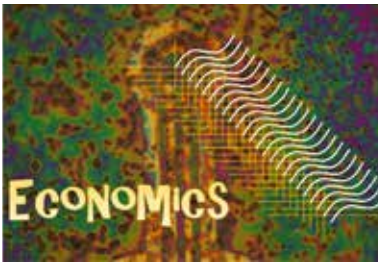


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JITSUGAKU

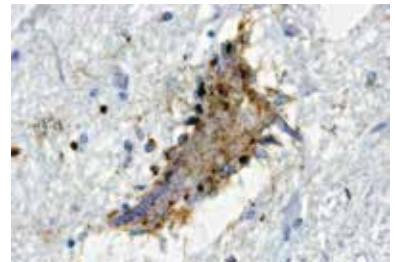
Showcasing the best research from Keio University



Applied econometrics



Quantum Computing:
Keio University launches
IBM Q Network Hub



A chance to slow
neurodegeneration



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ON THE COVER

Restoration work on the Old Library on Mita Campus is now complete after more than 2 years.

The restoration included a revolutionary retro-fitting technique to install base isolation devices underneath the building without altering its form. The work was both challenging and meticulous since the building is a nationally-designated important cultural property built in the Meiji era.

Over the coming months, there are plans underway to establish the "Keio Historical Archive Space (provisional name)" inside the newly restored Old Library. This space will be a venue to teach visitors about Keio's rich culture, history, and traditions, while sharing the founding principles that continue to guide the university to this day.



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Editorial

Excellence in Social and Economics Impact



Issue 5, September 2019

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.

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

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Keio University is one of only three Japanese universities to be ranked in the top 100 of the THE World University Impact Rankings 2019.

Yukichi Fukuzawa, the founder of Keio University, is internationally renowned for his visionary emphasis on encouraging scientifically-based knowledge (*jitsugaku*) for the betterment of society. More than 150 hundred years after the founding of the university, Fukuzawa's ideals continue to shape the activities of Keio as evidenced by the Times Higher Education University Impact Rankings 2019 announced on April 3, 2019, which underscore the university's global socio-economic impact. Keio was ranked 91st, behind only two other Japanese institutions: Kyoto University (48th) and the University of Tokyo (52nd).

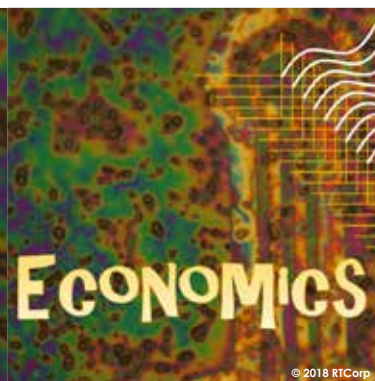
This global recognition of Keio's contributions to society is based on diverse and world-class research in areas ranging from the arts, humanities, and social sciences, to the natural sciences, engineering, and medicine. This issue of *Jitsugaku* offers insights into the latest research at Keio across all these disciplines.

Articles include a feature on "applied econometrics" regarding what happens when the "invisible hand" does not work.

There are eight articles in this issue covering natural sciences and engineering, including a closer look at the IBM Q Hub @ Keio University for quantum computing and an article about how mechanical engineers discovered differences in the brains of Neanderthals and early modern humans.

Medical subjects are also included, with a feature about an interdisciplinary approach to the treatment of hereditary hearing loss using regenerative medicine and artificial intelligence, and two articles on the effects of gut bacteria on human health and disease.

There is also an article that takes a deeper look at language, providing insights into how people communicate verbally by unconsciously adapting to different voices in noisy environments.



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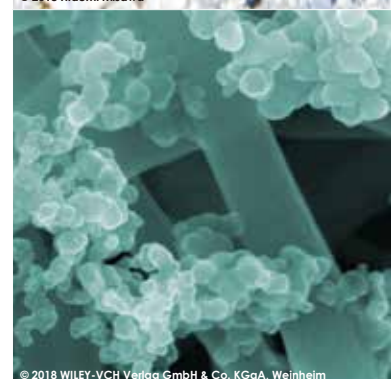
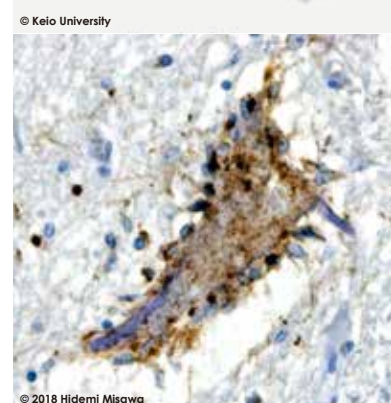
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* This article was made for Keio University by Nature Research Custom Media, part of Springer Nature.
This article was made for Keio University by RTCorp.



Applied econometrics

Empirical analysis of social interactions and knowledge spillover in which the 'invisible hand' does not work

Why study economics?

“I grew up with a keen interest in nature and wildlife in the greenery-rich suburbs of Tokyo,” says Ryo Nakajima, Professor at the Department of Economics of Keio University. “At high school I read a book that led me to think not only about nature itself but about the coexistence of human society with nature, especially in rural society. This was the reason I decided to major in agricultural economics at university.”

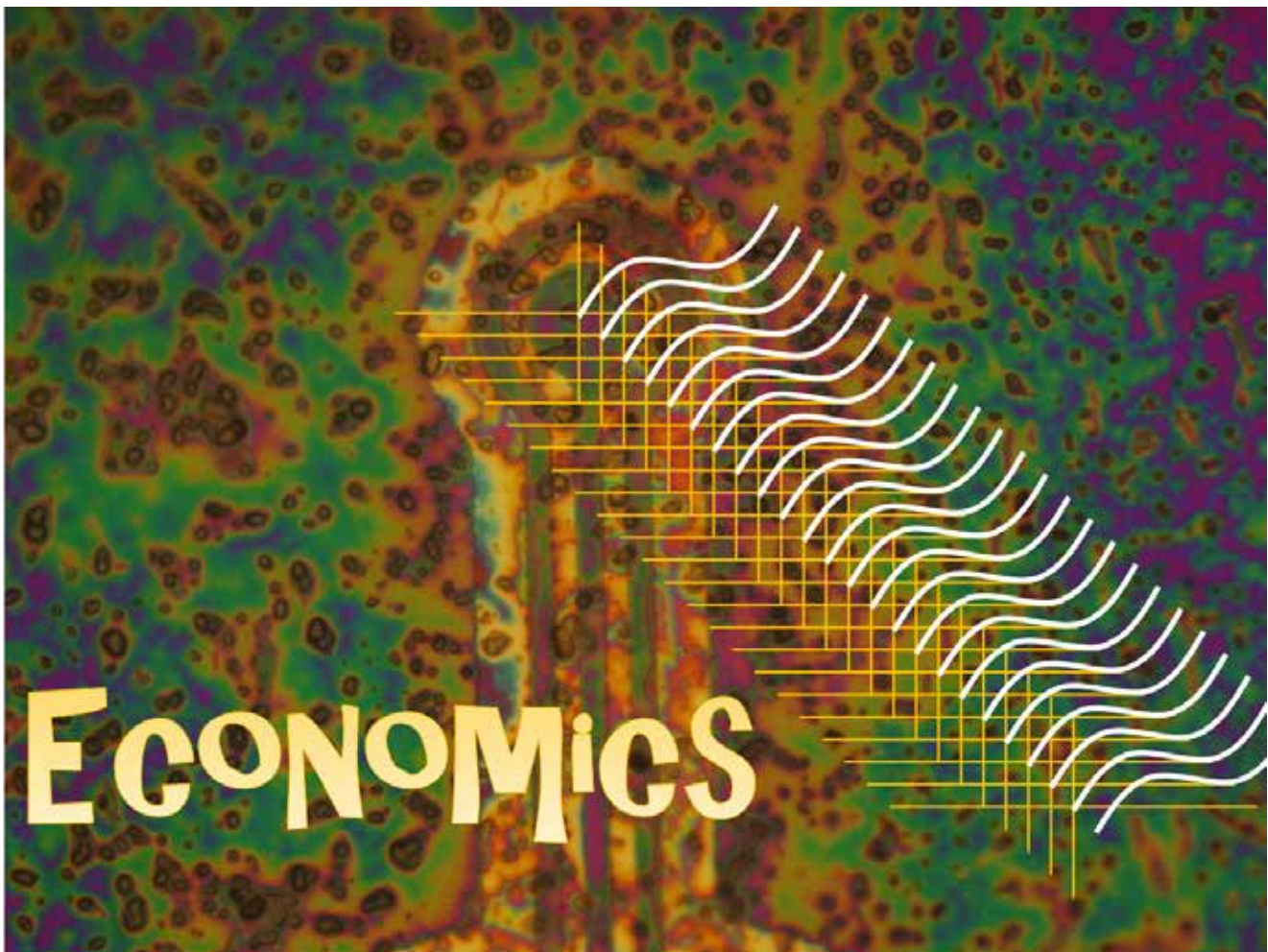
Nakajima became interested in the pragmatic aspects of economics in validating theories using data while taking a course on economics at the Department of Agricultural Economics at Kyoto University. “But I found that in other courses, such as rural sociology and farm management science, teaching tended to emphasize ideology based on hypotheses that were impossible to disprove; although in retrospect I realize that this impression was a product of inexperience,” recalls Nakajima. “I remember rebelling against these courses and decided to focus

only on economics.”

After completing his undergraduate studies at Kyoto University, Nakajima enrolled on a doctorate course in labor economics at the Faculty of Economics at New York University (NYU), specializing in methodology of applied economic analysis.

Features of economics courses in the US and Japan

In the mid-1990s when Nakajima was a student at NYU, the curricula taught at faculties of economics in Japan were



Economics is a dynamic and multifaceted area of research. © 2018 RTCorp

different from those in the United States. “The biggest difference was content on Marxian economics,” says Nakajima. “In Japan there were lectures on neoclassical economics, with Marxian economics also designated as a compulsory subject. Meanwhile, on curricula at American universities the focus was on microeconomics and macroeconomics; and this remains the case today.” Nakajima recalls studying Marx’s capital theory at the Department of Agricultural Economics at Kyoto University. “I remember being very surprised that there were opportunities to discuss this with American classmates and international students while I was studying in the USA.”

Nakajima has seen firsthand how the collapse of socialism led to the decline in the teaching of Marxian economics in Japan, with the result that there is very little difference in curricula taught in Japan and the US today. “I think that economics undergraduates, not only in Japan and the United States but also in other countries, use classic economics textbooks. Economics involves acquiring knowledge by means of step-by-step methodologies using standard textbooks. So the main difference in undergraduate lectures on economics given at Keio and at American universities is the language in which they are taught, rather than the content.”

Nakajima adds that lectures and teaching content vary greatly for graduate schools, with the differences reflecting the characteristics of each graduate school, or the personality of supervising teachers, rather than differences between Japan and the United States.

Research on empirical analysis of social interactions

In the traditional economic paradigm, people’s economic behavior is analyzed based on their interactions

via results of market transactions. As far as relying on market transactions, it has been shown that voluntary and self-interested behavior by individuals will lead to a desirable outcome without external intervention. Adam Smith expressed this as persons being controlled by the “invisible hand”.

In contrast, economic analysis of social interactions focuses on direct interactions occurring independently of transactions involving goods and services. For example, it is known that people’s health and longevity are greatly influenced by the people they interact with on a daily basis, such as family members, friends and acquaintances. This is because behavior that is harmful to health, such as smoking and excessive eating and drinking is influenced by interactions with people who are directly implicated in such habits. This behavior may be indirectly influenced by friends of friends and even the actions of strangers connected to them through social networks. The important point to draw from this is that even though decisions may seem to be the result of free will, people are influenced by their surroundings.

In circumstances in which individual actions are influenced by factors other than market transactions, the “invisible hand” does not work, so the overall results may not be desirable. Since it is not possible to predict the overall macroscopic outcomes from a simple summation of individual micro-actions, it is necessary to consider the influence of individuals on other individuals as part of a system of global social interaction.

“I wanted to find out more about the relationship between micro- and the overall macro-behavior so I decided to focus my research activities on the empirical analysis of social interaction,” says Nakajima. “In my NYU doctoral thesis I described this by means of research on how youth smoking is influenced by peers and how that influence

spreads. I published the results in *The Review of Economic Studies* in 2007¹.

“It may be of interest to note that my choice of this research theme was in fact influenced by social interactions with faculty members who were themselves studying social interaction at the Faculty of Economics at NYU at the time. They were not my academic advisors, but I cannot deny that contact with them affected my choice of research theme. I think this further goes to show that the range of voluntary decision-making by people is unexpectedly limited, and I conclude that decision-making depends on where you are and who you are with.”

Approach to research

Nakajima examines social interactions using large-scale micro data on individuals employing two main methods. The first is experimental research design. Since it is difficult to intervene in the decision-making of actual subjects by carrying out randomized control experiments, Nakajima uses situations that can be regarded as natural experiments, where random intervention occurs, formulates a hypothesis about social interactions, and quantifies the magnitude of interactions.

The second approach is an analytical method called structural estimation, consisting of the task of constructing an economic theory model that explains people’s behaviors and estimating the parameters of the model that might best describe the observed action pattern. “Based on the estimated model, we carry out predictive simulation about people’s behavior and verify the validity of the theoretical model by examining whether that prediction can explain the behavior of real people consistently,” explains Nakajima. “Predictive simulation by modelling is also used for policy evaluation. It is possible to quantitatively calculate

the effect of policies that have already been implemented and to compare the impact of alternate policies that may be executed in the future and to clarify in advance which is the best policy.”

Recent research highlights

Nakajima is looking into the social interactions of experts who create new knowledge and have carried out empirical research. Researchers and inventors are considered to “produce” new knowledge, but most of the knowledge “produced” is based on existing knowledge. Previous research shows that researchers and inventors incorporate knowledge through direct contact with their colleagues. In other words, most of the expert knowledge is transmitted and spread through social networks of peers, not by market transactions.

In a paper published in 2014, Nakajima and colleagues traced the flow of knowledge of inventors using US patent data and quantified the physical distances over which knowledge spreads².

In more recent collaborative research Nakajima and his collaborator analyzed the transmission of scientific knowledge across generations³. “We

quantitatively measured the degree of succession of scientific knowledge through guidance at the graduate school - in other words a guided relationship,” says Nakajima. “To that end, we introduced a value-added model that correlates the research results of graduate students with the “quality” of the supervisor and estimated the “quality” of research guidance. To identify the teaching guidance effect of teachers, we focused on the separation of faculty members due to mandatory retirement, transfer, death, and so on.”

When a professor leaves their job, the research guidance of students is handed over to another professor, so the approach to the supervision of master’s and doctoral students in the laboratory will differ. Meanwhile, in the laboratory of the generation before the professor left, the same person conducts research guidance for graduate students. By comparing differences between generations of such research guidance environments as natural experiments, this research identified the impact of changes in the quality of research guidance due to changes in supervisors on the growth of research findings by students. In empirical analysis for physics researchers who ob-

tained degrees at the Graduate School of Science of the University of Tokyo, the effect of supervisor turnover was measured. The results show that research guidance of university supervisors has a significant influence on the research achievements of students.

Future research

Nakajima is currently researching social interactions to measure the impact of generational changes in researchers on the inheritance of knowledge in Japanese manufacturing companies and the connection to the company’ productivity.

“We are also working on a project to study how companies can incorporate new knowledge and outside ideas, and what kind of organizational structure is most effective to utilize such knowledge.”

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Desperately seeking status: Sociology of organization

Researchers uncover patterns in the decisions of security analysts revealing status-seeking behavior.

Many professions involve decision making. But are professionals’ decisions always based on independent analysis, or are

social factors at play? Are decisions perhaps made to please a target customer group with the aim of increasing one’s status, implying actions that may objectively not be the best? Hitoshi Mits-

hashi at Keio University and colleagues conducted a quantitative study of this behavior, known as status seeking.

The researchers looked at a large group of security analysts, whose job



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it is to issue recommendations on publicly traded stocks. Every year, *Institutional Investor* magazine bestows 'All-Star Awards' on selected analysts. These are highly prestigious awards, and 'All-Stars' experience benefits and privileges not afforded to 'non-All-Stars'. All-Star status is temporary, and results from positive recommendations of investors — analysts' customers. Recommendations are largely service-oriented; criteria include responsiveness to investor needs, promptness of returning phone calls and providing extra insight when necessary. Mitsuhashi and colleagues argue that driven by the goal of becoming (or remaining) an All-Star, analysts act to increase their visibility to investors. In practice, analysts do this by continuously reassessing their portfolio of managed stocks; specifically, by dropping, keeping or starting coverage of particular stocks, taking

into account stock coverage by rival analysts. Normal, objective decisions, not resulting from status-seeking behavior, would be solely driven by stock investment value.

Mitsuhashi and colleagues tested their hypotheses using a dataset on analysts' coverage of US stocks from 1995-2007. The data consisted of more than 100,000 quarterly analyst stock portfolio snapshots. Of particular interest are the reactions of analysts covering a given stock to a rival analyst, All-Star or not, also taking on the stock. The researchers observed that such a competitive entry by an All-Star increases the likelihood of other analysts who already have the stock in their portfolio keeping it, but also of their initiating coverage of new stocks.

The researchers found that All-Stars behave differently compared to non-All-Stars, and that in general, the analysts' behavior is of a status-seeking

nature. Potential negative implications of such overt status-seeking behavior are that investors may make mistakes and that the assessment of firms may become analyst-specific rather than based on industry performance.

This research on the behavior of analysts is a valuable model for initial insights on competitive environments of actors aware of the importance of status, and it is notable for establishing links between dynamic markets and human competitive behavior with conclusions such as that award criteria for status may not be related to behavior that is beneficial to the market, and that consumers who use status as a basis of producer choice may make erroneous decisions.

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How costs related to changing the quality of products impact firms

The costs firms incur when changing the quality of their products can determine how they fare with respect to their competitors

Expanding into new markets is a key step in the growth of a firm, while understanding which factors give a competitive advantage is strategically important. However, models that predict the positioning of different firms in a new market often fail to capture all of the complex factors that determine the positioning of a particular firm in relation to its competitors. Now, Shogo Kurokawa and Nobuo Matsubayashi from Keio University in Japan have come up with a new theoretical model that accounts for the costs incurred when changing the quality level of products, revealing the significant impact this can have in the final equilibrium outcome.

If, when launching a new product or introducing an existing product to a new market, the said product has the same quality as existing ones, the only costs a firm incurs are those related to its manufacture. Otherwise, there

are additional costs related to the ‘repositioning’ the firm must undergo in order to shift from the quality level of existing products to that of the new one. These costs are higher if the gap in quality is greater, and include new production facilities, know-how, distribution networks, marketing, and advertising costs. Furthermore, repositioning costs remain high even if the quality of the product is lowered (for example, to sell in a market where prices tend to be lower). In such cases, costs are mainly related to maintaining the firm’s reputation and avoiding brand dilution.

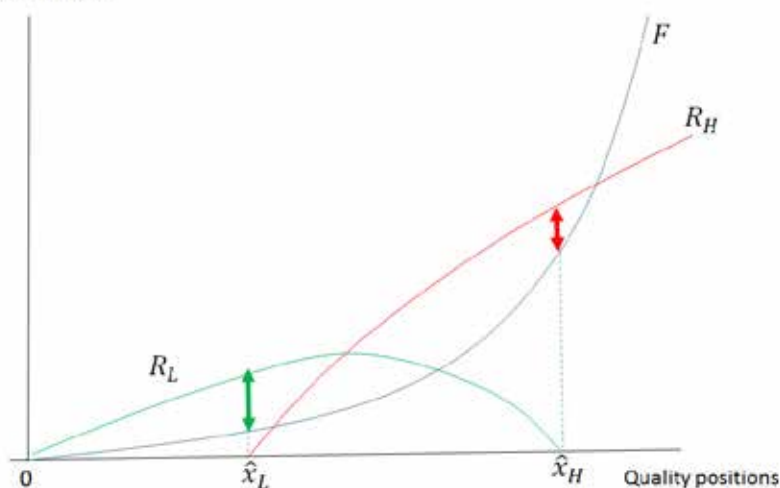
The authors studied a duopoly model of vertical differentiation (that is, their products differ in quality rather than features such as color) which took into account repositioning costs to analyze how they changed the outcome at equilibrium and the relative profitability of the two firms. They examined the case of two established

firms that entered a new market and chose a quality level and price. The decisions over quality and price made by the two firms were then modelled and analyzed using game theory.

The study found that repositioning costs reduced the ability of firms to differentiate themselves from each other vertically, resulting in highly-positioned firms being pushed to offer products of excessively high quality, and vice versa. When firms had similar quality positions, the quality levels of their products were sometimes the reverse of their respective quality positions, with the top-level product of the lower-quality firm being better than the bottom-level product of the higher-quality firm. Moreover, the firm with the higher-quality position sometimes generated smaller profits than its rival, even if its products were better. It was found that, in particular, when the repositioning costs differed significantly between the two firms, as in the case of pre-established and new firms, the lower-positioned firm could make higher profits by strategically choosing a lower-quality product.

The authors thus showed that conventional wisdom stemming from standard models claiming that higher-quality positions are always advantageous does not hold true in all situations.

Revenues and Costs



Revenues and Costs © Keio University

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Diamond

– the industrial scientist’s best friend –

From sensitive sensors to carbon dioxide recycling, diamond with a smattering of boron atoms has a diverse range of applications

There is more to diamond than its sparkle. The material’s exceptional hardness and thermal conductivity have seen it be used extensively in industry. And modifying diamond’s structure can make it even more useful. For example, adding boron atoms turns diamond into a good conductor of electricity. Such boron-doped diamond (BDD) is finding uses as wide ranging as wastewater treatment, biomedical sensing, and conversion of carbon dioxide emissions into useful chemicals.

For the past 17 years, Yasuaki Einaga from Keio University’s Department of Chemistry has been exploring BDD’s properties and pioneering new potential uses. Einaga and his team have shown that BDD is ideal for making electrodes. As well as combining high electrical conductivity with exceptional hardness and stability, “diamond electrodes show highly interesting and superior electrochemical properties compared to conventional electrodes,” Einaga explains. “They have great potential as next-generation functional materials.”



Conductive diamond in the form of needle-like microelectrodes makes excellent biocompatible sensors. © 2018 Yasuaki Einaga

Strength and sensitivity

Einaga initially focused on developing BDD electrodes for electrochemical sensors. These sensors exploit the fact that many substances undergo electrochemical oxidation at a characteristic voltage. When the analyte, such as a heavy-metal ion in a water sample, is present, an easily detectable spike in current occurs at that voltage. “The sensitivity is good because of the surface inertness of diamond,” says Einaga. “Because the background current is very small, the ratio of the signal to the background is high.” The team is currently collaborating with the private sector to develop various commercial sensors, including heavy-metal ones.

Being made of carbon, diamond electrodes are highly biocompatible and have many potential biomedical applications. In a recent animal study, Einaga co-led a team that used a BDD microelectrode sensor to monitor the concentration of a drug in the body in real time following intravenous injection¹. The system provided time-resolved, tissue-specific data that reveals the drug’s effects with unprecedented detail.

Recycling carbon dioxide

The array of potential uses for BDD is so broad that Einaga’s research has diversified far beyond sensors. One area is to use the BDD electrode as a stable, highly efficient electrochemical catalyst for organic synthesis. In par-

ticular, Einaga is focusing on BDD’s ability to electrochemically reduce carbon dioxide — the biggest contributor to global warming — to convert the waste gas into useful products². “Forming useful compounds such as alcohols, aldehydes or formic acid by electrochemically reducing carbon dioxide is a very important and urgent topic,” Einaga says. Electrochemical reduction has the potential to become a large-scale method for recycling carbon dioxide emissions.

The team is also developing BDD electrodes for generating ozone — an environmentally friendly disinfectant used in hospitals, for example — as a way to break down harmful compounds in wastewater³. “I can no longer say what is the main application we study in our lab, because we are studying all these fields in parallel,” Einaga notes.

After 17 years, diamond research continues to hold great appeal for Einaga. “I am still fascinated by this interesting material, which has many faces — jewelry, semiconductors, superior electrodes — in spite of its simple structure.”

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Solving the bucket challenge for remote-controlled excavators

Improving simulations of unmanned construction equipment can reduce risks for workers in challenging environments

The tsunami that struck the Fukushima Daiichi Nuclear Power Plant in March 2011 caused radioactive cesium to leak into the surrounding soil. Decontaminating this land will be a problematic legacy for generations to come — by some estimates, more than 20 million cubic meters of soil needs to be isolated. Researchers from Keio University are working on techniques to help with this clean-up and other dangerous situations by improving the physics behind systems for remote- and computer-controlled machinery^{1,2}.

Moving mountains with a model

Disasters such as the Fukushima incident and volcanic eruptions can make environments too dangerous for construction workers to enter, prolonging repairs by weeks or months. Companies in Japan are spearheading the development of driverless equipment such as bulldozers, excavators, and trucks that work autonomously or are guided by operators stationed hundreds of kilometers away.

While advances in aerial drones and computer sensors are improving how these machines interact with the environment, their efficiency is poor compared with that of directly controlled equipment.

“Most of the work taking place in this area is devoted to manufacturing real unmanned machines,” notes Genya Ishigami at Keio University’s Department of Mechanical Engineering. “But we believe that research into

high-fidelity simulators can solve some of the issues involved in planning an effective construction process.”

Ishigami cites an example of a typical challenge encountered by teleoperated excavators — remote operators cannot easily judge how much soil has been moved by the bucket, so may overload machines. Sensing how much material is in and around a bucket requires performing calculations in real time that are beyond the capabilities of most virtual control systems.

To produce an algorithm capable of quickly and reliably testing interactions between a bucket and the soil, the Keio team modified an existing model, which had originally been developed to simulate how robots walk on sand. Their technique calculates how much resistive force an object generates as it moves through granular particles, with data coming from parameters such as intrusion angle, penetration depth, and geometric factors that account for soil levels inside and outside the bucket during excavation.

Digging for answers

The team’s trials compared simulations of rotational and bulldozer-like excavator motions to the actions of a real bucket equipped with a grid of tiny sensors in a soil mechanics test bed. Measurements of the three-dimensional force distribution between the soil and bucket proved the validity of their model — the algorithm could predict the same trends in force ex-



Improved computer models of the interaction between an excavator bucket and soil could help to make unmanned operation of excavators a reality. © Avalon_Studio/Getty

perienced by a bucket during a half-minute excavation in just a fraction of a second.

“The sensor-embedded bucket directly measures the force distribution between the bucket and soil, which is unique,” says Ishigami. “It helps clarify the key issues we need to work on to improve our model’s accuracy.”

Because the team’s technique can be adapted to different shapes and sizes, it could be used in simulating other parts of construction machines, including wheels, tracks, and blades. Ishigami, with a background in robotic space exploration, also sees opportunities in extraterrestrial excavation and construction. “It would be interesting to apply the model on the Moon or Mars, where gravity is different,” he notes.

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Designer layered materials put a colorful twist on sensing

Layers of color-changing plastic can be tuned by hosting organic or metallic 'guests', enabling easy-to-read measurements of heat and friction

A smart polymer developed at Keio University responds to stimuli by absorbing different wavelengths of light, allowing minor changes to objects to be visualized that might escape other techniques¹⁻⁶. For example, the polymer can indicate how hard a pen presses on an object through vivid color transformations. This technology, which can also be used to display three-dimensional temperature changes, may be used to sense mechanical stress in material degradation, and for biomedical applications such as diagnosing pressure ulcers.

Inspired by dirt

The clay minerals found in soil naturally exemplify the versatility of layered materials. Consisting of stacked sheets of alumina and silica, clays

can swell and hold water by absorbing molecules between these sheets through a process known as intercalation. People learned as early as two millennia ago that the intercalation of different 'guest' particles into sheets could create rudimentary dyes, and applications based on this principle continue to this day.

One modern layered material being investigated by Yuya Oaki and his colleagues at Keio University's Department of Chemistry is a conductive plastic known as polydiacetylene. The conjugated electrons that flow through polydiacetylene make it sensitive to light — polymerization is usually indicated by a color change. Because the particular color that emerges depends on the length and twisting of the polymer backbone, researchers have explored ways to exploit these compounds as chemical and biomolecular sensors.

Oaki realized, however, that producing polydiacetylene sensors required a structure that was flexible enough to change in response to an external force. "Layered materials such as liquid crystals or lipids have soft structures that give them dynamic properties," he explains. "To get similar sensitivity and controllability, we used intercalation to tune the response to stimulus."

Many layers, many uses

In the team's approach, a substrate, such as filter paper, is dipped into a solution containing long, floppy hydrocarbon chains with rigid diacetylene cores, and then air dried. The resulting thin film self-organizes into highly aligned layers, similar to a liquid crystal. The sample is subsequently immersed in a solution of metallic ions, which intercalate between the organic sheets.

Experiments revealed that different metal ions enlarged the distances and altered the structures of the organic layers in distinct ways, creating a tunable output of possible colors. When one of Oaki's students tested for heat sensitivity, the results showed the intercalated material responded to rises or dips in temperature by changing color within seconds — a surprise, Oaki recalls, because most polydiacetylene hues are irreversible.

The team also discovered that mechanical force, such as grinding in a mortar, could initiate color switching. To refine this effect, they exchanged



The polydiacetylene material developed by Yuya Oaki and his team changes color based on responses to external stimuli such as temperature.

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the metallic guests for more flexible ones based on organic amines. The new system enabled innovative detection of friction - for example, it could readily indicate the number of times a pencil rubbed a particular spot.

“It’s not easy measuring and visualizing applied friction forces, but our color-change method can even indicate accumulated amounts,” says Oaki, who was recently awarded the Young Scientists’ Prize of the Commendation for Science and Technology by the

Japanese government for his research. “Next, we hope to enhance the sensitivity by using an informatics approach and also to realize materials that are based on this polydiacetylene material, and are responsive to multiple stimuli.”

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Quantum computing: Keio University launches IBM Q Network Hub

Keio University is the only host in Asia of the IBM Q Hub for quantum computing

On 17 May 2018 Keio University announced the launch of the IBM Q Network Hub at its Yagami Campus in Yokohama. “This is the first IBM Q Hub in Asia configured and authorized to access the IBM Q cloud computing system,” says Naoki Yamamoto, an associate professor and the chair of the Keio University Quantum Computing Center. “We are building on Keio University’s 20 years of expertise in quantum computing to work with specialists at IBM to support academic and industrial organizations to discover and harness the power of quantum computing for both scientific and business applications.” The first four industrial partners in Japan to join the IBM Q Hub are JSR Corporation, MUFG Bank, Mizuho Financial Group, and Mitsubishi Chemical Corporation.

To date IBM has offered free access to its IBM Q 5 qubit system, enabling



Entrance to the common room at the IBM Q Network Hub at Keio University’s Yagami Campus in Yokohama. © Keio University

more than 50,000 users from over 150 academic institutes worldwide to undertake over 1.5 million experiments and produce more than 25 research publications.

Meanwhile, members of the Keio University IBM Q Network Hub are

able to access IBM Q’s commercial 20 qubit cloud system, and will in future also be able to access a 50-qubit IBM Q system.

The Keio University IBM Q Hub is part of a network of six IBM Q Hubs across the world. The others are lo-

cated at IBM Research (USA), Oak Ridge National Laboratory (USA), The University of Oxford (UK), North Carolina State University (USA), and The University of Melbourne (Australia). The hubs provide access to IBM Q systems, technical support, educational resources, and networking for

collaborative research.

Members of the Keio hub have multidisciplinary backgrounds and include researchers from private industry, specialists hired to work at the hub, and Keio University students and researchers, including overseas invited researchers.

“Education and nurturing the next generation of experts in quantum computing, or ‘Quantum Natives’ is a major goal for us,” says Yamamoto. “We are organizing programs for both our domestic and international students to use the IBM Q Hub for writing algorithms. We have high expectations.”

Anatomy of the Neanderthal brain

Researchers reveal differences in the brains of Neanderthals and early modern humans

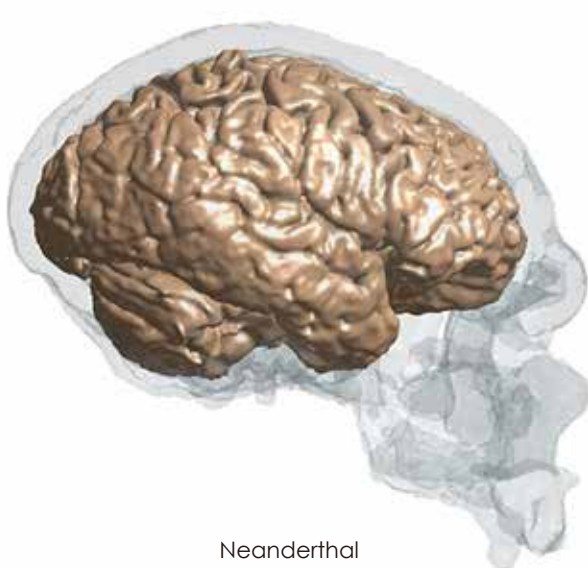
Why Neanderthals (Homo neanderthalensis), a subspecies of archaic humans that lived until at least 38,000 years ago, were ultimately replaced by modern humans (Homo sapiens) remains unclear. Various hypotheses have been put forward, but a growing amount of evidence suggests that the replacement may have come from differences in neural or cognitive function — in other words, from brain differences between the two species. Now, Naomichi Ogihara from Keio

University and colleagues have virtually reconstructed the brains of Neanderthals and early Homo sapiens, revealing variations in brain morphology that correspond to different social and cognitive abilities.

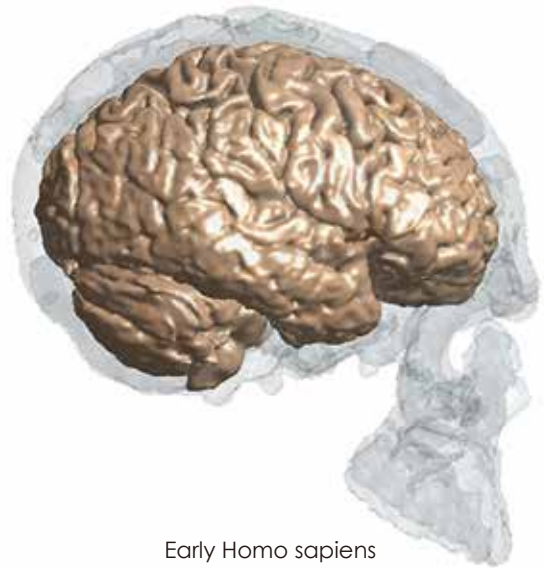
The researchers started from four adult Neanderthal and four adult early Homo sapiens fossil skulls, including the well-known 30000-year old Cro-Magnon 1 skull. Importantly, most of the skulls stem from an epoch during which the two species coexisted. Ogihara and colleagues used an algorithm to reconstruct the brain morphologies

from computer tomography data of the skulls - a technique called computational anatomy. The algorithm was developed and tested through comparing the skulls of living humans to their brain structures.

From the obtained morphologies, the scientists derived important parameters such as cerebral and cerebellar volume, and surface morphology. The cerebrum is the largest division of the brain and is divided into two hemispheres. The cerebellum, another part of the brain, lies in the hindbrain and two of its functions are regulation of



Neanderthal



Early Homo sapiens

Reconstructed brains of Neanderthals based on fossil skulls compared with those of early Homo sapiens. © Keio University

body movement (motor control) and higher cognition (including language and social abilities). Ogihara and colleagues found that the cerebellum was significantly larger for the early *Homo sapiens* than for *Homo neanderthalensis*. Specifically, they found that the right cerebellar hemisphere of Neanderthal brains are relatively small, implying minimal connection to that part of the cerebrum which plays a major role in language processing. Since more data concerning this connection is needed to make conclusions regarding Neanderthal brain function, and since preservation in the cerebellar region of the fossil skulls is not optimal, the researchers point out that

the morphology “of the Neanderthal cerebellum needs to be confirmed in future studies with a large number of cases”.

To examine the relation between cerebellar size and cognitive abilities in more detail, the researchers looked at large sets of data correlating (present-day) human brain morphology and cognitive performance. They concluded that the cerebellar regions are indeed involved in the so-called executive functions (cognitive processes required for the control of behaviour), as well as language processing and episodic memory.

The findings of Ogihara and colleagues show that the differences in

the cerebellum’s neuroanatomical organization may have caused different cognitive and social abilities of Neanderthals and European early modern humans. Citing the researchers, the “ability to adapt to changing environment by creating innovation may have been limited in Neanderthals and this difference possibly affected their chance of survival and drove the replacement process [of *Homo neanderthalensis* by *Homo sapiens*]”.

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New type of optical waveguide for handling cloud-computing data traffic

Researchers report a simple fabrication method for polymer-based single-mode optical waveguides

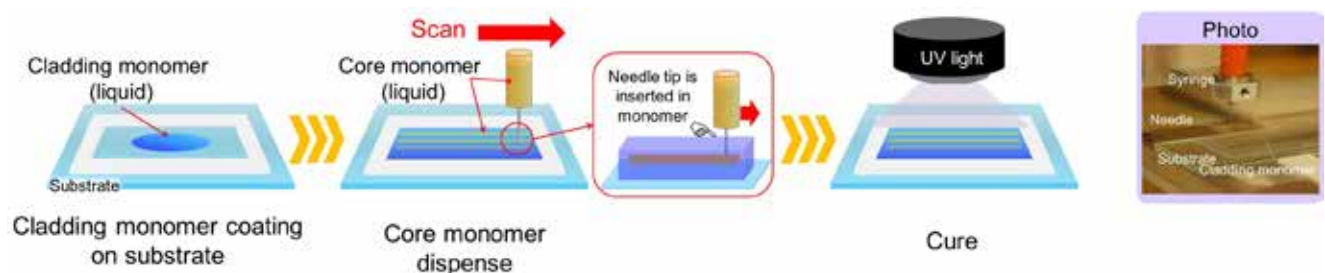
Cloud-computing activity has increased enormously in recent years, generating ever more data stored in ever-larger data centers. For users to be able to continuously access their data, networks capable of handling the rapidly growing amounts of data traffic within data centers are needed. Researchers from Keio

University have now developed a new kind of waveguide that is a promising component for state-of-the-art optical networks wherein data is transported as pulses of light.

A key property of the waveguide developed by the researchers is that it is “single-mode,” not “multimode.” This is important for ensuring low-loss integration with silicon waveguides

expected to be used in computer chips — multimode waveguides cannot achieve the necessary longer link distances and higher bandwidths.

The scientists developed a technique called the “Mosquito method.” An organic substance is first coated onto a substrate. Then, another organic viscous liquid (the core material) is dispensed into the coating through



The Mosquito method developed for fabricating polymer-based, single-mode optical waveguides with circular cores. © Takaaki Ishigure, Keio University

a syringe needle, followed by a curing procedure. It takes no more than 15 minutes to make a single-mode polymeric waveguide 5 centimeters in length with 12 channels. A main advantage of the technique is that it does not involve photomasks — relatively expensive templates used in lithographic methods for etching out parts of a thin material.

Another important aspect of the Mosquito method is that it not only enables the fabrication of circular wave-

guide cores, but also the control of the core diameter, which has to be small enough to achieve single-mode operation. The diameter can be reduced by lowering the dispensing pressure of the syringe and increasing the speed with which it moves along the coating.

The scientists performed quality-control checks of the waveguides they fabricated. Optical power profile, signal loss during propagation, misalignment tolerance (in connections between the waveguide and other optical compo-

ments) and “interchannel crosstalk” (disturbances due to interfering signals from neighboring channels) were all found to be of sufficient quality to warrant proper operation. In the words of the researchers, “the single-mode waveguides fabricated using the Mosquito method are very promising for off-chip interconnects.”

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Exciton fission for high-yield solar energy conversion

Quantifying multi-exciton generation for solar energy conversion in molecular materials

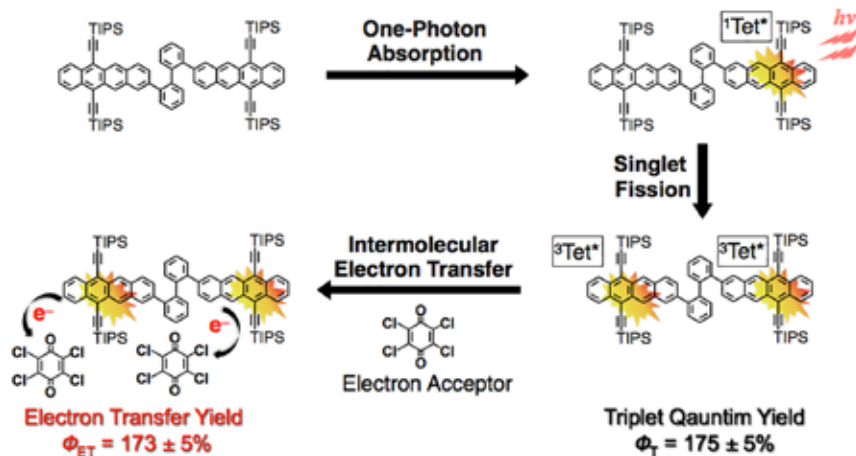
In molecular materials, the absorption of one photon can result in the formation of a singlet exciton — a state formed by an electron and a hole bound by their electrostatic attraction and with opposite spins. In a process called singlet fission, the singlet exciton splits into two triplet excitons, that is, two excitons in which the electron and hole

have their spins pointing in the same direction. The triplet excitons are initially strongly correlated, but they can be separated, and the electrons they carry can then be transferred to other molecules. This complex process is very promising for applications in solar energy conversion, because it opens up the opportunity of reaching very high power conversion efficien-

cies, as the absorption of a single photon results in the generation of multiple electrical charges (i.e., multi-exciton generation).

Singlet fission can happen within a single molecule in systems of two molecular units covalently linked by an organic bridge (the process in this case is called intramolecular singlet fission). This is advantageous because we can quantitatively evaluate the photophysical processes and parameters such as kinetic constants and quantum yields. Singlet fission theoretically enables the performance of the sequential photoenergy conversion process starting from the singlet state and leading to electron transfer with the radical ion pair quantum yield approaching 200%. However, the quantitative two-electron transfer process through singlet fission has yet to be reported.

Shunta Nakamura, Hayato Sakai, and Taku Hasobe of Keio University,



Sequential photoenergy conversion process from singlet fission to intermolecular electron transfer in this study © Keio University

together with colleagues from Kobe University and Tampere University of Technology (Finland) have quantitatively characterized a sequential process involving intramolecular singlet fission and intermolecular two-electron transfer by using two tetracene-based molecules linked by a biphenyl unit (Tet-BP-Tet) as the singlet fission and electron donor system, and chloranil as the electron acceptor system.

The structure of Tet-BP-Tet was studied theoretically by density functional theory, and experimentally by absorption and fluorescence spectroscopy. Femtosecond, nanosecond, and microsecond transient absorption

was used to characterize the ultrafast excited-state dynamics and measure the rate of intramolecular singlet fission, the triplet quantum yield, and the rate of dissociation of the triplet-triplet state into individual triplet states. Finally, the long lifetime of the triplet exciton, which is important for the electron transfer to happen, was verified. Performing experiments spanning very different timescales allowed the observation of each of these processes, which happen at very different speeds. Next, the intermolecular electron transfer process was studied, and its rate constant and yield were estimated.

Thus, the authors thoroughly characterized the sequential photoenergy conversion process from intramolecular singlet fission to intermolecular two-electron transfers. As they comment in the paper, “such a molecular system provides a new perspective for construction of future solar energy conversion systems.”

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Air pollution and environmental monitoring

Measuring the charging states of atmospheric particles offers accurate data for formulating advanced models on the effects of particulates for human health

Inhalation of particulate matter is one of the top ten risks to human health according to the World Health Organization

(WHO). In 2016, as many as 4.2 million people died due to the effects of particulates in the air. With these alarming statistics, it is not surprising that there

have been increased calls for greater awareness and monitoring of the air for potentially deadly particulates. “The health risks of inhaling par-



The Keio Measurement system of Aerosol Charging State (K-MACS) © RTCorp

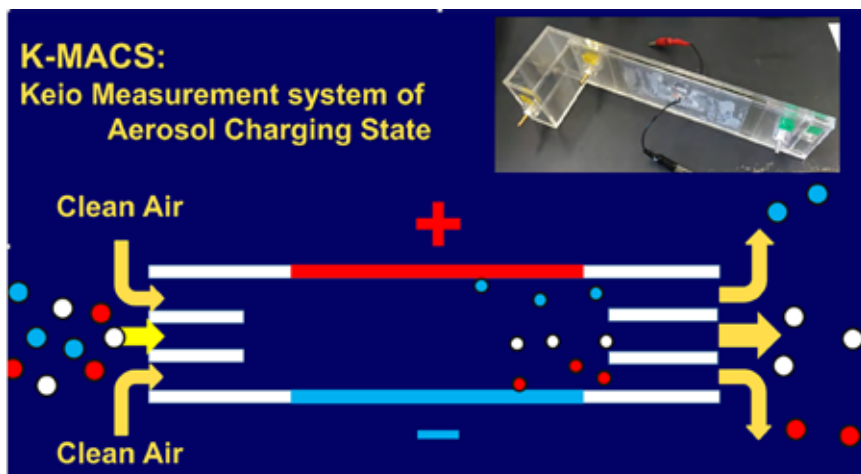


Fig. 1: Illustration and photograph of the Keio Measurement system of Aerosol Charging State (K-MACS) © Keio University

ticles less than 2.5 micrometers, so-called PM2.5, are well documented with environmental agencies monitoring particle-concentrations and issuing warnings to the public about dangerous levels of PM2.5 in the air,” says environmental scientist Tomoaki Okuda, an associate professor at the Department of Applied Chemistry, Keio University. “However, recent reports indicate that singly charged particles are about six times more likely to be adsorbed into the respiratory tract than uncharged particles. So, an accurate assessment of the effect of air-borne particles on human health requires a much deeper understanding of not only the size of particles, but also their physico-chemical properties including charge and surface struc-

ture. My research is focused on determining the charging state of particles in the air, which, surprisingly, is not well understood.”

Keio Measurement system of Aerosol Charging State (K-MACS)

Okuda and colleagues developed K-MACS (Fig. 1)^{1,2} as an inexpensive and versatile system to continuously separate and quantify the charging state of atmospheric particles ranging in size from 300 nm to 500 nm for short durations over a period of 12 months. “We studied this range of particles because they have a larger concentration in the air,” says Okuda. Measurements of these particles were taken at Keio University’s Yagami Campus from April

2017 to February 2018.

The two main findings were that the charging state of the atmospheric particles was different from the results of theoretical studies to-date (Fig. 2), and that the particle charging state fluctuated markedly with changing atmospheric conditions (water vapor amount and entrained air mass) due to seasonal variations.³

“These results offer new insights into the changes of the charging state of particles,” says Okuda. “They will play an important role in the accurate evaluation of the effects of atmospheric particles on human health on a global scale.”

Related research conducted by Tomoaki Okuda

Okuda conducted a theoretical assessment of the performance of a parallel plate particle separator (K-MACS) instrument designed to measure the charging state of PM2.5 particles. Results yielded an optimal voltage to maximize the types of particles.² This research addresses the question of what happens to aerosol particles in humid conditions, such as haze. A discrete element model showed a correlation between relative humidity and the amount of water contained in the particles that were found to be charged negatively or positively.⁴

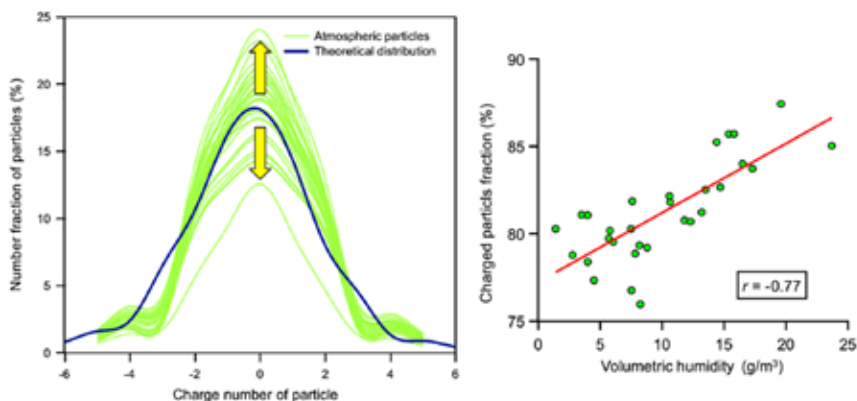


Fig. 2: (Left) Charge distributions of measured (green) and theoretically calculated particles. (Right) Variation of the volumetric humidity versus charged particles fraction. © Keio University

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A chance to slow neurodegeneration

Drugs targeting a protein with a key role in neurodegeneration may slow the advance of the neurological disorder ALS

A molecular pathway that becomes active in vulnerable subpopulations of neurons in people with the debilitating neurological disease amyotrophic lateral sclerosis (ALS) has been uncovered by Keio University researchers¹. Therapies targeting this pathway could slow the progress of this incurable condition.

The late cosmologist Stephen Hawking was the best known ALS sufferer. Hawking lived for 55 years after diagnosis, but about half of ALS patients die within three years of onset as the steady loss of motor neurons gradually robs sufferers of control over their bodies.

Different types of motor neurons control specific kinds of muscle movement, and some are more likely to succumb to ALS than others: motor neurons controlling slow-twitch muscles are largely resistant to degeneration, whereas those controlling fast-twitch muscles are susceptible. There is additional complexity — a subset of these latter motor neurons perishes early in ALS, while another survives until its second wave, during which patients lose most voluntary movements.

“The different vulnerabilities of different types of motor neurons is one of the long-standing mysteries for ALS researchers,” notes Hidemi Misawa at Keio University’s Faculty of Pharmacy. This has led to a search for biological markers that clarify the nature of this susceptibility and enable early discrimination of endangered motor neurons.

Misawa’s team recently obtained evidence that the cell signaling protein

osteopontin might be a key to understanding the selective disease process of ALS. “It’s expressed abundantly in motor neurons serving ALS-resistant muscles,” Misawa says.

The researchers have now determined that this protein plays a key role in establishing the tipping point of vulnerability to ALS, and they have identified osteopontin-activated molecular pathways that indicate which cells will go from being protected to becoming vulnerable to degeneration.

To assess this protein’s function, the researchers knocked out the gene that encodes it in a mouse model of ALS. Osteopontin deficiency initially delayed the onset of neurodegeneration and muscle loss in these animals, but the disease progressed faster than usual once it began to manifest.

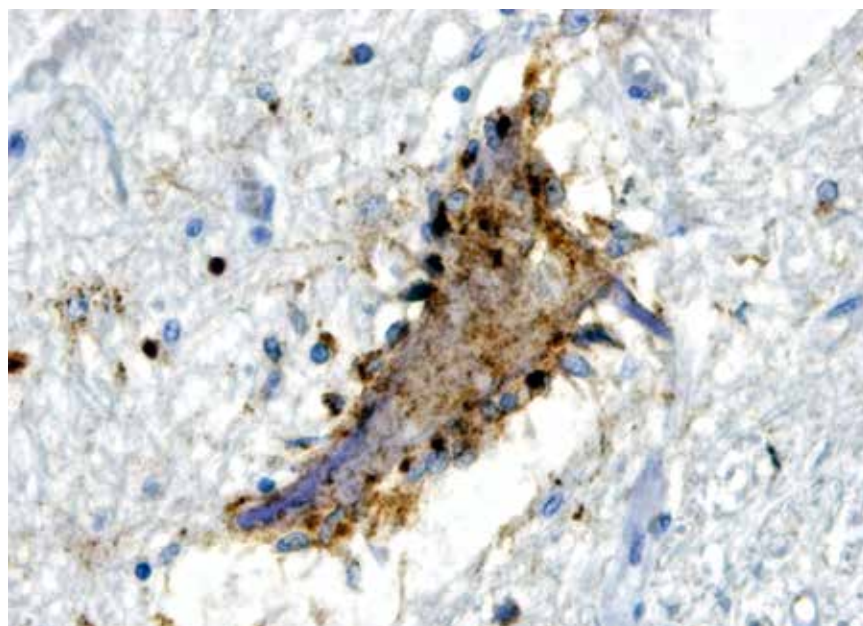
This reflects osteopontin’s dual role. On the one hand, it stimulates the induction and activation of the enzyme

matrix metalloproteinase-9 (MMP-9), which renders neurons susceptible to degeneration. This explains why osteopontin deficiency initially delays ALS. On the other hand, osteopontin sends signals that protect against inflammatory damage from brain glial cells, so that its absence ultimately leaves neurons vulnerable to destruction.

These findings suggest that osteopontin could be a potential drug target for ALS therapy. Misawa hypothesizes that blocking osteopontin’s activation of MMP-9 in early-stage ALS patients could slow disease progression. His team is now using more-sophisticated mouse models to study this pathway in greater detail.

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Motor neurons from a patient with ALS, where osteopontin is shown in gray. Blue indicates brain glial cells attacking the neuron. © 2018 Hidemi Misawa

Cell therapy stacks up

A fiber mat that releases a growth factor enhances the survival of heart muscle tissue transplanted in rats

A new tissue engineering technique co-developed by Keio University scientists promises to boost the regenerative capacity of cell transplantation therapy for heart disease¹. This technique could also assist the transplantation of other kinds of cells.

Heart cells regenerate themselves at a glacial rate, and consequently damage sustained during a heart attack is often permanent. An exciting avenue that researchers are exploring to repair damaged hearts is to artificially grow cells outside the body and then transplant them in the heart. But heart muscle cells grown in flat sheets can be transplanted only a few layers thick — any deeper and the cells start to die because they do not get enough oxygen and nutrients.

Now, Kenichi Nagase of Keio University's Department of Pharmaceutical Sciences and his co-workers have developed a simple strategy that overcomes this problem. It involves

fabricating a fibrous mat out of synthetic resin and then spraying it with nanoparticles containing a growth factor that accelerates the formation of blood vessels in transplanted cellular tissue.

To test the regenerative potential of the new biomaterial, Nagase's team cultured cells from the ventricles of rats to create pancake-like sheets of heart muscle tissue. The researchers placed six of these sheets on top of one another and then implanted the multilayered tissue stacks onto the dorsal subcutaneous tissue of rat — both with and without the growth-factor-impregnated fiber mat added to the top of the tissue pile.

Two weeks later, sheets with the mat produced cell layers that were about twice as thick as those generated by sheets lacking the mat. Mature blood vessels also more readily infiltrated the matted implants, bringing with them red blood cells that nurtured the transplanted heart muscle tissue with essential oxygen and nutrients. With-

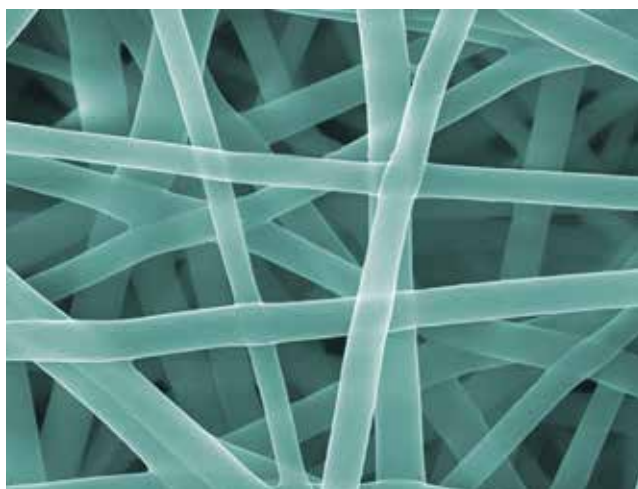
out the local release of the growth factor, the tissue tended to die off inside the rats.

“This research could expand the possibility of cellular tissue transplantation in regenerative medicine,” says Nagase, noting that his team is continuing to improve the method. “The system leads to the successful transplantation of relatively large cellular tissue, which cannot be transplanted using the conventional procedure.”

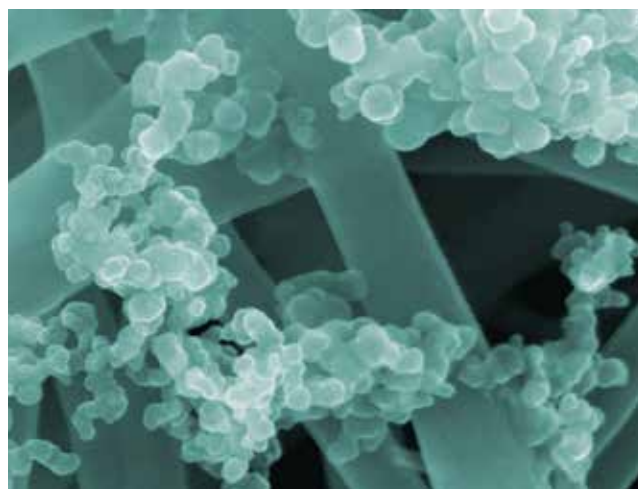
Nagase considers that adding a growth factor-releasing mat could also work for transplants of other kinds of cell sheets. For example, people with liver damage might benefit from therapies involving sheets of hepatocytes, the primary cell type in the liver. “The system could be broadly applied in transplantation medicine,” Nagase notes.

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To boost the regenerative capacity of heart cells, Keio University researchers first made a fibrous mat out of synthetic resin. © 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim



Kenichi Nagase and his team then sprayed the fibrous mat with nanoparticles containing a growth factor that accelerates the formation of blood vessels in transplanted cellular tissue. © 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

Regenerative medicine and artificial intelligence

Advances in iPS cell-based therapy for treatment of hereditary hearing loss

Masato Fujioka, Makoto Hosoya, and their colleagues at the Department of Otorhinolaryngology, Head and Neck Surgery, Keio University School of Medicine, are searching for methods to treat genetic hearing loss — an extremely challenging area of medicine with no potentially useful strategies to cure such ailments at present.

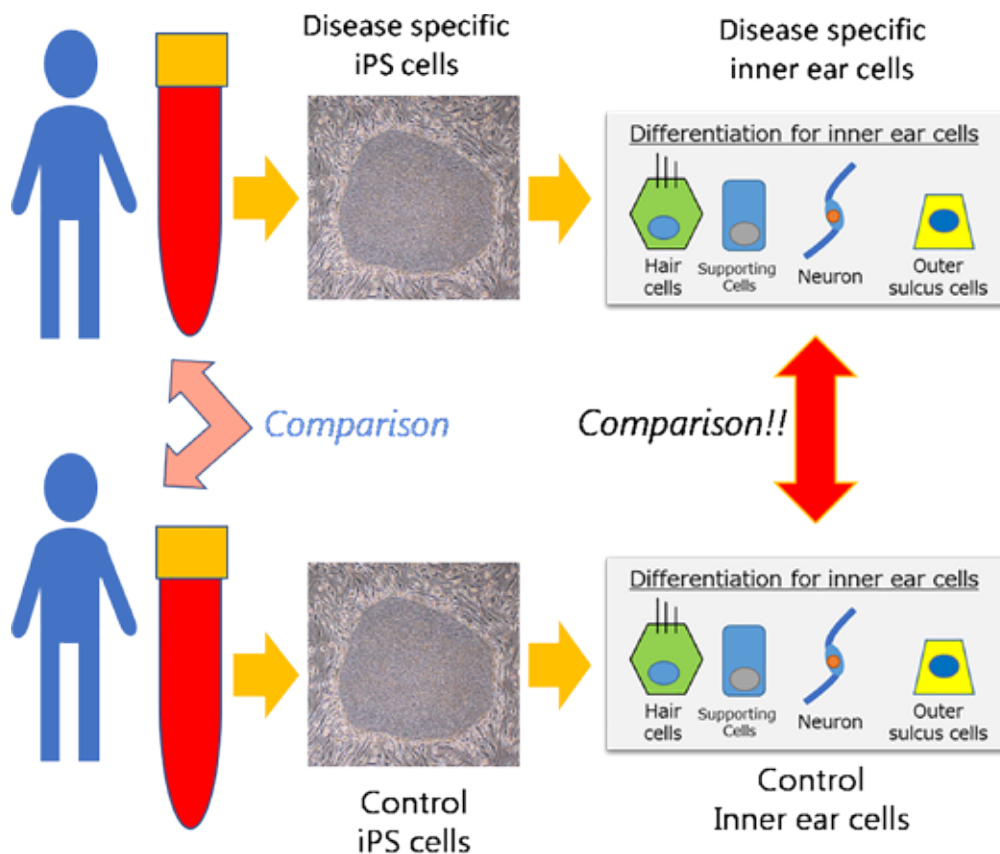
Fujioka and Hosoya are investigating the possibility of using regenerative medicine, specifically iPS cells, to model human inner ear cells. “Ideally we would like to obtain samples of inner ear tissues by direct biopsy,”

says Fujioka. “But in reality, this is not possible because the inner ear is filled with lymph inside the bone that makes it inaccessible to collect cells for examination and observation to monitor progression of hearing loss. So, we devised a new approach based on first producing iPS cells from patients and then inducing inner ear cells from these iPS cells. Our early results are very promising and we expect them to lead to in vitro procedures for pathophysiological analysis and drug screening.”

The Keio researchers used patient-derived iPS cells to discover the cause of one of the most common forms

of hereditary hearing loss, Pendred syndrome¹. Pendred syndrome causes progressive deafness and no effective therapies are available. In genetically modified mouse models, however, the disease does not lead to progressive deafness as is observed in humans.

The iPS cells were prepared from the blood of patients and used to induce cells of the inner ear. The mechanisms causing deafness were then studied. The results showed that the abnormal protein known as pendrin only accumulated in the patient’s cells of the inner ear, and notably, that this protein was made of aggregates similar to those of neurodegenerative



Application of iPS cells in studying hereditary hearing loss © Department of Otorhinolaryngology, Head and Neck Surgery, Keio University School of Medicine

diseases such as Alzheimer’s disease.

Further analysis showed the inner ear cells to be vulnerable to cellular stress, and that hearing loss gradually progresses due to the death of a particular type of inner ear cell—a finding proposed as “inner ear degeneration.”

The researchers also searched for therapeutic drugs to prevent cell death and discovered for the first time the possible therapeutic effects of rapamycin, which is already used as an immunosuppressant. This research utilizing patient iPS cells yielded unexpected findings that imply phenomena observed in Alzheimer’s disease are also occurring in the inner ear. This pioneering research opens up the possibility of a major breakthrough in the treatment of deafness, including senile deafness.

The future role of artificial intelligence and the Internet of Things

“I was interested in regenerative medicine during my high school days so I wanted to study at the Keio University School of Medicine,” says Hosoya. “I was really impressed by the research of Keio’s Professor Okano, Physiology, and Professor Fujioka, Otolaryngology, so I decided to start conducting research on inner ear regeneration. Now, as medical doctors we have to expand our horizons and learn about artificial intelligence (AI) as well.”

The Keio team stresses the increasing inroads AI is making in medicine, in particular radiology, pathology, dermatology, and diagnosis. “I think that similar waves of AI will reach otorhinolaryngological diseases,” says Fujioka. “I think that the biggest challenge for advances in inner ear medicine is collecting physiological data. The conditions of patients can change rapidly, such as in Ménière’s

disease, and physicians must be aware of them. So, I would like to develop secure procedures to collect accurate, time-dependent physiological data of the functions of the inner ear.”

As an example, Fujioka describes the treatment of Pendred syndrome, a disorder characterized by hearing loss and repetitive dizziness where the conditions of patients can vary significantly with time. Frequent hearing tests are required to monitor the effects of treatment. This is a perfect example of lending equipment to patients to collect biological information with Internet of Things (IoT) technology that could be monitored in real time by the patient’s physician.

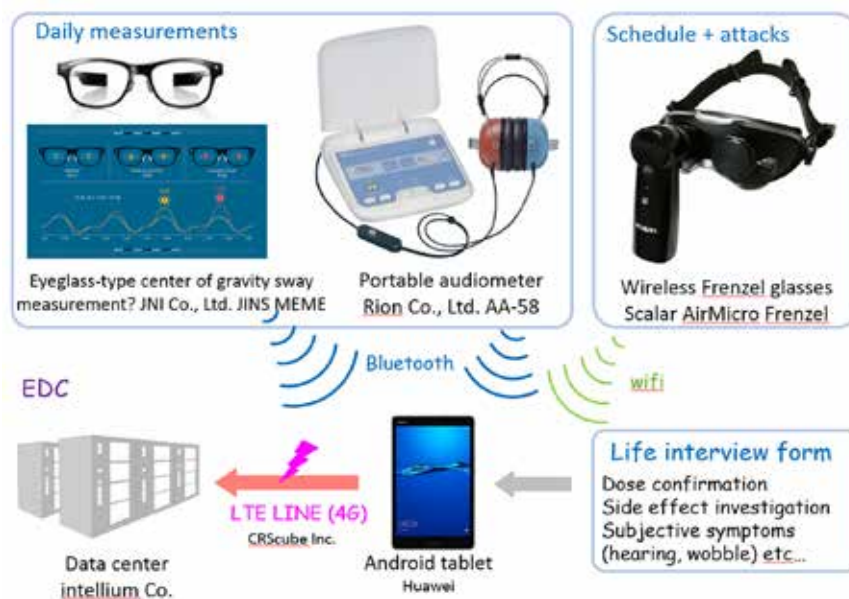
“We are planning IoT trials with 16 patients for 10 months,” explains Fujioka. “So, three physiological examinations per person per day will produce about 300 days of data. We will monitor the effects of drug administration on the patient’s symptoms.” Fujioka adds that by monitoring changes in the inner ear function in the same patient and using machine learning algorithms, it may be possible to predict vertigo attacks before they occur.

Trials on 16 people will yield 4,800 sets of data, and 14,400 measurement results—a significant amount of “big-data.” The point is that all 16 patients being monitored are limited to the mutations of the same gene, and “several different mutations in one single gene will be included in our trials,” says Fujioka. There are expected to be individual differences, but it is a homogeneous population compared to Ménière’s disease and senile deafness. It is expected to be an ideal group to create prototypes of analysis algorithms.

“I hope that this IoT clinical trial system can become a prototype for future clinical trials for inner ear disorders, as well as a health management tool for a wide range of users handling easy to use equipment that is not necessarily medical devices used in hospitals.”

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IoT-based monitoring of patients with ear ailments
© Department of Otorhinolaryngology, Head and Neck Surgery, Keio University School of Medicine

Measuring oxygen deficiency and blood vessel permeability in tumors

Researchers develop a method for simultaneously mapping oxygen level and spatially uneven vessel permeability in tumor tissue

In tumors, newly formed blood vessels tend to have an abnormal tissue distribution – vessel permeability and oxygen delivery are spatially more uneven than normal. To better understand tumor mechanisms and to optimize anti-cancer drug delivery strategies, it is important to be able to quantify both blood vessel permeability and local hypoxia (oxygen deficiency). Kosuke Tsukada and colleagues at Keio University have now developed a method enabling the simultaneous measurement of both permeability and hypoxia in tumor environments.

The researchers imaged the flow of blood, made fluorescent, in tumors implanted in mice. The mice were put on the stage of a confocal laser scanning microscope (a type of microscope used for reconstructing 3D structures) and

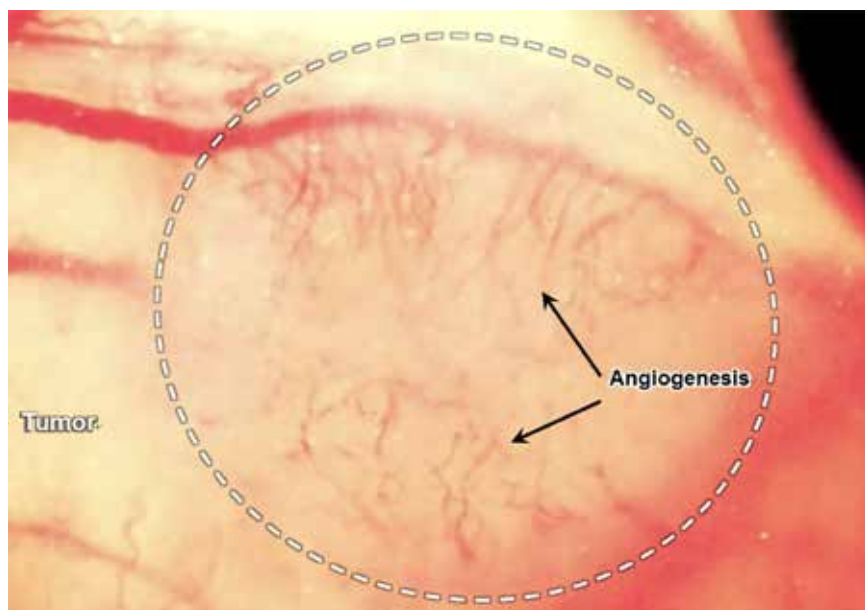
after injecting a fluorescent dye, fluorescence images were recorded every minute. Image processing techniques were then applied to quantify vessel permeability and how it changes over time. (Fluorescence was excited by irradiation with a continuous-wave laser.)

During the permeability measurement process, for the same field of view of the microscope, the tissue oxygen partial pressure (a measure for the presence of oxygen) was quantified through phosphorescence. A phosphorescent substance was injected in the mice, after which the phosphorescence lifetime was measured; the latter can be related to oxygen concentration. (In contrast to fluorescence, phosphorescence was triggered by a pulsed laser.)

The oxygen partial pressure was

found to be higher in normal tissue than in tumor tissue; in the latter, vessel networks were generally more complex. Regarding vessel permeability, the scientists found that for normal tissue it was generally evenly distributed, whereas for tumor tissue there was greater heterogeneity.

Previous methods could only achieve mean results for tissue regions or for the entire tissue, and combining oxygen partial pressure mapping with permeability measurements was not possible at all. This demonstration by Tsukada and colleagues shows that it is feasible to simultaneously measure tumor vessel permeability and oxygen partial pressure *in vivo*. The scientists believe that “[their] findings could be applied to improve anticancer drug delivery and radiotherapy by identifying the dependence of local tissue oxygenation on the vessel structure and hemodynamics,” and anticipate that “this method can be applied to investigate other issues, such as visualization of the relationship between parietal cell dynamics [processes taking place in the stomach] and vessel permeability caused by hypoxia.”



Tumor angiogenesis (black arrows) in murine breast cancer (white circle) grown on a mouse back skin
© Kosuke Tsukada, Keio University

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Understanding kidney failure caused by complications of muscle injuries

A study on mice and humans unlocks new insight in the molecular mechanism behind rhabdomyolysis-induced acute kidney injury

Rhabdomyolysis is a syndrome caused by muscle injury: damaged skeletal muscles break down and release myoglobin (a protein that stores oxygen in muscles) in the bloodstream. This can lead to kidney damage and acute kidney injury (AKI), a life-threatening condition. Different types of muscle injuries can lead to rhabdomyolysis, including excessive exertion during sports, lack of oxygen in the muscle, medications and drug abuse, as well as injuries sustained in natural disasters or wars.

The molecular mechanism underlying rhabdomyolysis-induced AKI is still largely unknown. There is strong evidence that myoglobin and heme (a molecule containing an iron ion) released from the necrotic muscle cells and reactive oxygen species play a role, as does the infiltration of macro-

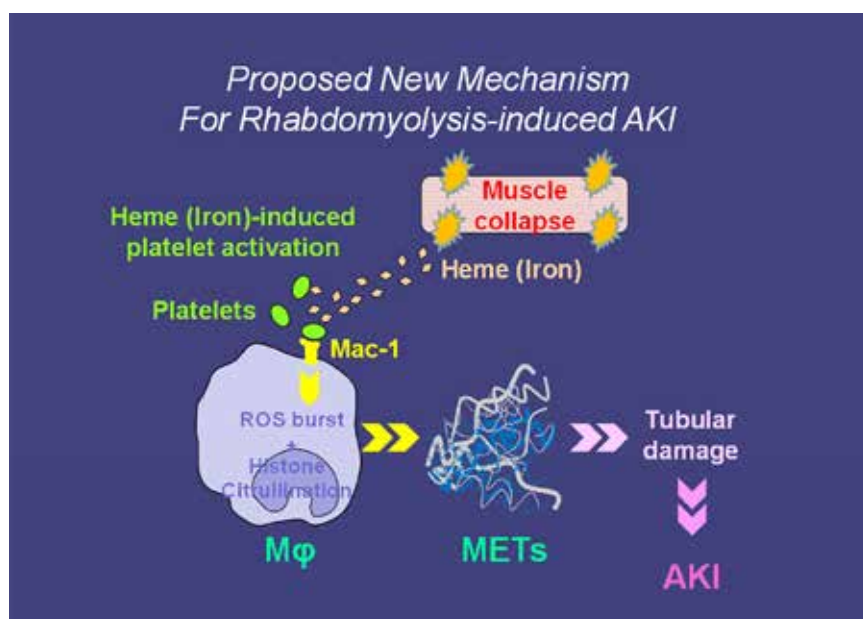
phages in the kidneys.

Now, writing in *Nature Medicine*, Junichi Hirahashi from the Keio University School of Medicine and colleagues put forward a new hypothesis for the mechanism: the released heme activates platelets that interact with macrophage antigen-1 (Mac-1, a receptor) and induces the generation of reactive oxygen species, histone citrullination, and the resulting release of macrophage extracellular traps (METs) — an immune response normally aimed at immobilizing and killing microorganisms. The METs damage tubules and promote AKI. It is the first time METs have been demonstrated to contribute to the pathogenesis of a disease.

The authors started by studying a mouse model of rhabdomyolysis. They verified the presence of METs in the kidneys, linking it to increased tubular damage, and observed that

extracellular traps are present in the blood of mice with rhabdomyolysis-induced AKI, but not in that of the control group. Macrophages and platelets clearly play a role, as depleting those cell types inhibits renal injury. The importance of Mac-1 in the disease is highlighted by the observation that mice not expressing it show a renal function similar to that of healthy mice, even though they exhibit evident muscle degradation; METs are reduced or absent in this case. Moving on to humans, the authors found evidence supporting the hypothesis that METs are responsible for rhabdomyolysis-induced AKI.

A treatment that reduces the formation of platelet-induced METs *in vitro* markedly prevented renal damage in mice. “Early volume-repletion and renal-replacement therapies have been established for rhabdomyolysis-induced AKI; however, the delivery of medical supplies is often not feasible shortly after disasters”, write the authors. “Our results suggest that inhibitors of Mac-1 and/or direct inhibitors of METs [...] might be new therapeutic strategies for the prevention of platelet-mediated MET formation and associated renal tubule injury in rhabdomyolysis-induced AKI.”



A Proposed New Mechanism For Rhabdomyolysis-induced AKI © Keio University

Reference

1. Koshu Okubo, Miho Kurosawa, Mako Kamiya, Yasuteru Urano, Akari Suzuki, Kazuhiko Yamamoto, Koji Hase, Koichiro Homma, Junichi Sasaki, Hiroaki Miyachi, Tatsuo Hoshino, Matsuhiko Hayashi, Tanya N Mayadas & Junichi Hirahashi, Macrophage extracellular trap formation promoted by platelet activation is a key mediator of rhabdomyolysis-induced acute kidney injury. *Nature Medicine*, 24, 232-238 (2018).

Can gut bacteria protect infants against infection?

Healthy bacteria in the gut of infants are a vital defence against gastro-intestinal infections

The human gut harbours a host of bacteria, known as the gut microbiota. In healthy individuals, microbiota is vital for proper digestive functioning, the synthesis of certain vitamins, and protecting the body against infections by external bugs. Infants are particularly susceptible to orally acquired infections, which is traditionally attributed to their underdeveloped immune system. However, given that their gut microbiota is considerably different from that of adults, could this also be a factor? In a collaborative study, researchers at Keio University now have an answer.

The team collected microbiota from infant/neonatal (4-day-old) and adult (7-week-old) mice and introduced them into age-matched germ-free mice, which subsequently had the

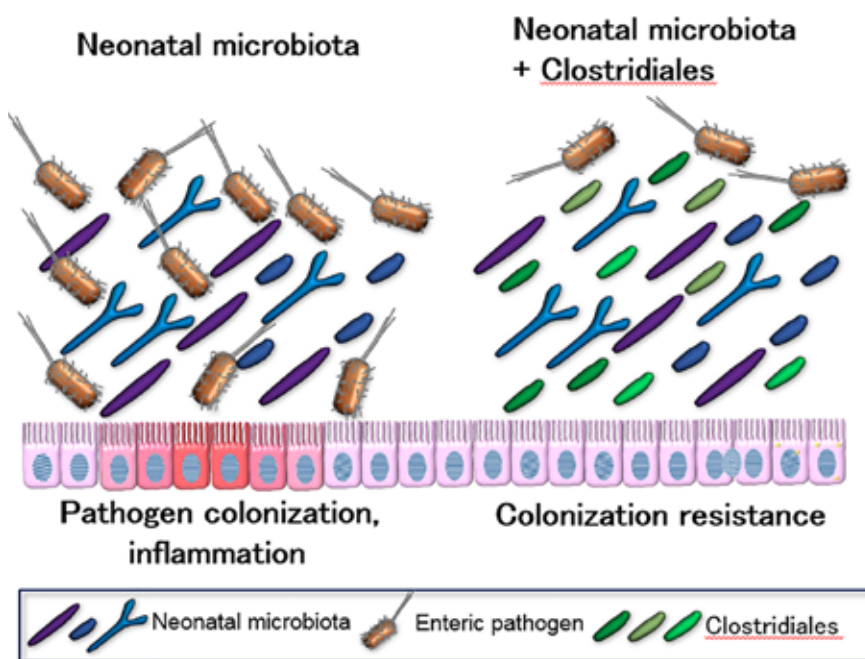
same microbiota that they were inoculated with present in their faeces.

The neonatal microbiota was devoid of two common orders of bacteria, Clostridiales and Bacteriodales. Like human infants, mice induced with neonatal microbiota were also more prone to colonization and infection by two disease-inducing bacteria. Interestingly, when these mice were supplemented with the adult microbiota, the incidence of infection was reduced. Could the reason for these differences lie in the two missing neonatal bacterial strains?

The neonatal microbiota mice were then supplemented with either Clostridiales or Bacteriodales strains. Upon exposure to the two infectious strains of bacteria, it was now seen that only the Clostridiales strain could protect the mice against a gastro-intestinal

infection. Modulation of their immune system did not affect their susceptibility to infection. The importance of the Clostridiales species was further highlighted by the fact that the neonatal microbiota played a role in harbouring this strain in later stages of life.

The researchers conclude that, “neonatal microbiota contribute to the acquisition of protective Clostridia before weaning and is a critical event that prevents the growth of enteric pathogens in the gut early in life.” The authors have previously shown the protective role played by gut bacteria in suppressing allergic airway inflammation, as well as potentiating the effects of the cholera vaccine. The regulation and maintenance of healthy gut microbiota is therefore important at all stages of life.



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2. Yun-Gi Kim, Kankanam Gamage Sanath Udayanga, Naoya Totsuka, Jason B. Weinberg, Gabriel Nunez, & Akira Shibuya. Gut Dysbiosis Promotes M2 Macrophage Polarization and Allergic Airway Inflammation via Fungi-Induced PGE₂. *Cell Host and Microbe* **15**, 95-102 (2014).
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Innovative polymer-based cancer drug delivery system

Modifying temperature and pH enhances drug delivery for cancer therapy

Successful delivery of drugs to cancerous tissues in the body remains a challenge. Current drug delivery systems are based on prolonging drug circulating in the bloodstream. However, these systems prevent the drug from entering cancer cells, which results in the loss of drug activity. Yuki Hiruta and colleagues at Keio University have devised a delivery system that can be tricked into doing so, successfully.

The research team used two unique polymers to build their system: one temperature-sensitive and one pH-sensitive. The two polymers were chemically bound together to form a diblock polymer. When several diblocks were immersed in water, they arranged themselves into micelles. The temperature-sensitive polymer being hydrophilic, or attracted to water, formed the outer “corona” of this micelle. The pH-sensitive polymer being

water repellent, positioned itself on the inside of the sphere and formed its core. Doxorubicin (DOX), an anti-cancer drug, was then loaded into the micelles.

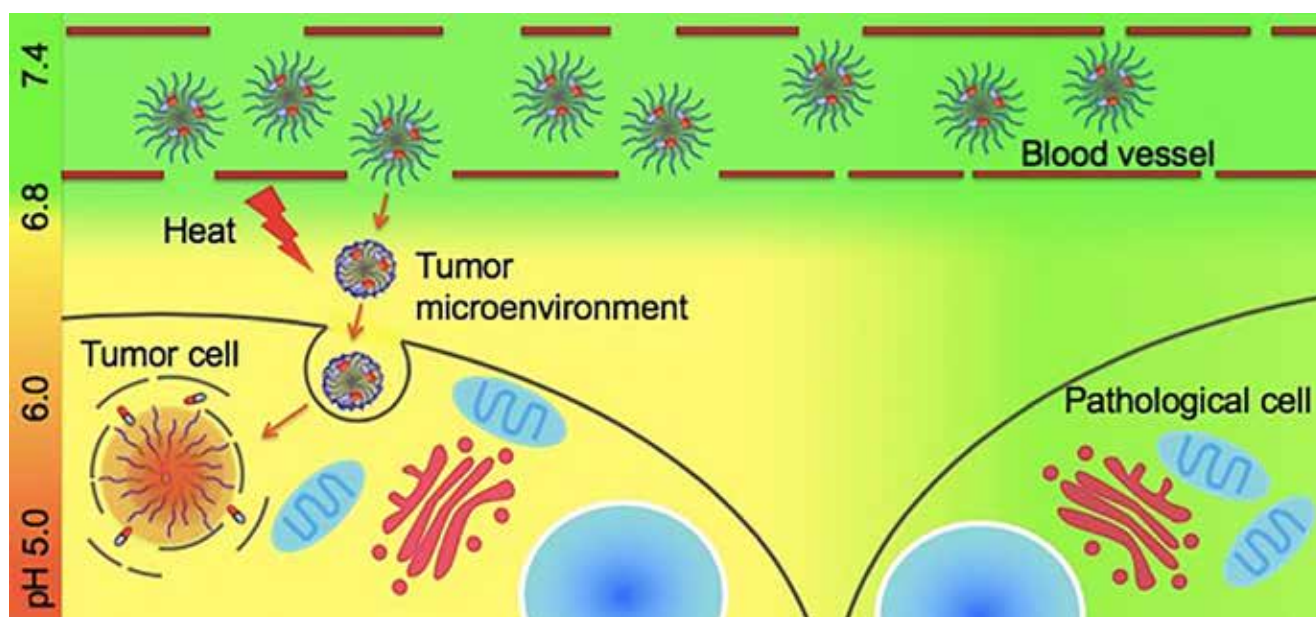
The next step was manipulating the temperature to facilitate a targeted uptake of these micelles. Cancer cells grown in the lab, were heated to 42°C. This temperature, well above normal body temperature, was enough to induce the polymer chain to change from hydrophilic to hydrophobic, resulting in several micelles clumping together. The aggregated micelles could then be easily taken up by the cancer cells. Intracellular endosomes/lysosomes have an acidic environment within, resulting in a low pH. This low pH disrupted the core polymer arrangement, releasing free DOX within the cancer cells. Free DOX cannot escape from the micelle core when a pH-resistant polymer was used for the core, indicating that pH-

sensitivity was indispensable for the release of DOX. Cells infiltrated by DOX were subsequently killed, proving the effectiveness of this system. It was also confirmed that only micelles, without DOX, had no effects on the cells, proving their safety.

“This two-step drug delivery system demonstrates potential for tumor-specific chemotherapy with the combination of local hyperthermia”, concludes the team. Since the micelles developed in this study will not enter cells at normal body temperature, these will be spared. Not only does the system devised here ensure entry of drugs into cancer cells, but also provides a strategy to specifically target them by increasing their temperature.

Reference

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A graphical representation of the micelles containing doxorubicin. © Yuki Hiruta, Keio University

Gut bacteria can cause liver cancer

Bacteria in the gut alter fat in the body which promotes the risk for liver cancer

Non-alcoholic steatohepatitis (NASH) is a common cause of liver damage, wherein there is an accumulation of fat in the liver. This condition often leads to hepatocellular carcinoma (HCC), i.e., liver cancer, at later stages. Scientists have linked bacteria in the gut, also known as gut microbiota, with the incidence of NASH-associated HCC. However, the exact nature of this relationship is unknown. Hidetsugu Saito and colleagues at Keio University and other institutions have recently

reported a mechanism by which the microbiota might induce NASH-associated HCC.

For their research, the team first induced NASH in mice. Feeding the mice with a high-cholesterol high-fat diet called STHD-01 without administration of tumor initiators not only led them to develop NASH, but also HCC within 41 weeks. As expected, the mice treated with antibiotics that reduced the microbiota showed almost no signs of HCC in their liver. This confirmed the involvement of the microbiota in the oc-

currence of NASH-associated HCC.

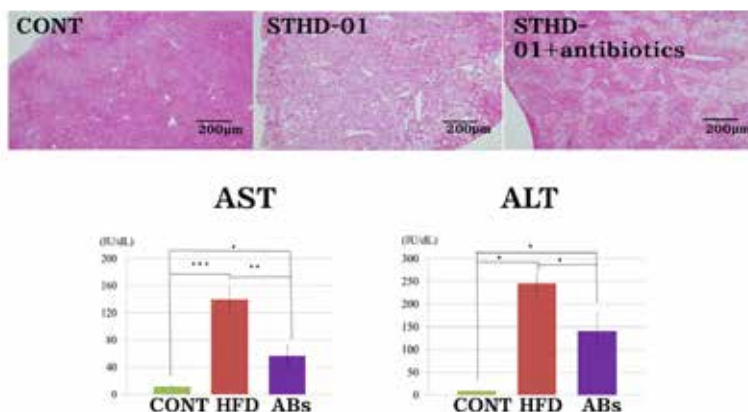
The fat content in the livers of these mice was then examined. Indeed, their livers contained high levels of certain fats such as cholesterol and bile acids. However, accumulation of these molecules was also found in the liver and feces of the antibiotic-treated mice. What changes did the gut bacteria induce then, that could have led to cancer? Upon rigorous investigation of the fat profiles, it was observed that long saturated fatty acids and secondary analogues of the bile acids were key players. Secondary bile acids were highly prevalent in the feces of HCC mice, but were depleted in the antibiotic-treated mice. It is therefore likely that the gut bacteria convert primary bile acids to secondary bile acids.

The next step was to see if secondary bile acids are directly linked to cancer. For this purpose, liver cells grown in the lab were treated with secondary bile acids. As expected, these acids activated a cancer-inducing pathway in the cells. This cancer pathway was also operational in the livers of STHD-01 fed mice.

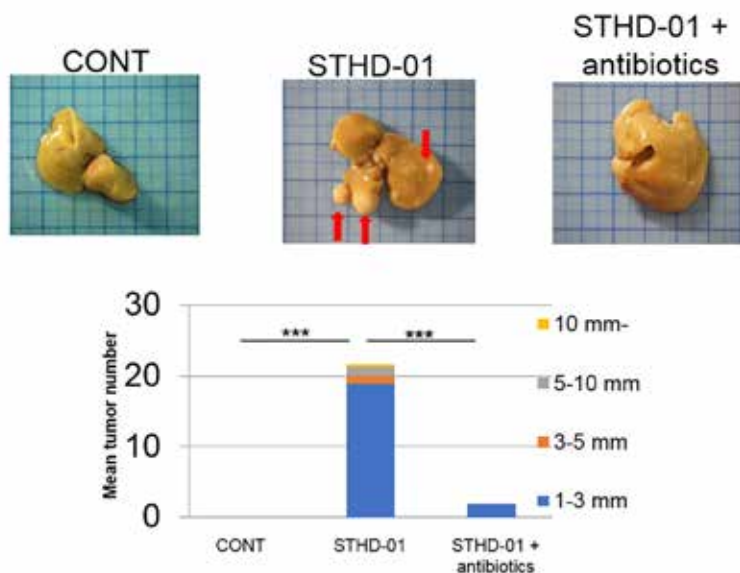
This study revealed a novel mechanism by which the gut microbiota can modulate the normal metabolism of fat to induce cancer. Patients suffering from NASH, who already have a high proportion of bile acids in their liver, are at a higher risk of developing HCC because their gut bacteria will convert those bile acids to their toxic counterparts. Monitoring gut bacteria closely in NASH patients might reduce this risk.

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Liver pathology and enzymes (9w) © Shoji Yamada, Keio University



Number of tumors (41w) © Shoji Yamada, Keio University

Genes and congenital disorders

Mutations in one gene can manifest as a multi-organ disease

CHARGE syndrome is a rare congenital condition. It results in a varied set of structural anomalies in the body, especially around the head and face. A conundrum in the world of genetics is how in conditions such as CHARGE, mutations in one single gene can lead to such a diverse set of abnormalities. Jun Kohyama and colleagues at Keio University have recently been studying the gene implicated in CHARGE syndrome, CHD7, and explained how it relates to head and facial deformities.

Given that these abnormalities arise during developmental stages of the fetus, the team first employed neuroepithelial (NE) cells: these cells give rise to the central nervous system (CNS), i.e., the brain, eyes, and ears, as the fetus develops. It was first noticed that CHD7 was mandatory for the NE cells to retain their identity. When CHD7 was suppressed, the NE cells started

showing properties of other cell types. CHD7 was thus the primary factor in maintaining the CNS “lineage” of cells. How then, did CHD7 single-handedly come to regulate an entire lineage?

To assess this, Kohyama’s team performed a gene analysis. Since genes drive all the different functions in our body, those that are the direct target of CHD7 would help understand its effects better. CHD7 was found attached to a specific set of genes known as “super-enhancers” (SE). The SEs play an important role in maintaining the identity of different cell types. Thus, CHD7 binding to SE in NE cells is important for controlling the fate and development of NE cells. Another interesting function of CHD7 that was revealed was its activation of “enhancers.” These enhancers are genes that are specific for CNS development.

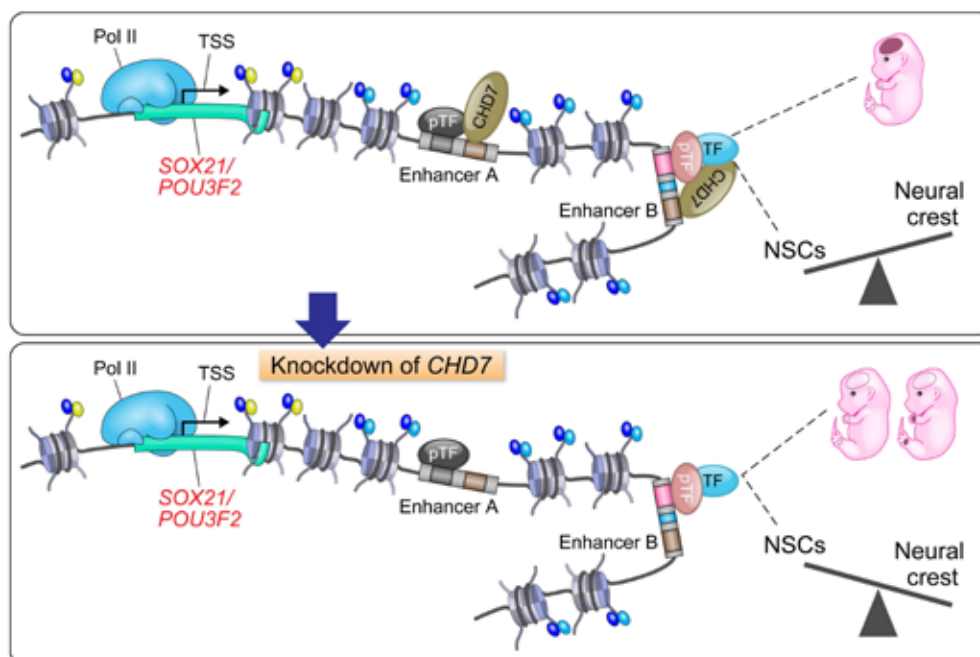
After understanding how CHD7 plays a role in maintaining the integrity of NE cells, the team finally at-

tempted to understand if it had a more specific role with regards to CHARGE. Gene analysis on CHARGE-patient derived cells revealed two candidates as its target: SOX21 and BRN2. Both of these genes are also involved in the healthy development of the nervous system.

“Our study provides insights into the longstanding question regarding the causes of multiple anomalies in CHARGE syndrome patients,” conclude the authors. They showed how anomalies in a single gene can switch the structural and functional integrity of cells during development, resulting in a multi-organ malformation. Given the advances we now have in genetic testing, this study highlights the importance of monitoring the CHD7 gene in human fetuses.

Reference

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Knockdown of CHD7 © MuhChyi Chai, Keio University

Human speech: Taking your cues in Japanese accents

Insights into how people communicate verbally by unconsciously adapting to different voices in noisy environments

Yukiko Sugiyama's interest in Japanese pitch accent began during her graduate studies in the US. "Spoken forms of languages can be roughly divided into either stress accent languages like English, or tone based languages like Chinese," explains Sugiyama. "But how do we classify pitch accent languages like Japanese? My goal is to answer this question."

Japanese employs the so-called fundamental frequency (F0) as the main cue to differentiate words that contrast only in accent. In the absence of F0, which is roughly analogous with the speech produced in whisper, listeners can use other acoustic information to infer the meaning of words. Is this true also for Japanese?

"Reports based on syllable duration and intensity — acoustics of speech — do not show if listeners can use them to distinguish words that differ only in accent," says Sugiyama. "My approach is completely different. I am focusing

on the perception of speech instead of its production."

Now, writing in *Phonetica*, Sugiyama describes the use of acoustic stimuli obtained by removing the periodicity of F0 from natural Japanese speech and substituting it with white noise, while keeping all the other acoustic properties intact, to see if a group of native Tokyo Japanese speakers would still be able to identify words.

Sugiyama selected 14 two-syllable words that differ only in respect to the presence or absence of an accent on the last syllable. Out of all the disyllabic words that differ only in accent, she selected those that cannot be produced with more than one accent type, and then restricted the set to words that would be likely familiar to participants, and excluded words that were typically used in compounds. Because the onset and offset of an utterance exhibit acoustic properties specific to their locations in a sentence, the words were embedded in the middle

of a sentence equivalent to the English 'he wants...' or 'he has a good...'.

Each listener was exposed to blocks of both natural and edited speech; the accuracy for edited speech was about 65%, compared to a little over 95% for natural speech. The fact that listeners' responses exceeded chance level indicates the presence of other cues for accent besides F0.

Analysis of the duration and amplitude of test words showed no significant differences in syllable duration between accented and unaccented words; a reliable difference in amplitude was, however, observed. The implication of this research is that amplitude acts as a secondary cue for Japanese accent, whereas duration does not play an important role.

"For practical purposes, I hope my research can help in the development of high performance hearing aids and cochlear implants."

Reference

1. Yukiko Sugiyama, Perception of Japanese Pitch Accent without F0. *Phonetica* 74, 107-123 (2017).



How do we communicate verbally by unconsciously adapting to different voices in noisy environments? © Shutterstock

THE KEIO MEDICAL SCIENCE PRIZE



The 2018 Keio Medical Science Prize Laureates



Feng Zhang

I am greatly honored and humbled to receive the Keio Medical Science Prize, which has been awarded to many brilliant scientists over the years. Having the work that my team and I have done to develop genome editing tools recognized in this way is an incredible distinction, and it inspires us to do even more to find ways to improve human health. On behalf of all the scientists that have contributed to this discovery, thank you.



Masashi Yanagisawa

I am truly honored to receive the prestigious Keio Medical Science Award and feel humbled going through the prominent list of previous laureates. My achievements would not have been possible without the teamwork of my lab members and esteemed collaborators and I would like to accept this award on behalf of my entire team. Looking back, I realize that exploratory research has always been my style ever since the start of my career. I went into the field of sleep research not because of my own planning but through simple observations of experimental phenomena. From here on out, I plan to remain free and unbiased, asking hard questions and exploring the scientific mysteries that lie before us.

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, 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 Committee reviews the nominations and submits a recommendation to the Board.
3. The Board makes the final decision and 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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