Issue 4
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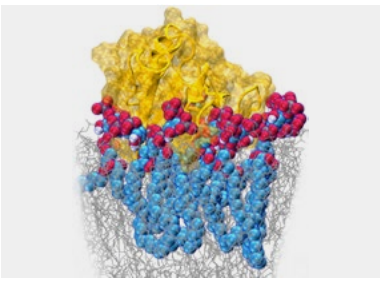
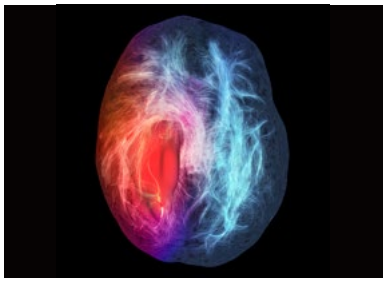
JITSUGAKU

Showcasing the best research from Keio University

Global Outlook of a Hundred Years of Nursing Education



Molecular jostling affects diffusion at cell membranes



Drug helps blood vessels but leaves lurking cancer cells

Tardigrade genomes explain life on the extremes

Keio University

Happy Centennial Anniversary!

The Keio University Faculty of Nursing and Medical Care

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ON THE COVER

In 1918, Keio University established one of Japan's earliest educational facilities to train nurses under the leadership of the first dean of the Keio University School of Medicine, Shibasaburo Kitasato, who foresaw the integral role of nurses in modern medical care. Now, 100 years after the first 54 nursing students enrolled at the Department of Medicine Nurse Training Center, Dean Hiroko Komatsu is bringing nursing education at the Faculty of Nursing and Medical Care into the future under the mantra of "training individuals who strive to build a healthful society."

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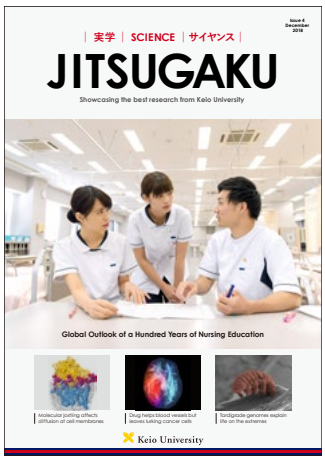
Global Outlook of a Hundred Years of Nursing Education at Keio



Issue 4, December 2018

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.

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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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The evolution of nursing education at Keio University over the last 100 years has been inspired by the spirit and philosophy of Keio University's founder, Yukichi Fukuzawa. His belief in *dokuritsu-jison*—independence and self-respect—and *jitsugaku*—empirical science—led to the advent of the Women's School of Welfare, the Keio Junior College of Nursing, and in 2001, the Faculty of Nursing and Medical Care.

Nursing entails an exploration of the multifaceted and practical aspects of science, and necessitates judgment and practical skills based on a spirit of mutual respect, humaneness, deep intellect, and ethics. Furthermore, nursing requires a lifetime of study and interaction with other academic disciplines to advance the development of nursing care as an "empirical science."

Utilizing its wide-ranging strengths as a comprehensive higher education institution, Keio University has established curricula and courses that includes tuition from faculty members of other departments, enabling students to take lectures and practical exercise classes in other disciplines. In particular, the Faculty of Nursing and Medical Care collaborates with the Faculty of Pharmacy and the School of Medicine to inspire and nurture students in their pursuit of education in health and medical care.

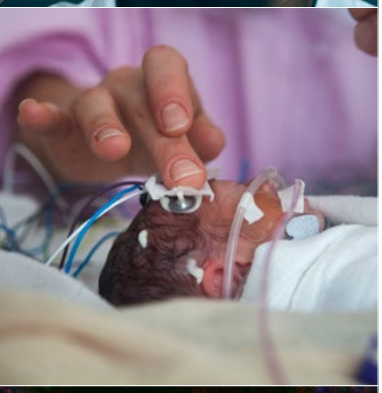
Notably, the Inter-professional Education program offered by the three medicine-related departments launched a compulsory course in 2011, where undergraduate students participate in group discussions with students from the other departments in their own year. The aim of such interaction is to learn to cooperate and respect the views of professionals from other areas of expertise in order to provide higher quality medical care and treatment for patients.

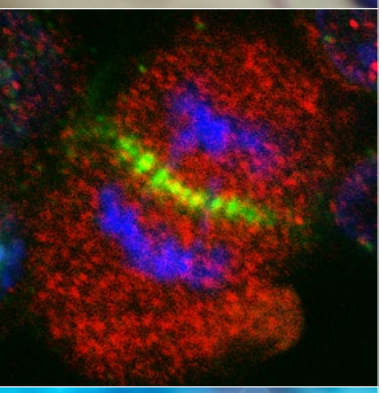
Advances in pharmaceutical treatments, innovative healthcare programs, and preventative measures against the spread of disease have necessitated a global approach to nursing. Anticipating social changes in the future, defining and prioritizing potential medical issues, and so on, require a global perspective on medical care. With such global concerns in mind, Keio University has implemented programs for accepting short-term international students and set up overseas training programs in the United States, the UK, and Laos.

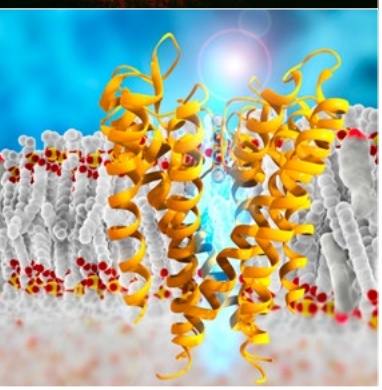
Students at the Faculty of Nursing and Medical Care nurture a rich human sensitivity and acquire expertise and a broad outlook that enables them to play leading roles in medical care once they graduate. Nursing education at Keio University is continuously evolving to foster practitioners in nursing and medical care suited for the challenges of the 21st century.

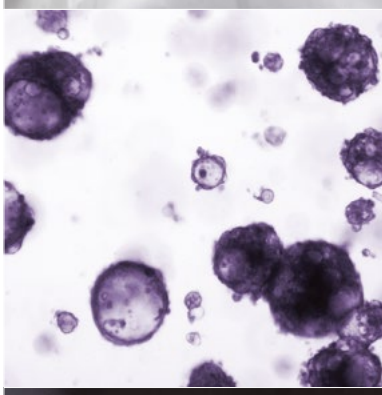
The articles in this issue of *Jitsugaku* reflect the pioneering, multidisciplinary, and global outlook of research and education at Keio University. Research highlights include 'Heavy coffee-drinking mice produce fewer fat cells, bringing broad health benefits' by Megumi Funakoshi-Tago; 'Economic researchers dismiss growing concerns about the negative impact of globalization' by Toshiyuki Matsuura; 'Innovative 3D-printed "caring-tools" to enhance the quality of life of elderly people' by Shoko Miyagawa; and 'DNA analysis shows how water bears survive extreme conditions, yet leaves evolutionary origin unclear' by Kazuharu Arakawa.

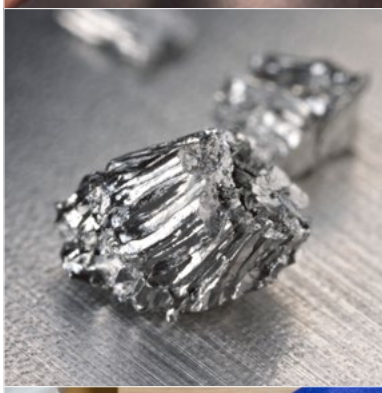
Contents

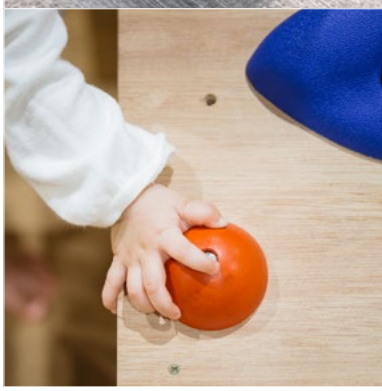












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The best drop for lean beans

Heavy coffee-drinking mice produce fewer fat cells, bringing broad health benefits

Coffee contains active compounds that can suppress obesity and its related health effects.

Can't begin the day without a coffee? A morning brew might have broader benefits than just an energizing jolt, new research shows. Previous health surveys have hinted that regular coffee drinkers have a significantly reduced chance of developing obesity and associated diseases such as type-2 diabetes and heart disease. Researchers at Keio University have taken a closer look at these claims, and discovered a molecular mechanism by which coffee inhibits fat cell formation[1].

"Our results provided evidence that drinking coffee has advantages for reducing obesity and its associated diseases," says Megumi Funakoshi-Tago from the Keio University Faculty of Pharmacy, who led the work.

The team's first step was a control experiment in mice. In a study involving 36 animals, just as earlier surveys had predicted, mice on a high-fat diet gained significantly less weight when given a diluted drip-filter coffee extract, the team discovered.

These lean, coffee-fed mice had accumulated less of a fat form called adipose tissue — the very tissue associated with obesity. "It is well understood that obesity is caused by abnormal 'adipogenesis'," the process by which immature fat cells become fully functional, fat-laden cells called adipocytes, Funakoshi-Tago says. The team homed in on coffee's effects on adipocyte formation, and confirmed that it inhibits the formation of mature adipocyte fat cells.

Drilling down into the cellular signaling pathway known to trigger adipogenesis, the researchers traced coffee's effect to a molecule called insulin receptor substrate 1 (IRS1). In the presence of coffee, a key phosphorus tag on IRS1 is removed, consigning the molecule to the cellular recycling bin and switching off adipocyte formation.

But to realize the full effects of drinking coffee on obesity would demand a serious coffee habit, says Funakoshi-Tago. Weight gain was restricted in mice given the equivalent of 6 to 7 cups of coffee per day. "To prevent obesity, we would have to drink more than 9 cups a day," she adds.

A more efficient route, would be to identify the coffee molecule responsible for the beneficial effect, which could be a lengthy task. "Coffee extract contains a large number of chemical components," Funakoshi-Tago says. "We tested the effects of caffeine, chlorogenic acid, and caffeic acid, which are known to be abundant in coffee extract, however, they had no effect on adipogenesis." The team is now grinding through coffee's other component molecules, looking for the elusive active compound.

Reference

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Taking the temperature of the tiniest things

Nanoscale thermometer takes precise heat readings of tiny spots, billionths of a meter wide

The temperature of tiny structures, thousands of times smaller than a grain of sand, can now be measured accurately, thanks to a technique developed by Keio University researchers[1]. The method could help to design more efficient electronic components, or monitor the behavior of individual cells.

The technique is a form of nanoscale thermometry, able to measure the temperature at a point just billionths of a meter wide, and it avoids some key problems of previous approaches. Scanning thermal microscopy techniques, which come in direct contact with a sample, have a spatial precision of less than 100 nanometers. But the microscope's probe tip can damage the sample, and heat exchange between the sample and the equipment can affect the temperature measurement. Meanwhile, non-contact methods using lasers have a spatial resolution that is usually limited to half the wavelength of the incoming light, which is typically several hundred nanometers.

Yoshihiro Taguchi of Keio University, and colleagues, have invented a non-contact technique called fluorescence near-field optics thermal nanoscopy (Fluor-NOTN), with a spatial resolution of just 70 nanometers. It relies on nanoscale-sized 'quantum dots' made of cadmium selenide, which fluoresce when light shines on them. Crucially, the time it takes for this fluorescence to fade away depends on the quantum dots' temperature.

The team coated a silicon surface with the quantum dots, and used a conventional electrical thermometer to monitor its temperature. They shot incredibly brief pulses of blue laser light at the surface through a specially modified optical fiber, its core tapered to a 70-nanometer-wide opening.

The pulses made the quantum dots fluoresce red light, which travelled back up the optical fiber to a detector. This showed that the fluorescence lifetime was just over 13 nanoseconds at room temperature. But as the temperature increased to 40 degrees Celsius, the lifetime decreased to about 12 nanoseconds.

By measuring the fluorescence lifetime of quantum dots in this way, the researchers hope to study the temperature distribution in minuscule straw-like structures called carbon nanotubes (CNTs). An electrical current causes some CNTs to heat up and emit light, which could be used to generate pulses that carry information in novel forms of computer chips. "Understanding the local temperature distribution is important for controlling the response speed of light emission, and the light spectrum," says Taguchi.

The researchers also aim to study living cells with Fluor-NOTN. "The temperature distribution of a cell is still unknown," says Taguchi. "We aim to map the local temperature of a single cell, such as a neuron."

Reference

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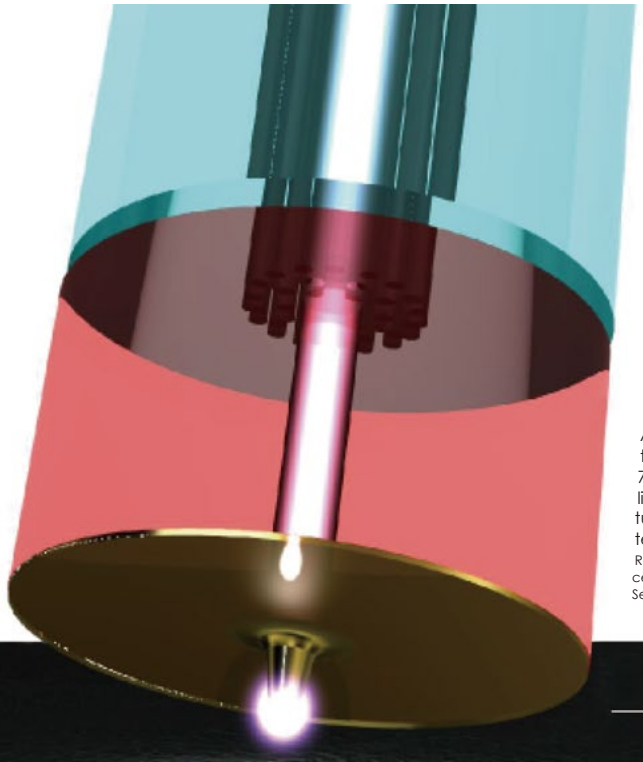

An optical fiber, its core tapered to an aperture just 70 nanometers wide, shines light onto fluorescent quantum dots to measure their temperature.

How 7-month-olds make sense of adult babble

Japanese infants determine where words start and finish by employing a neural circuit attuned to speech sounds

To newborns, adult speech sounds like a constant stream of babble. But at some point between their first squeals and first steps, babies begin to recognize the beginning and end of words — an important development in the process of language acquisition known as word segmentation. Keio University researchers have found that Japanese babies can segment words at seven months — two months earlier than previously thought — and have clearly identified the brain regions that help infants do this[1].

Previous studies into the neural basis of word segmentation have used a technique known as event-related potentials (ERP), which can measure electrical activity in the brain resulting from specific stimuli, but usually offers only a crude visualization of brain activity. In contrast, Yasuyo Minagawa and colleagues at Keio used functional near-infrared spectroscopy (fNIRS), which measures the concentration of hemoglobin associated with neuronal behavior, to reveal the exact brain regions engaged in word segmentation.

The researchers separated a cohort of 54 Japanese infants into three age-groups (5-6 months, 7-8 months, and 9-10 months) and introduced them to simple Japanese words, such as *tanishi* (mud snail) and *zakuro* (pomegranate).

In an initial training session, the researchers attracted the infants' attention to a screen, where single target words were read aloud together with a lively animation. This was followed by behavioral testing, in which the target words and control words were recited as part of a sentence.

The ability to recognize words by the age of seven months facilitates language acquisition in infants.

Infants aged 9-10 months spent significantly more time looking at the screen when sentences included the target words, indicating their ability to segment the words from the sentences.

Neuroimaging using fNIRS, however, indicated that this skill develops slightly earlier. During the training task, infants in the 7-8-month and 9-10-month age-groups showed significant activation in brain regions that play a role in encoding and storing short-term phonetic memory. The test session, in contrast, significantly activated regions associated with retrieving the phonetic memory.

These results corroborate with previous studies using ERP, but reveal for the first time the exact regions that play a role in infant word segmentation. These regions seem to be a part of the early cerebral circuit involved in articulating sounds (dorsal pathway) as opposed to the circuit that registers meaning (ventral pathway).

Furthermore, the study pinpoints when Japanese babies begin to segment words in their native language, which is around the same time as babies learning English and German, but slightly earlier than French.

Minagawa hopes to further study how Japanese babies learn the meaning of words; and to explore the role of social interaction in language acquisition.

Reference

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Space technology for a world of problems

The benefits of satellites are far-reaching and versatile. They can improve productivity on farms, locate people stranded in disaster zones, and even track sports performance

Naohiko Kohtake's research area of space once seemed among the least practical realms. But his work solves real-world problems for everyday people working on the land, looking for safety, or scoring their next try.

Kohtake is a system design scientist at Keio University, who thinks big about how satellites can collect, analyze, and even send out data. "The key is a holistic view," says Kohtake, who is also an adjunct associate professor at the School of Engineering, Asian Institute of Technology. "Many people focus on specific areas, but we focus on optimization, system thinking, and modeling to design a sophisticated, merged system."

A striking example of this is Kohtake's disaster management systems. He has used location data collected from mobile phones and taxi GPS to analyze how people behave during disasters across Asia, such as the 2011 Tohoku earthquake and resulting tsunami. "Data is useful for finding social issues," he says. "We can understand the program underneath — the human mind."

While developing these systems, Kohtake realized that satellites could also help with communication in the confusion of a natural catastrophe. "After a disaster it is difficult to maintain contact and communicate messages to people," he says.

Taking advantage of the fact that Japanese navigation satellites can broadcast messages directly to the GPS receiver built into mobile phones, Kohtake and students designed an app

Satellite technology is helping rugby players improve their sports performance.
© Keio University Rugby Football club

to get location information about designated meeting points or safe routes to people in disaster zones. Already, the system has been successfully trialed for bushfires in Australia and for tsunami warnings in several Asian countries.

This example, like many of Kohtake's diverse research areas, grew out of his passion to broaden the uses of satellite data.

"Nearly every university has a program on how to build rockets and satellites, but few have courses on how to use satellite technology," he says. To address this, Kohtake leads the Geospatial and Space Technology Consortium for Innovative Social Services (GESTISS), a collaboration set up in 2012 between several universities in Asia, including Keio University's Graduate School of System Design and Management. Every year, GESTISS organizes tutorials, seminars and summer camps for 100 students across Asia and inspires them to think about how to employ satellites for social good.

Kohtake's GESTISS students, in collaboration with Malaysian researchers, traveled to palm plantations in Malaysia, where they revolutionized the labor-intensive planting practices. Using satellite and drone data to create three-dimensional maps, they developed an app that enables a single person to calculate the optimal planting position — far more efficient than the traditional team method using long wires.

As well as rural settings, Kohtake is working in the most densely populated areas of the world. The obstacle of tall buildings can cause errors in navigation systems of several meters, which could lead to disaster for driverless cars. Kohtake's solution is to develop a navigation app that uses data from multiple satellite networks — the Japanese Quasi-Zenith Satellite System, the Chinese BeiDou and the United States Global Positioning System (GPS) — and is accurate to within a meter.

Kohtake's positioning system is so precise that he is now using it to benefit his favorite pastime, rugby. Each player is equipped with a small tracking device, enabling them to download a record of their every movement on the field, to analyze and improve their performance.

This revolution in sport science, believes Kohtake, who is an adviser at the Japan Sport Council, will also give professionals a career path when they retire from sport.

"Top athletes interested in their performance data develop analytical skills, which are good not only for sport but also can help them move to other domains."

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Molecular jostling affects diffusion at cell membranes

Dynamic interactions between proteins and lipids at cell membranes result in complex changes in diffusion rates

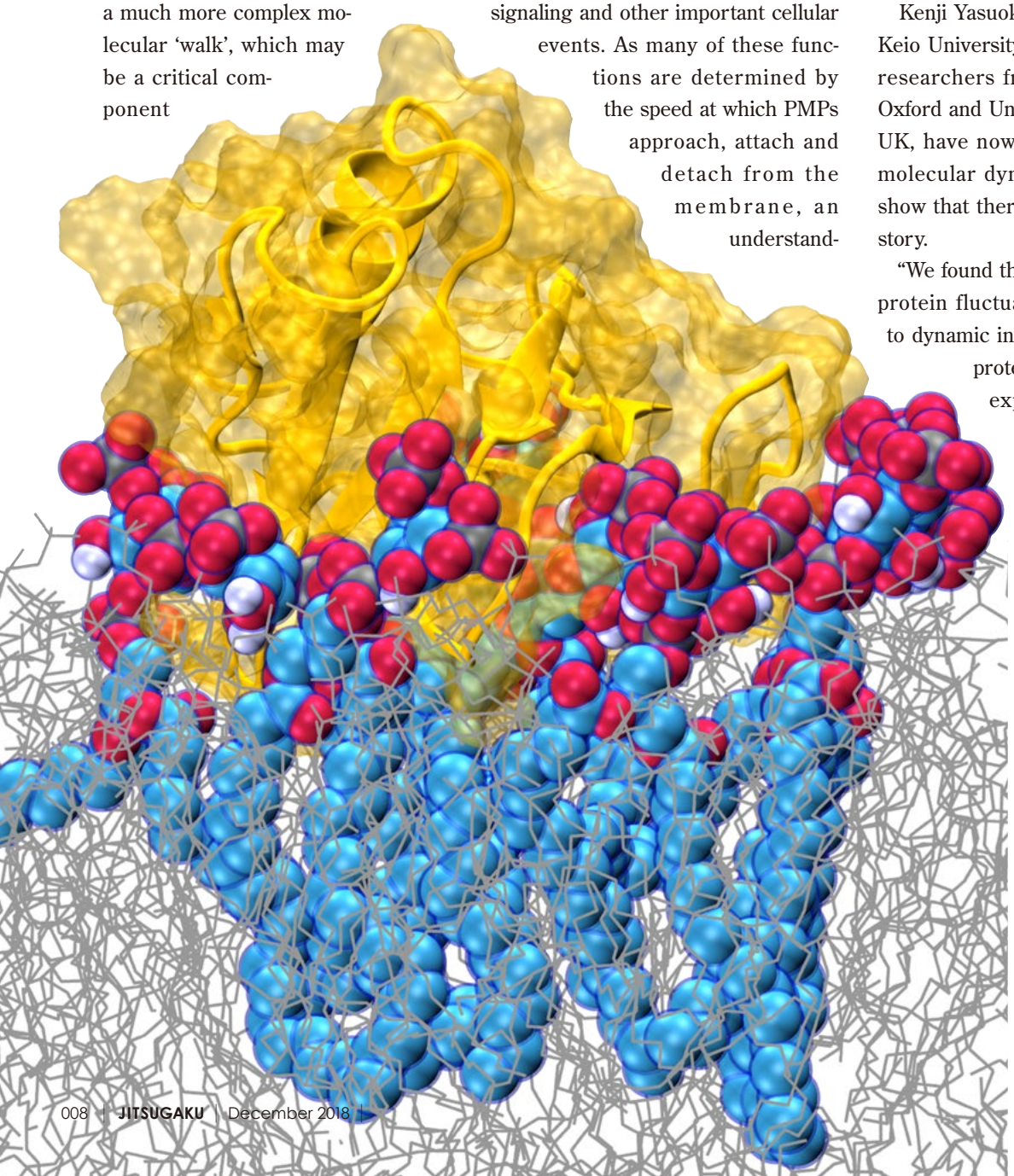
Molecular dynamics simulations have revealed that the diffusion of key biomolecules at cell membranes changes dramatically over short time scales due to complex molecular interactions, including clustering[1]. This suggests that the apparently steady diffusion of these molecules over longer time scales hides a much more complex molecular 'walk', which may be a critical component of biological processes.

The cell membrane is a remarkable biological structure that is selectively permeable to certain ions and biomolecules while being impermeable to most water-soluble molecules. Peripheral membrane proteins (PMPs) temporarily bind to the cell membrane to provide a range of biological functions, including the regulation of cell signaling and other important cellular events. As many of these functions are determined by the speed at which PMPs approach, attach and detach from the membrane, an understanding of the detailed molecular dynamics of these processes could provide important information on biological mechanisms. However, conventional methods for modeling and analyzing the diffusion of PMPs provide only general characteristics and are unable to resolve the detailed motion contributing to overall diffusion over long periods.

Kenji Yasuoka and colleagues from Keio University, in collaboration with researchers from the University of Oxford and University of Leeds in the UK, have now used high-resolution molecular dynamics simulations to show that there is much more to the story.

"We found that the diffusivity of the protein fluctuates anomalously due to dynamic interactions between the protein and specific lipids," explains Yasuoka. "This 'short-time' diffusivity is intrinsically different from long-time measurements, and shows that the overall mobility of signaling proteins on the surface of cell membranes is sensitive to lipid interactions."

The researchers used a new method to estimate the short-time diffusiv-



Molecular dynamics simulation snapshot showing the binding of a Pleckstrin homology domain (yellow) with lipids (red/blue) in the cell membrane (grey).

ity from a single molecular trajectory without relying on knowledge of changes in diffusivity, looking specifically at the dynamic interactions of the Pleckstrin homology (PH) domain — the PMP lipid recognition module that controls membrane binding. Their molecular dynamics simulations tracked the motion of a hundred Pleckstrin homology domains when placed within a few nanometers of a cell membrane surface over a period of just 10 microseconds.

The results show that cell membranes are complex spatially and temporally inhomogeneous environments where crowding of lipids and proteins is common.

"Determining the interactions of PMPs with the membrane at the molecular level is crucial for understanding the function of these biological important proteins," says Yasuoka. "We are also interested in investigating the diffusion process in more complex systems, such as the interaction between transmembrane proteins and PMPs."

Reference

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Future tech will read everything in your eyes

Researchers are creating smart eyewear that will measure your reading habits and will even tell you how much you understood

For the foreseeable future, making tech more intuitive will be about analyzing eye gaze and the delicate muscles and skin around your eyes, says Kai Kunze, a researcher at Keio University. "Eyes can tell you everything from where you're focused to your level of expertise in a topic," explains Kunze, a German-born, Tokyo-based expert in wearable computing, cognition-aware computing, and smart eyewear. "If you understand something well, for example, your gaze will usually flow nicely and you won't fixate on unfamiliar words for very long."

Kunze's doctoral students at Keio's Graduate School of Media Design are tweaking wearable headsets in ways that could change our everyday lives. One project is looking at how to allow the motion-sick to navigate virtual environments nausea-free while standing still — a key problem holding virtual reality (VR) technology back. Another is seeking to harness your natural squint to zoom in on hard-to-see objects.

Eye-interpreting equipment, Kunze says, is more advanced than other technologies and will be the first cab off the rank in the race toward VR headsets and wearable computing devices, such as Google Glass. "There's technology that can measure brain activity, but it's too hard to process that information in real time. For real-time feedback, eyes can provide a lot more information much faster."

Future virtual reality devices are likely to be fitted with eye-tracking technology. © mikkelwilliam/Getty

"We've already seen a couple of start-ups and kick-starter campaigns doing similar work. Three years ago, we implemented our own eye tracking in VR headsets because nobody had done it before. I suspect the next Oculus or Second Life head-mounted displays will come with eye tracking. It's relatively cheap to implement, and you gain a lot from it in the VR headset space."

Reading glasses that measure fatigue

Japan, says Kunze, is an amazing place to work on this type of tech because of the low resistance to incorporating new technologies into daily life. Some of his innovations have already hit the market.

For example, prescription glasses from Japanese eyewear company J!NS look like retro horn-rimmed glasses, but use electrooculography eye tracking to give wearers all sorts of information about their physical and mental state (see image). Using installable apps, the glasses can alert tired drivers and monitor concentration levels at work using feedback from blinks and eye movement.

Kunze, who was a consultant in the design, says that electrooculography is a promising form of eye tracking because it is computationally light. It involves measuring changes in electric fields caused by eye move-

Glasses being retailed by the Japanese eyewear company J!NS can monitor fatigue and concentration levels. © 2017 Keio University

ment using electrodes positioned on the skin around the eyes, which can be inserted into the nose pads and bridges of conventional glasses. "Eyes are basically like a dipole," says Kunze. "The electric charge the sensors detect varies as you move your eyes toward or away from a sensor."

J!NS commercially released these glasses in 2015. In many respects, they echo the roll out of physical activity trackers — like Fitbits for the mind. However, since more than 80 per cent of sensory information comes to humans via the head, Kunze points out that these devices are green pastures for researchers.

Are you in the right headspace to read that report?

Your glasses could soon reveal your intellectual habits — good and bad — doubling as a fitness tracker for your brain.

For example, research by Kunze and colleagues in Germany and Osaka Prefecture University has provided a basic proof of concept of Kunze's Wordometer, which uses the electrooculography technology in J!NS glasses to count the number of words the wearer reads in a day.

More-subtle mental processes such as cognitive load, attention distribution, and stress require a lot of psychological research, and so Kunze and his colleagues have been measuring facial temperature patterns and electrodermal activity (EDA). EDA technology uses spectacle touch points in a similar way to electrooculography, but measures sweat gland permeability, changes in skin resistance to a small electrical current, or the differences in the electrical potential between different parts of the skin. The advantage of EDA is there is a wealth of information on what these measurements can tell you about your psychological state — EDA has been used in psychological research since Carl Jung used it to study psychological arousal in the early 1900s.

In short, says Kunze, smart eyewear could very soon tell you whether it's time to read that difficult report or just go for a walk.

Born before their time

'Stuck' brain cells in extremely premature babies lead to impairment in later life

Up to half of babies born before 28 weeks develop significant difficulties later in life: attention deficit hyperactivity disorder, autism, and other developmental disorders. Keio researchers have discovered that such problems occur because neurons in the developing brain never complete their journey to the outer regions of the brain[1].

Extremely preterm births (those before 28 weeks) are on the rise, but no-one knows why. "Improved medical care increases survival, but the prevalence of preterm babies [in ratio to normal-term births] is increasing. It's a big problem," says Ken-ichiro Kubo of Keio University. "We're now discovering the impact of extremely preterm birth. The first of these babies are now in their teens or early twenties — go back further than this and these children simply didn't survive."

Separated from the umbilical cord, extremely preterm babies do not have the functional lungs or circulatory system they need to supply their brains with oxygen and blood, hampering brain development at a critical stage. It is this, rather than the early birth, that often causes issues.

Leading a team of 27 researchers in Japan and the United States, Kubo and his colleague Kimiko Deguchi hypothesized that this brain damage is caused by the impairment of 'neuronal migration'. In this process, neurons in the growing brain are produced in the innermost part of the brain and then migrate outward through the white matter to the gray matter at the brain's extremities. "Neuronal migration is an essential, early stage of development in mammalian brains," explains Kubo. "It needs to happen. Cells can't just pile up in the middle of the brain; they need to move to the brain's surface for the brain to be correctly wired and function appropriately."

The team studied brain samples of infants born before 28 weeks and found that significant amounts of neu-

Many babies born before 28 weeks develop significant difficulties later in life. Keio researchers have found that such problems are caused because neurons in the developing brain do not reach the outer regions of the brain.
© BSIP/Contributor/Getty

rons, frozen in time, never reached their destination — the cells were 'stuck' mid-migration. "The process apparently hasn't been completed in these cases," says Kubo.

To validate this suspicion, the team created a 'model' of this brain injury using mice. Having developed in the womb under a period of blood starvation, their mice exhibited the same learning difficulties as their human counterparts — failing to distinguish a novel object from one they had previously been exposed to. Examination revealed that these mice too exhibited incomplete neuronal migration. "Our mice model really mimics the disease presentation in humans," says Kubo.

Kubo and his team intend to research neuronal communication with a view to rescuing the development of children already living with affected brains.

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Foreign investment boosts productivity at home

Economic researchers dismiss growing concerns about the negative impact of globalization

There has been a backlash against globalization, as evidenced by the Brexit vote in the UK and the election of Donald Trump as US president, both in 2016. Increasingly, people are viewing corporate investment abroad as a threat to employment in their home countries.

A recent study shows that the opposite may be true — setting up or acquiring companies in foreign countries, known as foreign direct investment (FDI), "does not necessarily hollow out the domestic economy, but rather it could help raise productivity at home," says Toshiyuki Matsuura, an econometric researcher at Keio University[1].

Conventionally, econometric researchers have investigated how FDI affects domestic performance at a company level. But such studies tend to be too broad and have led to conflicting conclusions. Matsuura and his collaborators hoped that a more focused study based on appropriately selected data would give more consistent results.

By considering FDI at a plant level, the study by Matsuura and colleagues provided a more detailed analysis than previous studies. It was based on two sets of Japanese government data about overseas affiliates. The team looked at more than 2,700 plants of 2,100 manufacturers in the electrical machinery and electronics industry from 1985 to 2003. They selected this industry because it has the most FDI among all Japanese industries.

Matsuura and co-workers introduced new definitions for FDI. Conventional studies consider two types of FDI: horizontal FDI (HFDI) for investment in developed countries and vertical FDI (VFDI) for investment in developing countries. But Matsuura and colleagues defined HFDI as producing the same products both abroad and at home and VFDI as relocating a part of the production process (for example, assembly) to overseas.

In their analysis, Matsuura's team added various variables to conventional methodologies to minimize possible biases and calculated a key index called the total factor productivity.

The outcome was consistent with what the researchers had predicted — VFDI significantly raised productivity in Japan, whereas HFDI had no clear effect on productivity. This finding differed significantly from those of some firm-level analyses.

Many people view the globalization of production as a threat, but a recent study shows that investing in foreign countries can actually boost the domestic economy. © Philippe Roy/Cultura/Getty

The team also found that VFDI in East Asia greatly improved productivity in Japan. "We had thought that most companies produced parts in Japan and assemble them abroad where labor is cheaper, but we actually discovered that many companies do the opposite and that many labor-intensive upstream activities are still done in Japan," Matsuura says.

The study's findings have important implications for Japan's economic strategy. "It is important for policymakers to encourage companies to invest more abroad in order to raise national productivity," notes Matsuura.

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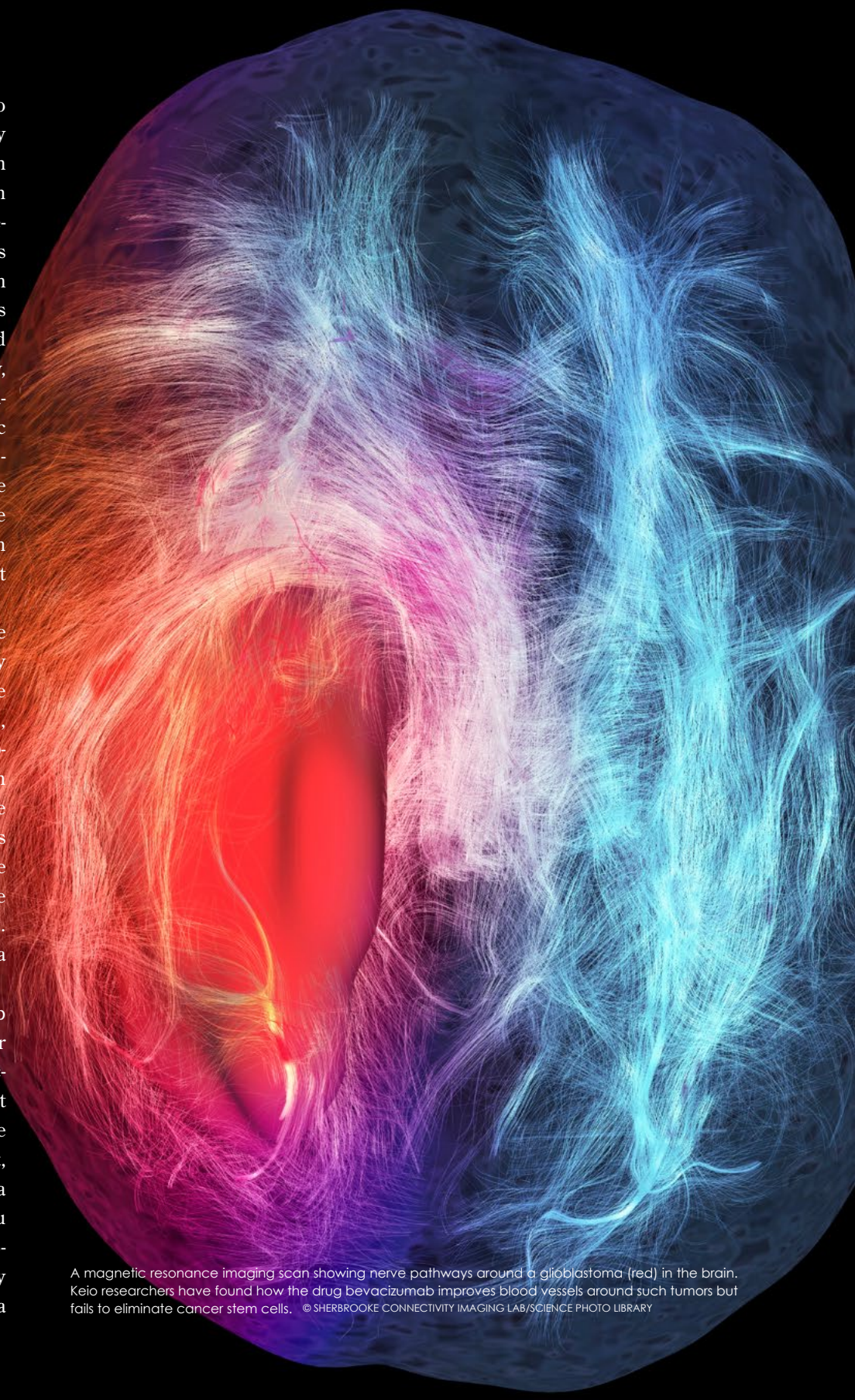
Drug helps blood vessels but leaves lurking cancer cells

Drug cuts the supply lines to brain tumors but doesn't eliminate cancer stem cells, which could explain resistance to the drug

When given to patients newly diagnosed with aggressive brain cancer, the drug bevacizumab reduces the density of blood vessels in tumors but shunts cancer stem cells to areas where blood vessels are still functioning normally, find Keio researchers. This discovery, from a first-of-its-kind investigation of bevacizumab's microscopic effects, should help cancer researchers better understand the mechanisms of resistance to the drug and so design combination strategies that promote patient survival.

Sold under the brand name Avastin, bevacizumab works by blocking a protein involved in the formation of new blood vessels, thereby choking off the blood supply that normally fuels the growth and spread of cancer cells. The drug is approved in many parts of the world for patients whose glioblastoma brain tumors have returned after initial treatment. In Japan, it is also available as a front-line therapy.

In clinical studies, bevacizumab has been shown to delay tumor growth and improve patient function. However, the drug did not extend patients' lives. When the cancer recurred after treatment, it tended to come back with a vengeance — and now Hikaru Sasaki and Ryota Tamura, neurosurgeons at the Keio University School of Medicine, have an idea



A magnetic resonance imaging scan showing nerve pathways around a glioblastoma (red) in the brain. Keio researchers have found how the drug bevacizumab improves blood vessels around such tumors but fails to eliminate cancer stem cells.

why that is.

Sasaki, Tamura and their colleagues collected tumor samples from six patients with glioblastomas who underwent surgery shortly after treatment with bevacizumab. They also analyzed tumor samples from eleven patients who did not receive the drug. Across the treated tumors, the researchers saw that bevacizumab dramatically affected blood vessels: they became less dense; they no longer proliferated; and oxygen levels recovered[1]. In a separate study, Sasaki and his team also found that blood vessel congestion might be involved[2].

However, the therapy never completely wiped out the cancer stem cells that seeded the recurrence of the disease. While it did eliminate one of the places where cancer stem cells are often found, when the researchers looked for nestin, a protein that indicates the presence of cancer stem cells, they found it clustered around the remaining blood vessels in a spot called the perivascular niche.

"Combination therapies that target the perivascular niche might be a rational approach to treat glioblastomas more efficiently," says Sasaki, noting that the persistence of cancer stem cells "might constitute one of the mechanisms of resistance to bevacizumab."

Sasaki and his colleagues are currently running a prospective trial to clarify the mechanisms of resistance and to identify biomarkers that might predict likely responders to bevacizumab.

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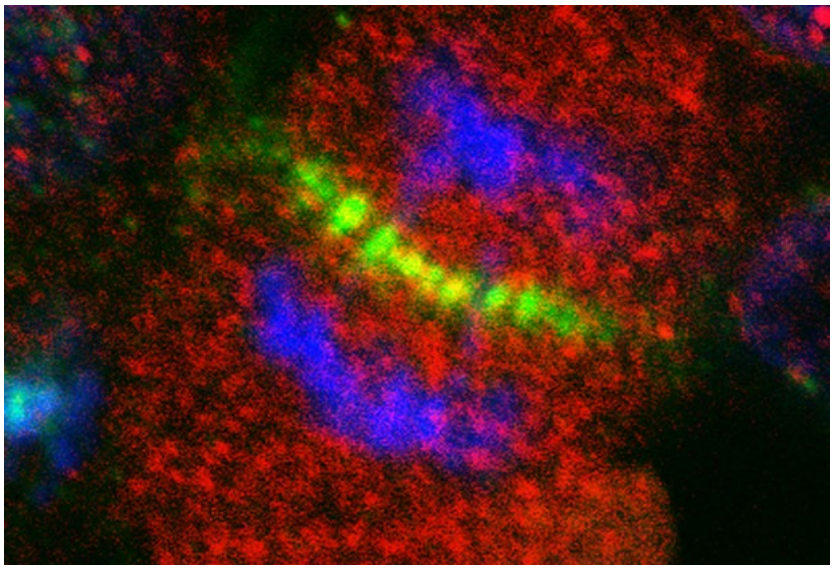
Chromosomal chaos gives cancer a survival advantage

Cancer cells adapt to genomic abnormalities by producing a protein that confers drug resistance

Resistance is a vexing problem in the world of cancer therapy, with many patients either failing to respond or benefiting only temporarily from a given drug. A recent study by Kohji Noguchi and colleagues at Keio University has uncovered a survival mechanism that tumor cells use to elude destruction, and a potential avenue for designing more effective cancer treatments[1].

Drugs that sabotage cell division, or mitosis, can help to slow down and stop tumor growth. "Classical anticancer drugs, such as vinca alkaloids and taxanes, target mitosis," explains Noguchi. "And mitotic aurora kinases have also been considered as a novel pharmacological target." These enzymes help manage the appropriate redistribution of genetic material during cell division, and several aurora kinase inhibitors are showing promise in cancer clinical trials. "However, we lack predictable biomarkers for these inhibitors to understand their effectiveness," says Noguchi.

Noguchi and his colleagues therefore exposed colorectal cancer cells to increasing doses of an aurora kinase inhibitor, VX-680, in order to isolate a variety of drug-resistant clones for closer study. One effect of aurora kinase inhibitors is the accumulation of abnormal numbers of chromosomes, a state known as aneuploidy. Aneuploidy is often observed in cancer cells, but this condition typically triggers a self-destruct mechanism in healthy cells. The researchers observed that their VX-680-resistant cells had become highly aneuploid, containing 70-80 chromosomes rather the normal complement of 46, but they had clearly acquired a mechanism



Fluorescence imaging of aurora kinase inhibitor-resistant cells reveals that aurora kinase B (green) and AKT3 (red) overlap at the center of the cell during cell division. The blue label indicates chromosomes.

that allowed them to survive despite their condition.

A closer examination revealed that four of these five drug-resistant cell lines were producing excessive levels of a signaling protein called AKT3. A series of experiments in other cell lines subsequently provided compelling evidence that AKT3 prevents both the cell death and chromosomal abnormalities caused by aurora kinase inhibition. According to Noguchi, this was unexpected. "The AKT family has multiple oncogenic functions and is usually considered to work in cell survival mechanisms, which would provide resistance to cytotoxic drugs," he says. "However, there were no reports connecting AKT with aneuploidy."

Aneuploidy is not uncommon in malignant cells, and Noguchi believes that these results reveal a connection between this characteristic and the emergence of drug resistance via AKT3. This highlights an important potential escape mechanism for tumors being treated with aurora kinase inhibitors, but it also shows a vulnerability that could be exploited in future treatments. "I hope to find novel molecular targets for the selective killing of aneuploid cancer cells," says Noguchi.

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Tarantula toxin reveals channel function

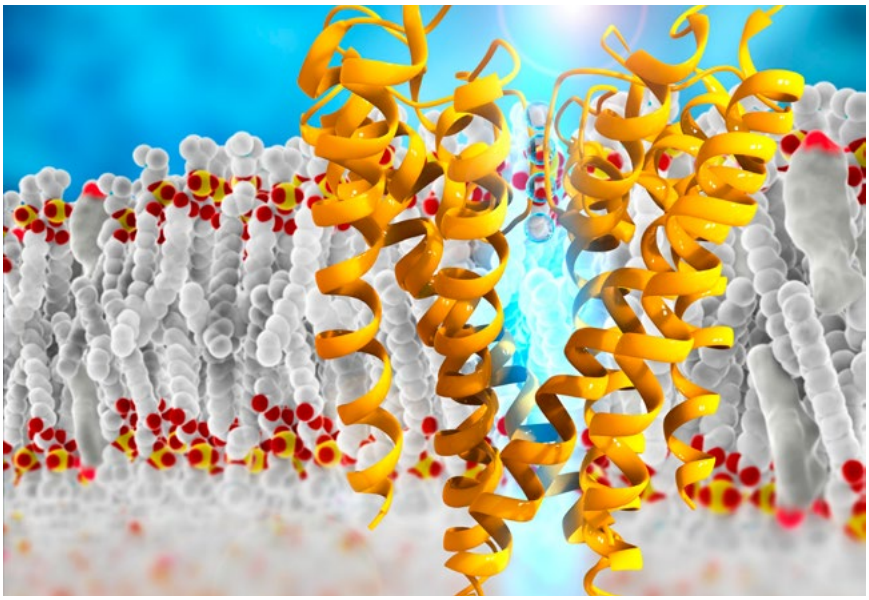
Revelation of how a spider toxin binds to a membrane protein could lead to new drug therapies

A structural analysis of how a toxin from tarantula venom disrupts electrical signaling proteins could help pave the way for new drugs to treat cancer, heart disease, neurological disorders, and other conditions.

The human genome encodes 40 different voltage-gated potassium ion channels (Kv), each of which allows potassium ions to flow across the cell membrane (see image). This generates electrical signals in cells that are involved in everything from neurotransmission to muscle contraction.

The Kv proteins consist of two domains that differ in function and structure: a pore that conducts ions and a sensor that reads the electrical gradient across the membrane. Toxins used by poisonous animals act by either blocking the pore or modifying the sensor. These two mechanisms are also promising for developing new drugs.

In theory, both domains offer potential drug targets, but completely shutting off the channels causes major problems such as heart arrhythmias. Consequently, most researchers — including Keio University's Masanori Osawa — are trying to find ways to fine tune the activity of the voltage-sensing domain (VSD), which acts as a gatekeeper for the ion pore.



Schematic image showing the molecular structure of a potassium channel in the cell membrane.

"The VSD is a fascinating drug target portion in Kv channels," says Osawa, a structural biologist at the Keio University Faculty of Pharmacy, "but no structural information had been obtained on the interaction between the VSD and a gating modifier toxin."

To rectify this, Osawa teamed up with scientists at the University of

Tokyo to look at how a toxin found in the venom of the Chilean Rose tarantula inhibits Kv channels by binding to the VSD[1]. Using a nuclear magnetic resonance method that the group had previously developed[2], the researchers identified the precise binding sites. They then used this information to build a structural model of how the toxin docks onto the domain and blocks the protein's function.

Their model indicates that the toxin stabilizes the VSD in a certain conformation, locking it in that position. "This stabilization provides a possible mechanism for a new drug targeting the VSD," says Osawa.

Other toxins known to bind the domain — such as those found in the venoms of scorpions, snakes, and sea anemones — probably connect at different sites to induce other conformations, Osawa notes. These too could provide a treasure trove of therapeutic drug leads and warrant study in greater structural detail, he says.

"We are only just beginning to understand the structural basis of how gating modifier toxins bind the VSD," Osawa says.

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Shaking up cell culture

Mechanical vibrations offer a gentler way to detach cells from culture dishes

A gentler method for removing cultured cells from their dishes that enables harvesting of stronger and healthier cells has been developed by researchers at Keio University[1].

Scientists have been culturing cells in dishes and flasks for more than a century, but the emerging technologies of tissue engineering and regenerative medicine are producing new challenges since they require a huge number of cells for a single treatment. For example, about a billion cells need to be grown to produce new heart muscle to treat a patient with weak myocardial tissue.

Cells anchor themselves to the surfaces of culture containers using proteins in their outer membranes. Researchers typically use an enzyme called trypsin to cut those anchors and liberate the cells when they are ready to be transplanted into a recipient. This enzyme, however, often damages cells, especially the proteins on their surface.

Now, researchers led by Kenjiro Takemura of Keio University have devised a less disruptive method that uses ultrasonic vibrations to release cells from culture dishes, which better preserves their health and function.

Takemura is not a cell biologist, but Keio colleague Yuta Kurashina thought his expertise in ultrasonics could lead to a useful alternative to trypsin. "I've been working on ultrasonic actuators for almost 20 years — since I was a student," says Takemura. The two researchers conceived an approach in which the culture surface is cooled, causing cells to loosen their grip, and then controlled mechanical vibrations are applied to shake the cells free.

An initial demonstration with mouse muscle cells showed that this gentler treatment made a significant difference. Although the relative number of detached cells was about 23 per cent lower for this new approach, the cells were generally healthier than those that had been exposed to trypsin. Their initial survival rate was nearly 20 per cent higher, and they had higher proliferation rates after several days of cultivation. The cells detached by

A scientist working with cultured cells in a clean room. Researchers at Keio have found a way to harvest healthier cells using ultrasonic vibrations to gently remove them from their dishes. © E+/Getty

vibration also retained key structural features that were more likely to be lost after detachment by trypsin.

Takemura is optimistic that this method will improve the overall efficiency of cell preparation for clinical applications. "Automation of cell culture should be easier with our method, which may make the mass culture of cells feasible," he says.

His team's top priority is moving from the stainless-steel culture surfaces used in this proof-of-concept study to the plastic surfaces used in conventional cell-culture systems. Preliminary data indicate that this transition should be smooth, making the approach more accessible to the broader cell-biology community.

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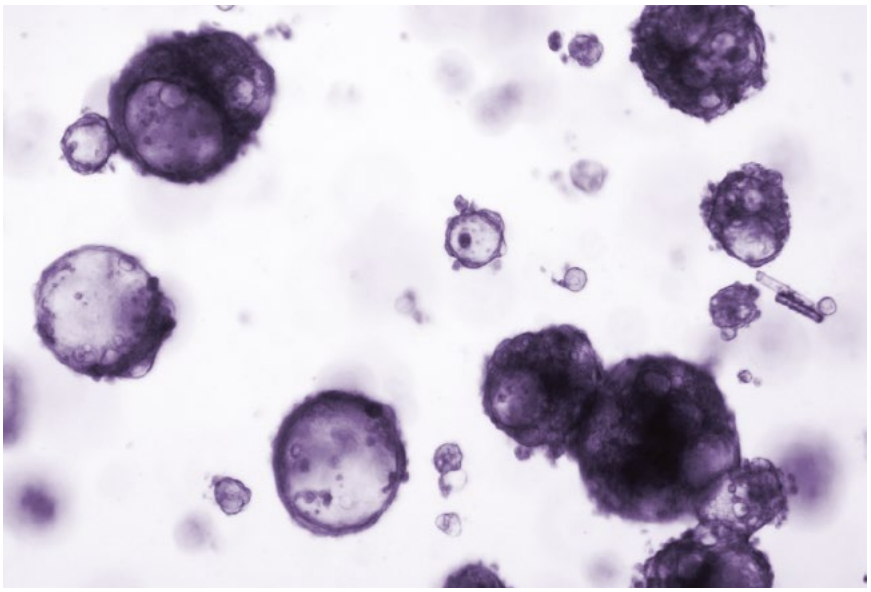
Ancient antiviral response could help treat cancer

A class of drugs can harness the power of the body's immune system to fight diverse tumors



Three-dimensional organoids derived from human cholangiosarcoma tumor cells.

By stimulating a patient's immune system, a drug already in use to treat a blood disorder can thwart the growth of a variety of solid tumors, find a team at Keio University[1].

The drug 5-aza-CdR is currently approved for treating a blood disorder that can lead to leukemia. It inhibits the methylation of DNA, preventing enzymes from chemically modifying genomic DNA. Such modifications can greatly alter the expression of genes that control a variety of critical cellular functions, including cell growth and survival.

Some studies have shown that methylation inhibitors such as 5-aza-CdR could be used to treat other cancers. These effects have generally been attributed to the drugs reactivating tumor-suppressor genes, but the actual mechanism remains poorly understood.

Yoshimasa Saito and his coworkers at Keio University set about figuring out how the drugs work. They began by assessing the effects of 5-aza-CdR on a mouse model of intestinal cancer. The team found that the drug cut the number of tumors that formed by roughly a third and that animals that received the drug tended to have smaller tumors than those that did not.

Having demonstrated that 5-aza-CdR can act on such cancers, the researchers then cultured cells derived from mouse intestinal tumors under conditions that promote the formation of three-dimensional 'organoids'.

"Organoids are budding, cyst-like structures that closely recapitulate the properties of the original tumors," explains Saito, "This makes them a powerful tool for studying how cancers respond to treatment."

The researchers found that 5-aza-CdR strongly inhibited the growth of tumor-derived organoids and were minimally toxic to healthy intestinal cells.

Delving deeper, Saito's team looked at which genes were turned off and on by this treatment and noticed a striking pattern. "Our findings indicated that DNA demethylation suppresses the proliferation of intestinal tumor organoids by inducing an anti-viral response," says Saito. He and his colleagues suggest that the methylation inhibitors are somehow reactivating endogenous

retroviruses — ancient viral DNA sequences that have accumulated over evolutionary history and now lie dormant throughout the genome. This initial antiviral response leads to immune activation and the shutting down of tumor proliferation.

"These findings represent a major shift in our understanding of the anti-tumor mechanisms of DNA demethylating agents," says Saito.

The team believes the strategy could be effective for treating other cancers, and it has already obtained promising results with organoids derived from challenging tumors such as cholangiosarcoma and pancreatic cancer. "We are trying to develop a personalized therapy for refractory cancers," says Saito.

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Digital 3D-fabrication technology for nursing and healthcare

Innovative 3D-printed 'caring-tools' to enhance the quality of life of elderly people

3D printing technology has important medical applications, such as manufacturing prosthetic parts, implants, and models of human organs. Here, researchers at Keio University in Tokyo, describe the potentially important role of 3D printing in nursing and long-term care for the elderly. Given Japan's rapidly ageing society, demand for terminal care in hospitals or care facilities will exceed capacity in the near future. Furthermore, there are insufficient visiting nurses to provide in-house care. Therefore, strengthening in-house care is an urgent task for healthcare of the elderly. The introduction of information technology (IT) is an essential strategy from both aspects of work efficiency and providing high quality care.

Specifically, Shoko Miyagawa and colleagues at Keio University noticed the increased availability of 3D printers in self-help community centers throughout Japan. Based on interactions with nurses, medical practitioners, engineers and material designers, Miyagawa and her collaborators established a benchmark for specific digitally fabricated objects needed by patients and classified them into three types.

Firstly, are self-help devices enabling individuals to carry out specific tasks. For example, someone with paralyzed fingers who is unable to pinch, is assisted by a customized 3D-printed penholder for signing important documents.

Second, 'caring tools' facilitate interaction between care-givers and care-receivers. For instance, cutting out plasters in fun shapes — such as animals — with a laser cutter helps patients overcome negative perception of surgical tape.

Third, Miyagawa and colleagues identified educational objects as tools to learn how to perform therapy actions. For example, a 3D-printed semi-transparent cranial model can be used for practicing the insertion of a tube for vacuuming phlegm from a patient's throat with light-emitting diodes acting as guides to follow its position inside the model. The researchers also addressed the question of safety, as the proposed 3D-printed objects must be washable and not produce skin irritation. Another important aspect of the research project of the Keio scientists is an assessment of the usage level of the objects. To this end, the researchers are currently developing an 'internet-of-things' sensing system: a data logger that can collect information about an object's use for one month.

A 3D printer used by Keio researchers to digitally fabricate objects such as a pen holder and cranial model for nursing and healthcare.

Having established the relevance of 3D printing techniques for improving the quality of life and the independence of elderly people, Miyagawa and colleagues conclude that, "in order to make digital fabrication more useful it is necessary to further reduce the cost of introduction and operation and to develop technologies to do so."

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Robotic arms with a human-like sense of touch

Birth of innovative touch sensitive avatar robotic arm based on real-haptics

The world's first 'real haptics' avatar-robot arm

Conventional haptic robots communicate with humans by transmitting the sense of touch to their operators through mechanical vibrations using touch sensors, which can be insensitive and prone to malfunction. Hence, this type of haptics technology is useful for games and entertainment but has limited industrial applications.

Takahiro Nozaki, an assistant professor at the Faculty of Science and Technology, Keio University and colleagues have developed a 'real haptics' avatar-robot with a General Purpose Arm (GPA) that transmits sound, vision, movement, and importantly, a highly sensitive sense of touch, to remotely located users in real time. "Our real-haptics technology is an integral part of the Internet of Actions (IoA) technology with potential applications in manufacturing, agriculture, medicine, and nursing care," says Nozaki.

This is the world's first high precision 'tactile force transmission technology' that remembers human movements, edits and reproduces them. Notably, the GPA does not employ conventional touch sensors, thereby making it cheaper, more compact and robust. The realization of the Keio University touch sensitive avatar-robotic arm based on real-haptics is a dream come true for Nozaki. "As a high school student I wanted to study robotics, and surveying my options enrolled at the Department of System Design Engineering at Keio University — the top department in Japan conducting this type of research."

Core technology for the real time haptic avatar arm

The two innovative key components of the Keio avatar-robot GPA are high precision motors in the avatar arm and algorithms to drive them. Importantly, the precise control of force and position is critical for transmitting the sense of touch without using touch sensors.

The real haptics robot GPA can recognize shapes and compositions of materials — soft or hard — position of objects in 3D-space, and manipulate them according to real-time instructions from a remotely located user, where the arm acts as a real-time avatar. Historically, the technical breakthrough in motor control and robotics that led to the successful development of the robotic-avatar developed by Nozaki and colleagues was first reported by Keio University's Kouhei Ohnishi in 1983 in his paper titled, "Torque-speed regulation of DC motor based on load torque estimation method" (*IPEC — Tokyo'83*, page 1209). Ohnishi continued to develop his ideas in his 1993 paper on 'sensorless torque control' (*IEEE Transactions on Industrial Electronics,* 40, 259, (1993)).

This report was followed by his proposals for 'motion control in mechatronics' (*IEEE Transactions on Mechatronics,* 1, 56, (1996)).

Commercialization of ideas and future work

Nozaki has launched the company Motion Lib to commercialize his 'real-haptics technology'. The main product is the 'ABC-CORE' IC force/tactile controller that uses two synchronized motors to adjust the force of DC/AC servomotors and transmission of tactile forces.

Furthermore, Nozaki is collaborating with 30 companies to conduct proof of concept projects for applications to Internet of Actions (IoA). "In one of our projects, the assist-avatar robotic GPA is being tested for real-life applications in supporting farmers to pick fruit and other agricultural applications," says Nozaki.

Touch sensitive avatar-robotic arm based on real-haptics developed by Takahiro Nozaki and colleagues at the Keio University Haptics Research Center.

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Health economics offers unique insights into modern Japanese society

Fusing expertise in medicine and health economics sheds new light on healthcare and gambling in Japan

"My family are all medical practitioners, so I followed in the tradition and studied medicine at Kyoto University," says Rei Goto, an associate professor at the Graduate School of Business Administration, Keio University. "But ever since my schooldays, when healthcare was free for the elderly, I have been interested in government policy and management of Japan's healthcare system."

During his final year at medical school Goto went to Newcastle, England, for a short course in clinical training and "discovered the field of health economics" that was at the heart of healthcare management in the UK. "My visit to the UK reignited my interest in healthcare management," says Goto. "So after completing my two year hospital residency, I started on a doctoral course in health economics at Kyoto University to study social issues in Japan, including healthcare costs and gambling."

Rationalizing costs of outpatient treatment for children with hospital admissions

In this study Goto and colleagues analyzed the effect of reducing medical care subsidies given to children receiving outpatient treatment on inpatient admissions in Japanese hospitals. "We obtained inpatient data for 366,566 children in 1,390 municipalities in Japan from 2012 to 2013 using the Japanese Diagnostic Procedure Combination (DPC) database," explains Goto. "Our aim was to elucidate the effects of increasing subsidies for outpatient care on hospital admissions."

Rei Goto is combining his expertise in medicine and health economics to analyze social issues in Japan such as healthcare and gambling.

The survey showed that in general decreasing cost sharing for outpatient care did not significantly affect admissions to hospital. However, hospitals in low income regions showed a decrease in admissions, and those high income areas, an increase. "These results are important because prior to our study we did not know the effect of income on hospital admissions," says Goto. "In low income areas, the increase in outpatient medical expenses may be offset by decreases in hospital medical expenses due to admissions.

Gambling on the future

Gambling in Japan is undergoing unprecedented changes as exemplified by recent government proposals to allow the construction of regulated casino resorts. "In this research we wanted to clarify the actual level of pathological gambling in Japan and verify whether easy access to gaming facilities is a risk factor for pathological gambling," says Goto.

The researchers conducted an internet-survey on 'lifestyle and leisure' covering the whole of Japan (excluding minors) from 17 to 22 November 2014, with responses from 6,576 people, and used the South Oaks Gambling Screen to determine signs of gambling dependence.

Generally, the survey showed that gambling dependence was not related to the ease of access to pachinko parlors. However, accessibility was a significant factor in gambling dependence for men, and people living in low income areas. Also, accessibility of pachinko parlors was not a factor for women and people living in high income areas.

"I hope that our research on health and social issues in Japan, which has the world's fastest aging population, will be a useful reference for scientists and policy makers in other countries," says Goto. "We will continue to publish and disseminate information about this research for a global audience."

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Tardigrade genomes explain life on the extremes

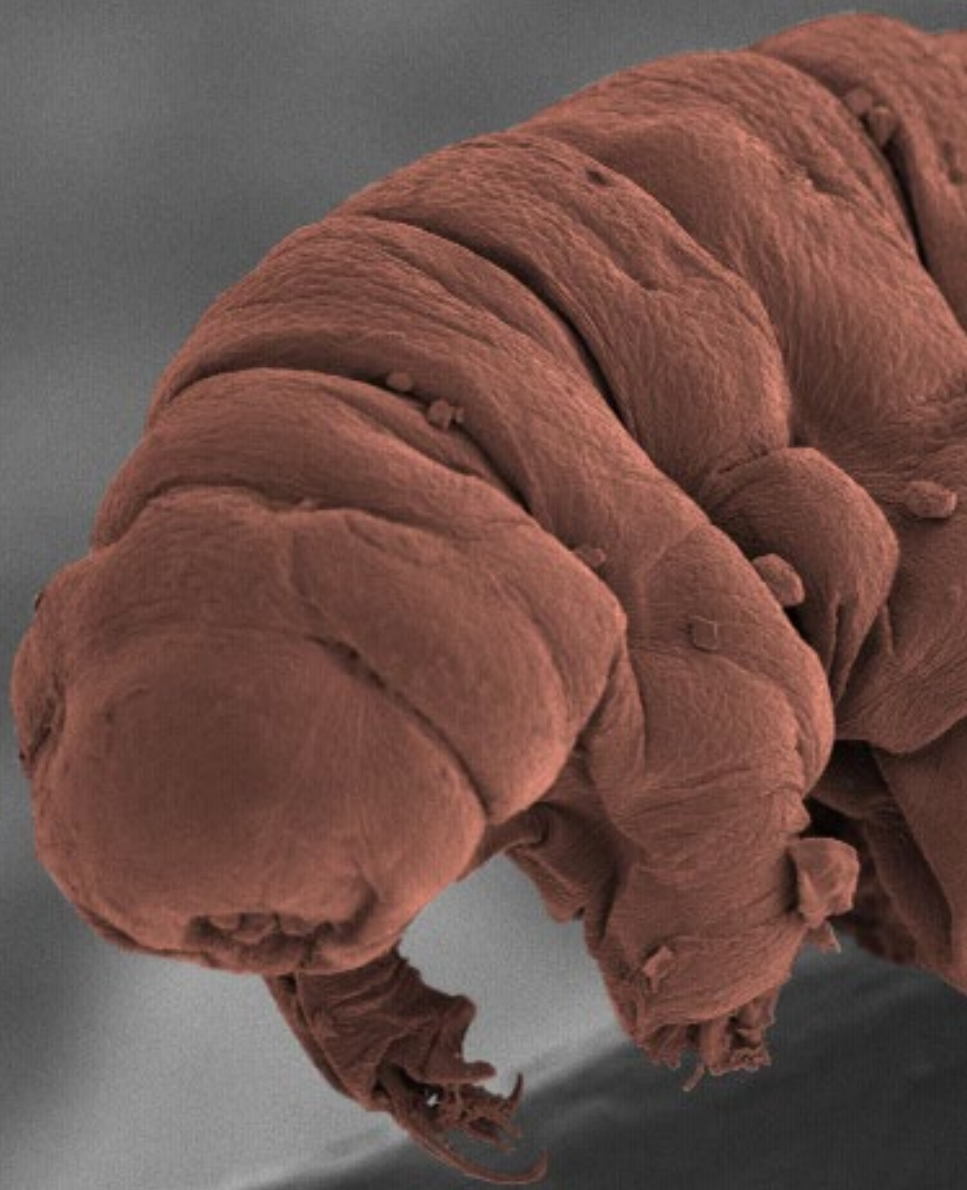
DNA analysis shows how water bears survive extreme conditions, yet leaves evolutionary origin unclear

Tiny water-dwelling creatures known as tardigrades can survive for years in the face of extreme temperatures, radiation exposure, desiccation, and even the vacuum of space. How these microscopic animals evolved and why they are invincible have long puzzled scientists.

A genomic study co-led by Keio University researchers sheds light on how these hardy beasties withstand rapid desiccation, freezing, and other environmental trials, and provides new clues on the contested evolutionary history of tardigrades, also known as water bears or moss piglets[1].

The findings hold relevance beyond this particular quirk of natural history, says Kazuharu Arakawa from Keio's Institute for Advanced Biosciences. "These mechanisms to withstand significant cell damage may lead us to better understand the integrity of human cells on stress and damage," he says.

What's more, insights about how tardigrades endure dehydration may help scientists develop more stable enzymes, vaccines, and cell therapies that can be freeze-dried and stored at room temperature. "We foresee significant impact on the preservation and logistics of these products," Arakawa says.



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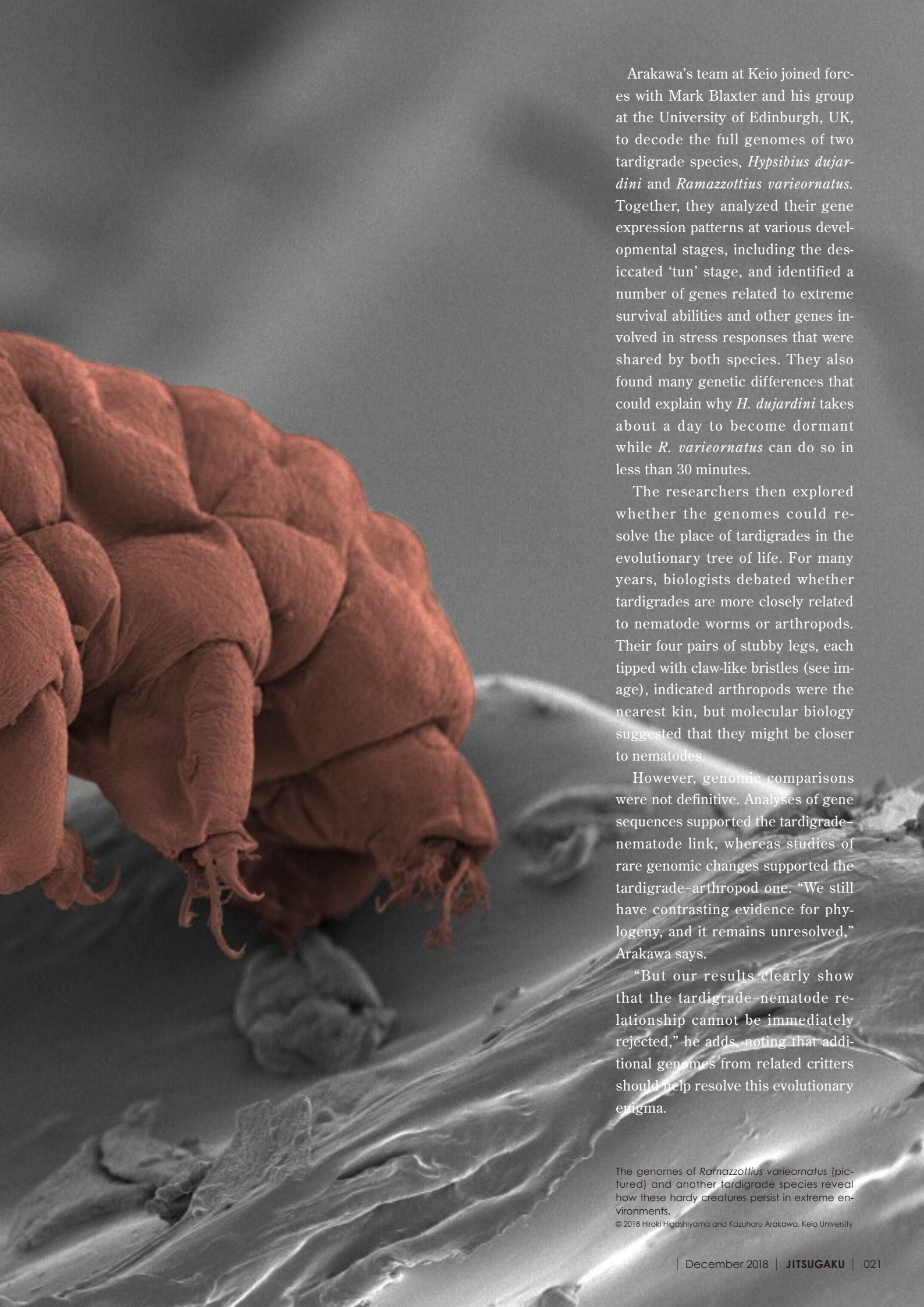

Arakawa's team at Keio joined forces with Mark Blaxter and his group at the University of Edinburgh, UK, to decode the full genomes of two tardigrade species, *Hypsibius dujardini* and *Ramazzottius varieornatus*. Together, they analyzed their gene expression patterns at various developmental stages, including the desiccated 'tun' stage, and identified a number of genes related to extreme survival abilities and other genes involved in stress responses that were shared by both species. They also found many genetic differences that could explain why *H. dujardini* takes about a day to become dormant while *R. varieornatus* can do so in less than 30 minutes.

The researchers then explored whether the genomes could resolve the place of tardigrades in the evolutionary tree of life. For many years, biologists debated whether tardigrades are more closely related to nematode worms or arthropods. Their four pairs of stubby legs, each tipped with claw-like bristles (see image), indicated arthropods were the nearest kin, but molecular biology suggested that they might be closer to nematodes.

However, genomic comparisons were not definitive. Analyses of gene sequences supported the tardigrade–nematode link, whereas studies of rare genomic changes supported the tardigrade–arthropod one. "We still have contrasting evidence for phylogeny, and it remains unresolved," Arakawa says.

"But our results clearly show that the tardigrade–nematode relationship cannot be immediately rejected," he adds, noting that additional genomes from related critters should help resolve this evolutionary enigma.

The genomes of *Ramazzottius varieornatus* (pictured) and another tardigrade species reveal how these hardy creatures persist in extreme environments.

Tracing the origins of the Japanese with 3D technology

By using computed tomography to analyze hominin bones, researchers at Keio are revealing the history of Japan's first inhabitants

A half-size, three-dimensional printed restoration model of a Shiraho skull.

Unbeknownst to the many tourists who flock to Ishigaki Island in Okinawa, the island harbors an archaeological site where the story of Japan's first people is being gradually revealed. A limestone cave set slightly back from Shiraho beach has yielded an unprecedented number of bone fragments, which date back more than 20,000 years — some of the oldest found in Japan.

Analyzing ancient bones using modern technology

We know much less about the first Asians than the early humans of Africa and Europe. Reiko Kono of Keio University's Faculty of Letters is taking advantage of the power of modern technology to improve the effectiveness of excavations in Asia. She is using computed tomography (CT) scanning and three-dimensional (3D) printing to virtually restore the bones of hominins — modern humans and extinct human species.

Kono begins her 3D virtual restorations with a CT scan. The bone fragments are converted into digital data made up of tiny pixelated cubes and triangular surfaces. Kono then uses this data to determine how the fragments should be pieced together.

"It may be time consuming, but it's a non-invasive way of restoring remains," says Kono. "Printing out and physically touching the restoration model also helps verify that the fragment connections make sense."

Recently, Kono's expertise in 3D restoration has helped advance research in Taiwan[1], China[2] and Indonesia[3]. Her models have allowed researchers to confirm that they had found groups of people distinct from other known hominins in Asia.

She is now applying her technique to sites in Japan. "We know that hominins came to the Japanese archipelago about 40,000 years ago, but we don't know much else about the time before the Jomon period, which started roughly 16,000 years ago," says Kono. "The Shiraho remains will definitely give us much more accurate insight."

One of the Shiraho remains had surfer's ear, a bone growth inside the ear induced by regular exposure to wind and cold water. Two had heavily worn teeth on both the upper and lower jaws, although the teeth on the upper jaw were more worn than those on the lower. These are just some of the details Kono and colleagues are trying to explain in order to understand the Shiraho people's lifestyle.

"One thing we can say for sure is that any information we obtain from the Shiraho bones will provide valuable new insights and be of great importance to the study of human remains in Japan," Kono comments.

Coming face-to-face with the Shiraho people

In addition to illuminating characteristic differences with other human remains in Japan, Kono has her eyes set on another ambitious goal: reconstructing the faces of the Shiraho people.

"The remains from Minatogawa on Okinawa Main Island[4] had been the 'industry standard' of what the first Japanese people looked like," says Kono. "The Shiraho bones are now telling us that our ancestors in Japan were also more diverse."

One challenge has been that faces, with small, delicate parts, shatter easily. But this is where 3D scanning can help. “With digital data, it’s possible to make mirror images of fragments,” says Kono. “If there’s a part missing on one side, we can complement it in this way.”

The 3D digital restoration of the Shiraho people is nearing completion. In the process, Kono reaches back to the beginning, shedding light on a buried chapter.

Doing a three-dimensional computed tomography scan of a Shiraho skull.

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Using iron to accelerate organic synthesis

A catalyst made from Earth-abundant iron can drive an important reaction for making organic compounds

A simple iron catalyst can replace costly ruthenium in a reaction that can be used to generate diverse libraries of complex organic compounds, three researchers at Keio University have shown[1]. This finding promises to make it cheaper to produce complex organic molecules such as organic electronic materials and therapeutic drugs.

Organic molecules consist mainly of carbon and hydrogen atoms plus a few other ‘heteroatoms’, such as nitrogen, oxygen or chlorine. Chem-

Keio University researchers have found a way to replace the expensive precious metal ruthenium (pictured) with a simple iron catalyst for the carbon-hydrogen alkylation of aromatic ketones by alkenes.

ists have traditionally exploited the reactivity of these heteroatoms to build complex products from simple starting molecules. This approach, however, can require long sequences of reactions to install the correct set of heteroatoms for a particular conversion, making synthesis expensive and time consuming.

A more efficient way to make organic molecules is to directly manipulate a molecule's carbon-hydrogen bonds. Known as carbon-hydrogen bond functionalization, this reaction involves breaking the bond between carbon and hydrogen and then swapping the hydrogen with another element such as carbon, oxygen or nitrogen. But because organic molecules typically contain many such bonds, it is difficult to selectively trigger a reaction at only the desired carbon-hydrogen bond.

One way to achieve this selectivity is to use a catalyst, but these are often expensive precious metals such as rhodium, palladium or ruthenium. There is thus a strong push to replace these precious metal catalysts with cheaper catalysts made from inexpensive, abundant metals such as iron.

Now, Fumitoshi Kakiuchi and coworkers Naoki Kimura and Takuya Kochi at Keio University have shown that a simple iron compound catalyzes the carbon-hydrogen alkylation of aromatic ketones with alkenes. The iron compound does this by bonding to the ketone group of the aromatic ring, which directs the incoming alkene molecule to attach to the adjacent, 'ortho' position of the aromatic ring. The trio showed that a wide variety of alkenes can be used for this reaction.

Previous research had suggested that iron could drive this transformation, but the iron was consumed in the process. "These precedent stoichiometric reactions gave us hints to develop iron-catalyzed ortho-selective carbon-hydrogen alkylation of aromatic ketones with alkenes," Kakiuchi explains.

The next frontier of carbon-hydrogen functionalization reactions is to develop 'regioselective' catalysts that selectively target a particular carbon-hydrogen bond without needing a directing group such as a ketone. "Regioselective carbon-hydrogen functionalization of aromatic compounds without using a directing group is still quite difficult," Kakiuchi notes. "We intend to develop this type of regioselective carbon-hydrogen functionalization using additives or ligands."

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Politics of populism behind Putin's 2016 victory

Keio analyst Atsushi Ogushi argues that rising populism contributed to Putin's definitive result in the 2016 Russian Duma election

The strong showing of Vladimir Putin's United Russia party in the 2016 Duma election can be ascribed to the recent rise in the politics of populism in Russia, according to Atsushi Ogushi, an associate professor in the Department of Political Science at Keio University and an analyst of Russian politics[1].

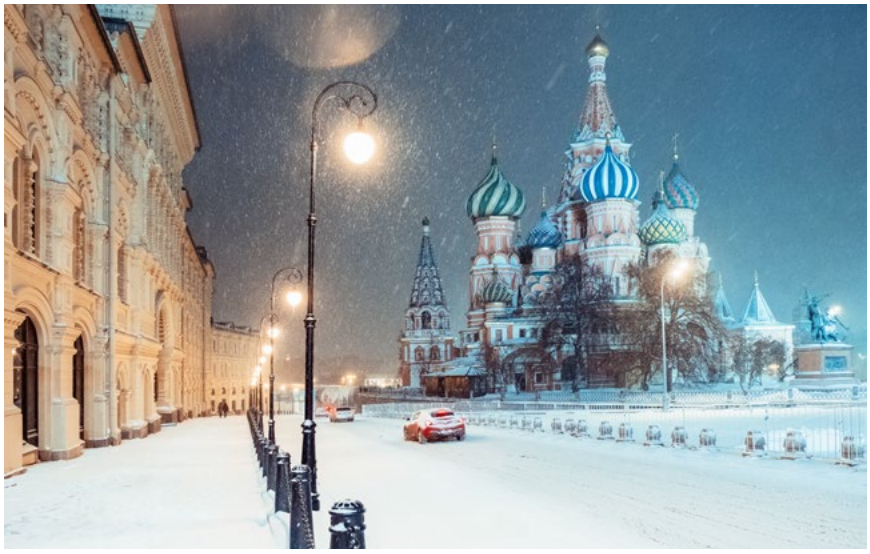
Ogushi argues that populism, however broadly it is defined, is the opposite of machine politics, where the party and its foot soldiers are all-important. He says that the rise of one signals the fall of the other, in direct proportion.

It was through this lens that Ogushi analyzed the 2016 Duma election, which saw United Russia win 76 per cent of the seats.

Putin's fluctuating popularity had received a boost due to his handling of the crisis in neighboring Ukraine. However, Ogushi argues that the shift from machine politics had been a prominent feature of Russian politics in the past and that the 2016 was simply the next wave in populism. He notes that changes to the electoral system should have seen a marshalling of the forces of the party machine, but there was little evidence that this took place. This implies that the changes, along with the relative popularity of United Russia, helped the party win many seats.

Two-pronged approach

Ogushi believes the Kremlin employed two strategies to bolster Pu-



Atsushi Ogushi has been interested in Russian politics at the Kremlin since before the demise of the USSR in 1991. © Elena Liseykina/Getty images

tin's personal appeal. The first was to distance Putin from the United Russia party so that he could appear as standing above party politics. In his analysis, Ogushi comments, "it is much safer for Putin to stand apart from all parties, and this may be his populist method for gaining support from people in general."

The second strategy was to cultivate a 'clean' image for Putin, with him attacking officials who were popularly perceived as being corrupt. A new director was appointed to oversee the running of the 2016 election, and surveillance cameras were deployed to encourage transparency at polling stations. Although voter turn-out remained low, Ogushi says "it is widely acknowledged that the 2016 Duma election was more open than the previous one."

Looking ahead

Ogushi notes that if Putin can sustain this level of popularity in the long run, it could signal a fundamental shift in Russian politics away from machine politics and toward a populist regime.

"There is little doubt that Putin will win the next presidential election, but that must be his last term," he says. "So successor struggles may take place within a few years, but the great power concentrated in Putin's leadership will complicate the succession. It will be very interesting to see how a personalized political system can overcome the succession problem."

Ogushi's analysis is born of on-the-ground experience with the Russian nation.

"I think it is very important for political scientists to conduct fieldwork," he says. "Sometimes they instead concentrate on creating theoretical models. That might be okay in a purely academic world, but political studies can have political and policy implications. I think the 'theory first' mentality that forms policies without a knowledge of the region can be dangerous."

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Frontiers of haptics science: Uncovering the secrets of the human body's perception of touch

Insights into human touch and body perception and their utilization for positive psychological and cognitive effects in our daily lives

The sense of touch: Who is shaking hands with whom?

Scientific research has yielded deep understanding on the human senses of sight, hearing, smell, and taste. But knowledge about bodily perceptions of the sense of touch is still limited. For example, during a handshake, who is shaking whose hand? The answer to this question is just one of the multifaceted aspects of touch being studied by 'haptics scientist' Masashi Nakatani. "I am intrigued by human somatosensory (touch and body) perception and its utilization for positive psychological and cognitive effects in our daily lives," says Nakatani, who commenced his research on the Shonan Fujisawa Campus (SFC), Keio University, in April 2017. "I start-

Figure 1: Children from 0 to 6 years old explore their environments to collect information necessary for their survival. © cocoiku by ISETAN SHINJUKU Store

ed studying touch modality 16 years ago as an undergraduate. My doctorate was about human tactile perception for developing tactile displays that can provide information through the skin surface." After his doctorate, Nakatani investigated touch receptors embedded in the skin in a dermatology laboratory[1] and also worked in industry on developing tactile sensors for evaluating cosmetics[2].

Focus on developmental psychology in infants

Now, Nakatani is concentrating on developmental psychology in infants, a topic that was triggered by a chance meeting with an educator developing parenting classes for children from 0 to 6 years old, who wanted to use state-of-the-art media technology that included haptics. "This sounded like a very cool concept and I decided to collaborate to develop a parenting service for children," explains Nakatani. "I'm studying how infants explore and 'feel their world' using their vision and touch before they have even acquired language skills. They are collecting information needed to survive." Underscoring concerns about the effects of modern technology on children's behavior, Nakatani is analyzing how current technologies such as smartphones and tablet PCs affect their visual and haptic exploratory behavior. "My working hypothesis is that some kids have less opportunities to explore with touch modality because of exposure to massive amounts of information and communications via visual modality, so that they explore environments less manually and actively," explains Nakatani.

Figure 2: Smartphone-based haptic text-based chat system with audio-vibrotactile feedback for sense of presence. © Kazuki Sakurada, SFC TOUCH LAB

Environment at the Keio SFC campus promotes interdisciplinary research

The Keio SFC campus is also conducive for interdisciplinary research, an important factor for Nakatani to be able to pursue his studies on haptics and other research field. "I am working with a music-neuroscientist, Dr. Shinya Fujii, on the relationship between auditory and haptic feedback on subjective frisson, that is the 'feeling of being chilled and touched'," says Nakatani. "One of my goals is to clarify how body perception helps us acquire cognitive skills that are unique to human beings, particularly in the modern information age" (Fig.1).

TECHTILE toolkit

Nakatani and colleagues invented the TECHTILE toolkit to promote people to appreciate the sense of touch[3]. "I think that modern haptic devices must provide greater value for us to enjoy our daily lives," says Nakatani. One of Nakatani's students, Kazuki Sakurada, has developed a smartphone-based haptic chat system with audio-vibrotactile feedback to provide a sense of presence of others during text conversations. "This study may yield clues about the importance of somatic feedback in emotional attachment with other people (Fig. 2)," says Nakatani. "In the long term, I would like to enhance human abilities to extract valuable knowledge from overwhelming, excessive information in the environment."

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Smart paper gives low-cost diagnostics in living color

Inkjet printing technology transforms ordinary filter paper into devices that can spot kidney disease or contaminated water

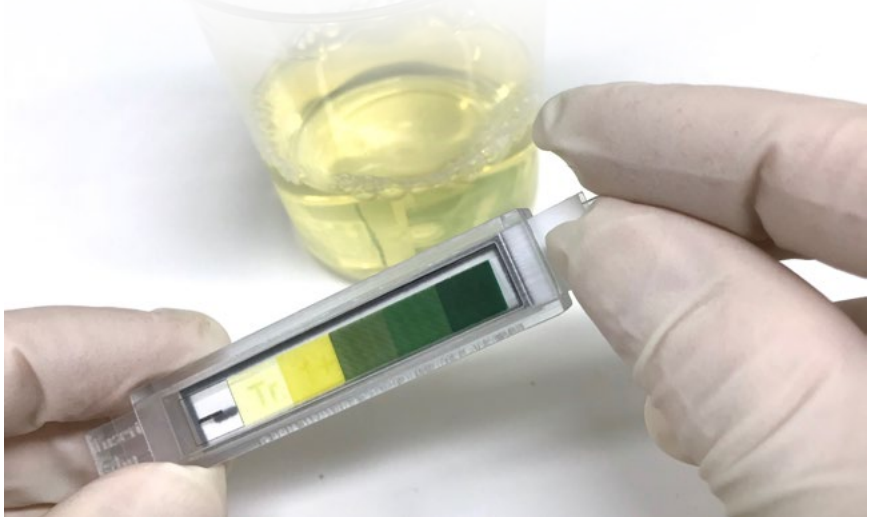
Paper-based analytical devices have come a long way from old-fashioned litmus strips used to measure pH. Advanced printing techniques now enable quick, accurate testing for multiple chemical or biological agents on substrates that cost just pennies to produce. Researchers at Keio University are showing how the efficient display of color-based information may take such paper-based devices out of the lab and into the real world for applications including medical and environmental diagnostics[1,2].

Guiding flow using water-repelling inks

When water droplets come into contact with conventional filter paper, they spread uncontrollably in all directions as they absorb. To direct the flow of samples such as tiny blood drops, Daniel Citterio from Keio University and his team employ microfluidic patterning techniques based on water-repelling inks. "We create hydrophobic barriers using common inkjet or solid wax ink printers," explains Citterio. "These barriers are three dimensional, extending throughout the thickness of the paper, and so they guide the liquid where we want it to go."

Citterio and his co-workers specialize in paper analyzers that indicate the presence of specific compounds through vivid color changes. One recent project involved creating optical electrodes, or 'optodes', that identify aqueous ions such as sodium, making them useful for various applications, including water monitoring.

Optodes are also extremely sensitive to pH because they rely on the exchange of protons against the target cation to initiate a color change. But this sensitivity normally requires users to simultaneously measure pH and apply a correction to the sample. "One big advantage of paper is that you can put almost anything on it, including a pH buffer," notes Citterio. By incorporating the buffer layer into their device, the researchers ensured it automatically adjusts for varying chemical conditions, including those arising from cellulose in the paper substrate.



Reading the results of home urine tests can be challenging. Daniel Citterio and his team have developed a system that makes it much easier to interpret results.

Most devices direct water along the paper's surface, but the team obtained better results when droplets were driven vertically. "Since optode membranes are highly hydrophobic, liquids will try to avoid these zones in lateral channels," says Citterio. "However, top-down flow forces the liquid to contact the hydrophobic area, generating stronger color signals."

Simpler testing of urine

Another diagnostic device developed by the Keio researchers aims to improve a basic diagnostic tool — the urine dipstick. Their device alters color in response to different protein levels. "People normally don't have urine dipsticks at home because the color change is quite faint," says Citterio. "But if used correctly, they can indicate signals of kidney disease. Doctors tell us that they can do more for patients with earlier warnings."

To avoid such uncertainties, the team developed a text-displaying dipstick. Using inkjet printers and a special ink that changes color at different biomolecular concentrations, they printed symbols signifying different levels of protein: from 'trace' to '+4'. The paper device is then inserted into the lower portion of three-dimensional printed housing, and a screening film is placed on top to hide the text. Briefly immersing these devices into urine samples demonstrated that this approach can give the same accuracy as commercial dipsticks but with readouts that are far simpler to interpret.

"This could benefit people with color vision anomalies," notes Citterio. "And

this same concept could be applied to any type of colorimetric indicator. As long as you can read, you can't go wrong."

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Faulty transporter protein could underpin delayed labor

A protein in the placental lining helps synthesize a fetal hormone that signals to pregnant mothers to begin contractions

Rates of childbirth by cesarean section are on the rise worldwide, and while there are some social reasons for this increase, an all-Keio team of researchers has identified a potential biological one[1]. Specifically, Masatoshi Tomi at Keio University's Faculty of Pharmacy and his colleagues found that a transporter protein called OAT4 is needed for the fetus to signal to its mother to begin contractions. When this protein is faulty, labor gets delayed, which may partially account for the high incidence of cesarean sections in Japan and elsewhere.

OAT4 is expressed in the placenta and kidney. It helps the developing fetus both to get rid of toxins and to synthesize various sex hormones, including estradiol, estrone, and estriol (collectively known as estrogens). The impact of OAT4 on estradiol and estrone signaling is better known than its effect on estriol signaling, despite estriol being the only estrogen that arises solely from a fetal-derived precursor.

To test the role of OAT4 in conveying the estriol precursor from the fetus across the placenta, Tomi and his team studied a population of placental cells called syncytiotrophoblasts, which cover finger-like projections from the placenta that invade the wall of the uterus and enable nutrients to circulate between the fetus and the mother.

In particular, the researchers looked at the part of the syncytiotrophoblast cell membrane that faces the fetal side. They created tiny capsules from this membrane and found huge numbers of OAT4 proteins, which proved to be essential for the passage of the estriol precursor.

According to Tomi, most studies on estrogen synthesis processes have focused on the action of enzymes. "In contrast, our study has highlighted the importance of membrane transporters," he says. "Our finding will be a trigger to put more emphasis on the transporter in estrogen synthesis by the fetoplacental unit."

Recent studies from Tomi and his colleagues have found that OAT4 proteins in the same syncytiotrophoblast cells help the fetus transport an antihistamine drug called levocetirizine and a blood pressure drug called olmesartan. Notably, OAT4 is found only in primate cells; it does not occur in rodents. That could help to explain a uniquely human side effect of antihypertensive drugs such as olmesartan. In mouse models, agents from this drug class caused no problems to developing pups, but there is a high risk of life-threatening kidney damage in the fetuses of human mothers who take the medicines. "It is plausible that this fetal toxicity is facilitated by the presence of OAT4-mediated transport," says Tomi.

A possible biological explanation for the increase in births by cesarean sections has been found by Keio researchers.

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THE KEIO MEDICAL SCIENCE PRIZE

The 2017 Keio Medical Science Prize Laureates

John E. Dick

It is with gratitude that I accept the Keio Medical Science Prize. Science is not done in isolation and I have had the good fortune to be surrounded by wonderful colleagues in Toronto who set the highest standards for scientific thought that continuously challenged me to tackle biological challenges with rigour and clear thinking. All of our work on the biology of normal and leukemic human stem cells was the cumulative effort of many students and post-docs who contributed so much to the thinking and execution of the experimental findings. I dedicate this award to them.

Seiji Ogawa

It is a great honor to receive the prestigious Keio Medical Science Prize and to join the ranks of the renowned previous laureates. The MRI phenomenon I encountered during my fundamental research a quarter of century ago has seen applications in brain science far beyond my expectations at the time. The successful development of the neuro-imaging field is the product of efforts by great many talented scientists around the world.

OBJECTIVE

The Keio Medical Science Prize 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 medicine and life sciences, 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 be researchers in medicine or life sciences closely related to medicine, and preferably currently active in their field of research. The Keio Medical Science Prize is an international award.

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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