Spotlight on Research

2021-22 Hokkaido University

HOKKAIDO UNIVERSITY

CONTENTS

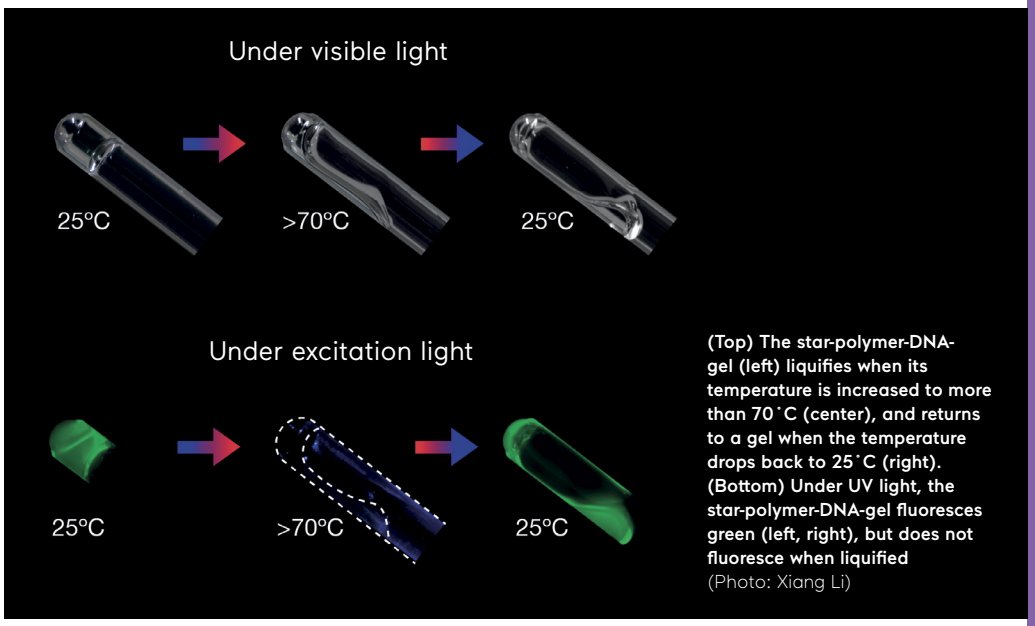
DNA design brings predictability to polymer gels

Simulations have led to the fabrication of a polymer-DNA gel that could be used in tissue regeneration and robotics.

Scientists have made a tuneable, elastic and temperature-sensitive gel by using complementary DNA strands to connect star-shaped polymer molecules together. The gel, and the method used to develop it, could lead to advances in tissue regeneration, drug delivery and soft robotics. Xiang Li at Hokkaido University led the team of researchers who reported their findings in the journal *Polymer Science*.

"Gels are made by using bonds to link polymer molecules together," explains Li. "When the bonds are connected, the material is more solid, and when they break in response to stress, the material turns to liquid."

Owing to their high biocompatibility, water solubility and temperature sensitivity, DNA strands would be highly suitable for linking polymer molecules by taking advantage of their ability to form complementary bonds. However, scientists have so far found it difficult to use DNA links to develop homogeneous gels with on-demand elastic properties.



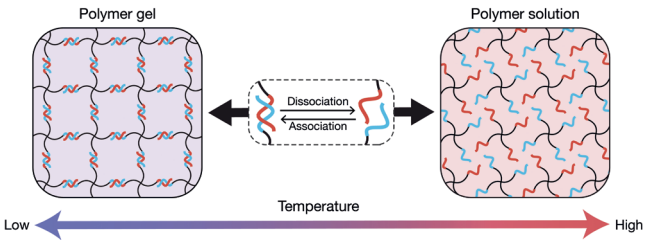
(Top) The star-polymer-DNA-gel (left) liquifies when its temperature is increased to more than 70˚C (center), and returns to a gel when the temperature drops back to 25˚C (right). (Bottom) Under UV light, the star-polymer-DNA-gel fluoresces green (left, right), but does not fluoresce when liquified (Photo: Xiang Li)

Looking to solve this problem, Li and his colleagues used software programs to simulate the formation of different DNA sequences and their complementary strands, and to determine how these double strands respond to changes in temperature.

Based on the software simulations, they chose a pair of complementary DNA sequences to link four-armed molecules of polyethylene glycol (PEG). They prepared the gel by dissolving DNA strands and PEG separately in buffer solutions before mixing them together. Finally, they conducted a series of experiments and analyses to evaluate the resulting gel's properties.

The gel performed as predicted by the simulations, remaining elastic, self-repairing and solid until its melting temperature of 63°C over multiple testing cycles. The experiments also showed that the PEG molecules were homogeneously linked together by the DNA double strands and that liquid formation happened when the strands separated.

"Our findings suggest that we will be able to fabricate DNA gels with on-demand viscoelastic properties by making use of already available data on DNA thermodynamics and kinetics," says Li. "The aim will be to improve the understanding and applications of this class of gel." ●



The star-polymer-DNA gel consists of complementary DNA strands (red and blue) linked to a molecule called polyethylene glycol (PEG, black). At lower temperatures, the DNA strands form complementary bonds leading to a gel; as the temperatures increase, the complementary bonds break and the gel liquifies. (Masashi Ohira, et al. *Advanced Materials*. January 16, 2022).

ORIGINAL ARTICLE
Masashi Ohira, et al. Star-Polymer-DNA Gels Showing Highly Predictable and Tunable Mechanical Responses. *Advanced Materials*. January 16, 2022.

FUNDING
This study was supported by the JSPS (JP17K14536, JP19K15628, JP20J22044, JP20K15338, JP16H02277), JST(JPMJFR201Z, JPMJCE1304, JPMJCE1305, JPMJCR1992). The SANS experiments were performed at J-PARC, Ibaraki, Japan (Proposal 2017B0138).

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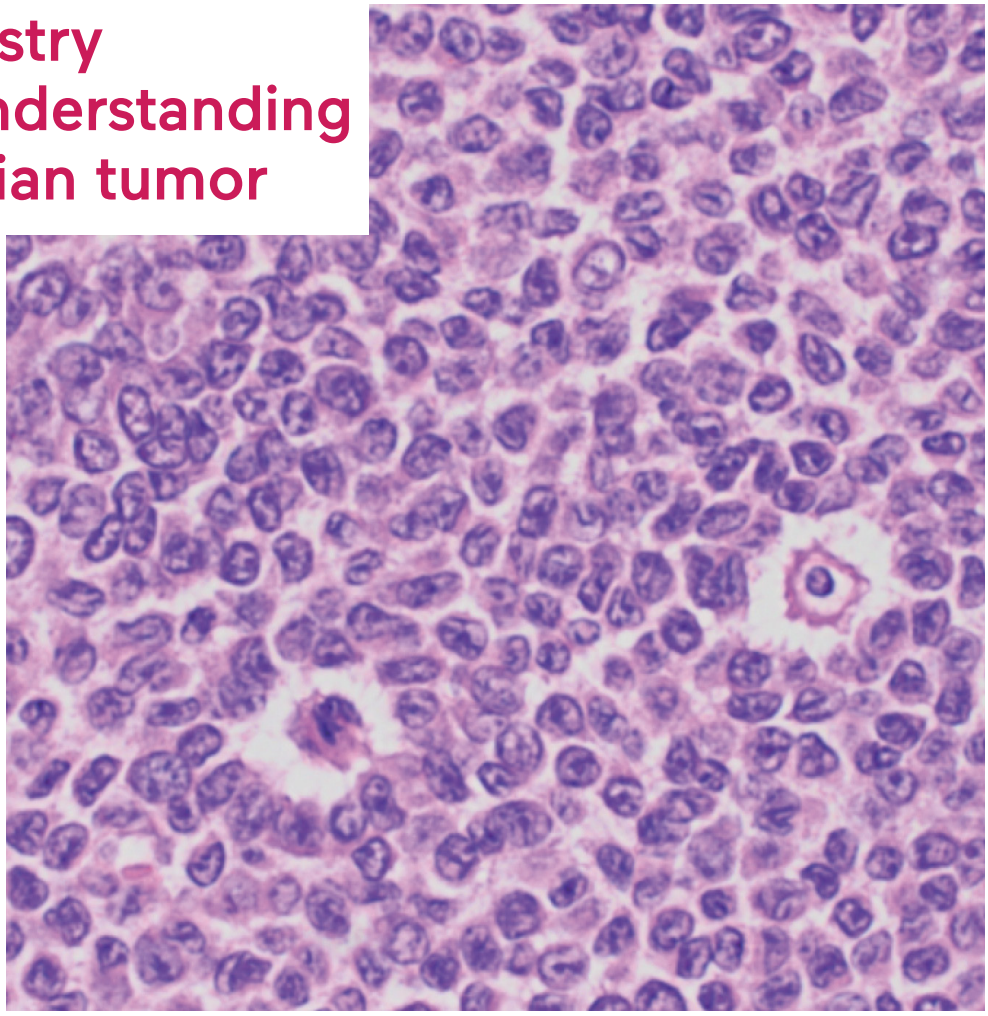
Cancer registry improves understanding of rare ovarian tumor

Examination of Japanese cases of gynecological cancer offers a better understanding of the profile of a rare ovarian tumor and could change treatment guidelines.



Ovarian granulosa cell tumor (Photo: Yasuhiko Ebina).

Ovarian granulosa cell tumors are a rare type of ovarian cancer that affect the ovaries and fallopian tubes, and can extend further into the pelvis and lymph nodes. Treatment typically follows the same guidelines as other ovarian cancers and often sees the lymph nodes removed via surgery.

Researchers at Hokkaido University and colleagues have analyzed the disease and treatment of hundreds of women with ovarian granulosa cell tumors and say more invasive surgery could be avoided in some cases. The findings, published in the journal *Gynecologic Oncology*, improve understanding of how the disease progresses and responds to therapy.

"Our main objective with this study was to improve understanding of the clinical, pathological and prognostic features of ovarian granulosa cell tumors," says Hokkaido University gynecological oncologist Yasuhiko Ebina.

To investigate the disease, Ebina and a team of scientists from several Japanese universities accessed the Gynecological Tumor Registry of the Japan Society of Obstetrics and Gynecology. They examined the data of 1,426 patients in the registry who were diagnosed with ovarian granulosa cell tumors between 2002 and 2015. This study represents analysis of the second largest sample size of ovarian granulosa cell tumors in the scientific literature and is the largest such cohort study in Asia.

They found that just under 2% of the women in the registry were diagnosed with this specific cancer, with a median age of 55. Importantly, microscopic examination of surgically removed lymph node tissue showed that early-stage tumors only rarely spread beyond the ovaries and fallopian tubes.

The team found a worse prognosis for patients with cancers that had spread beyond the ovaries and tubes. Those whose tumors were incompletely removed during surgery also had worse five-year survival rates.

They also found that surgery in patients under 50 designed to protect fertility, typically by removing only an early-stage tumor or the affected ovary and tube, did not worsen their prognosis. This suggests that fertility-sparing surgery could be considered for more women in the early stages of the disease.

"Our findings have led us to conclude that lymph node dissection can be omitted if the surgeon finds the tumor limited to the ovarian and fallopian tube tissue following a thorough exploration of the abdominal cavity," says Ebina. "At the same time, as much of the tumor should be removed as possible to ensure that residual tissue is not left behind at the end of the initial surgery." ●

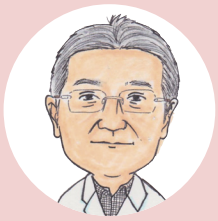


Illustration by Yasuhiko Ebina

ORIGINAL ARTICLE
Yasuhiko Ebina, et al. Clinicopathological characteristics and prognostic factors of ovarian granulosa cell tumors: A JSGO-JSOG joint study. *Gynecologic Oncology*. August 26, 2021.

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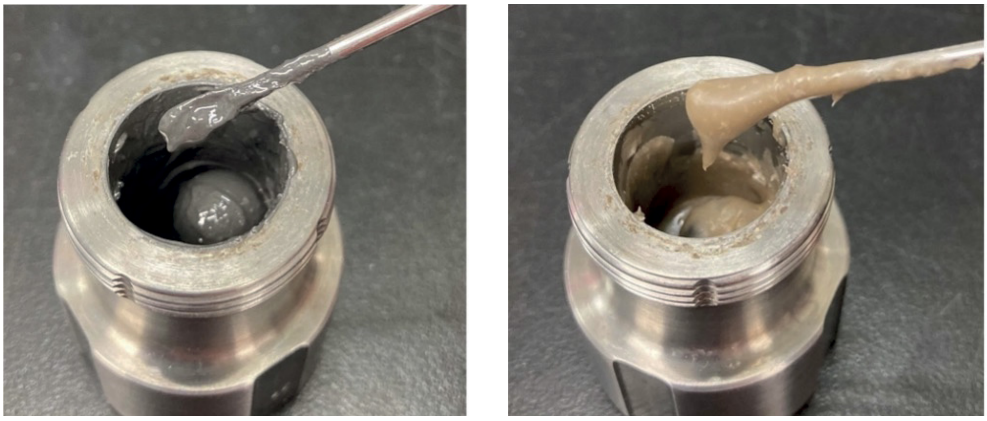
120-year-old reaction turned on its head with environment-friendly, paste-based method

A new method for creating one of chemistry's most widely used classes of compounds could revolutionize industrial processes, making them cheaper, simpler and more environmentally friendly.

A group of researchers led by scientists at Hokkaido University have developed a simpler, greener method for producing Grignard reagents—one of the most important and widely used type of reagents in the chemical industry—that drastically cuts down on the use of hazardous organic solvents and could lead to reduced production costs. This new process was reported in *Nature Communications*.

Grignard reagents are an essential ingredient in a common method for creating carbon-carbon bonds, the building blocks of organic molecules. These reagents were discovered 120 years ago, but due to their instability, the conventional production method still used today is carried out in toxic organic solvents and with no exposure to moisture and oxygen. This results in a complicated, delicate, and expensive process that produces environmentally hazardous waste.

Researchers sidestepped these problems by minimizing the amount of organic solvent used and by employing a mechanochemical technique called ball-milling to produce Grignard reagents. The reactants, magnesium metal and organohalides, were loaded into a metal chamber along with a stainless-steel ball. In a key step, a small amount of organic solvent—about one-tenth the amount used in conventional methods—was added to the solid reactants.

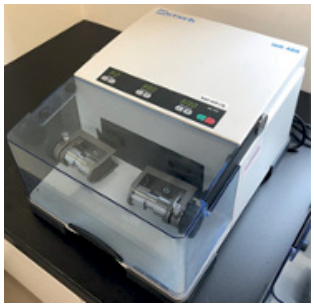


(Left) Reaction mixture of magnesium metal and organohalide after one hour of ball milling. Use of this material in subsequent reactions led to only a 6% yield of the desired product. (Right) Same process, but with a small amount of organic solvent also added at the beginning. Use of this paste form of Grignard reagent in subsequent reactions led to yields of up to 94% of the desired product (Photo: Koji Kubota).

The chamber was then spun for one hour, causing the ball to tumble around and slam into the solid-state reactants, helping them to mix thoroughly and react, forming a paste-like Grignard reagent.

It is more difficult for water or oxygen to affect the Grignard reagents when less organic solvent is used. This means that removing water and oxygen from the surrounding air is not required, making the process easier to perform and less costly. Given the potential economic and environmental benefits, this discovery could have a huge effect on chemical industries.

"With a growing need to address environmental concerns and reduce CO_2 emissions, it is important to develop chemical reactions that don't require organic solvents," commented Associate Professor Koji Kubota. "Grignard reagents are arguably the most well-known, commonly used reagents in industry, and so our work could fundamentally change the way a vast number of chemicals are produced at scale, leading to significantly reduced impact on the environment." ●



The ball mill used to produce Grignard reagents in the study (Photo: Koji Kubota).

Professor Hajime Ito (top) and Associate Professor Koji Kubota (bottom) of the research team at Hokkaido University and the Institute for Chemical Reaction Design and Discovery (ICReDD). (Photos provided by ICReDD).

ORIGINAL ARTICLE

Rina Takahashi, et al. Mechanochemical synthesis of magnesium-based carbon nucleophiles in air and their use in organic synthesis. *Nature Communications*. November 18, 2021.

FUNDING

This work was supported by JSPS (17H06370, 18H03907, 20H0479, 21H01926, 19J20824), JST (JPMJCR19R1, JPMJFR201I), and MEXT.

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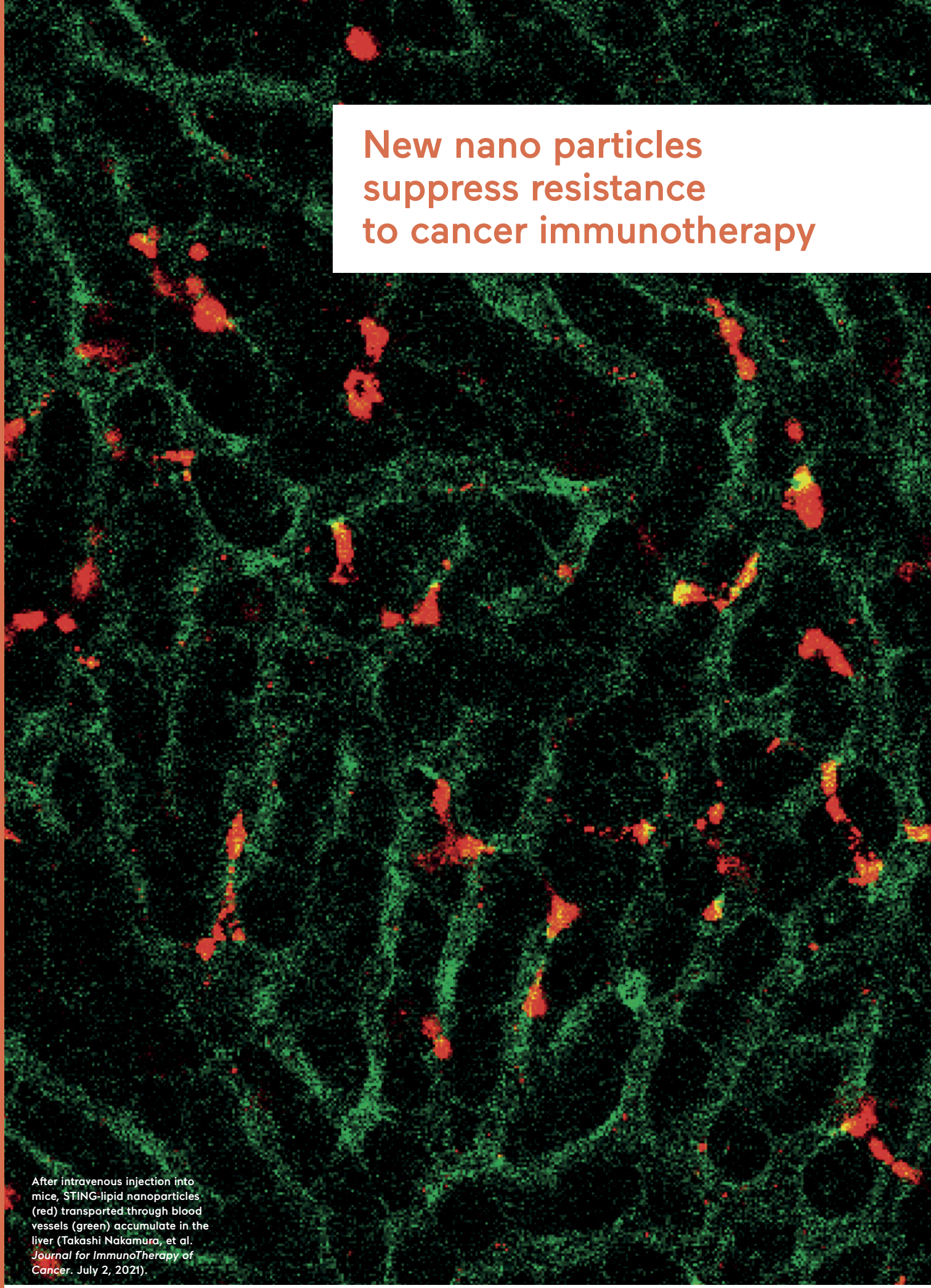
New nano particles suppress resistance to cancer immunotherapy



After intravenous injection into mice, STING-lipid nanoparticles (red) transported through blood vessels (green) accumulate in the liver (Takashi Nakamura, et al. *Journal for ImmunoTherapy of Cancer*. July 2, 2021).

A specially designed lipid nanoparticle could deliver immune-signaling molecules into liver macrophage cells to overcome resistance to anti-tumor immunotherapy.

Hokkaido University scientists and colleagues in Japan have found a way that could help some patients overcome resistance to an immunotherapy treatment for cancer. The approach, proven in mice experiments, was reported in the *Journal for Immunotherapy of Cancer*.

The activation of checkpoint proteins on the surfaces of immune cells help regulate the immune response by preventing them from indiscriminately attacking the body's other cells. But some cancer cells are able to hijack this mechanism, preventing an immune response against them as well. Scientists have recently developed immune checkpoint inhibitors that can counteract this strategy, but some people are resistant to the treatments.

Now, scientists at Hokkaido University and Aichi Institute of Technology have found a way around this by developing a specially designed lipid nanoparticle that can carry immunity-triggering molecules into immune cells in the liver called macrophages.

The lipid, called YSK12-C4, has a high affinity for immune cells. When intravenously injected into mice with metastatic melanoma, it was able to deliver signaling molecules, called cyclic dinucleotides, across the cell membranes of their liver macrophages, where they stimulated the production of immune-related proteins called type 1 interferons via a stimulator of an interferon gene (STING) pathway. These were released into the blood, activating another type of immune cell called natural killer cells in the spleen and lung, which produced interferon-gamma inside the lung metastases.

This treatment, on its own, only elicited a mild anti-tumor effect. This is because the type 1 interferons and interferon-gamma triggered the expression of a protein called PD-L1 on the cancer cells. PD-L1 prevents a strong tumor-killing immune response of natural killer cells that express PD-1. Administering an anti-PD-1 immunotherapy treatment, however, prevented the cancer cells from turning off those natural killer cells, which then became armed and able to launch a full-scale attack.

"The findings suggest that our lipid nanoparticles carrying immune-signaling molecules convert the immune status from immunologically cold to immunologically hot," says Takashi Nakamura of Hokkaido University's faculty of pharmaceutical sciences. "This could lead to the development of a promising adjuvant that reduces resistance to anti-PD-1 antibody treatment in some cancer patients."

Further studies will need to examine whether the treatment can cause liver toxicity and if different signaling molecules can be used. ●

> "Our lipid nanoparticles carrying immune-signaling molecules convert the immune status from immunologically cold to immunologically hot."

Takashi Nakamura, lead author of this study (Photo: Takashi Nakamura).

ORIGINAL ARTICLE

Takashi Nakamura, et al. STING agonist loaded lipid nanoparticles overcome anti-PD-1 resistance in melanoma lung metastasis via NK cell activation. *Journal for ImmunoTherapy of Cancer.* July 2, 2021.

FUNDING

This work was supported by MEXT, AMED and Hokkaido University

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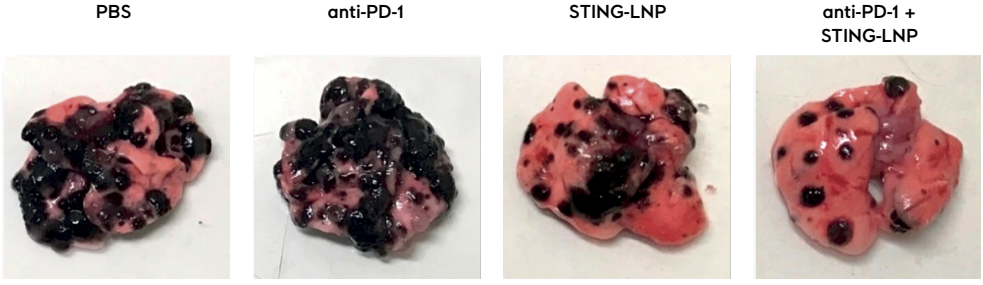
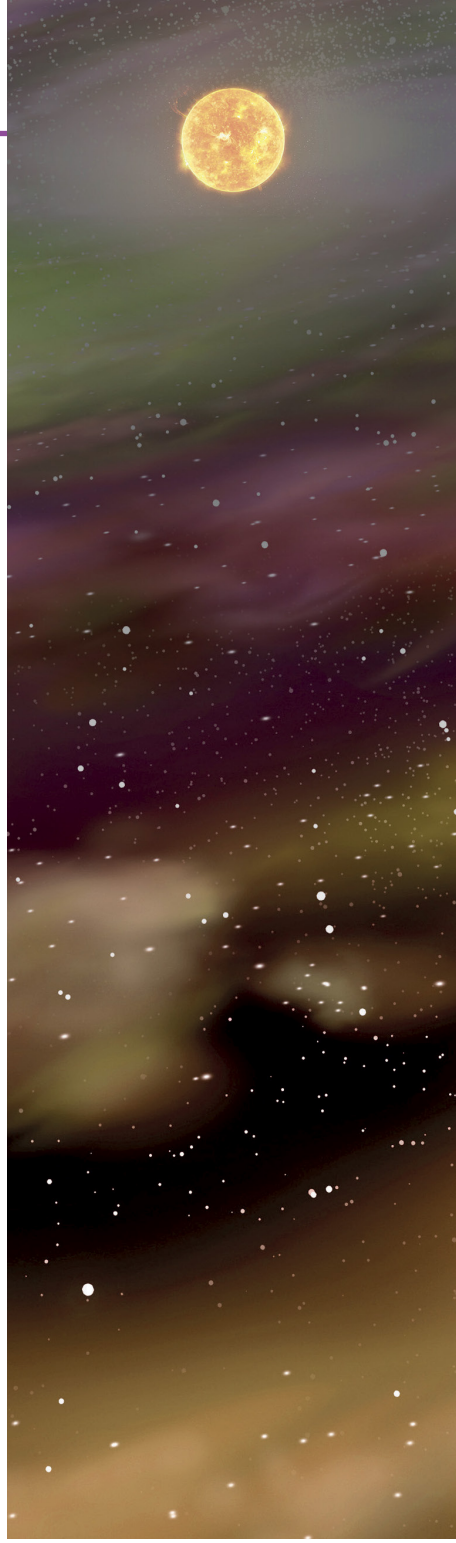


Combination therapy against anti-PD-1-resistant lung cancer. A combination of anti-PD-1 antibodies and stimulator of an interferon gene (STING)-loaded lipid nanoparticles (STING-LNP) had the maximum effect in reducing metastases (black regions) on lungs (pink tissue; far right). STING-lipid nanoparticles alone had a better effect (center right) than anti-PD-1 antibodies (center left), which were as effective as the control saline solution (far left; Takashi Nakamura, et al. *Journal for ImmunoTherapy of Cancer*. July 2, 2021).

Magnetic patterns hidden in meteorites reveal early Solar System dynamics

Researchers have developed a novel technique to investigate the dynamics of the early Solar System by analyzing magnetites in meteorites utilizing the wave nature of electrons.



"Our nanometer-scale paleomagnetic method will unveil a detailed history of the early Solar System."

Within meteorites, the magnetic fields associated with the particles that make up the object can act as a historical record. By analyzing such magnetic fields, scientists can deduce the probable events that affected the object and reconstruct a time-lapse of what events occurred on the meteorite and when.

"Primitive meteorites are time capsules of primordial materials formed at the beginning of our Solar System," said Yuki Kimura, an associate professor at the Institute of Low Temperature Science at Hokkaido University who led the study. "To understand the physical and chemical history of the Solar System, it is crucial to analyze various types of meteorites with different origins."

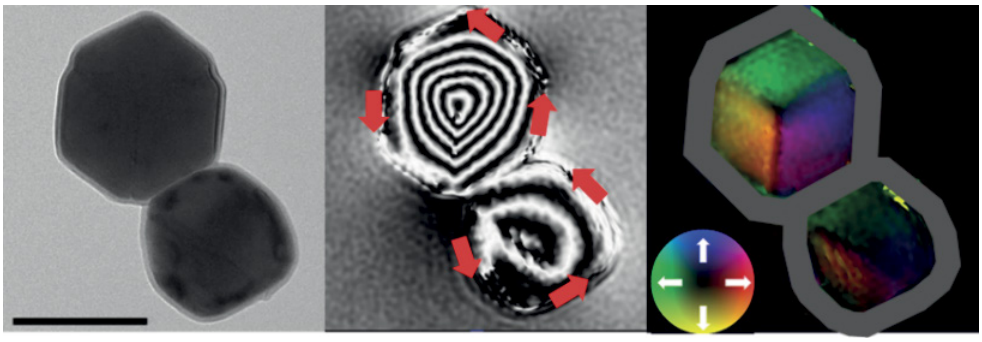
While there are many meteorites available for study here on Earth, most of them originated from the asteroid belt, between Mars and Jupiter. These samples are used to study what the early Solar System looked like. However, it becomes difficult to reconstruct events that happened farther out in the Solar System, well past the asteroid belt.

This is where the research team took great strides in understanding outer Solar System dynamics soon after the system formed. The paper, published in *The Astrophysical Journal Letters*, details a novel technique to study the remnant magnetization of particles in the Tagish Lake meteorite, believed to have been formed in the cold outer Solar System.

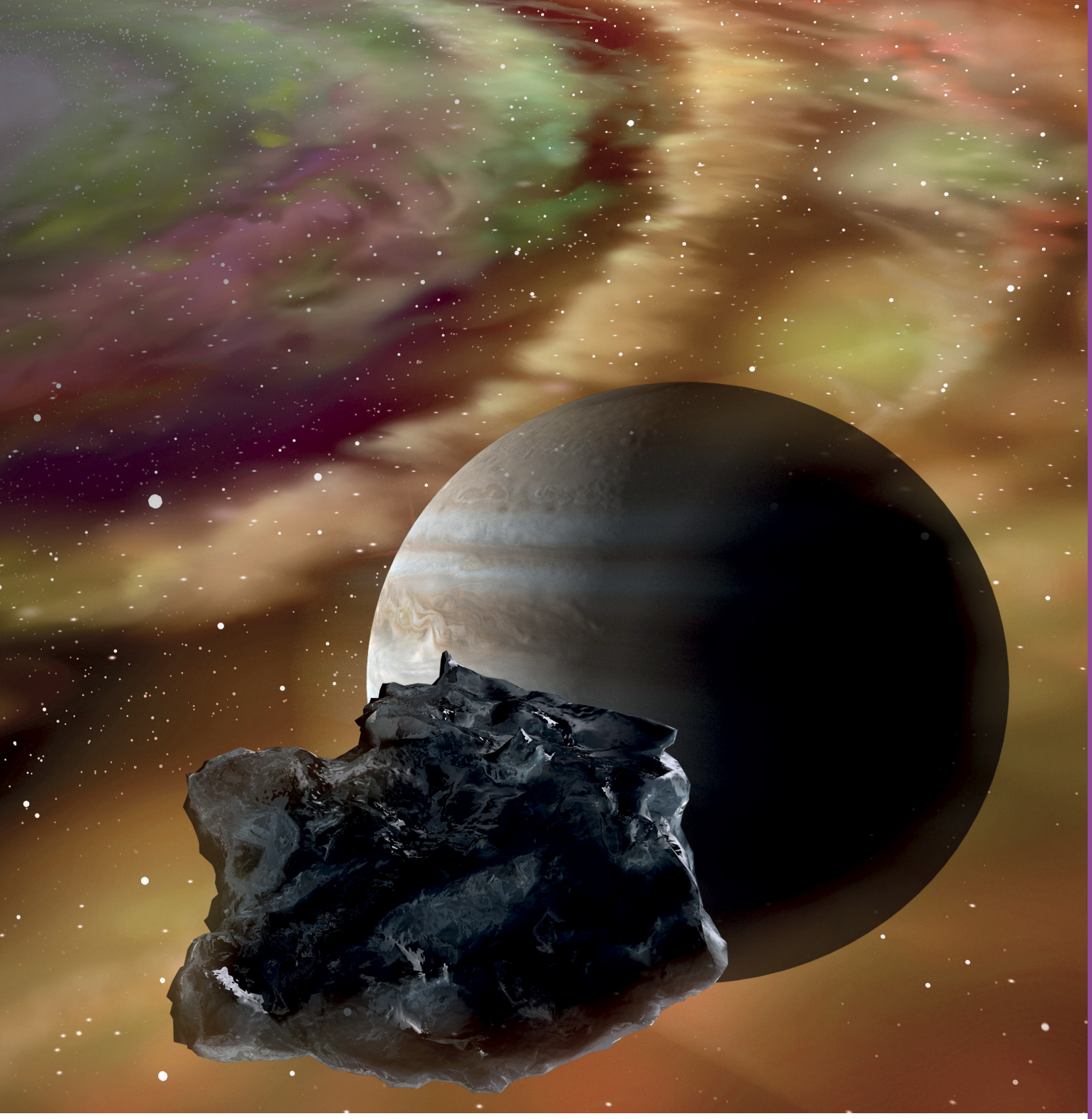
Using the technique, together with numerical simulation, the team showed that the parent body of the Tagish Lake meteorite was formed in the Kuiper Belt, a region in the outer Solar System, sometime around 3 million years after the first Solar System minerals formed. It then moved to the orbit of the asteroid belt as a result of the formation of Jupiter. The magnetite was formed when the parent body was heated to about 250°C by radiogenic heating and an energetic impact which is thought to have occurred during the body's transit from the Kuiper belt to the Asteroid belt.

"Our results help us infer the early dynamics of Solar System bodies that occurred several million years after the formation of the Solar System, and imply a highly efficient formation of the outer bodies of the Solar System, including Jupiter," says Kimura.

The new technique, called "nanometer-scale paleomagnetic electron holography," involves using the wave nature of electrons to examine their interference patterns, known as a hologram, to extract high resolution information from the structure of the meteorites. This high-resolution technique adds another crucial tool to the



The new technique to analyze magnetic fields reveals events that occurred on the Tagish Lake meteorite. Electron microscope image (left), a magnetic flux distribution image (middle), and a color-wheel map image (right) of magnetite particles from the Tagish Lake meteorite. The red arrows and white arrows indicate the directions of the magnetization vectors and the direction of the magnetization, respectively. (Yuki Kimura, et al., *The Astrophysical Journal Letters*, August 11, 2021)



Jupiter and a comet formed in a cold outer region of the early solar system. (Illustration provided by Yuki Kimura)

toolbox of researchers working to understand the early dynamics of the entire Solar System.

Armed with their new technique, the team hopes to apply it to more samples, including samples from an asteroid still in orbit around the Sun, called Ryugu. Kimura detailed their ongoing research plan: "We are analyzing the samples that Hayabusa 2 brought back from the asteroid Ryugu. Our nanometer-scale paleomagnetic method will unveil a detailed history of the early Solar System." ●

ORIGINAL ARTICLE

Yuki Kimura, Kazuo Yamamoto, Shigeru Wakita. Electron holography reveals early planetary dynamics of the Solar System. *The Astrophysical Journal Letters*, August 11, 2021.

FUNDING

This study was supported by the JSPS KAKENHI (16K13909, 20H05657).

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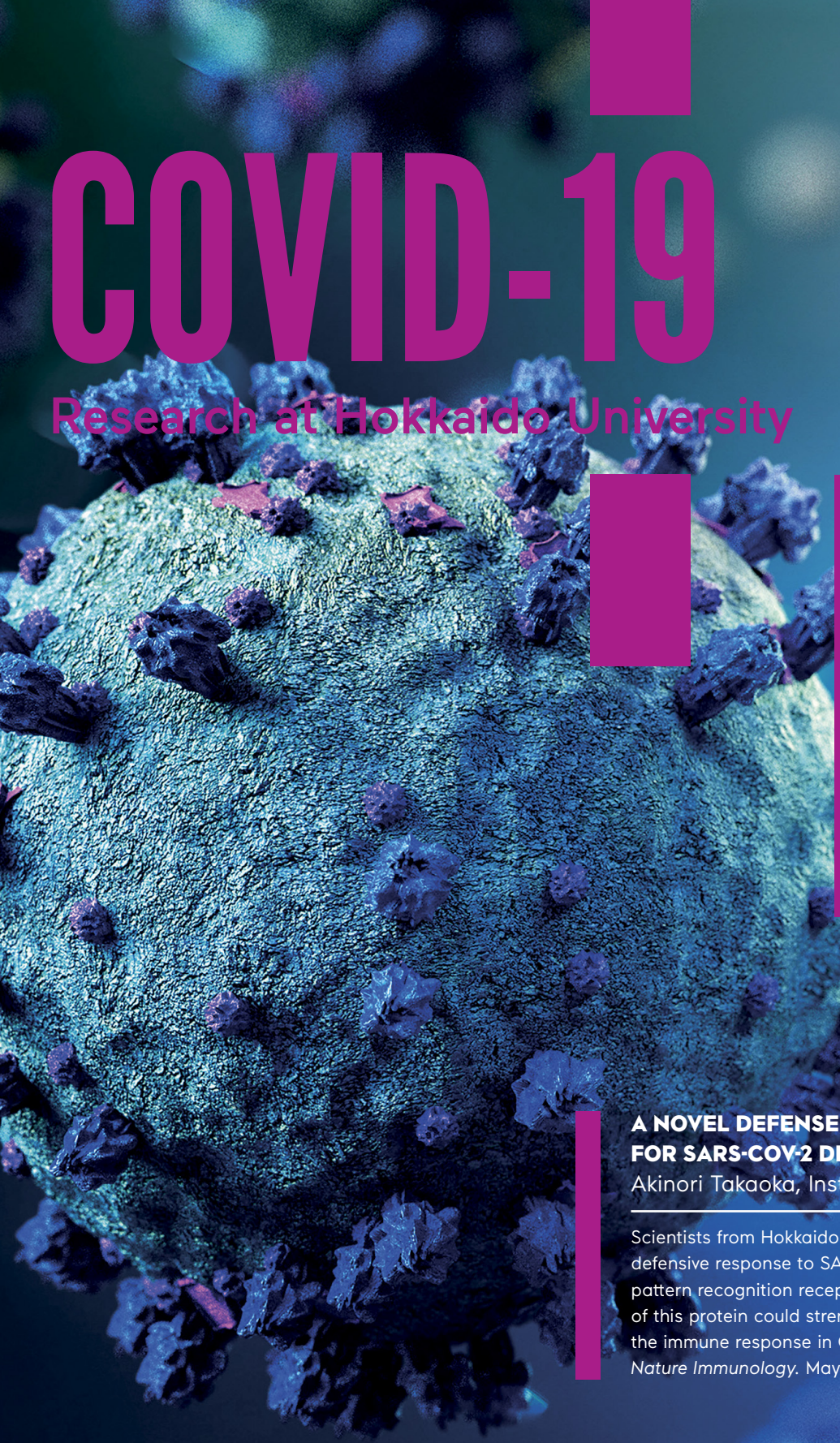
COVID-19

Research at Hokkaido University



REVEALED: HOW SARS-COV-2 EVADES OUR IMMUNE SYSTEM

Koichi Kobayashi, Graduate School of Medicine
Hirofumi Sawa, International Institute for Zoonosis Control

Scientists at Hokkaido University and Texas A&M University have identified a key mechanism used by the SARS-CoV-2 virus to evade host immune systems.
Nature Communications. November 15, 2021

A NOVEL DEFENSE MECHANISM FOR SARS-COV-2 DISCOVERED

Akinori Takaoka, Institute for Genetic Medicine

Scientists from Hokkaido University have discovered a novel defensive response to SARS-CoV-2 that involves the viral pattern recognition receptor RIG-I. Upregulating expression of this protein could strengthen the immune response in COPD patients.
Nature Immunology. May 11, 2021

A RAPID METHOD TO QUANTIFY ANTIBODIES AGAINST SARS-COV-2

Manabu Tokeshi, Faculty of Engineering

Scientists have developed a rapid, highly accurate test to detect antibodies against the spike protein of SARS-CoV-2 in human serum, opening a new avenue for understanding the full extent of the pandemic and evaluating the effectiveness of vaccines.
Biosensors and Bioelectronics. June 5, 2021

Check out the most recent COVID-19 Research at Hokkaido University

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PANDEMIC CHANGED PERCEPTIONS OF MASKED FACES

Jun I. Kawahara, Faculty of Letters

The Covid-19 pandemic has improved perceptions of facial attractiveness and healthiness of people wearing face masks in Japan.
i-Perception. June 27, 2021

TRACKING SARS-COV-2 DURING TOKYO 2020 VIA WASTEWATER

Masaaki Kitajima, Faculty of Engineering

Wastewater-based epidemiological tracking of COVID-19 in the Tokyo 2020 Olympic and Paralympic village showed that SARS-CoV-2 was present in areas without diagnosed individuals.
Journal of Travel Medicine. February 3, 2022

A NOVEL, QUICK, AND EASY SYSTEM FOR GENETIC ANALYSIS OF SARS-COV-2

Takasuke Fukuhara, Graduate School of Medicine

Researchers from Osaka University and Hokkaido University have developed a system for analyzing mutations in SARS-CoV-2 that is much simpler and faster than existing methods.
Cell Reports. April 1, 2021

A RAPID ANTIGEN TEST FOR SARS-COV-2 IN SALIVA

Isao Yokota and Takanori Teshima, Faculty of Medicine

Scientists from Hokkaido University have shown that an antigen-based test for quantifying SARS-CoV-2 in saliva samples is simple, rapid, and more conducive for mass-screening.
The Lancet Microbe. May 19, 2021

ESTABLISHING AN AUTOMATED SYSTEM FOR THE ANALYSIS OF SARS-COV-2 IN WASTEWATER

Masaaki Kitajima, Faculty of Engineering

On March 19, 2021, Hokkaido University, Robotic Biology Institute Inc., iLAC Co., Ltd., and Shionogi & Co., Ltd. have entered into a memorandum of understanding (MOU) toward the establishment of an automated system for the analysis of the novel coronavirus (SARS-CoV-2) in wastewater.

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Corals tell Arabian Sea story of global warming

Coral insights into 1,000 years of seasonal changes in the Arabian Sea warn of significant impacts caused by global warming.

Every year, the southwesterly winds of the summer monsoon sweep down the Arabian Peninsula, pushing the surface waters of the Arabian Sea away from the coast and driving an upwelling of deep waters to the surface. This rising seawater is colder and less saline than the surface water and is rich in nutrients, providing energy for the various organisms living in the Arabian Sea and Indian Ocean.

Scientists from Japan, Taiwan and Germany, including coral reef scientist Dr. Tsuyoshi Watanabe of Hokkaido University, have uncovered evidence from corals off the coast of Oman suggesting that global warming is causing changes to the Arabian Sea that could impact the climate, ecosystems and socioeconomics of the densely populated areas surrounding the Indian Ocean. The findings were published in the journal *Geophysical Research Letters*.

Stronger summer monsoon winds lead to a stronger upwelling in the Arabian Sea. Stronger winds form when the air over the Indian subcontinent warms more rapidly than the air over the Indian Ocean. Recently, however, the opposite has been happening. Scientists wanted to know how this change affects the Arabian Sea upwelling, but the phenomenon has not been monitored continuously, so available measurements aren't enough to tell the whole story.

Watanabe and his colleagues analysed fossil and modern corals off an Omani island in the Arabian Sea. They identified the ages of the corals they collected and established a correlation between coral data and seawater temperature changes over a very fine timescale, and used that information to extrapolate salinity changes. The four fossil corals they used dated to approximately 1167 CE, 1624 CE, 1703 CE and 1968 CE, respectively. They took samples from the corals at different depths towards their cores, and then analysed the ratio of strontium to calcium in the samples, as well as the amounts of oxygen and carbon isotopes. The growth rate of the corals is steady over centuries, and the skeletons contain a record of the changes in elements. Generally, as water temperatures rise, the strontium-to-calcium ratio and isotope oxygen-18 in coral decrease.

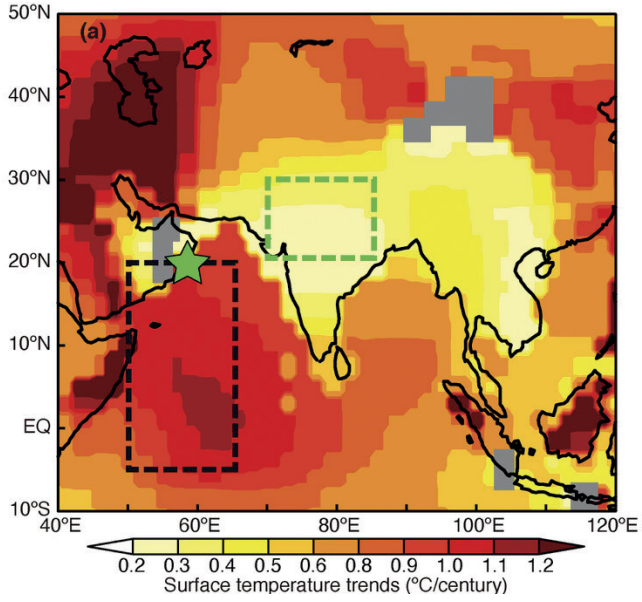
The results showed that the summer Arabian Sea upwelling was relatively stable through the warmer period of the medieval climate anomaly in the 12th century; the cooler little ice age, which extended between the 14th and 19th centuries AD; and up until the mid-20th century. After this period, however, the scientists observed a clear weakening of the Arabian

Collecting coral samples in the waters off Oman (Photo: Tsuyoshi Watanabe).

A piece of coral from one of the coral reefs in the Arabian Sea (Photo: Tsuyoshi Watanabe).

Sea upwelling. They reason this can most likely be explained by faster warming of the northern Indian Ocean, caused by greenhouse gases, and slowed warming of the Indian subcontinent, caused by the absorption of sunrays by aerosol emissions over South Asia. This then weakens the summer monsoon winds, impacting the strength of the Arabian Sea upwelling.

"The seasonal upwelling is vital for commercial fishing and has significant impacts on the regional climate, ecosystems and socioeconomics," says Tsuyoshi Watanabe. "Our findings imply that weakening of the Arabian Sea upwelling is likely to continue along with global warming, impacting monsoon rainfalls, sea levels, fisheries and even agricultural production." ●



"Our findings imply that weakening of the Arabian Sea upwelling is likely to continue along with global warming."

Warming trends of the northern Indian Ocean and the Indian subcontinent. The Arabian Sea has warmed to a much larger extent than the Indian subcontinent. The star indicates the sample site of modern and fossil Arabian Sea corals used in this study (Takaaki K. Watanabe, et al. *Geophysical Research Letters*. May 24, 2021).

Tsuyoshi Watanabe, corresponding author of the current study, in Oman (Photo: Tsuyoshi Watanabe).

ORIGINAL ARTICLE

Takaaki K. Watanabe, et al. Corals reveal an unprecedented decrease of Arabian Sea upwelling during the current warming era. *Geophysical Research Letters*. May 24, 2021.

FUNDING

This work was supported by JSPS KAKENHI (JP25257207), the Ministry of Science and Technology, Taiwan ROC (9109-2123-M-002-001), the National Taiwan University (109L8926), and the Higher Education Sprout Project of the Ministry of Education, Taiwan ROC (109L901001).

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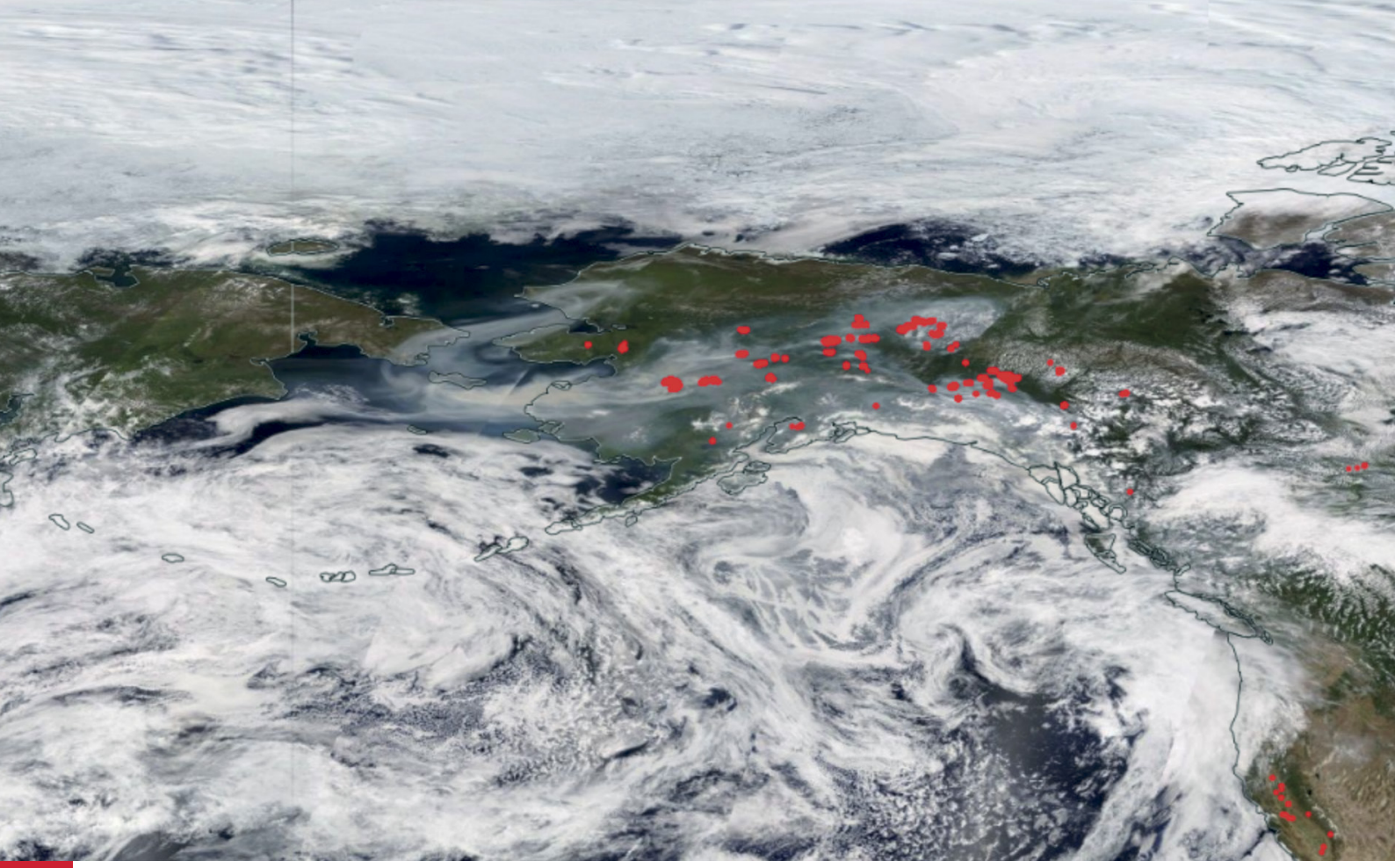


A satellite image of Alaska on July 9, 2019. The red spots indicate the locations of wildfires; the smoke from these wildfires is also visible (Terra/MODIS Corrected Reflectance True Color image with Suomi NPP/VIIRS Fires and Thermal Anomalies (Day, 375m), NASA Worldview).

FACING PAGE
The relationships among CAW, heatwaves, wildfires, and pollution. (Teppei J. Yasunari, et al. *Environmental Research Letters*. May 17, 2021).

Newly identified atmospheric circulation enhances heatwaves and wildfires around the Arctic

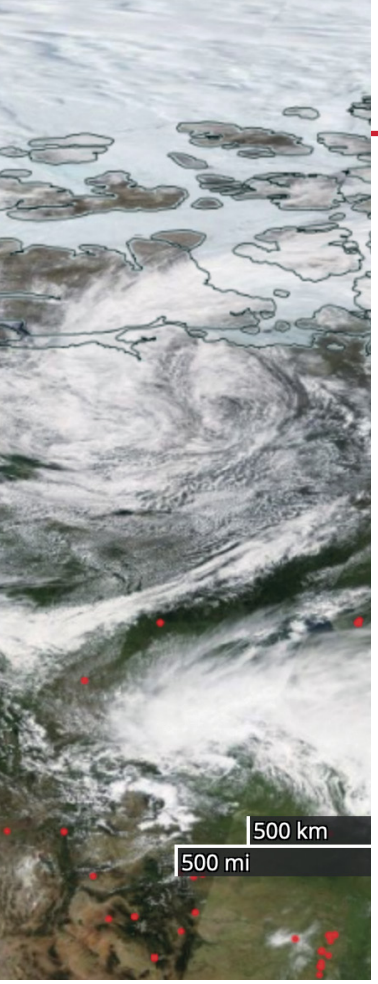
Scientists have uncovered a summertime climate pattern in and around the Arctic that could drive co-occurrences of European heatwaves and large-scale wildfires with air pollution over Siberia and subpolar North America.

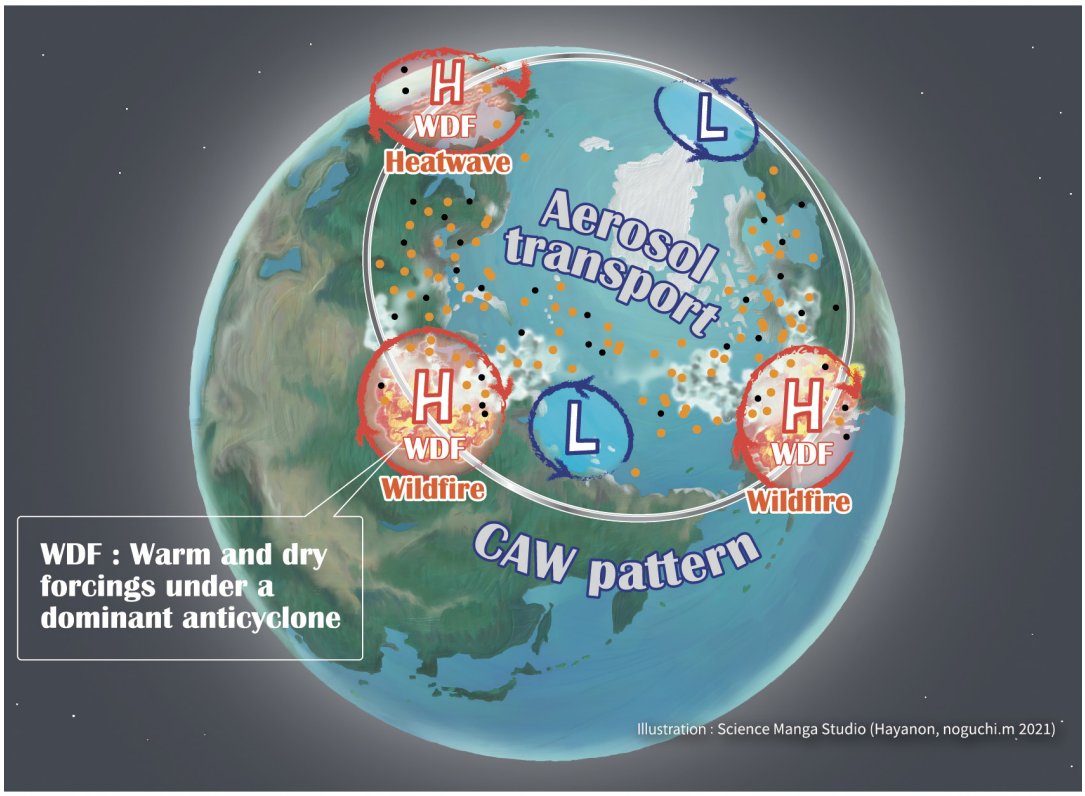
A team of scientists from Japan, South Korea, and the USA, including Hokkaido University's Assistant Professor Teppei J. Yasunari, have revealed relationships among wildfires, aerosols (air pollution), and climate patterns in and around the Arctic. They have published their discoveries in the journal *Environmental Research Letters*.

"Wildfires lead to extensive air pollution, primarily in the form of inhalable particulate matter with diameters of 2.5 micrometers or smaller (PM2.5). Arctic hazes during winter and spring are typical phenomena due to aerosols existing in the Arctic. In our scientific field, it is also known that deposition of light-absorbing aerosols onto snow surfaces can induce the so-called snow darkening effect, contributing to accelerated snow melting. For these reasons, long-term assessments of PM2.5 and aerosols in the Arctic and surrounding regions are required," said Yasunari.

For their investigations, the scientists used the MERRA-2 (Modern-Era Retrospective analysis for Research and Applications, version 2) dataset and fire data by satellite, both produced by NASA, focusing on the recent period from 2003 to 2017. They assessed comprehensive air pollution (i.e., PM2.5) in the Arctic for as long as the past 15 years, seeking to clarify the relationships between variations in PM2.5 and aerosols, wildfires, and the relevant climate patterns.

"We found 13 out of the 20 months with highest PM2.5 in the Arctic during the 15 year period were in summer. The elevated PM2.5 levels were highly correlated with relatively higher organic carbon aerosol concentrations, implying active wildfires. We concluded that the





summertime wildfires contributed to those months with exceptionally high PM2.5 in the Arctic. In those months, the wildfires likely occurred under extremely warm and dry conditions. Those were due to concomitantly persistent or developed high-pressure systems over Europe, Siberia, and subpolar North America, namely, Alaska and Canada," explained Yasunari.

The scientists named this climate (atmospheric circulation) pattern, the *circum-Arctic wave (CAW) pattern*, as a driver for enhancing the co-occurrence of heatwaves in Europe and wildfires in Siberia and subpolar North America. In fact, the CAW-like pattern was also seen in the early summer of 2019, which was outside the period of the MERRA-2 analyses.

This study has also revealed that the summertime CAW pattern in the atmospheric circulations became only prominent after 2002. This finding suggests the increasing climatic significance of the CAW pattern as a driver of possible co-occurrences of European heatwaves and wildfires over Siberia and subpolar North America in recent years. Both wildfire smoke that increases PM2.5 and heatwaves are of significant concern to human health.

This study has expanded conventional knowledge of the connections between weather conditions, wildfire-induced air pollution, and climate patterns. "We have just found the CAW pattern, but do not yet know its trigger mechanism and persistence under the present and future climate conditions," remarked Yasunari.

The elucidation of the CAW formation and activity is vital in future works; better projections in summer will help develop effective measures for people living in and around the Arctic in responding to large-scale summer heatwaves and severe wildfires.

Involved in this study were Professor Hisashi Nakamura, The University of Tokyo, Japan; Dr. Nakbin Choi and Professor Myong-In Lee, Ulsan National Institute of Science and Technology, Republic of Korea; and Professor Yoshihiro Tachibana, Mie University, Japan, and two scientists from the Goddard Space Flight Center, National Aeronautics and Space Administration (NASA), USA. ●

ORIGINAL ARTICLE
Teppei J. Yasunari, et al. Relationship between circum-Arctic atmospheric wave patterns and large-scale wildfires in boreal summer. *Environmental Research Letters*. May 17, 2021.

FUNDING
This study was supported by the MEXT ArCS (JPMXD1300000000) and ArCS II (JPMXD1420318865) projects; the JSPS KAKENHI (17H02958, 17KT0066, 18H01278, 19H01976, 19H05668, 19H05698, 19H05702, 20H01970, 20K12197); and the MOE (JPMEERF20192004).

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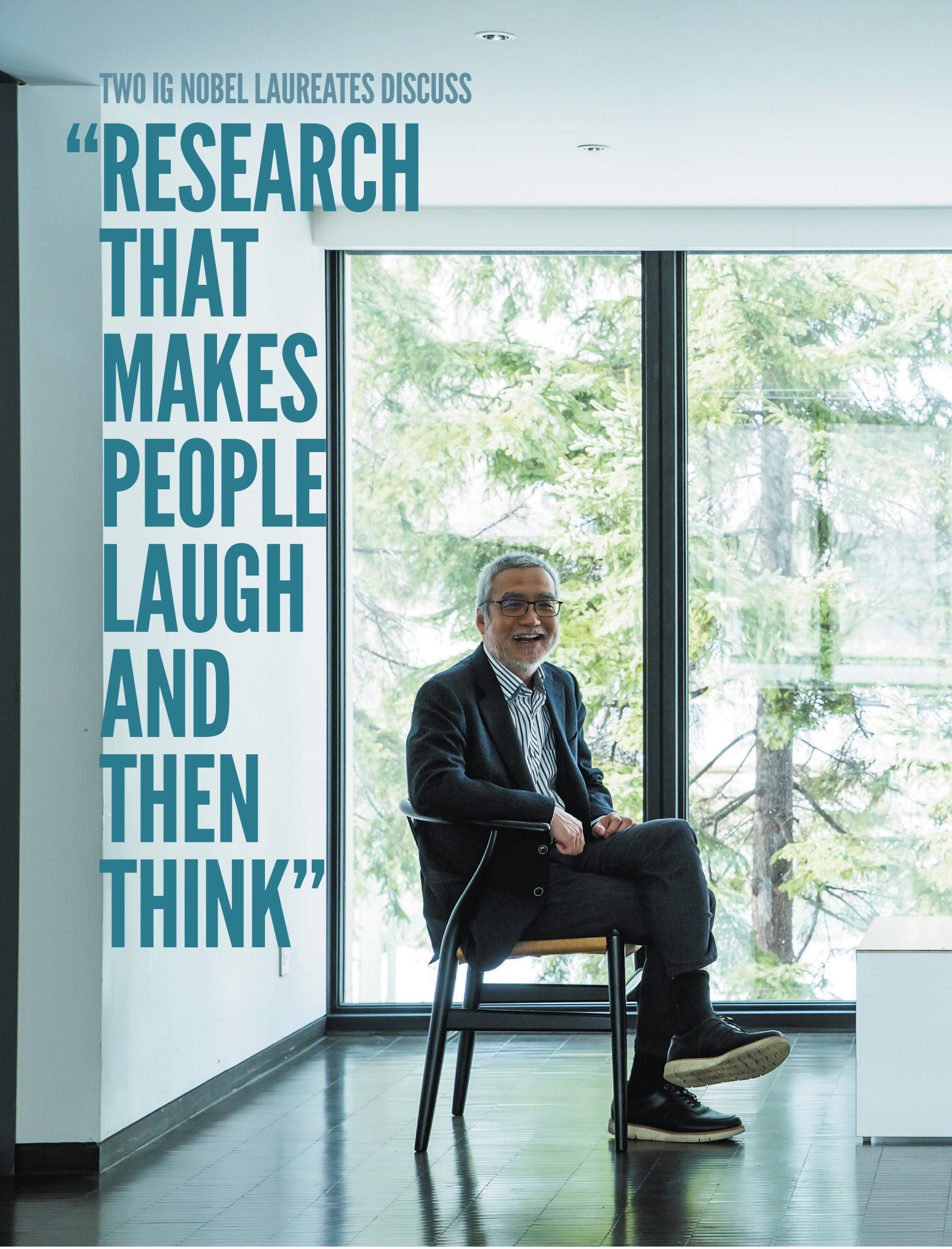
TWO IG NOBEL LAUREATES DISCUSS

"RESEARCH THAT MAKES PEOPLE LAUGH AND THEN THINK"



The Ig Nobel Prize, established in 1991, is awarded to "research that makes people laugh and then think" and is also known as the "behind-the-scenes Nobel Prize." In 2021, the online award ceremony was held on September 9 (Boston time, USA), and it was the 15th consecutive year that a Japanese researcher won the prize. Our university has two Ig Nobel Prize winners: Professor Toshiyuki Nakagaki of the Research Institute for Electronic Science, who won the Cognitive Science Prize in 2008 and the Transportation Planning Prize in 2010, and Associate Professor Kazunori Yoshizawa of the Research Faculty of Agriculture, who won the Biology Prize in 2017. The prize-winners, who have been researching "slime mold" and "barklice," respectively—both of which are unknown to most people—discussed each other's research and the environment of Hokkaido University.

Professor Toshiyuki Nakagaki (left), Research Institute for Electronic Science; Associate Professor Kazunori Yoshizawa (right), Research Faculty of Agriculture, Hokkaido University

Associate Professor Kazunori Yoshizawa, Research Faculty of Agriculture

The copulatory organ of female *Neotrogla*. The blue-colored part is the female penis. (Photo by Kazunori Yoshizawa)

Conveying the true joy of science through unexpectedly funny research

Yoshizawa: You have won the Ig Nobel Prize twice. What was it like when you won the first one?

Nakagaki: The Ig Nobel Prize is a parody of the Nobel Prize, so when I went to the first award ceremony, I thought the mood would be more chilly. I thought I would be the target of ridicule. But it was a very fun ceremony full of all kinds of tricks and little stories.

Y: I wasn't able to attend the ceremony when I was awarded, but I felt that way when I watched the broadcast of the ceremony. They used the Nobel Prize and the authority itself as a laughing stock.

N: The spirit of the prize is to make people laugh and then make them think, isn't it? In addition to conveying the true joy of science to the world through research, people also laugh when they see something truly unexpected.

Y: Researchers, including us, are extremely serious, and that's why it's so interesting.

Discovery of Insects with Male and Female Sex Organs Reversed

N: Mr. Yoshizawa, you won an award for your research on a new insect species in which the male has a vagina, and the female has a penis.

Y: Reproduction is a competition between sexes to maximize benefit. The insect I studied, a genus of barklice called *Neotrogla*, lives in a very nutrient-poor cave in Brazil, so the semen of the male is a valuable source of nutrition for the female. So the female has evolved to have a switching valve to increase the amount of semen receiving ports to two, so that it can receive twice as much semen. And the female penis evolved as a structure to actively receive semen from males.

N: That's interesting; semen is required as nutrition.

The Ig Nobel Prize award ceremony is usually held at Harvard University (Photo provided by Teruyoshi Furusawa, Associate Professor, Rikkyo University)

Y: During mating, the female inserts her penis into the male's body and sucks out the sperm and nutrition. There is a fierce struggle between the male and female, like, "Give me the semen!" "No, I won't do it so easily!" (laughs)

N: So it's the opposite of ordinary creatures.

Y: My current guess is that females came to have penises as the power relationship during mating was reversed.

N: Just by talking about it, it changes the way we look at males and females. I think it's research that makes us fundamentally reconsider the evolution of males and females.

Demonstrating the cleverness of slime mold, a single-celled organism that solves mazes

Y: Your paper was published in *Nature*, wasn't it? I happened to be flipping through the magazine, and the moment I saw a photo of slime mold solving a maze, I immediately thought, "This is interesting!" Even if you don't understand the logic, you can intuitively understand the essence of the research.

N: Originally, I was studying the behavior of single-celled organisms, and I was always thinking about how to show their performance in an easy-to-understand way. For my research, I kept a true slime mold called "mozihokori" or "the blob" (*Physarum polycephalum*) and fed it oatmeal. And I tried placing the food far away, putting obstacles in the way, and creating situations that would be difficult for the slime mold.

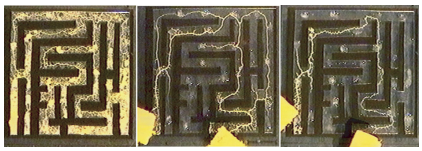
Y: Did it avoid the obstacles to move forward?

N: Yes. When it hit a dead end, it went back. Then I thought it would be a good experiment to do this in a maze.

Y: Your second award was for your research on transportation networks using slime mold.

N: When I increased the number of feeding sites to seven, I thought it would be interesting to try this on a map. Based on a map of the Tokyo metropolitan area, I placed devices that slime mold dislikes in places where it is difficult to set up a transportation network. Then, it would find an efficient route while avoiding those places. We thought this could be applied to the design of transportation infrastructure in society.

Y: When you put it side by side with the actual traffic network, you can clearly see the similarity. I was very impressed with this brilliant demonstration.



Slime molds solving a maze (Photo by Toshiyuki Nakagaki)

Accumulation of knowledge and experience broadens one's horizon

Y: As a researcher, what I find is that—even if you are looking at the same thing—the way you see it is completely different depending on the person. For example, small differences in small insects are immediately apparent to me.

N: Yes, yes! It's interesting that the way you see things changes depending on your knowledge and experience. It's like training your observational eyes and sensitivity.

Y: Nowadays, people are using genome data to estimate the phylogenetic evolution of insects, and it is generally thought that this phylogeny is the most accurate. However, from the perspective of a researcher focusing on the shape of living things, there is a part of me that says, "That's not true. I want to go against the trend and keep focusing on the shape."

N: It's important to observe carefully first. I want students to see a lot of real things.

Y: In that sense, fieldwork is also necessary. There are things you can't see unless you're in the actual environment.

N: In that respect, Hokkaido University is good. You can do fieldwork right on campus. (laughs)

Marc Abrahams (center), the founder of the Ig Nobel Prize, with Nakagaki (left) and Yoshizawa (right) in front of the Clark statue (Photo courtesy of Like! Hokudai)

The field where you can do what you really want to do

Y: Don't you think that you are often asked, "How can your research help the world?"

N: That's true. When reporters write an article, I think it would be easier for readers to understand if they conclude with that point.

Y: However, I would like to say out loud that basic research, like what we are doing, research that seems "useless" at first glance, is actually important. Really important.

N: It is the role of science to stimulate intellectual curiosity, not just to provide concrete benefits to the world.

Y: I thought that the point of the Ig Nobel Prize is how interesting the researcher makes the research, and I thought my research was too straightforward.

N: I think my research is also too straightforward, but I hear that all the Ig Nobel winners say the same. (laughs)

Y: I think the fact that we can do research that could win an Ig Nobel Prize shows the diversity and breadth of the academic field at Hokkaido University. A very simple discipline like insect taxonomy has survived for over 100 years.

N: That's really true. I want to welcome people who have a passionate desire to study something to Hokkaido University.

Y: Let's hope that the future winners will follow in our footsteps. (laughs) ●

> "The role of science is to stimulate intellectual curiosity, not just to provide concrete benefits."

Professor Toshiyuki Nakagaki, Research Institute for Electronic Science

Causes of concrete and asphalt deterioration explained

Scientists reveal that the deterioration of modern concrete and asphalt structures is due to the presence of trace quantities of organic matter in these structures.

A close-up of a bridge, showing deteriorated asphalt pavement and concrete (Photo: Akihiro Moriyoshi).

Cement and asphalt are vital to modern construction materials; cement is used for the construction of various buildings and structures, while asphalt is primarily used for highways and runways. They have been widely used for these purposes since the 1800s. It has been observed that modern concrete structures and asphalt structures tend to deteriorate much faster than historical structures, but the reason for this phenomenon was unknown.

A team of scientists from six institutions, including Akihiro Moriyoshi, Emeritus Professor Hokkaido University, have revealed that the presence of trace quantities of organic matter in modern concrete structures and asphalt pavements drive the deterioration of these structures. Their findings, which include novel methods to assess deterioration, were published in the journal *PLOS ONE*.

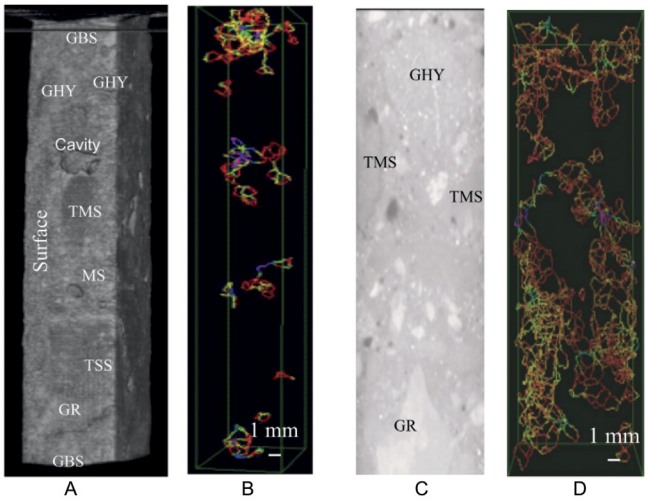
The deterioration of modern concrete structures and asphalt pavements are a major issue. The features that lead to deterioration include cracks, disaggregation (breakdown into fine white powder) and delamination (separation into layers). These deteriorated structures are unsafe for their intended purposes; rapid deterioration reduces the expected lifespan of structures, thereby increasing the costs for maintenance or replacement.

The scientists set out to develop a new method to assess the rate of deterioration in concrete. The current method is based on the width of surface cracks in concrete and a simple chemical test; however, it only gives an incomplete picture of the level of damage. During their experiments, the scientists happened to notice that a strange odor developed when commercial cement was mixed with water. They hypothesized that organic matter was responsible for the odor, and investigated the effect it has on deterioration of concrete.

The scientists developed the one-dimensional transient moisture permeation apparatus to accurately reproduce the field environmental conditions that concrete structures and asphalt pavements are exposed to, in the laboratory, over a period of 24 hours. When combined with CT scans, this method can be used to evaluate the precise extent of the damage. They tested a variety of asphalt samples from Japan dating back to 1960; a number of concrete samples from across the world were also tested, and a 120-year-old concrete sample was used as a reference.

The scientists showed that there are a number of organic molecules, from diverse sources, present in modern concrete structures and asphalt pavements: phthalates, diesel exhaust particulates, surfactants, and windshield washer fluids. These molecules are either introduced during the manufacturing process or absorbed from the environment, and cause rapid deterioration of concrete structures and asphalt pavements.

Of the organic matter present in cement, phthalates have the highest effect on deterioration more than phosphates and air entraining water reducing agents. Organic matter in water accelerates deterioration of asphalt pavements. The scientists also showed that crack width and length is the best determinant of concrete damage, while the degree of formation of amorphization is the best determinant of deterioration. They believe that their findings can be used to develop novel formulations for long-lasting concrete structures and asphalt pavements. ●



CT scans showing cracks in damaged concrete. A and B show cracks in the first layer while C and D show cracks in the second layer. GBS, GHY, TMS, MS TSS and GR refer to different types of aggregates in the mortar (Akihiro Moriyoshi, et al. *PLOS ONE*. May 13, 2021).

ORIGINAL ARTICLE
Akihiro Moriyoshi, et al. Deterioration of modern concrete structures and asphalt pavements by respiratory action and trace quantities of organic matter. *PLOS ONE*. May 13, 2021.

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Plant flowering in low-nitrogen soils: a mechanism revealed

Scientists from Japan, Europe and the USA have described a pathway leading to the accelerated flowering of plants in low-nitrogen soils. These findings could eventually lead to increases in agricultural production.

FBH4 is necessary for accelerated flowering in *Arabidopsis*. Accelerated flowering is only seen in the wild type(left), but not in FBH4 deficient plants (right) plants, under low-nitrogen conditions (Miho Sanagi, et al. *Proceedings of the National Academy of Sciences of the United States of America*. May 11, 2021).

Nitrogen is one of the three macronutrients required by plants for growth and development, along with phosphorus and potassium. Nitrogen-rich condition induces plant growth, particularly the growth of stems and leaves, while delaying flowering. On the other hand, in some plants, low-nitrogen conditions lead to a change from growth mode to reproductive mode, therefore accelerating flowering. However, the molecular mechanisms that regulate flowering under these conditions are not known.

A team of scientists led by Associate Professor Takeo Sato of Hokkaido University's Graduate School of Life Science has revealed the molecular mechanism responsible for the acceleration of flowering in *Arabidopsis* under low nitrogen conditions. Their findings were published in the journal *Proceedings of the National Academy of Sciences of the United States of America* (*PNAS*).

Arabidopsis, a cruciferous plant, is well known as a model plant in biology and has an extensive database of its protein expression. In the current study, the team first identified a set of proteins involved in flowering that became active as a result of changes in nitrogen level. One of these was the gene regulation factor FLOWERING BHLH 4 (FBH4). Through experiments using FBH4 deficient plants, this protein was found to be responsible for accelerated flowering under low-nitrogen conditions.

Further investigation suggested that FBH4 is extensively phosphorylated by another protein called SnRK1. Low-nitrogen conditions suppress SnRK1 activity, which in turn results in the dephosphorylation of FBH4. The dephosphorylated FBH4 moves to the nucleus to activate genes responsible for flowering. Dephosphorylated FBH4 is also responsible for controlling the expression of other genes vital for plant survival under low nitrogen conditions, particularly those related to nitrogen recycling and remobilization.

The scientists concluded that, in response to inadequate nitrogen, *Arabidopsis* plants appear to precisely control gene expression related to developmental and metabolic processes required for flowering through FBH4. "The FBH family of genes is present in major crop plants," says Takeo Sato. "Crop plants exhibit early flowering under low-nitrogen conditions; if we can control FBH activities in these crop plants, it might be an effective way to sustainably increase agricultural production." ●

***Arabidopsis* plants used in one of the experiments during the study (Photo: Takeo Sato).**

Takeo Sato, with Arabidopsis plants in the culture room (Photo: Takeo Sato).

ORIGINAL ARTICLE

Miho Sanagi, et al. Low nitrogen conditions accelerate flowering by modulating the phosphorylation state of FLOWERING BHLH 4 in *Arabidopsis*. *Proceedings of the National Academy of Sciences of the United States of America*. May 11, 2021.

FUNDING

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The Silence of INDIGENOUS PEOPLE

Assistant Professor
Mai Ishihara

Assistant Professor Mai Ishihara is the first female full-time researcher at Hokkaido University's Center for Ainu and Indigenous Studies (CAIS) and is the first female faculty member who openly reveals her Ainu ancestry. As a quarter-Ainu, Ishihara talked about how she had been subdued by her own ignorance, and later by silence, of her Ainu ancestry. She transformed her struggle and her views on the pain faced by her Ainu (indigenous people of Hokkaido) ancestors into a book based on her long-term research.

Ishihara reminisced about the moment when she had just learned about her Ainu ancestry. At the age of 12, her mother revealed the story of her bloodline and added that she ought not to reveal the fact to other people unless they have a certain amount of knowledge in the history of Hokkaido and Ainu people. Henceforth, Ishihara led her life as a "Silent Ainu." Ishihara coined and used this term to refer to people who are aware of their Ainu heritage, but do not know how to address this no matter how much they want to talk about it.

"I was taken aback by that revelation. Up until that point, I had grown up with zero contact with anything that is related to Ainu. My mother chose to bring up the subject out of the fear that I would have grown up with discriminatory perspectives towards the Ainu people — including my own ancestors," said Ishihara.

Ishihara had only started to publicly come out about her ancestry in her 20s. However, after telling people around her, Ishihara realized that most of them were unable to exhibit deeper understanding about this fact. She came to see that the struggle and the pain caused by the marginalization towards the indigenous people need to be widely addressed.

"Japan is widely believed to be monocultural. On the other hand, I can see that the Japanese government is trying to embrace multiculturalism. Coexistence is beginning to be seen as an essential element to handle the demographic problem, such as the low fertility rate and the decreasing population. We are just entering the beginning phase of this discussion," explained Ishihara.

Compared to previous decades, when revealing one's Ainu ancestry

was still a taboo, there are now more efforts to boost Ainu people's visibility and to preserve their cultural heritage. Ishihara noted how daily lives in Hokkaido regions are beginning to be more imbued with Ainu culture. She thought that the effect was rather powerful, but it is not yet sufficient.

"In 2019, a legal act that recognizes Ainu as Japan's indigenous group was passed. While such measures certainly form a degree of safety for Ainu people, however, the law does not mention specific indigenous rights. In places such as Scandinavia, North America, Taiwan, Australia and New Zealand, indigenous people have indigenous rights. More international comparative studies are needed to find out why the debate on indigenous rights does not seem to progress in Japan. Studying the Ainu people as a matter of transitional justice and multiculturalism will expand international and interdisciplinary research around this subject," added Ishihara.

Ishihara spent ten years on an autoethnographic research that she submitted as her PhD dissertation. This work was turned into a book, newly re-released by Hokkaido University Press in 2021, entitled "Autoethnography of 'Silence': The Story of the Pain of Silent Ainu and Their Care". In this book, Ishihara listed and described the details on the different stages of being a Silent Ainu. Another highlighted issue is the importance of discussions on mixed-race people. This book is the first publication in Japan containing "autoethnography" in the title.

"Autoethnography is indeed quite novel and challenging in many ways, but I was driven to perform a study on myself, on my historicity as a Silent Ainu, to provide descriptions on Ainu studies that have long been insufficient in reaching people like myself," disclosed Ishihara, who has just finished editing yet another book depicting Ainu people that soon will be published by the same publisher. Ishihara received the 38th Masayoshi Ohira Memorial Prize for this book, one of 5 recipients this year. The prize is given annually to individual authors, collaborations or compilations, whose works contribute to the development of "the Pacific Basin Community Concept" and regional studies of the Pacific Basin region.

Up until the early Meiji period (late 19th century) Ainu Kotan (settlements) used to exist in the present-day Central Lawn of Hokkaido University. Salmon could be found swimming in the Sakushukotoni River which ran through this area. (Credits: Hiroshi Oda, Faculty of Humanities and Human Sciences)

Currently, Ishihara is also a part of Global Station for Indigenous Studies and Cultural Diversity (GSI) collaborative research group, a part of Hokkaido University's Global institution of Collaborative Research and Education (GI-CoRE).

"In particular, I have a great interest in conducting research on women of indigenous groups because women of different cultural backgrounds share the same feelings and concerns, which makes it easier for indigenous female researchers to connect and establish networks. We hope our activities will be able to provide useful resources for diverse networking, which is important in the post-COVID-19 era."

"Women of different cultural backgrounds share the same feelings and concerns, which makes it easier ... to connect and establish networks."

BOOK INFORMATION
Source: Hokkaido University Press
Title: 『〈沈黙〉の自伝的民族誌―サイレント・アイヌの痛みと救済の物語』("Autoethnography of 'Silence': The Story of the Pain of Silent Ainu and Their Care".)
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BENJAMIN LIST AWARDED NOBEL PRIZE IN CHEMISTRY 2021

On October 6th, 2021, the Royal Swedish Academy of Sciences awarded the 2021 Nobel Prize in Chemistry jointly to Benjamin List of the Max-Planck-Institut für Kohlenforschung and David W. C. MacMillan of Princeton University "for the development of asymmetric organocatalysis." He was conferred the Nobel Prize in Chemistry 2021 in a ceremony held in Berlin, Germany, on December 7, 2021

Dr. List has been working on the development of new chemical reactions using organocatalysts as a Principal Investigator at the Institute for Chemical Reaction Design and Discovery (WPI-ICReDD) at Hokkaido University since 2018, and he has also been a Specially Appointed Professor since May 2020.

What follows is a condensed, edited transcript of the video conference with Nobel Laureate Dr. Benjamin List, held at ICReDD, Hokkaido University on October 7, 2021.

How do you feel about receiving the Nobel Prize?

It's like a dream come true. It's almost unreal in a way. I was in Amsterdam with my wife [on the day of the announcement]. In the back of my mind, I knew that today the prize would be given. But I did not expect this at all. Certainly not at my "relatively" young age.

Sometime around 11.00, the phone rang in my pocket. On the phone, it said a phone number I didn't know but underneath it said "Sweden". I went outside and it was the call, it's the call and that was such an incredible moment and it was just incredible.

What is the key to this important achievement in Chemistry?

Of course, the component of luck is always involved, but also, sort of serendipity. From my PhD supervisor, Johann Mulzer, I knew about the old proline work in the 70s, that was somehow forgotten. And then, at Scripps Institute, when I looked at the crystal structure of the enzymes I was working with, I saw there's an amino group and there's an acid, and then — I know it's really naïve, but — amino acid came to mind. Everything fell into place.

But I felt a little bit silly and maybe naïve, because everybody knew that this is a stupid idea. Because at the time, the thinking was that small molecules could not be catalysts. So, I did this experiment and I kept it a secret. I think we should cherish this feeling of insecurity; it's really special. We should not feel too confident about our work.

What made you want to participate in ICReDD?

First of all, it's the general inspiration of the Japanese-style chemistry, like this radical innovativeness about it, this courage to try new things. Of course, Maeda-sensei's approach to computational chemistry, to theoretical chemistry, is unique. I think we are at the phase where the potential of computational chemistry can be realized, for the first time in the history of chemistry. I'm very curious and I want to be part of this.

Has your impression of research in Japan changed after joining ICReDD?

I love this interdisciplinarity and your enthusiasm about opening up to other countries, other people, other

Benjamin List receiving his Nobel Prize medal and diploma in Berlin, Germany at Harnack House, Max Planck Society for the Advancement of Science.
© Nobel Prize Outreach. Photo: Bernhard Ludewig.

influences. I love this mixing up of computation, scientific experiments and artificial intelligence.

What kind of Chemistry research do you want to conduct in the future?

I'm waiting for the day that we sit down and design chemical reactions from scratch. Maybe one day we'll be able to design enantio-selective catalysts. Right now, just predicting the right enantiomer would be an incredible challenge.

Ultimately, maybe this work might make chemists superficial, in a certain way. Maybe we won't need this style of chemistry that we do, at some point. I don't think this is happening very soon, though. I am not worried about that time, because then we can do other great things. There are so many things we can do and be excited about.

Do you have a message to young researchers?

It's a simple message, it's not a revolutionary one, but it's an important one: Follow your enthusiasm, do what you really love to do, and don't anticipate the outcome. Don't get attached to the outcome. ●

ICReDD establishes the Akira Suzuki Awards in Chemical Reaction Design and Discovery

The Akira Suzuki Award and the ICReDD Award, both sponsored by the Tosoh Corporation, were established in 2021 by the Akira Suzuki Award Organizing Committee, led by professors at the Institute for Chemical Reaction Design and Discovery (ICReDD), in commemoration of Professor Akira Suzuki's winning of the 2010 Nobel Prize in Chemistry and in celebration of his 90th birthday. The purpose of these awards is to recognize outstanding contributions to chemical reaction design and discovery defined in the broadest sense, and to contribute to the advancement of science and technology. The Akira Suzuki Award honors contributions made via experimental chemistry, while the ICReDD Award honors contributions made via computational (theoretical) chemistry and information science.

The awards consist of a medal and a monetary prize of 10,000 US dollars. The awards are bestowed each year during the annual ICReDD International Symposium, at which recipients give an award lecture. Winners are selected by the Award Selection Committee, separate from the Award Organizing Committee, based on the above criteria. The award selection committee for the Akira Suzuki Award includes Professor Benjamin List, 2021 Nobel Laureate in Chemistry.

The inaugural award ceremony and lectures will take place as part of the 4th ICReDD International Symposium at Duke University, Durham, North Carolina, USA, on March 12th and 13th, 2022.

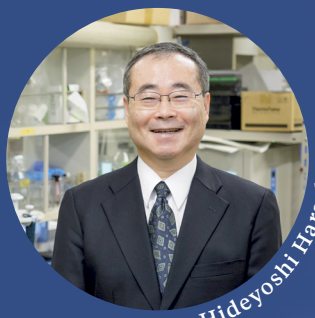
The winner of the inaugural Akira Suzuki Award for 2021 is **Stephen L. Buchwald**, the Camille Dreyfus Professor of Chemistry at the Massachusetts Institute of Technology. He completed his PhD with Jeremy R. Knowles at Harvard University in 1982. He then was a postdoctoral fellow at Caltech with Robert Grubbs before joining the faculty at MIT in 1984. Professor Buchwald is well-known for developing the Buchwald-Hartwig amination, which enables aromatic carbon-nitrogen bond formation. His group focuses on the creation of catalysts that enable carbon-carbon and carbon-nitrogen bond formation and as well as other methods for the synthesis and modification of bioactive molecules.

The winner of the inaugural ICReDD Award for 2021 is **David J. Wales**, Professor of Chemical Physics at the University of Cambridge and Chair of the Theoretical Chemistry group. He completed his PhD at Cambridge in 1988 under the supervision of Anthony J. Stone and then held a series of research fellowships, including a Royal Society University Research Fellowship from 1991 to 1998. He became a lecturer at Cambridge in 1998 and a professor in 2008, and was elected a Fellow of the Royal Society in 2016. His research focuses on understanding how structure, dynamics and thermodynamics are encoded in the potential energy landscape, with applications to protein folding, cluster chemistry, and glasses.

OTHER AWARDS & RECOGNITIONS
received by Scientists at Hokkaido University


Yuma Yamada

Associate Professor Yuma Yamada of the Faculty of Pharmaceutical Sciences, Hokkaido University was declared as the recipient of the American Pharmacists Association's 2022 Ebert Prize—the oldest existing pharmacy award in the US—on December 8, 2021, in recognition for his paper *Mitochondrial Delivery of an Anticancer Drug Via Systemic Administration Using a Mitochondrial Delivery System That Inhibits the Growth of Drug-Resistant Cancer Engrafted on Mice* (Yuma Yamada, et al. Journal of Pharmaceutical Sciences. May 3, 2020; 10.1016/j.xphs.2020.04.020).


Hideyoshi Harashima

Professor Hideyoshi Harashima of Hokkaido University is the latest awardee of the Høst-Madsen Medal, the highest scientific honour awarded by the International Pharmaceutical Federation (Fédération Internationale Pharmaceutique, FIP). This is the second recognition he has received from the FIP; he was bestowed with the Distinguished Scientist Award in 2010.


Reiko Kishi

Distinguished Professor Reiko Kishi of the Hokkaido University Center for Environmental and Health Sciences was honored with the International Society for Environmental Epidemiology (ISEE)'s prestigious 2021 John Goldsmith Award, on August 26, 2021, for her life-long efforts and innovative contributions to the development of the field of environmental epidemiology, which have led to sustainable and outstanding contributions to society.


Madoka Ono

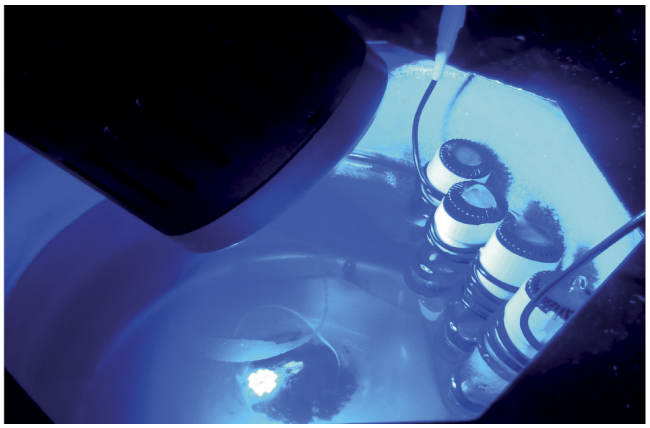
Associate Professor Madoka Ono of Research Institute for Electronic Science (RIES), Hokkaido University is to be awarded the 12th Promotion and Nurturing of Female Researchers Contribution Award, also known as the Kashiko Kodate Award, sponsored by the Japan Society of Applied Physics (JSAP). The award is given in recognition of her study on the development of high-performance oxide glasses through its structural control.


Akira Kakugo

An international team including **Associate Professor Akira Kakugo** has been selected as one of 28 recipients of the HFSP (Human Frontier Science Program) Awards 2021. The project *Structural damage to axons resulting from repetitive mechanical motion* — which is led by Henry Hess (Columbia University, USA), Akira Kakugo (Hokkaido University, Japan), Vittoria Raffa (Università di Pisa, Italy) and Orit Shefi (Bar-Ilan University, Israel) — was one of 21 Program Grants selected by the HFSPO Board of Trustees; it will seek to address unresolved questions in the field of mechanobiology, such as how nerve cells repair damage and maintain function over a long period of time.

Blue LEDs light the way toward sustainable development

A new method for creating a highly useful chemical subunit eliminates the need for precious metals, potentially leading to the sustainable production of pharmaceuticals and electronics.



Reaction vials being exposed to blue light from an LED (Photo: Yusuke Masuda).

Light-emitting diodes (LEDs) are commonly used in the electronic displays in our TVs, smartphones, and other devices; now, researchers at the Institute of Chemical Reaction Design and Discovery (ICReDD) at Hokkaido University have utilized blue LEDs to develop a more sustainable way to make key chemical subunits that have potential uses in pharmaceutical and photoelectronic development.

Researchers utilized blue LEDs in combination with a copper-based molecular catalyst to perform what is known as a cross-coupling reaction, in which two molecules are joined via a carbon-carbon bond. This is one of the most widely used types of reactions and is essential for creating most of the chemical products used today. The use of copper—a cheaper and more commonly available metal—as a catalyst for a cross-coupling reaction is a major breakthrough in sustainability, since this reaction typically relies on the use of precious metals such as palladium.

The new method is also advantageous because the copper metal in the molecular catalyst itself absorbs the blue light, rather than needing a separate light-absorbing compound in addition to the catalyst. This makes the synthesis not only cheaper and simpler to perform, but also easier to control, since there are fewer moving parts.

The blue light plays a key role in activating the copper-based catalyst. Theoretical calculations showed that this light exposure causes electrons to move from the metal copper atom to a connected subunit of the molecular catalyst. This excited state has separated electrical charges, making the catalyst much more reactive, and researchers were able to use it to carry out a cross-coupling reaction that creates an acyl group, which are useful for the synthesis of pharmaceuticals and photoelectronic materials.

Implementation of this new method is expected to both provide cost savings and increase the sustainability of the production of a wide variety of chemical compounds with potential uses in medicine and electronics. Its utilization of commonly available materials makes it especially appealing.

"This synthetic method is a breakthrough because it combines two easily obtainable items, blue LED light and copper, to achieve a coupling reaction that did not exist before," commented Assistant Professor Yusuke Masuda. "Technology that produces useful compounds from resources which are abundantly available on Earth is critical for the sustainable development of humanity. I expect this advance will become a milestone in the development of sustainable molecular synthetic methods."

ORIGINAL ARTICLE
Yusuke Ueda, et al. Photoinduced Copper-Catalyzed Asymmetric Acylation of Allylic Phosphates with Acylsilanes. *Journal of the American Chemical Society*. January 6, 2022.

FUNDING
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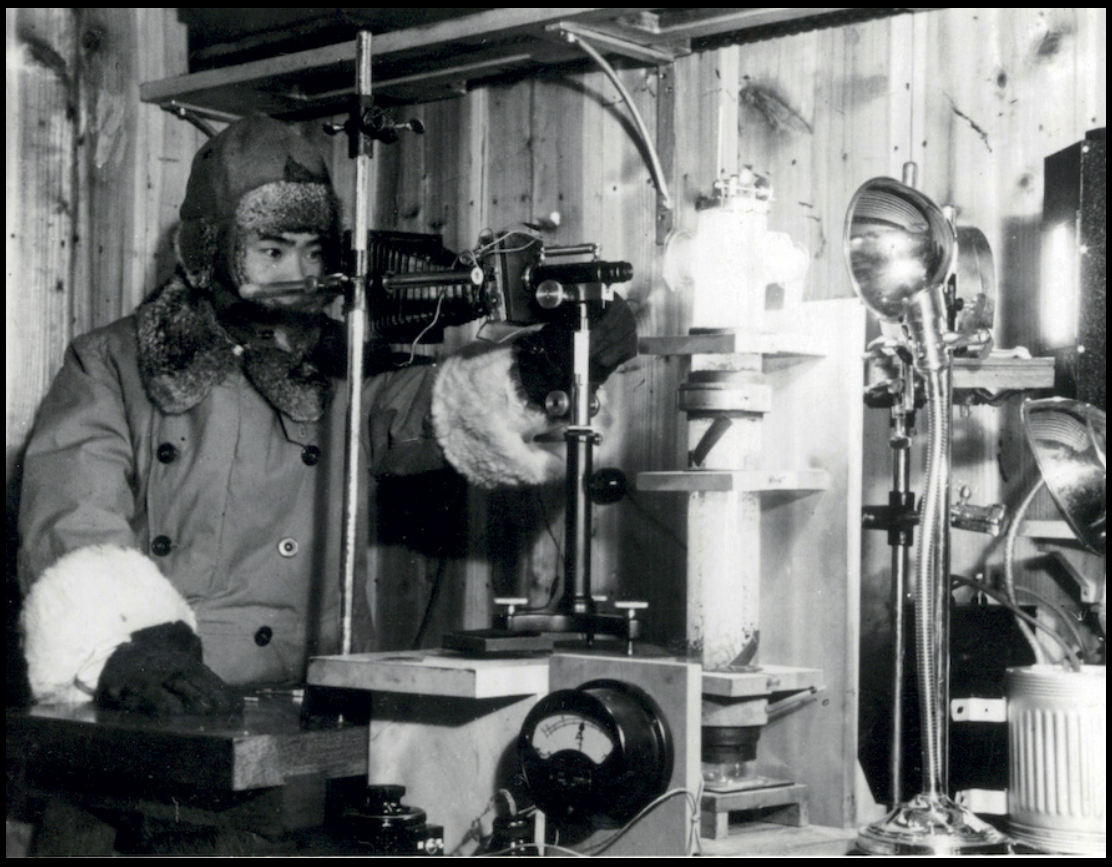
Professor Masaya Sawamura (top), Professor Jun-ya Hasegawa (middle), and Assistant Professor Yusuke Masuda (bottom) of the research team at the Institute for Chemical Reaction Design and Discovery (ICReDD), Hokkaido University (Photos provided by ICReDD, Hokkaido University).



Ukichiro Nakaya working in his low temperature laboratory (Photo: Hokkaido University Archives)

Low temperature science: THE PAST, THE PRESENT, AND FUTURE

Hokkaido University put the cornerstone of the development of low temperature science upon the birth of the Institute of Low Temperature Science (ILTS) in 1941. Prior to its establishment, the institution owes gratitude to the founding father, Ukichiro Nakaya (1900-1962). Through his groundbreaking research and innovations, Nakaya made his name known to the world, particularly in the scientific findings on snowflakes. The year 2020 marked the 120th anniversary of Nakaya's birth, in which we also commemorate his achievements and influence in the development of low temperature science.

Ukichiro Nakaya – An individual ahead of his time

Born in 1900, in what is now Kaga City of Ishikawa Prefecture, Nakaya moved to Hokkaido in 1932 to fill in the position of Assistant Professor at Hokkaido Imperial University's (current Hokkaido University) School of Science. Relocating to the cold area tweaked his curiosity and challenged him to carry on scientific observations on snow crystal formations in the Tokachi Region and Mount Asahidake of Hokkaido. In 1935, a special low temperature science laboratory was finally erected on the campus which allowed Nakaya to gain deeper insights on snow regardless of the season.

In March 1936, using a convective snow-making apparatus they had constructed out of cylindrical glass, a historical moment took place within the lab. By adjusting the air temperature and humidity, Nakaya and his colleagues managed to form the very first artificial snowflake at the tip of a thin sliver of rabbit's hair, taken from the fur coat of one of his assistants.

Following this success, Nakaya proceeded to produce more snow-related findings such as the "Nakaya Diagram" — a diagram of snow crystal morphology — that has been developed ever since and significantly contributes to meteorological

studies. Illustrating different shapes of snowflakes, scientists could refer to this diagram to analyze the situation up in the clouds by scrutinizing the snow crystal's structures. This direct correlation between the atmospheric condition and the morphology of snow crystal is poetically reflected in what is arguably his most famous remark:

"Snowflakes are letters sent
from heaven."

Nakaya even went as far as applying interdisciplinary approaches in his research and frequently embarked to different places around the world to study any subject related to the cold climate: not just snow but ice, fog, winter clothes, etc. In 1957, Nakaya visited Greenland for the first time to join a research project on ice cores; he visited several more times until his passing in 1962.

By having initiated the scientific experiments on low temperature science — a field of science that had almost been overlooked during his era — Ukichiro Nakaya laid the foundation upon which the current low temperature scientists unveil more discoveries that may answer some fundamental questions of human life.

From a small-sized laboratory, to a forerunner facility

As a result of Nakaya's labors, the small-sized cold room which had served as his experimental ground gradually expanded to the very first research institution of Hokkaido University, ILTS, formally established in November 1941. Currently housing 45 faculty members, ILTS works in collaboration with several domestic and international universities and research institutions. Living up to Nakaya's principles, ILTS is extending the scope of its research activities through interdisciplinary studies. The research topics are greatly diverse; from determining mammalian hibernation systems through a physiological perspective, to geomorphological observations of snowy regions.

The previous ILTS building at Kita 10 (left, photo provided by Hokkaido University Archives) and the current building at Kita-19 (right) at Hokkaido University Sapporo Campus.

ILTS's expansion of the research scope even takes on a literal level out of this world after having established a research group of astrophysical chemistry, in which the scientists are focusing on molecular evolution in space.

"This particular branch of science is certainly beyond Nakaya's thinking," commented Dr. Manabu Fukui, the director of ILTS. "By virtue of the seed planted by Ukichiro Nakaya, the discipline of low temperature science has now soared to the uncovering of humanity's and the universe's origins through interstellar molecular studies."

To keep up with the current exigency in the global environment, the institution is continuously performing research to gain important viewpoints regarding climate change. Research expeditions to both of the earth's polar regions have been conducted, such as the 61st Japanese Antarctic Research Expedition in November 2019 that was led by ILTS's very own Associate Professor Shigeru Aoki. Benefitting from these kinds of expeditions, the participating scientists obtain scientific specimens and discoveries on the past and present outlook of our planet's condition, based on which one could calculate the upcoming prospects.

In terms of educational advancement, ILTS serves as an academic institution for graduate students affiliated with Hokkaido University. ILTS is also a member of an interuniversity cryosphere science education program called International Antarctic Institute (IAI), in which the institution actively takes part in the exchange of pedagogic activities and resources. Special lectures have been conducted as Hokkaido Summer Institute (HSI) courses that are available for students around the world to attend.

The research institute has reached other milestones in their network expansion. In 2004, Pan-Okhotsk Research Center was opened in Sapporo Campus, inviting more joint-projects in the evaluation of environmental conditions around the Sea of Okhotsk area, whose conditions are sensitive to climate change and global warming. In 2010, ILTS was designated as one of Japan's nationwide joint-use institutes by the Ministry of Education, Culture, Sports, Science and Technology (MEXT). As we are heading towards ILTS' 80th anniversary in 2021, Dr. Fukui expressed his aspirations for the institution.

"I have expectations on ILTS that it will devotedly continue advancing and producing scientific achievements that can contribute to many people's lives and the advancement of basic science." ●

Ice cores drilled out and brought from Antarctica for various research subjects (left) are being stored in a special -50°C low temperature storage room of ILTS (right).

Executive Vice President Atsushi Yokota (second from left), Head of the SDGs Initiative Office, at the press conference announcing the Institute for the Advancement of Sustainability.

PURSUING A SUSTAINABLE FUTURE

Institute for the Advancement of Sustainability launched

Hokkaido University officially announced the establishment of the University's Institute for the Advancement of Sustainability in a press conference held in the Centennial Hall, Hokkaido University on June 29, 2021. The new institute was launched and is active from August 1, 2021.

Hokkaido University's enduring journey towards sustainability officially started in 1996, far before The United Nations (UN) set up the Millennium Development Goals (MDGs), the precursor of the running Sustainable Development Goals (SDGs), in 2001. The Hokkaido University's 1996 Campus Masterplan sowed the seeds of a practical long-term plan to realize a sustainable campus. This plan has been evolved several times, each time adjusted to the local and global demands. In 2008, concurrent with the 2008 G8 Summit in Hokkaido, Hokkaido University hosted the first G8 University Summit in Sapporo.

With this new Institute, the University is determined to further progress in this area and "offer solutions to global problems through contributions towards SDGs". This initiative anticipates more engagements and cooperation with various stakeholders: citizens, local governments, companies, and also national and international universities.

President Kiyohiro Houkin will preside over the Institute for the Advancement of Sustainability. Under the Institute, a new office called SDGs Initiative Office has been established, headed by Executive Vice President Atsushi Yokota; the existing Sustainable Campus Management Office is now headed by Executive Director Nobuyoshi Sugawara. Both offices will work in tandem to oversee SDGs-related initiatives by the University.

Hokkaido University among top universities in THE Impact Rankings 2021

The Times Higher Education (THE) Impact Rankings measures higher education institutions' performances in delivering the United Nation (UN)'s Sustainable Development Goals (SDGs) and the impact. For the 2021 rankings, data was collected from 1240 institutions worldwide.

Hokkaido University topped in Japan along with six other universities, all of which ranked 101-200th worldwide. The University is 15th place worldwide for the contributions towards Zero Hunger (SDG 2). For the other individual SDG rankings, Hokkaido University is also placed within the top 100 university worldwide, including: 47th for Industry Innovation and Structure (SDG 9), 82nd for Life below Water (SDG 14), and 94th for Life on Land (SDG 15).

Hokkaido University joined the International Universities Climate Alliance

The International Universities Climate Alliance (IUCA) was established in April, 2020 to help communicate research insights on the most effective means to meet the unprecedented global challenge of climate change. On November 11, 2020, Hokkaido University joined the alliance as the only member from Japan as of the date.

The University of New South Wales (UNSW Sydney), Australia is facilitating the establishment of the Climate Alliance and 48 institutions are working together on this platform (as of November 30, 2020). The Climate Alliance is made up of seven regional committees, linked to the IUCA Executive Committee and the Climate Alliance Assembly. Under the five research themes and four sub-themes proposed by the alliance, researchers will exchange information and form networks in the same field.

ASTEROID RYUGU

SAMPLES ARRIVED AT HOKKAIDO UNIVERSITY

Professor Shogo Tachibana (far left), Professor Hisayoshi Yurimoto (far right), and the members of Yurimoto's laboratory with the Ryugu samples.

Retrieved by the Hayabusa2 exploration mission, the samples of asteroid Ryugu arrived at Hokkaido University on June 21, 2021. The samples were personally delivered by Professor Shogo Tachibana from the School of Science, The University of Tokyo. Hokkaido University's Professor Hisayoshi Yurimoto will lead a chemistry analysis team, one of the teams that will conduct the initial analyses on the samples, using Hokkaido University's isotope microscope.

Born 4.6 billion years ago, withstanding the tectonic forces and heat, Ryugu is believed to have recorded the memory of the solar system in its infantile period. Abundant with carbon, the asteroid is classified as a C-type asteroid, from which it is expected that we can find organic materials and water that are essential components of life on earth. Over the next one year, the preliminary analysis teams aim to uncover the mysteries surrounding the formation/birth of the ocean and life, as well as the origin and evolution of the solar system.

In addition to the chemical analysis by Yurimoto's team, these valuable samples will also be analyzed by different teams from the perspectives of the coarse grain compositions, fine grain compositions, volatile compounds, solid organic components, and soluble organic components.

The chemical analysis team will analyze the samples using the isotope microscope which has been developed at Yurimoto's laboratory for over 30 years. In their research activities, this device captures the images of the fine distribution of elements' isotopes from meteorite and asteroid samples. Isotopes are the same elements with different atomic weights. By analyzing the isotope ratios, they can learn about the age and origin of components/substances/material.

Yurimoto is enthusiastic about this preliminary analysis. "The treasure chest has just been opened. From now on, we will inspect its content down to every nook and cranny," he said. ●

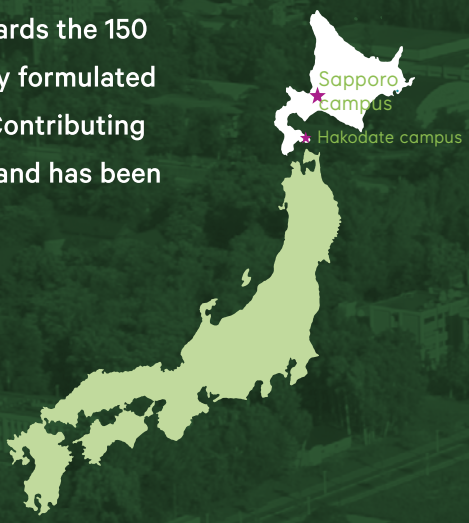
Ryugu samples were packed and carried in a sealed pack of nitrogen gas to avoid contamination by the earth's atmosphere.

Professor Hisayoshi Yurimoto (left), the leader of the chemical preliminary analysis team for the Hayabusa2 project. / Supervisor for the entire preliminary analysis team of Hayabusa2 Project, Professor Shogo Tachibana (right) of The University of Tokyo.

Hokkaido University *at a glance*

A Long History

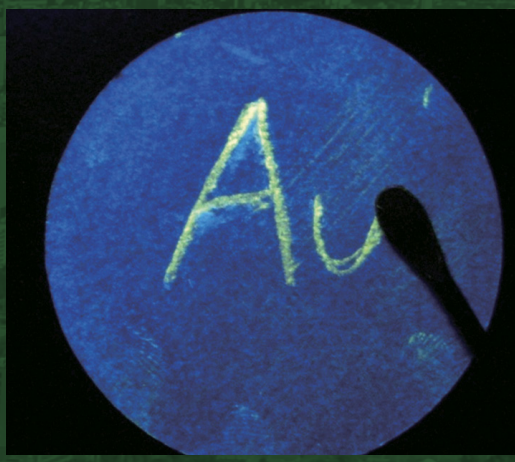
Founded in 1876 as Sapporo Agricultural College, Hokkaido University is one of the oldest, largest, and most prestigious universities in Japan. Boasting one of the largest campuses in Japan, the university houses cutting-edge research facilities, a university hospital, and a number of field research 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.

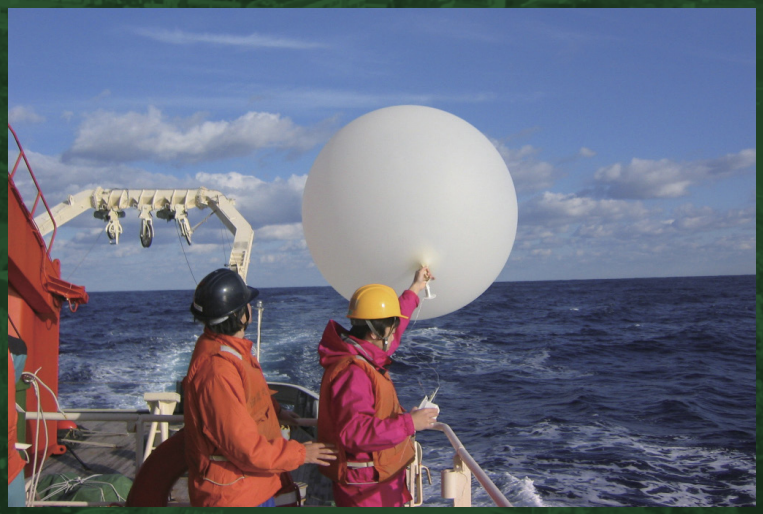


Contributing towards
the **resolution**
of **global** issues

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 150 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 2021

1876
established

12
undergraduate schools

21
graduate schools

11
overseas offices

11
overseas offices

227,860
alumni

689***
partner institutions
***Located in 63 countries/regions

18,171*
students
*Including 2,104 international students from 100 countries/regions

3,893**
faculty & staff
**Including 853 International Staff

RANKING

1st in Japan* **101-200th** in the world
Times Higher Education (THE) World University Impact Rankings 2021 *(shared with 6 other universities)

98th
in Asia
Times Higher Education (THE) Asia University Rankings 2021

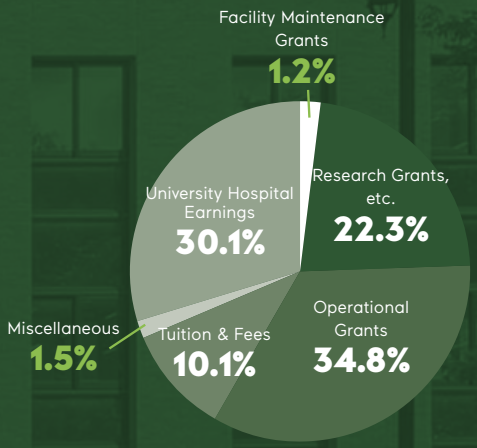
8th in Japan **145th** in the world
QS World University Rankings 2022

5-7th in Japan **151-200th** in the world
Academic Ranking of World Universities (ARWU) 2021

7th in Japan **114th** in the world
Nature Index Top Academic Institutions 2021

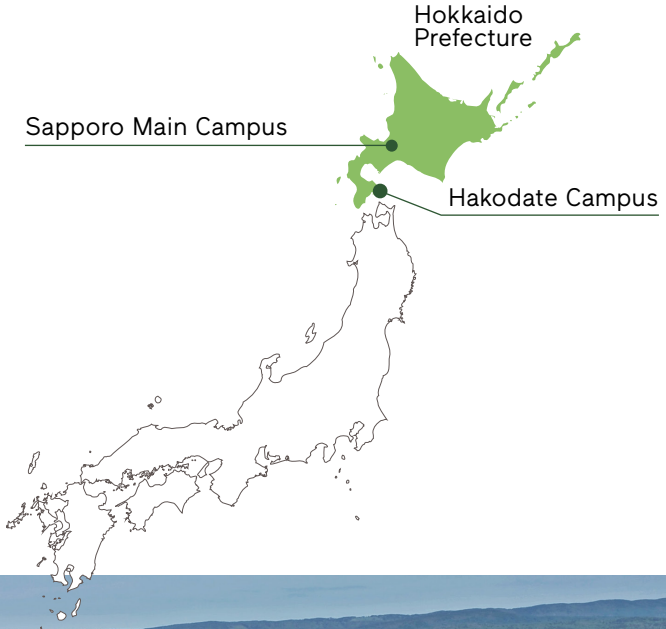
REVENUE

¥104,568m
revenue in 2021



HOKKAIDO UNIVERSITY

Founded in 1876 as Sapporo Agricultural College, Hokkaido University is one of the oldest, largest, and most prestigious universities in Japan. The university attracts prospective students all around the globe with the diverse degree programs offered and the all year round scenic beauty. The campuses are located in the cities of Sapporo and Hakodate of Hokkaido and 21 facilities are spread throughout Hokkaido and mainland Japan, contributing towards the resolution of global issues.



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