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Training plants in self-defense

Screening of a chemical library reveals a bounty of molecules that could help protect food crops against infection

When plants become infected, they rally an immune response by producing the hormone salicylic acid (SA). This molecule not only marshals defenses at the immediate site of initial infection and destroys affected cells, but also triggers a distributed response that elevates resistance throughout the plant. Since SA governs a generalized pathogen response, this pathway represents a potentially useful target for chemically boosting the immunity of crops against a broad spectrum of threats.

Unfortunately, the SA response also stalls plant growth. Thus, scientists have been searching for compounds that indirectly increase plant ‘readiness’ against infection by priming the SA pathway for rapid activation, rather than directly switching on SA signaling. For example, soil treatment with the compound probenazole results in robust immune-priming, but only for a subset of crops. “Probenazole works well for rice, but less so for dicotyledon plants such as vegetables,” says Ken Shirasu of the RIKEN Plant Science Center in Yokohama. He notes that although other probenazole-like priming chemicals are commercially available, these too are largely limited to use with rice (Fig. 1).

To isolate and characterize new molecules that might offer a useful foundation for more broadly effective immune-priming agents, Shirasu teamed up with colleague Yoshiteru Noutoshi, now at Okayama University, Japan. Starting with a library of 10,000 commercially available molecules, they



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Figure 1: Immune-priming chemicals such as probenazole help protect rice against infection, but leave other critical crops vulnerable.

examined the extent to which pre-treatment with each could induce a defensive ‘self-destruct’ response in thale cress (*Arabidopsis thaliana*) cells infected with the bacterial pathogen *Pseudomonas syringae* (Fig. 2). Their work uncovered a broad family of candidate-priming compounds called ‘imprimatins’, which could ultimately provide plant scientists with the starting material for a far more effective armor against infection¹.

Different approaches to priming

The researchers initially selected two molecules that had no ill effect on healthy *Arabidopsis* cells, but induced rapid cell death following bacterial exposure. Because of their similar

effects, Shirasu and Noutoshi classified both molecules as imprimatins, but categorized them as two different subtypes based on clear differences in their chemical structure. The researchers then searched a public chemical database using imprimatins A1 and B1 as references; they identified an additional ‘relative’ for each, and named them A3 and B2, respectively. Pretreatment of *Arabidopsis* seedlings with each of the four compounds effectively suppressed bacterial growth, confirming the compounds’ effectiveness as immune-response primers.

The PATHOGENESIS-RELATED1 (*PRI*) gene is an early target for activation by SA, and as none of these four compounds induced *PRI* expression in

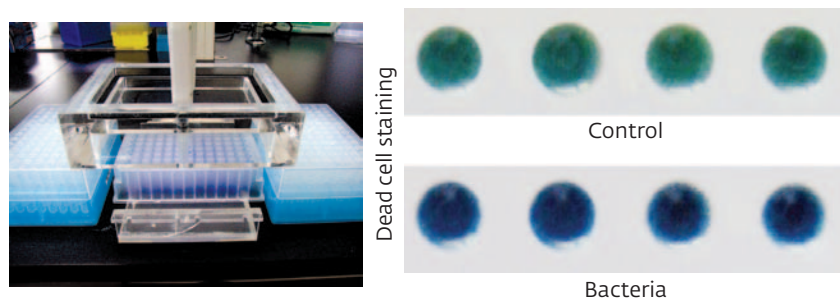


Figure 2: After pretreating *Arabidopsis* cells with a variety of different molecules (left), the researchers sought out compounds that induced cell death following pathogen infection (right).

uninfected plants, it was clear that they were not simply switching on the signaling pathway. Once infected, however, the treated plants showed increased *PR1* activity relative to controls. The researchers were able to link this response to elevated levels of SA.

Because of its growth inhibitory effects, plants gradually stop SA signaling via a process called glucosylation: an enzyme tacks a glucose sugar molecule onto SA to transform it into the inactive derivative SA-2-O- β -D-glucoside (SAG). The A and B imprimatins halt this transformation by inhibiting enzymes responsible for converting SA to SAG. Noutoshi and Shirasu identified two specific SA-glucosylating enzymes that appear to be primary targets for these compounds.

In a subsequent study, the researchers investigated another imprimatin identified in their initial screen². This molecule differed sufficiently from the others to merit its own category; Shirasu and Noutoshi dubbed it imprimatinC1. Similar to its counterparts, imprimatinC1 triggered cell death specifically in response to infection and thereby conferred bacterial resistance to plants. Further experiments, however, indicated that this molecule acts by a distinct mechanism. Unlike the A and B imprimatins, imprimatinC1 appears to act as a partial mimic of SA, and treatment with this compound directly stimulated *PR1* expression.

Careful chemical analysis revealed that imprimatinC1, and related imprimatin compounds, most likely undergo a transition to become metabolites that

trigger certain downstream events in the SA pathway. The researchers suggest that C1 may act by interacting with a specific subset of the various receptors that normally bind this hormone.

Just the tip of the beansprout

The molecules from this screen are unlikely to move directly into the agricultural world, as they currently lack the required potency. However, they do offer promising starting points. For example, the researchers were able to confer strong antibacterial protection to plants by inactivating the genes encoding the two SA glucosyltransferase (SAGT) enzymes targeted by the A and B imprimatins. This confirmed that direct inhibition of SA-to-SAG conversion is a viable approach for effective immune priming. Furthermore, ‘prodrugs’ such as imprimatinC1—which need to be metabolically processed before they become active—are often more stable than compounds that are already metabolically active. This is a desirable trait for agricultural chemicals. At least some of the SA-responsive pathways present in *Arabidopsis* seem to be evolutionarily conserved in other vegetable crops. This suggests to the researchers that the imprimatins may confer protection to the crops that are presently left vulnerable by probenazole.

Noutoshi and Shirasu are still examining several other promising candidates from their initial screen. “We have more to analyze, and the most interesting compounds have not yet been published,” says Shirasu. He notes that one of the major challenges has been

identifying molecules that are truly protective. Several of the candidates trigger cell death in infected cells while failing to stimulate an accompanying immune response. Fortunately, several molecules have made the cut, so the researchers are now working hard to characterize the ‘best of the best’. “We already know their target proteins,” says Shirasu, “and now we’re trying to elucidate their biochemical function.” ■

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2. Noutoshi, Y., Jikumaru, Y., Kamiya, Y. & Shirasu, K. ImprimatinC1, a novel plant immune-priming compound, functions as a partial agonist of salicylic acid. *Scientific Reports* **2**, 705 (2012).

ABOUT THE RESEARCHER



Ken Shirasu graduated from the University of Tokyo, Department of Agricultural Chemistry in 1988, and was awarded his PhD in genetics from the University of California, Davis, in 1993. He then served as a Salk-Noble postdoctoral fellow at the Salk Institute, USA, where he studied plant immunity. In 1996, he joined the Sainsbury Laboratory, UK, as a researcher, and in 2000 became a group leader. He joined the RIKEN Plant Science Center as a group director in 2005, and since 2008 has also held a position as a visiting professor in the Department of Biological Sciences at the University of Tokyo.

Magnets in which less is more

A new class of magnets in which fewer electrons mean stronger magnetism could lead to new energy-saving technologies

Magnetism in semiconductors arises mainly through the interaction of magnetic ions and electrons. Normally, the more electrons that contribute to the magnetism, the stronger the magnet. However, researchers at the RIKEN Advanced Science Institute at Wako have now discovered a magnet that becomes weaker as the number of electrons increases¹. The work has implications for both fundamental science as well as future energy-saving technologies.

“Our results have verified the most basic features of this long hypothesized magnetic state—the stability of the magnet without excess electrons,” says research team member Joseph Checkelsky. “A potential byproduct of such an unusual state of matter is the presence of an energy-dissipation-free electrical mode for low power electronic applications,” he says.

The new magnet, made from bismuth telluride to which the magnetic material manganese is added, belongs to a recently discovered class of materials known as topological insulators. In these materials, electrons on the surface behave very differently to those in the rest of the material. For example, they do not scatter easily, which has advantages for electronic applications. Electrons in the surface state also occupy a special electronic state, the so-called Dirac cone (Fig. 1, left). In the magnetic topological insulator, the electrons near the Dirac point are responsible for the material’s magnetic properties. However, only a limited number of electrons can be in this surface state. As

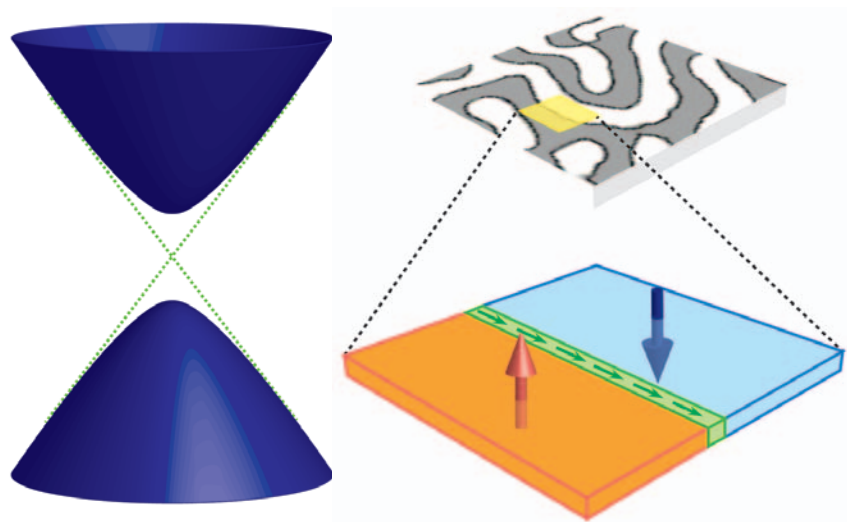


Figure 1: Magnetic topological insulators. The electronic states of the magnetic topological insulator (blue) are slightly different to those of the original Dirac cone (green lines) (left). At the interface between two magnetic domains (blue and red), a current with almost no losses can flow (right).

electrons are pumped into the system, the crucial electronic states are filled and the magnetism is weakened.

The researchers observed this effect by controlling the injection of electrons into the material. At low electron densities the critical temperature above which magnetism disappears is higher than for the case of a higher number of injected electrons. Above a certain threshold the magnetism even disappears completely.

Another effect occurs at the interface between magnetic domains of different orientation on the surface that form a kind of patchwork within magnets. At these domain walls, magnetism falls to zero, which brings out another property

of magnetic topological insulators—the electric currents flow without loss around the edges, in this case along the domain walls (Fig. 1, right). Thus, the conductivity of the sample is also influenced by magnetism and therefore the carrier concentration.

Controlling the quality of the material is an issue for the development of actual applications. Checkelsky believes new developments in thin film technology could be one way to facilitate the transition to applications. ■

1. Checkelsky, J.G., Ye, J., Onose, Y., Iwasa, Y. & Tokura, Y. Dirac-fermion-mediated ferromagnetism in a topological insulator. *Nature Physics* **8**, 729–733 (2012).

In it for the long haul

Longer transmission lengths boost spin electronic applications

All modern electronics are based on the fundamental concept of electrical charges moving through a circuit. There are, however, alternative schemes that promise faster and more efficient types of computing. An example is spintronics, which is based on the use of the electron's magnetic property—its spin—instead of its electric charge.

Researchers at the RIKEN Advanced Science Institute in Wako have moved a step closer to realizing spintronic devices by showing that 'spin information' in various materials can travel much further than previously thought¹. "Our experimental results could be useful for developing new devices such as the spin transistor and spin-logic devices," explains Yasuhiro Fukuma from the Quantum Nano-Scale Magnetics Team.

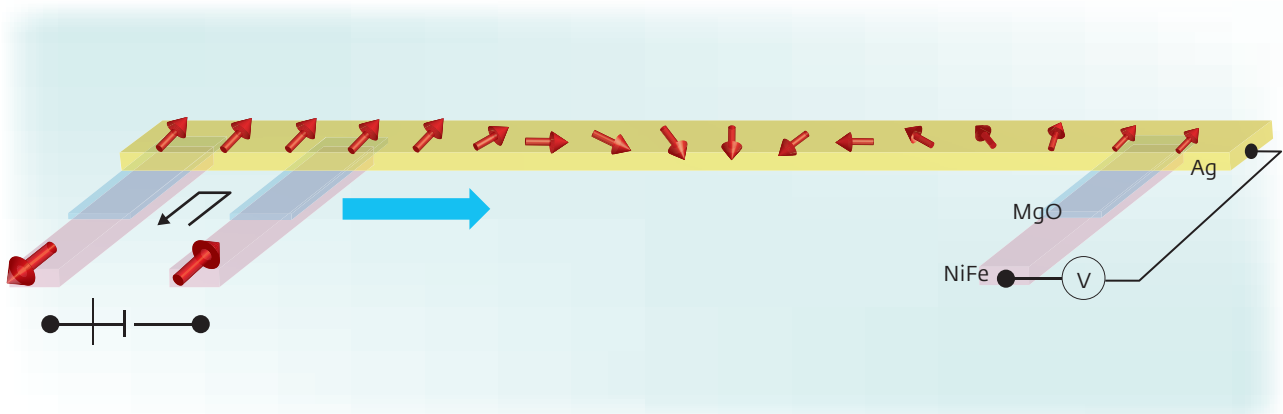
The basis for spintronics is to use the direction of the electron spins—up or down—in computing. The difference to conventional electronics is that

there is no need for electrons to travel in order to pass on information about spin. Instead, the polarization of spin in one direction cascades along the device as the electrons influence their neighbors, one by one. However, measuring this spin diffusion in detail has been challenging. The spin signals are small and difficult to detect because their creation in spintronic devices is generally very inefficient. The research team has solved this problem by using two magnetic contacts to inject the spin signal into a thin silver wire (Fig. 1), enhancing the amount of spin polarization present in the wire. This degree of polarization can then be measured at several distances along the wire by using a third contact that picks up the signal.

In the experiments, spin currents could even be detected at distances of over 10 micrometers. Even though the absolute magnitude of the spin signal

may have decreased, the quality of the spin precession signal, the so-called coherence, is improved as travel distances increase. This is due to the fact that the collective coherent precession of the spins has a beneficial effect on the overall spin polarization over time, which recovers the output signal of the precession at greater distances. Moreover, the coherence of the spin precession as a function of the travel distance shows a universal behavior that is independent of the material used. This is welcome news for the realization of future devices, says Fukuma. "The universal behavior will be beneficial for designing spin current-based memory and logic devices by using a variety of metallic and semi-conductive materials, including graphene." ■

1. Idzuchi, H., Fukuma, Y. & Otani, Y. Towards coherent spin precession in pure-spin current. *Scientific Reports* **2**, 628 (2012).



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Figure 1: Measuring spin propagation. Two magnetic contacts (left) are used to create a spin polarization (red arrows) at one end of a silver nanowire (yellow), whose value after travelling a defined distance is measured by a third contact.

Neutrons get back together

A method for reversing the velocity spread in neutron beams should boost the accuracy of precision experiments

Neutrons offer a combination of properties that make them exquisitely sensitive and versatile sensors. They are charge neutral, which means they do not interact with electric fields, and they possess a magnetic momentum, making them perceptive to magnetic fields. To achieve the highest sensitivity in neutron-based experiments, researchers aim to produce very dense neutron beams. But they also have to ensure that the density does not decrease as the neutrons are transported from source to target. Addressing this latter issue, an international research team including Yoshichika Seki of the RIKEN Nishina Center for Accelerator-Based Science, Wako, has demonstrated a method for refocusing a neutron beam that has lost its initial density¹.

As neutrons exit their source, they behave in a similar way to marathon runners. Initially they are densely packed but gradually they spread

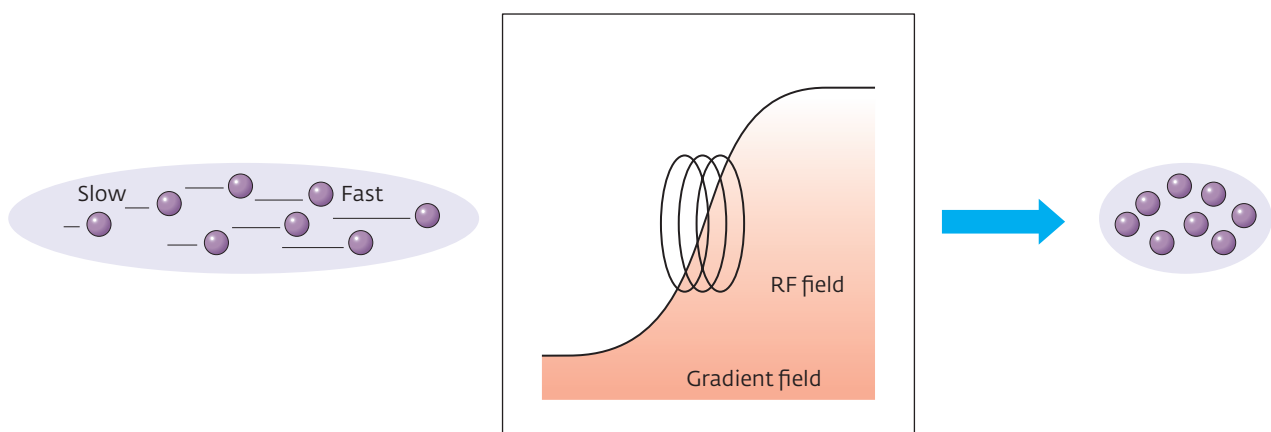
out over the course. For neutrons, this decrease in density is difficult to prevent. Conventional focusing techniques fail, precisely because neutrons carry no charge and so cannot be controlled with electric fields. Seki and colleagues have now found another way. Consider the marathon runners: if after some time into the race all athletes are asked to return to the starting line, then the advantage of the faster runners will become a disadvantage. By the time the runners are back at the starting point, they will all be bunched together again.

Seki and his colleagues used a similar trick to undo the velocity spread in a neutron beam. Their ‘runners’ moved at a velocity of a few meters per second through a magnetic field. As they did so, their magnetic moments could be flipped using radiofrequency fields, causing a change in energy—and thus in velocity. When the strength of the magnetic field changed within the

region through which the neutrons passed, the flipping could be done in a way to ‘punish’ the fast neutrons that have already established an advantage, while ‘rewarding’ the slow ones (Fig. 1). Eventually, the neutrons regained their initial density.

The new method will help in experiments to search for the neutron’s so-called electric dipole moment, which in turn could provide a clue about the origin of matter in the Universe. The researchers expect the technique to also be useful in practical applications. “Nowadays neutron beams are widely employed in material science and in the medical field, so our method should have a very broad impact,” says Seki. ■

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Figure 1: An ensemble of dispersed neutrons (left) in a neutron beam can be regrouped by passing the beam through a spatially varying magnetic field and flipping the neutrons at suitable times with a radiofrequency (RF) field. Eventually the neutrons will regroup tightly (right).

Anomaly approximated

A ten-year study provides an extraordinary level of accuracy to estimate intrinsic magnetic properties of two subatomic particles

The electron is found in every atom and plays a key role in almost every chemical reaction. So, a complete understanding of its physical properties is vital. Researchers from the RIKEN Nishina Center for Accelerator-Based Science, together with their colleagues from Nagoya University, Japan, and Cornell University in the US, have completed the most precise calculations of the magnetic properties of the electron¹ and a similar, heavier particle known as a muon². Their results provide a stringent test of physicists' understanding of the subatomic world.

The most accurate theory for describing elementary particles that scientists have yet created is called the 'standard model'. This model divides fundamental particles into three broad categories: quarks, which make up most of the mass around us; gauge bosons, which are responsible for forces that hold this matter together; and leptons, which include both the electron and the muon. Leptons are characterized by their mass, their electric charge and their magnetic moment—a measure of the particle's intrinsic magnetic properties.

British scientist Paul Dirac predicted that the magnetic moment of leptons should be exactly 2. However, scientists have known for a long time that the actual value varies very slightly from this perfect number because of quantum effects. RIKEN researcher Makiko Nio and her colleagues have performed state-of-the-art computational analysis of this anomalous magnetic moment of both the electron and the muon.

Particle physicists describe the behavior of elementary particles using

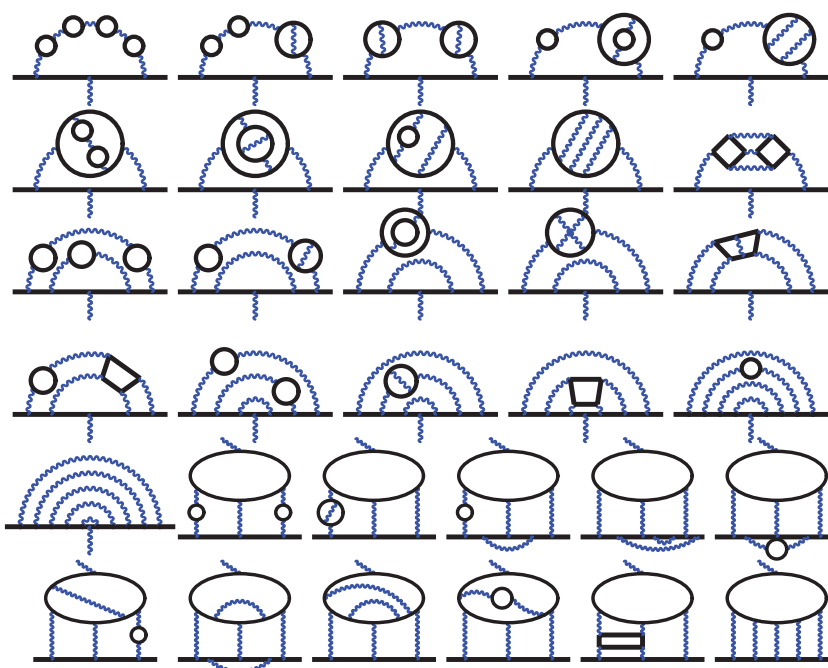


Figure 1: Calculations incorporating a complete set of Feynman diagrams give the most accurate estimates of the anomalous magnetic moment of the electron and the muon to date.

pictorial representations known as Feynman diagrams (Fig. 1). Nio and her co-workers included in their calculations all of the 12,672 Feynman diagrams relevant to the anomalous magnetic moment of the electron, far more than any previous work. "To handle these enormous and tedious calculations, we developed an automated code-generating system, and carried out computations using supercomputers at RIKEN for almost 10 years," says Nio. They were thus able to provide a value for the electron anomalous magnetic moment that was accurate to 0.24 parts per billion. "With these results we have also obtained the world-best value of the fine-structure constant, which determines the strength of electromagnetic interactions," she says.

The researchers also performed similar calculations to provide a more accurate estimation of the muon anomalous magnetic moment. Their improved value confirms the previous result which does not fully agree with that expected from the standard model. The researchers believe that this discrepancy between the measurement and theoretical prediction may lead to new physics beyond the standard model of elementary particles. ■

1. Aoyama, T., Hayakawa, M., Kinoshita, T. & Nio, M. Tenth-order QED contribution to the electron $g-2$ and an improved value of the fine structure constant. *Physical Review Letters* **109**, 111807 (2012).
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Seeing symmetry surfacing

A novel form of electron–molecule interaction on metal surfaces provides fresh prospects for molecular electronics

When a piece of metal is cooled down, it becomes easier for electrons to move through the material. Therefore, the electrical resistance of a metal normally decreases with lower temperatures. However, in the presence of magnetic impurities—tiny imperfections in the material—the resistance increases again below a certain temperature. This phenomenon has to do with how electrons scatter from the impurity and is generally known as ‘the Kondo effect’. It can come in many forms—one of which has now been discovered by Emi Minamitani of the RIKEN Advanced Science Institute, Wako, and co-workers at the University of Tokyo, Japan, and Osaka University, Japan. They have shown that in the case of magnetic molecules deposited on a metal surface, a Kondo effect appears that reflects the local symmetry of the molecule at the adsorption site¹.

The team studied the molecule iron phthalocyanine, which they deposited on a gold surface (Fig. 1). The Kondo effect had been reported before in this system but a mystery remained—the effect depended on where exactly on the surface the molecules were located. When the iron atom of the molecule was on top of a single gold atom, the Kondo effect was much stronger than when the iron built a bridge between two gold atoms. Minamitani and her co-workers have shown that this unexpected adsorption-site specificity is due to the interplay between the geometry and symmetry of both the molecule and the surface. Only in the ‘on top’ case, the symmetry of the molecule is preserved, leading to a more pronounced Kondo effect.

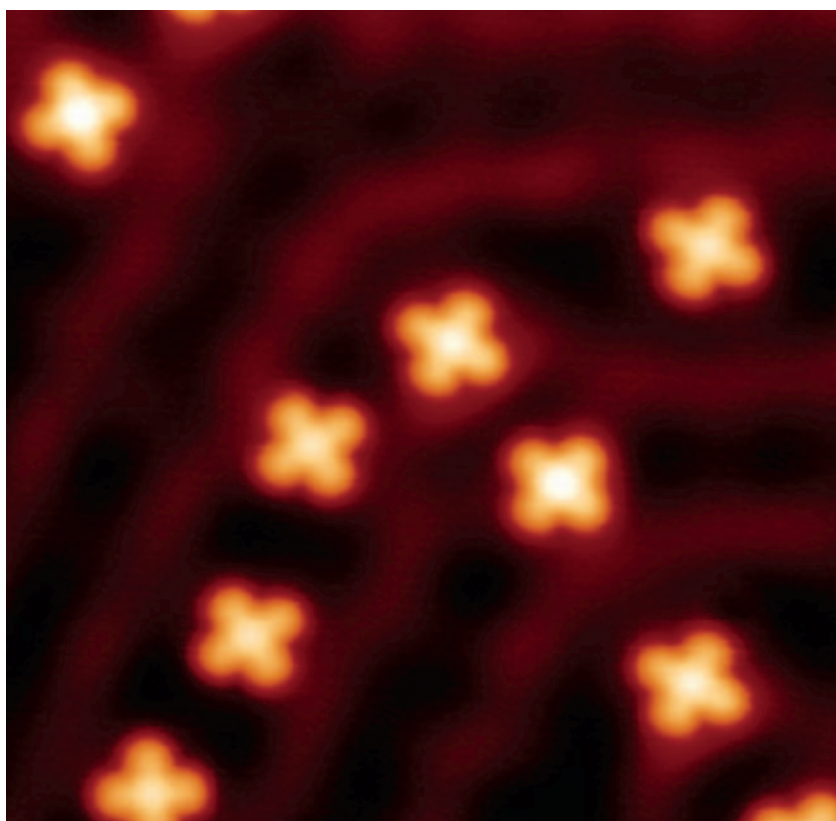


Figure 1: A scanning-electron micrograph of iron-phthalocyanine molecules (seen as bright crosses) adsorbed on a gold surface. The image size is 15 x 15 nanometers.

So far, the researchers have shown the new manifestation of the Kondo effect for one specific type of molecule–surface combination, but the phenomenon should also be present in other systems where magnetic molecules are deposited on metallic surfaces. “There are many candidate systems in which the Kondo effect and variants of it should appear,” says Minamitani. Moreover, the geometry of the molecule-on-surface system allows researchers to tune the Kondo effect by chemical or mechanical manipulation.

“Our next step is to find ways of controlling and tailoring such novel types of

Kondo systems,” says Minamitani. And while the Kondo effect is a low-temperature phenomenon that may not affect devices operating at room temperature, Minamitani expects that their work will provide a route to exploring fundamental phenomena in the field of molecular electronics. “Our findings suggest that the electronic states of molecules exhibit a richer variety of behaviors than we expected,” she says. ■

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A new leaf in the carbon capture playbook

‘Green chemistry’ using carbon dioxide and low-cost catalysts provides a new way of producing potent carbon–boron synthetic reagents

Because carbon dioxide (CO₂) gas is a freely available resource, there are concerted efforts worldwide to convert this molecule into a chemical feedstock. Zhaomin Hou and colleagues from the RIKEN Advanced Science Institute in Wako have made important progress toward this goal by developing the first protocol for attaching both CO₂ and boron atoms to unsaturated carbon–carbon triple bonds¹. This procedure uses inexpensive organic–copper catalysts to construct valuable ‘building blocks’ for chemists under mild, one-pot conditions.

The strong double bonds inside CO₂ make this molecule particularly inert and hard to use in most chemical reactions. Current tactics have focused on using transition metals to catalyze addition of electron-rich organic ‘nucleophiles’ to CO₂’s central carbon atom. This technique has successfully generated simple carboxylic acids. However, production of more complex substances containing non-hydrocarbon atoms has remained mostly out of reach.

Hou and his team used a groundbreaking approach to help turn CO₂ into organoboron reagents—valuable synthetic compounds because of the wide number of transformations possible at carbon–boron bonds. First, they turned alkynes, molecules with carbon–carbon triple bonds, into nucleophiles. Nucleophilic species are highly reactive with many types of chemical groups but they are also difficult to control. To achieve the necessary precision, the team used N-heterocyclic carbene (NHC) copper complexes, a hybrid organic/inorganic

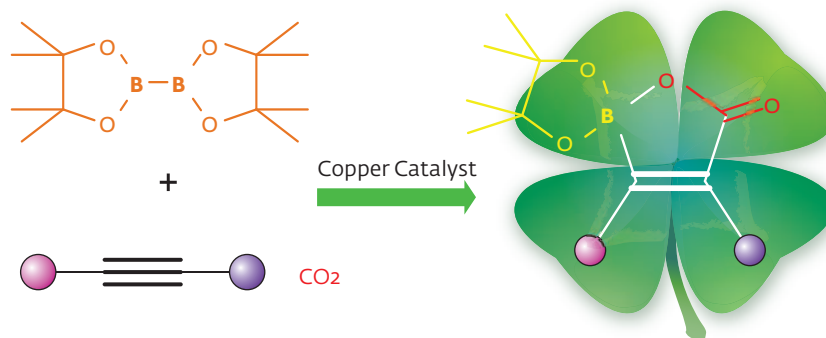


Figure 1: In a new demonstration of ‘green chemistry’, researchers have used copper catalysts to turn waste carbon dioxide (CO₂), alkyne molecules and boron complexes into a uniquely shaped ring system suitable for organic synthesis.

system with a strong track record of catalyzing CO₂ additions².

X-ray experiments revealed that the strategy had paid off: NHC–copper complexes could indeed catalyze the addition of CO₂ and diborane molecules to alkynes through a three-step catalytic insertion process. This reaction generates a final product with a unique, previously unknown cyclic structure containing a boron atom, a carbon–carbon double bond and a carboxyl group that the authors termed ‘boralactone’ (Fig. 1).

By tweaking the structure of the NHC–copper catalyst, the researchers were able to apply the technique to a wide range of alkyne-type molecules with no side reactions. Intriguingly, the catalyst delivered the same geometric arrangement—high regio- and stereoselectivity—no matter which substituents were attached to the carbon triple bond. Hou explains that this advantageous

behavior occurs because the diborane–catalyst complex always attacks the alkyne bond from a specific direction due to electronic interactions. Furthermore, the cyclic boralactone helps to drive this selectivity.

“Our reaction may serve as an attractive method for the synthesis of multifunctional alkenes, as it uses CO₂ and easily available alkynes as building blocks with a relatively cheap copper catalyst,” concludes Hou. ■

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Oxide flips from open to closed

A transistor made from vanadium dioxide could function as a smart window for blocking infrared light

The transistor is the ultimate on-off switch. When a voltage is applied to the surface of a semiconductor, current flows; when the voltage is reversed, current is blocked. Researchers have tried for decades to replicate these effects in transition metal oxides by using a voltage to convert the material from an insulator to a metal, but the induced change only occurs within a few atomic layers of the surface.

Now, Masaki Nakano and colleagues at the RIKEN Advanced Science Institute in Wako have discovered that applying a voltage to a vanadium dioxide (VO_2) film several tens of nanometers thick converts the entire film from an insulator to a metal¹. The findings point to the specific material properties needed to make such devices work. They may also lead to new types of ‘smart’ technology.

The electronic properties of transition metal oxides can be tuned by changing their chemical composition or temperature. For example, VO_2 is an insulator at room temperature, but heating it or replacing a small fraction of the vanadium atoms with tungsten (an electron donor) causes a phase transition where the vanadium ions, which are paired up at low temperature, unfasten into a different crystal structure in which electrons are mobile. In principle, applying a positive voltage to the surface of an insulating VO_2 film can accomplish the same effect by inducing electrons to the surface, making this region metallic.

Researchers have assumed that this charging effect would be limited to a few atomic layers just below the surface because the excess of electrons cancels

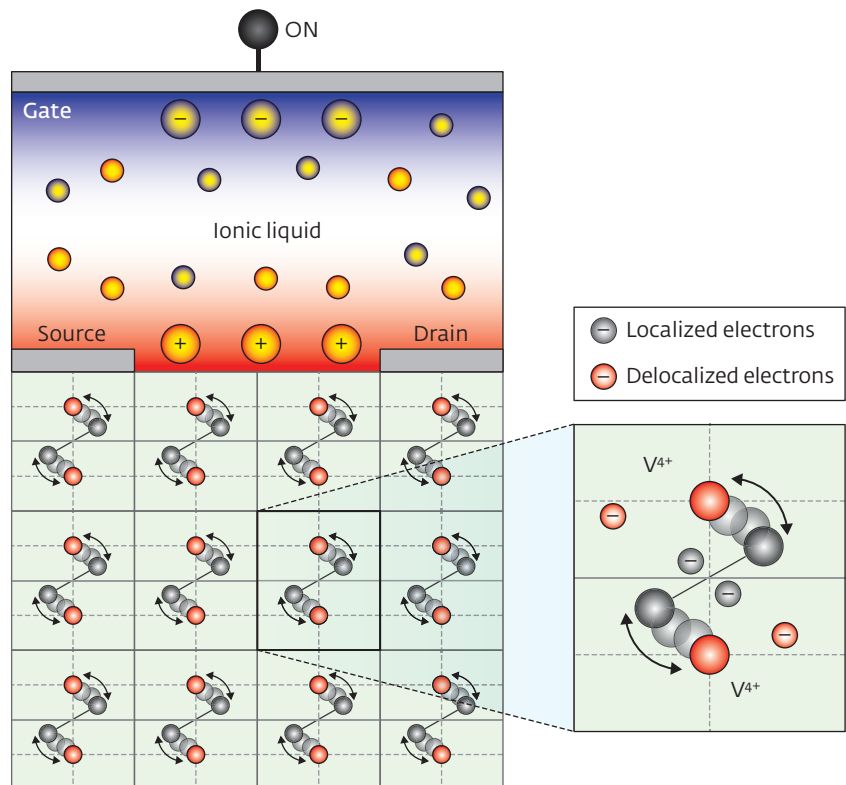


Figure 1: Below 47 °C, the vanadium ions in a film of VO_2 pair up into a different crystal structure and the electrons no longer conduct freely. The transition can be reversed with a positive voltage, applied at the top of the film. The voltage induces electrons to move to the region near the surface, which restores the high-temperature structure and metallic behavior throughout the entire film.

out the applied electric field (an effect called screening). But Nakano and his colleagues found that the excess electrons were enough to ‘trigger’ the crystal structure change associated with metallic behavior (Fig. 1). “The surface lattice distortion propagates through the entire film, followed by an electronic phase transition inside the bulk region,” he says. The voltage-induced transition decreases VO_2 ’s resistance by a factor of 100.

The team is actively seeking other materials like VO_2 , as well as technological applications. One is a heat switch. Since temperature determines whether VO_2 is a metal or an insulator, it also

determines the frequency of light the material absorbs. VO_2 -coated glass could therefore act as a ‘smart window’, passing or blocking infrared light depending on the temperature outside. “Normally, this switching temperature is fixed,” says Nakano. “Our device adds electrical switching functionality to a smart window, which is very promising for energy-saving applications.” ■

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Protein modification marks cancer

The discovery that a specific protein modification is important in cancer development could lead to new approaches for treating the disease

All proteins are made from chains of amino acids and their functions can be modified by adding small molecules to specific amino acids. One such modification is the addition of a methyl group, which is made of one carbon and three hydrogen atoms, that is attached to the amino acids lysine or arginine. This methylation occurs in many proteins, but its function is unclear.

Heat-shock protein 70 (HSP70) is one protein that is methylated on a specific lysine amino acid. HSP70 is found in all animals and plays a role in many biochemical processes within cells. Other HSP70 modifications have been directly linked to diseases such as cancer and Parkinson's disease.

Now, an international team, including researchers at the RIKEN Advanced Science Institute, Wako, has demonstrated that lysine methylation has similar implications¹.

Staining HSP70 with fluorescent markers showed that the methylated protein was concentrated in the chromosomes, while the unmethylated protein was spread throughout the cell, outside of the chromosomes (Fig. 1). By capturing the methylated protein from cells and identifying the proteins that came with it, the team found an important interaction with an enzyme called Aurora kinase B (AURKB).

"AURKB is an important protein that promotes cell cycle progression and can encourage cancer cell proliferation," explains co-author Minoru Yoshida. "Indeed, its expression is often deregulated in cancer and its inhibitors have been developed for cancer therapy."

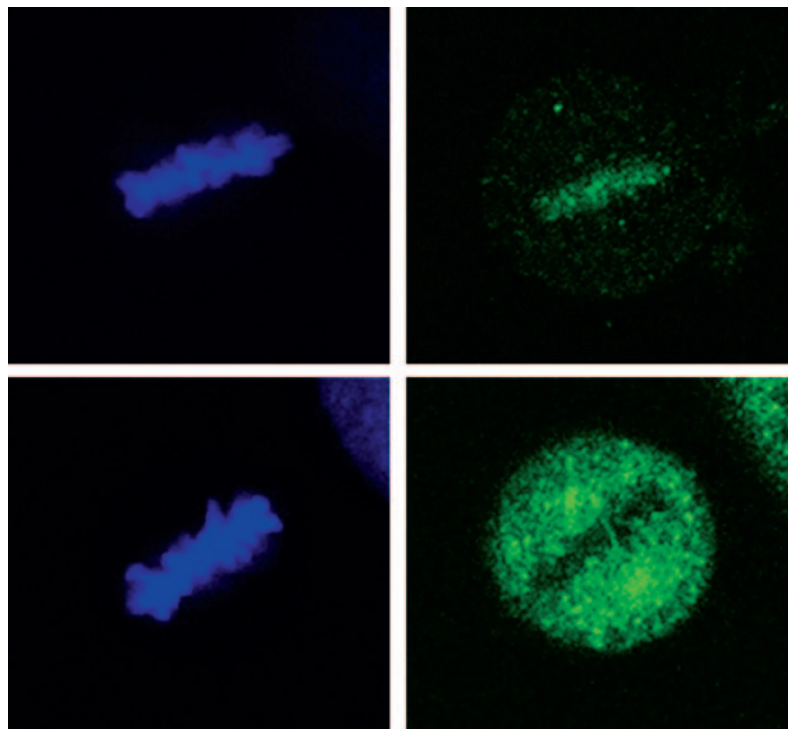


Figure 1: Visualising DNA (blue) and HSP70 (green) during cell division shows that methylated HSP70 associates with DNA (top row), but unmethylated HSP70 is distributed throughout the rest of the cell (bottom row).

AURKB activity was enhanced by its interaction with HSP70, and introducing mutant HSP70 into cultured cells showed that this interaction altered cell growth: HSP70 methylation accelerated cell growth and division. Having found that levels of methylated HSP70 are higher than normal in cultured tumor cells and tissue from human cancer patients, the team concluded that the modification of the protein is important in the development of cancer.

Despite these findings, Yoshida says there is still much to understand about HSP70 methylation: "It is necessary to do more detailed analyses of why HSP70 is highly methylated in cancer cells, how it is specifically localized in the

nucleus, and how it activates AURKB," he says. But he also thinks that this work provides a new tool in the battle against the disease. "We expect that methylated HSP70 will be a remarkable new cancer diagnosis marker," he says. "As for therapy, not only AURKB inhibitors but also HSP70 methylation inhibitors or a combination of both will be new chemotherapeutic strategies in future." ■

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Understanding the role of the first responder

A recently identified receptor helps trigger the first wave of immune response and also facilitates the launch of subsequent defense mechanisms

B cells can generate different ‘classes’ of antibodies, each of which carries a specific type of protein chain that triggers a specific downstream cascade of immune responses. Immunoglobulin M (IgM) antibodies, which are the first on the scene, play a particularly important role in fighting off pathogen infection.

It took scientists nearly 40 years to finally isolate FcμR, a receptor molecule that enables immune cells to respond to IgM. Hiroshi Ohno’s team at the RIKEN Research Center for Allergy and Immunology (RCAI) in Yokohama was among the first to identify the gene encoding this receptor, and he and his RCAI colleague Ji-Yang Wang recently set out to characterize its function by generating a strain of FcμR-deficient mice¹.

FcμR is predominantly produced by B cells in mice, and Ohno and Wang did not observe any significant differences in overall B cell numbers in the genetically modified animals. When the researchers triggered an immune response in B cells from these mice, however, they found that these cells divided more slowly and subsequently began dying off. FcμR-deficient mice also generated significantly fewer plasma and memory B cells (Fig. 1), which are respectively responsible for antibody secretion and coordinating the immune response to recurring infection. Collectively, these results indicate that although this receptor is not required for B cell maturation, it is likely to play a critical role in mounting the initial immune response in the presence of an infectious threat.

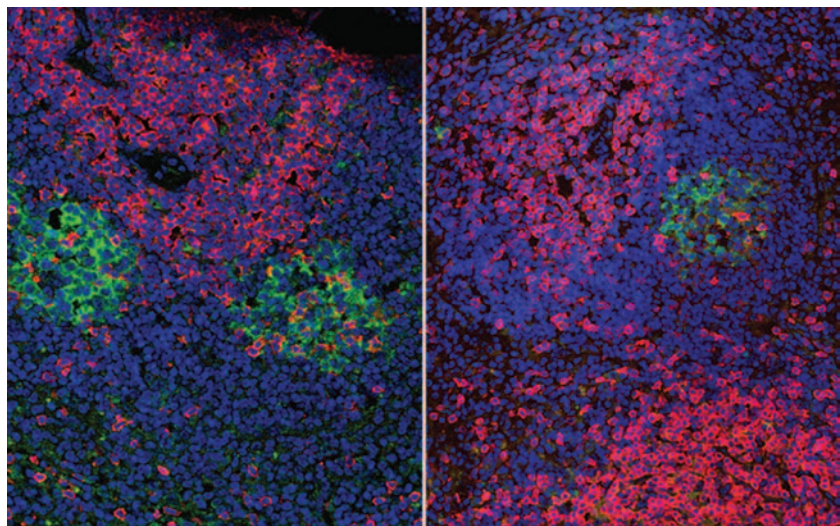


Figure 1: In wild-type mice, immune stimuli cause B cells (green) to interact with T cells (red) within structures known as germinal centers (left), giving rise to antibody-secreting plasma cells and memory cells that facilitate long-term immunity. In mice lacking FcμR, however, these germinal centers are greatly diminished (right). Blue dye indicates cell nuclei.

As the FcμR-deficient mice grew older, they produced sharply elevated numbers of antibodies targeting host tissues, similar to those produced in autoimmune conditions like lupus or rheumatoid arthritis. Such ‘auto-antibodies’ are of the immunoglobulin G (IgG) subtype, which appears later in the immune response relative to IgM, suggesting that FcμR is required for B cells to properly manage the shift from IgM- to IgG-mediated immunity. “Our work defines and closes an auto-regulatory loop that ensures adequate B cell activation during the early phase of an antibody response, yet prevents excess activation at the late phase,” explains Wang.

These results do not tell the entire story about IgM signaling, which also

employs a parallel network known as the complement pathway, but Wang and Ohno believe their findings could offer clinical opportunities for patients with malfunctions in IgM production as well as other immune disorders. “FcμR might contribute to human chronic lymphocytic leukemia (CLL) and, if so, inhibition of FcμR signaling by inhibitors or blocking antibodies could offer therapeutic benefit,” says Ohno. ■

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A natural sense of rhythm

Shifting levels of molecules in the blood provide a snapshot of internal ‘body-time’, helping doctors to assess disorders linked to circadian rhythm malfunctions

Anybody who has worked the overnight shift will testify that sometimes the time displayed on the clock is not the same as the one in your head. This disconnect is not merely perception; many physiological functions follow an internal chronological rhythm. ‘Body-time’ can profoundly affect overall health and even the response to therapies for cancer and other disorders.

By charting rising and falling concentrations of molecules in the bloodstream, researchers led by Hiroki Ueda of the RIKEN Center for Developmental Biology in Kobe and Tomoyoshi Soga of Keio University, Japan, have developed a first-generation ‘metabolite clock’ that enables easy monitoring of the human body’s internal timetable¹.

“The goal of our study was to develop a method that would be available for clinical situations,” says Takeya Kasukawa, a researcher in Ueda’s laboratory and lead author on the study. Doctors can track physiological rhythms via changes in levels of the hormone cortisol, but this is a laborious procedure as subjects have to stay in the hospital for a few days and have blood taken every few hours. By using mass spectrometry—a technique for identifying and quantifying the various components within a mixed sample—Kasukawa and his colleagues were able to characterize temporal changes in levels of metabolic by-products in the blood.

The researchers had previously generated such a metabolite timetable in mice² and attempted to replicate this success with six human volunteers. For a week, these subjects lived on a 28-hour

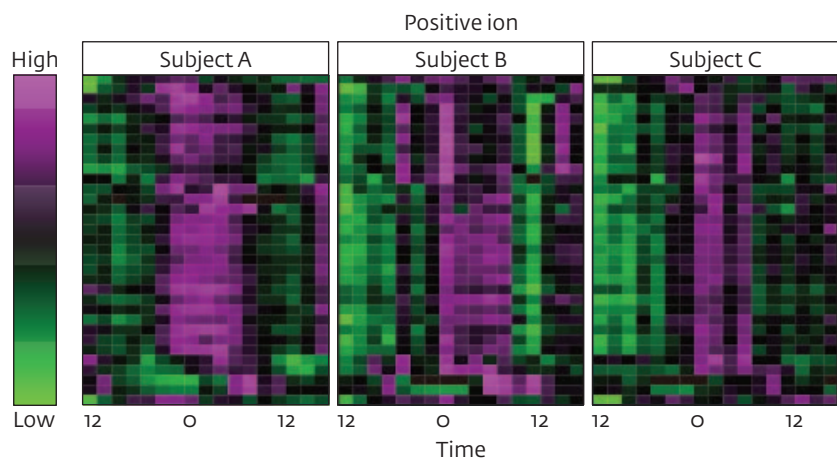


Figure 1: By analyzing the ionic fragments generated through the process of mass spectrometry, it becomes possible to identify the molecules contained within a complex mixture. Analysis of human blood via this technique reveals dozens of metabolites whose levels cyclically rise (purple) or fall (green) with the body’s internal clock.

cycle that desynchronized their internal time relative to the normal sleep/waking schedule. The researchers used blood samples collected from three of these individuals prior to the desynchronization process to generate a timetable, and identified dozens of metabolites whose levels shifted cyclically (Fig. 1). They then used these metabolite signatures to determine the post-desynchronization body clock in all six individuals.

The results proved remarkably accurate compared to conventional cortisol measurements, with a difference generally not exceeding a few hours, even with one subject whose body-time was especially disrupted relative to the others. Kasukawa expects that future iterations of this metabolite clock will achieve greater accuracy through the identification of new timetable molecules in the blood and more sensitive instrumentation.

Even this first-generation clock, however, allows reasonably accurate body-time estimation from only a few blood samples and the research team plans to push forward with clinical feasibility studies. “We are planning to apply our molecular timetable method to patients with sleep disorders or irregular circadian clocks,” says Kasukawa. ■

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YASUYUKI AKIBA

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Reproducing the Universe immediately after the Big Bang

The Universe began with the Big Bang approximately 13.7 billion years ago. In the immediate aftermath, the Universe was a superheated and highly-condensed fireball known as the ‘quark-gluon plasma’ (QGP)—a state of matter where the quarks and gluons that constitute protons and neutrons are roaming randomly. An international collaborative research group, in which RIKEN is participating, succeeded in reproducing the QGP using the Relativistic Heavy Ion Collider (RHIC) at the Brookhaven National Laboratory (BNL) in the United States. In 2010, Yasuyuki Akiba, group leader of the RIKEN BNL Research Center Experimental Group, and co-workers found that the initial temperature of the QGP is about 4 trillion °C. The reproduction of the QGP and subsequent experiments carried out to study its properties are contributing to our understanding of the primitive Universe.

Reproducing the Universe immediately after the Big Bang

“More than 1,000 researchers and students from around the world have come to the RHIC in Long Island, located on the outskirts of New York City. They have been engaged in equipment development and experiments for many years. What brings so many people from around the world together in the RHIC?” asks Akiba. “It is because the experiment in the RHIC is a completely new one that can create a physical state nobody has ever accomplished,” he says. “To put it in a nutshell, we are performing an experiment to reproduce the Universe immediately after the Big Bang.”

“According to physics, a substance can be divided into smaller pieces until we get down to elementary particles that cannot be divided any further. These particles interact with each other to cause all physical phenomena. At present, quarks and gluons are considered to be types of elementary particles. The force that arises when quarks interact with gluons is called the ‘strong interaction’—it is so strong that quarks cannot be separated from each other,” explains Akiba.

The smaller pieces, or atoms, can be divided into a nucleus and electrons; and the nucleus into protons and neutrons. A proton or neutron consists of three quarks, which combine with each other by exchanging gluons (Fig. 1, part A).

Scientists proposed the existence of quarks and gluons in the 1960s. A decade later a theory—‘quantum chromodynamics’—emerged that explains the strong interactions between the two. “Since that time, instead of separating quarks from each other, scientists have proposed the idea of producing quark-gluon matter by compression and heating,” says Akiba. “This idea is based on the assumption that with increasing compressive force and heat, quarks become free of the confines of protons or neutrons at a certain temperature and concentration, resulting in quarks and gluons being scattered randomly. That state is the ‘quark-gluon plasma’. The Universe immediately after the Big Bang is considered to be a QGP.”

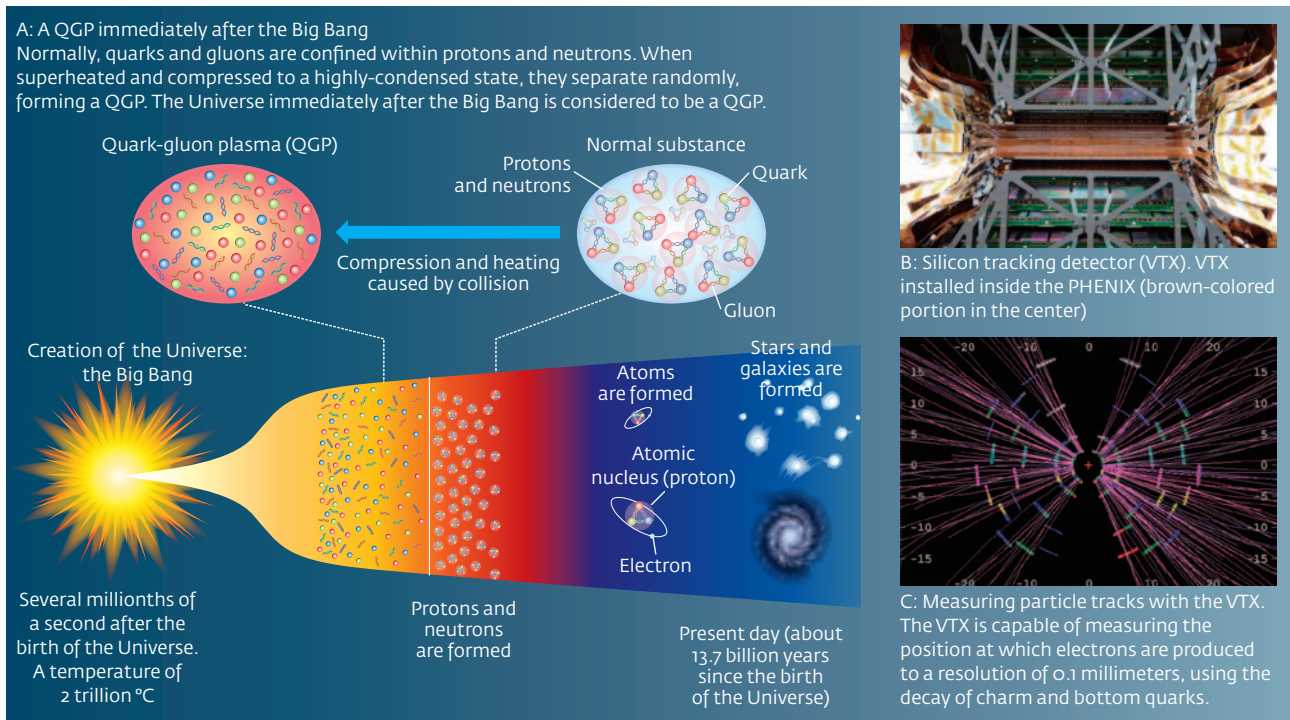


Figure 1: Measuring the QGP immediately after reproducing the Big Bang

Observations of stars and galaxies show that the further a star is from the Earth, the faster it moves away. This suggests that the Universe is expanding and, if we went into the past, it would be smaller and at a higher temperature and density. Calculation based upon the rate of expansion suggests that the Universe of 13.7 billion years ago was a superheated, highly-condensed fireball.

Akiba expands on these initial conditions: “The fireball at the birth of the Universe, or immediately after the Big Bang, is considered to be a QGP. However, the plasma lasted only about several millionths of a second. With the expansion of the Universe, it is estimated that the Universe cooled down to below 2 trillion °C and that quarks and gluons became confined in protons and neutrons.” Over time, nuclei consisting of protons and neutrons captured electrons to form atoms, eventually leading to the creation of stars and galaxies.

The initial Universe was a “drop” of liquid

“To collect many protons and neutrons for compression and heating, you only have to make accelerated, heavy atoms collide with each other,” says Akiba, of

the particles required to create a QGP. For example, the nucleus of a gold atom contains 197 densely packed protons and neutrons. When accelerated and forced to collide with each other, these nuclei are compressed. Upon collision, part of their kinetic energy is converted into mass in the form of particles, resulting in the formation of a high-density state. “The famous equation $E = mc^2$, derived by Einstein, suggests that energy is equivalent to mass. In other words, energy can be transformed into mass and vice versa. Part of the kinetic energy of atomic nuclei is changed into thermal energy when they collide with each other. At sufficiently high energy, this method should be able to create a superheated, highly-condensed state with a temperature of more than 2 trillion °C.”

In 1991, construction began on the RHIC, with the aim of creating a QGP. In collaboration with the BNL and research institutions from more than ten other countries, RIKEN developed and constructed the PHENIX, a large measuring instrument for observing QGPs. This was followed by the establishment of the RIKEN BNL Research Center (RBRC) in 1997, and the completion of the RHIC in 1999.

The RHIC facility, with two accelerator rings and a total circumference of 3.8 kilometers, is capable of accelerating ionized gold nuclei at up to 99.995% of the speed of light. This is accomplished by circulating nuclei in opposite directions through separate rings before colliding them with one another. A successful collision experiment was first achieved in 2000.

To understand whether or not a QGP has been created, the researchers must predict and observe particles within the RHIC. “Colliding two nuclei of gold can produce up to about 10,000 particles, which are observed and analyzed with measuring instruments such as the PHENIX,” says Akiba. These 10,000 particles have varying levels of energy and include high-energy particles that are produced when quarks and gluons crash head-on into each other. “We theoretically predicted that the number of high-energy particles produced when atomic nuclei of gold collide head-on with each other was about 1,000 times the number of particles produced when protons collide with each other. However, the number actually observed was about 200 times—only 20% of the predicted number.”

As to the location of the ‘missing’ 80% of high-energy particles, Akiba suggests: “We think the high-energy particles were produced as predicted. If no obstacles were around them, we would have been able to observe all of the particles. The high-energy particles were slowed down because of the presence of some high-density matter that was created immediately after the collision: the particles lost their energy when they were passing through it. This high-density matter is the QGP.”

To describe the properties of the QGP, Akiba and co-workers considered the collisions of gold nuclei, which are rarely head-on. Instead, they are almost always slightly off-center and thus, the QGP immediately after the collision has an elliptical shape (Fig. 2, left) and soon begins to expand because of its high density. “By studying how this QGP expands, we will be able to understand its properties. Before the data, the QGP was considered to have properties similar to gases through which quarks and gluons can move freely.”

If a QGP is similar to a gaseous state, it will soon change its shape from elliptical to spherical and expand uniformly in all directions. “However, the elliptical shape began to expand in the lateral directions. This was an unexpected phenomenon.” Akiba termed it ‘elliptic flow’ (Fig. 2, right). “The elliptic flow suggests that the QGP has properties similar to those of liquids, but it has almost zero viscosity and is very thin and smooth.” The findings were published in 2005. In this paper, the initial Universe was expressed as a ‘drop’ of liquid.

Measuring the temperature of the QGP

By 2005, researchers were almost certain that a QGP had been created within the RHIC. “However, whether the temperature of the QGP was more than 2 trillion °C was not confirmed because no means to measure the temperature were available at that time,” says Akiba.

Unfortunately, no thermometer exists that can measure a temperature of above 2 trillion °C. There is, however, an

alternative way to monitor temperature, as Akiba explains: “As the temperature of a substance increases, the substance emits light of higher energy and shorter wavelength. In other words, we can determine the temperature of a substance by measuring the light emitted by the substance.” For example, the surface temperature of the Sun is estimated to be around 6,000 °C, which is derived from the wavelength and brightness of the light emitted by the surface of the Sun.

“The energy of the light emitted by a substance with a temperature of 2 trillion °C is several hundred million times the energy of visible light. At present, we can use instruments that have been developed to measure such intense light. The problem is that when atomic nuclei of gold collide with each other, they emit light not only from the QGP but also light from other sources. The light from other sources is ten times more powerful than the light from the QGP and, unfortunately, we have no reliable means to measure the light emitted exclusively by the QGP.”

Measuring the temperature of the QGP had therefore become a long-standing challenge for Akiba. “I have been considering how to measure the temperature of the QGP since just after the beginning of our experiments in the RHIC. One day, I had an inspiration: we should measure electron-positron pairs rather than measuring the light itself.”

As previously mentioned, energy can be transformed into mass, and vice versa, because the two are equivalent. So when the energy of light exceeds a certain level, the light immediately turns

into an electron-positron pair with a fixed probability—that is, the light turns into mass. “We are able to distinguish the light from the QGP from the light from the other sources by measuring the electron-positron pairs. In fact, we had already developed an electron-measuring device for different measurement purposes and installed it in the PHENIX. We used the device to measure electron-positron pairs,” says Akiba (Fig. 3).

By 2002, the PHENIX had been used to measure over 20 million collisions between gold nuclei. “Light, however, turns into electron-positron pairs with a probability of only 0.001. Thus, the experimental data obtained from the 20 million collisions is insufficient for a rigorous determination of the temperature,” points out Akiba. “We continued the collision experiment, obtained several tens of sets of collision data by 2004, and continued our analysis. In 2006, we finally determined the approximate temperature of the QGP. Later, after careful follow-up work, we published the results in the science journal, *Physical Review Letters* in 2010. The initial temperature of the QGP is about 4 trillion °C.” Excitingly, these results confirmed that a QGP had actually been created in the RHIC.

“Quantum chromodynamics explains the strong interactions, and no researchers think that the theory is incorrect. However, calculation efforts based on the quantum chromodynamics equations did not provide us with detailed explanations of the phenomena occurring in a QGP because of the massive amount of calculation and technical difficulties involved in the calculation,” Akiba concedes. As a consequence, theoreticians propose

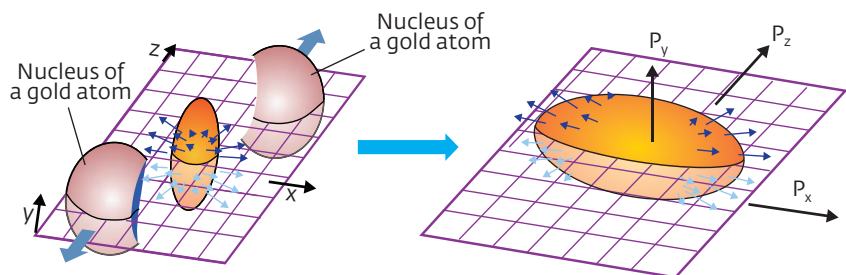


Figure 2: Elliptic flow

Two gold nuclei often collide with each other off-center, forming the elliptical shape of a QGP (left). The QGP has almost zero viscosity, causing a phenomenon known as ‘elliptic flow’, which is an expansion of the QGP in the lateral directions (right).

different results and predictions for the phenomena occurring in a QGP at a particular temperature.

“The successful measurement of the temperature of the QGP created by the RHIC enabled us to compare theoretical predictions with the experimental results in the RHIC. In other words, we have obtained a means to check whether the proposed theoretical predictions are correct or not,” comments Akiba, on the relationship between theory and experiment. “Reviewing the experimental results at the RHIC, theoreticians are continuing to advance their theories and to create new theoretical predictions. Today, this cycle of creating new predictions and verifying them by RHIC experiments is repeated continuously with the aim of deepening our knowledge of strong interactions and the QGP.”

Using heavy quarks to study the QGP

The properties of a QGP can also be studied using heavy quarks and their previously developed electron-measuring device, according to Akiba. There are six types of quarks: up, down, strange, charm, bottom, and top—listed in order of increasing mass. Protons and neutrons contain the lightest types: the up and down quarks. “The quarks in the QGP created by the RHIC are mostly up and down quarks, although a small number of charm and bottom quarks are also created,” says Akiba. “Top quarks are very heavy compared to other quarks—these quarks are not created by the RHIC. We have continued measurements to study the properties of a QGP on the basis of the behavior of the heavier charm and bottom quarks. They decay and emit electrons as soon as they are created. By measuring those electrons, we can study the behavior of heavier quarks in a QGP.”

“While measuring the electrons to study the behavior of charm and bottom quarks, we found an amazing phenomenon,” Akiba notes. “The charm and bottom quarks were slowed down, and dragged by the elliptic flow of the

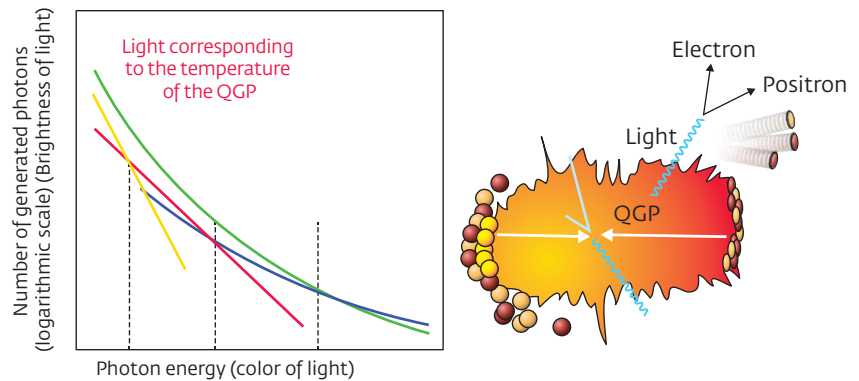


Figure 3: Measured temperature of the QGP

When gold nuclei collide with each other they emit light, not only from the QGP, but also from other sources. This light is ten times more powerful than the light from the QGP. The temperature of the QGP is determined by measuring electron-positron pairs transformed from light energy (right), and by measuring the color and brightness of the light (energy) emitted from the QGP (left).

QGP—a phenomenon similar to that observed when heavy rocks are dragged by water flow. Quarks and gluons in the QGP appear to interact with each other more strongly than predicted.”

Akiba and co-workers have developed a new device to study the phenomenon further. “With conventional equipment, we cannot distinguish electrons emitted by charm quarks from those emitted by bottom quarks. However, we must be able to find detailed information on the properties of a QGP by studying the behavior of charm and bottom quarks separately—they have different masses.”

They have also found a method to distinguish between charm and bottom quarks. “On average, upon decay, charm quarks emit electrons at a distance of 0.1 millimeters from the site of a collision between gold nuclei, whereas bottom quarks emit electrons at a distance of 0.5 millimeters. We detect the difference in the decay point. To this end, we have developed a high-resolution silicon tracking detector, known as the ‘VTX,’” (Fig. 1, part B).

December 2010 saw the installation of the VTX detector in the PHENIX by Akiba and his group (Fig. 1, part C). Given the remarkable phenomena that occur in a QGP, it is clear that there will be further findings for the team to report. In addition, Akiba’s work on the temperature measurement of a QGP was recognized with the 2011 Nishina Memorial Prize, which is presented annually to

researchers who have made great contributions to the field and application of atomic physics. Going forward, Akiba speculates about his research: “The main point of attention is the difference in how quarks are dragged. Our prediction is that the heavier bottom quarks will be dragged by the elliptic flow of the QGP less than the lighter charm quarks. Our goal is to measure quantitatively the difference of energy loss and the flow of charm and bottom quarks.” ■

ABOUT THE RESEARCHER

Yasuyuki Akiba was born in Tokyo, Japan, in 1959. He graduated from the Faculty of Sciences at the University of Tokyo in 1982, and obtained his PhD in 1988 from the same university. He was a research associate at the Institute of Nuclear Study, part of the University Tokyo, and KEK, the High Energy Accelerator Research Organization, prior to joining RIKEN in 2003. Akiba was promoted to vice chief scientist in the same year, and he was named experimental group leader of the RIKEN BNL Research Center in 2008. Currently, he is a deputy spokesperson for the PHENIX experiment at the RHIC. His research focuses on the quark-gluon plasma (QGP), a new form of matter produced in high-energy heavy ion collisions. He received the prestigious Nishina Memorial Prize in 2011 for his research at RHIC on lepton-pair production.



ANIMAL TECHNICIAN TEAM

Laboratory of Evolutionary Morphology
RIKEN Center for Developmental Biology

Caring for RIKEN's aquatic animals

How long have you worked at RIKEN?

We began working at the RIKEN Center for Developmental Biology (CDB) in 2003 (Ms. Shibuya) and 2006 (Ms. Yamamoto). At that time, we were in charge of breeding and raising zebrafish for research. This is now our third year of working in the Laboratory for Evolutionary Morphology, where we deal with a more diverse range of animals.

Please tell us about your work at RIKEN.

Our laboratory houses a variety of aquatic animals including 80 cloudy catsharks, 40 axolotls, 20 bichirs, 20 gars, numerous lancelets, 30 zebrafish, 30 African clawed frogs and 1 lungfish. On a daily basis we feed the animals, test and change the aquarium water, and switch our aquarium tanks. The two of us work part-time at the research aquarium, each undertaking three days per week on rotation. We both share the same responsibilities in the laboratory.

How did you become interested in working at RIKEN?

The work that we could perform at the RIKEN CDB was quite unique compared to ordinary part-time jobs. Also, the opportunity to work at a famous research laboratory in Kobe, where we live, was very intriguing.

What parts of your job require special attention?

The animals are extremely sensitive to changes in their environment, which can affect their appetites. We always try to keep their living conditions stable so that they will eat a lot, grow healthily and produce many eggs that can be used for experiments. Since most of the animals in our laboratory do not easily produce eggs, we are very happy and relieved when we find them.

Also, because the animals we raise are aquatic, it is important to maintain excellent water quality. They are directly affected by changes to the water, and may become ill or produce fewer eggs as a result. Therefore, we always closely monitor their well-being and any fluctuations in water quality.

What are some difficult aspects of your job?

Whenever we begin to raise a new type of animal, many conditions must be checked to ensure that the environment is suitable for them. Additionally, some animals depend on diatom algae for their diet, but growing this kind of algae in the laboratory can be a challenging trial-and-error process.

What are some memorable experiences you have had at RIKEN?

Animals have been known to jump out of the aquariums! One time a gar—which has a large body and long ‘spear-like’ jaws—managed to propel itself straight up and through a 10-centimeter-wide hole in the lid of the aquarium. It bounced off the wall behind the tank, landed on the floor, and set off a frantic search for the lead researcher to come and assist us! Another time, we found an axolotl walking around on the laboratory floor. These were very memorable incidents for us.

What is the best thing about working at RIKEN?

We have the chance to work with rare species, which is a unique experience. Also, as most of our work can be done independently, we have a lot of autonomy in setting up apparatus and can work at our own pace. The researchers entrust us with a variety of tasks for raising the animals, which makes our work particularly enjoyable.

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Sweden's Future Leaders Forum visits RIKEN

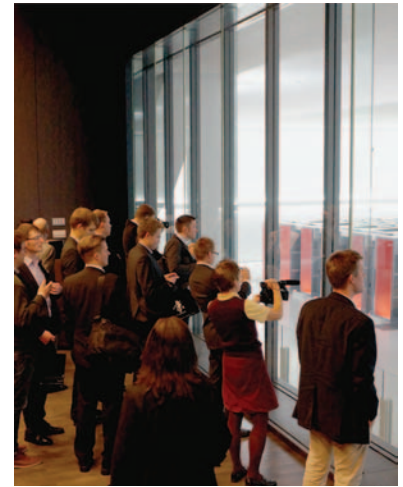
A delegation of 21 young Swedish research leaders paid a visit to the RIKEN Kobe Institute and the Advanced Institute for Computational Science (AICS) in Kobe on 26 November 2012, as part of a two-week tour that took them to a number of research institutes in both Japan and Korea. The visitors, who were accompanied by staff from the Swedish Embassy in Japan, came as part of a Swedish program for leadership development called the Future Leaders Forum, a yearlong program where people identified as having the potential to become future leaders of academic or industry

research in Sweden are given training in various fields of leadership. One part of the program is a tour abroad to learn about leadership development in other countries.

Following a series of presentations on RIKEN, the RIKEN Center for Developmental Biology (CDB) and the Future Leaders Forum program, the visiting researchers and RIKEN members in Kobe gave short talks introducing their own research themes. They next attended a luncheon at the CDB, where the members discussed leadership programs in Japan and Sweden.



Researchers from the Swedish Future Leaders Forum and staff from the Swedish Embassy in Japan visited RIKEN, Kobe.



The K computer was a tour favorite.

In the afternoon, the group was taken to the nearby AICS, home to the K computer, one of the world's fastest supercomputers. They were given a tour of the facilities and a presentation by Akinori Yonezawa, deputy director of the AICS. A highlight of the tour was the pillar-less room that holds the 700,000 cores that make up the K system, and the visiting delegation asked numerous questions about the operations of the computer, including its construction cost, electricity usage and availability for use. ■

The K computer earns awards for excellence at SC12 conference

On 13 November 2012, the K computer, jointly developed by RIKEN and Fujitsu and open for shared use since September 2012, took top honors at the High Performance Computing (HPC) Challenge Class 1 Awards, presented at the International Conference for High Performance Computing, Networking, Storage and Analysis (SC12) in Salt Lake City, USA. The awards evaluate supercomputers in four different performance categories, and the K computer was first in the Global HPL, EP STREAM (Triad) per system and Global FFT categories. The K computer also took second place in the Global Random Access category.

The Gordon Bell Prize for outstanding achievement in HPC was also awarded on 15 November at SC12 to research performed on the K computer. A research group from the University of Tsukuba, the Tokyo Institute of Technology and RIKEN used the K computer to perform extremely large simulations with an unprecedentedly high level of efficiency. This is the second year in a row that work utilizing the K computer has been awarded this prize.

The target of the award-winning simulation was the gravitational evolution of dark matter in the early Universe. The number of dark matter particles simulated was two trillion, making it the world's largest dark matter simulation to date. The simulation's execution performance was 5.67 petaflops on 98% resources of the

K computer system, and the calculation speed achieved was 2.4 times faster than that of a rival team on a similar simulation due to the advanced numerical algorithm developed by the Tsukuba group. The work is also an exciting example of the K computer's powerful capability in simulation research. ■





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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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