Keio University

実学 | Science | サイヤンス

Issue 2
August 2016

JITSUGAKU

Showcasing the best research from Keio University

A change of heart

Reprogramming connective tissue cells to repair damage

Catch of the day on ice

Netting carbon from natural gas reserves

Positioned for excellence

A sensing system to measure performance in motion

Seiyo Jijo (*Things Western*), vol. 1
by FUKUZAWA Yukichi
1866 (Keio 2)
Three volumes, woodblock
L. 22.5 cm, W. 15.4 cm ea.
Fukuzawa Memorial Center for Modern Japanese Studies,
Keio University

ON THE COVER

In 1862, London hosted its second world's fair. More than 6 million people from 39 countries attended the London International Exhibition on Industry and Art, including a mission representing the Tokugawa shogunate in Japan. Keio founder Yukichi Fukuzawa was appointed official translator for the delegation, and documented his experiences in one of the most widely read books of the time, *Seiyo Jijo*, or *Things Western*.

Published in 1866, the first volume of *Seiyo Jijo* was a bestseller and introduced revolutionary ideas that influenced a feudal Japan on the cusp of major social, economic and political upheavals. By 1868, the Meiji Restoration had restored power to the emperor and ushered in a period of modernization and Westernization to Japan. Two later volumes of *Seiyo Jijo* were published in 1868 and 1870.

Seiyo Jijo clearly details many foreign concepts and major technological advances that Fukuzawa observed during his travels. It offered the most current guide to the West for a globally isolated Japanese public. Even the idea of an exhibition would have been a novelty, which Fukuzawa described as "a convention of products." While museums are important repositories of knowledge and innovation — "a new gadget of yesterday can be a useless thing today," explained Fukuzawa. "The point of holding expositions is to teach and learn from each other, and to take advantage of each other's strengths. It is like trading intelligence and ideas." The book also formulates political systems of the West — democracy, monarchy and the parliamentary system.

The title page of *Seiyo Jijo* depicts many of the most impressive technologies, including the steam engine, electricity and telegraphy. A courier in a Western outfit runs above electric power cables — representing a new form of instantaneous communication. A hot-air balloon glides high above the mountains, a steamship sails across the open sea and a steam-driven locomotive cuts through a tunnel. "There was nothing that didn't look new," wrote Fukuzawa, "learning about their origins and functions, there was nothing not amazing."

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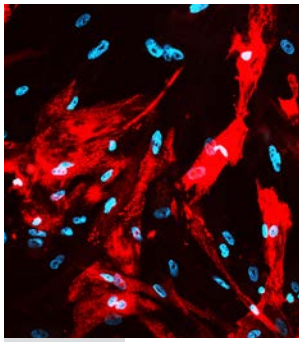

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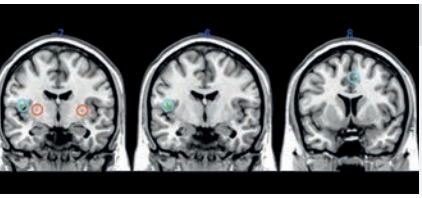

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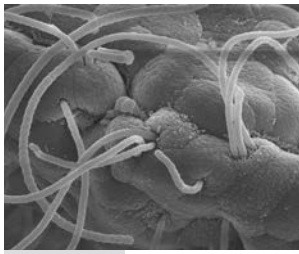

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Further information
Keio University is Japan's oldest institute of higher education, founded in 1858 by educator and intellectual leader Yukichi Fukuzawa.

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Keio University

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JITSUGAKU

Longevity, security, and creativity

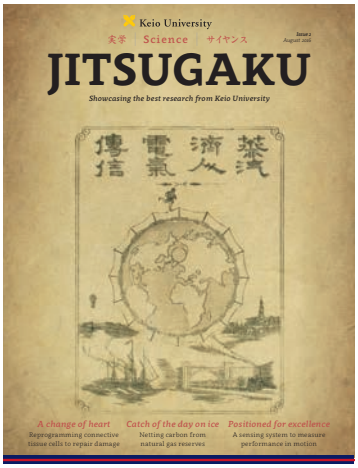
Since its founding, Keio has upheld the principles of social responsibility, lifelong learning, and leadership

As one of 13 top-tier universities selected under the Japanese government's Top Global University Project, Keio University continues to lead Japan's internationalization efforts. The ten-year initiative, launched in 2014, seeks to raise Japan's profile in global university rankings. To achieve this goal, Keio has committed to investing significant resources in sharpening its edge as a world-leading research university and extending its legacy of contributing to society.

Japan and the world currently face many critical challenges, including rapidly aging populations, declining birthrates and environmental, economic and social instability. There is also an urgent need for innovative solutions. In these times of great change, Keio is following the advice of its founder, Yukichi Fukuzawa, to contribute to humanity through learning and *jitsugaku* (science). He aspired for students, alumni and faculty members at Keio University to be model leaders in society.

To address these challenges, Keio has launched transdisciplinary research and education initiatives in three key areas: longevity, security and creativity. These global, cross-cutting initiatives will help to realize a world in which, inspired by innovative ideas, people live longer, better lives in safer, more sustainable communities.

The second issue of *Jitsugaku* offers a peek into this new world and is a testament to the multidisciplinary nature of research at Keio University. The 5 feature articles and 12 research highlights in this publication cover areas as wide ranging as robotics, agriculture, disaster risk reduction, immunology, clean energy and sports science. From discovering the secrets of successful aging to reducing healthcare costs, research at Keio University is original, progressive and socially responsible.



Issue 2, August 2016

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.

The Old University Library on Keio's Mita campus.

IGNITING JAPANESE SOCIAL INNOVATION

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

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

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

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

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

Thinking for oneself, taking responsibility for one's actions and *jitsugaku* are basic principles held dear by Fukuzawa that Keio continues to uphold to this day. Fukuzawa emphasized the importance of freedom, equality and lifelong learning. He noted, "Heaven does not create one man above or below

another man." Fukuzawa is honoured on the 10,000 yen note, Japan's highest denomination.

Applying *jitsugaku* to solve global problems

Keio is a comprehensive higher education institution located on six campuses across the greater Tokyo area. It has 10 undergraduate faculties, 14 graduate schools and approximately 30 research centers and institutes, including a university hospital. The institution's affiliates include two primary schools, three junior high schools, and five high schools, including one in New York. Keio is a unique academic entity that offers lifelong education. Keio has partnerships which include 300 overseas institutions and 7 international organizations in 49 countries. Partner universities include Harvard Medical School, Columbia University, Stanford University, the University of Oxford, and the University of London. International organization partnerships include the Asian Development Bank, the International Bank for Reconstruction and Development and UNESCO. To further boost its research capacity, the university has intensified existing collaborations with 16 research universities and institutions, primarily in the United States and Europe.

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

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

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

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

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

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

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

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

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

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

Keio University founder Yukichi Fukuzawa's autobiography, *Fukuo Jiden*, has been translated into almost a dozen languages.

Motion sensors for sporting excellence

Lightweight smartphone sensors and Newton's laws of motion can help athletes maximize their performance

As a young man, Yuji Ohgi spent several hours a day in the swimming pool perfecting his stroke. These countless hours of practice paid off — at the age of 20 he competed in the preliminary trials to join the Japanese swimming team for the 1988 Olympic Games in Seoul.

While he was not quite fast enough to make the team, the experience helped shape his career. Ohgi soon hit on the idea that accelerometers and gyroscopes (used by today's smartphones to get their bearings) might help athletes and their coaches work out the optimal body positions and movements to improve performance. This inspiration laid the foundations for 20 years of innovation and discovery in the field of sports biomechanics.

Most of Ohgi's work focuses of human athletes, but not all of it. In one project, he is applying his expertise to better characterize the movements of thoroughbred racehorses using special treadmills designed to take their weight.

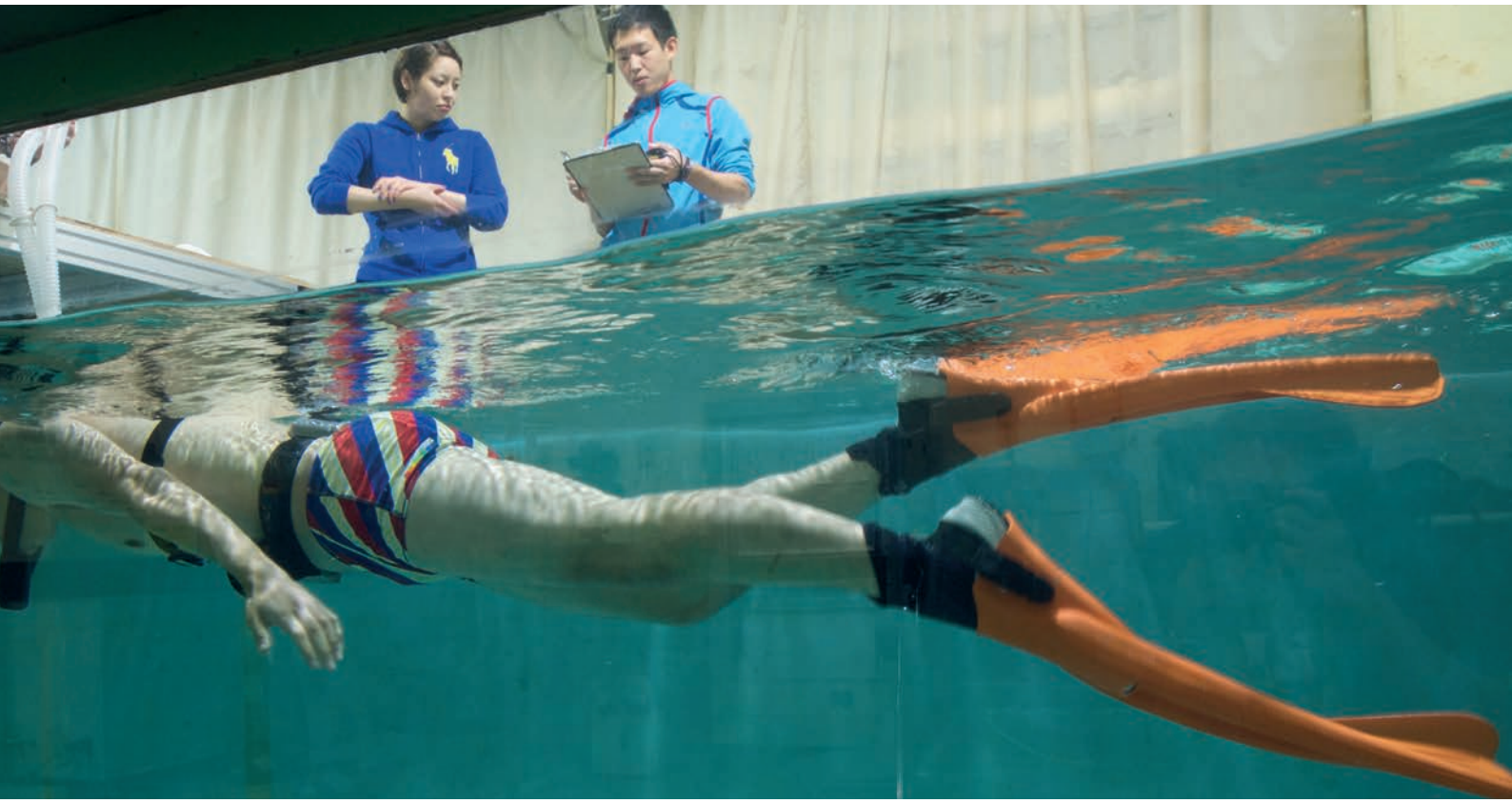
"Newton's laws cover all sporting activities," says Ohgi, now an associate professor at Keio University's Graduate School of Media and Governance. "The mechanical properties can be formulated in almost the same way for people and horses. Once we understand the fundamental physics involved, we can comprehend the mechanics of any sport."

Stroke by stroke

Ohgi first worked on using accelerometers and gyroscopes, known as inertial sensors, to analyze athletic performance in 1995, when the watch manufacturer Casio provided his supervisor with funding to research the development of a sporting wristwatch. After investigating the technology's potential in martial arts and baseball, he naturally turned to the sport he excelled at — swimming.

Traditionally, coaches used cameras to visually assess sports performance, but the bubbles and splashes generated as swimmers ploughed through the water would often obscure the picture, limiting the capture of key data. "Usually swimming training is a matter of trial and error, with swimmers and coaches trying out new stroke techniques. But nobody really knows which techniques are best," says Ohgi. "Using inertial sensors, we can calculate the stroke propulsive force to assess the most efficient techniques."

The accelerometers and gyroscopes found in today's smartphones can be used to improve the performance of swimmers, ski jumpers, and golfers, among other athletes.



After scrapping some earlier models, in 2006 he developed a waterproof data logger that could be strapped around a swimmer's wrist and wirelessly send data on acceleration and angular velocity to a poolside device[1]. More recently, he has used chest-strap-based sensors, and he is currently developing software for swimming training.

Jump and swing

Ohgi has applied the same ideas he developed for swimming to many other sports.

In ski jumping, for example, athletes move at great speeds over large distances, making it difficult to capture movement and positioning in detail, even with high-speed cameras. Since 2005, Ohgi has been refining a system that deploys seven inertial sensors on a jumper's body and one each per ski, as well as a laser scanner to track trajectory[2]. The system can be used to measure aerodynamic forces during jumps and provides better understanding of the effects of small changes in body positioning.

Ohgi also worked with Keio University colleague, Associate Professor Ken Ohta, in a collaboration with the Japanese electronics company Seiko Epson Corporation to develop a lightweight golf-swing analysis tool. Again using inertial sensors, the device provides players with data on swing path, club and club-head speed, face angle and efficiency of energy transfer from the body to the club shaft. The device was launched in Japan in 2014, and the United States and South Korea in 2015.

Not only sportspeople benefit from Ohgi's work; he is involved in a study led by colleagues at Keio's Sports Medicine Research Center on whether regular exercise can reduce cognitive decline and dementia. As part of the study, he is using Microsoft's Kinect motion-sensing device to develop a way to analyze elderly people's gaits.

Looking to the future, Ohgi envisions technologies that generate data on sporting performance will come into their own at the 2020 Tokyo Olympics. As co-chair of the scientific committee of the Japan Swimming Federation, he hopes to initiate a project using machine learning to identify the characteristics of swimmers from video footage.

This, says Ohgi, will form part of the research foundations for a much more technologically advanced experience for those watching the games and other sporting events remotely. "I believe that by 2020, television audiences will be able to monitor things like the speed and energy expenditure of their favorite athletes," he says.

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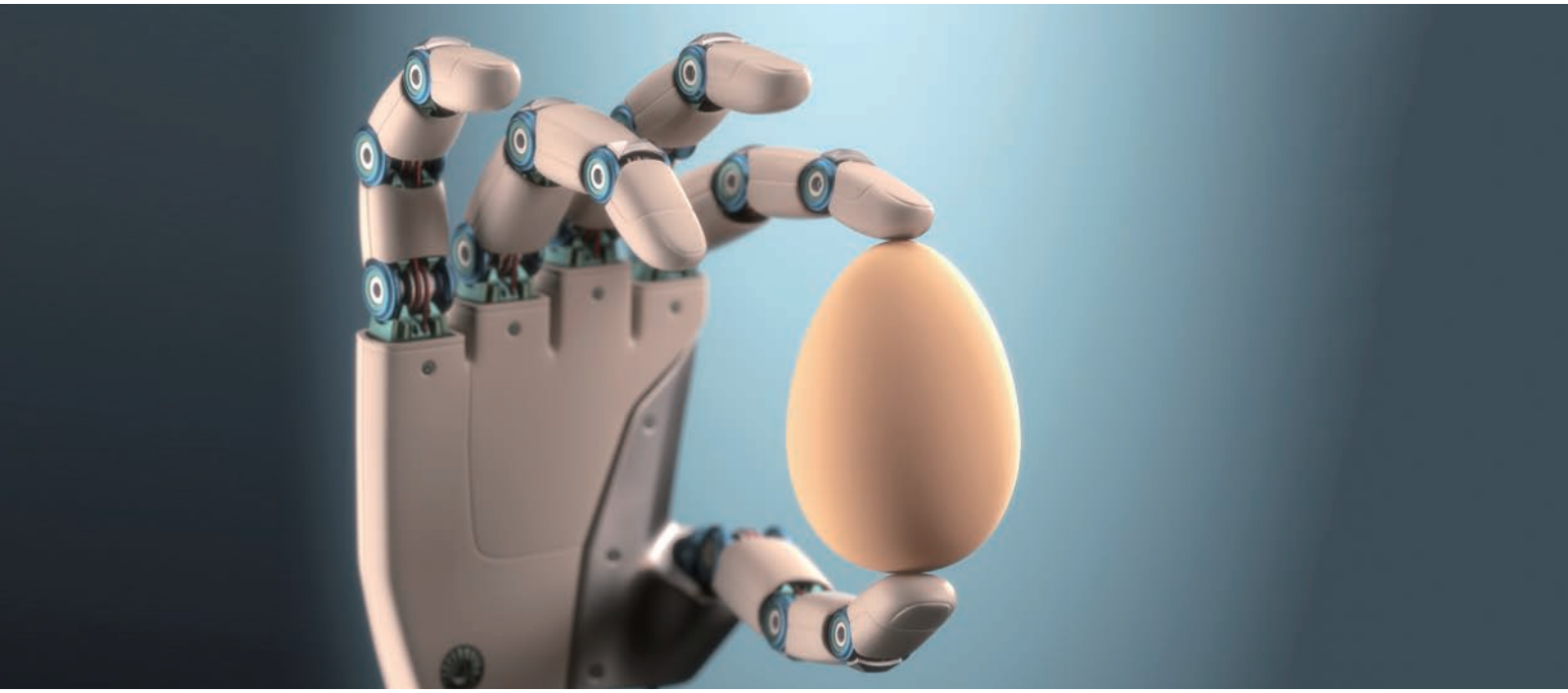

Improving the communication between remote mechanical systems and their human controllers can lead to more precise movements.

A gentler approach to remote control

Unstabilizing vibrations in remotely controlled systems can be reduced using an elastic feedback method

Remotely controlled devices offer a safe way to perform hazardous tasks, such as bomb disposal or activities in radioactive areas. Eiichi Saito and Seiichiro Katsura from Keio University's Department of System Design Engineering have developed a method for increasing the stability and precision of these remotely controlled systems[1].

Remote-controlled robots in risky settings may need to grab an object firmly enough not to drop it, but not so tightly as to damage it. This balance is achieved through a concept known as feedback: the robot's movements are automatically adjusted based on measurements of the forces between the grabbing tool and the object. The same type of give-and-take is needed to direct robots to precise locations.

However, because the robot and its human controller are at different locations, there is a time delay between the input from the controller reaching the robot and the feedback reaching the controller. This time delay can make the system vibrate and become unstable.

The Keio team proposed a novel time-delay compensation scheme that models the system as a series of oscillating masses connected by springs. They introduced infinity-order equations to this mass-and-spring concept to predict vibrations across a wide range of frequencies. Since time delay is a type of infinite-order problem that works across all frequencies, using these equations in the algorithm that determines the feedback in their system helped to reduce the deleterious effects of the vibrations.

"From an engineering point of view, it is better to use a simple model, but high-speed adjustments in position lead to high-frequency vibrations," explains Katsura. "So there is a trade-off between simplicity in control design and suppression of these vibrations. We introduced so-called infinite-order modeling and control to solve the trade-off issue."

The researchers experimentally validated their approach in a simple mechanical system comprised of a computer-controlled motor that moves an object to a desired position. This system was then controlled by a second computer that acted as the remote controller. A time delay of 25 milliseconds was artificially added between the two computers. The team first tested a common alternative approach for reducing the negative effects of time delays known as the Smith predictor. This alternative method achieved a steady final position, but fell almost a millimeter short of the intended target. Saito and Katsura's method reached the steady end-state in the same time but with a higher accuracy.

"At present, the system only considers a position-control system," says Katsura. "In future work, we hope to extend this to force-control systems too."

Reference

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T cells launch targeted attack on tumors

Discovery of a protein fragment gives rise to a new strategy for harnessing the immune system against leukemia

A protein fragment newly identified by Keio researchers[1] and expressed in leukemia cells points to a target for developing novel immunotherapies to combat the deadly blood cancer.

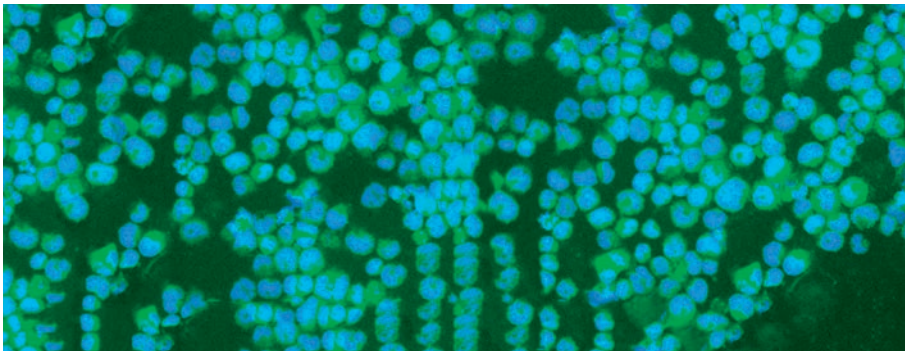
Scientists have known for more than a decade that many tumor cells, and cells from leukemia blood cancers in particular, express a protein called PEPP2 that can trigger an immune response (see image). However, it was unclear what part of the protein specialized immune cells called killer T cells recognized and latched on to.

A team led by Maiko Matsushita, a hematologist and cancer immunologist at Keio University, went in search of the elusive site on PEPP2 to which white blood cells bind — a site known as the epitope. They synthesized 24 fragments of the PEPP2 protein. Using immune cells from healthy donors in the laboratory, they singled out one PEPP2 fragment — a nine amino-acid stretch — that roused the killer T cells into action.

With this small protein fragment, "we could induce anti-PEPP2 killer T cells with strong activity," Matsushita says. "This encouraged us to believe that this epitope might be useful for many leukemia patients."

To boost the expression of PEPP2 on leukemia cells, and increase the potency of the anti-PEPP2 T cells, Matsushita and her colleagues exposed the leukemia cells to a drug that removes chemical marks from the DNA. These marks, known as methyl tags, restrict gene expression, and the researchers found that the 'demethylating' drug increased levels of PEPP2 expressed in the leukemia cells. The cells were subsequently more vulnerable to attack from killer T cells.

The findings could pave the way for a new therapeutic strategy for combatting leukemia, a disease that kills more than 250,000 people globally each year. Matsushita envisions a scenario in which scientists genetically engineer a patient's own T cells in the laboratory so that they respond to PEPP2 more actively and efficiently. Those cells could then be infused back into the patient together with a drug that takes away the methyl tags from the DNA of the cancerous cells in the body.



Leukemia cells expressing the surface protein PEPP2 (labeled bright green) that immune cells in the body can recognize.

The approach would need to be tested in animal models and then in human clinical trials. But if it proves safe and effective, it could greatly benefit patients who don't respond to existing drugs or who experience disease recurrence.

"For those patients," Matsushita says, "immunotherapy targeting PEPP2 might be a good treatment option, since PEPP2 is also expressed in leukemia stem cells, which are one of the reasons for disease relapse."

Reference

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The price of a personal touch for lung cancer therapy

Personalized treatments are an affordable option for improving the lives of lung cancer patients in Japan

Personalized treatments for lung cancer patients can help them live longer, with fewer side effects, at a marginal expense to the Japanese healthcare system, finds an analysis by Keio University researchers[1]. The analysis justifies adopting personalized treatments for the most fatal form of cancer worldwide, which kills around 1.6 million people every year.

"We're facing a new era of personalized medicine," says study lead Hisashi Urushihara, from Keio University's Research Laboratory of Drug Development and Regulatory Science. He foresees that screening for specific genetic traits will soon be standard in medicine in the form of companion diagnostic tools that assess the potential benefits and risks of a specific drug to a specific patient. "Companion diagnostics will drastically improve treatment outcomes, making optimal therapy possible," says Urushihara.

Consider the drug gefitinib, which inhibits a protein called epidermal growth factor receptor (EGFR). EGFR is elevated only in certain types of cancer, including the most common form of lung cancer, non-small-cell lung cancer. A landmark study in 2009, the Iressa Pan-Asia Study, showed that gefitinib treatment slowed lung cancer progression in patients with EGFR gene mutations (between 10 and 30 per cent of patients), but was almost completely ineffective for patients lacking this mutation.

The challenge for Urushihara's team was to justify the increased cost to the healthcare system of a genetic test and tailored gefitinib treatment compared to standard chemotherapy. "Every country is suffering from the increased cost of medical care," says Urushihara. Several countries have adopted policy measures to incentivize healthcare that carries the best value for money.

Using models of disease progression and EGFR prevalence, the researchers estimated the quality of life gained by personalization of lung cancer treatments. EGFR-positive patients were given gefitinib, while EGFR-negative patients underwent standard carboplatin–paclitaxel chemotherapy.

Then they asked if the treatment was good value, assuming that patients would be happy to pay JP¥5 million for a year of good health (reduced to JP¥1.5 million after accounting for the percentage covered by the national healthcare system). The answer was yes: for only JP¥122,000 (US$995) per patient, adopting standard EGFR screening for non-small-cell lung cancer would improve all patients' survival by the equivalent of 13 days of good health because they received the best treatment for their condition. In all the scenarios modeled, around 89 per cent of patients would gain outcomes justifying the small premium for EGFR screening and

Offering the best medicine while addressing growing healthcare costs is a serious challenge for many countries.

treatment. Targeted gefitinib treatment allows "patients to spend more time with their families and lead more active lives, while contributing to society," he says.

Reference

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Survival threat emerges from within industrial clusters

A combination of microeconomics and quake-engineering reveals greater vulnerability of clustered manufacturing plants to natural disasters

Setting up local factories in close proximity to competitors can bring enormous opportunities for growth, but poses a high risk of long-term failure to recover from a massive earthquake, according to a study by an international team of economists led by Toshihiro Okubo at Keio University[1].

"Many people believe that industrial agglomeration in large cities makes companies resilient to natural disasters," Okubo says. "But our study reveals a lot of negative aspects."

Many studies have looked at how natural disasters undermine global, regional and local economies in developing countries, but few have focused on developed economies. This type of analysis matters for Japan because of the imminent threat of another large earthquake following the devastating shake that hit the northeastern Tohoku region of Japan in 2011.

The researchers looked into the 6.9-magnitude earthquake that struck the western port-city of Kobe in 1995, claiming 4,500 lives. They used the government's highly detailed mapping data, building-level surveys, and plant-level economic surveys, created using an advanced geographic information system. The data assigned one of five colors to each of the 1,846 manufacturing plants across the city according to the degree of damage they had incurred. The researchers used this information to calculate the associated percentage loss of value for each building, area and road. Leveraging Okubo's expertise in theoretical and empirical studies of economic geography and international trade in the presence of firm heterogeneity[2], the team created various parameters for assessing the effect of earthquake damage on plant survival and the impact of clustering on long-term survival.

"By combining an economic approach with earthquake engineering, we learned that even though plants in clusters survived the earthquake, many of them suddenly failed after five to ten years," says Okubo.

Manufacturing industries such as the rubber and non-ferrous metals industries were heavily clustered and their plants were severely damaged. Damaged plants were more likely to fail than undamaged plants within the same cluster amid increased competition and cannibalization, rather than cooperation to survive difficult times. Such negative impacts of building damage persisted much longer than expected. "The result also reaffirmed the importance of strengthening structures to make them more quake resistant," says Okubo.

Okubo's cross-disciplinary approach matches well with Keio's commitment to practical research. "We were able to understand the long-term impact of earthquakes, which economic data alone could not have explained." He is now expanding his research scope to cover the aftermath of other disasters, including the Tohoku quake and nuclear accidents in Fukushima.

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Factories that group together in industrial clusters are exposed to a high risk of failure up to ten years after suffering damage from a major earthquake.

Leading the race against dementia

Exercise could hold the key to reducing cognitive decline in aging populations

Modern medicine faces a dilemma of its own making. While people have longer lifespans, aging populations can become an unmanageable burden for healthcare systems. The resolution could lie in readjusting what we classify as healthcare.

As the country with the world's oldest population, Japan is particularly attuned to the specific ailments of senior citizens. Dementia already afflicts more than three million Japanese and will affect more lives as the population continues to age. At Keio University's Sports Medicine Research Center, researcher Yuko Oguma is investigating whether regular exercise, which reduces the risk of obesity, heart disease, and depression, could also help delay cognitive decline. "Preventing cognitive decline is a national problem," she says. "It is very important for our society to work on health management and not just medication."

Step by step

Oguma's approach focuses on prevention over treatment. Recalling her early career as a physician at Keio University Hospital, she says: "I saw lots of patients with serious diseases, such as cardiovascular diseases and cancer, and I started to think about how to prevent or postpone their diseases by improving their lifestyles." Oguma continued this research when she moved to Boston to attend the Harvard T.H. Chan School of Public Health as a graduate student. Now an associate professor at Keio, she aims to reduce the number of people with obesity and cognitive decline by improving public health and reducing society's healthcare burden.

Research by Oguma[1] and others has shown that even a modest increase in daily physical activity can make a difference. Regular activity, such as walking to work or the store, climbing stairs, or even gardening, lowers the risk of heart disease, diabetes, and depression, as well as helping to prevent obesity and knee or lumbar pain. Oguma incorporated these findings as part of a team conducting a systematic review for Japan's Ministry of Health, Labour and Welfare into new guidelines for physical activity in 2013. The guidelines recommend 60 minutes of moderate to vigorous daily physical activity as optimal, but emphasize that as little as 10 minutes a day is beneficial.

An activity a day

Oguma now runs the Graduate School of Health Management's '+10 project', a combined research program and public health initiative, which aims to increase senior citizens' daily physical activity by 10 minutes. The program targets elderly communities in the coastal city of Fujisawa, organizing calisthenics groups and offering training videos and support. "Doing ten minutes of physical activity is better than nothing," she explains. "Sixty minutes would be much better, but ten minutes is a good start."

Elderly residents in the central-eastern city of Fujisawa, Japan, exercising as part of Keio University's '+10 project' to increase their daily activity by ten minutes.

Physical activity is known to increase blood flow to the brain and to increase the concentration of a protein important for neuronal growth and maintenance called brain-derived neurotrophic factor. Using data from the +10 project, Oguma hopes to discover whether increased physical activity can prevent cognitive decline. Her team, in collaboration with dementia specialists at Keio University's School of Medicine, uses questionnaires and an iPad application to assess participants' cognitive function.

The graduate school is also using the 2020 Tokyo Olympics to raise awareness. "Instead of just watching athletes do sports on television, this is a very good opportunity to increase physical activity in the population," Oguma says. "I want physical activity to become part of people's routine. If people can lead healthier lives within their communities, our aging population will put less strain on the healthcare system."

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Anti-inflammatory interactions

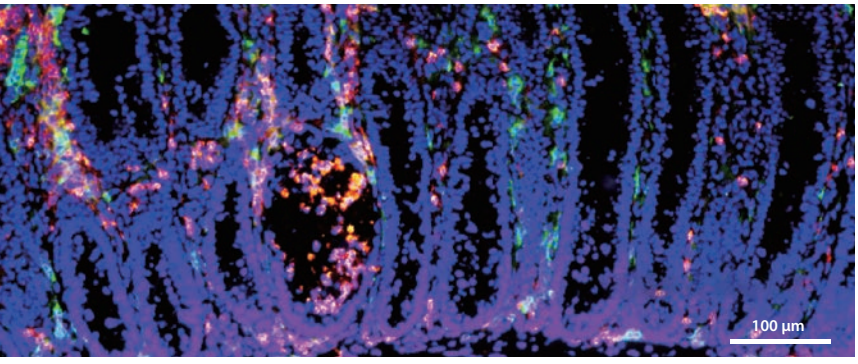
The influence of intestinal bacteria on gene expression in immune cells could be the key to treating inflammatory bowel disease

The past 100 million years of evolution have developed a complex relationship between bacteria and the human gut. These bacteria are essential because they break down nutrients that we cannot process, but, conversely, our immune systems must be constantly alert to the possibility that they will trigger an inflammatory response. Rapidly unfolding research that includes cutting-edge work at Keio University is revealing the importance of epigenetic mechanisms to this interplay, in which intestinal bacteria influence gene expression in immune cells. The findings present novel opportunities for the treatment of inflammatory bowel disease, which affects more than 3.5 million people worldwide.

Epigenetics and immunity

Epigenetic mechanisms involve chemical modifications of DNA molecules and histones, the proteins around which they are wrapped. These modifications alter gene expression and, consequently, cell function. The significance of epigenetics was described by the British biologist and geneticist, Conrad Waddington, as early as 1942, but the mechanisms and their full implications are still being unraveled.

"Nowadays, human epigenetic studies are common," says Koji Hase from the Keio University Graduate School of Pharmaceutical Science. The US National Institutes of Health (NIH), for example, launched the Roadmap Epigenomics Mapping Consortium in 2008, which has since revealed the epigenomic landscape in various human tissues and cells, and could lead to state-of-the-art therapies for cancers and autoimmune diseases. "Epigenetics in the immune system, however, is an emerging research field that has rapidly developed since the turn of the century," says Hase[1].



Disrupting the epigenetic regulation of regulatory T cells in the intestinal lining of mice causes inflammation, shown by the green fluorescent markers.

Immunity to inflammation

Research at Keio University, undertaken by several scientists, has focused on the epigenetic effects of intestinal bacteria on immune cells. "Keio University is now the center of microbiome and epigenetic studies in Japan, and researchers here are leading the worldwide initiative in microbiome studies," says Hase. Notable researchers include Kenya Honda, who heads research on the regulatory effects of the microbiome on the immune system, Takanori Kanai, who was the first to initiate fecal microbiota transplantation in Japan, and Akihiko Yoshimura, who leads studies on the epigenetic regulation of immune cells.

Hase's own work has shown that a metabolite called butyrate that is produced by intestinal bacteria is involved in the epigenetic regulation of regulatory T cells[2,3], which are central to the suppression of inflammatory responses. Butyrate was found to induce the differentiation of regulatory T cells in mice. Disruption of this epigenetic regulation caused severe inflammation of the intestinal lining known as colitis (see image)[3], but the disease was prevented by treatment with butyrate[2].

"Our findings not only link butyrate to microbe-mediated induction of regulatory T cells in the colon, but also provide evidence for the therapeutic application of butyrate in inflammatory bowel disease," says Hase.

Although the Keio University research has established the importance of intestinal bacteria in the epigenetic regulation of immune function, the precise molecular mechanisms behind this regulation are not known. Determining them is Hase's next step. "Gut-derived metabolites might behave as 'external hormones' to regulate host immunity and metabolism," he says. "I would like to take advantage of metabolomics to identify the molecular components of such host–microbe signaling."

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Stretching out speech components such as vowels in English or consonants in Japanese can be used to emphasize just how much we mean something.

Emphasizing words with a bit of a stretch

Consonants can be lengthened to convey both meaning and emphasis in Japanese

Japanese speakers adjust the length of consonants to convey the strength of their conviction about a subject, according to a study by Shigeto Kawahara at The Keio Institute of Culture and Linguistic Studies[1].

Unlike in English, the meaning of words in Japanese can vary dramatically depending on whether the consonants are pronounced as long or short sounds. Lengthen the 't' in the word for 'outside' (*soto*), for example, and you could be saying 'softly' (*sotto*). But consonant lengthening can also be used to emphasize the degree of meaning a speaker wishes to convey, as in the English vowel-based example, 'Thank you sooooo much for reading'. "Nobody really studies these phenomena of lengthened consonants and vowels even though it is very common in everyday speech," says Kawahara, who wanted to experimentally quantify the levels of distinction that could be conveyed through lengthening.

Kawahara and his colleague Aaron Braver at Texas Tech University selected four consonants — t, d, s, and z. Seven undergraduate students were given two adjectives for each consonant and instructed to lengthen the consonant to indicate emphasis in the context of a sentence. For example, for '*uzai*', which means 'annoying', the phrase would be '*ano koogi uzai*' or 'That lecture is annoying'. Participants were asked to repeat the sentence with varying levels of emphasis, in a randomized order, either with no emphasis or with anywhere up to five levels of emphasis, as in '*ano koogi uzzzzzzai*'.

The researchers used a phonetics software package called Praat to generate waveforms and spectrograms from the recordings that could be used to visually and statistically pinpoint the number of durational distinctions participants were able to convey. Kawahara was surprised by the results: "We initially thought that 3 or 4 degrees would be the most, but they managed to do 6!"

But are people able to recognize these subtle distinctions without technological intervention? In a previous study about English vowel lengthening conducted in the United States, Kawahara found that listeners are not very good at picking up on these distinctions. "The exact value of emphasis doesn't practically matter — it is sort of a selfish thing like 'Here's what I want to say'." Kawahara plans to carry out a similar perception analysis for the Japanese consonant lengthening study.

"This is a very understudied area," he points out. "It would be interesting to branch out and examine other languages." The findings could potentially be used to improve artificial intelligence or voice recognition software.

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Fine-tuning the brain's circuitry

A protein pair manages the proper development of neuronal connections essential for motor learning and neurological health

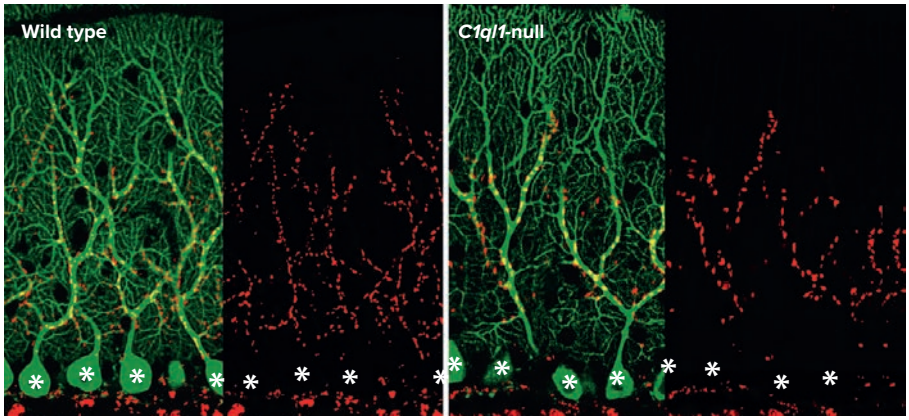
A mechanism that controls the formation and elimination of neuronal connections in the brain's motor center, the cerebellum, has been discovered by researchers led by Michisuke Yuzaki and Wataru Kakegawa at Keio University[1]. The process remains active over the course of a lifetime, and may be associated with certain neurological disorders.

Voluntary movement in the cerebellum is governed by signals transmitted at synaptic junctions between climbing fibers and neurons called Purkinje cells. "In immature animals, each Purkinje cell is innervated by numerous climbing fibers," says Kakegawa. "But as the animal grows, one climbing fiber — referred to as the winner — is strengthened, and the remaining weak climbing fibers are gradually eliminated." Kakegawa and Yuzaki identified a protein that might control this 'pruning', and set out to test their hypothesis.

They generated genetically modified mice lacking the protein known as C1ql1, which is specifically produced by climbing fibers. Purkinje cells in these mice retained multiple climbing fiber connections, but failed to establish the formal synaptic linkages needed for normal signaling (see image). In contrast, mice producing high levels of C1ql1 initially established excess connections, but pruned these down to a single winner within days. "This suggests that C1ql1 contributes to the strengthening of winner climbing fibers and the elimination of excess weak climbing fibers during development," says Kakegawa.

Subsequent experiments revealed that C1ql1 establishes fully functional climbing fiber–Purkinje cell synapses by binding a receptor protein called Bai3. The effects of Bai3 deficiency were essentially indistinguishable from those seen in mice lacking C1ql1, generating disruptions in synapse formation that interfered with the capacity to learn motor skills. The climbing fiber pruning process normally initiates roughly a week after birth, but the researchers were surprised to discover that the signals remain active throughout adulthood. Experiments that prevented C1ql1–Bai3 interaction in genetically normal adult mice undid the pruning process, resulting in impaired motor learning. However, the researchers could restore normal connectivity in adult mice that grew up lacking C1ql1 or Bai3 by enabling production of these proteins.

Kakegawa believes that these findings may offer important insights into human health. "Synapse dysfunctions have been observed in mouse models of psychiatric disease and in individuals with neurological disorders," he says. "Furthermore, the Bai proteins have been associated with psychiatric symptoms." A top priority for Yuzaki's team will be to explore this signaling pathway and to learn whether these proteins and their relatives perform similar roles elsewhere in the brain.



Climbing fibers form numerous synapses (red) with Purkinje cells (green; asterisks indicate cell bodies) in the cerebellum of normal, wild-type mice (left). In mice lacking the protein C1ql1 (right), climbing fibers form a greatly reduced number of synapses with Purkinje cells.

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Learning from master farmers

Keio researchers are applying information technology to capture and spread the agricultural wisdom of Japan's aging farmers

Computer scientist Atsushi Shinjo is using modern technology to gather and disperse the accumulated wisdom of Japan's expert farmers thanks to an encounter in 2009 with prize-winning tomato farmer Yutaka Ooyama from Tochigi Prefecture, a few hours' drive north of Tokyo. "I watched Ooyama as he inspected his tomatoes and found differences between his viewpoints and those of novice farmers," says Shinjo. This observation inspired Shinjo to establish the Agri-infoscience Laboratory at Keio University's Shonan Fujisawa Campus, an institution dedicated to maintaining "a balance between the latest technology and the rich natural environment."

An expert farmer records his work using an eye camera system.

Old wisdom

The seeds of Shinjo's initiative were actually sown years earlier in conversations with his grandfather, a vegetable farmer. "My grandfather would ask his vegetables how much water they needed," Shinjo recalls. Of course, the vegetables could not respond, but Shinjo remembers that his grandfather evaluated the condition of his plants in a very similar way to Ooyama.

Japanese farmers are some of the most productive and efficient in the world, but this admirable status is under threat because the most experienced farmers are aging fast. In terms of calories per acre, Japanese agricultural output is almost ten times greater than that in the United States and more than twice that of the most efficient agricultural nations in Europe, such as Germany. Yet the average age of Japan's farmers is rising steadily; it increased from 59 years in 1995 to nearly 66 in 2010.

"Two million of our 2.6 million experienced farmers will retire in the next ten years, and successors are in short supply," says Shinjo. "We need to act fast to capture and spread their knowledge."

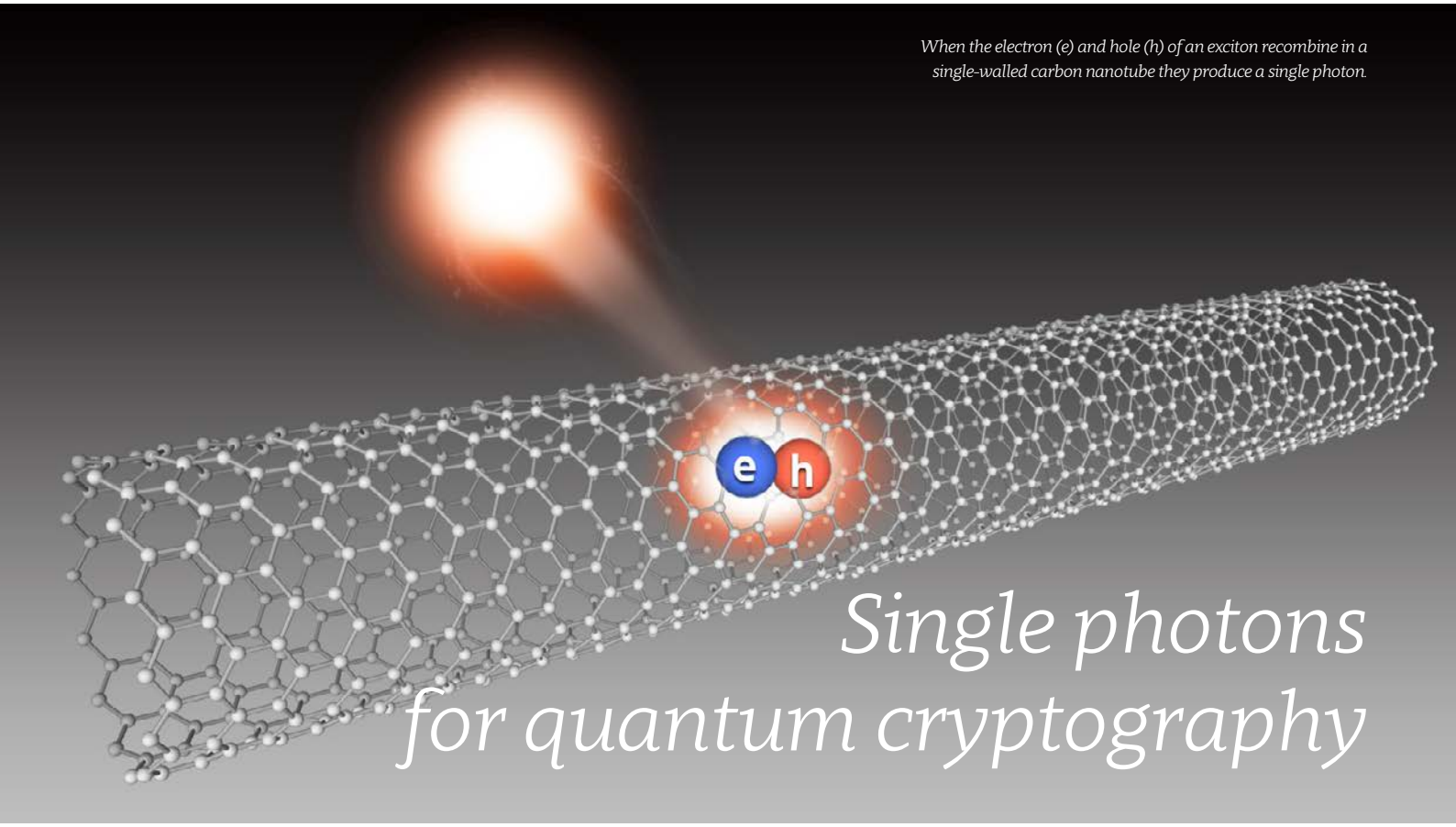
Agri-informatics

The Keio Agri-infoscience Laboratory uses information technology to capture the methods of the most successful farmers and then applies a software system to assess the data and distribute the best methods to younger farmers. This 'AI Agri-Culture' process offers advice through a decision-making support system. The precious input to the system comes from the wisdom and good practice of a network of exemplary farmers, or *takumi* ("masters" in Japanese).

The farms of the *takumi* experts are monitored using sensors to capture data on growing conditions, including temperature, irrigation and water levels, and chemical treatments. These technical data are combined with information on farming decisions and activities throughout the year, which the farmers record on software developed for mobile phones. The Keio researchers then collate and analyze the data and present it for use by less experienced farmers on computer tablets linked to a cloud-based network. The end users can install sensors on their own farms to help them replicate the conditions used by the *takumi* farmers, while also benefiting from more descriptive guidance.

Trials of this approach have already proved successful in Japan and Thailand. "Mandarin orange farmers have achieved a 20 per cent improvement in fruit quality using our system," reports Shinjo. A trial version of the software will be further evaluated during 2015 and a vendor will provide a commercial version before the end of 2017.

"Eventually, I want to apply our system to underdeveloped countries that already face food crises," says Shinjo. "This is one of the most important issues facing the world. Hopefully, we can help novice farmers to become experts as fast as possible," he adds.



When the electron (e) and hole (h) of an exciton recombine in a single-walled carbon nanotube they produce a single photon.

Single photons for quantum cryptography

Carbon nanotubes that emit single photons at telecommunication wavelengths and room temperature could be useful for quantum cryptography

Single-walled carbon nanotubes can emit single photons at room temperature and at wavelengths used for telecommunications, according to research by Keio University scientists[1]. This makes them very attractive as single-photon sources for quantum cryptography systems.

Quantum cryptography is an emerging technology that uses the quantum-mechanical properties of photons to encrypt information. The laws of quantum mechanics ensure that any attempt to intercept the information would garble it. For quantum cryptography to become commercially viable, light sources are required that produce just one photon at a time and at wavelengths used for telecommunications.

Takumi Endo, Junko Ishi-Hayase and Hideyuki Maki at Keio University have discovered that single-walled carbon nanotubes meet both criteria with an unexpected bonus — they generate single photons at room temperature. "We expected that single-walled carbon nanotubes would be suitable materials for single-photon sources at telecommunication wavelengths," says Maki, who led the research. "But we were very surprised that they produced single photons at room temperature."

The researchers used a superconducting single-photon detector to measure and analyze the light emitted from the nanotubes for temperatures from 6 to 300 kelvin (room temperature). The results revealed that the nanotubes exhibited 'photon antibunching' over the full temperature range — a sure indicator that they were emitting single photons.

Single-walled carbon nanotubes contain quasiparticles called excitons that consist of a negative electron and a positive hole. In the case of 'localized' excitons (that is, those restricted to a narrow area), a single photon of light is emitted when the electron fills the hole in a process called recombination (see image).

Localized excitons tend to become non-localized with increasing temperature, making it less likely that single-photon emission will occur. The scientists suspect, however, that a sleeve of randomly arranged carbon atoms on the nanotube shields it from direct contact with air, which allows the localized excitons to exist at high temperatures. This means that the nanotube's optical properties could potentially be fine-tuned using external coatings, for example.

A further advantage of these nanotubes is that they can be readily incorporated on silicon chips.

"Since single-walled carbon nanotubes can be directly grown on silicon chips, nanotube-based emitters can be easily combined with silicon photonics," notes Maki. This, together with the fact that the nanotubes do not require cooling, makes on-chip single-photon sources a feasible proposition — something that would greatly facilitate widespread uptake of quantum cryptography. The researchers intend to improve the efficiency of single-photon generation by nanotubes and apply a nanotube-based single-photon source to current quantum cryptography technology.

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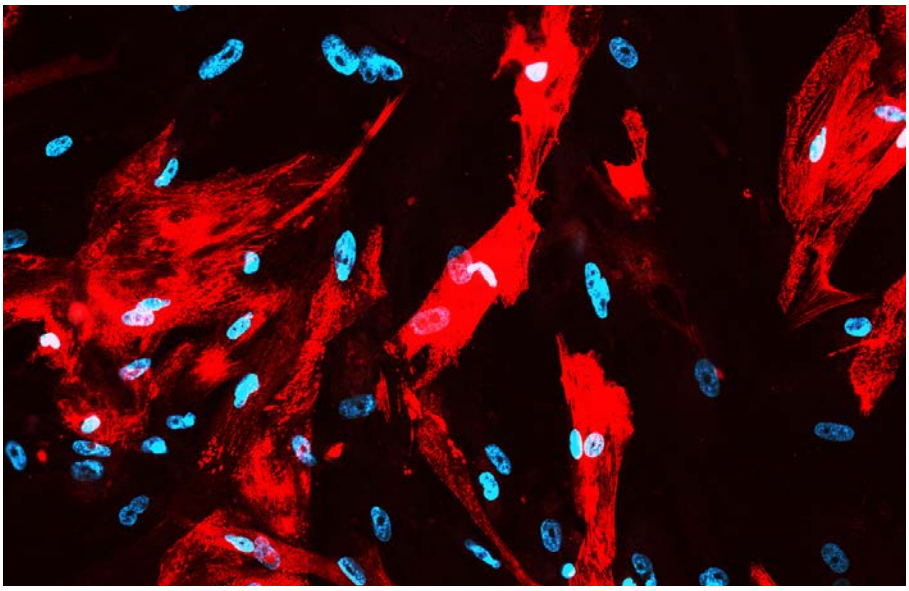
Mending broken hearts

A small RNA molecule can convert fibroblast cells directly into beating heart muscle cells

Keio researchers have found a direct and efficient way to convert mature cells from one type to another. The technique could eventually be used to stimulate a patient's connective tissue cells to become the beating heart muscle cells that will repair their damaged hearts.

"Heart failure is the number two killer in Japan," says Masaki Ieda at Keio University School of Medicine, who led the study. And cardiovascular diseases remain the leading cause of death worldwide, affecting an estimated 17.5 million people annually.



Human heart muscle cells (red) generated from fibroblasts by direct reprogramming.

Many research groups are trying to create mature cell types that could be used in regenerative medicine, but mostly via the stem cells route. Ieda and his co-workers are world leaders in exploring an alternative, direct path. In 2010, they were among the first groups to report direct reprogramming, when working with neurons and cardiac cells[1].

"Direct reprogramming is faster and simpler than stem-cell-based methods and carries no risk of tumor formation," says Ieda.

In their most recent study, Ieda and his colleagues, in collaboration with other Japanese research centers, found an efficient way to convert connective tissue cells known as fibroblasts into beating heart muscle cells called cardiomyocytes[2].

The researchers found that a small RNA molecule known as miR-133 can repress the activity of a key regulatory gene in a way that promotes the desired reprogramming into cardiomyocytes[1]. The miR-133 molecule is one of many microRNAs that can silence gene activity by binding to the larger messenger RNA molecules that carry genetic information from DNA to be decoded into active proteins. Overall, the miR-133 molecules block the activity of a large set of genes that make cells fibroblasts, while at the same time allowing other sets of genes that generate cardiac cells to become active.

Uncovering this fine detail about the mechanism by which fibroblasts can be reprogrammed into heart muscle cells should greatly assist efforts to move the current exploratory studies into real treatments. While Ieda used cultured cells in his study, he believes that similar techniques might eventually be possible in human patients. "We think we could reprogram fibroblasts into beating heart cells *in situ*," says Ieda.

Ieda now plans to explore ways to make the reprogramming process more efficient. In addition to the ultimate aim of repairing beating hearts, this work could also generate

cells that can be used for modeling heart disease and testing potential new drugs.

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Locating people using radio waves

A person's whereabouts could soon be tracked without the aid of a portable device

Keio researchers have devised a way to accurately locate an individual's position using only a remote antenna by exploiting the way that the human body interacts with radio signals[1]. The scheme has the potential to revolutionize remote patient monitoring, ambient intelligence for smart homes, and intrusion detection in security applications.

To be located, a person usually needs to hold a device containing a transceiver designed to interact with global positioning system (GPS) satellite signals or wireless or cellular networks. Mobile phones serve this purpose well, but in applications where relying on a device is too risky, such as in patient monitoring, location methods without a device are necessary.

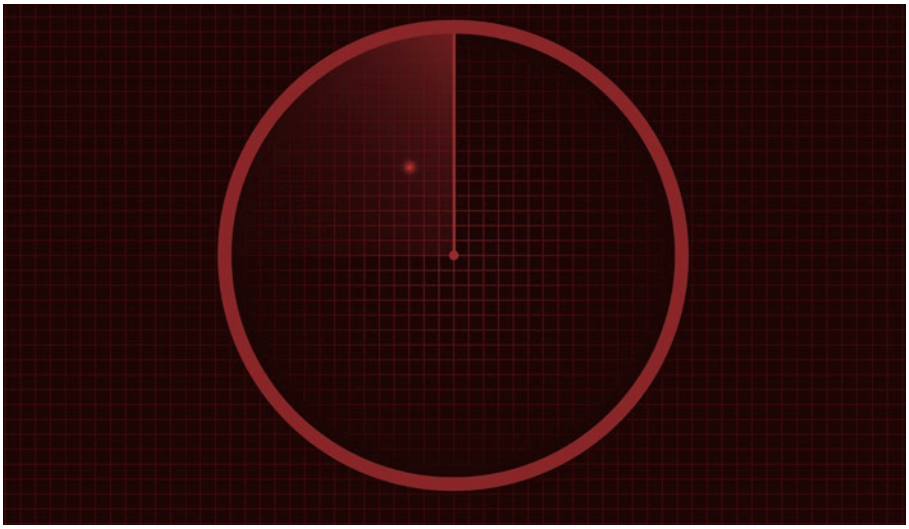
Several device-free localization methods that do not require the involvement of individuals have been proposed, but their accuracy is often poor due to the difficulty in separating the location signal from signal 'noise'. Tomoaki Ohtsuki and Jihoon Hong from the Department of Information and Computer Science at Keio University have developed a system that combines sophisticated signal processing with a specific distribution of antennas to detect the 'fingerprint' of human-body interaction with ambient wireless radiation without the noise interference that has plagued previous attempts.

The human body is an electrical conductor, which means that it diffracts, reflects and refracts radio signals emitted by wireless network transmitters in a very specific way. By analyzing these wireless signals using a mathematical concept called the eigenvector, Ohtsuki and Hong have been able to extract not just the fingerprint of human-modified wireless signals, but also the direction of signal, with unprecedented accuracy.

"Using special signal processing techniques, we can extract enough information from the signals to estimate the direction of the individual," says Ohtsuki. "While conventional schemes are subject to signal noise, our technique separates the signal and noise components, making signal processing stable and robust and allowing us to achieve high localization accuracy."

One of the most important features of Ohtsuki's localization system is its compatibility with existing network infrastructure. "Our scheme involves some antennas and signal processing, just as in current cellular systems and WiFi networks, so our approach can substitute into existing systems relatively easily."

Ohtsuki and Hong have further refined their approach to be able to detect specific movements of the tracked individual, such as falling, adding value to an already promising technique. The team is also working on expanding the system's capacity to track multiple individuals.



A new signal processing scheme can locate a person by detecting their body's interaction with ambient wireless signals.

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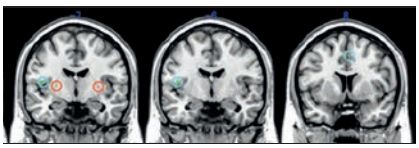
Finding where mind, brain, and body meet

Emotions arise in brain regions that link the triad of mind, body and brain



Magnetic resonance imaging scans comparing volumes of gray matter in postural tachycardia syndrome (PoTS) cases with controls. Brain areas where people with PoTS have less gray matter than controls are shown in green. Areas where controls have less gray matter than people with PoTS appear in red.

Satoshi Umeda loves music. In his youth, he learned to play the piano, trumpet, and double bass. Beautiful music evoked "marvelous" emotions in him, and he often wondered how these feelings were created inside his body and mind.

So began his interest in psychology. In 1992, he joined a master's program at Keio University's Department of Psychology, later going on to complete a PhD. He enjoyed Keio's "free and independent" atmosphere and became intrigued by the James–Lange theory of emotion, which emphasizes the mind–body interaction for understanding emotion. "It suggests that bodily feelings come first and emotional feelings follow," says Umeda.

"A turning point for me was reading Antonio Damasio's book *Descartes' Error*. The error was to think that the mind and the body were separate," he explains. "I decided then to scrutinize the mind–brain–body triad." Now a professor at Keio, Umeda has spent the last 15 years studying this triad and has gradually homed in on certain brain regions where he suspects it is embodied.

The heart of the matter

Our ability to feel our own bodies, including our awareness of sensations like sweating and heartbeat, is known as interoception. Umeda reasons that regions of the brain that process interoception might be where the mind, brain and body meet.

> ***"We understand others' emotional states by feeling our own bodily states simultaneously."***

A prime candidate appears to be a brain region known as the salience network. It consists of two adjacent brain areas: the anterior cingulate cortex, which controls bodily functions such as heart rate and blood pressure, and the insular cortex, which receives input from the heart and other organs and is known to be involved in emotions. Processing of both emotions and interoception within this network probably explains why bodily feelings accompany emotions.

Looking for evidence of a connection between interoception and emotions, Umeda and his team investigated whether there was a link between people's awareness of their own heartbeat and their ability to read the emotions of others. They discovered that those who are more aware of their own hearts beating are better able to tell whether other people are happy or sad[1].

"The key brain area involved in understanding other people's emotions appears to be the medial prefrontal cortex," he says. And it is no coincidence that this region is located next to the salience network, he adds. "We understand others' emotional states by feeling our own bodily states simultaneously."

Frightening palpitations

Damasio's book also reminded Umeda that studying faulty or damaged brain areas can often illuminate what the intact area does.

So he is investigating people whom he suspects may have a faulty salience network, with a view to better understanding its function. These people have postural tachycardia syndrome (PoTS) and experience an abnormal increase in heart rate when they stand up.

"They feel unpleasant and frightening symptoms such as palpitations, light-headedness, clouding of thought, and blurred vision. They are also prone to chronic fatigue and psychiatric symptoms such as depression, panic attacks, and anxiety," says Umeda.

He was lead author of a ground-breaking magnetic resonance imaging study published in 2015, which compared the brains of 11 patients with PoTS with 23 normal controls[2]. This was the first study to show that the brains of people with PoTS are different — their salience networks are smaller than normal (see image).

He is now using functional magnetic resonance imaging to see whether people with the condition respond normally to emotional challenges.

Beautiful music, and the strong emotions and bodily feelings it elicits, continue to inspire Umeda and his research. For a long time he conducted the university orchestra, and he still plays the piano at home.

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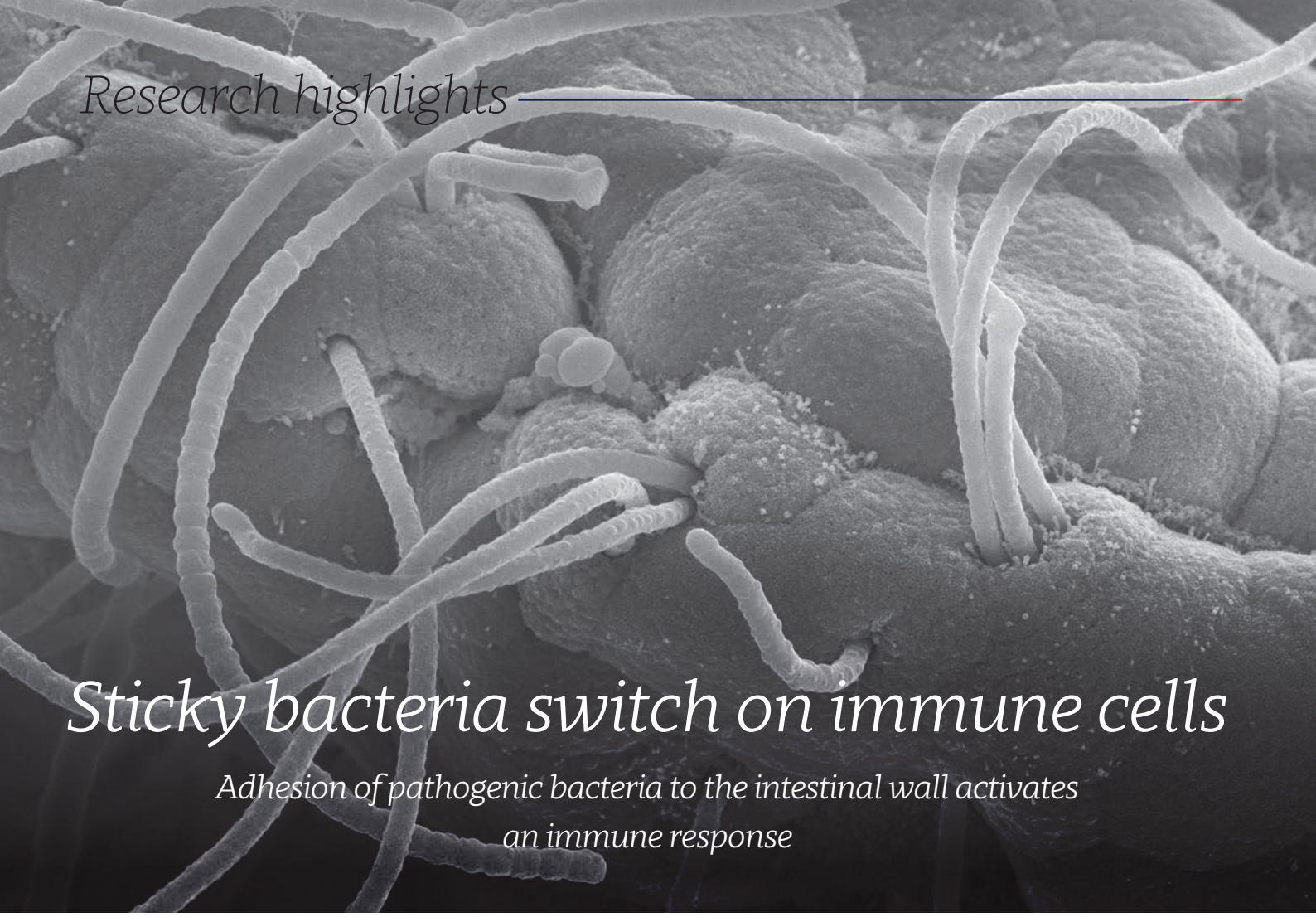

Sticky bacteria switch on immune cells

Adhesion of pathogenic bacteria to the intestinal wall activates an immune response

Electron micrograph of sticky segmented filamentous bacteria (long strands) attached to epithelial cells.

Intestinal immune cells are spurred to action by the attachment of pathogenic bacteria to the gut lining, according to research from Keio University[1]. Their discovery highlights the importance of physical interaction in triggering the immune response, and could improve treatments to balance the overproduction or underproduction of these immune cells in various diseases.

Pathogenic bacteria invade the intestinal wall by adhering to the epithelium and disrupting the epithelial barrier, explains Kenya Honda, who led the study. "That's pathogenic bacteria's pattern: adhesion, disruption, and invasion."

Immune cells which are abundant in the small intestine, known as Th17 cells, block this process by stimulating epithelial cells to produce anti-microbial peptides and strengthen the tight junctions between them, which maintain the epithelial barrier In rodents, resident gut microbes known as segmented filamentous bacteria are potent inducers of Th17 activity. Receptors on the Th17 cells are known to recognize the foreign antigens, but Honda suspected that adhesion might also play an important role in triggering the immune response. "Segmented filamentous bacteria are very sticky bacteria," he says (see image).

To test the importance of physical contact, however, Honda's team first had to overcome the challenges of culturing the bacteria and developing non-adhesive mutants.

The breakthrough came with an experiment by Yoshinori Umesaki at the Yakult Central Institute. Umesaki introduced segmented filamentous bacteria from rats into microorganism-free mice, and vice versa. The reciprocal colonization experiments showed that adhesion is host-specific — the foreign bacteria couldn't adhere to the intestinal lining of their new hosts — and that Th17 cells weren't induced in the absence of bacterial adhesion.

To study the process in humans, the researchers had to identify similar Th17-inducing bacteria colonizing the human intestine. They isolated 20 strains present in fecal samples from ulcerative colitis patients that were not present in healthy patients. When these strains were introduced to microorganism-free mice, they adhered to the lining of the colon, where they activated Th17 cells.

Diseases like ulcerative colitis and Crohn's disease have been linked to an imbalance in the gut microbiome, so correcting the imbalance could cure the disease, or at least alleviate symptoms.

Eventually, Honda's team aims to use microbiome engineering as a way to treat

patients with an overactive immune response, such as in autoimmune disorders, or a weak immune response. "For example, HIV-infected patients have fewer Th17 cells in their gut," explains Honda. "If we could identify a nice set of Th17-inducing bacteria, those could be applied to treat HIV or other diseases."

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Icy cages hold a clean energy secret

Water crystals can purify natural gas by selectively trapping carbon dioxide molecules

Unconventional sources of natural gas, such as so-called 'flammable ice' reserves located in the Sea of Japan, may soon find wider use thanks to carbon capture technology developed by Keio researchers[1].

Generating electricity from natural gas instead of coal or oil is a promising way to reduce greenhouse gas emissions. This energy, composed primarily of methane (CH_4) and other light hydrocarbons, burns cleaner than other fossil fuels because it is relatively free of impurities like carbon dioxide (CO_2) and hydrogen sulfide. However, rising demand means that lower-quality natural gas supplies, with trickier purification requirements, are being targeted for extraction.

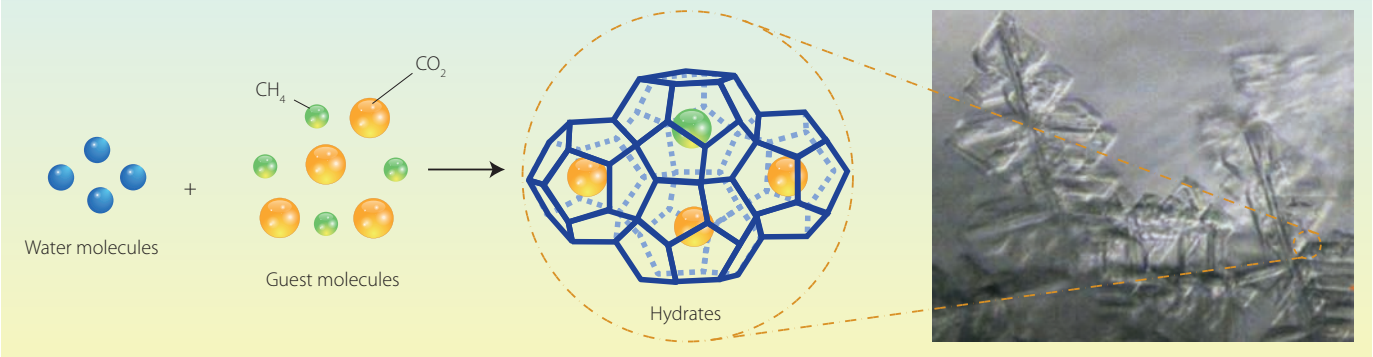
Chemical absorption and membrane separation are typical techniques used to remove CO_2 impurities from natural gas. But these treatments suffer from disadvantages such as the use of corrosive liquids and the need to constantly clean clogged filters. Ryo Ohmura and colleagues from Keio University's Department of Mechanical Engineering investigated a way to avoid such complications by using simple water molecules with surprising gas-trapping abilities.

Clathrate hydrates are ice-like complexes that form naturally on ocean seabeds, where temperatures plummet and pressures are enormous. These conditions cause water molecules to hydrogen-bond into cages and trap gases such as CH_4 or CO_2 at densities tens to hundreds of times greater than possible through typical compression techniques (see image).

The hydrates are also selective, explains Ohmura, and only stabilize when the gas compound fits suitably inside the aqueous cage: molecules too big or too small cause the complex to collapse. Since CO_2 molecules are larger than CH_4 molecules, the hydrates can be used to purify natural gas by selectively encapsulating and removing unwanted CO_2.

The team tested the carbon-capturing performance of hydrates under conditions that model the continuous operations of natural gas refineries. Using a small-scale reactor, they passed a CO_2–CH_4 mixture through a hydrate slurry and analyzed compositions for over 35 hours. Eventually, steady-state conditions — with significantly reduced CO_2 concentrations — were reached.

The researchers then compared the experimental data to computational algorithms designed to uncover the thermodynamic and kinetic factors behind hydrate purification. "With more accurate models,



Hydrates, compounds that trap gas molecules inside cages of ice, have diverse applications, from carbon capture to consumer goods.

we can identify ways to improve the hydrate formation, and understand long-term CO_2 capture more precisely," says Ohmura.

This technology has other, intriguing applications that could even change what we eat for dessert. Ohmura and his team are developing hydrates embedded with CO_2 that can carbonate frozen food — a potential way to inject champagne-like effervescence into ice creams and jellies.

Reference

1. Tomita, S., Akatsu, S. & Ohmura, R. Experiments and thermodynamic simulations for continuous separation of CO_2 from CH_4 + CO_2 gas mixture utilizing hydrate formation. *Applied Energy* **146,** 104–110 (2015).

The secret to successful aging

Keeping inflammation at bay can help people live past 100

A large study of the elderly in Japan has found that having low levels of inflammation in the body is the most important predictor of a long and healthy life[1].

The findings suggest that drugs that regulate the body's immune system could also help people remain mentally sharp and disease-free well into their 80s, 90s, 100s, and possibly beyond. "Anti-inflammatory medications are a potential intervention to slow aging," says Yasumichi Arai, a geriatrician-scientist at the Keio University School of Medicine in Tokyo.

About 0.05 per cent of Japan's population is aged 100 and older, which means the country has more so-called centenarians per capita than anywhere else in the world. Arai and his colleague Nobuyoshi Hirose (see image) have been studying these elderly people for more than 15 years.

In 2000, they launched the Tokyo Centenarians Study to look at people aged 100 years and older; in 2002, they began the Japanese Semi-supercentenarians Study to examine those over 105; and in 2008, they started the Tokyo Oldest Old Survey on Total Health, which considered people aged 85 and up. All participants in these studies underwent extensive medical examinations, including DNA analyses, cognitive studies and various physiological functions tests.

Arai, Hirose and their colleagues pooled data from the various cohort studies, including some of the centenarians' children, and, in total, investigated the health of 1,554 individuals to determine the most important biological driver of successful aging. They found that low levels of markers for chronic inflammation trumped all other indicators of whether a person might reach extreme old age, including blood cell numbers, metabolism, and liver and kidney function.

The Keio team also looked at the length of telomeres — the caps at the ends of chromosomes that are thought to continuously shorten with age and eventually lead to the cessation of cell growth — in collaboration with researchers at Newcastle University in the United Kingdom. They found that telomere size was not a predictor of successful aging, although most of the centenarians and their children managed to maintain long telomeres.

"People with the lowest inflammatory burden have the best chance of survival, and have higher physical and cognitive function," Arai says.

Arai is now looking for safe and effective anti-inflammatory drugs that could be prescribed to improve the quality of life of older people. "Because aging is the greatest risk factor for a majority of chronic diseases," Arai says, "interventions targeting aging itself are promising to elongate human health-span."

Reference

1. Arai, Y. *et al.* Inflammation, but not telomere length, predicts successful ageing at extreme old age: A longitudinal study of semi-supercentenarians. *EBioMedicine* **2,** 1549–1558 (2015).

Keio researcher Nobuyoshi Hirose (left) with the oldest man in history, Jiroemon Kimura, who died in 2013 at the age of 116.

The Keio Medical Science Prize

The 2015 Keio Medical Science Prize Laureates

"I thank the Selection Committee for this wonderful award. I am fortunate to work alongside students and colleagues committed to identifying new ways to enhance the nutritional health of infants, children and adults, living in different parts of the world, by studying the interrelationships between our gut microbiomes and diets. Studies of the microbiome are allowing us to see ourselves as intimately connected to the microbial world, prompting us to consider another dimension of our human biology and evolution, and inspiring us to be better stewards of our precious microbial resources."

Jeffrey I. Gordon

"It is a great honor for me to receive The Keio Medical Science Prize 2015. I have been working on autophagy, an intracellular degradation system, for more than 27 years by using yeast. Identification of the genes in yeast responsible for autophagy changed the research. It is becoming clear that autophagy plays an important role in a variety of cellular events and is related to certain diseases. It has been a great pleasure for me to share many exciting findings with my very talented colleagues. I would like to express my sincere thanks to all of them."

Yoshinori Ohsumi

Objective

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

Prize

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

Nomination and Selection

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

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

Yearly Schedule (Subject to change)

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

www.ms-fund.keio.ac.jp/prize

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