Spotlight on Research

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2018-19 Hokkaido University

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Obesity inhibits key cancer defense mechanism

Obesity could enhance cancer development while aspirin might prevent it — a new insight into potential targets for cancer prevention.

ORIGINAL ARTICLE
Sasaki A. et al., Obesity Suppresses Cell Competition-Mediated Apical Elimination of RasV12-Transformed Cells from Epithelial Tissues. *Cell Reports*, April 24, 2018.

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Obesity is a known risk factor for certain types of cancer, including colon, pancreatic and breast cancer. Studies have shown its role in promoting tumor growth and malignant progression. But its role in cancer initiation has been uncertain.

"Epithelial" cells lining the surfaces of organs have the intrinsic ability to remove potentially malignant cells from their midst. This is called the "epithelial defense against cancer" mechanism. Normally, the cells sense harmful cells and push them out by the process called cell competition.

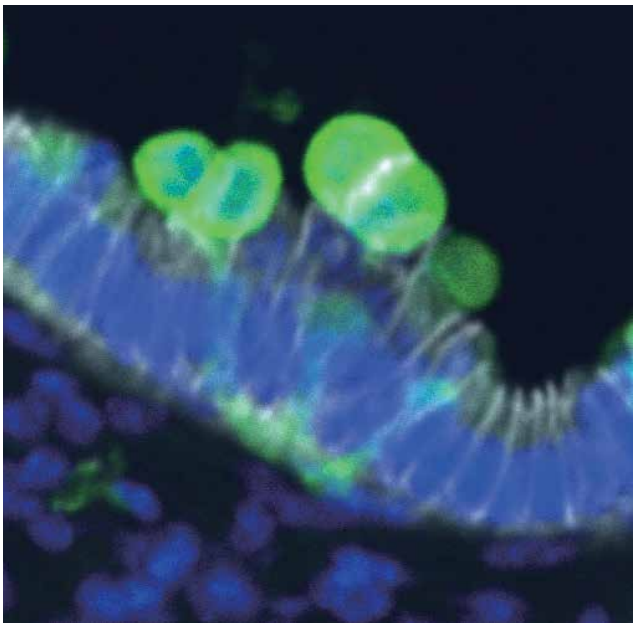
To study how obesity affects this defense mechanism, researchers from Hokkaido University and their collaborators bred mice that were designed to express a known cancer-inducing mutant protein called Ras. Epithelial cells usually remove the potentially malignant Ras-transformed cells.

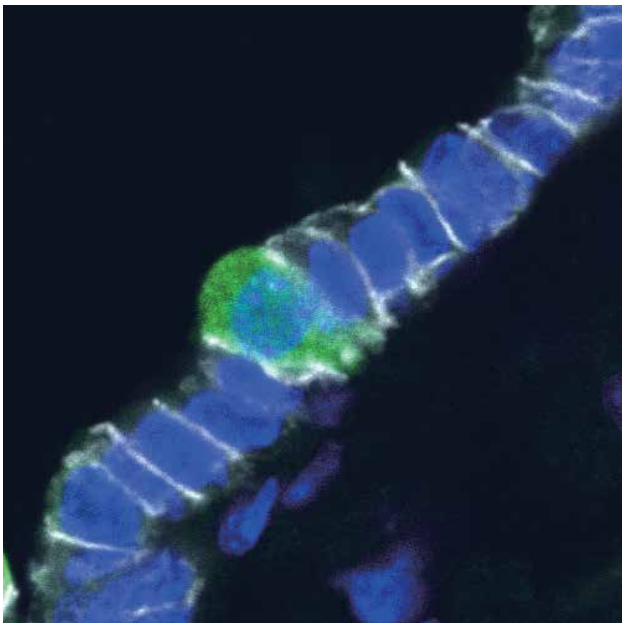
Feeding the Ras mice high-fat diets, which resulted in severe obesity, suppressed the defense mechanism and therefore increased the number of Ras-transformed cells remaining in the tissue. This suppression was seen in the intestine and pancreas, but not in the lungs. Furthermore, a month later the Ras-transformed cells developed a tumor in the pancreas of mice with the high-fat diet. The result supports previous correlations made between intestinal and pancreatic cancer and obesity, but not lung cancer.

Following experiments using the mice model and cultured cells revealed that fatty acids and chronic inflammation cause the suppression of the defense mechanism.

When mice fed a high-fat diet were treated with aspirin, known for its anti-inflammatory properties, the defense mechanism was substantially enhanced. This implies that reinforcing the epithelial defense mechanism with anti-inflammatory drugs could be utilized for cancer prevention.

"This is the first report to show that obesity and chronic inflammation can influence competitive interaction between normal cells and transformed cells. It implies other factors such as infection, smoking, sleeping patterns and aging may also affect cell competition," says Yasuyuki Fujita of Hokkaido University who led the study. ●





▼ **Transformed cells (green) were eliminated from the epithelium of the pancreas in mice fed a normal-diet (left) while the cells remained in the tissue of mice fed a high-fat diet (right). (Sasaki A. et al., *Cell Reports*, April 24, 2018)**

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Measuring the risks of extreme temperatures on public health

Heat and cold waves affect people with certain health conditions differently, highlighting the need for tailored public service risk communication.

Extreme hot and cold weather increase the number of deaths and emergency room visits but affect specific at-risk populations differently, according to new research from the U.S. and Japan.

The study, published in the journal *Risk Analysis,* found that extreme cold increased mortality and morbidity risks for people with cardiovascular and respiratory diseases, while extreme heat was risky for people with renal diseases. "We analyzed the data from Twin Cities, Minnesota, in the U.S., and found patterns with universal validity across the globe," says Matteo Convertino, an Associate Professor of Hokkaido University who led the study. The results highlight the potential for tailoring public service messages for people with specific health conditions.

While well known that extreme weather can be dangerous, not enough analysis has been done to compare specific temperatures against deaths and disease to know when public service messaging will be most effective.

Convertino teamed up with the University of Minnesota Twin Cities and the Minnesota Department of Health to determine which critical temperatures should trigger critical public health warnings. The Twin Cities are known for their harsh winters and hot, humid summers. The team gathered extreme temperature data and compared it to deaths in the city between 1998 and 2014 and emergency department visits from 2005 to 2014.

They found that the relative risk for mortality and morbidity increased generally with more extreme temperatures, but that at-risk populations were affected differently depending on their health conditions. Risk for people with cardiovascular disease or respiratory illness increased in the winter, but not significantly in the summer, which was the opposite for people with renal diseases. Diabetics showed no clear response to extreme temperature. They also found that percentile-based temperature thresholds and heat index are more appropriate than absolute temperatures for determining when to initiate emergency risk communications.

"Considering climate variability over space and time, tailored emergency risk communication programs are extremely important for informing the general public about potential health risks, such as severe heat waves or cold snaps, and how individuals can protect themselves. Our model can determine such temperature thresholds to start risk communications, which is important for saving human lives," says Convertino. ●

ORIGINAL ARTICLE
Liu Y. et al., Threshold evaluation of emergency risk communication for health risks related to hazardous ambient temperature. *Risk Analysis*, April 10, 2018.

FUNDING
U.S. Centers for Disease Control and Prevention (5H13EH001125-03).

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Global fisheries could still become more profitable despite global warming

Global commercial fish stocks could provide more food and profits in the future, despite warming seas, if adaptive management practices are implemented.

> " If we continue to work toward developing adaptive fishery management strategies, the future may be overall brighter than so far anticipated."

Researchers from Hokkaido University, the University of California, Santa Barbara (UCSB), National Center for Ecological Analysis and Synthesis, and Environmental Defense Fund (EDF) found that harvesting sustainable amounts of seafood globally over the next 75 years can lead to higher total food production and profits, even taking into consideration the fish populations which are projected to decline as the ocean warms and habitats change.

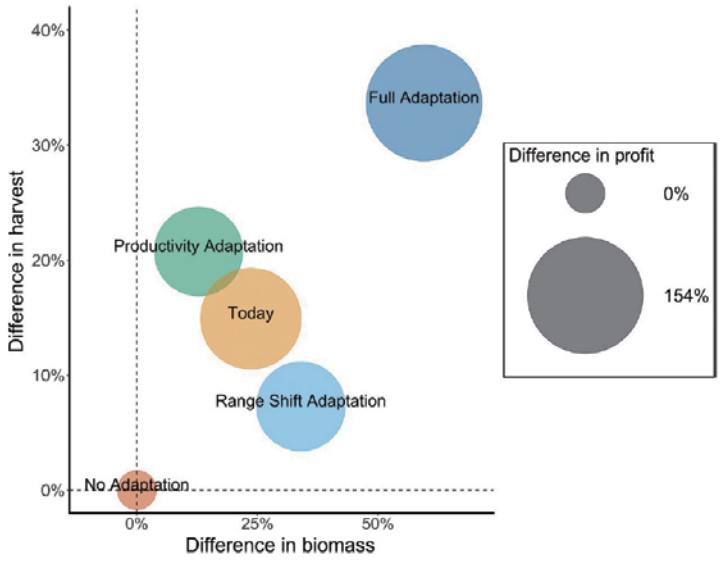
This is because, under what has been determined as the best management scenario, some major fish and shellfish stocks that are commercially harvested, broadly referred to as fisheries, will grow and become more profitable, offsetting the many others projected to shrink or even disappear. On a global average, profitability could rise by 14 billion USD and harvest by 217 million metric tons above today's levels, according to the study.

There is a catch. In the model, the growth was achieved under the projected moderate warming of 2.2°C (3.9°F) above average global temperatures by 2100. But if temperatures rise further, global fish harvest and profits are expected to decline below today's levels even with the best management in place.

The researchers say their study, published in *Scientific Advances*, conveys an important message: the oceans can continue to be a source of healthy seafood and sustainable livelihoods for billions of people, but only if action is taken to manage the stocks well and limit the carbon emissions that drive climate change.

"If we continue to work toward developing adaptive fishery management strategies, and we commit to the international agreements for climate change mitigation and emission reductions, the future may be overall brighter than so far anticipated," says aquatic ecologist Jorge García Molinos of Hokkaido University.

He noted that this potentially brighter future appears unattainable for nearly half of the 915 species and mixed groups of species analyzed in the study. The tropics will be hit especially hard, where warming is projected to be the greatest.



Fishery management simultaneously addressing both range shift and productivity changes generates much greater benefits in profits (154%), harvest (34%), and biomass (60%) than focusing on either challenge alone. (Gaines S.D., *Science Advances*, August 31, 2018)

Photo @orandfm / Adobe Stock

This work represents the first study incorporating both climate change projections and alternative management approaches into predictions of future fishery status. The authors first modelled the effect of climate warming on geographical fishery range distributions and productivity, affecting where and how much can be fished, using four contrasting climate change scenarios (rises of 1.0°C to 3.7°C in average global temperatures by 2100). For each of these climate scenarios, the team then projected how biomass, harvest and profits for each stock would change under four management scenarios. The management scenarios include: no changes to current fishing rates; varying fishing rates according to changes in stock populations; varying fishing rates according to changes in distribution patterns; or full adaptation that maintains sustainable harvest levels even as stocks fluctuate and shift throughout fishing territories.

Addressing both productivity and distribution changes through a fully adaptive management strategy led, on average, to higher yields and profits in all but the most extreme climate scenario. This is something unattainable if either challenge is addressed alone. The researchers admit that achieving such comprehensive management may be idealistic, but note that improved management of just 10% of the global stocks could still lead to a rise in global profits.

In an effort to capture a global picture, the models did not incorporate other factors that influence marine populations, including species interactions and other stressors besides warming. “Fitting more of these elements into the big picture will be important for improving predictions and should be the subject of future work,” says García Molinos.

ORIGINAL ARTICLE

Gaines S.D., Improved fisheries management could offset many negative effects of climate change. *Science Advances*, August 31, 2018.

FUNDING

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Group bonding on fire

Christopher Kavanagh looks into the psychological effects of participating in or witnessing rituals using empirical methods.

Participants in a Japanese fire-walking ritual share a drastic and painful experience. (Photo: Christopher Kavanagh)

Walking on fire, bathing in ice-cold water, traversing a continent in pilgrimage – the world is full of demanding rituals. And there are countless many ubiquitous and low-key rituals such as meditation practices or attending a regular church service.

"Rituals are in every society and a big part of human interaction. Even where societies are secular, state rituals and public festivals are an important part of the fabric of society," says Christopher Kavanagh, Postdoctoral Visiting Researcher from the University of Oxford, who is working at Professor Masaki Yuki's Social Ecology and Psychology Lab at Hokkaido University. He is studying the psychological effects of participating in or witnessing different rituals, whether rituals result in tighter bonds with fellow participants and if patterns are consistent cross-culturally.

What really distinguishes his research, however, is his emphasis on combining anthropological field research with empirical methods to provide a quantitative foundation for building and testing theory.

There is no shortage of theories within anthropology on why humans in different cultures perform rituals. However, researchers are often unable or uninterested in making predictions and testing their theories. "If we employ open science methods, such as the pre-registration of hypotheses, sharing data, etc., this will improve our predictions and make the tests clearer. We need a framework to allow other researchers to independently reproduce individual results," emphasizes Kavanagh, who wants to give a voice to anthropologists who see their research as a scientific endeavor.

He shares the empirical approach to studying society with psychologists, while classical anthropologists usually focus on long term intensive field work, interviews and their interpretation. However, he notes that "Psychologists tend to be less interested in field studies and more in experimental studies with much more controlled environments." This is where he thinks an anthropological mindset can be useful as experimental anthropologists typically strive to make things more similar to the actual world at the cost of control.

Consequently, his data are collected in multiple ways: in online questionnaires targeting specific groups, in carefully designed lab experiments using both self-report questions and implicit tasks, and from surveys and interviews collected at festivals. All data are then analyzed statistically to determine whether they lend support or conflict with specific hypothesized interactions between itemized cultural phenomena such as "pleasantness of common experience" and "preference of in-group members over out-group members."

Kavanagh elaborates: "Doing experiments in the field is messy but important." He can tell of many examples where the techniques they brought into the field produced very different results from what was anticipated by the theory. However, he suggests these are not always due to flaws of the experimental tools themselves, nor are they shortcomings in the way people respond or behave. "Sometimes we find very different patterns, so while there may be universal aspects to rituals, context matters," he explains, adding: "You don't find that by only looking at recruited students in a lab."

But instead of despairing at this messiness, Kavanagh points out that this is why collecting data in many regions and in many contexts is so important, because it can help us understand which mechanisms are universal and which are culturally specific.

And Japan is an especially important data point for him. "Japan is unique in that people report very low interest in religious identities, but it still is a highly ritualistic society," he explains. This gives him a chance to separate the effects of ritual and religious belief.

Kavanagh is part of the international "Ritual Modes Project" funded by the European Research Council and headed by Professor Harvey Whitehouse of the University of Oxford. The project also includes historians trying to apply a quantitative approach to the analysis of rituals recorded in historical cultures. In addition, there are psychologists on the project interested in employing rituals as interventions where people are at risk of engaging in (e.g., terroristic) self-sacrifice to help them bond to different kinds of groups. While he acknowledges the importance of such work, Kavanagh restrains that such efforts are still in preliminary stages and that "I feel that it might be difficult considering our current limitations in understanding ritual psychology." Nevertheless, he thinks that it is important to inform people about the power rituals have over us so that people are better equipped to understand them and avoid being exploited. "Understanding the basic psychology of rituals is important to understanding human society." ●

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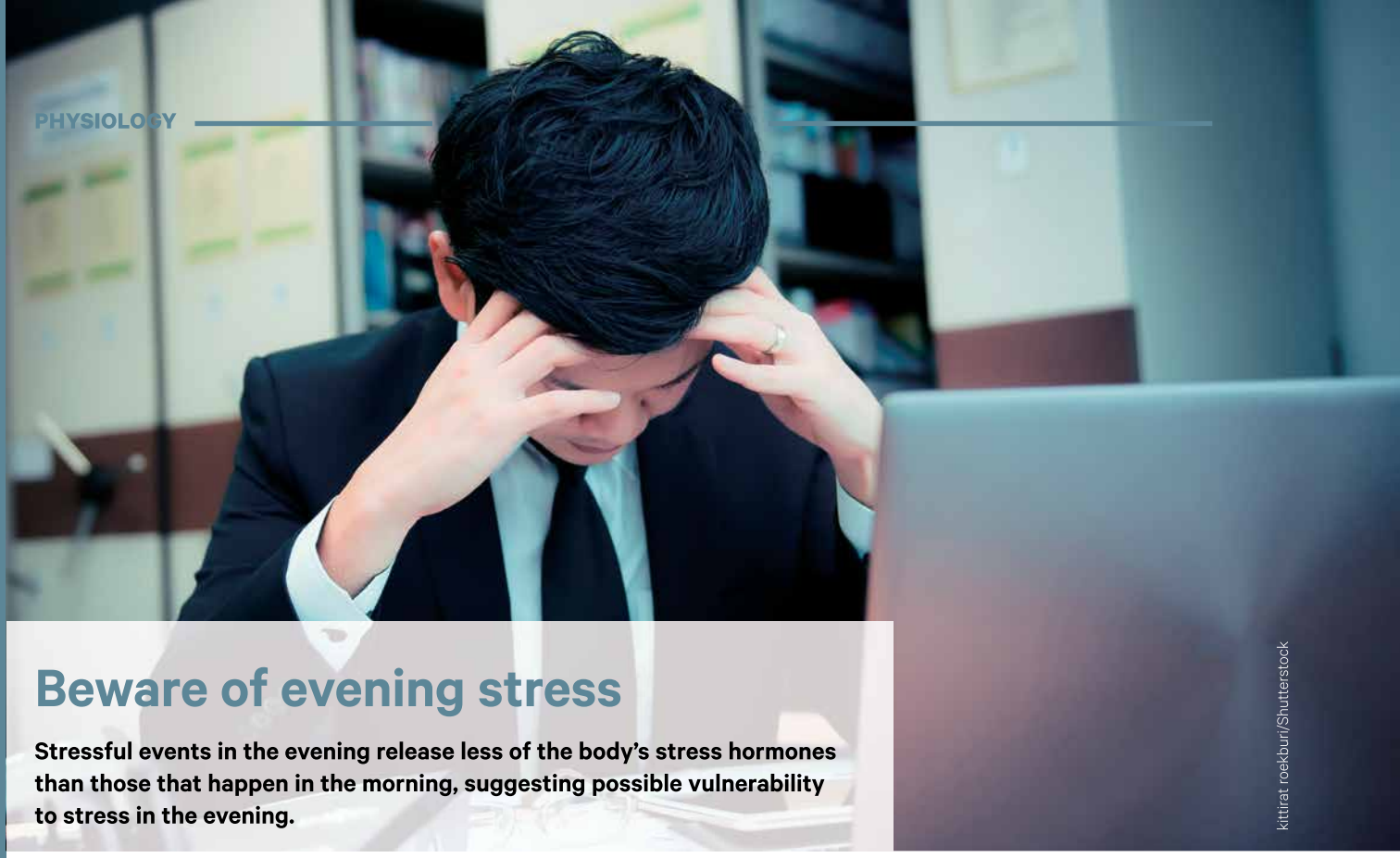

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Beware of evening stress

Stressful events in the evening release less of the body's stress hormones than those that happen in the morning, suggesting possible vulnerability to stress in the evening.

The body's central system reacts less strongly to acute psychological stress in the evening than it does in the morning, according to research conducted at Japan's Hokkaido University.

In the study published in the journal *Neuropsychopharmacology Reports*, medical physiologist Yujiro Yamanaka and his colleagues recruited 27 young, healthy volunteers with normal work hours and sleep habits to find out if the "hypothalamic--pituitary-adrenal" (HPA) axis responds differently to acute psychological stress according to the time of day.

The HPA axis connects the central nervous and endocrine systems of the body. Cortisol, the primary stress hormone in humans, is released for several hours when the HPA axis is activated by a stressful event. This helps provide the body with energy in the face of a perceived need for fight or flight. Cortisol levels are also regulated by a master circadian clock in the brain, and are normally high in the morning and low in the evening.

The team first measured the diurnal rhythm of salivary cortisol levels from the volunteers to establish a baseline. The volunteers were then divided into two groups: one that was exposed to a stress test in the morning, two hours after their normal waking time, and another that was exposed to a stress test in the evening, ten hours after their normal waking time.

The test lasted for a period of 15 minutes and involved preparing and giving a presentation in front of three trained interviewers and a camera, and conducting a mental arithmetic. Saliva samples were taken half an hour before starting the test, immediately after, and at ten-minute intervals for another half hour.

The researchers found that salivary cortisol levels increased significantly in the volunteers that took the stress test in the morning while no such response was observed in those that took the test in the evening. The volunteers' heart rates on the other hand, an indicator of the sympathetic nervous system which immediately responds to stress, did not differ according to when the test was taken.

Yujiro Yamanaka commented "The body can respond to the morning stress event by activating the HPA axis and sympathetic nervous system, but it needs to respond to evening stress event by activating the sympathetic nervous system only. Our study suggests a possible vulnerability to stress in the evening. However, it is important to take into account each individual's unique biological clock and the time of day when assessing the response to stressors and preventing them."

ORIGINAL ARTICLE

Yamanaka Y., Motoshima H., and Uchida K. HPA axis differentially responses to morning and evening psychological stress in healthy subjects. *Neuropsychopharmacology Reports*, November 21, 2018.

FUNDING

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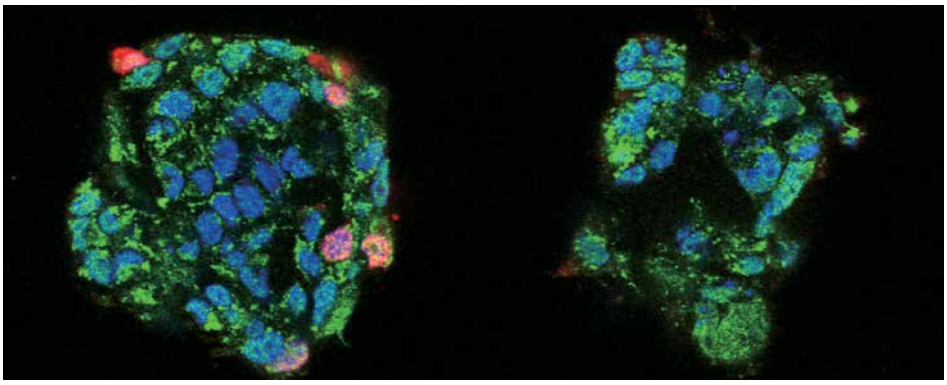
Key molecule for flu infection identified

Scientists have discovered the key receptor molecule that enhances the infection of the influenza A virus, providing a novel target for anti-flu drug development.



Human bronchial epithelial cells cultured with (right) or without (left) a calcium channel blocker (CCB) prior to exposure to IAV. Red signals show infected and replicated IAV. Treatment with CCB significantly suppressed IAV infections. (Fujioka Y. et al., *Cell Host & Microbe*, May 17, 2018)

Viral infection starts when a virus particle attaches to a receptor molecule on the surface of a host cell. The virus particle then hijacks cellular machinery to enter the cell and replicate itself, establishing the infection. The key receptor molecule for the influenza A virus (IAV) has remained unidentified despite decades of research.

A research team led by Professor Yusuke Ohba of Hokkaido University previously demonstrated that changes in Ca2+ concentration in host cells play an important role in IAV infections.

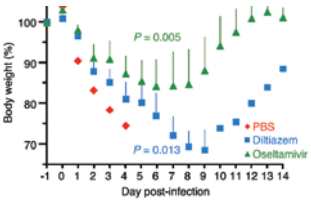
In the latest study published in *Cell Host & Microbe*, the same team has discovered that the Ca2+ channel, a transmembrane protein that allows Ca2+ to move across the cell membrane, is the key receptor molecule for IAV infections. Furthermore, treating human cells with calcium channel blockers (CCBs), which are commonly used as anti-hypertension drug, significantly suppressed IAV infections.

In experiments using cultured human cells, the team found that IAV binds to the Ca2+ channel on the cell's surface to trigger an influx of Ca2+, followed by entry of the virus and infection. Knocking down Ca2+ channels inhibited IAV-induced Ca2+ influx and virus entry. They also revealed that sialic acid on the Ca2+ channel is crucial for the virus to bind.

Finally, the team tested the effect of CCB on IAV infections using mice. When they treated the animals with CCB intranasally, a significant and dose-dependent reduction in the amount of replicated viruses was observed. When the animals were treated with high amounts of IAV, administration of CCB significantly prolonged survival and allowed weight recovery of the survivors whereas the untreated group died within five days.

"There were cases when the suppressive effect of CCB on IAV infections was comparable to that of an existing anti-flu drug. We expect that the interaction between IAV and the Ca2+ channel could be a novel and important target for future drug development," says Yusuke Ohba. ●

Cultured monkey cell showing IAV-induced Ca2+ influx (oscillations). (Fujioka Y. et al., *Cell Host & Microbe*, May 17, 2018)



Changes in body weight after IAV infection. Mice untreated with CCB died within five days after IAV infection while the group treated with CCB (diltiazem) survived and recovered their body weights, as did a common anti-flu drug oseltamivir-treated group. (Fujioka Y. et al., *Cell Host & Microbe*, May 17, 2018)

ORIGINAL ARTICLE

Fujioka Y. et al., A Sialylated Voltage-Dependent Ca2+ Channel Binds Hemagglutinin and Mediates Influenza A Virus Entry into Mammalian Cells. *Cell Host & Microbe*, May 17, 2018.

FUNDING

Grants-in-aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan (#26115701 and #15H01248), Japan Society for the Promotion of Science (#26293041 and #16H06227), Japan Agency for Medical Research and Development (JP17fk0108124j0601), Mochida Memorial Foundation for Medical and Pharmaceutical Research, the Waksman Foundation of Japan, the Sumitomo Electric Group Corporate Social Responsibility Foundation, and SENSHIN Medical Research Foundation.

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The right squeeze for quantum computing

A new theoretical model involving squeezing light to just the right amount is bringing us closer to a new era of computing.

Scientists at Hokkaido University and Kyoto University have developed a theoretical approach to quantum computing that is 10 billion times more tolerant to errors than current theoretical models. Their method brings us closer to developing quantum computers that use the diverse properties of subatomic particles to transmit, process and store extremely large amounts of complex information.

Quantum computing has the potential to solve problems involving vast amounts of information, such as modelling complex chemical processes, far better and faster than modern computers.

Computers currently store data by coding it into "bits." A bit can exist in one of two states: 0 and 1. Scientists have been investigating ways to employ subatomic particles, called "quantum bits," which can exist in more than just two separate states, for the storage and processing of much vaster amounts of information. Quantum bits are the building blocks of quantum computers.

One such approach involves using the inherent properties in photons of light, such as encoding information as quantum bits into a light beam by digitizing patterns of the electromagnetic field. But the encoded information can be lost from light waves during quantum computation, leading to an accumulation of errors. To reduce information loss, scientists have been experimenting with "squeezing" light. Squeezing is a process that removes tiny quantum-level fluctuations, referred to as noise, from an electromagnetic field. Noise introduces a certain level of uncertainty into the amplitude and phase of the electromagnetic field. Squeezing is thus an efficient tool for the optical implementation of quantum computers, but the current usage is inadequate.

In a paper published in the journal *Physical Review X*, Akihisa Tomita, an applied physicist at Hokkaido University, and his colleagues suggested a novel way to dramatically reduce errors when using this approach. They developed a theoretical model that uses both the properties of quantum bits and the modes of the electromagnetic field in which they exist. The approach involves squeezing light by removing error-prone quantum bits, when quantum bits cluster together.

This model is ten billion times more tolerant to errors than current experimental methods, meaning that it tolerates up to one error every 10,000 calculations.

"The approach is achievable using currently available technologies, and could further advance developments in quantum computing research," says Akihisa Tomita of Hokkaido University. ●

ORIGINAL ARTICLE
Fukui K. et al., High-Threshold Fault-Tolerant Quantum Computation with Analog Quantum Error Correction. *Physical Review X*, May 25, 2018.

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FUNDING
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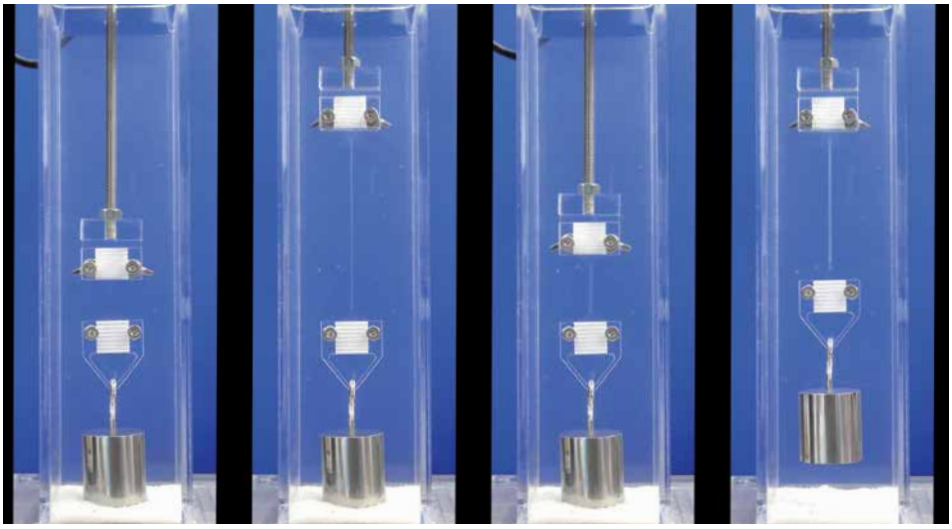
Self-growing materials that strengthen in response to force

A strategy inspired by the process responsible for muscle growth could lead to the development of stronger, longer-lasting materials.



This image depicts the process in which double-network hydrogels were stretched, leading to the strengthening of the material. (Gong J. P. et al., *Science*, February 1, 2019)

Watch the video to learn about the new gel.

Hokkaido University researchers have developed a strategy to fabricate materials that become stronger in response to mechanical stress – mimicking skeletal muscle growth. Their findings, published in the journal *Science*, could pave the way for long-lasting materials that can adapt and strengthen based on surrounding conditions.

The strategy was inspired by the process that makes human skeletal muscles become stronger. As a result of strength training at the gym, for example, muscle fibres break down, encouraging the formation of new, stronger fibres. For this to happen, the muscles must be supplied with amino acids, the building blocks of proteins, which join together and form muscle fibres.

Hokkaido University's Jian Ping Gong and her research team developed a strategy employing 'double-network hydrogels' that emulates the building process of skeletal muscles.

Double-network (DN) hydrogels are a soft, yet tough material formed of about 85 weight percent water and two types of polymer networks: one rigid and brittle, and the other soft and stretchable.

The team placed a double-network hydrogel inside a solution containing molecules, called monomers, which can be joined to form larger compounds called polymers. This solution emulates the role of circulating blood carrying amino acids to skeletal muscles.

Applying tensile force (stretching) to the hydrogel causes some of its rigid and brittle polymer chains to break. This leads to the generation of a chemical species called 'mechanoradicals' at the ends of the broken polymer chains. These mechanoradicals can trigger the joining up of the monomer absorbed into the hydrogel from the surrounding solution into a polymer network, strengthening the material.

With successive stretching, more breaking down and building up occurs. Through this process, the hydrogel's strength and stiffness improved 1.5 and 23 times respectively, and the weight of the polymers increased by 86%. The team was further able to tailor the material's response to mechanical force by using a specific monomer that altered the gel's reaction to heat; heated at high temperatures, the gel's surface became more water-resistant.

Gong explained "Since many types of DN gels have similar mechanical features, this process could be applied to a wide range of gels, expanding the range of potential applications." ●

ORIGINAL ARTICLE
Gong J. P. et al., Mechanoresponsive self-growing hydrogels inspired by muscle training, *Science*, February 1, 2019

FUNDING
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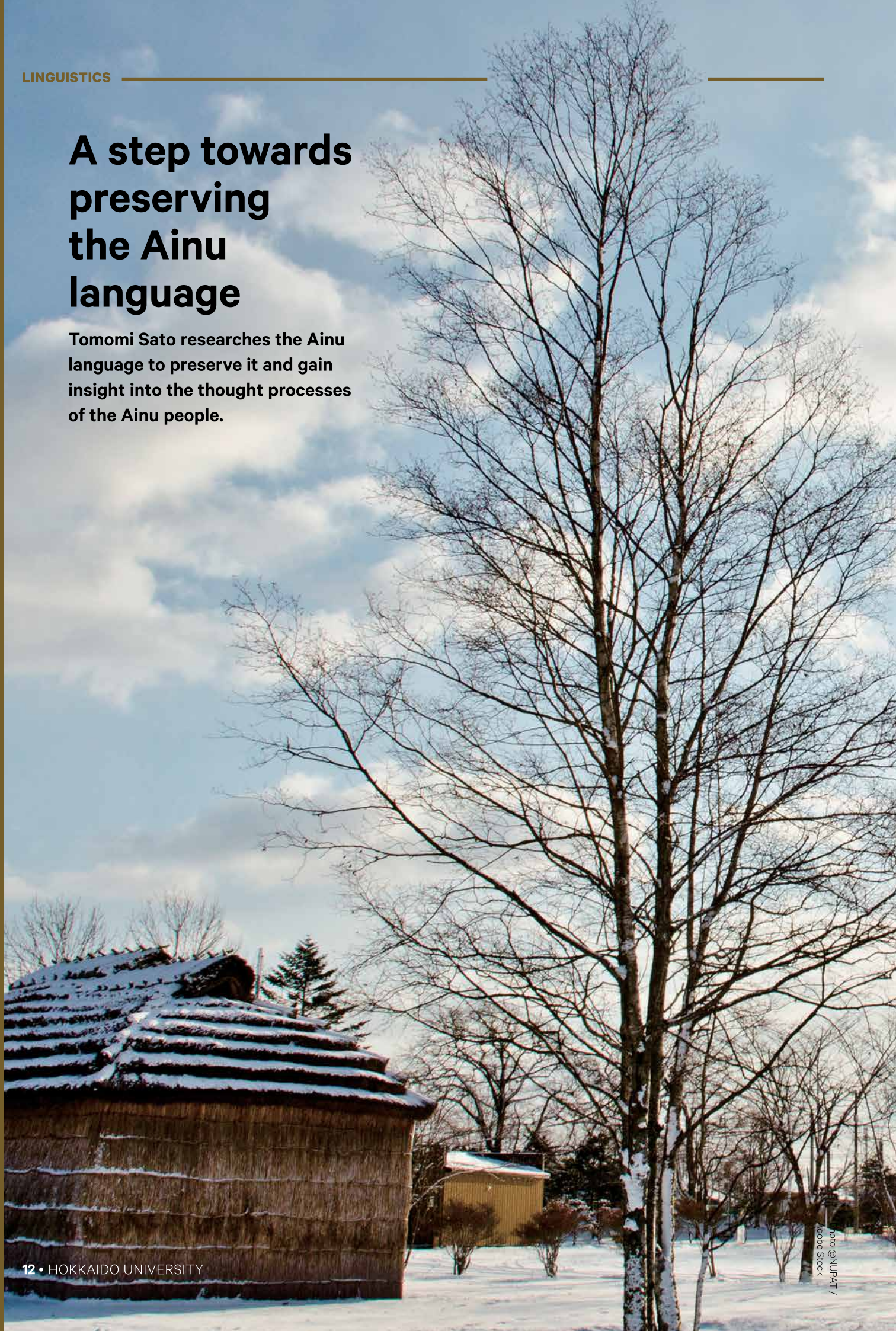
A step towards preserving the Ainu language

Tomomi Sato researches the Ainu language to preserve it and gain insight into the thought processes of the Ainu people.



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The Ainu people are the indigenous population of Hokkaido, Sakhalin and the Kuril islands. Having suffered a great deal of discrimination in modern history, there have been many recent efforts to preserve Ainu culture and its endangered language. The first law to protect the rights of the Ainu people was established in 1899, although the name of that law ("The Former Savage Preservation Law") as well as its historical evaluation are now controversial. In 1997 came the "New Ainu Law," and in 2005 Hokkaido University established its Center for Ainu and Indigenous Studies, created to deepen our understanding of Ainu culture as well as to increase awareness and appreciation of indigenous peoples.

Tomomi Sato, an affiliate of the center, is an example of someone involved in preserving Ainu culture, especially its language. Specializing in linguistics and the Ainu language, he estimates that most speakers of the language are of an elderly age. Although this makes it increasingly more difficult to conduct research about the Ainu language, Sato has yet to fully analyze all of the recordings he has on file. It is his hope that his studies will be of use to people looking to learn the Ainu language; and indeed in 2008 he published a book titled "The Foundation of Ainu Grammar" for just that purpose.

For most of its history, Ainu was an unwritten language, and other than a few notable occasions (such as the "Collection of Ainu Mythologies" published in 1923) the language was not properly recorded in writing until fairly recently. For this reason, there is no set orthography in which Ainu should be transcribed. It is usually written either in Roman letters or Japanese katakana, but as Sato explained – perhaps it is more appropriate to use Roman letters since it is a more neutral way to portray words, whereas a transcription into Japanese katakana may in a way be relating it to the Japanese language.

Not unlike studying languages widely spoken, analyzing the Ainu language gives us an insight into the thought processes and mindset of the Ainu people. For example, word structures in Ainu are usually quite complex. *K-e-yay-ko-tuyma-si-ram-suy-pa* in Ainu means "I'm thinking about..." However, a direct translation into English would actually be "I swing my mind to distant places many times by myself about something," conjuring up the image that Ainu people truly do think about something when they say it.

The lexicon of the Ainu language only begins to touch upon the subject, Sato's recent research surrounds the linguistic phenomenon of "noun incorporation." Noun incorporation is the combination of a verb and a noun to create a compound verb. An example in English would be the word "to baby-sit." Noun incorporation is uncommon in English (and also relatively rare in Japanese), but this is not the case for the Ainu language. Simple examples of this include *cep-koyki* – "fish catch" – or more naturally "to catch fish." As mentioned before, Ainu words are often complex and full of imagery. An example of this is *sir-pirka*, which is also an example of noun incorporation and means "the surroundings are favorable" – or simply "it's fine." The rich imagery of the language is further exemplified by the incorporated verb *teke-pase* – "(his) hand is heavy" – meaning "he moves slowly because of his age." This last example is also worthy of note since it contains the nominal stem, *teke* "one's hand," which has its possessor on the outside of its grammatical element. This type of linguistic construction is called "morphological stranding" and is very rare for a language to have.

Although previously considered a "primitive" language, it is by no means such from a linguistic point of view. In Sato's words, "Language can provide us with strong empirical evidence that human beings are the same in their basic capacity and must not be discriminated according to their ethnicity. But even today, outside linguistics, and partly even inside linguistics, there still remains strong prejudice and a discriminative attitude to unfamiliar minor languages and cultures."

The intricacy of the Ainu language in turn highlights the complexity of Ainu culture. Subsequently, it draws out the diversity of culture in Hokkaido, showing that Hokkaido too has a rich history worth re-discovering. ●

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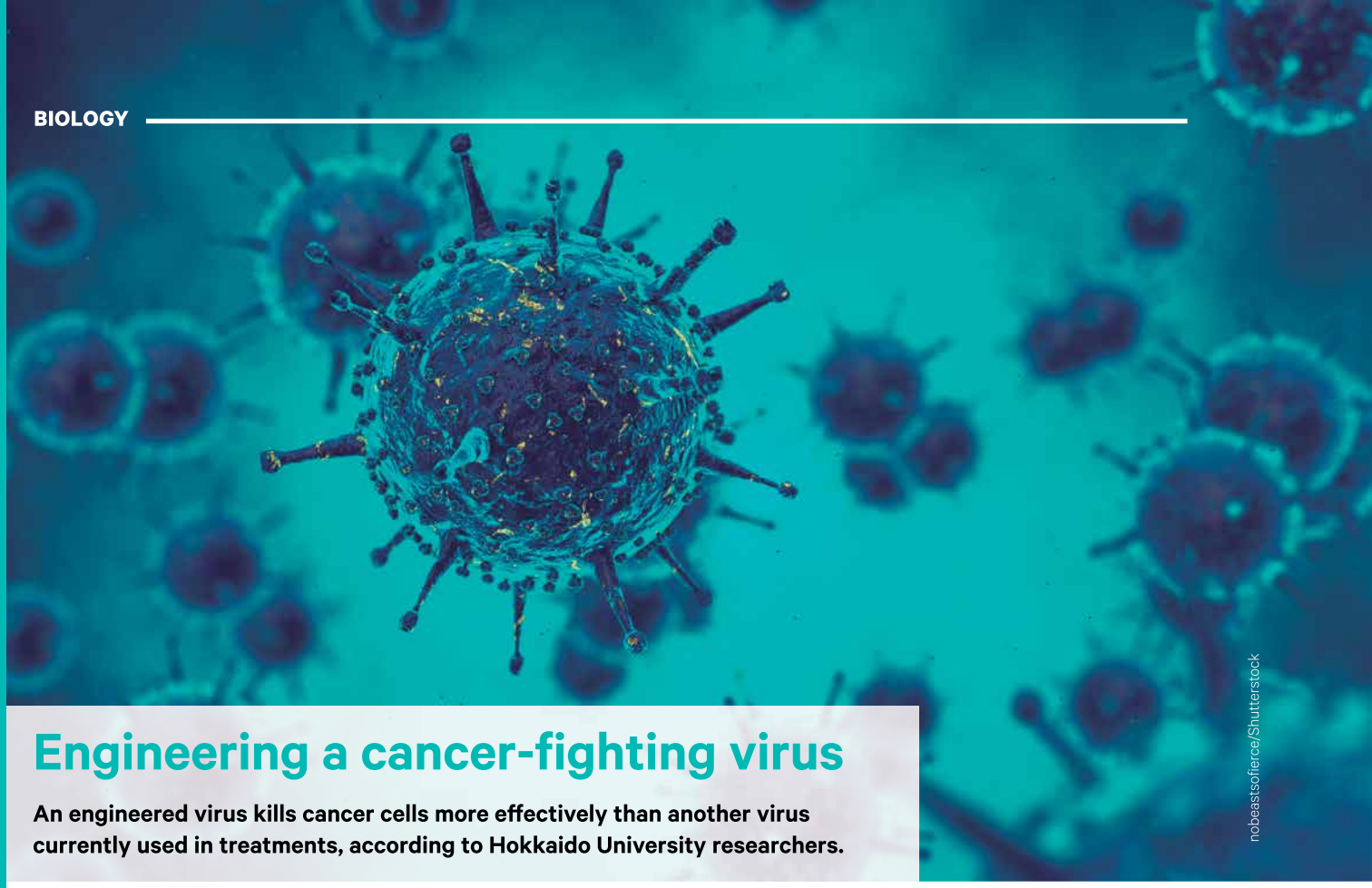

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Engineering a cancer-fighting virus

An engineered virus kills cancer cells more effectively than another virus currently used in treatments, according to Hokkaido University researchers.

Hokkaido University researchers have engineered a virus that selectively targets and kills cancer cells. The virus, called dl355, has an even stronger anticancer effect than another engineered virus currently used in clinical practice, according to a study published in the journal *Oncology Reports*.

Molecular oncologist Fumihiro Higashino and colleagues deleted a gene involved in viral replication, called E4orf6, from a type of adenovirus. The team previously discovered that E4orf6 stabilizes a type of mRNA called ARE-mRNAs in the infected cells enabling viral replication. ARE-mRNAs are known to be stable in stressed cells and cancer cells, but rapidly degrade in normal cells.

In laboratory tests, they found that their modified adenovirus, called dl355, replicated and increased its number significantly more in cancer cells than it did in normal cells. Higashino explains "The E4orf6-lacking virus relies on the stable ARE-mRNAs in cancer cells for its replication."

Some viruses can be used to treat cancers, as they replicate within the cells until they burst and die. The researchers infected several types of cultured cancer cells with 100 dl355 virus particles per cell and found that nearly all the cancer cells died within seven days. In contrast, most normal cells infected with the virus did not die, even after seven days. Several cancer cell lines managed to survive low doses of dl355, but all cancer cells were killed by the virus as the dose was increased. Tumor growth was also significantly suppressed when dl355 was administered to human tumor cells grown in mice.

Finally, the team compared the anticancer effects of dl355 with another anticancer adenovirus currently used in clinical practice, called dl1520. dl355 replication was higher in all cancer cell lines tested, including cervical and lung cancer cells, and was better at killing all but one type of cancer cell, compared to dl1520. Both viruses only killed very few normal cells.

The findings suggest that dl355 has potential to be an effective anticancer treatment, the team concludes. They suggest enhancing the stabilization of ARE-mRNAs in cancer cells could even further strengthen its effect, but Higashino notes that further research is required. "While we think dl355 has the potential to be an effective treatment method in dealing with many types of cancers, much more research needs to be done. When we think of a timeline, at least five more years of further research may be required, possible more, on top of clinical trials," Higashino noted.

ORIGINAL ARTICLE
Yanagawa-Matsuda, et. al, Oncolytic potential of an E4-deficient adenovirus that can recognize the stabilization of AU-rich element containing mRNA in cancer cells, *Oncology Reports*, November 12, 2018

FUNDING
Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan (26293423 and 23659928).

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Genetics doesn't matter much in forming society

New insight into a decade-long debate indicates that genetics isn't as important as once thought for the evolution of altruistic social behaviour in some organisms.

▲ The sweat bee (*Lasioglossum baleicum*) used in the study commonly forms a eusociety.

Photo © Norihiro Yagi

This is the first empirical evidence that suggests social behaviour in eusocial species—organisms that are highly organized, with divisions of infertile workers—is only mildly attributed to how related these organisms are to each other.

This finding is contrary to earlier theories that attribute altruistic selfless behaviour in eusocial species to genetic relatedness and a want to ensure the propagation of their genes. In some insect species, genetic similarity is higher between sisters than between a sister and its own offspring, and this has been considered the key driver in the formation of eusocieties.

When evolutionary biologist Eisuke Hasegawa and his colleagues at Hokkaido University studied the foraging and nesting behaviours of the eusocial sweat bee (*Lasioglossum baleicum*), they found that their fitness—an organism's reproductive success and propagation of its genes—was more a result of the bees' cooperative behaviour than it was a result of their genetic similarity.

The team investigated five aggregations of sweat bee nests in various areas on the Japanese island of Hokkaido. In each aggregation, there were two types of nests: those in which multiple females worked together to take care of the offspring of a single queen, and those in which a mother bee took care of her offspring on her own.

Queen bees lay several eggs at a time. They hatch as predominantly infertile females, who grow to become workers. The team studied how often and for how long each adult female left the nest to forage over a 12-hour period.

They found that the females working in the cooperative nests foraged more often than the females from the solitary nests. In addition, solitary nests were devoid of adult females much more often than social nests, leaving the nests more vulnerable to predators.

Ants are the main predator of sweat bees. A female sweat bee protects the offspring in her nest from scout ants, which can recruit many other ants to attack, by plugging the nest opening with her head. This is why solitary adult females can only leave their nests for short periods of time. Cooperative nests, on the other hand, are more efficiently defended.

Individual females in social nests are known to have higher fitness than solitary females, meaning that social bees are more successful in propagating their genes. The team has found that 92% of the increase in fitness can be attributed to the benefit of grouping—efficient foraging and defense—while the rest is due to the genetic similarity between the individuals.

"There has been a decade-long debate among scientists as to whether genetic similarity or the benefit of grouping is the primary drive of sociality. Our study could help reveal some of the factors behind the evolution of cooperation, including cooperation between humans, by quantifying how much cooperative behaviour contributes to the increased fitness of altruistic individuals in a group," says Hasegawa. ●

ORIGINAL ARTICLE
Ohkubo Y, Hasegawa E. et al., The benefits of grouping as a main driver of social evolution in a halictine bee. *Science Advances*, October 3, 2018.

FUNDING
Grants-in-aid from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (26440228, 15H04420, 18H02502).

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ICReDD is situated in the Creative Research Institution building at Sapporo Campus.

THE INSTITUTE FOR CHEMICAL REACTION DESIGN AND DISCOVERY (ICReDD) LAUNCHED

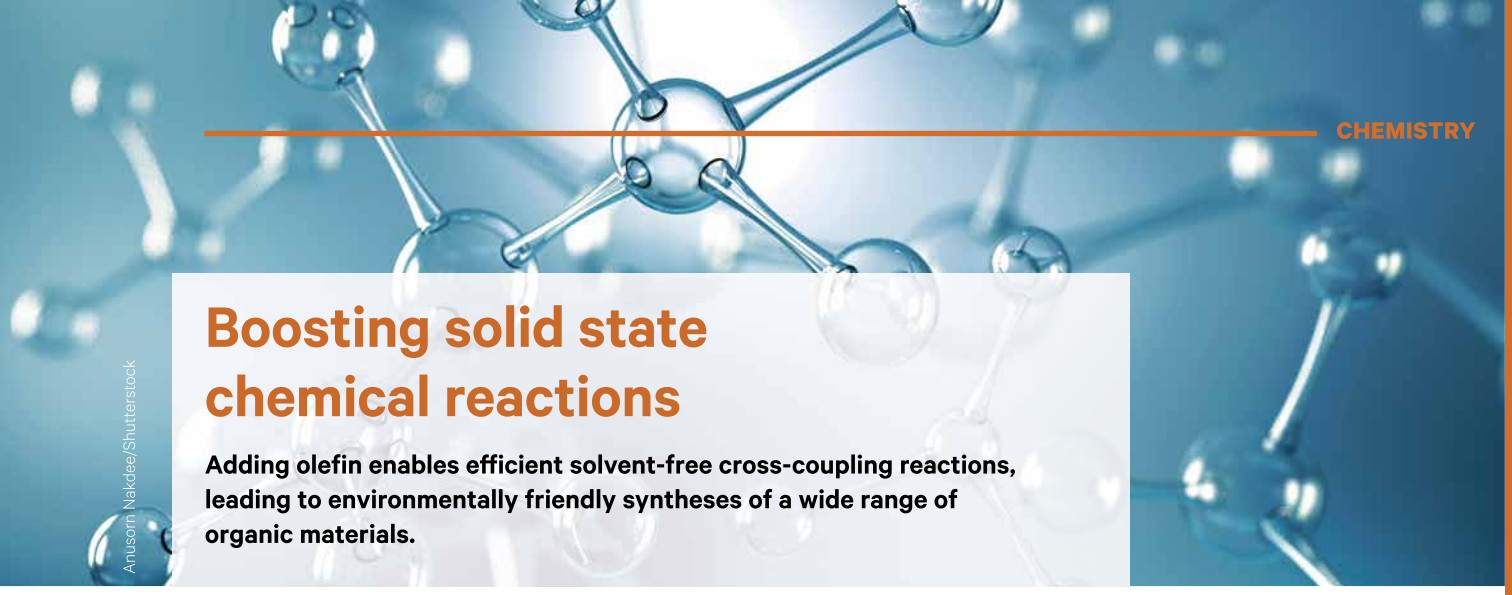
Hokkaido University launched the Institute for Chemical Reaction Design and Discovery (ICReDD) in 2018 as part of the World Premier International Research Center Initiative (WPI) by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan. The institute aims to conduct research to acquire an in-depth understanding of complex chemical reactions and to accelerate the efficient development of new chemical reactions. Professor Satoshi Maeda from the Faculty of Science has been appointed the center director. The WPI will support the program for ten years, providing seven hundred million yen each year.

Finding new chemical reactions is indispensable for generating advanced materials and chemicals as well as reducing energy consumption and environmental burdens. So far, such development requires a trial-and-error approach which tends to be time-consuming, laborious, expensive, and inefficient. The new institute will tackle this issue by integrating the fields of computational science, information science, and experimental science.

The institute aims to build an international research environment with 30% of the researchers from overseas. It has already appointed three internationally renowned scientists from the United States, France, and Germany as Principal Investigators (PIs) as well as eleven from Japan.

Professor Maeda says “Fundamentally new scientific approaches have been much anticipated” for the development of new chemical reactions. “We are excited to start new challenges to provide innovative solutions through collaborations.”

ICReDD members at Hokkaido University gathered to prepare for the international kick-off meeting.



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Boosting solid state chemical reactions

Adding olefin enables efficient solvent-free cross-coupling reactions, leading to environmentally friendly syntheses of a wide range of organic materials.

A cross coupling reaction is typically performed in an organic solvent, and leads to the production of a large amount of solvent waste, which is often harmful to the environment. A new strategy developed by Hokkaido University researchers in Japan opens the door for more environmentally friendly solvent-free solid-state cross coupling processes using mechanochemistry. It also has many potential applications, including the development of organic materials found in solar cells and light-emitting diodes.

Cross-coupling reactions proceed efficiently in the presence of a metal catalyst to form a wide range of organic molecules with novel properties. In particular, the Nobel-prize-winning palladium-catalysed cross-coupling reactions have long been used in the synthesis of natural products, in medicinal chemistry, and in polymer and materials science.

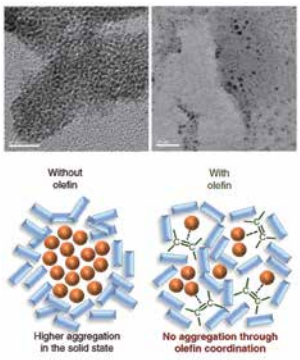
To reduce environmental waste, researchers have been looking at methods to enable efficient organic syntheses that use less or no solvent. In this context, "solid-state organic transformations" have received considerable research attention, but improving the efficiency of cross-coupling reactions in solid media remains a challenge.

In a study published in *Nature Communications*, Hokkaido University organic chemists Koji Kubota, Hajime Ito and their colleagues developed a new strategy for solid-state palladium-catalysed cross-coupling reactions using mechanochemistry that enables efficient solvent-free synthesis of organic materials.

Two solid organic materials were placed inside a ball milling jar that contains a stainless steel grinding ball. A palladium-based catalyst was also added. The jar undergoes a shaking process that causes the ball to grind the solid compounds, initiating a cross-coupling reaction.

They found that the palladium-based catalyst tended to aggregate during the reaction, which may lead to catalyst deactivation. But, when olefin such as 1,5-cyclooctadiene was added to the mixture, it acted as a dispersant for the palladium-based catalyst, facilitating a more efficient solid-state cross-coupling reaction. When olefin was added, the conversion rate of the reaction went up from less than 30% to 99%.

"Our protocol should be particularly useful for reducing the amount of organic solvent used in industry that is harmful to the environment. It will also make the production process less costly," said Hajime Ito. "The new method could be applied to, for example, the production of triarylamines that can be found in a wide range of organic materials including solar cells and light-emitting diodes." ●



▲ Electron microscopic images of palladium nanoparticles in the reaction mixtures. After 99 minutes of the reaction, the palladium catalyst was found aggregated and deactivated itself (left) while the addition of olefin kept the catalyst dispersed (right). The schematic illustration shows the function of olefin as a dispersant. (Kubota K. et al., *Nature Communications*, January 10, 2019)

ORIGINAL ARTICLE
Kubota K. et al., Olefin-accelerated solid-state C–N cross-coupling reactions using mechanochemistry. *Nature Communications*, January 10, 2019.

FUNDING
MEXT/JSPS KAKENHI (JP17H06370, JP18H03907) and the Institute for Chemical Reaction Design and Discovery (ICReDD) which was established by the World Premier International Research Initiative (WPI), MEXT, Japan.

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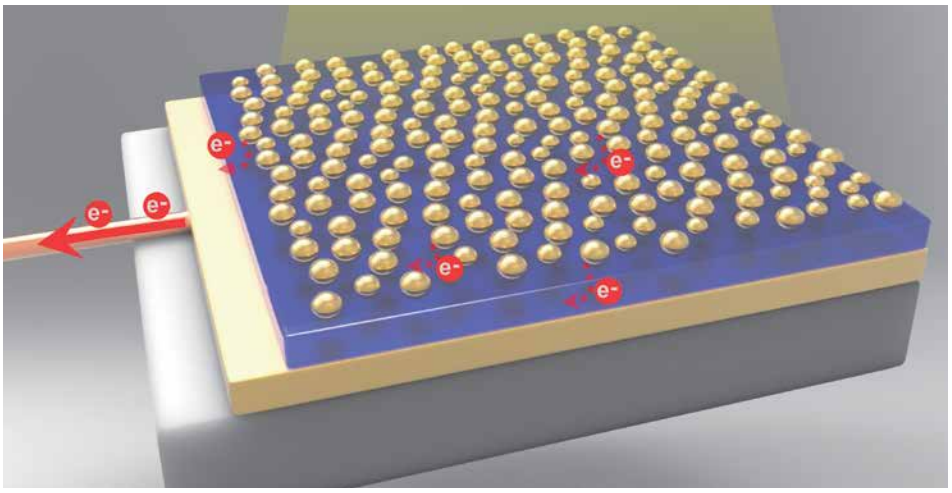
Golden sandwich soars photoelectron conversion efficiency

Scientists have developed a photoelectrode that can harvest 85 percent of visible light in a 30 nanometers-thin semiconductor layer between gold layers, converting light energy 11 times more efficiently than previous methods.



▸ The newly developed photoelectrode, a sandwich of semiconductor layer (TiO_2) between gold film (Au-film) and gold nanoparticles (Au-NPs). The gold nanoparticles were partially inlaid onto the surface of the titanium dioxide thin-film to enhance light absorption.

▲ The photoelectrode (Au-NP/TiO_2/Au-film) with 7nm of inlaid depth traps light making it nontransparent (left). An Au-NP/TiO_2 structure without the Au-film are shown for comparison (right). (Misawa H. et al., *Nature Nanotechnology*, July 30, 2018)

In the pursuit of realizing a sustainable society, there is an ever-increasing demand to develop revolutionary solar cells or artificial photosynthesis systems that utilize visible light energy from the sun while using as few materials as possible.

The research team, led by Professor Hiroaki Misawa of the Research Institute for Electronic Science at Hokkaido University, has been aiming to develop a photoelectrode that can harvest visible light across a wide spectral range by using gold nanoparticles loaded on a semiconductor. But merely applying a layer of gold nanoparticles did not lead to a sufficient amount of light absorption, because they took in light with only a narrow spectral range.

In the study published in *Nature Nanotechnology*, the research team sandwiched a semiconductor, a 30-nanometer titanium dioxide thin-film, between a 100-nanometer gold film and gold nanoparticles to enhance light absorption. When the system was irradiated by light from the gold nanoparticle side, the gold film worked as a mirror, trapping the light in a cavity between two gold layers and helping the nanoparticles absorb more light.

To their surprise, more than 85 percent of all visible light was harvested by the photoelectrode, which was far more efficient than previous methods. Gold nanoparticles are known to exhibit a phenomenon called localized plasmon resonance which absorbs a certain wavelength of light. “Our photoelectrode successfully created a new condition in which plasmon and visible light trapped in the titanium oxide layer strongly interact, allowing light with a broad range of wavelengths to be absorbed by gold nanoparticles,” says Hiroaki Misawa.

When gold nanoparticles absorb light, the additional energy triggers electron excitation in the gold, which transfers electrons to the semiconductor. “The light energy conversion efficiency is 11 times higher than those without light-trapping functions,” Misawa explained. The boosted efficiency also led to an enhanced water splitting: the electrons reduced hydrogen ions to hydrogen, while the remaining electron holes oxidized water to produce oxygen — a promising process to yield clean energy.

“Using very small amounts of material, this photoelectrode enables an efficient conversion of sunlight into renewable energy, further contributing to the realization of a sustainable society,” the researchers concluded. ●

ORIGINAL ARTICLE
Misawa H. et al., Enhanced water splitting under modal strong coupling conditions, *Nature Nanotechnology*, July 30, 2018.

FUNDING
Grant-in-aid for specially promoted research (grant-in-aid for scientific research) from the Japan Society for Promotion of Science (JSPS).

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Watch the videos of ItoP test-running at Hokkaido University.

BRAND-NEW CONCEPT CAR "ItoP" DEBUTS ON CAMPUS

The brand-new concept car "ItoP" made its debut at Hokkaido University's Sapporo Campus. Journalists were invited along for test rides as the research and development team held the ItoP's first public demonstration drive during a three-day event lasting from November 16th to 18th, 2018.

The ItoP was developed as part of ImPACT, a national research project which aims to bring about disruptive innovation in society and industry through an integration of the finest R&D capabilities in academia and industry in Japan.

Among sixteen ImPACT programs, Professor Kohzo Ito from The University of Tokyo leads the project called "Realizing Ultra-Thin and Flexible Tough Polymers," involving more than 20 universities, including Hokkaido University, and corporations in Japan. This program attempts to develop tough and yet flexible polymers that achieve a level of both thinness and toughness which exceeds conventional limits. Such polymers are expected to help realize a more energy-efficient, safe, and sustainable society.

Named for the concept of "Iron to Polymer," ItoP was developed in Professor Ito's program to showcase its R&D concept and technological achievements. About 80 percent of the components used to build the car are made from different types of polymers the team has developed, successfully reducing the body weight by 38% and greenhouse gas emissions by 11% to those of a conventional car.

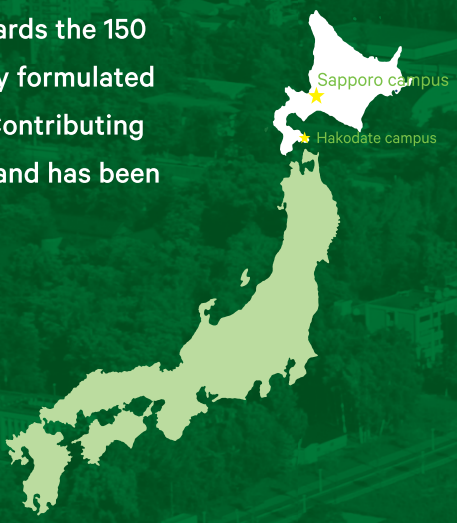
The rubber used for the tires was developed by the Bridgestone corporation based on the double network gel technology devised by Professor Jian Ping Gong's laboratory at Hokkaido University. The technology integrates two different kind of polymers, one rigid and brittle and the other flexible and stretchable, to make the material far tougher than conventional polymer-based materials. This has enabled the ItoP's tires to be lighter and thinner than conventional tires, contributing to higher fuel efficiency.

The novel polymers developed in this program could have a widespread ripple effect throughout the polymer industry in the future.

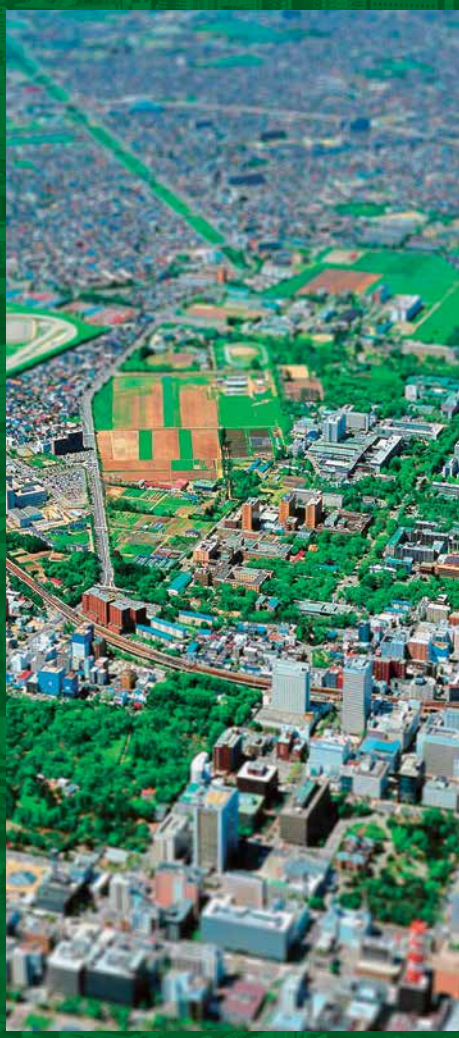
Hokkaido University *at a glance*

A Long History

Founded in 1876 as Sapporo Agricultural College, Hokkaido University is one of the oldest, largest, and most prestigious universities in Japan. Boasting one of the largest campuses in Japan, the university houses cutting-edge research facilities, a university hospital, and a number of field research centers including one of the world's largest research forests. Towards the 150 anniversary of its founding, the university formulated an action strategy under the slogan of "Contributing towards the resolution of global issues," and has been implementing a number of reform plans.



Contributing towards
the **resolution**
of **global** issues



Hokkaido Universal Campus Initiative (HUCI)

Aiming to further internationalize the university and foster more world leaders who can contribute to the resolution of global issues, the university launched the Hokkaido Universal Campus Initiative (HUCI) in 2014 as part of Top Global University Projects by the Japanese government. Under the initiative, the university has implemented a number of programs to develop global leaders and promote international collaborations.

Research

Since its establishment as an agricultural college, Hokkaido University has expanded its research strength to encompass a variety of fields in the sciences and humanities. It has produced experts in the areas such as low temperature science, life science, veterinary science, and fisheries science.

In 2014, to further strengthen international collaboration and conduct top-level research in strategic areas including quantum medical science and engineering, the university established the Global Institution for Collaborative Research and Education (GI-CoRE). In 2018, the university launched the Institute for Chemical Reaction Design and Discovery (ICReDD) as part of the World Premier Institutional Research Initiative (WPI) by the Japanese government.

International programs

In addition to the regular 12 undergraduate and 21 graduate schools, Hokkaido University runs a number of degree programs taught in English for international students such as Modern Japanese Studies Program (MJSP) and Integrated Science Program (ISP) for undergraduate students. At the graduate level, courses in engineering, veterinary medicine, agricultural science, science, and environmental science among others, are offered in English.

During the summer, the Hokkaido Summer Institute (HSI) offers more than 100 short programs in English covering a wide range of disciplines from material science to archaeology which are run by top-level researchers from the university and around the world.

Today

Data as of May 2018

660 km²
total area
campuses & facilities

12
undergraduate schools

21
graduate schools

1
Nobel prize
Akira Suzuki, Nobel Prize in Chemistry (2010)

8
overseas offices

218,277
alumni

18,605
students

12%
international students

3,974
faculty&staff

24
Research centers and institutions

RANKING

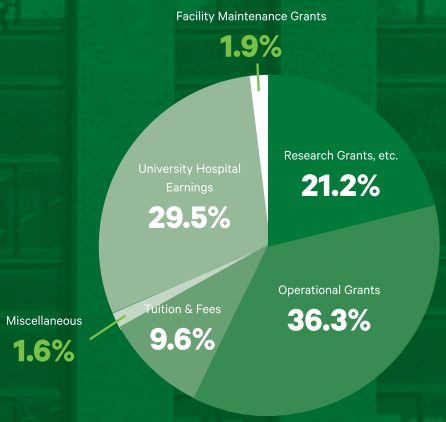
6th
in Japan
THE Japan University Rankings 2018

32nd
in Asia
QS Asia University Rankings 2018

90th
World's Most Innovative University
Reuters 2018

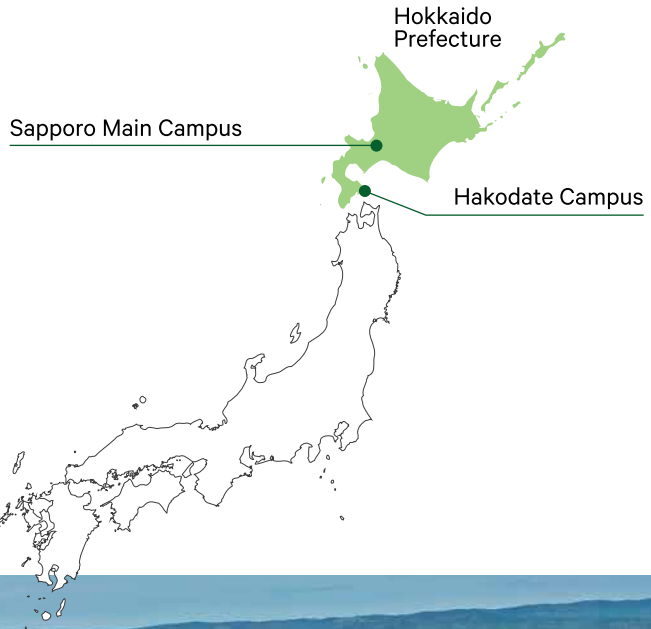
REVENUE

¥98,366m
revenue in 2018



HOKKAIDO UNIVERSITY

Founded in 1876 as Sapporo Agricultural College, Hokkaido University is one of the oldest, largest, and most prestigious universities in Japan. Boasting one of the largest campuses in the country, the university houses cutting-edge research facilities, a university hospital, and a number of field research centers including one of the world's largest research forests. Today, our researchers in the social and natural sciences, as well as in the humanities, are advancing human knowledge through their outstanding works.



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