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Issue 3
May 2017

JITSUGAKU

Showcasing the best research from Keio University

100 years of excellence

Medical innovation since 1917

Stroke of genius
Healing the brain with robots

Junk food
Bacterium found that digests plastic

Physics rewritten
Dark matter jolts LHC experiment

Keio University

since 1917
Keio University School of Medicine

Celebrating 100 years of Keio medicine in 2017

The Keio University School of Medicine was established in 1917, with renowned microbiologist Shibasaburo Kitasato serving as its first dean. Kitasato's vision of unity between basic medical research and clinical medicine has guided the school since its inception.

Over the past 100 years, Keio University School of Medicine has become a major center for world-leading medical research and education, and plays an indispensable role in the development of medical care in Japan.

ON THE COVER

1920 KEIO UNIVERSITY HOSPITAL OPENS

The opening ceremony for the Keio University Hospital was held on November 6, 1920 and the first general meeting of the Keio Medical Society was held on November 8 of the same year. *Keio Igaku*, the Journal of the Keio Medical Society was first published in 1921. The Building for Preventive Medicine & Public Health (Institute of Preventive Medicine) was completed in 1929, thanks to donations from the Rockefeller Foundation.

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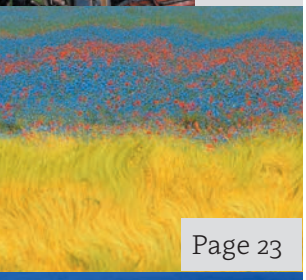
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Further information
Keio University is Japan's oldest institute of higher education, founded in 1858 by educator and intellectual leader Yukichi Fukuzawa.

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Keio University

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JITSUGAKU

Hundred years of medical excellence

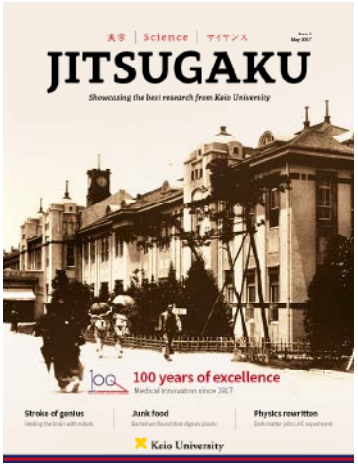
Keio celebrates a century of education, research, and clinical service in the medical and life sciences

The year 2017 marks the 100th anniversary of Keio University School of Medicine, a global center of learning, medicine, and research in the heart of Tokyo. For the past century, the school has upheld the mission set out by its founding fathers: visionary leader and educator, Yukichi Fukuzawa, and respected microbiologist, Shibasaburo Kitasato. Fukuzawa was a strong advocate for social change informed by reason and education, which Kitasato, who served as the School's first dean, realized through an equal commitment to basic and clinical medicine.

The School of Medicine inspires young students to become pioneers in the world of medicine, and backs scientific developments that lead to paradigm shifts in the medical and life sciences. Every year, Keio University rewards researchers that exemplify these ideals, with the Keio Medical Science Prize. This prize has gained global prominence as a prestigious reward for excellence and innovation, even anticipating seven Nobel laureates (see page 4).

For more than 150 years, Keio University has thrived under the motto of *jitsugaku*. In November 2016, it established a new institute that will strengthen its promise to realize a world where people live safer, longer, and more creative lives. The Keio University Global Research Institute will coordinate multidisciplinary research aimed at addressing the challenges facing Japan and the rest of the world in an era of political, social, and environmental upheaval (see page 17).

The articles in this third issue of *Jitsugaku* reflect Keio's ongoing efforts in this direction, from revealing the links between manga and western literature, to discovering how crows' beaks adapted to tool use, and discovering plastic-eating bacteria. We hope that you will join us on our journey into the next hundred years.



Issue 3, May 2017

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.

since1917
Keio University School of Medicine

A prize for science visionaries

The Keio Medical Science Prize recognizes scientific developments that have led to paradigm shifts in medical and life sciences

The 21st Keio Medical Science Prize went to Japanese immunologist Tasuku Honjo (center right) and Swedish evolutionary biologist Svante Pääbo (center left). Keio University President Atsushi Seike (right) and professor and dean of the Keio University School of Medicine, Hideyuki Okano (left), congratulated the laureates at an awards ceremony in Tokyo.

Every year since 1996, Keio University has honored the world's most outstanding medical researchers with The Keio Medical Science Prize, a globally recognized award that reflects the university's commitment to excellence and innovation in education, research and medicine. Remarkably, the prize has anticipated the Nobel Prize on multiple occasions, and seven winners of the Keio Prize have gone on to become Nobel Laureates.

The history of the Keio Prize dates to the early 1990s, when a Keio alumnus called Mitsunada Sakaguchi presented a gift to the university that aimed to spur research in the life sciences and stir the aspirations of young medical scientists.

Sakaguchi had graduated from the prestigious Keio University School of Medicine in 1940. Half a century later, he had not forgotten his alma mater and in 1994, his donation of five billion Japanese yen was used to establish the Keio University Medical Science Fund. His donation, equivalent to US$50 million, was followed several years later by an additional two billion yen. Sakaguchi wished for the money to be used to commend outstanding researchers, encourage medical research and its creative progress at Keio through grants, and promote worldwide medical advances.

The Keio Medical Science Prize is a key project of the Keio University Medical Science Fund, which also provides grants for research and international exchange. It recognizes outstanding researchers of any nationality, nominated and selected through a rigorous evaluation process. Laureates today receive a certificate of merit, a medal, and a monetary award of 10 million yen (equivalent to US$88,000).

Over the past two decades, the prize has gained prominence as the only one of its kind bestowed by a Japanese university focusing on medical and life sciences. It receives a large number of nominations from all over the world and has recognized researchers from Japan, the United States, Australia, Sweden, and France, covering a wide range of research, from the discovery of infectious proteins to cellular self-digestion.

Global pioneer

Keio University, Japan's oldest private institute of higher learning, was established in 1858 by educator and leading intellectual Yukichi Fukuzawa, who championed reason, observation and verification in science. Today, it ranks among the top ten universities in the world for the number of degrees it has conferred to chief executives, according to the *Times Higher Education*. Its well-connected network of alumni include three former prime ministers, the first Japanese woman to go to space, and many Olympic medalists.

The Keio University School of Medicine was established in 1917, with microbiologist Shibasaburo Kitasato serving as its first dean. Kitasato was a strong defender of the egalitarian ideals of science for society. He fostered not just doctors, but the next generation of 'physician scientists' committed to pursuing knowledge for the public good.

Keio's mission "is to be a constant source of honorable character and a paragon of intellect and morals for the entire nation," Fukuzawa said in 1896. He aspired for every member of Keio "to apply this spirit to elucidate the essence of family, society, and nation. They will not only articulate this essence in words, but also demonstrate it in their actions, and by so doing make Keio a leader of society." These words resonate today in the high standards set for laureates of The Keio Medical Science Prize.

Significant contributions

Selection of those laureates — one Japanese and one non-Japanese each year — is a painstaking task. Every winter, the Keio Prize committee gathers to begin a year-long process that considers recommendations from all over the world. Candidates are critically assessed for their accomplishments through a rigorous, four-stage vetting process. By the autumn, the winners are announced.

The result of those deliberations is a prize that is unique in recognizing "not just world-firsts, as is often the case with the Nobel Prizes, but also cumulative research that has an impact on human health," says Hideyuki Okano, professor and dean of the Keio University School of Medicine and chairman of the prize selection committee. This distinction is an important one, he says. Significant contributions to medical science can take many different forms.

Keio laureates are selected for having precipitated a paradigm shift in the life sciences. Their original research must have contributed to medical advances. Prizewinners are revered not only for what they have already revealed about the world, but also for the many more discoveries to come. As such, the committee favors younger researchers who are likely to maintain an active involvement in their work long after receiving the accolade — a criterion that distinguishes the Keio Prize from the Nobel.

Nobel promise

From the beginning, the Keio Prize proved its acuity. The first two laureates in 1996 were American neurologist Stanley Prusiner and Japanese neuroscientist Shigetada Nakanishi. Prusiner had discovered prions, a type of infectious protein that causes many neurodegenerative diseases such as scrapie in sheep and mad cow disease in cows. One year later, in 1997, he received the Nobel Prize in Physiology or Medicine for uncovering this "new biological principle of infection".

For his part, Nakanishi developed a ground-breaking technique for determining the structure, and eventually the function, of neural receptor proteins. In the years since winning the award, the tools he developed have brought into view a deeper understanding of the inner workings of the brain, from learning to memory and movement.

One in every five laureates has since gone on to receive a Nobel Prize.

In 1999 Keio recognized Australian-American biologist Elizabeth Blackburn for her discovery of telomerase, the enzyme responsible for capping the ends of chromosomes. The protective caps, known as telomeres, have been found to play an important role in cellular aging and the immortality of cancer cells. A decade after receiving the Keio Prize, Blackburn was awarded a Nobel in 2009.

Most recently, the Nobel Prize in Physiology or Medicine 2016 went to Japanese molecular biologist Yoshinori Ohsumi, one year after he received the Keio Prize. Ohsumi determined the process by which cells degrade and recycle their own contents, known as autophagy. He described the Keio medal as "a great honor".

Cancer targets and Neanderthals

On 1 December 2016, Keio inducted its newest laureates at a grand event complete with a student string orchestra at Kitasato Memorial Hall, Keio University School of Medicine. Japanese immunologist Tasuku Honjo, who discovered a promising drug in the fight against cancer, and Swedish evolutionary biologist Svante Pääbo, who is responsible for sequencing the entire genome of our distant ancestors, the Neanderthals, were the recipients.

"Both professors, Honjo and Pääbo, are outstanding researchers who exemplify the criteria of the prize: advancing medical and life sciences, cultivating new paradigms and continuing to be active in research," says Okano, who welcomed the audience of 300, including many high-profile guests. Keio University President Atsushi Seike congratulated Pääbo and Honjo on their accomplishments before conferring them with certificates and medals decorated with the Keio colors, blue and red. "This year's awards celebrate a truly wide scope of research, with one having an impact on lives in the future and the other reaching far back in time," he said.

Both laureates gave commemorative lectures after receiving their awards. Honjo described The Keio Medical Science Prize as a "visionary" award that takes a long-term view of the value of basic research. "I am very honored by the prize and extraordinarily humbled to be among such outstanding recipients," he said. "Curiosity was the starting point of my career as a medical researcher. Fortunately, this has led to results that may be beneficial to many people."

"I am deeply honored to receive the prize," said Pääbo in his acceptance speech. "I share this award with many people in my laboratory and elsewhere."

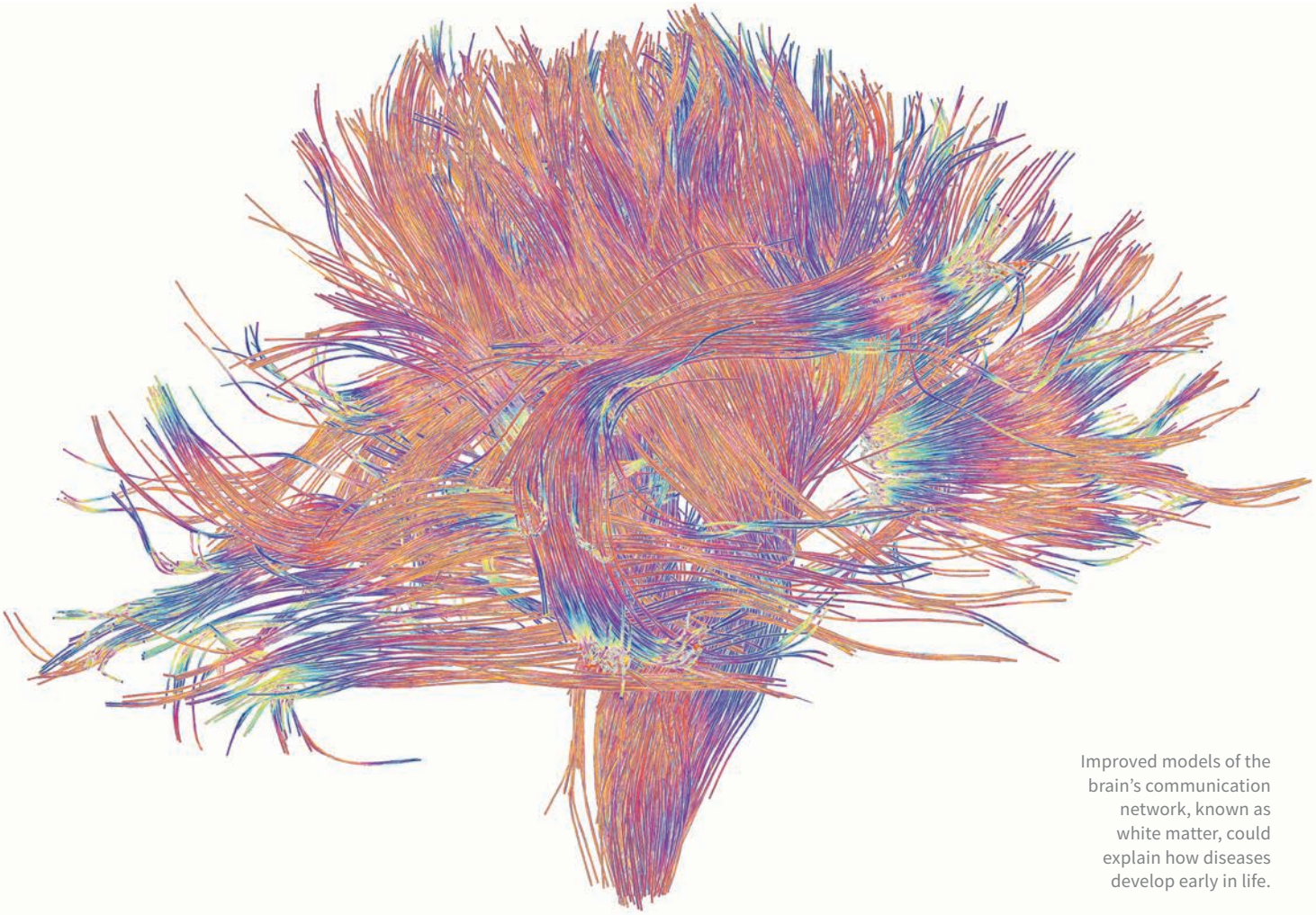
The 2016 nomination process involved a total of 3,142 academics and researchers from Japan and overseas, representing 40 countries. More than 100 nominations were put forward and assessed by members of the selection committee together with a large panel of experts from external institutions and Keio University. "The selection, the achievement, I find it very rewarding," says Okano, who has already begun the exhaustive process of choosing the 2017 laureates.

A lasting legacy

In many ways, The Keio Medical Science Prize encapsulates the founding principles of Keio's School of Medicine, which strives to be a pioneer in the world of clinical and medical studies. In 2017, the school will turn 100, and it has invited former prize laureates to give commemorative lectures at the centennial celebrations.

By honoring researchers who embody Keio's ideals in their work, The Keio Medical Science Prize acts as a driving force for ambitious young scientists. Students at Keio's School of Medicine are welcome at the annual award ceremonies, and given an opportunity to see researchers who are active in the global frontlines.

"We hope that the prize will inspire young students in particular," says Okano. "It is our hope that Keio Medical Science Prize Laureates serve as role models in terms of how they approach and conduct their research."



Improved models of the brain's communication network, known as white matter, could explain how diseases develop early in life.

Star-crossed models of white matter disease

Neural support cells implicated in childhood diseases of the brain's fatty high-speed transmission lines

Japanese researchers have gained new insights into childhood brain diseases by manipulating gene expression in laboratory mice[1]. The work, led by Kenji Tanaka at Keio University's School of Medicine, offers a new view of the tissue that constitutes almost half the human brain.

White matter is the brain's communication network. It consists of long neural projections wrapped in fatty tissue that acts as insulation to speed up transmission of electrical signals between brain regions.

Destruction or defective development of white matter leads to diseases called leukodystrophies, which include two disorders that Tanaka's work focused on — Alexander disease and megalencephalic leukoencephalopathy with subcortical cysts (MLC).

Alexander disease and MLC both develop in infants and both are caused by mutations in genes expressed in star-shaped brain cells called astrocytes. In Alexander disease, the gene *GFAP* seems to be involved, and *MLC1* is implicated in MLC. Healthy astrocytes are known to help

maintain white matter, but how the genetic mutations in these cells cause white matter degeneration is unclear.

One obstacle to solving the mystery was that mouse versions of these diseases either did not exhibit the characteristics of human leukodystrophy, or the disease only developed in old age. "We needed a new model in which the onset is in the developmental period to mimic the human disease," explains Tanaka.

His team developed new mouse models of astrocyte-related leukodystrophy using a technique they had previously developed to manipulate gene expression, called Flexible Accelerated STOP Tetracycline Operator (tetO)-knockin (FAST). The FAST system enabled the researchers to create mice in which *Mlc1* was deleted and mice in which *Mlc1* was overexpressed.

Deletion of *Mlc1* caused leukodystrophy in old, but not young, mice. By contrast, mice with overexpressed *Mlc1* developed white-matter abnormalities early in life, similar to the infantile onset of MLC in humans. Further experiments showed that overexpression of *Mlc1* in astrocytes disrupted the energy-dependent balance of sodium and potassium inside and outside the cells, leading to astrocyte swelling and white matter damage.

While the implications for humans are not yet clear, Tanaka has some ideas. "Disruption of energy balance or the balance of sodium and potassium might cause human leukodystrophy, and correction of these imbalances could improve the disease."

The team plans to further investigate the role of astrocytes in the development and maintenance of white matter. They are also using the FAST technique to study the role of proteins that support neural growth and survival in resilience and susceptibility to stress in models of neuropsychiatric diseases.

Reference

1. Sugio, S., Tohyama, K., Oku, S., Fujiyoshi, K., Yoshimura, T. *et al.* Astrocyte-mediated infantile-onset leukoencephalopathy mouse model. *Glia* **65,** 150–168 (2016).

Building a colorectal cancer library

Biobank of colorectal cancer 'organoids' reveals cancer's secrets

Three-dimensional tumors grown from cells of colorectal cancer patients are being used by Japanese researchers to explore how benign tumors transform into malignant metastatic cancer that claims nearly 700,000 lives around the world each year.

Their library of 'organoids' offers a unique opportunity to observe colorectal cancers as they would behave inside the human body.

"Until recently, cell lines and rodents have been the only living tools for cancer research, but these models may not fully reflect the characteristics of the clinical cancers. This has caused a bottleneck in translation from basic science to clinics," says Toshiro Sato of the Department of Gastroenterology and Hepatology at Keio University School of Medicine, who led the study.

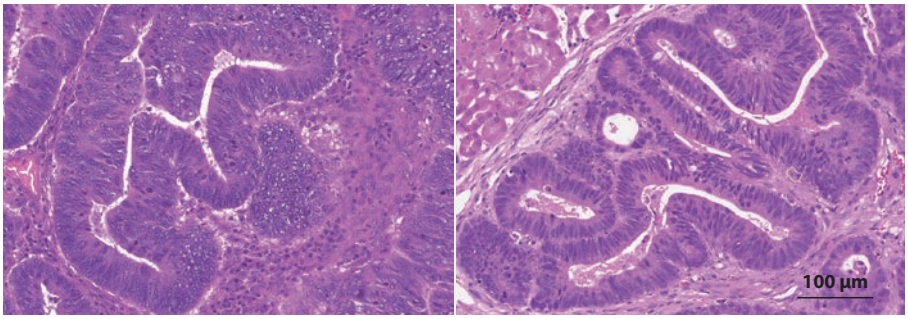
Colorectal cancer organoids are clusters of cells that form a mini-tumor, with the same structural features as the original tumor.

To build the library, Sato and colleagues collected cells from 52 tumors in 43 patients with colorectal cancer, including a number of rare subtypes. These samples were cultured with factors that might activate or repress particular signaling pathways known to affect cell growth. Each tumor sample thrived under a unique 'niche factor' microenvironment.

The result was a library of 55 colorectal cancer organoids, each with the same molecular signature as its *in vivo* counterpart. They also replicated the same cellular structure when transplanted into an animal model (see image)[1].

The biobank has already provided some valuable insights into colorectal cancer growth and metastasis. For example, because the team tailored the niche factors to each tumor, they were able to see which niche factors the tumors needed for growth, and which ones they didn't require.

While healthy intestinal stem cells are dependent on certain niche signals to grow, the researchers noted that tumors appear



Three-dimensional tumors grown on a dish and transplanted into animal models (right) develop similar cellular structures as the original colorectal cancer cells taken from patient tumors (left).

to have negated some of these growth restrictions through genetic mutations.

"We referred to this phenomenon as niche-independent growth," says Sato. "By profiling the niche factor requirements of each tumor organoid, we found that the transition from a benign adenoma to cancer, frequently accompanies this loss of niche-dependency." Interestingly, this same process did not appear to influence the transition from early cancer to advanced metastatic cancer.

The study showed that while samples from the original tumor and from its metastases were almost identical genetically, the metastatic organoids were still much more likely to metastasize when transplanted into the animal model.

This suggests some other mechanism, unrelated to genetic mutation is causing cancers to spread; a mechanism that we are yet to identify and target with treatment.

Reference

1. Fujii, M. *et al.* A colorectal tumor organoid library demonstrates progressive loss of niche factor requirements during tumorigenesis. *Cell Stem Cell* **18,** 827–838 (2016).

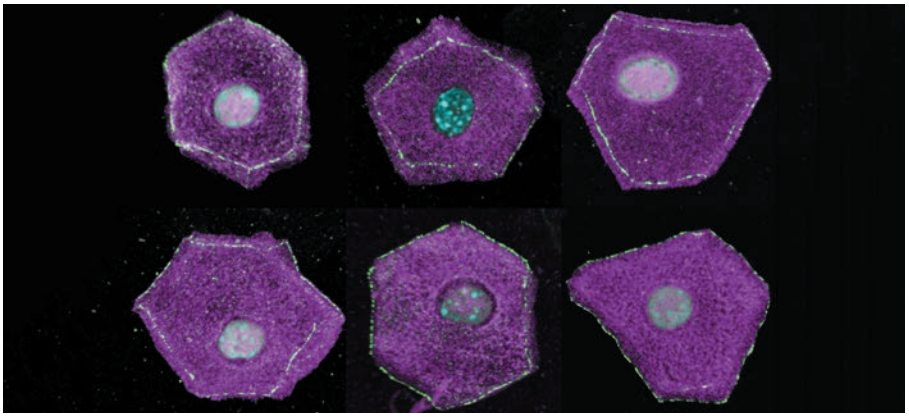
Sealing the deal on leak-proof cells

Scientists discover the unusual geometry that holds mammalian skin together, even while shedding

The human body sheds an estimated 200 million skin cells every hour, but doesn't leak. How the body maintains this protective barrier, despite such extensive cellular turnover has long puzzled scientists. The explanation, find researchers at Keio University, lies in the unusual shape of cells on the skin's surface.

A team led by Akiharu Kubo and Masayuki Amagai at Keio University School of Medicine found that epidermal cells, which make up our external coating, adopt the shape of a tetrakaidecahedron, a 14-sided geometrical structure consisting of 6 rectangular and 8 hexagonal sides[1]. "Such beautiful shapes are rarely observed in animal cells," says Kubo. "The discovery has changed the concept of the epidermis," — on a basic biological level, and for understanding what goes wrong when the skin's barrier is breached, as happens with inflammatory diseases such as eczema.

The epidermis — the body's largest and fastest-growing organ — consists of a thick outer layer of dead cells that are constantly shedding. Below this sits a multilayered sheet of living epidermal cells, sealed together like sewing thread by protein complexes known as tight junctions in a particular upper layer. The cells eventually die, and get replaced by newer cells from lower down in the epidermis. The Keio team wanted to know how this replacement happens without disrupting the physical seal of the tight junctions.



The 14-sided tetrakaidecahedron shape of epidermal cells (seen here from different angles) explains how the skin maintains a physical barrier against disease.

The researchers used a sophisticated imaging technique called confocal microscopy to examine the process in mice ears. A snapshot showed that the cells resembled a flattened version of a tetrakaidecahedron, a shape proposed 130 years ago by British physicist, Lord Kelvin, as optimal for packaging equal-sized objects with the least amount of surface area between them.

Kelvin conceived the space-filling shape when thinking about how bubbles fit together to form foam, a concept that can also be applied to skin cells.

The researchers used mathematical models to show that the mix of rectangular and hexagonal sides allow tight junctions to form with no gaps between adjacent cells. Further imaging revealed that during cell turnover the junctions form between three different cells to allow a new one

to swap in and an old one to move out, while maintaining a continuous barrier in the mouse skin, and presumably also in human skin.

As Kubo sees it, the process involves a balancing act between cell formation and old cell shedding at the tight junctions — all made possible by the 14-sided shape of the epidermal cells. Tip the balance and the skin barrier is weakened, leading to eczema, or too many new cells are produced, resulting in psoriasis.

Reference

1. Yokouchi, M., Atsugi, T., van Logtestijn, M., Tanaka, R. J., Kajimura, M., Suematsu, M., Furuse, M., Amagai, M. & Kubo, A. Epidermal cell turnover across tight junctions based on Kelvin's tetrakaidecahedron cell shape. *eLife* **5,** e19593 (2016).

Beta-blockers not better for heart surgery patients

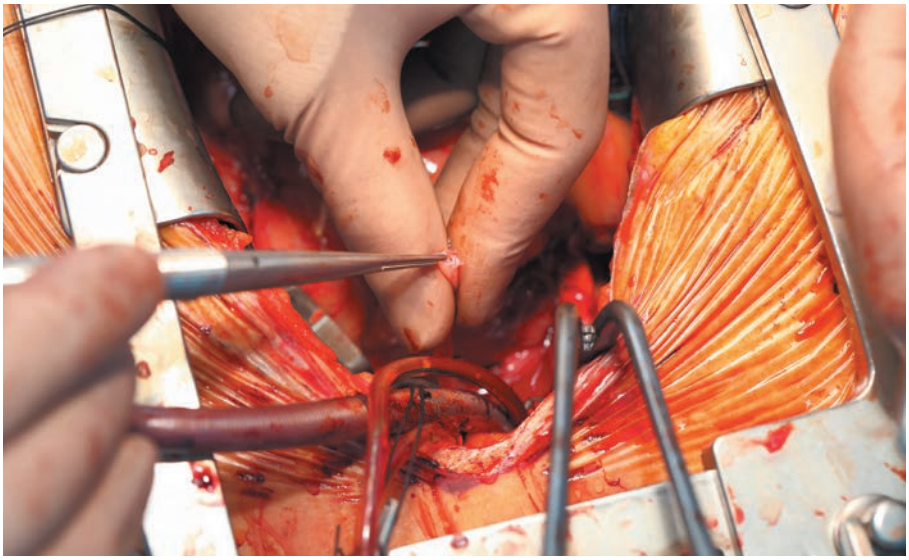
Japan-wide study shows a widely used heart drug does not improve bypass results

A class of drugs traditionally used to protect the heart from disease may have no effect on cardiovascular surgical outcomes, according to a study by Keio University researchers[1].

The drugs, known as beta-blockers, are among the most widely prescribed medications for controlling high blood pressure, and were recognized as being "cardioprotective" under surgical conditions, says Shun Kohsaka, from Keio University's Department of Cardiology. This is because the drug causes the heart to beat slower and to contract with less force, Kohsaka says.

"When heart rates are lower the oxygen consumption within the heart is kept low," says Kohsaka. Theoretically, this would allow the heart to tolerate a longer period under stress if any problems occur during surgery.

However, he says, in recent years there has been growing debate around the use of beta-blockers for bypass operations, which involve routing blood through healthy arteries.



The use of beta-blockers to slow down the heart rate during bypass surgery has no clinical benefit.

Recent studies have suggested beta-blockers have little effect on short-term, post-operative mortality and in some cases were shown to push the heart rate or blood pressure too low.

To investigate this, Kohsaka and colleagues analyzed 34,980 cases of coronary bypass surgery undertaken in Japan between January 2008 and December 2011.

The data, from the Japan Cardiovascular Surgical Database, involved 333 centers, accounting for almost 74 per cent of sites performing open-heart bypass surgeries in the country. The average age of patients was 68 years, with women comprising one-fifth of the patients.

Beta-blockers were used in 10,496 patients — around 30 per cent of cases. Patients receiving the drugs were slightly younger, but more likely to have other risk factors such as diabetes.

The researchers used rigorous statistical modeling to compare outcomes for patients undergoing the surgery with and without beta-blockers. This modeling was then extended to isolate subgroups that included low- and high-risk patients and those known to have left ventricular dysfunction.

The study found no major benefit in beta-blocker use under any of the analyses they performed — confirming recent findings of studies in the West.

Kohsaka says because East Asians are known to be genetically sensitive to beta-blockers, any effect should be more marked in his cohort. "Within beta-blocker-sensitive patients, we would

assume beta-blockers work very well, but in this study we do not see any benefits," says Kohsaka.

"No matter which ethnic group you are in, or what type of beta-blockers you prescribe, it does not seem to show any benefit, retrospectively."

Kohsaka is now looking at using the same approach to investigate the use of statins and aspirin in cardiac patients.

Reference

1. Kohsaka, S. *et al.* Effects of preoperative β-blocker use on clinical outcomes after coronary artery bypass grafting: A report from the Japanese cardiovascular surgery database. *Anesthesiology* **55,** 45–55 (2016).

Brain regions controlling emotion pass from mothers to daughters

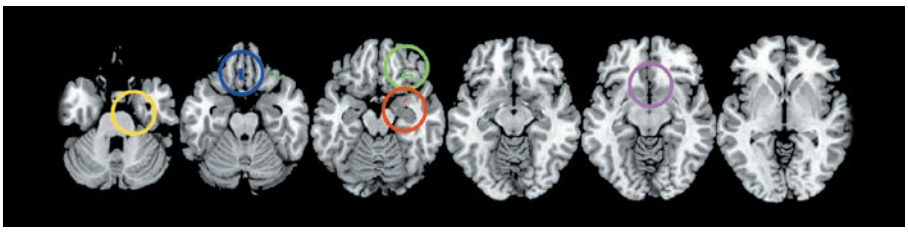
Women are more likely to inherit brain structures linked to depression from their mothers than their fathers

A brain-imaging study by neuroscientists at Keio University School of Medicine begins to explain the close association between depression in mothers and teenage daughters[1].

Scans revealed that the size of the brain area controlling mood and emotion correlated more between mothers and daughters than between mothers and sons, or between fathers and children of either gender.

If a parent has a family member with a mood disorder, there is approximately a 40 per cent chance that his or her offspring will develop that psychiatric condition, and the risk is even greater for mothers passing on their family's mental illness to daughters. As such, the insights gleaned through brain imaging can help answer critical questions about maternal effects on brain development and female susceptibility to developing depression and other female-biased psychiatric disorders, says Bun Yamagata, the study's lead author, who is now an assistant professor at Keio University's Department of Neuropsychiatry.

While working as a postdoctoral fellow at Stanford University in the United States, Yamagata collaborated with Fumiko Hoeft, who holds a joint appointment at Keio University, to study the heritability of brain circuitry. They recruited 35 healthy families from California and placed the parents and their biological children in a magnetic resonance imaging machine.



Mother–daughter similarities in the brain are most pronounced in regions involved in controlling emotion: the amygdala (red), gyrus rectus (blue), orbitofrontal cortex (green), parahippocampus gyrus (yellow), and anterior cingulate cortex (pink).

Their analysis showed that the volume of gray matter in the brain's amygdala, hippocampus and other parts of the so-called corticolimbic circuit, which plays a critical role in mood disorders like depression, correlated most strongly in mother–daughter pairs than in other parent–offspring relationships.

The reason remains unclear, but Yamagata speculates that genetic, prenatal and postnatal environmental factors and their interactions may underlie the intergenerational patterns.

To tease out those contributors, Hoeft and her colleagues are now repeating the experiment with mothers who used donor eggs, families that used other women to carry their genetic offspring to term, and, as controls, mothers whose eggs were fertilized using assisted reproductive technology. The research, Hoeft says, "will establish a new and complementary paradigm for noninvasively studying genetic and environmental influences of the human brain."

Meanwhile, Yamagata is running similar brain-scanning experiments at Keio University with families in which the parents have been clinically diagnosed with depression. He hopes the study will offer further justification for early interventions in female mental health.

Understanding how psychiatric diseases persist from one generation to the other can help to develop novel therapeutics and prevention paradigms that target high-risk individuals such as women, says Yamagata.

Reference

1. Yamagata, B., Murayama, K., Black, J. M., Hancock, R., Mimura, M., Yang, T. T., Reiss, A. L. & Hoeft, F. Female-specific intergenerational transmission patterns of the human corticolimbic circuitry. *Journal of Neuroscience* **36,**1254–1260 (2016).

Preserving more than words

A vast collection of rare books at Keio University is attracting worldwide interest through a new online course

Surrounded by floor-to-ceiling bookshelves filled with ancient scrolls, original manuscripts and rare artworks, Takahiro Sasaki, a professor at Keio University's Shido Bunko (Institute of Oriental Classics), reflects on his career. "When I studied medieval Japanese literature here at Keio University, I was struck by the sheer beauty of books. That was my first step into the world of bibliography," he says.

Housing 175,000 works, mainly Japanese classical texts, as well as pieces from China, Korea, and Vietnam, and a collection of rare Western books, Shido Bunko's library was amassed largely through items donated to the institute after World War II.

The world gained digital access to its collection through an online course guided by Sasaki. The course, Japanese Culture Through Rare Books, launched in collaboration with the UK's social learning platform FutureLearn in July 2016, explored the role of books in Japan's culture and history.

Books as time capsules

"Books are not just a way of preserving words and images," says Sasaki. "They are time capsules; their binding method, format and cover style can tell us a great deal about authorship and where they were made. We can learn about the cultural background, paper-making methods, fashions and technologies that led to their creation."

"For example, we have the single extant scroll-format copy of the first volume of *Shinsen Tsukuba shū*, written in the 15th century by imperial decree," says Sasaki of the anthology of Japanese collaborative poetry known as *renga* (see image). "Through research, I have found that the copyist of this work was not the master poet Sōboku as previously thought, but Anegakōji Mototsuna, a feudal lord who may have drafted the preliminary copy of the text."

Sasaki's detective work to unravel such mysteries using techniques such as handwriting analysis and comparative studies of textual lines is detailed in his book, *The Bibliographical Study of Classical Japanese Texts*, published in Japanese in June 2016. The book contains examples taken from popular works such as *The Tale of Genji*, *The Tale of the Heike* and *The Pillow Book*.

Opening up to the world

Unfurling a scroll dating back to 740 — the oldest known in the university's collection — Sasaki explains that Buddhist texts in the form of sutras came to Japan from China and Korea during the Nara period (710–794).

The single extant scroll-format copy of *Shinsen Tsukuba shū* (first volume) housed at Keio University's Shido Bunko (Institute of Oriental Classics)

"Among all formats, including the 'multi-section-binding' and 'pouch-binding' styles used for classical texts, my research has shown that the scroll format symbolises the highest rank, meaning that the scroll is at the top of the cultural hierarchy in terms of both the content and readership," says Sasaki.

The "multi-section-binding" format (*tetsuyōsō*) refers to single-folded pages sewn together along the fold and the "pouch-binding" style (*fukuro-toji*) refers to double-leaved pages forming a pouch as they are bound along the spine.

The scroll format subsequently influenced the placement of titles on bound books. For example, a vertical title on the left-hand side of a book cover often indicates that the book originated as a scroll, while a title placed in the center suggests that the book is a work of fiction, not derived from a scroll.

Japanese literature and the art of bookmaking flourished in the Heian (794–1185) and medieval (1185–1600) periods; this synergy of creativity is reflected in the diverse bookbinding techniques developed during this time and, for example, in the innovative use of minerals, such as mica powder to create luminous patterns.

"Today, we can see the influence of these features in Japanese stationery, which is famed for its intricate designs," says Sasaki. "*Manga* and *anime* also have their roots in these classical Japanese texts."

Sasaki observes that there is growing interest in Japanese rare books overseas. "We've had tremendous interest in our online course from around the world," he says. "I hope the course will deepen people's knowledge of Japanese culture and history," says Sasaki. "Books are an excellent gateway to understanding Japan."

Mind over machine

Chronic stroke sufferers boost the brain's ability to heal itself through brain–machine interfaces

Chronic stroke patients can regain lost movement by training their brain to control a robotic exoskeleton.

Junichi Ushiba works in the science-fictional world of brain–machine interfaces, but he doesn't like the term 'cyborg'.

"'Cyborg' sounds like 'technology's invasion of human beings,'" says Ushiba, from Keio University's Laboratory for Rehabilitation Neuroscience. He's more interested in how technology can be used in a more benign way to promote the brain's self-healing abilities in people whose neurological function has been compromised by neuromuscular disease. The results have been impressive; by connecting stroke patients' brains to computers, Ushiba is helping damaged neural regions come alive.

Wiring up

An engineer by training, Ushiba became interested in the interface between engineering and neurology in 2009 when a student came to him and suggested the idea of a brain–machine interface that used noninvasive electroencephalogram (EEG) technology, involving electrodes on the surface of the skin. This approach was first developed in the 1980s to help people with 'locked-in' syndrome to communicate.

Having studied rehabilitation, Ushiba realized there was a lack of treatment options for people whose disease had affected their ability to control their arms, and who therefore couldn't manually interact with a machine or computer.

"I realized that helping the damaged brain to rewire itself using brain–machine interfaces could become an essential and unique therapy to such patients," Ushiba says. He thought that using the brain to direct actions on a computer or machine might stimulate rewiring and healing in the damaged parts of the brain that normally control those same physical movements.

So he and his research team began working with people with muscular dystrophy; a group of inherited diseases characterised by gradual muscle wastage. The aim was to see if they could control a machine with the power of their mind.

Moving thoughts

The first question was whether brainwaves recorded through the skin would be an accurate measure of activity in the parts of the brain associated with muscle control. Ushiba and his team conducted experiments in which they used EEG to look at brain and spinal cord activity in healthy volunteers who were asked to imagine moving their wrist[1, 2]. This showed that just imagining the movement of a limb was enough to excite the neurons in the brain and spinal cord that would normally trigger this movement.

The next step was to see what effect this approach might have in people paralysed by stroke. By this time, Ushiba's work was garnering international attention, and he began working with overseas collaborators — including neuroscientists Surjo Soekadar from Germany and Hartwig Siebner from Denmark — to develop the next generation of brain–machine interfaces. The international partnership has since seen one of Ushiba's master's students, Shuka Shibusawa, working in Soekadar's lab to continue the collaboration.

The team conducted an experiment in which they used real-time brain imaging to see what happened when stroke patients tried to move a paralysed finger.

After one hour of finger extension training, every day, for a month, Ushiba and colleagues observed increased brain activity in the damaged parts of the brain that normally would control this movement[3].

The results were testament to the brain's remarkable plasticity — its ability to 'rewire' around damage — and showed how a brain–machine interface might facilitate this process.

Stroke therapy

But, the researchers aren't stopping there. If the neural activity associated with imagining a physical movement can be recorded, can it also be used to activate that movement?

He and his collaborators are now working to use the EEG-based brain–machine interface in humans to control a robotic exoskeleton. Animal studies by other research groups already suggest that the approach not only enables robotic-assisted movement, but the movement feeds back into the brain to further promote functional reorganisation around damaged areas.

"We believe that our brain–machine interfaces would be far more effective compared to simple robotic movement support," Ushiba says, referring to passive exoskeleton-style robotics that simply translate physical movement to robotic movement.

The team have already published numerous case studies of brain–machine interface work in people suffering chronic stroke, and found that around 70 per cent of patients show improvements in lost motor function. It offers hope to people for whom there currently are few prospects for improvement.

References

1. Takemi, M., Masakado, Y., Liu, M. & Ushiba, J. Sensorimotor event-related desynchronization represents the excitability of human spinal motoneurons. *Neuroscience* **297,** 58–67 (2015).
2. Takemi, M., Masakado, Y., Liu, M. & Ushiba, J. Event-related desynchronization reflects downregulation of intracortical inhibition in human primary motor cortex. *Journal of Neurophysiology* **110,** 1158–1166 (2013).
3. Ono, T., Tomita, Y., Inose, M., Ota, T., Kimura, A., Liu, M. & Ushiba, J. Multimodal sensory feedback associated with motor attempts alters BOLD responses to paralyzed hand movement in chronic stroke patients. *Brain Topography* **28,** 340–351 (2015).

In March 2011, a devastating earthquake hit Japan's eastern coast, destroying livelihoods, as seen in this aerial shot of Ishinomaki city, and changing people's perception of risk.

Measuring the tremors of an earthquake-savvy public

Understanding how people perceive risk during natural disasters could save lives

Everyone in Japan knows what to do when the Earth begins to shake — the small island-nation sits above one of the world's most seismically active regions. While this familiarity with earthquakes helped save many lives in the 2011 Tohoku earthquake, it also caused many to underestimate the danger of being hit by a tsunami. An estimated 19,000 people died in the Tohoku disaster, more than 14,000 from drowning.

Satoko Oki, a geophysicist at Keio University's Faculty of Environment and Information Studies, has studied the Japanese public's response to the earthquake and come up with some unexpected observations about how the brain processes risk. Her research will help to improve communication and education in an earthquake-savvy community.

Paradox of perception

Oki was a teenager when in 1995 a devastating earthquake hit Kobe city, killing more than 6,000 people. She spent hours glued to the television news coverage of the disaster unfolding. It was then she decided to become a seismologist, but not just any seismologist. Oki wanted to engage the public in her work.

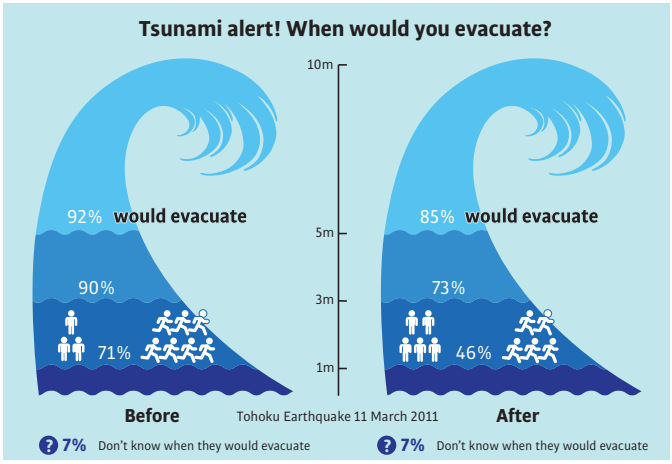
In 1981, Japan introduced more stringent standards for new buildings to be constructed to withstand ground motion of magnitude 7 or higher. People living in coastal areas were also advised to evacuate to higher ground to escape an impending tsunami. "We don't know when the 'big one' will occur, but we already know how to survive," says Oki.

Oki wanted to know what height of tsunami the general public thought presented a serious threat. In 2010, about a year before the Tohoku quake, she conducted a survey of more than 2,000 people, providing answer choices from 'don't know' to 'more than 10 centimeters' to 'more than 5 meters'.

To help explain the results, Oki sought the advice of Kazuya Nakayachi, a psychology researcher at Doshisha University in Kyoto. Before they had an opportunity to analyze the data, however, the magnitude 9 earthquake hit.

About a month after the quake, Oki and Nakayachi surveyed 1,036 participants and compared their answers to those of 733 respondents in the same prefectures from the previous survey. Oki assumed that the participants, out of fear of reliving the harrowing experience, would be ready to evacuate for smaller tsunamis. Nakayachi instead, "assumed that their risk perception would decrease," recalls Oki. The survey data validated Nakayachi's hypothesis (see image), which was based on a psychological model known as the anchoring effect[1].

The anchoring effect describes how people judge data in relation to a previously known value, and either inflate or diminish it. In the case of the tsunami survivors, having just witnessed a 40-meter-high wave, many believed a 3-meter-high wave, which is still capable of ripping a house apart, to be 'no big deal'.



Japanese perceived waves under 10 meters high to be less risky after experiencing the magnitude-9 earthquake and 40-meter high tsunami that hit Tohoku on 11 March 2011.

Unfortunately, people love reporting record-breaking events — from the fastest 100-meter sprint to the largest collection of gnomes. Oki cautions that for natural disasters, to somewhat mitigate this anchoring effect, records should be accompanied with a baseline, such as a 1-meter-high tsunami — "which is still dangerous."

Finite pool of worry

The Tohoku earthquake also caused one of the world's worst nuclear accidents at the Fukushima Daiichi power plant. Oki and Nakayachi went on to investigate whether the high level of public anxiety around earthquakes and radioactive contamination following Tohoku affected the way people felt about other unrelated hazards[2]. They compared survey results from 2008 and 2012 for changes in public anxiety about 51 hazards ranging from nanotechnology to international conflict.

Overall anxiety about these hazards decreased significantly, in a manner not commensurate with the larger loss of life associated with them. The lowered risk perception for other hazards in the wake of a severe natural disaster could dilute harm-reduction measures, warn Oki and Nakayachi.

In April 2016 Japan was hit with another powerful series of shakes in southern Kumamoto. Oki is keeping a close eye on the public communication. "It is not enough to conduct research into earthquake science, we also need to develop our communication skills to improve public awareness and promote preparation," she says.

References

1. Oki, S & Nakayachi, K. Paradoxical effects of the record-high tsunamis caused by the 2011 Tohoku earthquake on public judgments of danger. *International Journal of Disaster Risk Reduction* **2,** 37–45 (2012).

2. Nakayachi, K., Yokoyama, H. M. & Oki, S. Public anxiety after the 2011 Tohoku earthquake: Fluctuations in hazard perception after catastrophe. *Journal of Risk Research* **18,** 156–169 (2015).

Western roots in Japanese manga

Delving into Japanese subcultures reveals surprising literary links with works of Western literature

At the closing ceremony of the Rio Olympics, Prime Minister Shinzo Abe famously dressed up as Super Mario. He was teleported to the stage at the end of an animated trailer promoting the Tokyo Olympics in 2020, which featured Hello Kitty, Pac-Man, and Doraemon — some of Japan's best-known exports from its *manga* (comic books), *anime* (animations), and gaming culture. The global popularity of these characters forms a major part of the government's Cool Japan initiative designed to boost the creative industries.

Beneath the variously *kawaii* (cute) or deadpan masks of these characters there are long histories, and in some cases, unexamined literary connections, according to Hisayo Ogushi, professor of literature at Keio University's Faculty of Letters.

"The influence of Western literature, particularly works by 19th century women writers, on *Shojo manga*, or manga for girls, is particularly striking," she says.

Other worlds

Ogushi started reading manga at a young age, and soon began burrowing into translated works of Western literature. — stories by Edgar Allan Poe, Gaston Leroux, Arthur Conan Doyle, and other classics such as Louisa May Alcott's Little Women. "Those books opened the door for me to 'the other world'," says Ogushi. "I love both manga and literature, though I never thought I'd combine the two genres in my research."

While Ogushi was writing *Hybrid Romance*, her study of cultural identity and women's roles in American literature published in Japanese in 2002, she "began incubating ideas about gender, race, and genre studies," which would become a "launchpad for exploring the links between manga and Western influences in greater depth."

"Take the historical romance *Candy Candy*, for instance — a hugely popular Shojo manga series published in the 1970s," says Ogushi, explaining that the novelist Keiko Nagita wrote the text, which was illustrated by the renowned manga artist Yumiko Igarashi. "Both of these women later revealed that they were conscious of describing Western settings held to be 'otherworldly' at the time. So although young readers might not have caught on, Nagita and Igarashi knowingly recreated the story of *Daddy-Long-Legs* by the American writer, Jean Webster (1876–1916), and alluded to the world of Lucy Maud Montgomery (1874–1942), the Canadian author of *Anne of Green Gables*."

Ogushi points out further parallels between the March sisters in *Little Women* and characters in Chieko Hara's *Three Swings*, as well as the more recent influences of Western films on manga creations by Akimi Yoshida (*California Story*), Taeko Watanabe (*Family*), and Minako Narita (*Alien Street and Cipher*).

In many cases, the "re-imaginings" of Western settings can be interpreted as homages or pastiches, says Ogushi. "*Banana Fish* by Akimi Yoshida is another example of a respectful riff on the original, *A Perfect Day for Bananafish* by J. D. Salinger."

Many fictional lives

In addition to these individual influences cited by manga artists, Ogushi contends that Shojo manga as a genre has a longer, more tangled history with Western literature. She argues that the roots of Shojo manga can be traced back to Shojo novels of the 1910s and 1920s, a portion of which were based on abridged versions of Western domestic fiction, or narrative literature, largely written by and for women in the 19th century. Works by Harriet Elizabeth Beecher Stowe, Susan Warner, Lydia Maria Child, and others were highly influential during this era, selling more books than male Western authors. Ogushi continues to conduct comparative literature analyses to build a more comprehensive picture of Western influences on Japanese fiction pre- and post-World War II.

In October 2016, Ogushi and her colleagues launched an online course on Japanese Subcultures, in collaboration with the education platform FutureLearn. "This course is open to anyone interested in learning more about Japan's multifaceted culture. Many foreign students at Keio University tell us that manga or subcultures were their first step to getting to know Japan," she says. "As I always tell my students: you only live once, but through books, you can live as many times as you want."

19th century Western literature has influenced many popular Japanese manga comic books.

A global research hub

Keio University Global Research Institute launches an international mission to help society through interdisciplinary research

Keio University Global Research Institute (KGRI) was founded in November 2016 to address the challenges facing Japan and the rest of the world in an era of political, social, and environmental transformation.

Established in a year of significant global change, the institute aims to contribute to the modern world through interdisciplinary collaborations between Keio University and global partners in industry, academia, and government.

By encouraging researchers from diverse disciplines and cultures to share their work and perspectives, the center will foster new connections between people and link their ideas. The institute represents an acceleration of Keio University's globalization and will further its already valuable contributions to society.

Learning from Japan

Keio, Japan's oldest private institution of higher learning, was among 13 top-tier academic institutions chosen in 2014 by the Japanese government to be part of the Top Global University Project, a funding program designed to enhance the international competitiveness of Japan's leading schools.

As part of the initiative, Keio is committed to enhancing the sustainability of global society through *jitsugaku* (science), as a natural continuation of the philosophy of Keio's founder, Yukichi Fukuzawa. Keio University president, Atsushi Seike, identified three key areas of research on which it would focus: longevity, security, and creativity.

These comprehensive research initiatives are pertinent to the current situation in which Japan finds itself in the 21st century. With a rapidly aging population and declining birthrate, longevity is at the forefront of Japan's agenda. The nuclear accident in Fukushima is evidence of the danger of increasing risks to environmental, economic, and regional security. And Japan faces a rising demand for innovation to maintain global competitiveness.

"The Top Global University Project has been at the center of Keio University's strategy over the last three years," says Jiro Kokuryo, vice-president for international affairs. Among the many changes it has introduced have been institutional reforms to extend Keio's reach through cross-appointments, assignments of international staff in tenure-track positions, and expansion of the English-language syllabus.

"I hope KGRI will become a trigger for change," said Keigo Komamura, Keio University vice-president and director of the new center, Keio University Global Research Institute, at an inaugural symposium.

The KGRI represents the next stage of this strategy, providing platforms to promote, foster, and support current research projects. "The proliferation of efforts has made us aware of the need for a central program to integrate the various programs and maximize output. KGRI is our response to these needs. I hope it will contribute to providing effective solutions to the issues encountered by society."

Giant steps

KGRI will have three major missions: actualizing research through funding, making research more visible through effective publicity, and exploring new forms of interdisciplinary research.

Keigo Komamura, Keio University vice-president and director of KGRI, explains that the institute will have a loose, decentralized structure that will promote free-flowing exchanges between researchers. It will be an open platform, going beyond traditional working styles to connect academia with business, government, and international initiatives.

"The institute is destined to be a growing and unfinished project and that's why it has no fixed form."

Komamura particularly welcomes "idle talk" between researchers because it can lead to great discoveries. "I hope KGRI will become a trigger for change," he says.

At the inaugural KGRI symposium in December 2016, two commemorative lectures provided a glimpse of the kinds of research that KGRI will encompass.

"Economic integration and uncertainty define the world," said Huang Jing, director of the Centre on Asia and Globalisation at the Lee Kuan Yew School of Public Policy, National University of Singapore, who described a changing economic, social, and

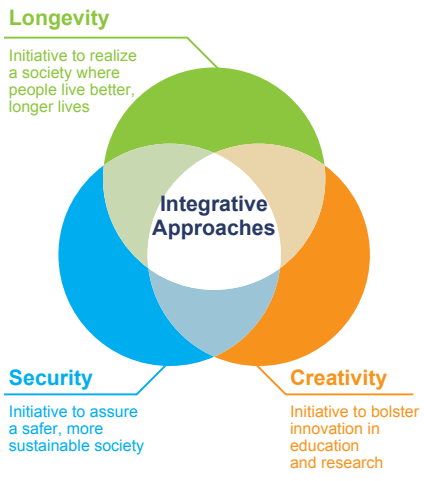
political landscape fueling global insecurity in the 21st century.

"We need to do global research to find out why we are having these problems," he said. "We are human beings and we see facts from different perspectives and we have different opinions about the same truth. That's why we need communication and thorough international, global research projects to help us to understand each other better. We have to build networks of researchers on platforms provided by institutions such as KGRI."

The need for international dialogue on research was echoed by Thibaut David of Grenoble Innovation for Advanced New Technologies (GIANT), one of the principal research centers in France. David, a scientific program coordinator at the French Alternative Energies and Atomic Energy Commission (CEA), gave a briefing about GIANT, a center in the French Alps that groups roughly 30,000 people from academia, industry, and research labs.

David emphasized the relationship between Keio University, CEA and the French National Center for Scientific Research, which signed a five-year collaboration agreement in 2014. Keio and GIANT have engaged in student and researcher exchanges in such fields as microfluidics, the Internet of Things, cyber-physical systems, and nanotechnologies.

"We are focused on people who share the same vision as us but who come from a different culture," David said. "The goal is really to be stronger."



Keio University President Atsushi Seike introduced a bold global research initiative to focus on the three areas of longevity, security, and creativity.

"We are focused on people who share the same vision as us but who come from a different culture," said Thibaut David of Grenoble Innovation for Advanced New Technologies. "The goal is really to be stronger."

Keio's three global initiatives

The world has much to learn from how Japan deals with the global challenges being tackled by KGRI's three research initiatives. Considering aged-studies, more than a quarter of Japan's population is 65 years or older and other countries are quickly joining the 'super-aged' bandwagon. Finland, Germany, Italy, Bulgaria, Portugal, Sweden, and Greece all have an elderly population of 20% or higher, lifting the global average of people in this bracket to 8%.

"Aging is not a unique issue to Japan — it's an issue for the entire world," says Hideyuki Okano, professor and dean of the Keio University School of Medicine, who leads KGRI's longevity initiative. "We aim for initiatives to realize a society where people live better and longer lives."

In one example, Keio researchers are gaining ground in tackling the growing incidence of dementia in Japan. The social cost of the disease has been estimated at ¥14.5 trillion per year, or 3% of GDP, a ratio that is expected to increase as the population ages. Early diagnosis and intervention can reduce those figures, and Keio researchers are exploring the role of nicotinamide adenine dinucleotide (NAD), a naturally produced anti-aging molecule. A precursor substance has been used in a clinical study to examine its safety and effectiveness in humans.

Another important part of Keio's focus on aging is the Center for Supercentenarian Medical Research, which brings researchers and clinicians together to better meet the needs of elderly patients. The center collects and analyses data from multiple surveys of centenarians to develop preventative care measures.

In the area of security, Keio covers a broad range of domestic and international issues including military tensions, climate change, and natural disasters. These include an analysis of the mass media's coverage of Japan in the aftermath of the Fukushima nuclear disaster, particularly its discussion of risk related to nuclear power technologies. "I believe that this security initiative project will contribute not only to academic research, but also to policy and practice," says law professor Yutaka Oishi, leader of the security initiative.

The creativity initiative, led by Tojiro Aoyama, includes projects such as multilingual search tools for social scientists that can be used to access data accumulated in various countries and languages, as well as vaccine adjuvants that use near-infrared laser light to prompt a more robust immune response.

Another project in the realm of creativity is the adaptation of brain-scanning technology to measure electrical activity in the brain associated with mental states like enjoyment, interest, stress, concentration, and calm. The Kansei Analyzer has been commercialized for testing people's responses to new products.

By fostering this kind of interdisciplinary research, KGRI will bind the many threads of investigation at Keio into a whole, says Komamura. "KGRI will be a kind of tapestry," he says, "into which we will interweave many research projects."

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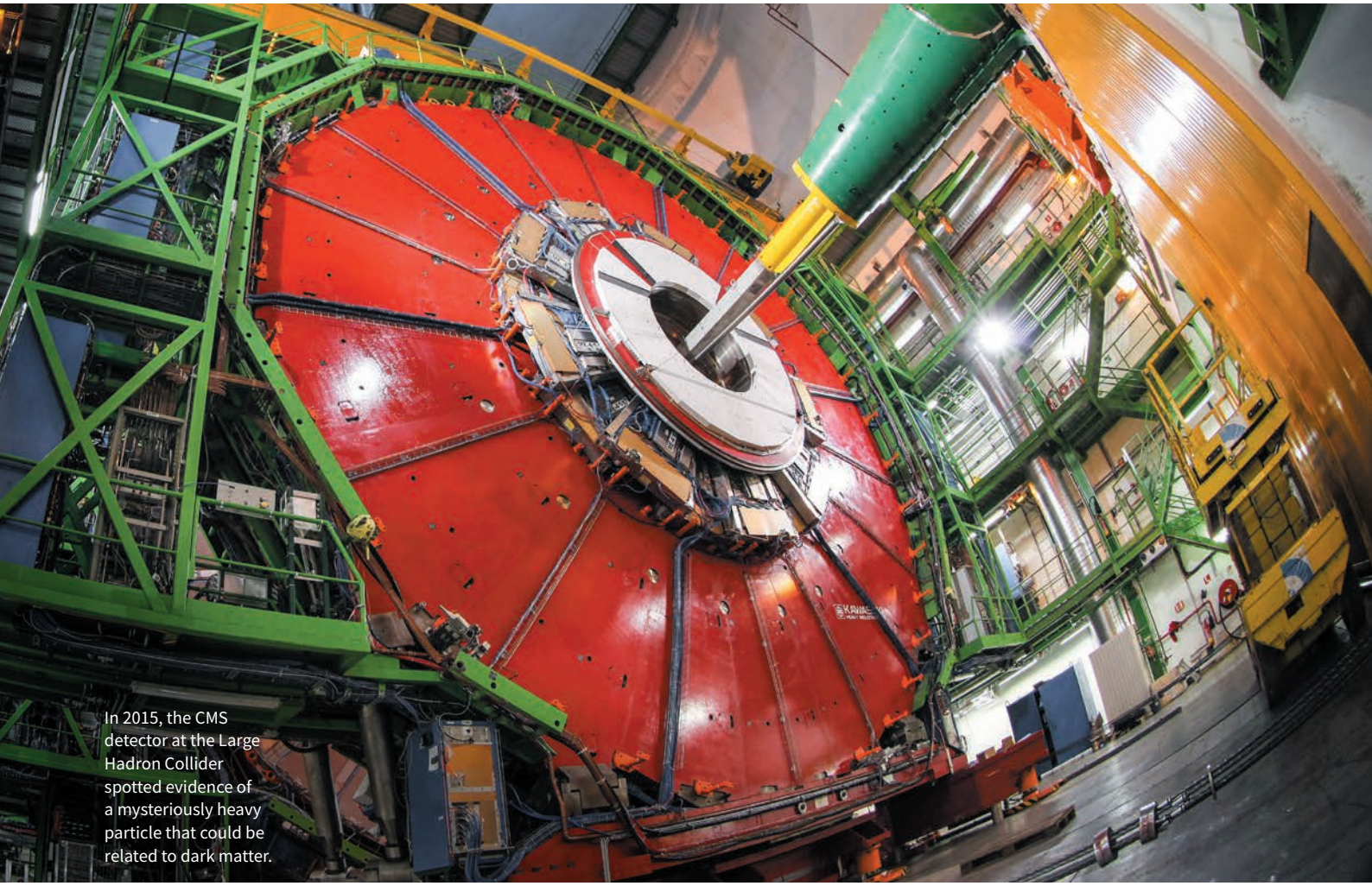


In 2015, the CMS detector at the Large Hadron Collider spotted evidence of a mysteriously heavy particle that could be related to dark matter.

Making light of a dark matter

The see-sawing behavior of dark-matter particles might have jolted experiments at the Large Hadron Collider

Unexpected signals in experiments at the Large Hadron Collider (LHC) could have been caused by heavy and light versions of a potential dark-matter particle known as the axion, propose researchers at Keio University[1].

Studies indicate that the Universe contains about six times more mass than can be seen with normal telescopes. Researchers once believed that this transparent or 'dark' matter was made mostly from abundant subatomic particles known as neutrinos, but recent cosmic observations disproved their hypothesis. Instead, researchers are now focusing on finding the axion, a theoretical particle predicted 40 years ago as a way to solve problems in the standard model of particle physics.

Similar to a photon, but with definite mass, axions should exist in sufficient quantities to account for dark matter in the Universe. Physicists are methodically searching for these particles by scanning the microwave spectrum for weak resonance signals, and looking for the creation of a new photon — a key indicator that an axion was captured. But spotting extremely miniscule axion resonances amid a constant background of cosmic microwave radiation left over from the Big Bang requires extraordinary luck.

To better their odds, researchers are smashing light beams together in the most powerful accelerator ever built

in the hope that scattering particles can illuminate previously inaccessible parts of the microwave spectrum. In late 2015, an LHC team uncovered evidence of something resembling an axion, but different in key ways — the resonance signal had an excess of energy — decaying into, not one, but two photons — and had a mass much heavier than predicted theoretically.

"When we saw this signal, we honestly had no idea whether it was genuine because there weren't any good reasons for a new state to exist," says Tetsutaro Higaki from the Department of Physics at Keio University. "But if it was real, we thought it had to be related to dark matter."

Higaki and his colleagues from Japan and South Korea theorized that the excess resonance belonged to a different type of axion. Through a model known as a see-saw mechanism, they predicted that heavy axions could align and generate the lightweight axions expected from particle physics through a mixing of quantum states. This theory concurs with models of the Universe's expansion, and explains why axions have been so tricky to find — scientists may have been looking in the wrong energy region.

"The heavy axions might be observed as new excesses when the LHC can get to higher energy scales," notes Higaki.

Reference

1. Higaki, T., Jeong, K. S., Kitajima, N. & Takahashi, F. The QCD axion from aligned axions and diphoton excess. *Physics Letters B* **755,** 13–16 (2016).

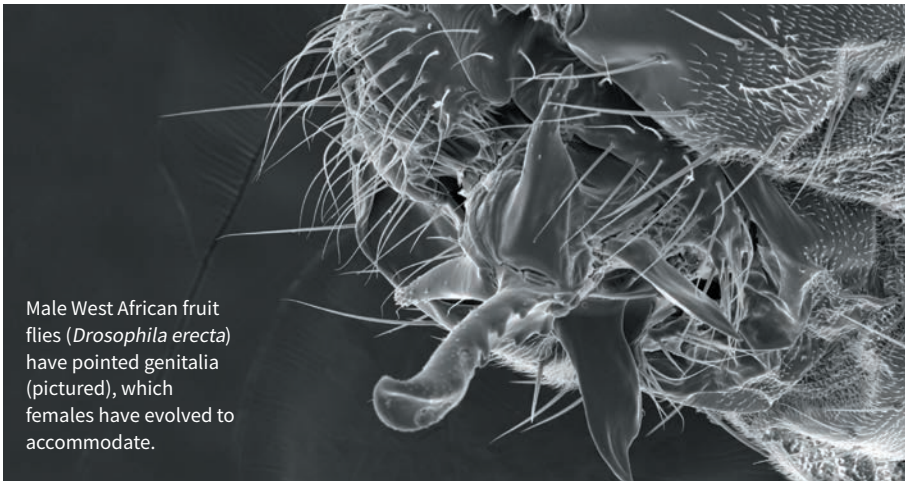
Female flies have soft spots for male genitalia

The reproductive tracts of female fruit flies have evolved to minimize damage caused by mating

Pity the poor female fruit fly. When she mates, the male inserts his pointy genital organ into her reproductive tract, where it opens like an anchoring device, inflicting what are known as copulatory wounds.

However, a new study by Yoshitaka Kamimura shows that female flies have developed an adaptation that protects them from this traumatic penetration[1]. The female genitalia have evolved soft pouches that ensure the resulting damage does not interfere with reproductive success.

"This sexual conflict over mating is likely to be the major evolutionary force underlying the observed genital coevolution," says Kamimura, an entomologist and evolutionary biologist at Keio University. While most scholars of sexual conflicts in the animal kingdom have focused on male adaptations, Kamimura's study demonstrates that the evolution of female genitalia can be just as complex.



Male West African fruit flies (*Drosophila erecta*) have pointed genitalia (pictured), which females have evolved to accommodate.

Kamimura had previously found that the females of several species of fruit flies and other insects have copulatory wounds after mating. However, in the West African fruit fly, *Drosophila erecta*, it seemed the female genital tract had evolved to limit these injuries, but it wasn't clear how. Did their soft pouches serve a protective function? Or was it the nearby hardened shields that mitigated the harmful effects of mating?

To better understand the evolutionary forces shaping female genitalia, Kamimura artificially damaged each structure and examined how it affected reproductive output. With each female fly, he anesthetized the insect and gently pushed aside the tips of the abdomen to reveal the internal structures of the reproductive tract. He then punctured the genital tract in one of three sites: the pouch, the shield, or the plate above the ovipositor tube through which the female lays her eggs. "The pouches were especially difficult to manipulate because they are colorless, tiny, and inconspicuous," Kamimura says.

Kamimura didn't use special equipment — only forceps, pins, scalpels, glass slides, sticky tape, and a microscope. "What I needed," he says, "was just practice, practice, and practice."

The flies generally survived the surgery but subsequent reproductive success depended on the site of the damage. Injury to the vaginal shield resulted in fewer eggs being successfully laid, and a harmed ovipositor plate led to lower rates of successful insemination. Wounding the pouch had little effect on mating and egg-laying success, suggesting that the soft structures evolved to help direct the spiny male appendages to locations where sex-induced injuries do not reduce female fecundity.

"Developing hardened structures is not always the optimal way to counter male harassment," says Kamimura.

Reference

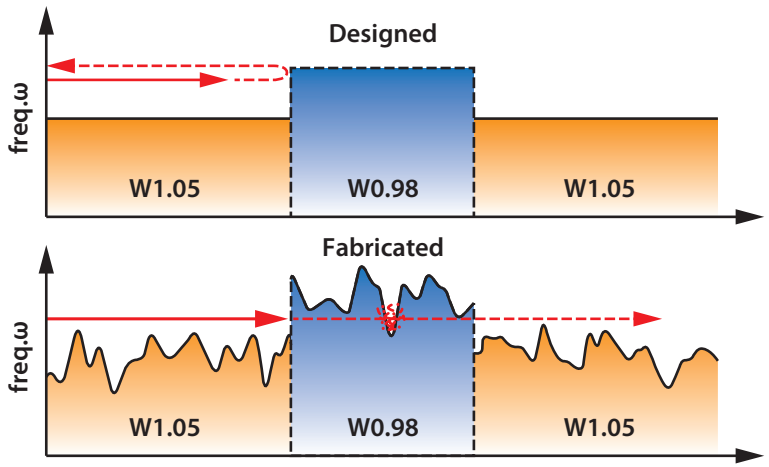
1. Kamimura, Y. Significance of constraints on genital coevolution: Why do female *Drosophila* appear to cooperate with males by accepting harmful matings? *Evolution* **70,** 1674–1683 (2016).

A bit of chaos benefits light-driven devices

Random features in nanoscale photonic cavities can help miniaturize devices that control optical data

Researchers usually try to avoid structural flaws when constructing photonic devices that manipulate, amplify, and switch signals from light beams. A team from Japan, however, has reported a high-speed photonic system that uses random fabrication errors to localize light for more compact optical devices[1].

Computing and shuttling data with light instead of electrons can hugely boost the speed and energy efficiency of signal processing. Such applications require strong interactions between photons and silicon crystals to produce nonlinear effects. One way to focus light waves at atomic targets is with photonic waveguides: ordered arrays of circular dimples, hundreds of nanometers wide, carved into a silicon surface, one by one, through a technique called electron-beam lithography.



Photonic waveguides fabricated using a speedy nanoscale patterning technique known as photolithography have more errors than a perfectly designed structure would, but can also tap into chaotic light-trapping capabilities.

For the past decade, Takasumi Tanabe from Keio University and colleagues have been developing waveguides with strong light-confinement capabilities. One of the team's most efficient designs sandwiches one waveguide, compressed to 98% of its normal spacing (W0.98), between two others at 105% spacing (W1.05). This setup causes photons at a specific 'cutoff frequency' to propagate very slowly through the waveguide, interacting with many silicon atoms along the way.

To better integrate their W1.05–W0.98–W1.05 device with electronic silicon circuits, the researchers investigated whether it could be produced using photolithography — a speedy way of forming nanoscale patterns using masks and etching solutions. These experiments produced dimples with larger fabrication errors than hoped for, but also modified the character of the propagating light so it became dominated by random scattering effects (see image).

Tanabe explains that when randomness increases in a photonic structure, scattering can cause light to localize and form 'nanocavities' that offer high confinement. This localization could be used to make photonic devices much smaller, but only if the randomness can be controlled by some method.

To accomplish this, the researchers varied the width of the W0.98 portion of their waveguide nanocavities until localized

resonances due to randomness appeared close to the cutoff frequency. The design confined randomized light to the central region of the waveguide, and yielded sufficient optical power for practical applications. As proof, the team integrated the random photonic system into a semiconductor diode circuit to produce a device that modulates electro-optic signals at high-speed gigahertz rates.

"Our device has a much smaller footprint than conventional modulators and is compatible with photolithographic fabrication," says Tanabe. "By studying this random behavior in more detail, we might be able to develop different devices such as all-optical switches or logic gates."

Reference

1. Ooka, Y., Daud, N. A. B., Tetsumoto, T. & Tanabe, T. Compact resonant electro-optic modulator using randomness of a photonic crystal waveguide. *Optics Express* **24,** 11199 (2016).

Beaks of canny crows adapted to tool use

Bill structure assists New Caledonian crows in using twig hooks to catch grubs

An international team of researchers discovered the unusual beak shape of the New Caledonian crow (*Corvus moneduloides*) is an adaptation to the smart bird's use of tools for catching insect prey[1].

The beak, with its short, straight upper bill and upturned lower bill, enables the species to grip and precisely manipulate the stick and leaf tools that it makes and uses to hook larvae out of wood. This is the first time scientists have discovered evidence that the physical shape of a non-human species has evolved and changed for better tool manipulation.

Securely holding a stick tool in its bill, a New Caledonian crow fishes out larvae hidden in decaying wood.

"If you look at the bill structure of the New Caledonian crow it is clear to the eye that you have a strange bill structure that is quite different from other crows," says one of the paper's lead authors, Ei-Ichi Izawa of the Department of Psychology at Keio University.

Izawa, a biological psychologist, had previously completed the first crow 'brain atlas' — a detailed brain analysis and map of a Japanese jungle crow (*Corvus macrorhynchos*). He also studied the behavior of these bold, city-smart crows.

In 2012, he met ecologist Gavin Hunt from the University of Auckland at a conference in Tokyo, and the two scientists discussed ways to analyze the distinctive beak structure of the more reticent New Caledonian crow. These forest-dwelling crows are endemic to certain islands in New Caledonia and, although their population is declining, are still common.

Hunt had discovered that wild New Caledonian crows made two types of tools, which they used to fish out plump longhorn beetle grubs from tree trunks. The canny birds fashioned hooks from twigs and ripped saw-toothed probes from pandanus leaves that they found in their natural habitat.

Izawa says: "My Japanese colleague Naomichi Ogihara suggested that the morphology of the bill enhanced and improved the use of tools." The team used computed tomography and a statistical technique known as three-dimensional landmark analysis to compare and measure how the beak structure of the New Caledonian crow differed from that of nine related corvids, and a woodpecker.

They found the New Caledonian crow's upper bill was deeper and shorter than that of the related crow species, and had a straight cutting edge. The thickened lower bill curves slightly upwards, giving the crow a secure grip on its tools. Izawa says: "This shape protects the bill from being bent by the strong forces exerted when probing for food and also allows the bird a clearer view when using tools to fish out prey."

Now Izawa wants to pinpoint how long ago the gene expression related to the 'strange upturned bill' occurred.

Reference

1. Matsui, H. *et al.* Adaptive bill morphology for enhanced tool manipulation in New Caledonian crows. *Scientific Reports* **6,** 22776 (2016).

Electrical brain stimulation can alter our appreciation of art.

Beauty is in the prefrontal cortex of the beholder

Noninvasive electrical brain stimulation can alter our appreciation of art

Electrically stimulating certain pleasure-sensing regions of the brain can change a person's subjective experience of beauty, researchers at Keio University have discovered[1].

In a study of 47 female Japanese students, researchers found participants whose medial prefrontal cortex was inhibited with an electrical current were significantly less likely to find beauty in a series of 20th century abstract artworks. However, the stimulation had no effect on their experience of ugliness, supporting the idea that beauty and ugliness are not opposite ends of the same scale but independent subjective experiences.

"This can help us understand the conflicting experience elicited by recent works of modern art, in which there is beauty and ugliness together in a single art work," says Hideaki Kawabata from Keio's Department of Psychology, who led the study.

In previous studies using brain imaging machines, Kawabata and his colleagues showed that the medial prefrontal cortex is activated when a person sees a face, painting or even mathematical formula they consider to be beautiful. "This brain area also responds when we observe

good, moral or social behaviors in others," Kawabata adds.

Ugliness, in contrast, lit up the left motor cortex of the brain, a region whose primary function is to plan and execute movement — suggesting it primes neural circuits to "escape from aversive stimuli or situations, or flick away incoming aversive objects," Kawabata says.

Kawabata and his team investigated the human experience of beauty and ugliness in more detail using a brain stimulation technique called transcranial direct current stimulation (tDCS). tDCS involves placing electrodes at certain positions on the scalp, to either enhance or suppress brain activity in areas beneath the electrode.

Although enhancing activity in the medial prefrontal cortex had no effect on participants' experience of beauty or ugliness, suppressing activity in the brain region made them less likely to find abstract paintings beautiful.

The results surprised Kawabata because they suggested that the medial prefrontal cortex is not just responding to the feeling of beauty — it actually has a role in causing the feeling.

In contrast, stimulating or inhibiting the medial prefrontal cortex had no effect on the number of paintings participants considered ugly, confirming that ugliness is not the opposite of beauty, but must arise as a separate cognitive mechanism in a different part of the brain.

The team plans to test whether, by adjusting the placement of electrodes, it is possible to enhance people's perception of beauty. Kawabata also raised the ethical dimension of being able to manipulate a person's subjective experiences using brain stimulation.

Reference

1. Nakamura, K. & Kawabata, H. Transcranial direct current stimulation over the medial prefrontal cortex and left primary motor cortex (mPFC-lPMC) affects subjective beauty but not ugliness. *Frontiers in Human Neuroscience* **9,** 654 (2015).

Simulation solves Venus atmosphere mystery

Waves of air create cold regions around the poles of our nearest planetary neighbor

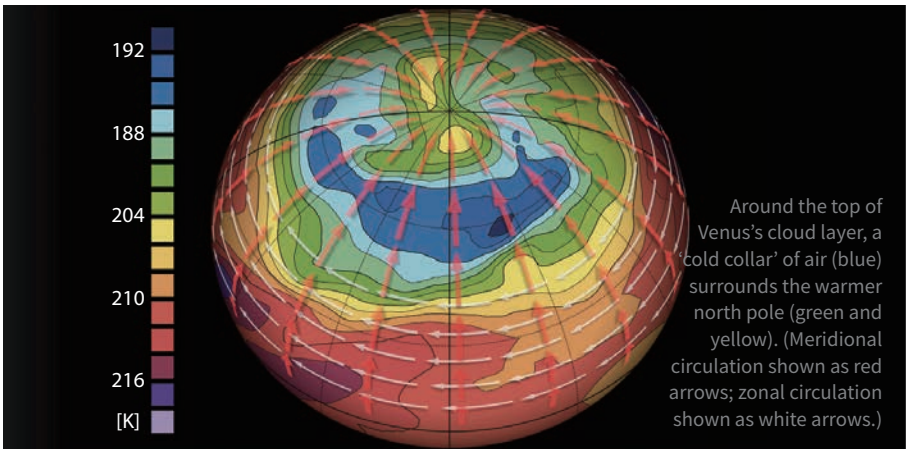
A detailed simulation of the Venusian atmosphere created by a team of researchers in Japan explains, for the first time, some of its mysterious features[1].

The winds that swirl around the poles of planets are called polar vortices. On Earth, the polar vortex is colder than the air at mid-latitudes. But Venus has a relatively warm polar vortex surrounded by a 'cold collar', a band of cooler air at around 60 degrees latitude. Moreover, the clouds above Venus's south pole are thicker than in its cold collar, and the air there is rich in carbon monoxide. Many studies have observed these features, but none have been able to explain how they form.

Norihiko Sugimoto of Keio University's Research and Education Center for Natural Sciences and colleagues have adapted a model of Earth's atmosphere to reproduce these features on Venus and reveal the underlying causes. While similar in size to Earth, Venus has a noxious atmosphere of dense carbon dioxide and sulfuric acid clouds.

The model showed that the cold collar was formed partly by the flow of air from equator to poles — known as meridional circulation — but was intensified by the thermal tide, a large wave of air driven by heat from the Sun. The thermal tide is most significant at cloud level, between altitudes of 50 and 70 kilometers, where most of the solar flux on Venus is absorbed. It can generate winds of 360 kilometers per hour at the cloud tops.

In the simulations, these atmospheric circulations caused a cold collar to appear around 60 degrees latitude at an altitude of 68 kilometers; its air was about -77 degrees Celsius, some 10–20 degrees cooler than at the north pole (see image). And at an altitude of 75 kilometers, the polar air temperature varied from -81 to -57 degrees Celsius, up to 40 degrees warmer than at 30 degrees latitude. Crucially, the simulation



Around the top of Venus's cloud layer, a 'cold collar' of air (blue) surrounds the warmer north pole (green and yellow). (Meridional circulation shown as red arrows; zonal circulation shown as white arrows.)

only matched observations when it featured the effects of the thermal tide. "We've reproduced these features for the first time in a general circulation model," says Sugimoto. "This makes it the best model of Venus's atmosphere so far."

The air currents and temperature patterns in the simulation also suggest how the south pole might accumulate more carbon monoxide and thicker clouds through photochemical reactions.

Japan's Venus Climate Orbiter 'Akatsuki' is currently circling Venus, and the team plans to use the probe's high-resolution observations to improve their simulation. They also hope to use their model to propose future observations for Akatsuki.

Reference

1. Ando, H., Sugimoto, N., Takagi, M., Kashimura, H., Imamura, T. & Matsuda, Y. The puzzling Venusian polar atmospheric structure reproduced by a general circulation model. *Nature Communications* **7,** 10398 (2016).

Plastic-munching bacterium found

New discovery could lead to a safer solution to plastic pollution

The discovery of a bacterium that feeds on polyethylene terephthalate (PET), by a team of Japanese scientists, has been hailed as a potential international breakthrough in dealing with the major pollution caused by the tough plastic[1].

The bacterium, named *Idoenella sakaiensis*, pitted the surface of a PET film with holes within just 60 hours. In six weeks, it almost completely degraded the plastic. "This is the first PET-degrading bacterium found," says Kenji Miyamoto, an associate professor in the Department of Biosciences and Informatics at Keio University and one of the study's authors. The team plans to build on the discovery "to develop a new and nature-friendly system" of recycling PET.

The bacterium *Idoenella sakaiensis* feeds on plastic bottles for energy and carbon.

More than 55 million tons of PET is produced each year to make products such as soda bottles, clothing and even car bumpers. First manufactured 70 years ago from petroleum products, PET's crystalline structure is difficult to break down. With only 14 per cent of plastic recycled, most of it ends up contaminating the environment, especially rivers and oceans.

The team, led by Kohei Oda of the Kyoto Institute of Technology, went in search of a microorganism that could degrade PET so it could be recycled without posing an environmental burden.

They collected 250 samples of contaminated soil, waste water and sludge from a PET bottle recycling factory in Osaka. Each sample was screened for microorganisms that could grow on the polymer. To make it easier for the bacteria to consume the polymer, they used an amorphous form of PET film, heat treated at 260 degrees Celsius to break down its crystalline structure.

In one sample, a consortium of microbes degraded the PET film and catabolized 75 per cent of the carbon into carbon dioxide. The researchers isolated the PET-eating bacterium from the sample.

"We were very excited," says Miyamoto. Further investigations found that *I. sakaiensis* had evolved to use PET as its major source of energy and carbon.

Electron microscope photographs showed clusters of bacterial cells, resembling tiny grubs, connected to the PET film and each other by thread-like appendages (see image).

Through DNA analysis the researchers discovered that the bacterium uses two enzymes — PETase and MHETase — to break down the plastic into its basic building blocks.

In follow-up research, Miyamoto says the team intends to determine the three-dimensional structure of the two enzymes "in order to know their reaction mechanism". The enzymes could potentially be manufactured and used to convert heat-treated PET waste into environmentally benign and useful materials.

Reference

1. Yoshida, S. *et al.* A bacterium that degrades and assimilates poly(ethylene terephthalate). *Science* **351,** 1196–1199 (2016).

Chain-walking chemistry installs new carbon bonds

Wandering catalyst activates carbon atoms to form carbon–carbon bonds

Inspired by a reaction that has become a mainstay of polymer synthesis, Keio University researchers have discovered a novel way to construct small organic molecules. Their method uses a 'chain-walking' catalyst to activate otherwise unreactive parts of simple molecules, catalyzing the formation of new carbon–carbon bonds[1].

The conventional formation of new carbon–carbon bonds — which turn simple starting molecules into complex structures, such as therapeutic drugs — is to first install a chemical 'handle'. For example, a chlorine atom might be used to pre-activate a particular carbon atom toward bond formation. Adding and manipulating these handles can make the synthesis of complex molecules slow and inefficient, so there is much interest in finding ways to directly install new bonds at unreactive carbon atoms.

Chain walking could be just such a reaction, realized Takuya Kochi from the Department of Chemistry at Keio University. Chain-walking chemistry was pioneered in the 1990s, when polymer chemists discovered a palladium catalyst that would attach to the end of a chain of carbon atoms, then 'walk' along the polymer chain before adding the next building block to the chain. "It is not a conventional way to form a carbon–carbon bond," says Kochi.

Polymer chemists use bulky substituents around the palladium atom to slow a competing reaction, alkene exchange, in which the palladium drops off the growing polymer chain. "We felt that if we just removed the bulky substituent, we could switch the rates," says Kochi, favoring alkene exchange over polymerization — the desired pathway when making small molecules rather than polymers.

The researchers tested their slimmed-down catalyst on a variety of starting molecules, each of which contained two parallel 'arms' consisting of carbon atoms. They showed the catalyst would attach to the end of one arm, then walk from atom to atom until it was opposite a carbon–carbon double bond on the other arm. It would join the two arms of the molecule at that point — activating the otherwise unreactive carbon it had walked to — to form the new carbon–carbon single bond.

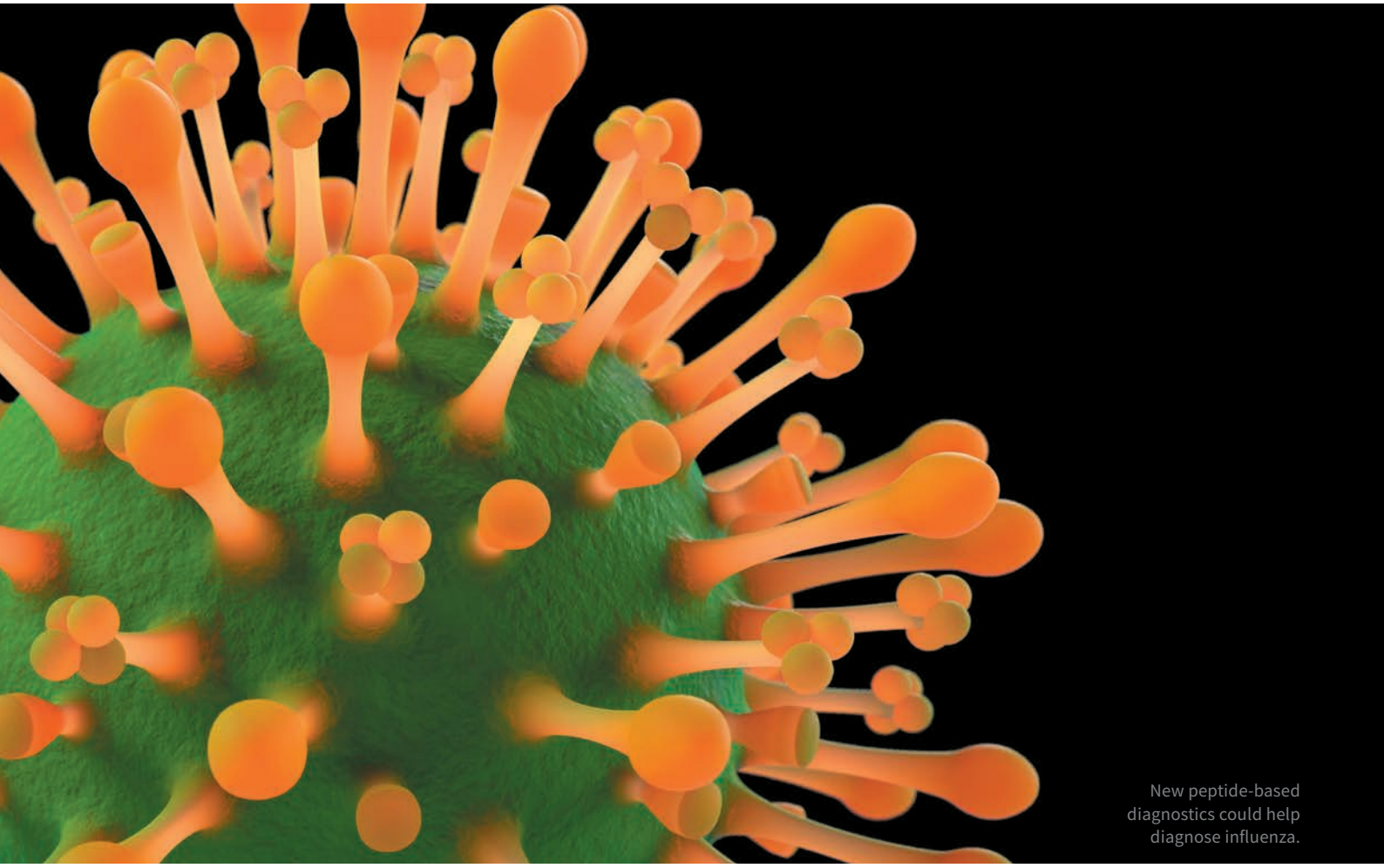
> **"It's not a conventional way to form a carbon–carbon bond."**

Using their reaction, the team has been able to synthesize a structure called prostane, the underlying carbon framework of a family of natural products. They are now investigating the reaction to identify which molecules are particularly suited to chain walking. "The chemistry is still in its initial phase," says Kochi.

Reference

1. Hamasaki, T., Aoyama, Y., Kawasaki, J., Kakiuchi, F. & Kochi, T. Chain walking as a strategy for carbon–carbon bond formation at unreactive sites in organic synthesis: Catalytic cycloisomerization of various 1,*n*-dienes. *Journal of the American Chemical Society* **137,** 16163 (2015).

Like a tightrope walker on a high wire, a chain-walking catalyst traverses a chain of carbon atoms before activating the middle of the chain toward bond formation.



New peptide-based diagnostics could help diagnose influenza.

Catching up with the influenza virus

New diagnostic tests could quickly reveal a flu infection in its early stages

Two new detection methods for the influenza virus could help prevent the next global pandemic.

Seasonal influenza is responsible for up to 500,000 deaths around the world, every year, and pandemic strains of the virus have periodically killed many more. Current methods to diagnose and track flu outbreaks are cumbersome, expensive or both.

A simpler technique for identifying patients in the early stages of infection could help get anti-influenza therapies faster to those who need them, and so limit the infection of others.

A team led by Toshinori Sato from Keio University's Department of Biosciences and Informatics exploited the fact that influenza invades the human respiratory tract and bloodstream by focusing on a sugar molecule found on the surface of our cells called sialic acid. Through a special kind of binding between sialic acid and a flu protein called hemagglutinin, viral particles can enter the human body, replicate and make us sick.

Sato and his colleagues previously identified a short chain of amino acids that mimics sialic acid, which they used as a decoy to bind viral hemagglutinin and prevent cell infection in the lab. In their most recent work, they took the same short peptide chain and developed two diagnostic assays for revealing the presence of influenza in a throat swab or other form of patient sample.

For the first test[1], Sato's team created a membrane that combined the peptide with a fatty molecule called a phospholipid. This preparation was fixed to a surface where it selectively attached to hemagglutinin when incubated with a flu-containing sample. Once all the flu particles had been collected, the researchers could then count them using traditional chemical and genetic techniques.

The other test[2] also started with the sialic-acid-mimic peptide, but in this case the researchers attached it to a highly sensitive electrode made of a diamond enhanced with the mineral boron. Any time a flu particle attached to the peptide, Sato and his colleagues could then detect its presence though electrochemical changes in the diamond sensor, without the need for additional assays.

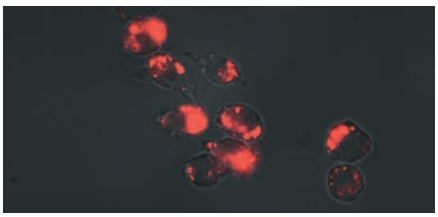
By avoiding the use of complex biological molecules, Sato says that his peptide-based diagnostics offer several advantages over existing ones in terms of manufacturing, storage and engineering. But, perhaps the biggest benefit comes from the peptides mimicking a part of the flu virus essential for its survival. So, whereas other tests need to be designed anew whenever a novel flu strain arises, according to Sato, "we expect that our strategy will be applicable to the detection of new influenza viruses that will appear in the near future."

References

1. Matsubara, T., Shibata, R. & Sato, T. Binding of hemagglutinin and influenza virus to a peptide-conjugated lipid membrane. *Frontiers in Microbiology* **7,** 468 (2016).
2. Matsubara, T., Ujie, M., Yamamoto, T., Akahori, M., Einaga, Y. & Sato, T. Highly sensitive detection of influenzavirus by boron-doped diamond electrode terminated with sialic acid-mimic peptide. *Proceedings of the National Academy of Sciences USA* **113,** 8981–8984 (2016).

Dimming the lights on cancer cells

Fluorescent probes selectively taken up by tumorous tissue could be used for early disease detection



Stimuli-responsive fluorescent polymers light up to reveal the temperature inside cells.

A stimuli-responsive fluorescent polymer that is readily taken up by living cells could become a useful diagnostic tool for identifying diseased cells, Keio University scientists suggest. The research team developed fluorescent polymers whose light output dims in response to warmer temperatures and more acidic pH — conditions typical of pathological tissue in patients with diseases ranging from cancer to Alzheimer's disease.

The polymers' responsive properties could eventually be used to selectively deliver drugs to diseased cells.

At the heart of the polymer, developed by Hideko Kanazawa and her team at Keio University's Department of Pharmacy, is a molecule called Poly(N-isopropylacrylamide), or PNIPAAm. This polymer is well known for significantly changing its structure in water above a critical temperature.

At low temperatures, a strong interaction between water molecules and the polar nitrogen-rich amido groups in the PNIPAAm polymer means the polymer spreads out into an expanded coil formation. But, warming the solution disrupts the water–polymer interaction, until the critical temperature of 32°C is reached and the polymer suddenly contracts, forming a compact globular structure.

Kanazawa and her team created four new forms of PNIPAAm polymer that incorporate different fluorescent side-chains. Previous work showed these fluorescent groups are pH-responsive, dimming under acidic conditions. But the team showed that, once combined with the PNIPAAm polymer, they also became responsive to temperature. Below the polymer's critical temperature the side-chains fluoresce brightly. But as soon as the polymer collapses, the fluorescence is switched off[1].

This responsive behavior remains active inside living cells, Kanazawa showed (see image). The researchers attached a non-polar lipid additive called DOPE to the polymer to help draw it through the non-polar cell membrane and into the living cell. They were surprised to find just how effective the strategy proved. "DOPE caused a strong preference for cellular uptake, allowing the polymers to be rapidly internalized without the requirement for a delivery system," Kanazawa says.

The team is already working on new versions of the fluorescent polymer with enhanced functionality, Kanazawa adds. For example, it has developed versions of the polymer that, under the mildly acidic pH around diseased cells, switch from a polar to a non-polar state. This polarity switch dramatically boosts the rate at which the fluorescent probe is taken up by diseased cells compared to healthy ones. "This polymer may offer the potential for development as a diagnosis tool for early tumor detection," Kanazawa says. "Furthermore, it could be used as a tumor-selective intracellular drug delivery system."

Reference

1. Yamada, A., Hiruta, Y., Wang, J., Ayano, E. & Kanazawa, K. Design of environmentally responsive fluorescent polymer probes for cellular imaging. *Biomacromolecules* **16,** 2356–2362 (2015).

The Keio Medical Science Prize

The 2016 Keio Medical Science Prize Laureates

"I am greatly honored to receive The Keio Medical Science Prize. For more than 30 years I have worked on the retrieval of DNA from long dead organisms. It has now become possible to go back in time and study the genomes of extinct hominins, past human populations, ancient pathogens and extinct animals. Many talented collaborators both in my lab and elsewhere have helped make this dream come true. I thank them all."

Svante Pääbo

"It is my great honor to receive The Keio Medical Science Prize 2016, which has been awarded to many excellent medical scientists. I encountered the PD-1 molecule and found that PD-1 serves as a brake in the immune system. Based on the findings in animal models, the PD-1 blockade cancer therapy became available 22 years after its discovery. I deeply appreciate the active investment in basic research in Japan about 20 years ago, which made this innovative application possible."

Tasuku Honjo

OBJECTIVE

The Keio Medical Science Prize is an international prize that recongizes 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 research 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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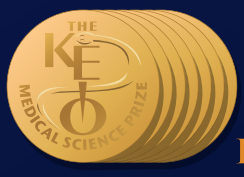

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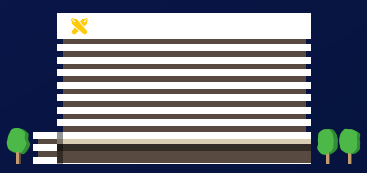

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