interest in, my studies. I feel most stimulated, however, while I am trying something that nobody has ever attempted, or studying something that is considered very difficult," says Uchiyama.

His motto is: "I want to be a researcher who will not be easily forgotten rather than a researcher who earns a name in the record of literature publication." "We can write lots of research papers if we study popular research themes, and I think that many researchers are happy to choose such research themes. Instead, I would rather work actively on low-profile themes that few researchers are interested in and themes in which study results are not expected quickly. Basic chemical research is one of these themes. I want to establish my own unique discipline of basic chemistry, and expand the discipline to every field of research surrounding basic chemistry by faithfully following my own curiosity."

One of his curiosities is the mystery of the functions of elements. "Why do elements have specific properties? Chemistry has not succeeded in explaining this mystery." The chemical functions of matter are considered to depend on the state of the electrons in the atoms. "For example, we can combine organic molecules and a metal element into a molecule with new functions. This is because electrons in the organic molecules are attracted to the metal element, resulting in a change in its electronic state. Furthermore, two elements in a similar electronic state, such as Cu(I) and Zn(II), show different properties. I want to take advantage of synthetic chemistry, spectroscopy and computational chemistry to explain the functioning of electrons based on their electronic states. I think this will lead to an understanding of biological phenomena at the molecular, atomic and electronic levels."

A completely new chemistry of elements is being explored through basic research into the roots of chemistry. This new chemistry will lead to the creation of new molecules having functions that can support our society in the future, and the creation of therapeutic agents for uncommon diseases. ■

About the researcher

Masanobu Uchiyama was born in Saitama, Japan, in 1969. He graduated from the Faculty of Pharmaceutical Sciences, Tohoku University, in 1993, and obtained his MSc in 1995 at the Graduate School of Pharmaceutical Sciences, the University of Tokyo. He was appointed as an assistant professor at Tohoku University in 1995, and then received his PhD in 1998 from the University of Tokyo. He rejoined the Graduate School of Pharmaceutical Sciences at the University of Tokyo in 2001 as an assistant professor, and was promoted to lecturer in 2003. From 2001 to 2004 he served concurrently on the three-year 'Synthesis and Control' project supported by the Precursory Research for Embryonic Science and Technology (PRESTO) program of the Japan Science and Technology Agency. He has been with RIKEN since 2006 as an associate chief scientist, and is director of his own research group. His research interests are in the area of synthetic organic chemistry based on organometallic, physical and computational chemistry.

Joint ISIS and RIKEN Muon Facility Developments Symposium

A Joint ISIS and RIKEN Muon Facility Developments Symposium was held on May 18 of this year in response to recommendations of RIKEN's International Advisory Committee. Hosted in the beautiful setting of the Cosener's House at the Rutherford Appleton Laboratory (RAL) in Oxfordshire, UK, located on the grounds of the mediaeval Abbey of Abingdon, the symposium aimed to strengthen collaborative research ties between RIKEN and RAL, and to deepen mutual understanding of muon science and the experimental technology used in its pursuit.

RAL's ISIS proton synchrotron facility, the site of experiments discussed at the symposium, houses two muon beam lines, one each for the RIKEN–RAL Muon Facility and the ISIS European Muon Facility. Over the past twenty years, the RIKEN–RAL Muon Facility has supported a wide range of research, including muon-catalyzed fusion, the use of muons in investigating the electromagnetic properties of various materials, and the use of ultralow-energy muon beams in surface science.

The Cosener's House symposium featured a total of nine presentations by representatives from the RIKEN–RAL Muon Facility and the ISIS European Muon Facility. RIKEN presentations focused on the construction of a new muon spin rotation (μSR) spectrometer having 600 plastic scintillation counters embedded with wavelength-shifting fibers, and on experimental high-pressure μSR apparatus. RAL presentations centered on an experimental high magnetic field μSR apparatus with 7T superconducting magnet, and on muon spin radiofrequency resonance equipment.

The assortment of presentations at the symposium provided an invaluable opportunity for participants to exchange views on experimental equipment currently under development, discuss plans for future facilities, and share experiences in overcoming common challenges. As the largest research collaboration project between Japan and the United Kingdom, the success of the RIKEN–RAL Muon Facility depends on these discussions, which play a central role in upholding the facility's track record of groundbreaking research in muon science.

Discussion of phenotype data sharing at the International Phenome Integration Meeting

An International Phenome Integration Meeting, sponsored by RIKEN and co-sponsored by the Society for the Study of Mammalian Genetics, was held in Kyoto, Japan, on July 12–13 of this year. The meeting focused on the integration of phenotype data produced in large-scale mouse phenotyping projects (mouse clinics) and the standardization of a wide range of parameters.

Following opening remarks by Tetsuro Toyoda, director of the RIKEN Bioinformatics And Systems Engineering division, the meeting continued with a discussion of efforts in countries around the world to establish mouse phenotype databases. An example of such efforts was presented by Joel Richardson of the Jackson Laboratory, USA, who outlined phenotype data integration in the Mouse Genome Informatics (MGI) database — an international resource providing integrated genetic, genomic and biological data. Paul Shofield of Cambridge University, UK, discussed the principles and challenges of sharing and integrating data and resources, and Hiroshi Masuya of the RIKEN BioResource Center outlined progress in data sharing between RIKEN and the European Mouse Disease Clinic (EUMODIC) program.

On the second day of the meeting, a roundtable discussion was held on phenotype data sharing, focusing in particular on the integration of data, such as minimum information requirements for reporting mouse phenotype data, as well as on plans to share more detailed phenotypic information via the Resource Description Framework (RDF) standard. The encouragement of free community access to data was also discussed. RIKEN, EuroPhenome, MGI and TCP came to an agreement to develop a portal providing minimal phenotype information. RIKEN will also establish an RDF channel for machine access from third parties. It is expected that the progress made through the development of these facilities will provide a basis for further data integration at an international level.

In the months and years ahead, decisions reached at this meeting will be further discussed and implemented, ultimately leading to systems better able to index and search large quantities of phenotype data, supporting cutting-edge advances in health treatment.

RCAI–JSI International Symposium on Immunology 2009

The fifth RCAI–JSI International Symposium on Immunology, hosted by the RIKEN Research Center for Allergy and Immunology (RCAI) in conjunction with the Japanese Society for Immunology (JSI), was held in Yokohama on July 9–10 of this year. Organized jointly by RCAI Director Masaru Taniguchi and JSI President Kayo Inaba, the symposium is part of a series of annual conferences aimed at providing a forum for discussions on cutting-edge immunological research. This year's event proved a great success, drawing more than 350 participants from around the world including 21 internationally recognized speakers presenting their research on cellular and genetic views on autoimmunity.

The symposium was divided into four sessions focusing on different aspects of autoimmunity: negative regulation of autoimmunity, the cellular and molecular basis of autoimmunity, genetics in autoimmunity, and inflammation and autoimmunity.

In the session on the cellular and molecular basis of autoimmunity, Kiyoshi Takeda of Osaka University presented his research on lamina propria dendritic cells (DC). Findings from his group indicate that ATP, the molecular unit of currency in intracellular energy transfer, also acts as a bacterial mediator in the development of T_H17 cells, a helper T cell subset thought to play a key role both in defending against certain pathogens and, conversely, in driving autoimmune diseases. This discovery is an important example of the interplay between intestinal microbiota and the host immune system.

In the later session on inflammation and autoimmunity, Toshio Hirano of Osaka University and RCAI described an 'IL-6 amplifier' that appears to be involved in the etiology of autoimmune and inflammatory diseases. Josef Penninger of the Austrian Academy of Sciences outlined his group's research on the RANK/RANK ligand (RANKL), which plays an important role in bone metabolism. In experiments using a knockout strategy, Penninger found that mutant mice without RANKL could no longer mount a febrile response to a variety of stimuli, and that humans with RANK deficiency, like the mice, also suffer from both life-threatening osteopetrosis and an absence of the physiologically important febrile response.

In bringing together cutting-edge immunological researchers, this year's RCAI–JSI symposium provided participants with a unique opportunity to share ideas and learn about the latest discoveries. Next year's symposium promises to reveal further advances in this rapidly evolving field.

Dr. Makoto Taiji
Group Director
Computational Systems Biology Research Group
RIKEN Advanced Science Institute, Wako, Saitama, Japan

Hello Taiji-san:

I hope this postcard finds you well. I've been thinking about the time I spent at your lab at RIKEN in 2005 and 2007 and the fruitful experience I had there.

I have fond memories of working with you and your team at the Computational Systems Biology Research Group in Yokohama. The experience the first time, I remember, was fantastic, which is why we made the second project, the three-year collaboration among RIKEN, Cambridge University, Kobe University and the University of Hakodate.

It really was the best possible environment for this kind of research—the support was great, everything worked perfectly, and the technology was the best in the world in this field. We all felt very relaxed and were able to concentrate on our research.

This is especially true of your MDGRAPE special-purpose computer system for molecular dynamics simulations—without this exceptional machine, my work in protein modeling would not have been possible.

The research we're doing now, applying our methodology to simulating biomolecular systems, we developed here in Cambridge, but I used your machine to do the first simulations, so my current work is a direct result from that.

Since then, based on our findings at RIKEN, we have made some significant advances in our understanding of spontaneous self-organization of biomolecular systems, such as protein folding and the self-assembly of membranes, which are critical to the function of these molecules.

I'm continuing to look in these directions, studying the dynamics of these complex biomolecular systems, and have found some very interesting new phenomena that basically confirm the presence of long-term memory in molecular systems, much longer than anyone anticipated. This work will provide a basis for modeling of this fundamental property of complex biomolecular systems, and we expect it to find widespread application in biology, medicine and biotechnology.

Please say hello to your family from us. Both of the times I visited RIKEN, I came with my wife and daughters, and my eldest, 13 at the time, attended a regular Japanese school—a bit challenging, since nobody really spoke English, and she didn't speak Japanese at the time, but she still had a great time. We still talk about our trips with your family to Mt. Fuji and other places, and the good times we had there.

I wish you all the best in the future.

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