Issue 1
September 2015

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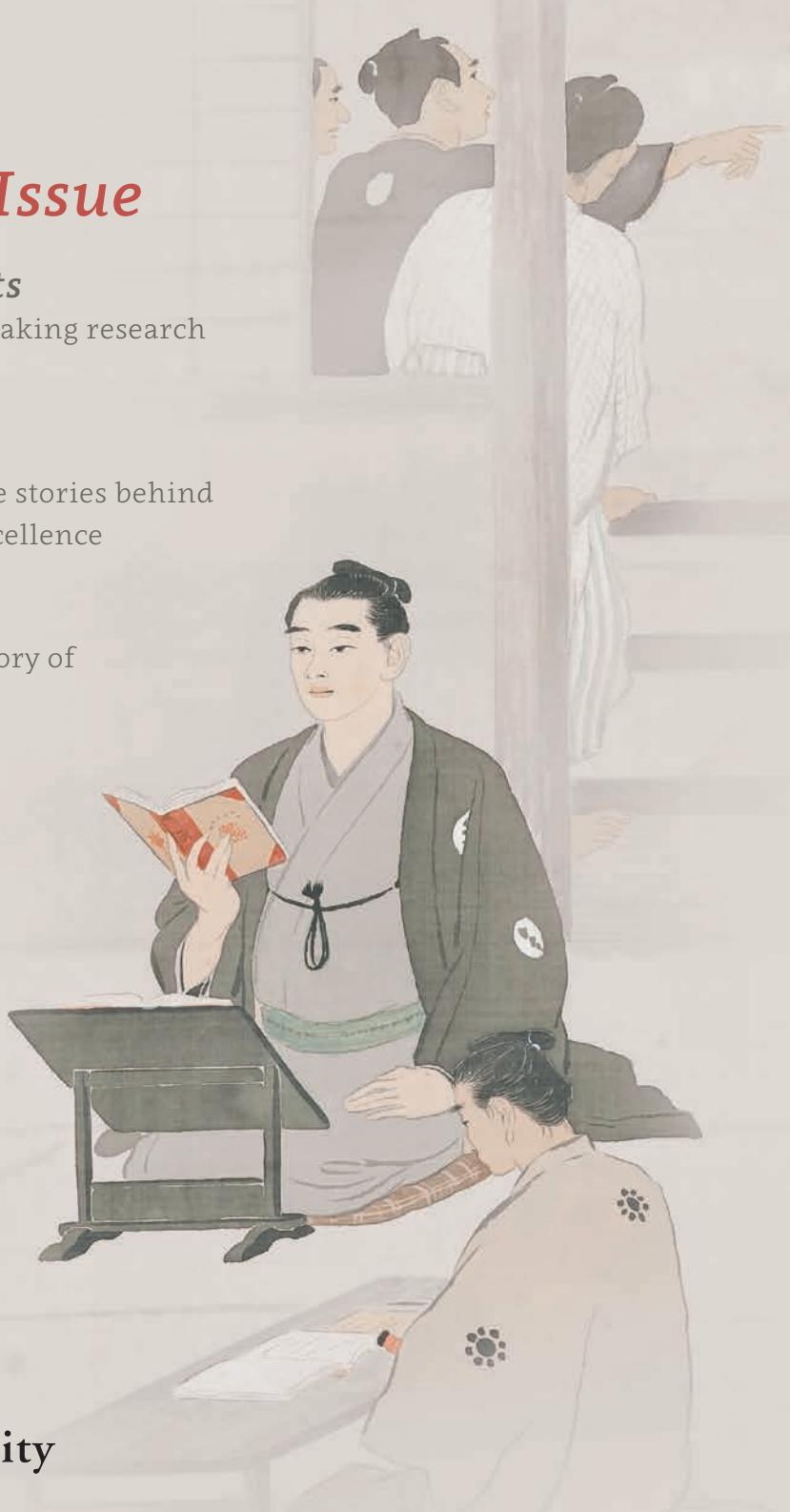
JITSUGAKU

Showcasing the best research from Keio University



Inaugural Issue

Research highlights
Discover the groundbreaking research produced at Keio

Features
Immerse yourself in the stories behind Keio's creativity and excellence

Inside Keio
Explore Keio's long history of social innovation

Keio University

ON THE COVER

The Boshin War from 1868 to 1869 between Imperial forces and Tokugawa loyalists threw Edo, present-day Tokyo, into a state of chaos. On May 15, 1868, despite the battle raging just five miles from his school, Yukichi Fukuzawa remained calm and delivered a lecture from a text by the American political economist Francis Wayland. In doing so, Fukuzawa demonstrated to his students that when it came to pursuing education and research, there was not a moment to be lost. The scene was depicted in 1910 by traditional Japanese painter Yasuda Yukihiko. Every year, Keio University commemorates the day with a special lecture at *Mita Enzetsu-kan* (Mita Public Speaking Hall).

Mita Enzetsu-kan *(Mita Public Speaking Hall), one of nine National Treasures and Important Cultural Properties at Keio University.*

(cover): "FUKUZAWA lecturing on Wayland's *Elements of Political Economy*" by YASUDA Yukihiko
1910 (Meiji 43)
Hanging-scroll, colors on silk
L. 114.8 cm, W. 42.8 cm
Fukuzawa Memorial Center for Modern Japanese Studios, Keio University.

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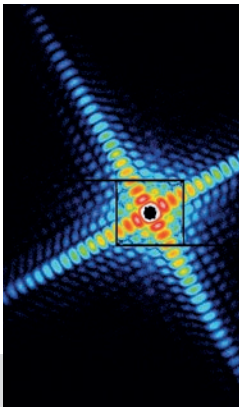

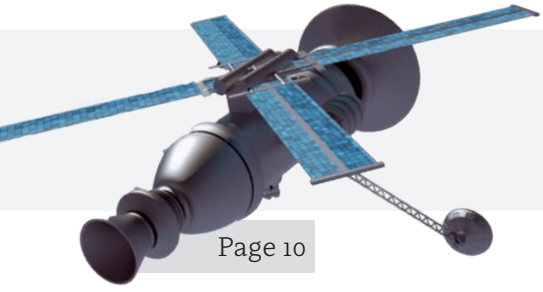

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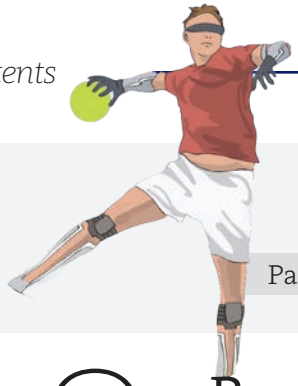

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JITSUGAKU

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Further information
Keio University is Japan's oldest institute of higher education, founded in 1858 by educator and intellectual leader Yukichi Fukuzawa.

Jitsugaku is a print publication of the online platform Keio Research Highlights, *which offers a taste of the important research and scientific developments from Keio University.*
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Keio University

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JITSUGAKU

Traditional yet innovative

Keio has a legacy as Japan's first modern institution of higher learning and continues to be one of Japan's top research universities.

Keio University has been selected as a Top Type research university for the Japanese government's Top Global University Project. Under this project, Keio is committed to further contribute to global society to bolster its position as a world-leading research university.

Keio continues to follow in the footsteps of its founder, Yukichi Fukuzawa, who aspired to contribute to society through learning and who especially valued *jitsugaku* (science). Science has a particularly important role to play in Japan, which will be the first to face many societal challenges requiring global attention. These challenges include an aging population and declining birth rate, increased risks to environmental, economic, and regional security, and a high demand for innovation.

Keio is well prepared to address these important global issues, drawing from research that extends across the humanities, social sciences, and natural sciences. And Keio is currently integrating its efforts through three transdisciplinary research and education initiatives focusing on longevity, security, and creativity.

This inaugural issue of *Jitsugaku* includes three feature articles and a selection of eighteen shorter research highlights covering a broad range of fields from biology and medicine, to physics, chemistry, law, and media studies. These articles offer a taste of Keio's groundbreaking discoveries and global contributions to social change. The Inside Keio article chronicles Keio's long history of social innovation, which is grounded on the principles of scientific realism, progressive thinking, and wise leadership.

We hope that our global initiatives will contribute to a sustainable, secure, and highly creative world where people live better, longer lives.

Issue 1, September 2015

WHAT IS *JITSUGAKU*?

Jitsugaku is a way of learning about the world pursued by Keio University's founder Yukichi Fukuzawa through the application of reason, observation, and verification. It is science in the true sense of the word and a powerful tool in Keio University's never-ending search for practical solutions to real-life problems.

Keio University Library is the only library in Asia to own a copy of the Gutenberg Bible.

IGNITING JAPANESE SOCIAL INNOVATION

Keio university is the oldest and one of the most prestigious universities in Japan, with a history that dates back more than 150 years. Located in the heart of Tokyo, Keio is a forward-looking, progressive institution founded on principles of scientific realism and Western philosophy, and is focused on enhancing the globalization of education in Japan.

Keio was founded by Yukichi Fukuzawa (1835–1901), an educator and intellectual leader who is considered a pioneer of modern Japan. Fukuzawa was born to a samurai family during the final years of the Edo period. He founded Keio Gijuku in 1858, as a school for Western learning in Edo, today's Tokyo. Keio Gijuku was characterized by its tenets of self-respect and independence of mind combined with an emphasis on *jitsugaku* (science). The school began offering university education in 1890, setting up its first departments in literature, economics and law, and has since continued to establish a firm reputation as a leading university in Japan. Indeed, Keio has a long history of attracting some of the world's brightest minds. For example, in 1922, the year after he won the Nobel Prize in Physics, Albert Einstein visited the university to deliver a five-hour speech, his first in Japan, in front of an audience of over 2,000 people.

Handwritten manuscripts and letters by Albert Einstein donated to Keio University.

Fukuzawa believed the best way for Japan to catch up with Western technology and social systems was to always strive for progress and enlightenment, and provide the academic and moral education needed to create a generation of wise and capable leaders. Graduates of Keio include prominent leaders and historical figures in all walks of life, including former prime minister, Junichiro Koizumi, and highly regarded people in the Japanese business world such as Toyota Motor Corp's incumbent chief executive officer, Akio Toyoda. Notable astronauts, writers, scientists, intellectuals, and artists also number among Keio alumni.

This is also reflected by Keio's 9th place ranking in the *Times Higher Education* Alma Mater Index: Global Executives in 2013. The index ranks institutions by the number of degrees they have awarded to CEOs of Fortune Global 500 companies.

Thinking for oneself, taking responsibility for one's actions and *jitsugaku* (science) are basic principles held dear by Fukuzawa that Keio continues to uphold to this day. Fukuzawa emphasized the importance of freedom, equality, and lifelong learning.

He noted: "Heaven does not create one man above or below another man." Fukuzawa is honored on the 10,000 yen note, Japan's highest denomination.

Applying *jitsugaku* (science) to solve global problems

Keio is a comprehensive higher-education institution located on six campuses across the greater Tokyo area. It has 10 undergraduate faculties, 14 graduate schools and approximately 30 research centers and institutes, including a university hospital. The institution's affiliates include two primary schools, three junior high schools, and five high schools, including one in New York. Keio is a unique academic entity that offers lifelong education. Keio has partnerships which include 266 overseas institutions and 9 international organizations in 41 countries. Partner universities include Harvard Medical School, Columbia University, Stanford University, the University of Oxford, and the University of London. International organization partnerships include the Asian Development Bank, the International Bank for Reconstruction and Development, and UNESCO.

Drawing on its vast research expertise, Keio is now focused on solving challenges in order to realize a prosperous super-mature society. This includes finding ways to promote a sustainable society while nurturing the next generation and maintaining the health of those in the prime of life and beyond.

"Today, Japan has the world's highest longevity rate. If we can establish our country as a model for a vibrant and prosperous aging society, it means that we can set a precedent for other countries that are also graying. Keio University continues to make intellectual contributions to Japan and the world to create such affluent aging societies," says Keio University President Atsushi Seike.

In recognition of its strengths in research and education, Keio University was recently selected by Japan's Ministry of Education, Culture, Sports, Science and Technology as one of the 13 top Japanese universities in the 2014 Top Global University Project. This 10-year grant will further strengthen Keio's capacity to promote research and education in various important fields.

> ***"Keio University continues to make intellectual contributions to Japan and the world to create such affluent aging societies."***

Under the Top Global University Project, Keio will set up three clusters focusing on Longevity, Security, and Creativity, which will all contribute to its goal of attaining sustainable development of a super-mature society. These three multidisciplinary clusters will draw on Keio's unique heritage of innovation and *jitsugaku* (science), and harness the power of the university's strong network of collaborations with industry, academia, and international organizations.

For example, the Longevity Cluster will focus on developing innovative solutions to the problems posed by aging societies. It will adopt a three-pronged holistic approach that will involve considering health matters, socio-political issues, and technological solutions; examples of each of these aspects include the development of regenerative medicine based on stem cell technology, research into the politics of aging societies, and the use of robots to undertake nursing duties, respectively.

Keio Founder Yukichi Fukuzawa.

In the Security Cluster, Keio researchers will explore security issues relating to social, economic, and geopolitical risks. Such security issues include global pollution, cyber security in financial markets, and regional security in East Asia.

Meanwhile, researchers in the Creativity Cluster will investigate telecommunication and analytical technologies as well as new materials such as plastic optical fibers. In addition, they will investigate new forms of expression in new media and participate in inter-university consortia such as the Global Innovation Design program. Finally, Keio Business School, the first in Japan to be accredited by the Association to Advance Collegiate Schools of Business, will undertake research on topics that include value creation through outstanding marketing and human resource management.

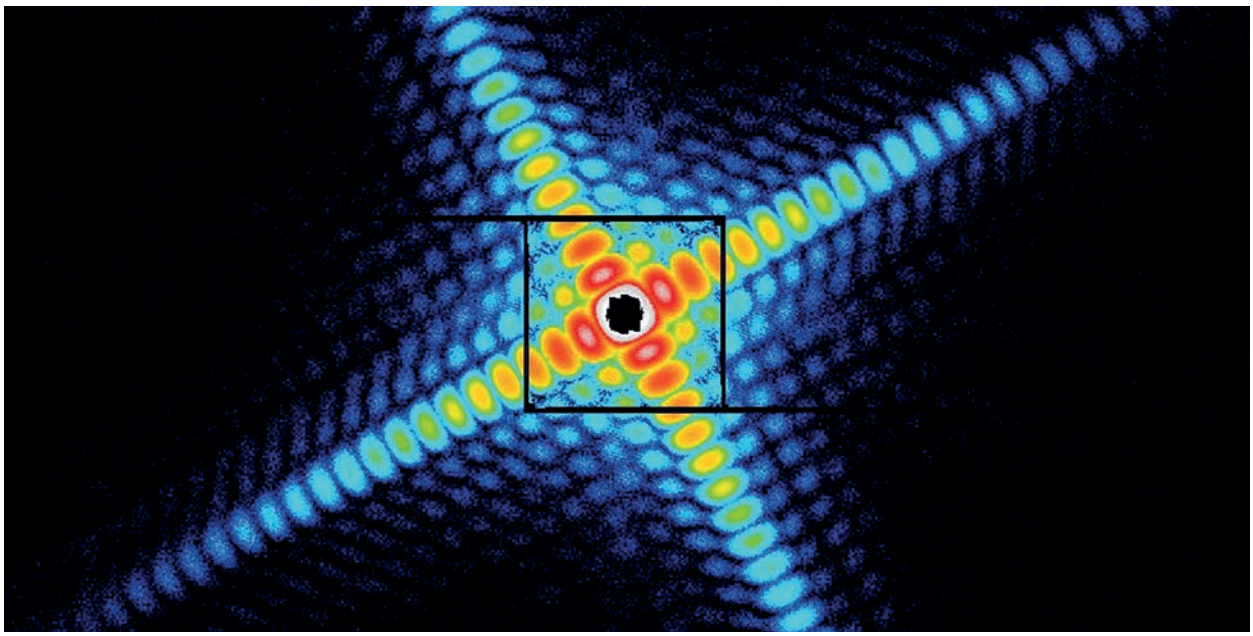
By consistently emphasizing the philosophy of *jitsugaku* (science), Keio will continue to provide leadership for the future through its commitment to education, research, and medicine. Its progressive environment helps students and researchers in their pursuit of excellence, both as researchers and as individuals, and enriches global society.

The Pen Mark has been an official symbol of Keio University for more than a hundred years.

The Old University Library on Keio's Mita campus.

Enhanced X-ray imaging

Improved coherent X-ray diffraction imaging makes it possible to analyze the internal parts of cells



X-ray diffraction pattern from a cube-shaped copper oxide particle, approximately 500 nanometers in size.

By employing a ring-shaped mask and appropriate signal processing, scientists in Japan have found a way to overcome a common limitation of coherent X-ray diffraction imaging and dramatically improve the quality of analysis[1]. As a result, they have succeeded in using the imaging technique to analyze the internal structures of biological cells and a collection of metallic nanoparticles.

Masayoshi Nakasako from the Department of Physics at Keio University and the RIKEN SPring-8 Center and his co-workers have been using the X-ray free electron laser at the SACLA facility in Japan for their experiments.

Imaging the diffraction patterns that result when X-rays interact with a sample is a very powerful approach for visualizing the structure of materials. Indeed, the discovery of the double-helix structure of DNA was based on analysis of an X-ray diffraction image, the famous 'photo 51' in 1952.

X-rays can deeply penetrate into materials beyond the reach of electron microscopy and their short wavelength yields an imaging resolution of just a few tens of nanometers, far better than optical microscopy. Applying phase-retrieval algorithms to the two-dimensional X-ray diffraction pattern captured on an image sensor with an array of pixels allows the electron density map of the sample to be reconstructed.

However, there is a problem that hinders coherent X-ray diffraction imaging experiments based on X-ray free electron lasers, especially those experiments involving clusters of metal particles with large scattering cross-sections or cellular organelles. At small diffraction angles, the image sensor receives such an intense X-ray signal that it saturates the detector, resulting in missing data. Nakasako's team solved the problem by employing an annular mask (see image) and dark-field phase retrieval.

"Through developing a diffraction apparatus called KOTOBUKI-1 and data

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processing software, we have succeeded in the structure analyses of bacterial cells and organelles in biology and the determination of the size distribution and the structures of synthesized metal nanoparticles from industry," explains Nakasako. "Recently we have succeeded in visualizing the structure of chloroplasts with the dimension of approximately 1 micron at effective resolutions of 70 nanometers, better than the resolution limit of optical microscopy."

The capabilities of this new form of coherent X-ray diffraction imaging are said to be a valuable addition to the other forms of imaging such as fluorescence and electron microscopy, for example. "The complementary use of [coherent X-ray diffraction imaging] together with other imaging techniques will bridge the resolution gap between cellular and structural biology," concludes Nakasako.

Reference

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Multi-tasking protein wires brain

Two roles are performed by one protein to ensure the correct wiring of brain networks

A single cell-surface protein is crucial for the precise wiring of a specific brain network, according to work by Keio University researchers[1]. The discovery might reveal a general mechanism by which a family of proteins controls development of the nervous system.

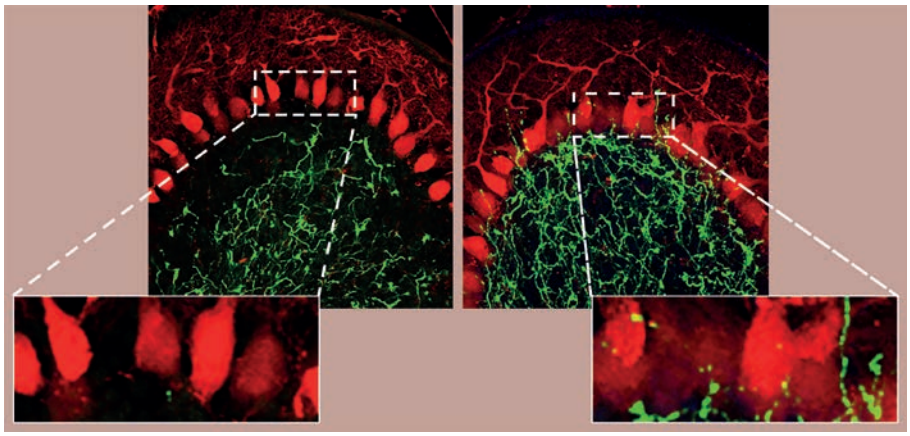
During development, neurons extend projections called axons, which make connections called synapses with other neurons to build specialized neural networks. For accurate wiring of these networks, axons must stop growing when they reach the right place and form synapses with the correct neurons. To identify the molecular mechanisms underlying this process, Ken-ichiro Kuwako from Keio University's School of Medicine and colleagues focused on an area of the brain called the cerebellum.

"The cerebellum is an excellent model for studying circuit connectivity because it has a well-characterized simple structure that consists of a small number of neuronal cell types," explains Kuwako.

Previous studies showed that two of these cell types — mossy fiber neurons and climbing fiber neurons — make different connections during development. Kuwako and colleagues aimed to determine which molecules underlie these differences by analyzing the proteins expressed in the two cell types at specific developmental stages

"This *in vivo* screening was a time-consuming step," says Kuwako. "It took us almost a year to complete." But the team's patience paid off: they showed that Cadherin-7 (Cdh7) — a cell-surface protein that mediates interactions between cells by binding to itself — is expressed at the developing synapses of mossy fiber neurons but not of climbing fiber neurons. They also discovered Cdh7 expression in the neurons with which mossy fiber neurons form specific synapses.

To examine how Cdh7 affects axon growth, the researchers grew a type of mossy fiber neurons called pontine nucleus (PN) neurons alongside cells that either did or did not express Cdh7. They observed reduced axon growth when PN neurons were surrounded by



Sections of the cerebellum in mice show that when the cell-surface protein Cadherin-7 (Cdh7) is expressed (left), pontine nucleus (PN) neurons (green) do not connect to Purkinje cells (red). However, reducing levels of Cdh7 in PN neurons (right) causes abundant connection of PN axons to Purkinje cells.

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Cdh7-expressing cells, indicating that interactions between Cdh7 molecules on the two types of cells impede axon growth.

Cdh7 also proved important for the formation of specific synapses. In mice, reduced Cdh7 expression in PN neurons led to the formation of fewer synapses with granule cells, which are normally specific targets, and more with Purkinje cells, which are not (see image).

"This study provides the first evidence that a single bifunctional cell-surface receptor orchestrates precise wiring by regulating axonal growth termination and synaptic specificity," says Kuwako. "Over 100 members of the same protein superfamily are expressed in a circuit-specific manner and may also play a dual role to establish precise wiring."

Reference

1. Kuwako, K., Nishimoto, Y., Kawase, S., Okano, H. J. & Okano, H. Cadherin-7 regulates mossy fiber connectivity in the cerebellum. *Cell Reports* **9,** 311–323 (2014).

A quick spin unleashes waves of the future

Spinning crystals allow researchers to peer inside objects in just milliseconds using terahertz light

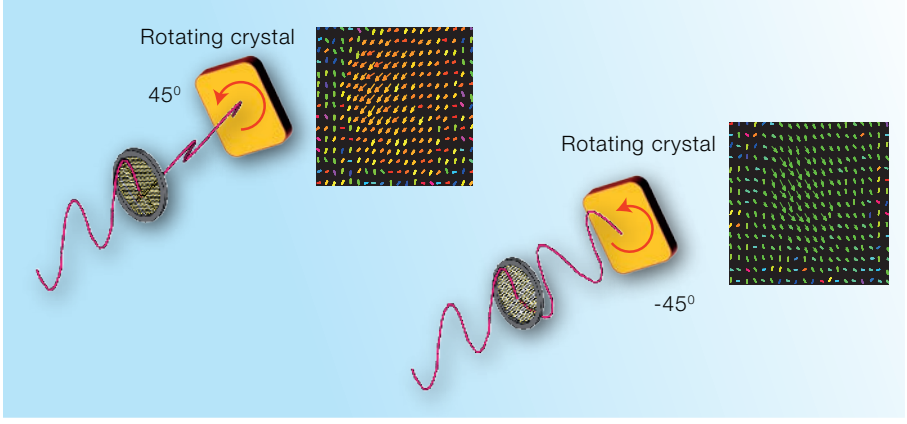
A new imaging device developed at Keio University[1] dramatically shortens the time needed to perform 'terahertz electric-field vector sensing' — a technique of interest to art historians and materials scientists alike for examining molecular-scale surface properties using low-power radiation. The high-speed optical probing characteristics of this device may find use in real-time manufacturing monitors or hidden-object detectors at security checkpoints.

Situated between the infrared and microwave regions of the electromagnetic spectrum, terahertz radiation has unique characteristics ideal for high-tech applications. For example, it has an intrinsic low energy, making it is less damaging than X-rays but penetrating enough to see through opaque materials such as plastics or paper. However, it has proved challenging to find ways to controllably generate terahertz light and detect how the amplitude, phase, and polarization of these beams change after interacting with a sample — data that can precisely identify material composition and properties.

Since 2012, Shinichi Watanabe and his team from Keio University's Department of Physics have been working to advance this experimental technology through 'terahertz time-domain spectroscopy'. In this approach, terahertz light is mixed with pulses of short-wavelength, near-infrared light inside a special electro-optic crystal before hitting the target. By varying the timing of the near-infrared light pulses, the researchers can monitor the amplitudes and phases of the terahertz waves on a video screen, similar to an oscilloscope.

Now, the Keio researchers have improved upon their concept by developing a way to probe time-dependent changes to the terahertz beam polarization. Watanabe explains that traditional devices for tracking how light behaves in different planes, such as wire-grid polarizers, limit the bandwidth of collected data. Fortunately, the team found a superior solution — the electro-optic crystal they used to mix terahertz and near-infrared light pulses had a natural symmetry that could detect polarization changes with extreme precision.

By shining terahertz light onto a mechanically spinning electro-optic crystal, the researchers used the polarized beams and high-speed cameras to capture the terahertz electric-field vectors (see image). These images provide real-time information of the magnitude and spatial distributions of the terahertz radiation passing through a substance — data that Watanabe says can improve understanding of materials such as birefringent polymer optical components and light-harvesting biomolecules.



Researchers have used light, naturally polarized by a rotating crystal, to generate two-dimensional, real-time snapshots of terahertz electric-field vectors (colored arrows in panels on right) for high-tech, subsurface imaging applications.

© 2015 Shinichi Watanabe, Keio University

"Seeing the amplitude, phases, and polarization of terahertz light gives us triple the amount of possible information," explains Watanabe. "And since the technology utilizes the natural symmetry of the electro-optic nonlinear crystal, it is versatile, precise, and suitable for real-time video mapping of terahertz electric-field vectors."

Reference

1. Takai, M., Takeda, M., Sasaki, M., Tachizaki, T., Yasumatsu, N. & Watanabe, S. Video-rate terahertz electric-field vector imaging. *Applied Physics Letters* **105,** 151103 (2014).

Lab-grown uterus could reverse infertility

Tissue-engineered uteri produce successful and healthy pregnancies in rats

Rats with bioengineered uteri can achieve normal pregnancies, show researchers at Keio University in Japan[1]. This work could lead to novel treatments for women who have abnormalities of the uterus that interfere with embryo implantation and fetal growth.

"The techniques might be clinically applicable for treating partial defects of the uterus and, in the future, perhaps for the reconstruction of the whole uterus," says Tetsuo Maruyama, a reproductive medicine specialist at Keio's School of Medicine.

A recellularized uterine graft being cultured in the laboratory.

Uterine-related infertility can sometimes be corrected surgically, but for most women with severely damaged or misshapen uteri the only way to genetically mother a child is through uterine transplantation or through the services of a surrogate — a woman who carries the baby to term and delivers it. Both of these approaches are fraught with ethical, legal and societal issues.

Tissue engineering offers a potential alternative. The technique involves fabricating organs from an individual's own body cells and then implanting these tailor-made organs into patients. So far, doctors have only tested the approach in people who need relatively simple, hollow organs, such as bladders and windpipes. But bioengineers around the world are using similar techniques to build more complex organs, including livers, kidneys, lungs and even hearts. Perhaps the uterus would be possible, too.

Maruyama and his colleague Kaoru Miyazaki set out to test that idea in a rodent model. They surgically removed the uterus from rats and used detergents to strip the organs of all their cells. This procedure left only the underlying matrix of collagen and other structural proteins, together with the cell-free architecture of the blood vessels that surround the uterus. The researchers then reseeded this scaffold with tens of millions of primary uterine cells and mesenchymal stem cells (see image). After three days in a bioreactor, tissue analyses showed that the lab-grown organs had uterine-specific structural integrity.

The bioengineered uteri could also yield healthy pregnancies. Maruyama and Miyazaki showed that pregnancy rates and average fetal weights in rats implanted with the uterine scaffold were comparable with control rats.

Many technical obstacles remain before the same method can be applied to humans. For example, scientists will need to figure out the best ways to surgically remove uteri from donors, safely strip all the cellular remnants to avoid immune rejection, and reconstruct the organs in the lab. Once these techniques have been optimized, however, bioengineered uterine grafts could offer a revolutionary new fertility treatment.

Reference

1. Miyazaki, K. & Maruyama, T. Partial regeneration and reconstruction of the rat uterus through recellularization of a decellularized uterine matrix. *Biomaterials* **35,** 8791–8800 (2014).

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Lawyers in space

A new legal field has sprung up to regulate humanity's ever-growing activities in outer space

Traffic police are not issuing speeding tickets in space, but the long arm of the law is far from absent in the 'final frontier'. A fast-growing body of national and international laws, known as space law, is now being used to regulate human activities in outer space, and Keio University is at the forefront of this young but increasingly important field.

In January 2012, the university, in collaboration with the Japan Aerospace Exploration Agency (JAXA), established the Center for Space Law (Institute of Space Law), which aims to examine and offer legal solutions to issues arising from space activities, as well as to foster and enhance research in the field of space law in Japan and countries across Asia. The center also runs a space law master's program. "It is the only institute of its kind in Japan and one of only about a dozen in the world," says Setsuko Aoki, a professor at the center.

Space exploration

Space activities have grown rapidly through large international space missions and satellites for communication, scientific research, espionage and remote sensing. Technology that relies on these activities is fast becoming a normal part of life — we use it every time we check our position on a navigation device or view a sports event screened on satellite television. Even space tourism is close to becoming a reality.

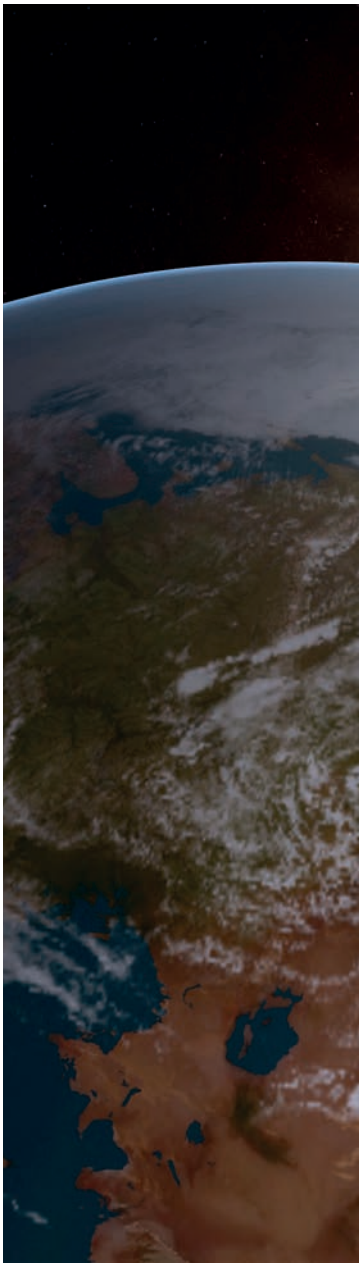
"Space is potentially very beneficial to humankind and can help us overcome many of the problems we face today," says Aoki, who became enamored with the field while studying law in Canada.

Examples of the benefits of space include the use of satellite data to combat infectious diseases and predict ozone depletion, she says. But legislation is needed to manage these inherently dangerous activities. "Space law can act as a vital facilitator for reducing risk and to cover compensation issues that arise when accidents do occur," Aoki explains.

For Aoki, the field offers an appealing mix of international relations and science, such as calculating satellite orbits. Space law covers the financing of off-planet enterprises, insurance, navigation, export control, security, intellectual property protection, and more. It also encompasses international politics, as typified by the Outer Space Treaty brokered by the United Nations. About 100 countries are parties to this treaty, which was produced in 1967.

Debris damage and militarization

Keio is researching aspects of space law that particularly affect Japan, such as the problem of space debris. NASA tracks over half a million pieces of debris orbiting the Earth, of which more than 2,000 are larger than a softball. According to Aoki, the Japanese satellite operator SKY Perfect JSAT Corporation has to adjust the orbits of its 16 satellites almost daily to dodge space debris hurtling toward them. Regulations are now in place that assign responsibility for damage caused



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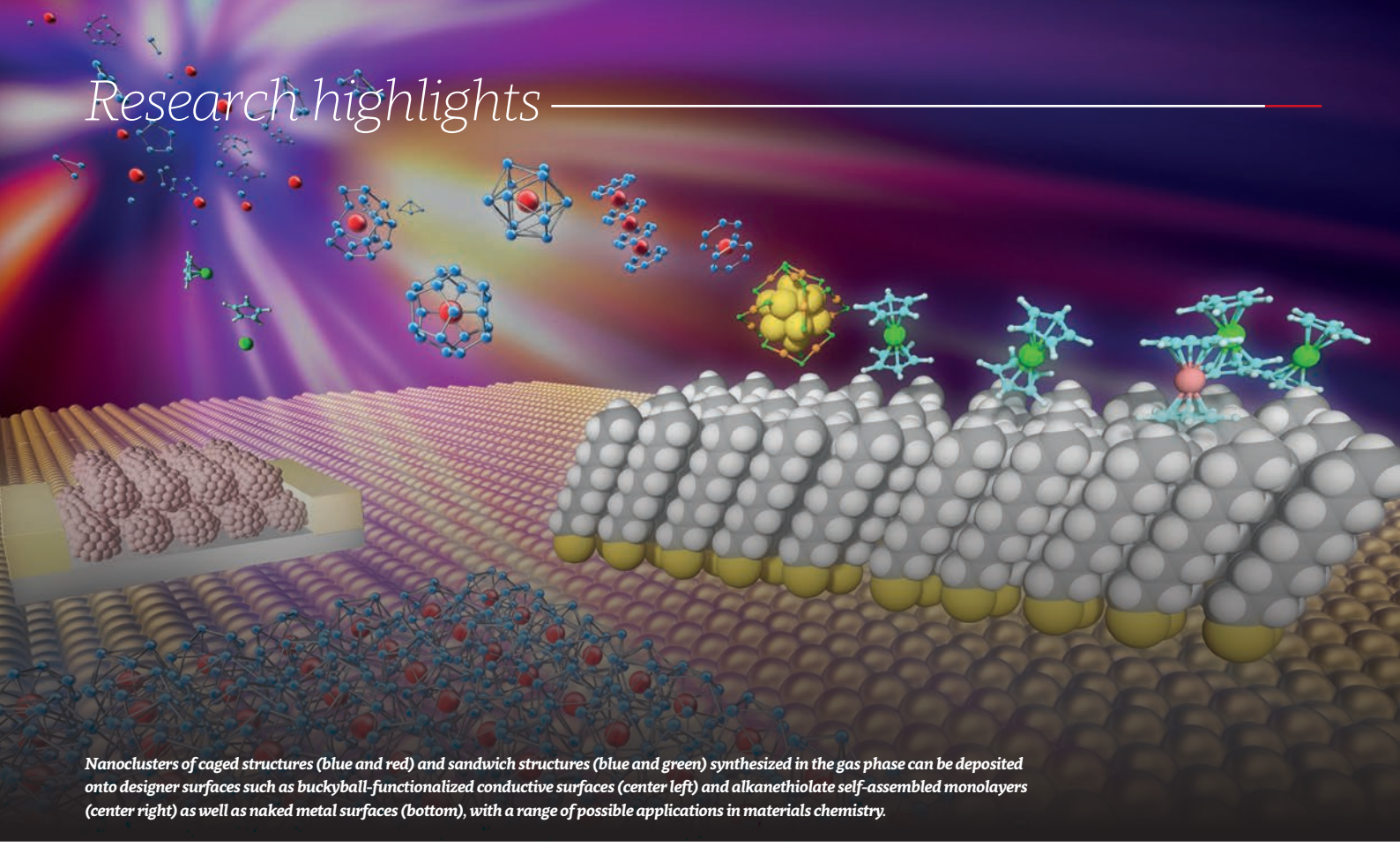
Space has great potential to benefit humankind, but judicious regulation is needed to facilitate the utilization of space.

by debris whose source is known, while non-legally binding guidelines stipulate ways to minimize the generation of new debris.

A more sinister aspect of space law is the militarization of space, particularly anti-satellite attacks. This area has become especially urgent since the anti-satellite missile tests conducted in 2007 by China, which involved the physical destruction of a Chinese satellite and generated thousands of pieces of trackable space debris. International treaties such as the Outer Space Treaty limit the deployment of weapons of mass destruction in space, and are expected to become increasingly important in preventing an arms race in space as technology advances.

The year 2015 is particularly important for space science in Japan as the Japanese government will begin to adopt national space laws in compliance with the Outer Space Treaty. "About 20 countries have already created such laws, and now it is Japan's turn," explains Aoki. She and other members of the Center for Space Law will be contributing to this process through their participation in various guiding committees. Thus, the center will be playing a major role in shaping space law policy in Japan. "This is a really exciting time to be active in this developing field," says Aoki.



Nanoclusters of caged structures (blue and red) and sandwich structures (blue and green) synthesized in the gas phase can be deposited onto designer surfaces such as buckyball-functionalized conductive surfaces (center left) and alkanethiolate self-assembled monolayers (center right) as well as naked metal surfaces (bottom), with a range of possible applications in materials chemistry.

Door opened to novel nanomaterials

A simple route to immobilizing nanoclusters opens up new possibilities in materials chemistry

Researchers have developed a technique for assembling novel nanomaterials from clusters of gaseous ions, with potential implications for solar energy, energy storage, and high-performance catalysis[1].

Small clusters of silicon cages holding single metal atoms or ions have long been identified as potential building blocks for nanomaterials. Before they can be used, however, these gaseous nanoclusters need to be immobilized on a solid surface. Previous attempts have resulted in undesirable changes to the shape and electronic charge of the clusters.

Atsushi Nakajima from the Keio Institute of Pure and Applied Sciences and colleagues at Keio University have immobilized tantalum cations trapped inside cages comprised of 16 silicon atoms ($Ta@Si_{16}^{+}$) onto a conductive surface while retaining their vital original properties.

The team selected a conductive surface functionalized with buckyballs (C_{60}) that are able to act as electron acceptors, theorizing that the $Ta@Si_{16}^{+}$ cations and buckyballs would form charge-transfer complexes ($Ta@Si_{16}^{+}$-C_{60}^{-}). "The immobilization process consists of two steps," explains Nakajima. First the $Ta@Si_{16}^{+}$ is neutralized, and then it transfers an electron to the buckyball and becomes cationic again. This transfer of an electron between each cluster and the buckyball it lands on is "a crucial factor in maintaining its symmetric cage shape and cationic state," he explains.

The researchers experimentally verified their theory by vaporizing tantalum and silicon atoms in a vacuum chamber to make the $Ta@Si_{16}^{+}$ cations. They then used mass spectrometry to identify the desired ions from the range of differently sized nanoclusters that had formed. The selected ions were fired onto the buckyball-functionalized graphite surface at a tightly controlled rate to ensure a gentle landing.

The researchers used scanning tunneling microscopy and scanning tunneling spectroscopy to study the structure of the resulting nanomaterial. A charge-transfer complex had indeed formed, creating a monolayer of the $Ta@Si_{16}^{+}$ cations on top of the anionic buckyballs attached to the conductive surface.

"This fabrication approach can be used to make a range of nanomaterials comprised of both different nanoclusters and different

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surfaces," explains Nakajima. Such nanomaterials made of monolayers of cations next to monolayers of anions could act as electrical junctions in a range of devices such as solar cells and supercapacitors. The technique could also lead to the design of high-performance catalysts. It has been predicted that the cationic state of supported nanoclusters is a key factor for controlling their catalytic reactivity, says Nakajima. "A novel avenue for developing nanocluster-based material science and technology has opened to us."

Reference

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Giving heart patients a breath of life

Animal studies show that hydrogen gas can minimize damage caused by the production of potentially lethal compounds following cardiac arrest

Inhalation treatment with hydrogen gas protects against neurological damage in a rat model of cardiac arrest, increasing the likelihood of survival and recovery, find researchers at Keio University and Nippon Medical School in Japan.

Many patients who survive cardiac arrest remain at increased risk of death. "Neurological dysfunction, cardiac damage, and systemic inflammation can contribute to their ultimate demise," explains Motoaki Sano, a cardiologist at Keio University. The stress from the one-two punch of oxygen deprivation and subsequent sudden restoration of blood stimulates the production of damaging molecules known as reactive oxygen species. These trigger inflammation and create regions of damaged tissue known as infarcts in the brain and other organs.

Sano's group has obtained evidence that this damage might be mitigated by treating patients with hydrogen after manually restoring blood circulation through cardiopulmonary resuscitation (CPR)[1]. "Hydrogen gas has antioxidant and anti-inflammatory properties, and limits infarct volume in the brain and heart," he explains. His team previously demonstrated that they could reduce post-cardiac arrest mortality by treating animals with hydrogen at the same time as they initiated CPR, but their investigation did not look at longer-term recovery or assess physical brain damage.

The researchers therefore embarked on a more thorough assessment of this approach in a rat model of cardiac arrest. To make their investigation more clinically realistic, they mixed hydrogen gas with normal air rather than pure oxygen, and delivered it only after normal circulation had been restored via CPR. They also tested their treatment in parallel with targeted temperature management (TTM), where a patient's body is cooled to minimize post-recovery tissue damage. "To date, TTM is the only approach proven to improve patient outcomes," says Sano.

Hydrogen treatment greatly improved survival and recovery, and even more so in combination with TTM. Of the rats that received both interventions, 86 per cent were alive one week post-cardiac arrest, compared with 38 per cent of control animals. This combination also reduced neurological damage and improved

A dose of hydrogen gas following cardiopulmonary resuscitation could potentially improve outcomes in patients who survive cardiac arrest.

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cognitive performance post-recovery. Most importantly, histological analysis showed that hydrogen treatment greatly reduced cell death and inflammation in vulnerable regions of the brain.

"This shows that hydrogen could be used as a brain resuscitation gas," says Sano. His team observed no adverse effects from treatment and has since initiated pilot safety studies in humans in preparation for formal human trials. While differences in human and rodent physiology make it difficult to predict precisely how effective this treatment will be, Sano sees a clear road to the clinic.

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Purer silicon promises perfection

An electronic circuit made from isotope-engineered silicon creates a better basic unit for a quantum computer

A fundamental element of a quantum computer that is scalable and retains its state for much longer than comparable approaches has been demonstrated by an international team of researchers[1].

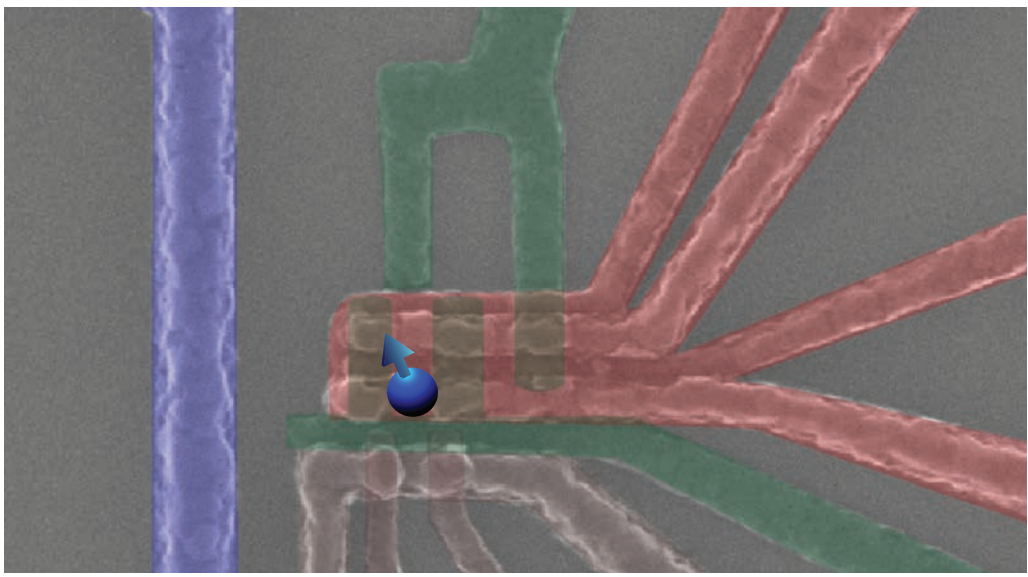
Quantum computers promise to solve problems far beyond the capabilities of modern machines. Whereas conventional computers store and process information as a sequence of electrical pulses, the quantum equivalent uses a physical system that is small enough to exhibit its quantum properties.

These quantum equivalents of classical bits, known as qubits, can come in many forms, and each has its own advantages and disadvantages. One approach is to use atomic impurities in otherwise perfect crystal structures, while quantum dots are another type of qubit. Quantum dots are larger than atomic impurities and are hence easier to connect to electrical contacts for inserting and extracting data. Atomic impurities, on the other hand, can maintain their quantum properties for much longer.

Kohei Itoh from Keio University, Japan, and colleagues from Australia and the Netherlands have now created a qubit that offers the advantages of both approaches.

The team made their qubit from a thin film of silicon. Crucial to their success was the high purity of their material. In addition to the common silicon-28 atoms, standard silicon often includes atoms of the isotope silicon-29. The samples at Keio University were carefully created to reduce the number of these heavier atoms. "Our work shows that isotope engineering of silicon has a crucial role to play for quantum information applications," says Itoh. He and his co-workers fabricated quantum dots by laying down electrical contacts. The electrical field between the contacts trapped an electron in an area approximately 30 nanometers in diameter (see image). A nearby transistor monitored the quantum state of this electron and the magnetic field created by a microwave transmission line controlled the properties of the quantum dot.

The researchers tested the operation of the qubit by applying a sequence of pulses that created a device known as a Clifford



Electrical contacts (red) trap a single electron (blue sphere) that is monitored by a nearby transistor (gray). The properties of this quantum-dot qubit are tuned using the magnetic field around a transmission line (blue).

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gate. They measured a control accuracy, or fidelity, of 99.59 per cent. The quantum properties of their dot could remain stable for 28 milliseconds — an order of magnitude longer than other types of semiconductor-based qubits.

"Moving on to two and more qubits is the next step," says Itoh. "We also intend to develop materials that will allow qubits to be buried under the surface and thus reduce the negative influence of interface defects."

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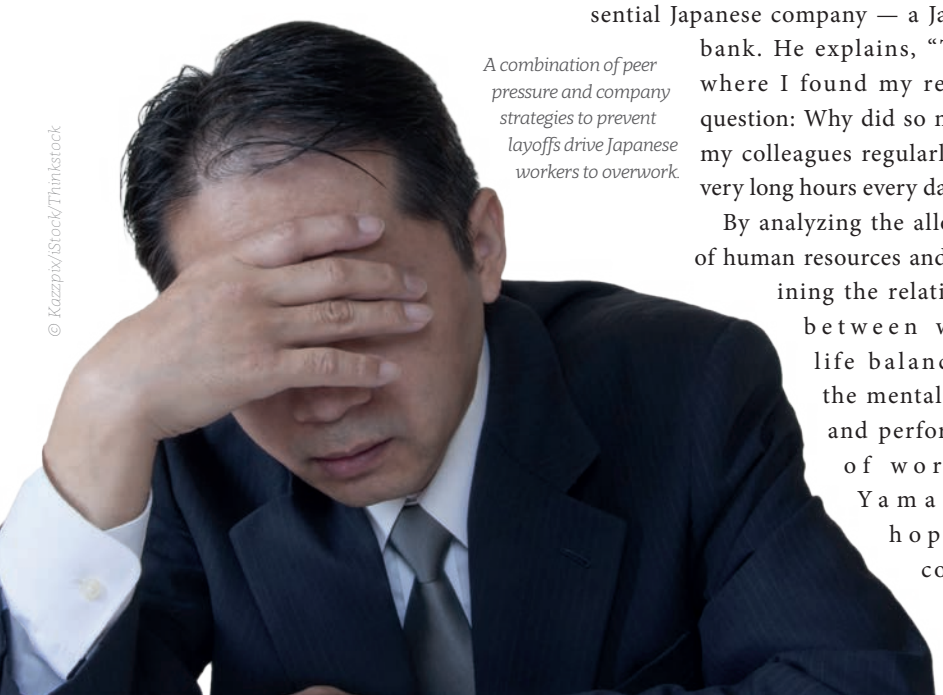
Bringing hard labor to account

One man's effort to rationalize Japan's infamous grueling work culture has yielded some fascinating insights into the Japanese work ethic

Karoushi is a Japanese word that means 'death by overwork'. In a country notorious for its long working hours and tradition of lifetime commitment to a single company, this term is familiar to many. Isamu Yamamoto at the Faculty of Business and Commerce, Keio University, has been studying this characteristically Japanese work culture for the last seven years with the aim of identifying some of its underlying motivations and effects on productivity.

Yamamoto developed an interest in the subject prior to joining Keio University during his years of working at a quintessential Japanese company — a Japanese bank. He explains, "That is where I found my research question: Why did so many of my colleagues regularly work very long hours every day?"



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A combination of peer pressure and company strategies to prevent layoffs drive Japanese workers to overwork.

By analyzing the allocation of human resources and examining the relationship between work–life balance and the mental health and performance of workers, Yamamoto hopes to contribute to the development of better labor systems in Japan.

His research makes extensive use of government statistics and census data, but also involves surveying hundreds of workers and firms over time, a type of longitudinal data called panel data — an area where Yamamoto is assisted by Keio University's Panel Data Research Center.

Using a unique data set on managerial-level employees who were transferred from Japanese to European branches of the same global firms, Yamamoto found that the daily hours worked by Japanese workers dropped significantly when they were relocated to European offices that did not have a long working-hour culture[1]. This finding shows that Japanese workers are no more inclined to work long hours than workers in other countries, but are instead influenced primarily by the work habits of their peers.

Using another data set for Japanese male workers and their matched firms he also discovered that long hours is a product of a rational strategy by Japanese companies to maintain a skilled workforce[2]. Companies value and honor the lifetime commitment and skill accumulation of their employees, and to avoid the need for layoffs during downturns, they tend to understaff, resulting in chronic overwork of incumbents — the downside of lifetime employment.

Yet with long hours comes an inevitable drop in human productivity. "Japanese employees are now working so long that the labor productivity is among the lowest of the developed countries," notes Yamamoto. He hopes that his team's research will one day lead to these issues being addressed at the level of national policy.

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The Superhuman Sports Committee is developing technologies that can enable individuals of varying physical ability, including the elderly, to compete in sports events.

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Faster, higher and more technological

Japanese researchers are engineering the technology and rules of superhuman sports, just in time for the Tokyo Olympics

The famous victory of supercomputer Deep Blue over world chess champion Garry Kasparov in 1997 proved that machines were beginning to challenge the intellectual ability of humans. Kasparov soon turned his digital adversaries into allies, introducing Advanced Chess in which human players compete with the assistance of computer programs. These hybrid teams have defeated even the most advanced supercomputers.

At Keio University's Graduate School of Media Design, human augmentation and virtual-reality researcher Masahiko Inami is now applying this concept of transhumanism — using technology to enhance the human condition — to the physical arena.

"Man–machine integrated systems will become the strongest systems in the world," asserts Inami. In 2014, soon after the announcement of the Tokyo Olympics, he brought together a group of researchers, sports psychologists, video game designers, and magicians to form the Superhuman Sports Committee, which aims to encourage the development of human–machine integrated systems to transform the experience of sport for players, trainers, and audience alike.

In the lead-up to the 2020 Olympic Games, the committee plans to test the functionality, strength, and entertainment value of such integrated systems in a series of public annual competitions.

Spider vision and flying balls

As a high school student, Inami was fascinated with the technology culture embodied by technology-inspired anime and Tokyo's electronics wonderland of Akihabara. "I visited Akihabara almost every day," says Inami, who would go exploring with his friends and sometimes purchase used computer parts or electronic circuits. Later as an undergraduate, he built small robots and virtual reality equipment, including a mechanical arm that could serve beer perfectly. During his doctorate, inspired by the manga and film series *Ghost in the Shell*, Inami developed an 'invisibility cloak' that used projection-based technology and a special retroreflective material to optically camouflage objects.

Now a professor at Keio University, Inami is continuing these projects through the Superhuman Sports Committee. His team is developing tactile communication systems that can convey to audiences what it feels like to hit a tennis ball traveling over 200 kilometers an hour back over the net. Using liquid-crystal goggles, the crowd can get a clearer view of the ball's fuzzy surface as it speeds across the court. Inami's team is also developing a way to mimic the vision of spiders, to give players a 360-degree field of view through head-mounted displays.

Another member of the committee, Jun Rekimoto at the University of Tokyo has designed what he calls a Flying Head, in which a camera attached to a floating drone can follow athletes across the court and send real-time footage of their movements from a third-person perspective via a head-mounted device. This device could be used to train basketball players the way that wall-to-wall mirrors give dancers and gymnasts perspective. Rekimoto's team has also designed a drone-powered ball that evokes scenes from quidditch matches in *Harry Potter*.

More accessible sports

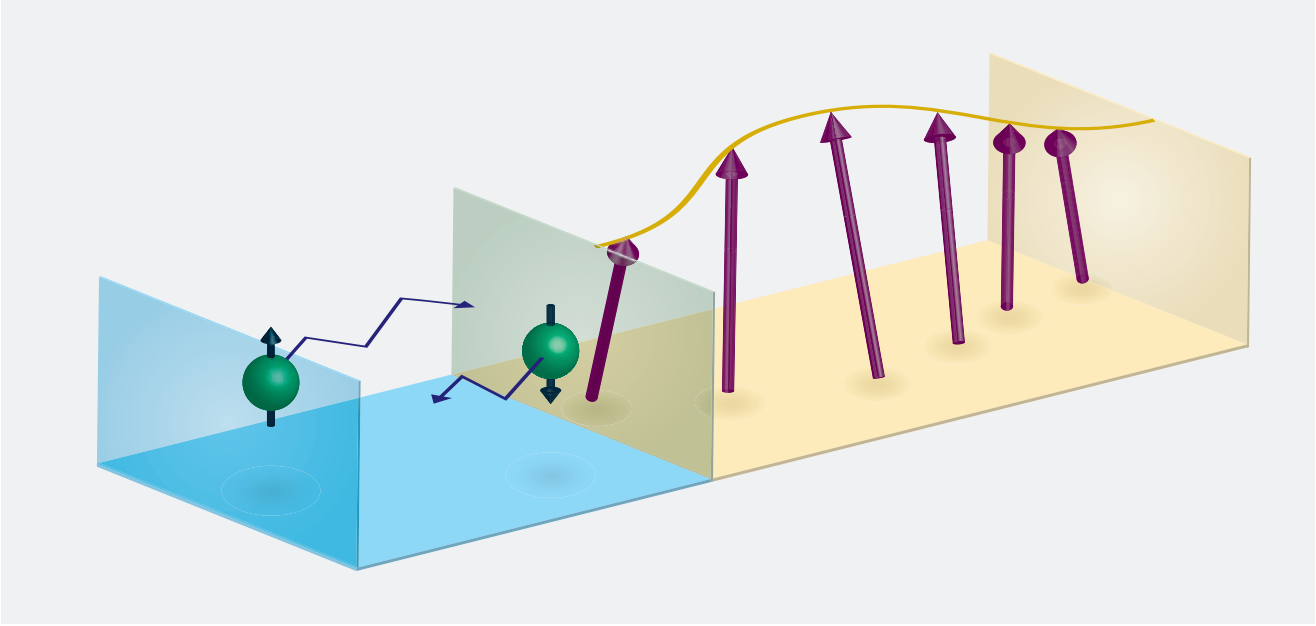
These technologies will force sports engineers to modify the rules of existing sports or invent entirely new sports, says Inami. Exoskeleton suits that can make sprinters run several orders of magnitude faster, for example, could make speed the lesser challenge. "Running fast is not so hard, but stopping safely is difficult." Perhaps the 100-meter dash could be made into a start-and-stop test, where runners are required to end the race exactly on the finish line.

> ***"World records in the Paralympics could soon surpass those of the Olympics."***

"Technology can also balance out differences in physical ability, for example due to age or disability," adds Inami, who foresees the emergence of more athletes like the German champion long-jumper and amputee Markus Rehm who beat able-bodied competitors at the German Athletics Championships in Ulm last year with a leap of 8.24 meters. Officials from Germany's track-and-field governing body raised questions as to whether Rehm's carbon-fiber prosthetic leg gave him an unfair advantage. Superhuman sports are likely to see such situations abound, says Inami. "World records in the Paralympics could soon surpass those of the Olympics."

A new degree of control for spintronics

Scientists in Japan have uncovered novel physics controlling spin-based electronics



Diffusing electrons in a metal (blue) establish a collective spin excitation in a neighboring insulator (beige) for the long-distance transmission of spin information in spintronic devices.

As successful as modern electronics has become, it cannot overcome one fatal flaw: pushing electrons down wires dissipates a lot of power. A new generation of spintronic devices can achieve much-improved power efficiencies by encoding information in electron spin, but they also face a steep challenge — spin information is quickly lost. Now, Hiroto Sakimura, Takaharu Tashiro and Kazuya Ando of the Department of Applied Physics and Physico-Informatics at Keio University in Japan have uncovered physics that may help make the long-distance transmission of spin information a reality[1].

The researchers focused on a spintronic system in which an electrical signal in a metal contact induces a traveling spin wave in a neighboring insulating wire (see image). This wave is a collective excitation of the spins of many immobile electrons and comes in discrete chunks (or quasiparticles) called magnons. The wave can travel long distances down the wire before creating a readout current in a second metal contact, which makes the system suitable for transmitting spin information in realistic devices.

Various unconventional techniques exist for controlling the size of the spin current flowing through the insulating wire. Among these is the process of splitting a single magnon into two magnons to increase the spin current. Interactions between magnons have also been observed to increase the magnitude of the current. Researchers, however, have been unclear about the underlying physics driving these enhancements.

Ando and his colleagues used the inverse spin Hall effect, in which a flow of spins creates a constant voltage, to demonstrate that these spin-current enhancements result from an increase in the average magnon lifetime. In the case of a single magnon splitting into two, the increase in steady-state spin current is not, as one might expect, directly the result of the two particles carrying a greater total angular momentum.

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Instead, magnons interact with each other through a process called spin damping in a way that increases their average lifetime. The researchers found that this process can increase spin currents even in the absence of magnon splitting.

By revealing the central role that magnon lifetimes and magnon–magnon interactions play in determining the magnitude of spin currents, these results may allow for a new way to control signal strengths — and therefore signal encoding — in spintronic devices. "The ability to create a spin current is an essential component of any spin-based technology," says Ando. "Our discovery therefore will be the basis for a new generation of spintronic devices."

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A therapeutic lead for heart muscle disorder

Reprogrammed stem cells show how a druggable hormone helps drive the problems associated with hypertrophic cardiomyopathy

An *in vitro* model of the hereditary heart disorder hypertrophic cardiomyopathy has revealed how genetic backgrounds interact with environmental factors to cause the hallmark phenotypes of the disease[1].

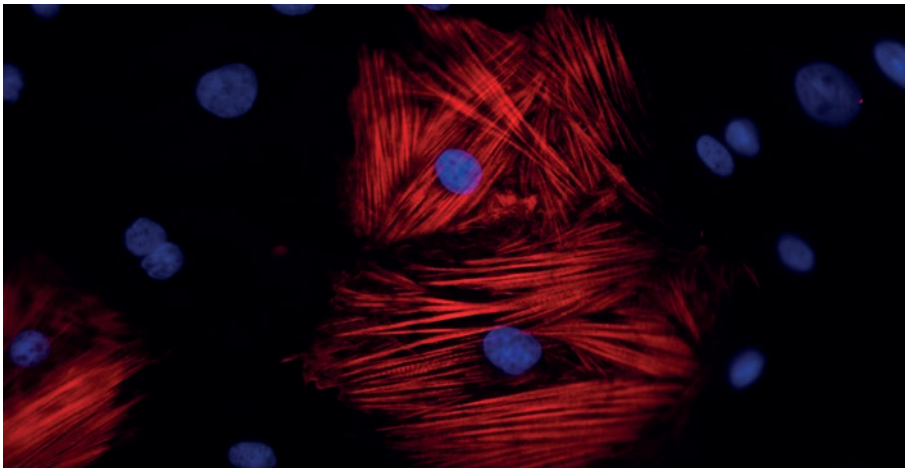
In hypertrophic cardiomyopathy, heart muscle cells increase in size, leading to thickening that makes it hard for blood to flow. The alignment of the cells also becomes disordered and irregular, causing changes in electrical signals that can trigger life-threatening abnormal heart rhythms. The condition is the leading cause of sudden unexpected death in young athletes and can cause debilitating cardiac problems in any age group.

To better understand the root cause of the disease, a team led by Keiichi Fukuda and Shinsuke Yuasa from Keio University School of Medicine took skin cells or blood cells from three unrelated patients with hypertrophic cardiomyopathy and three healthy controls. They introduced a virus expressing four pluripotency genes — the so-called Yamanaka factors, named after the Japanese Nobel laureate Shinya Yamanaka — and created embryonic-like 'induced pluripotent stem cells'. The researchers then coaxed these reprogrammed stem cells to form heart muscle cells called cardiomyocytes.

Under normal culture conditions, the morphological features and cellular behaviors of the cardiomyocytes from the healthy and diseased subjects appeared largely the same. However, when the researchers exposed the cells to endothelin-1, a hormone known to trigger the constriction of blood vessels, they observed large differences in the architecture of rod-like muscle fibrils (see image).

High-speed imaging studies further revealed that the heart muscle cells from patients with the condition beat out of sync when subjected to treatment with endothelin-1. This was true whether the cardiomyocytes came from stem cells derived from someone with a mutation in *MYBPC3*, a gene that is often dysfunctional in people with hypertrophic cardiomyopathy, or from patients with the disease but no known causative mutation.

The researchers confirmed their findings in a mouse model. Using cardiomyocytes derived from newborn mice with a heterozygous mutation in the mouse version of the *MYBPC3* gene, they showed that endothelin-1 induced similar problems in muscle fibrils to those seen in the human cells.



Cardiomyocytes derived from the reprogrammed cells of a patient with hypertrophic cardiomyopathy show augmented disarray in the presence of the hormone endothelin-1.

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Several drugs that block endothelin receptors are already on the market to treat another heart condition called pulmonary arterial hypertension. The findings from Fukuda, Yuasa and their colleagues suggest that these same agents might help people with hypertrophic cardiomyopathy as well. "We are planning a clinical study to know if an endothelin-1 blocker could be a standard therapy," says Yuasa.

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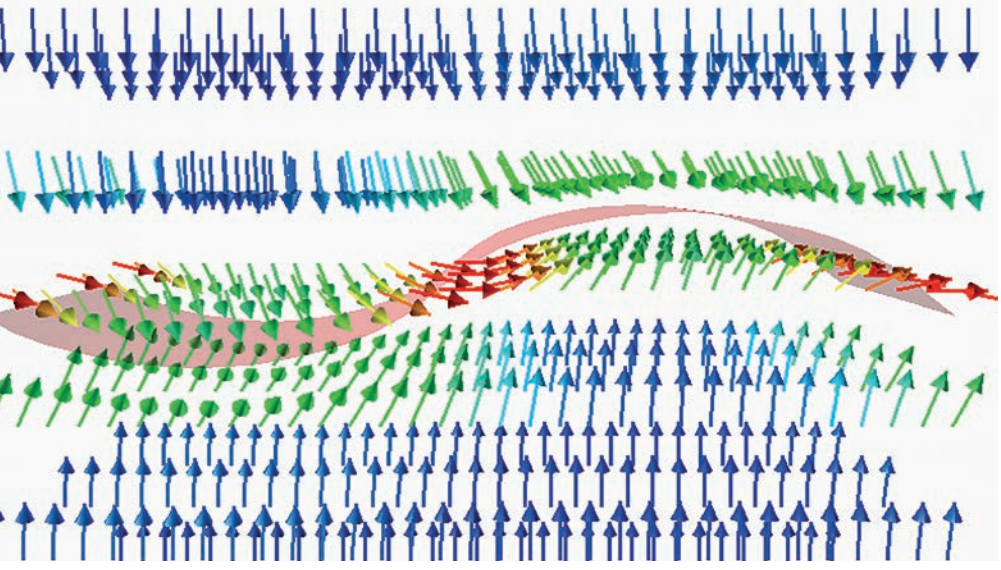
The not-so-symmetric Universe

Broken symmetries may provide a pathway to a unified theory of the Universe

Symmetry is an important mathematical concept that forms the basis of fundamental laws of the Universe. Researchers in Japan have now uncovered that imperfections rather than perfect symmetry might hold the key to understanding the forces that drive the Universe.

The fundamental forces of the Universe such as gravity, magnetism, and even space and time itself are inherently symmetric, which means that they exhibit the same properties in all directions. Therefore, physicists searching for a unified theory that can describe the Universe and all its forces are looking for theories that are based on perfect symmetries.

Their efforts, however, have run into a dead end. While it has been possible to unify most fundamental forces based on symmetry principles, adding gravity has been impossible. Muneto Nitta from Keio University and Michikazu Kobayashi from Kyoto University have now discovered that looking for perfect symmetries might be the wrong approach. "Our finding suggests a possibility of unification of gravity with other fundamental forces, if the relativistic symmetry is spontaneously broken," says Nitta.



Domains are regions in magnets where the magnetism points in different directions (blue arrows). Separating these domains are domain walls, which can show dynamic wave motions of the magnetic direction (green, red arrows).

Rather than studying forces and their symmetries at the high energies that were present in the cosmos right after the creation of the Universe, the researchers focused on low energies, such as conventional magnets. Magnets that are fully magnetized are symmetric, meaning that their magnetic components all point in the same direction. However, at intermediate magnetizations magnetic domains form, which are regions with different magnetic orientations. Separating these regions are domain walls, across which the magnetic orientation of atoms switches (see the arrows in the image).

Domain walls break the symmetry of magnets and this results in energetic excitations, like when a stone is thrown into a pond. The energy created by the stone breaking the perfect symmetry of the water's surface creates small ripples. Similarly, the magnetic fields across a domain wall can also create ripples.

Applying a theoretical framework of equations describing broken symmetries, Kobayashi and Nitta showed that some of these ripples are the consequence of a coupling of the magnetic force and the space and time symmetry of the material[1].

Given the difficulties in unifying symmetries of fundamental forces with space and time at high energies, this coupling was unexpected, and, says Nitta, "can provide some hints for unified high-energy theories." While

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the present findings apply only to low-energy dynamics, the strategy of unifying fundamental forces through broken rather than perfect symmetries could lead to an entirely new understanding of the Universe.

Reference

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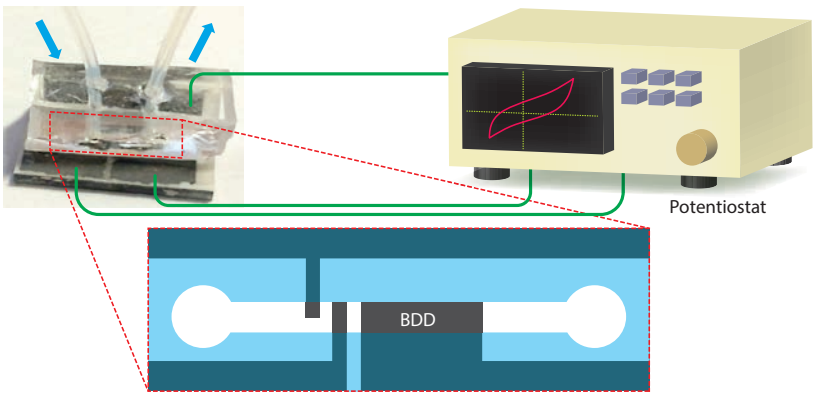
Winning the super-enzyme lottery

A microfluidic instrument that can rapidly screen millions of electron-transferring enzymes may uncover the next biofuel device



Microchip devices containing boron-doped diamond (BDD) microelectrodes can screen enzymes for catalytic activity with remarkably high throughput, measured using a potentiostat.

The power output and stability of biofuel cells that generate cheap electricity with catalytic enzymes can now be improved thanks to an analytic instrument developed at Keio University[1]. Nobuhide Doi from the Department of Biosciences and Informatics and colleagues have fabricated a device that screens libraries of potential enzyme catalysts hundreds to thousands of times faster than conventional methods using micro-sized electrodes and microfluidic sample handling.

NAD(P)-dependent oxidoreductases are enzymes that catalyze electron transfer between a broad range of biomolecules. This versatility has led researchers to investigate if the enzyme could replace heavy metal catalysts in electricity-generating fuel cells. So far, however, the oxidoreductases tested in biofuel cells have shown insufficient activity and stability for practical applications.

One way to improve the properties of existing oxidoreductases is with a process called directed enzyme evolution that mimics natural evolution to build up massive libraries of enzymes bearing slight mutations in their structures. Then, screening and selection experiments test the mutated enzymes' catalytic properties to help guide the evolution process. Current screening techniques based on light adsorption can assess thousands of clones at once, but higher-throughput methods are needed to advance fuel cell development.

Doi and his team explored whether the catalytic ability of NAD(P)-dependent oxidoreductases could be detected by measuring their electrochemistry — a significantly faster screening method that requires only tiny sample volumes. Achieving this goal required special 'boron-doped diamond (BDD) microelectrodes' developed by Yasuaki Einaga at Keio University. These robust, needle-shaped devices can survey a wide range of electrochemical conditions while having very low background current, making them ideal for ultra-sensitive detection of enzyme activity.

The team constructed a tube-shaped microfluidic device that continuously flows small volumes of enzymes past a BDD microelectrode detector (see image). After optimizing for pH and anti-protein aggregation effects, they tested the activity of two important catalytic enzymes: glucose-6-phosphate dehydrogenase and alcohol dehydrogenase. Remarkably, the new instrument needed only a millisecond to detect part-per-trillion concentration levels of the dehydrogenases, and required mere nanoliters of sample volumes. "The cost and time can be saved significantly compared with conventional methods," says Doi.

The speed and accuracy of the microfluidic–BDD microelectrode device implies it could handle much larger screening libraries than current techniques — potentially up to one million enzyme clones. Doi is confident this approach can narrow the search for 'super enzymes' appropriate for biofuel cells, likening it to a gambler improving his odds. "The more lottery tickets you buy, the higher your chance of winning," he adds.

Reference

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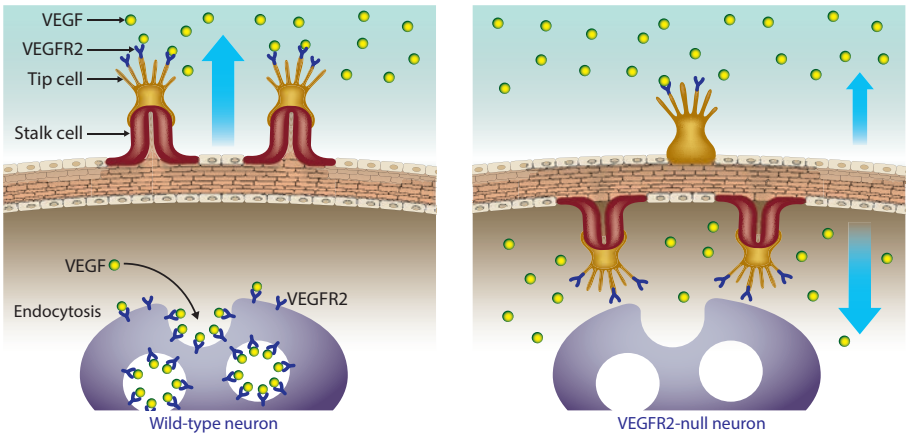
Preventing abnormal eye vessel growth

A molecular process crucial to the postnatal development of the retina is uncovered by an international team of researchers

A key molecular process governing the healthy development of the eye in mice has been uncovered by researchers at Keio University, along with international collaborators. Their unexpected findings may inform new treatments for eye diseases[1].

The eyes are a good example of the essential role played by complex interactions between the central nervous system and the blood and lymph vessel networks that ensure the healthy development of the body after birth. Without the correct development of the retina, signals sent via neurons to the central nervous system would be disrupted, potentially affecting our ability for sight.



A growth receptor called vascular endothelial growth factor receptor 2 (VEGFR2) prevents over-vascularization of retinal neurons by binding excess VEGF. In mouse models that do not express the VEGFR2 receptor in their retinal neurons, the vessels grow inward toward the neurons instead of outward.

> *This unprecedented mode of VEGF regulation may help to uncover strategies for targeting human diseases related to excess vessel growth, such as cancer and rheumatoid arthritis.*

The growth, pattern, and distribution of blood vessels in the body is regulated by a signaling protein called vascular endothelial growth factor (VEGF). New blood vessels emerge from pre-existing vessels when VEGF activates receptors present in endothelial cells that line all of the veins in the body — a process called angiogenesis.

Yoshiaki Kubota and co-workers at Keio University, together with scientists from across Japan, the United States, and Australia, made a surprising discovery when they set out to investigate angiogenesis in the development of the eye, and in particular the retina, after birth.

"Most researchers are focusing on the signaling and function of a VEGF receptor called VEGFR2 in endothelial cells," says Kubota. "However, to our surprise we discovered that VEGFR2 is much more abundantly expressed in neurons than in endothelial cells in mouse retinas."

This initial discovery enticed the researchers to examine why VEGFR2 was so strongly expressed in retinal neurons. The team painstakingly generated multiple lines of mice with the *Vegfr2* gene deleted from their retinal neurons. They found that the absence of neuronal VEGFR2 in the retina led to misdirected angiogenesis — instead of sprouting new vessels outward, the vessels began to grow inward toward the neurons themselves (see image). This caused unusually dense vascular growth around the retinal neurons. "VEGFR2 essentially acts as a barrier, binding VEGF and therefore preventing excess vessel growth in the retina," explains Kubota. "This process ensures that the eye receives the appropriate level of vascular supply and prevents over-vascularization."

Further analysis is required to determine if a lack of VEGFR2 receptors in the retina could have an impact on eye diseases such as diabetic retinopathy.

"We also hope that this unprecedented mode of VEGF regulation may help to uncover strategies for targeting human diseases related to excess vessel growth, such as cancer and rheumatoid arthritis," says Kubota.

Reference

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Reframing the language of dementia

A structured approach to language shows promise for improving the lives of dementia patients and their families

A diagnosis of dementia is likely to instill something akin to terror. But consider what could happen if we stopped using the language of loss when talking about the condition. This is the approach advocated by Takashi Iba from the Faculty of Policy Management and the Graduate School of Media and Governance at Keio University. In a booklet specifically designed to provide a structured way to communicate about dementia, Iba describes the onset of dementia as the beginning of a journey.

Words for a Journey provides a structured way for families and caregivers to communicate with loved ones living with dementia.

An aging society

With the global rise in average life expectancy, it is more likely than ever that we or someone close to us will be affected by dementia. In Japan — the world's first super-aged nation with more than 25 per cent of its present population above the age of 65 — the number of people with dementia is projected to reach 7 million by 2025.

Iba's research involves developing 'pattern languages', for which practical knowledge is mined from a variety of data sources and then organized into a pattern format. Pattern languages are used in a range of fields, including architecture, software design and creative activities.

Iba was giving a seminar on the creation of pattern languages in early 2014, when Makoto Okada of Fujitsu Laboratories approached him and asked whether he was interested in collaborating with him to create a new type of pattern language that would help people living with dementia. "I was immediately struck by the importance of developing such a support system, especially in Japan, and also, of course, around the world," says Iba.

The work was fast-tracked. Iba initiated the project with his students and several external collaborators in June 2014. They interviewed dementia patients and their caregivers and then organized the mined information into a pattern language. But for the work to make an impact, they realized that they needed to find a way of sharing the new language with patients, families, caregivers, doctors, and people for whom dementia is not a current concern. To realize that goal, they published the booklet *Words for a Journey* in Japanese and English in October 2014, a mere five months after commencing the project.

Words of care

The researchers constructed a pattern language for three separate groups: people with dementia; families and friends; and society as a whole. Accordingly, *Words for a Journey* is divided into three sections: "Words for the cared", "Words for the caring", and "Words for everyone". Each section is divided into a context, problem, solution, and name.

For example, "Words for the cared" describes how dementia patients tend to spend less time outside the home — the *context*. One *problem* that can arise from this is that patients may become depressed staying indoors or feel lost if they venture out by themselves. A *solution* would be to find a place that the cared can travel to by themselves and which their family knows; this place is called their 'favorite place' (*name*). To make living with dementia more manageable, Iba and his collaborators suggest reframing dementia as a 'new journey' and viewing it as an opportunity to learn more about one's loved ones.

To date, 500 copies of the booklet have been distributed. "It is touching to see the booklet welcomed by people who are affected by dementia," Iba notes. "We hope that these patterns will help to solve their problems and improve their daily lives."

As a firm believer in the capacity of pattern languages to improve lives, Iba hopes that the approach will encourage a social movement in which individuals share their experiences and mine information to establish a practical knowledge base for living well with dementia. His group plans to build on their work through community-centered dialogue workshops to demonstrate that "everyone can use patterns as a source of imagination and innovation."

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Measuring the galactic center

Surveys of a huge gas disk orbiting the center of our Galaxy can improve our understanding of black holes and star formation

The Milky Way has a supermassive black hole at its center. Telescope surveys can be used to identify the chemicals in a huge gas disk around the center to learn how the black hole functions and how stars are formed.

Our Galaxy, the Milky Way, rotates around a supermassive black hole at its center. Spinning around this center is a large disk of molecular gas, known as the circumnuclear disk, which was likely formed when the intense gravity of the black hole captured surrounding molecular clouds. Given its great size and density, the circumnuclear disk is believed to be a likely site for the formation of stars, but little is known about its composition.

Now, researchers at Keio University have collected spectral data that reveal the molecular make-up of the circumnuclear disk in great detail[1]. Tomoharu Oka and co-workers at Keio's School of Fundamental Science and Technology and Department of Physics used the radio telescope at the Nobeyama Radio Observatory to measure the intensity of radio waves from the disk, and from two neighboring giant molecular clouds that may be feeding it.

"The Nobeyama Radio Observatory 45-meter telescope is one of the world's best instruments for this work, having the largest diameter dish, wide frequency coverage, and high mapping efficiency," says Oka. He and his team sampled frequencies from 81 to 116 gigahertz, and attained the first unbiased spectra, meaning they had uniform quality over the frequency range.

The biggest challenge for the researchers was to identify which spectral lines came from which source. This was only possible because the circumnuclear disk rotates much faster than the nearby giant molecular clouds, producing a greater so-called Doppler shift in frequency.

"The spectral line shapes were highly complicated, so it was difficult to analyze," says Oka. "However, we believed that there

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must be some difference in nature between the molecular gas in the circumnuclear disk and giant molecular clouds." The team's analysis revealed that these huge astronomical features contain a mix of 30 molecular species, including some rare organic molecules.

We cannot see black holes, of course, and the main evidence that ours exists is a very bright source of radio waves, called Sagittarius A*. However, Sagittarius A* is not as bright as theory predicts. Oka and co-workers hope that their observations of the circumnuclear disk could help to solve this mystery and reveal other secrets about the center of our Galaxy and others.

"The circumnuclear disk is a potential reservoir for material flowing into the center, and so it could determine the future activity of the black hole," he says. "Its physical conditions and chemical composition must reflect the central activity."

Reference

1. Takekawa, S., Oka, T., Tanaka, K., Matsumura, S., Miura, K. & Sakai, D. Millimeter-wave spectral line surveys toward the galactic circumnuclear disk and Sgr A*. *The Astrophysical Journal Supplement Series* **214,** 2 (2014).

An emerging new focus for heart disease

A critical regulatory protein offers a potential new opportunity for treating the frequently fatal heart condition cardiac hypertrophy

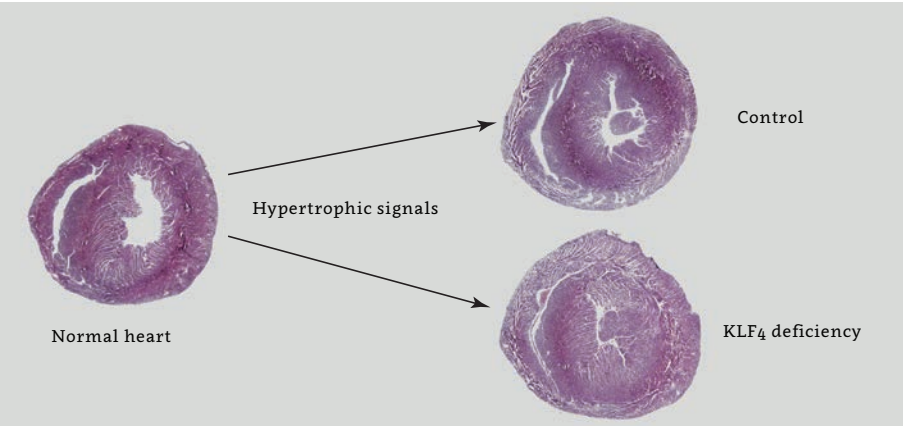
A team of researchers from Keio University has shown that a key transcription factor protein plays a role in regulating cardiac hypertrophy in mouse models of the disease[1]. The condition is characterized by thickening of the heart muscle and a reduction in the size of the heart's chambers, including the left and right ventricles. It is commonly caused by high blood pressure which, according to statistics by the World Health Organization, afflicts an estimated one billion people worldwide.

The transcription factor Krüppel-like factor 4 (KLF4) plays a crucial role in reading and interpreting the coded messages written in DNA. KLF4 binds directly to DNA to influence the behavior of multiple genes related to cellular differentiation, proliferation, and inflammation. The protein is known to function throughout the body but has been shown to be particularly active in the body's cardiovascular system — the heart and blood vessels.

Physician and biochemist Tadashi Yoshida and his colleagues at Keio University School of Medicine have been working on the intriguing protein for almost a decade. Most notably, since 2008 they have been exploring and explaining the critical role KLF4 plays in regulating the tough fatty build-up that accrues along the walls of arteries. This build-up is known as atherosclerotic plaque, and it narrows arteries and restricts the flow of oxygen-rich blood, ultimately causing potentially fatal heart attacks and strokes. Yoshida and colleagues, in collaboration with researchers from other institutes, had previously shown in mice that removing the genes responsible for expressing KLF4 accelerates the appearance of this plaque.

In their most recent investigation, Yoshida's team found that in mouse models of cardiac hypertrophy that lacked the *Klf4* gene in their cardiac muscle cells, or cardiomyocytes, the heart condition became worse (see image). The researchers further showed that KLF4 plays a role in mediating the antihypertrophic activity of a compound called trichostatin A (TSA) — TSA repressed the development of cardiac hypertrophy in control mice, but not in the *Klf4*-deficient mouse models.

These findings suggest that KLF4 is worthy of further investigation as a treatment



The hearts of mouse models deficient in Krüppel-like factor 4 (KLF4) protein show enhanced development of cardiac hypertrophy relative to control mice following stimulation by signaling molecules to induce the disease.

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for cardiac hypertrophy. Moreover, the response of TSA to KLF4 suggests other lines of inquiry. TSA is known to have epigenetic effects on cardiomyocytes, a process that could provide useful insights into the function of KLF4 if further explored. "It is of significant interest to find out how a cardiomyocyte-specific epigenetic modulator regulates cardiac hypertrophy through the regulation of KLF4," says Yoshida.

Reference

1. Yoshida, T., Yamashita, M., Horimai, C. & Hayashi, M. Kruppel-like factor 4 protein regulates isoproterenol-induced cardiac hypertrophy by modulating myocardin expression and activity. *The Journal of Biological Chemistry* **289,** 26107–26118 (2014).

Organic synthesis with light-coupled carbohydrates

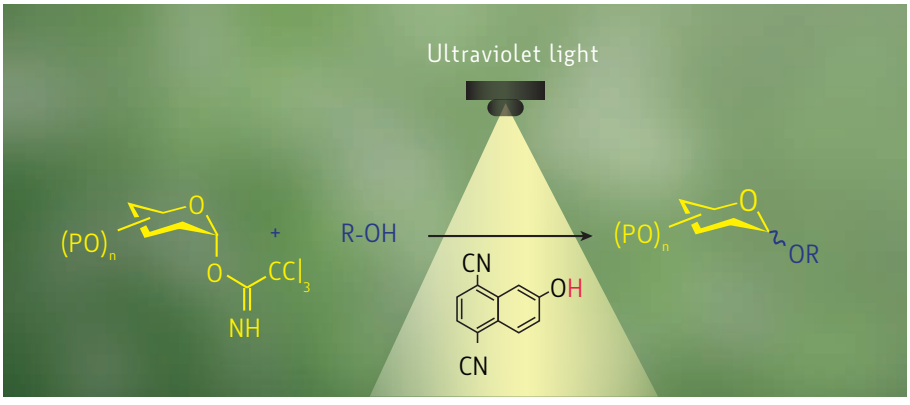
A reusable reagent offers a greener way to make carbohydrate-containing molecules

The synthesis of organic molecules using methods that result in minimal waste and take advantage of renewable energy sources has been a long-term goal for chemists. Researchers at Keio University have shown that certain organic acids can facilitate the coupling reaction between carbohydrates and various alcohols, and then be recovered and reused without any loss of reaction efficiency[1]. The glycosylation reaction, as well as benefiting from the recyclability of the acidic reagent, is triggered by light — a clean energy source. "Our glycosylation reaction is highly environmentally benign compared with conventional methods," says study author Kazunobu Toshima. "Moreover, it is the first example of a synthetic organic reaction employing reusable organic acids, which have been activated by photo-irradiation."

Glycosylation involves attaching a carbohydrate to other sugars or organic molecules to yield oligosaccharides or glycosides. Carbohydrate-containing molecules such as glycoproteins and glycolipids are vital participants in many biological processes. Glycosylation reactions are also common steps in the synthesis of bioactive and functional products, ranging from antibiotics to biodegradable surfactants. Given their widespread application, novel and environmentally benign routes to glycosylated products are highly sought after.

With this in mind, Toshima and colleagues identified several organic acids that can act as photo-activated reagents for glycosylation (see image). The organic acids comprise aromatic molecules with hydroxyl groups attached directly to the aromatic system — more specifically, phenol or naphthol derivatives. Irradiation with ultraviolet light increases the acidity of the organic acids, which causes a trichloroacetimidate group to leave the glycosyl donor and creates an intermediate suitable for reaction with various alcohols. The electron-donating capability of the organic acids was not sufficient to react with this intermediate, so no unwanted coupling with the hydroxyl group of the acids occurred.

The researchers then removed the ultraviolet light source to neutralize the reaction mixture and applied heat at a relatively low temperature to isolate the glycosylated product from the recyclable organic solvent, ether. The organic acids could be recovered in greater than 90 per cent yield,



The environmentally benign glycosylation reaction for the coupling of carbohydrates (yellow) and alcohols (blue) using organic acids (black).

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after purification of the reaction mixture using column chromatography, and reused with no loss of efficiency.

Toshima sees few hurdles in scaling up the reaction. "A large-scale reaction would only need a more powerful light source and a larger reaction vessel," he says.

"We envisage the development of different types of synthetic organic reactions using these light-activated organic acids, for example, carbon–carbon bond formation reactions, such as Mannich or Strecker reactions," he notes.

Reference

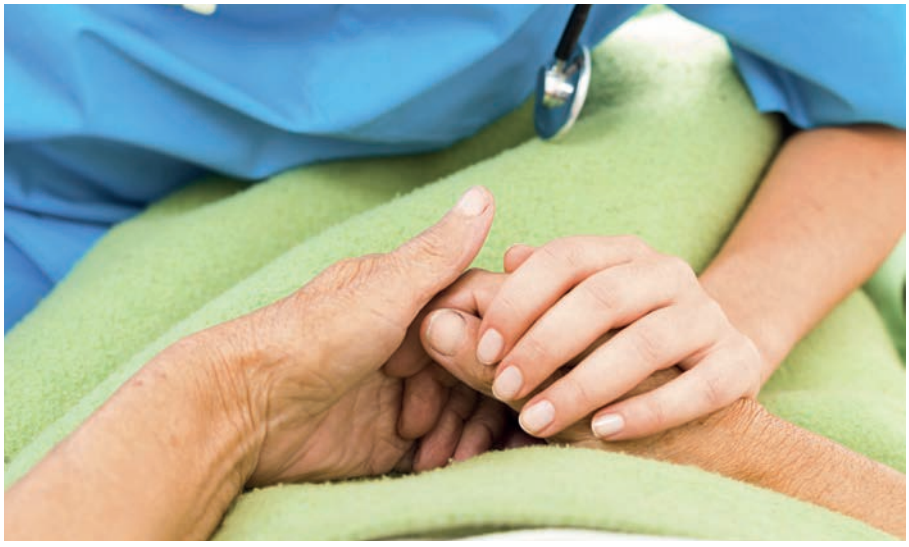
1. Iwata, R., Uda, K., Takahashi, D. & Toshima, K. Photo-induced glycosylation using reusable organophotoacids. *Chemical Communications* **50,** 10695–10698 (2014).

Combined therapy for breast cancer

A multi-pronged approach appears to be the most effective early treatment against a common and aggressive form of breast cancer

Women suffering from breast cancer fueled by the overexpression of human epidermal growth factor receptor-2 (HER2) have the best chance of eliminating the disease when receiving two presurgical treatments in conjunction with chemotherapy, a Keio University School of Medicine research team has discovered[1].

Breast cancer — the most common cancer in women — kills about half a million women each year worldwide. Of the more than 1.5 million new cases diagnosed annually, about 20 per cent are HER2 positive — an aggressive form of the disease characterized by elevated levels of the HER2 protein, which promotes cancer cell growth and division.



Combining two presurgical treatments with chemotherapy offers women with an aggressive form of breast cancer the best chance of eliminating the disease.

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Historically, HER2-positive breast cancer has had a poor prognosis. This has made it the focus of an expanding range of neoadjuvant therapies — treatments administered prior to primary treatments such as the surgical removal of cancerous tissue. As a result, HER2-positive breast cancer has become highly treatable, with four US Food and Drug Administration-approved anti-HER2 therapies now available. Of these, the monoclonal antibody trastuzumab has become the preferred therapy option for the metastatic form of the disease.

To identify the most effective treatment, Tetsu Hayashida and his colleagues at Keio University conducted a 'network meta-analysis' of the available relevant research on neoadjuvant therapies. Unlike conventional meta-analysis, which compares two subjects and determines which is better, the network meta-analysis approach compares and ranks all available subjects, resulting in improved decision making. "Network meta-analysis synthesizes information from a network of trials and combines direct and indirect evidence on the relative effectiveness of the treatments," explains Hayashida.

By using an electronic database, the Keio research team assessed 1,047 studies from which they identified 10 studies that met the eligibility criteria for their analysis, covering a total 2,247 patients in 7 different treatment arms.

To measure the efficacy of the different neoadjuvant therapies, the researchers compared for each treatment the number of patients with no residual histological evidence of a tumor at the time of surgery, a measure known as the pathological complete response. Patients who achieve this response are at a reduced risk of disease recurrence, which is associated with long-term survival — "one of the most important values in cancer treatment," says Hayashida.

The researchers' analysis identified that the most effective neoadjuvant treatment for HER2-positive breast cancer is to combine chemotherapy with two anti-HER2 agents — trastuzumab plus lapatinib and trastuzumab plus pertuzumab. This finding will directly impact the clinical treatment of HER2-postive breast cancer, says Hayashida.

Reference

1. Nagayama, A. *et al.* Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: A network meta-analysis. *Journal of the National Cancer Institute* **106,** dju203 (2014).

Quantum dots with temperature-dependent color

Nanometer-sized quantum dots whose color varies with temperature could be used for thermal sensing and solar protection

Researchers in Japan have produced quantum dots with sizes of around 1 nanometer by using the tiny pores in microporous silica as a mold[1]. The color of these quantum dots can be reversibly changed from pale blue to deep green by varying their temperature from 25 to 400 degrees Celsius (see image). This ability to change color with temperature, known as thermochromism, is promising for use in a wide range of applications, including solar protection and thermal indicators.

The color of quantum dots generally changes with their size (as shown here), but microporous silica can be used to produce nanometer-scale quantum dots whose color also varies with temperature.

"One-nanometer and sub-nanometer quantum dots have been little explored because of the difficulty of synthesis," says Hiroaki Imai who led the research with co-workers from Keio University and Tokyo Metropolitan Industrial Technology Research Institute. "Our findings provide a versatile method for producing size-controlled quantum dots in this size range."

Quantum dots are tiny particles of a semiconducting material with diameters generally in the 2 to 10 nanometer range, containing only a few tens of atoms. At these small sizes, quantum mechanical effects become significant. One manifestation of this is that their bandgap — the energy gap between the valence and conduction bands — increases with decreasing size.

Various methods have been developed to produce nanoscale quantum dots, but the synthesis of sub-nanoscale quantum dots has proven difficult. Such a method is highly desirable as it is anticipated that most transition-metal oxides will exhibit significant quantum effects only when they are approximately one nanometer or smaller.

Imai's team has demonstrated a versatile and controlled method to produce such quantum dots. The researchers grew copper oxide quantum dots in three porous silica samples with pore diameters of 0.6, 0.9, and 1.7 nanometers. Scanning transmission electron microscopy confirmed that this technique produced quantum dots whose diameters corresponded closely to the pore sizes of the silica templates.

The researchers found that the color of the copper oxide quantum dots depends on their size and varies reversibly with temperature. They attribute the variation of color with temperature to a shift of the bandgap and enhanced coupling between electrons and phonons induced by the confined volumes of the quantum dots.

This strong coupling came as a surprise to the researchers and suggests that quantum dots that are 1 nanometer or smaller in size may harbor other unusual properties.

"Conventional thermochromic materials are generally used at around room temperature due to their poor heat resistance," explains Imai. "The good thermal stability of these size-dependent thermochromic quantum dots means that they could be applied in durable temperature gauges in high-temperature systems."

Reference

1. Tamaki, H., Watanabe, H., Kamiyama, S., Oaki, Y. & Imai, H. Size-dependent thermochromism through enhanced electron–phonon coupling in 1 nm quantum dots. *Angewandte Chemie International Edition* **53,** 10706–10709 (2014).

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The Keio Medical Science Prize

The 2014 Keio Medical Science Prize Laureates

"It is a tremendous honor to receive the 2014 Keio Medical Science Prize, in recognition of our efforts to develop optogenetics, and to apply this technology to deepen the understanding of the brain in health and disease. This Prize is particularly meaningful because optogenetics originated as a tool to study the basic science of biology, not medical illness, and yet is enabling discovery of insights into disease states, as well as into healthy brain function. From both the neuroscience and psychiatry perspectives, I hope that this story helps further encourage and strengthen fundamental biology research."

Karl Deisseroth

"I am grateful to the selection committee for awarding me the Keio Medical Science Prize, by which I was greatly honored. This award recognizes our 20 years of efforts to understand how morphological asymmetries develop in the mouse embryo. I have been fortunate to share a number of exciting findings with many talented colleagues in Tokyo Metropolitan Institute of Medical Science and Osaka University. Collaborations with many scientists all over the world were also essential. My thanks go to those colleagues and collaborators."

Hiroshi Hamada

Objective

The Keio Medical Science Prize is an international prize that gives recognition to the outstanding and creative achievements of researchers in the fields of medicine and life sciences, in particular those contributing to scientific developments in medicine. It aims to promote worldwide advances in these fields to encourage the expansion of researcher networks throughout the world and to contribute to the well-being of humankind.

Prize

Laureates receive a certificate of merit, a medal, and a monetary award. The award ceremony and commemorative lectures are held at Keio University.

Nomination and Selection

Nominees must have made an outstanding contribution in the fields of medicine or life sciences closely related to medicine, and must be currently active in their field of research.

1. An invitation is sent out to academics and researchers all over the world each year, inviting them to nominate a candidate for the Prize.
2. The Keio Medical Science Prize Selection Committee reviews the nominations, selects laureates through a rigorous review process, and submits a recommendation to the Board.
3. The Board makes the final decision and the President of Keio University formally announces the laureate(s).

Yearly Schedule (Subject to change)

- Call for Nominations: Late January
- Deadline for Nominations: Early March
- Prize Announcement: Mid-September
- Award Ceremony: November or December at Keio University

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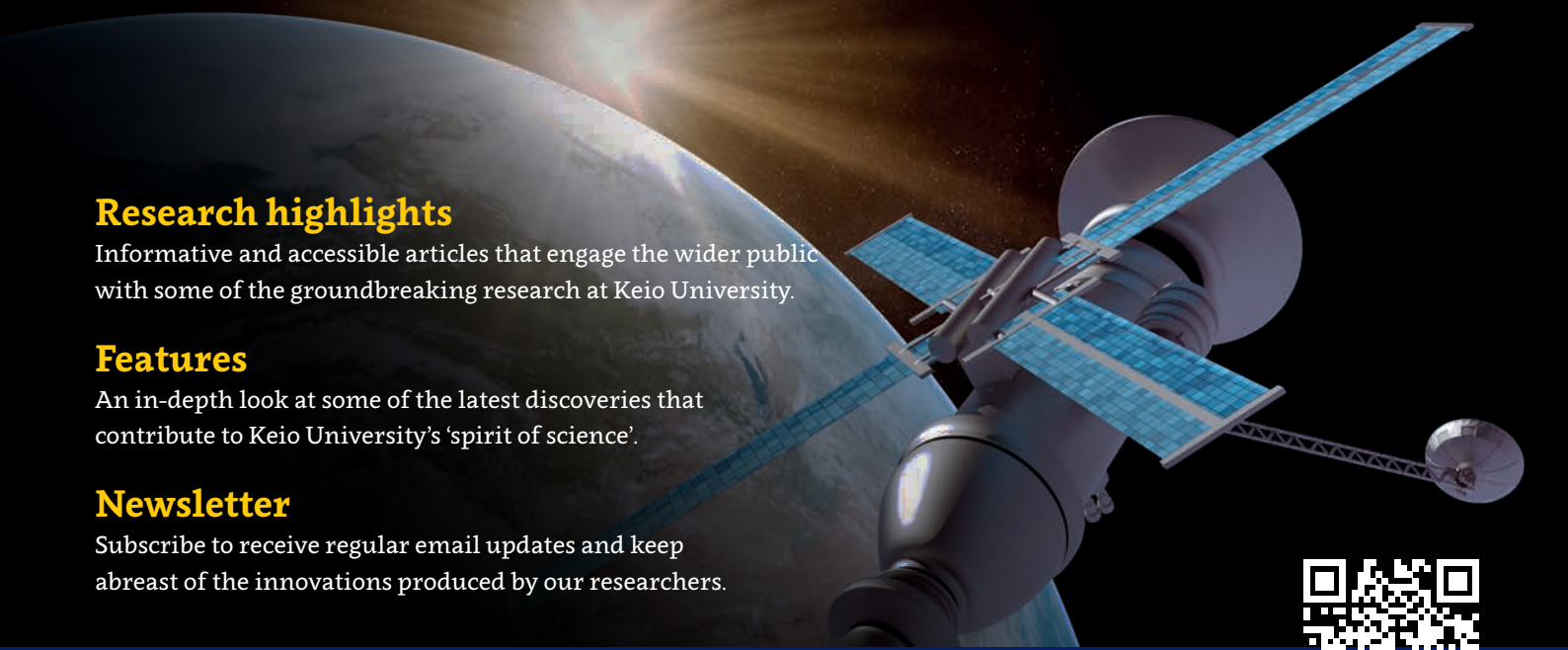
A new website, bringing Keio University science to the world



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