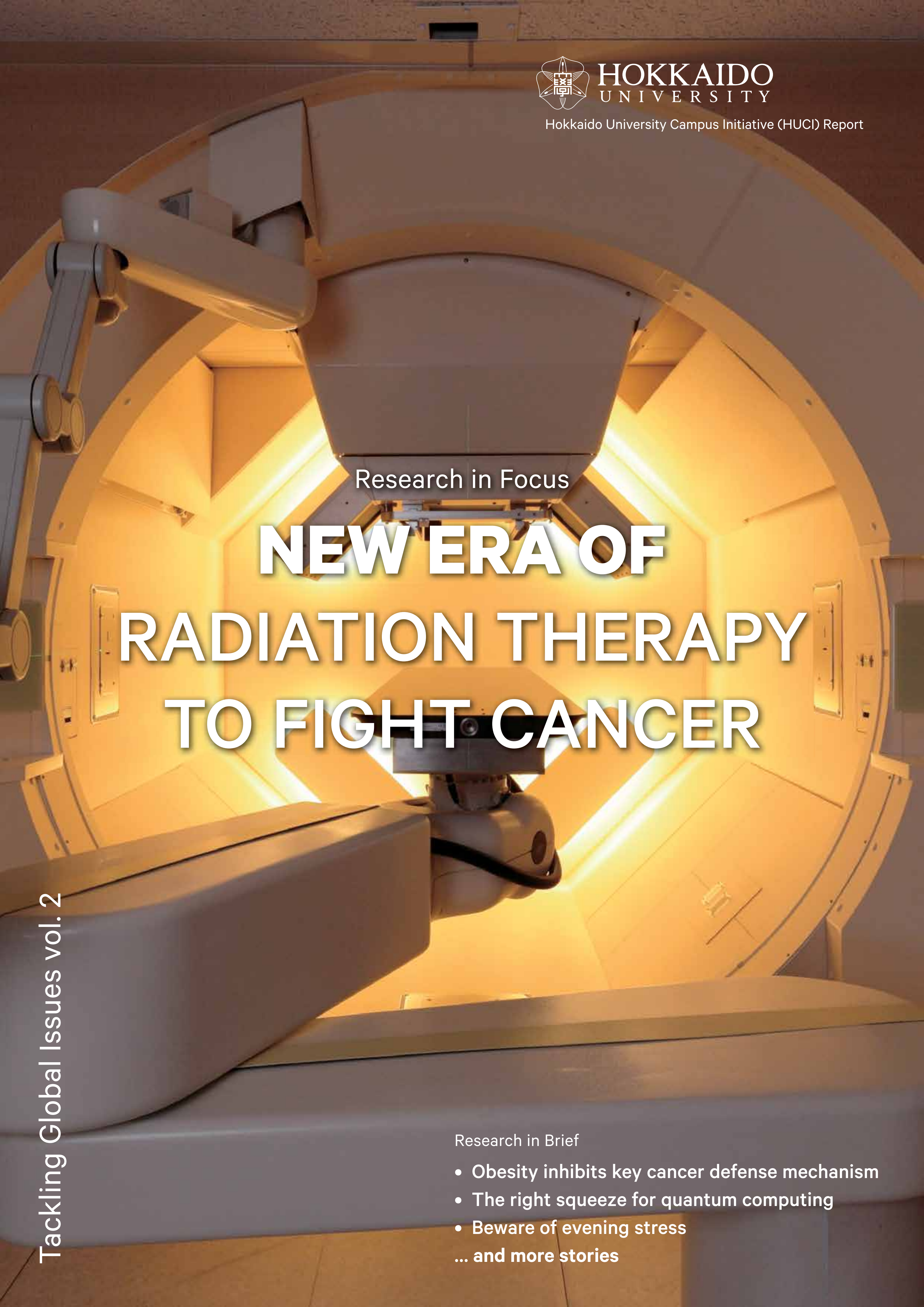

HOKKAIDO UNIVERSITY

Hokkaido University Campus Initiative (HUCI) Report

Research in Focus

NEW ERA OF RADIATION THERAPY TO FIGHT CANCER

Research in Brief

- Obesity inhibits key cancer defense mechanism
- The right squeeze for quantum computing
- Beware of evening stress

... and more stories

Tackling Global Issues vol. 2

Contents

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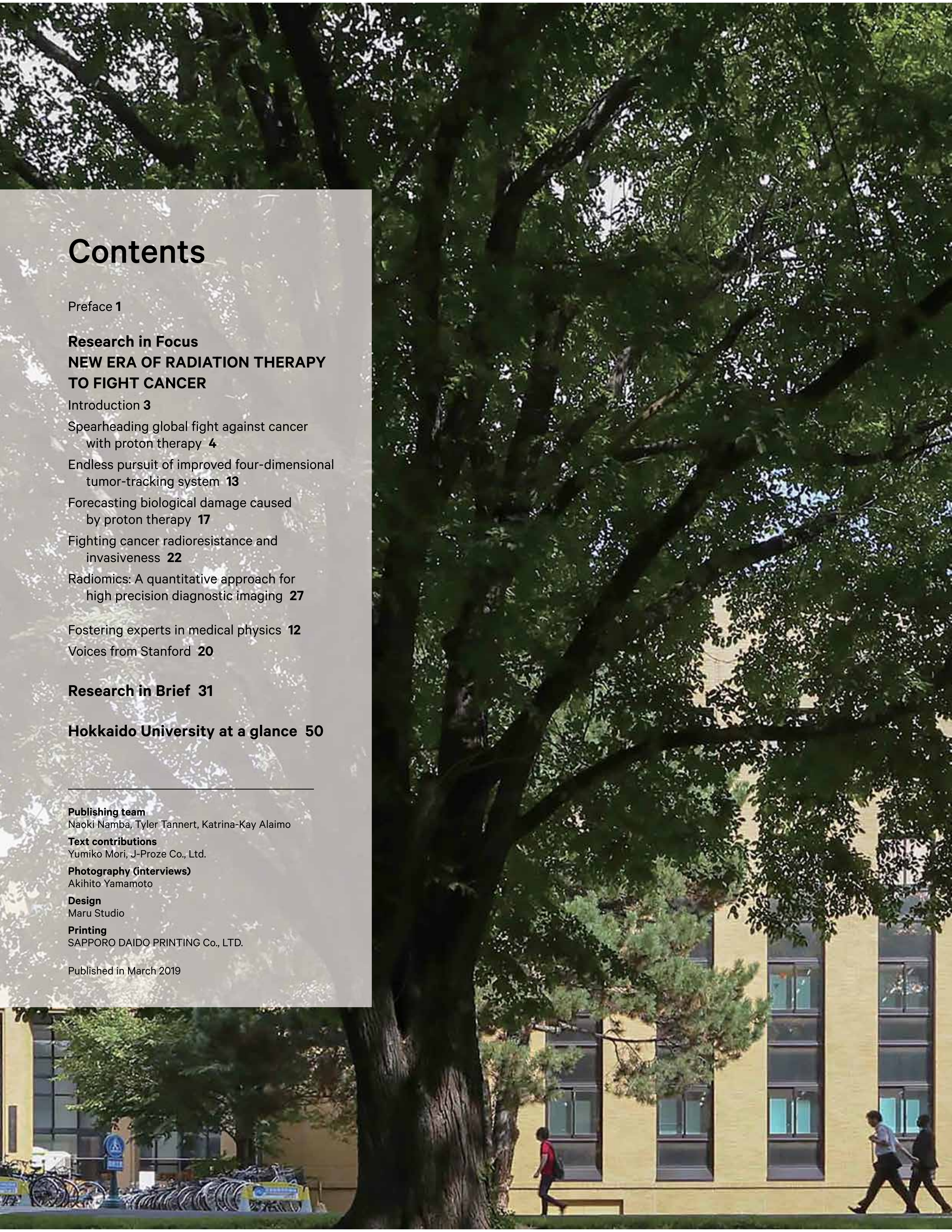

Preface

Hokkaido University originates from Sapporo Agricultural College, which was established in 1876 as one of the first modern higher educational institutions to grant Bachelor's degrees in Japan. Dr. William S. Clark from Massachusetts Agricultural College was invited as the vice president and taught modern agriculture and other sciences as well as a Western moral education, setting the course for what has become one of Japan's leading universities. Dr. Clark left the university with his famous words "Boys, be ambitious," which still remains in the minds of students at the university and throughout the country.

In its long history, Hokkaido University has produced a number of internationally recognized alumni including Dr. Inazo Nitobe, who later served as an undersecretary general of the League of Nations from 1920 to 1926 and wrote the book *Bushido: The Soul of Japan*, which explored the ethos of the nation. More recently, Dr. Akira Suzuki received the Nobel Prize in Chemistry in 2010 for discovering "Suzuki-Miyaura cross-coupling reactions." His discovery led to numerous developments and applications in everyday items, including pharmaceuticals and liquid crystal materials.

In 2018, Hokkaido University's proposal was adopted by the World Premier Institutional Research Center Initiative (WPI) of the Japanese government and the university launched the Institute for Chemical Reaction Design and Discovery (ICReDD). The institute aims to understand complex chemical reactions in-depth and to accelerate the efficient development of new chemicals.

In 2026, Hokkaido University will celebrate the 150th anniversary of its founding. To mark this upcoming milestone, the university formulated an action strategy under the slogan of "contributing towards the resolution of global issues." One of the applied strategies was the establishment of an international research and educational organization called the Global Institution for Collaborative Research and Education (GI-CoRE). The organization aims to conduct top-level international research in collaboration with world-leading researchers from around the globe. Some of the programs in GI-CoRE, including quantum medical science and engineering, the highlight in this issue, have also developed into graduate schools to bring their international and interdisciplinary approaches to education.

Studies of quantum medical science and engineering have brought about real-time tumor-tracking technology, enabling high-precision cancer treatment when combined with Hitachi's proton therapy system. Now, in close collaboration with Stanford University scientists, we strive to bring more innovations to cancer treatment.

This magazine, following the first issue covering our cutting-edge research on soft matter, will highlight on-going research on quantum medical science and engineering and also showcase a variety of research activities at the university. We hope readers of this magazine will gain insight into how Hokkaido University strives to contribute to a global society by promoting research that transcends the boundaries of nations and academic fields.

Masanori Kasahara

Masanori Kasahara, M.D., Ph.D.
Vice President and Executive Director
Institute for International Collaboration
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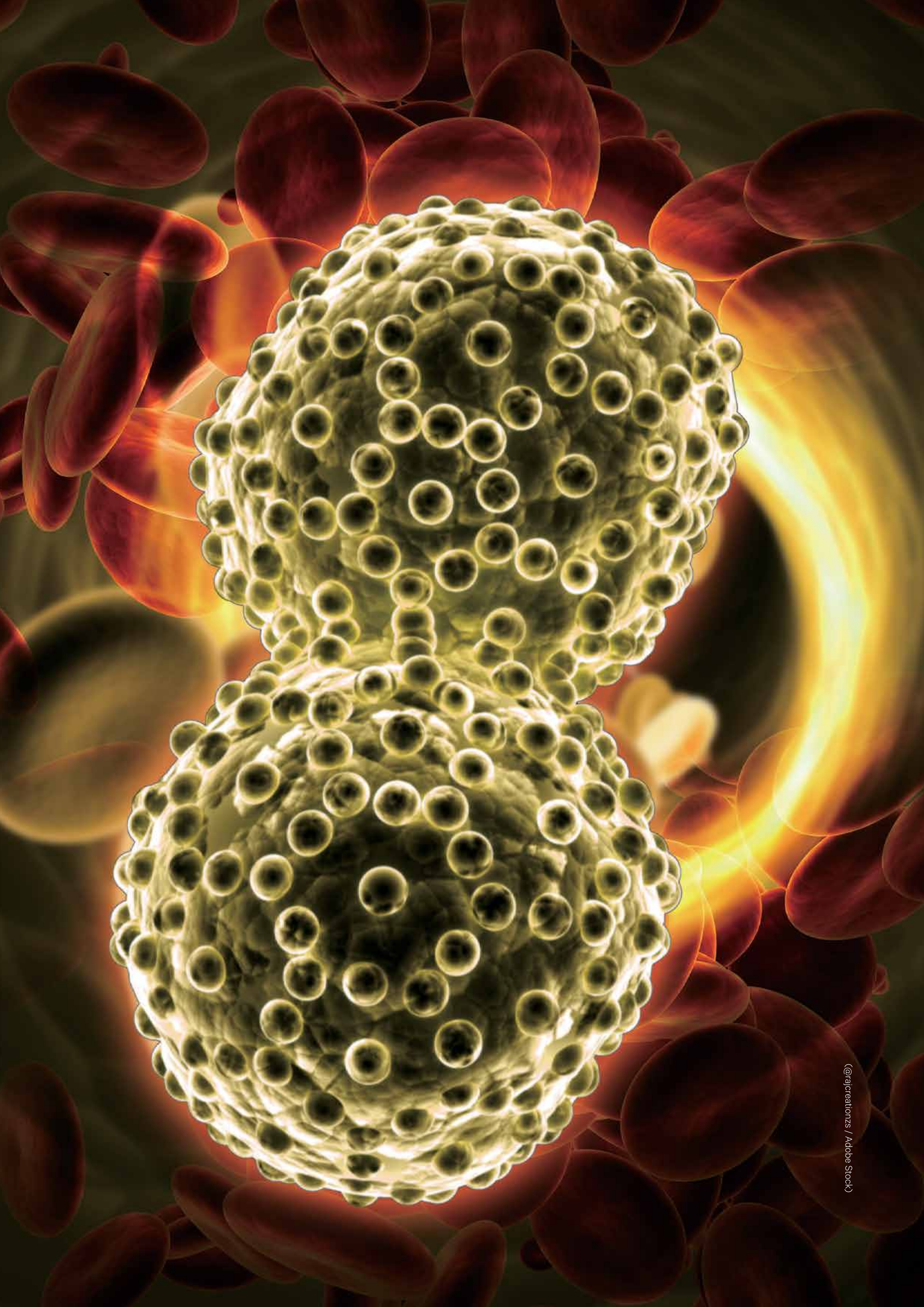


introduction

NEW ERA OF RADIATION THERAPY TO FIGHT CANCER

Cell proliferation, a property essential to life, sometimes puts life itself at risk. Modern medicine has waged a constant battle against cells that proliferate aggressively and uncontrollably, which can eventually spread throughout the entire body invading normal tissues: cancer.

Conquering cancer is of special importance to aging societies such as Japan, where government records show that the disease has been the number one cause of death since 1981. In 2016, about 370,000 people died of cancer, accounting for 28.5 percent of the deaths in the country. According to the World Health Organization, in 2016 tracheal, bronchial, and lung cancers were among the top 10 causes of death worldwide.

In the global fight against cancer, Hokkaido University is one of the world's leading institutions. The university's proton therapy system employs real-time tumor-tracking technology capable of treating patients with cancers that "move" due to respiration and other bodily movements — cases that have long been regarded as difficult, if not impossible, to treat. Combined with spot-scanning proton beam technology developed by Hitachi, Ltd., this therapy is seen as one of the most advanced methods for delivering radiation to tumors with sub-millimeter precision and reduced side effects. This state-of-the-art technology was developed as part of a national project conducted under the leadership of Hokkaido University Professor Hiroki Shirato.

The use of particle beams to treat cancer was first proposed in 1946 by Robert Wilson, an American physicist. In 1955, the Lawrence Berkeley National Laboratory began clinical research into proton beam therapy, and in 1961 Harvard Cyclotron Laboratory and Massachusetts General Hospital started treating cancer patients with proton beams. In Japan, clinical research began at the National Institute of Radiological Science in 1979 and at Tsukuba University in 1983. In 1998, National Cancer Center Hospital East became the first hospital-based institution to provide cancer treatment using proton beams. Since then, the number of proton beam therapy facilities has grown rapidly, totaling 17 facilities in Japan and more than 50 facilities worldwide as of 2018, with numbers expecting to increase in the coming years.

Since its development, radiation therapy, including proton therapy, has become one of the four major methods used to treat cancer, along with surgery, chemotherapy and immunotherapy. Hokkaido University's proton beam therapy is seen as one of the world's leading radiotherapy methods, and has treated approximately 300 patients since 2014.

Hokkaido University, now in collaboration with Stanford University and other institutions, is continuing to develop improved cancer therapies using proton beams and other forms of radiation. This special feature provides a glimpse into some of the university's latest efforts to improve real-time tumor monitoring, along with research on the biological effects of proton beams and the development of individualized treatment plans for cancer patients.

Dr. Hiroki Shirato

- Professor of Radiation Medicine at Hokkaido University
- The Director of the Proton Beam Therapy Center
- Introduced real-time tumor-tracking radiotherapy

> “I thought the outright rejection showed how original and creative the system was.”

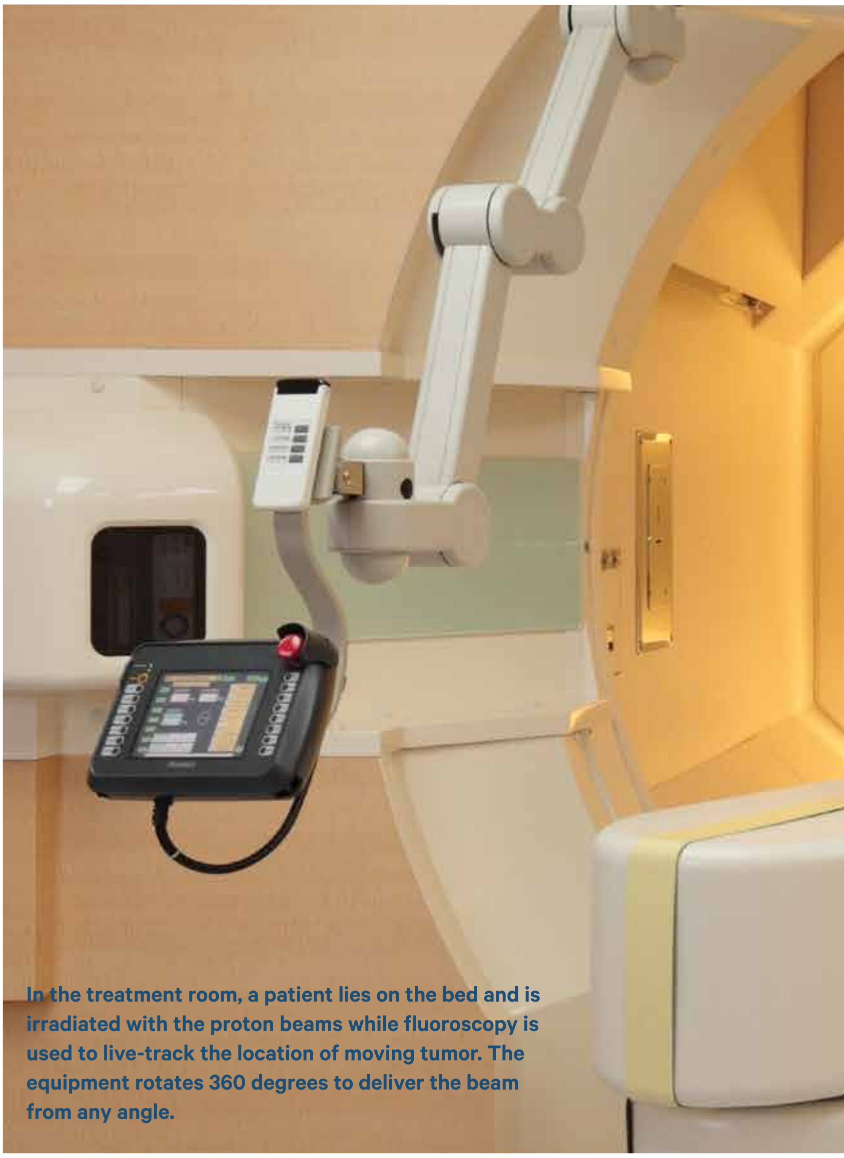
Spearheading global fight against cancer with proton therapy

Hiroki Shirato defied skeptics to introduce the world’s first real-time tumor-tracking radiation therapy system two decades ago. Now, Shirato’s idea has been adopted at the state-of-the-art Proton Beam Therapy Center and bringing a revolution in cancer treatment.

When he introduced the idea to make the world's first real-time tumor-tracking radiation therapy (RTRT) system in the late 1990s, Professor Hiroki Shirato was met with skepticism and criticism from many of his colleagues.

"Despite their doubts, I was confident the system would work," recalled Shirato. "In fact, I thought the outright rejection showed how original and creative the system was." His idea was eventually put into practice in 1998 for radiation therapy using X-rays. Twenty years later his vision has been fully embraced by the medical community and is an integral part of Hokkaido University's real-time-image gated proton therapy (RGPT) system, one of the most advanced radiation therapy systems in the world. The RGPT system, which fuses an upgraded RTRT system with discrete spot scanning technology from Hitachi, Ltd., was built in 2014 as part of the national Funding Program for World-Leading Innovative R & D on Science and Technology (FIRST).

The real-time tumor-tracking system is designed to locate, with millimeter precision, tumors in organs that are constantly "moving" due to respiration, peristalsis and other bodily motions. A two-millimeter gold ball is inserted near the tumor, then images of the diseased area are taken by computed tomography in order for the computer to learn the spatial relationship between the tumor and the gold marker prior to a radiation therapy. On the day of treatment, with the patient lying on a bed in the radiation therapy room, the gold marker is identified using fluoroscopy, or X-ray beams, coming from two directions, and its location is tracked automatically using pattern recognition technology. The proton beams are delivered only when the gold marker enters the gating window, therefore irradiating the tumor more precisely while avoiding unwanted irradiation of the adjacent healthy tissue. The system repeats this process every 0.03 seconds enabling precise tracking and irradiation.

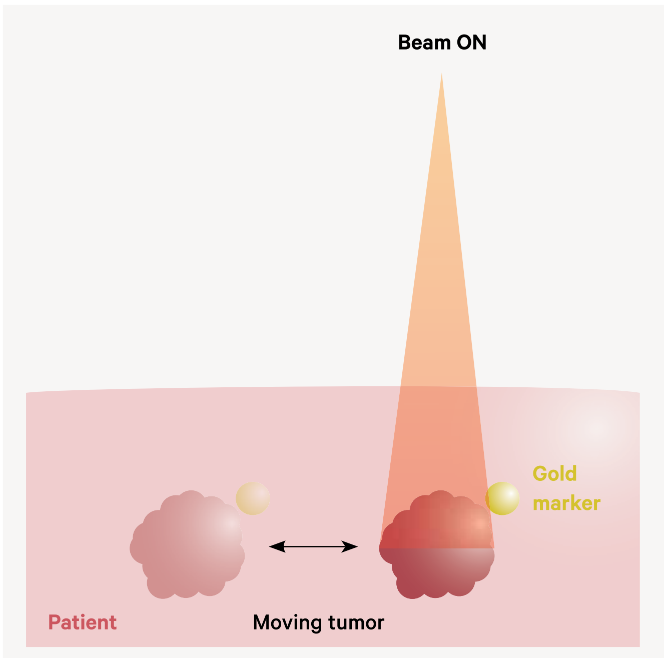


In the treatment room, a patient lies on the bed and is irradiated with the proton beams while fluoroscopy is used to live-track the location of moving tumor. The equipment rotates 360 degrees to deliver the beam from any angle.

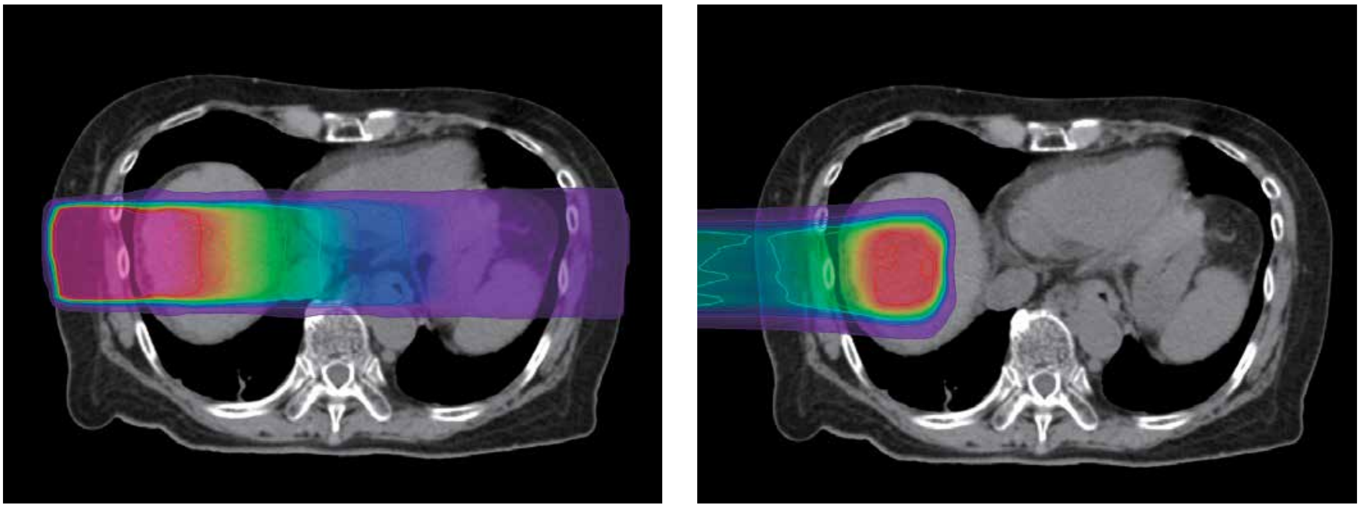
The use of a gold ball as a reference for irradiation, however, was the target of the original criticism, because there was little understanding at that time that a spherical marker could be located when irradiated by two X-ray beams set perpendicular to each other. There was also a doubt about placing the marker near the tumor, not directly on the tumor.

"Before this system appeared, irradiating moving organs had to be done by guesswork because we were unable to see the moving tumor during the treatment. So, an advanced radiation therapy, called stereotactic radiation therapy, was mainly used for tumors in the brain, head and neck, and other organs that do not move," Shirato said. "I was determined to fundamentally change how radiation therapy was conducted."

The marriage of Shirato's tumor-tracking system with the Hitachi's spot scanning technology used in proton therapy achieved the breakthrough Shirato had aspired to because of the superiority of proton beams over X-rays for treating both static and moving tumors.



▲ A gold marker to be implanted near the tumor (top). The tumor is irradiated only when the gold marker is in a certain position so as to reduce the dose delivered to healthy tissues (right).



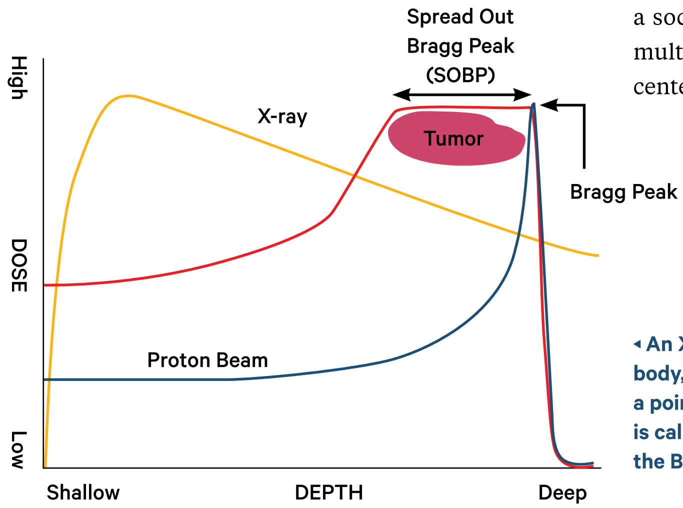
▲ X-rays (left) deliver the largest dose of radiation near the skin and gradually lose energy as they approach the tumor before exiting the body. In contrast, proton beams (right) release most of their cancer-fighting energy around the tumor and then stop immediately.

Proton beams have much better dose distribution for treatment

Accelerated protons separated from hydrogen atoms expend the bulk of their cancer-fighting energy at a designated depth in the body while sparing nearby healthy tissue, thus minimizing side effects. In contrast, X-rays are composed of photons and deliver radiation both before and after reaching cancerous cells — to healthy tissue and organs alike. In some cases, X-rays are better suited for projections of the tumor for diagnosis than for therapy because they travel though the body.

The advantage of using protons is that the doctor can control where the bulk of the energy is discharged by changing the speed of the particles released by the accelerator, ranging from 60 to 70 percent of the speed of light. The point where the greatest amount of energy is released is called the “Bragg Peak.” The proton enters the body by releasing small doses of radiation for a short time, then releases a large amount of radiation all at once near the tumor. After the Bragg Peak, the energy level quickly plummets to zero. X-rays, on the other hand, release the most energy 2 or 3 centimeters from the skin and then gradually lose energy as they approach the tumor before exiting the body.

Although proton beams are known to have excellent dose distribution, making the beam conform to the correct shape is another issue. In the conventional passive scattering method, a modulator and scatter foil are used to make the proton beam fit the shape of the tumor. A collimator, usually made of brass, and a resign compensator can be used to further shape the beam. However, these systems are incredibly large, requiring as much space as a soccer field when combined with the accelerator and multiple gantries, which was the standard size for proton centers globally.

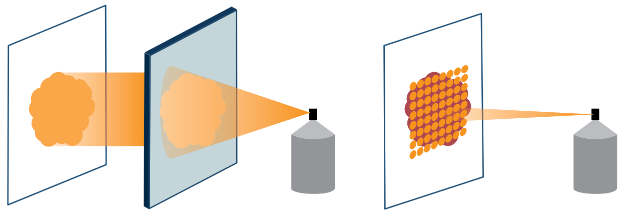


◂ An X-ray releases the largest amount of energy shortly after entering the body, while a proton beam can be controlled to release most of its energy at a point called the Bragg Peak. The red line shows a proton beam with what is called a Spread Out Bragg Peak, which is created using a device to widen the Bragg Peak and irradiate tumors more effectively.

In Hitachi's spot scanning system, fine proton beams are used to "paint" a radiation dose onto a prescribed spot on the tumor, without the need for the special equipment used in passive scattering. In this system, the proton beams conform to the shape and the depth of the tumor, making it possible to effectively treat complex tumors such as those in prostate and brain, and those seen in children. The system also allows large tumors measuring up to 30 cm x 40 cm to be treated in a single session, while conventional facilities can only treat tumors up to 15 cm x 15 cm.

The Proton Beam Therapy Center has been treating prostate cancer, head and neck carcinoma (excluding pharyngeal cancer), bone and soft tissue tumors, and pediatric cancers that are covered by health insurance. It also offers treatment for tumors of the liver, lungs, pancreas and other organs that are not yet covered by health insurance. "In theory, any cancer that can be treated with standard X-ray therapy we can treat with proton therapy," Shirato said "I expect more and more people will opt for proton therapy once the cost issue is settled."

Clinical research has shown many outstanding results from proton therapy, often curing cancers previously declared incurable. For instance, a man in his 80s with inoperable hepatocellular carcinoma who received 20 proton beam treatments exhibited a drastic reduction in tumor size and a significant drop in tumor marker levels within three months after the treatment started. In a recent finding, patients with nasopharyngeal cancer reported not losing their sense of taste after proton therapy. "I was really surprised by this because patients with nasopharyngeal cancer who undergo standard radiation therapy always lose their sense of taste," he said. "Reduced side effects could be a huge benefit of proton therapy. One of our faculty members has started quantitative research on this."



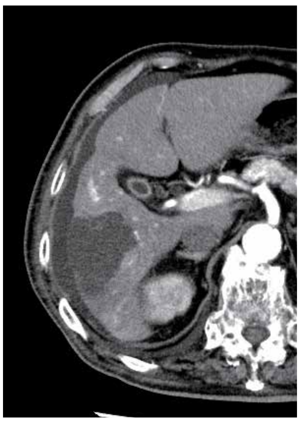
▲ **In the passive scattering method (left), special devices are needed to make the proton beam fit the tumor, while in spot scanning (right), fine proton beams are used to "paint" a precise radiation dose.**

> "I was determined to fundamentally change how radiation therapy was conducted."

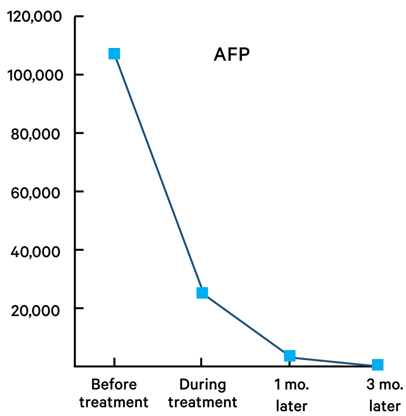
▼ **A case of hepatocellular carcinoma in a male in his 80s. The images show the tumor before treatment, after 20 proton beam sessions and after three months. Levels of the tumor markers AFP and PIVKA-II dropped as therapy progressed.**

Before treatment

During treatment (60 GyE/20 times)



3 months later



> “I am telling my students to come up with something so innovative that people will laugh at you at first.”

Smaller equipment helps the technology spread

Soon after his project was selected to be part of the FIRST program, Shirato's funding from the program was slashed in half due to a governmental policy change. With less funding, the team was forced to simplify the equipment so it could be housed in a space equivalent to two tennis courts, rather than the size of a soccer field. Further improvements to Hitachi's spot scanning system increased proton beam usage efficiency, which made the equipment much more compact. The circumference of the accelerator was reduced to 18 meters, compared with the conventional 23 meters, while the gantry's maximum outer diameter was reduced to 9 meters from 11 meters. Furthermore, because this system was the first in the world to only utilize the spot scanning method, and not also the passive scattering method, the thickness of the protective concrete wall could be drastically reduced.

"As the saying goes, 'Necessity is the mother of invention'. The funding cut prompted us to do something to downsize the equipment, which in turn made it commercially viable. World-famous hospitals like the Mayo Clinic in the United States suddenly became interested in the equipment because they believed it could be accommodated in their buildings," Shirato said.

In addition to the Mayo Clinic, the equipment has been adopted by the Singapore National Cancer Center, St. Jude Children's Research Hospital and Johns Hopkins University Hospital, among others.

Under the leadership of Shirato, a team of doctors and researchers has continued striving to update the RGPT system. A key member of this team is Professor Shinichi Shimizu, vice-director of the Proton Beam Therapy Center, who was instrumental in developing the current system. Since 2015, the system has been capable of performing intensity modulated proton therapy (IMPT), which gives doctors electromagnetic spatial control of proton beams of variable energy and intensity. IMPT is effective in delivering precise doses of protons to complex tumors located near vital parts of the body. Later that year, the Proton Beam Therapy Center began using a Cone Beam Computed Tomography (CBCT) device mounted inside the gantry. CBCT is better at depicting normal tissue adjacent to tumors, in particular the location and shape of soft tissue, which enables more precise dose delivery.

Shirato says his immediate goal is to further disseminate this kind of proton therapy by finding a better way to teach doctors how to insert the gold markers, which can be difficult for beginners. "Beyond that, we are trying to find a radiation beam that is better than protons for cancer treatment," said Shirato, whose desire to eradicate cancer is insatiable. "I am telling my students to come up with something so innovative that people will laugh at you at first."

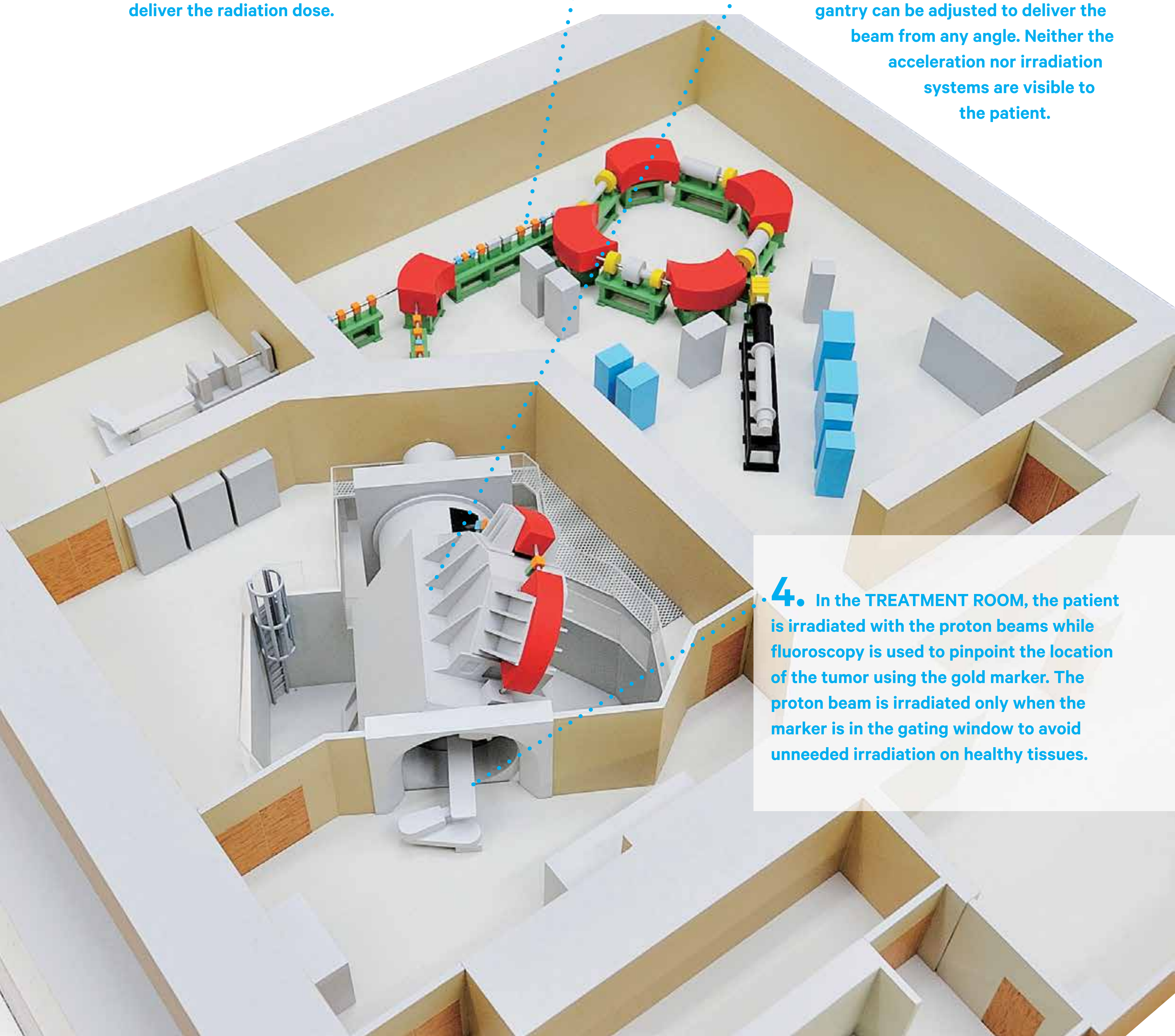
Patient treatment at the PBTC

The diagram below shows the state-of-the-art facility at Hokkaido University's Proton Beam Therapy Center (PBTC), where a cancer patient undergoes treatment with the real-time-image gated proton therapy (RGPT) system.

1. The patient lies on a bed in the TREATMENT ROOM. Well before treatment, a 1.5 to 2 mm gold ball is inserted near the tumor, or directly above it for prostate cancer. CT images are taken to locate the tumor within the moving organ, based on which a team of professionals, including a medical physicist, makes an elaborate plan to deliver the radiation dose.

2. In the ACCELERATION SYSTEM, hydrogen atoms are separated into negatively charged electrons and positively charged protons, the latter of which are accelerated to 60 percent to 70 percent of the speed of light.

3. The beam is then transported to the IRRADIATION SYSTEM, where a 360-degree gantry can be adjusted to deliver the beam from any angle. Neither the acceleration nor irradiation systems are visible to the patient.



4. In the TREATMENT ROOM, the patient is irradiated with the proton beams while fluoroscopy is used to pinpoint the location of the tumor using the gold marker. The proton beam is irradiated only when the marker is in the gating window to avoid unneeded irradiation on healthy tissues.

Fostering experts in medical physics

When Hokkaido University opened its Proton Beam Therapy Center in 2014, it simultaneously launched the Summer School for Medical Physics in order to provide young researchers and medical doctors with intensive lectures and hands-on practice in radiation physics.

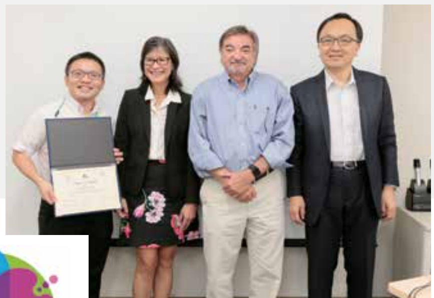
The summer school, organized by the Global Station for Quantum Medical Science and Engineering (GSQ) within the Global Institution for Collaborative Research and Education (GI-CoRE), invites internationally renowned professors from Stanford University, who are also members of the GSQ, to cover many of the fields falling under the umbrella of medical physics, including particle beam therapy, radiomics, and real-time tumor-tracking technology. The program also includes topics such as big data and deep learning, as well as practical trainings in treatment planning and quality assurance in proton therapy. This annual event has drawn global attention welcoming participants from throughout Asia, Europe, and North America.

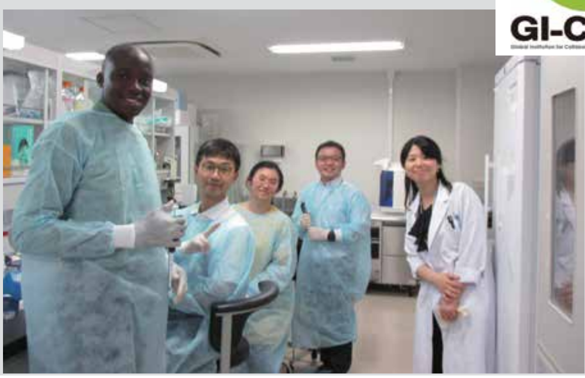
In 2018, Hokkaido University's GSQ took a step forward in education by launching another program: the Summer School for Radiation Biology. Another collaboration with experts from Stanford University, this course focuses on molecular biology and radiation biology of cancer cells. In addition to lectures, the program includes laboratory work to practice techniques such as detecting DNA damage following radiation treatment.

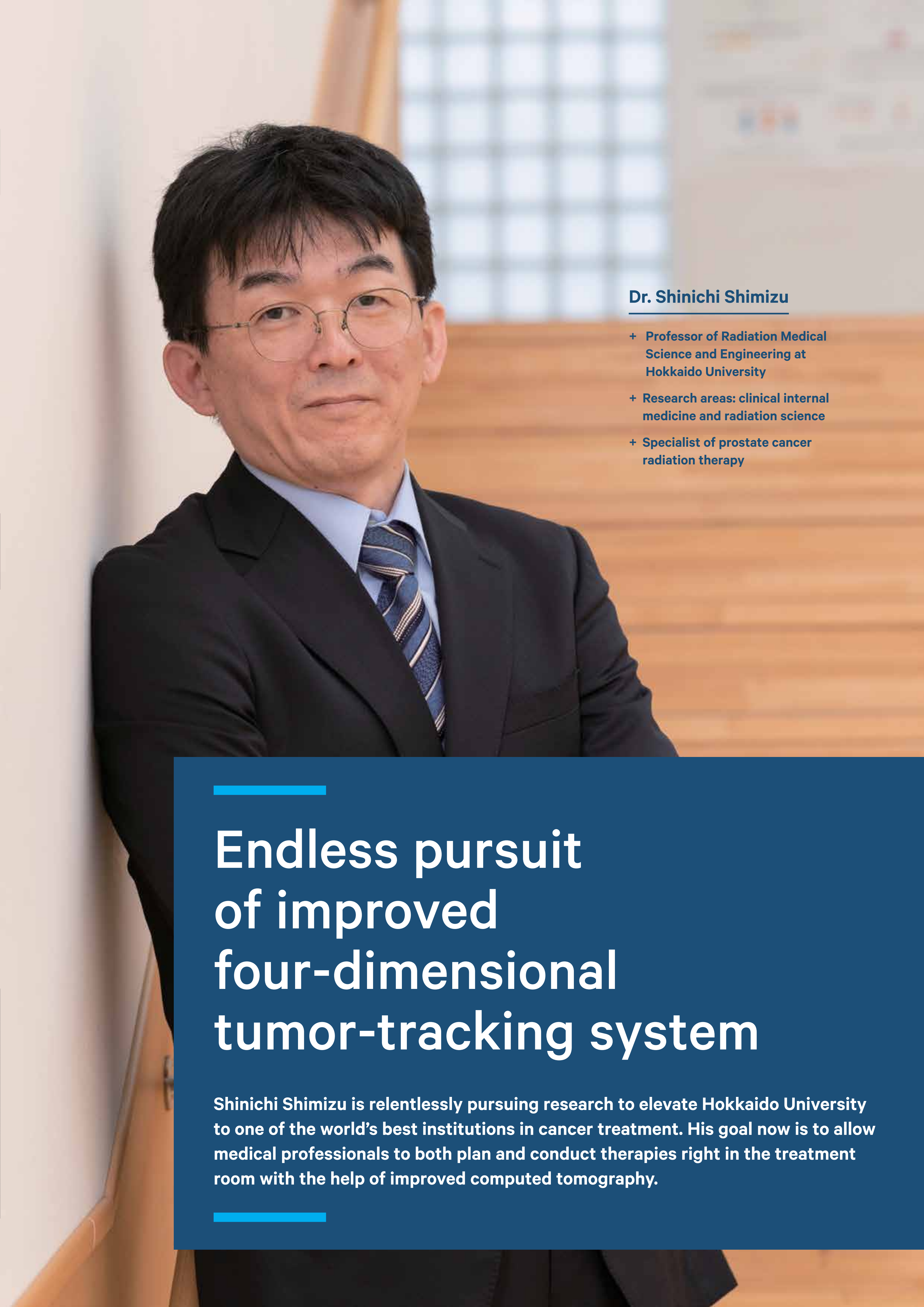
Since 2018, these summer programs have been made open to enthusiastic students from around the world as part of the Hokkaido Summer Institute (HSI), which features more than 100 courses in a large variety of academic disciplines. Through these programs, the university serves as an excellent platform for both students and experts from different backgrounds to meet and begin to develop collaborative ideas.

Furthermore, the success of the research activities at the GSQ led to the development of the Graduate School of Biomedical Science and Engineering, allowing the GSQ to bring its collaborative and interdisciplinary approaches to education. The graduate school aims to foster specialists who can apply the latest developments in science and engineering to medicine as well as medical physicists. Graduates will play indispensable roles at the forefront of radiation therapy. The graduate school started accepting both Master's course students and Ph.D. students in its Quantum Biomedical Science and Engineering Course and Molecular Biomedical Science and Engineering Course in 2017.

Photos from the Summer School for Medical Physics 2018 and the Summer School for Radiation Biology 2018.







Dr. Shinichi Shimizu

- Professor of Radiation Medical Science and Engineering at Hokkaido University
- Research areas: clinical internal medicine and radiation science
- Specialist of prostate cancer radiation therapy

Endless pursuit of improved four-dimensional tumor-tracking system

Shinichi Shimizu is relentlessly pursuing research to elevate Hokkaido University to one of the world's best institutions in cancer treatment. His goal now is to allow medical professionals to both plan and conduct therapies right in the treatment room with the help of improved computed tomography.

Professor Shinichi Shimizu was dispatched to the University of Texas MD Anderson Cancer Center for three months in 2012 to gain first-hand experience with proton therapy in anticipation of the establishment of Hokkaido University's Proton Beam Therapy Center in 2014. Now, several highly-rated cancer treatment centers in the U.S. have already or are considering adopting a proton therapy device developed jointly by Hokkaido University and Hitachi, Ltd. for its superior performance.

"We can safely say that the system jointly developed by Hokkaido University and Hitachi is one of the best in the world," Shimizu said. With his expertise in radiation medicine and computer programing, Shimizu played a pivotal role in developing the four-dimensional tumor tracking system, which is called the real-time-image gated proton therapy, resulting in 43 patents in Japan and 20 abroad. Yet he is by no means satisfied with the system and is trying to improve it further through ongoing research on Real-world Adaptive Proton Beam Therapy (RAPT).

One of the daunting challenges in proton therapy is pinpointing the exact location and shape of moving tumors. Tumors move with respiratory movements and other bodily motions, and their shape and location during a radiation treatment may differ from what they were before, making precise dose delivery difficult. "There is still a certain level of uncertainty in proton therapy because we can't actually see the tumor during the treatment," Shimizu said. "The exact shape and location of a tumor can be different from what is in CT images taken a day before."

> "If we have clear images, we can reduce the area of proton beam irradiation and increase the dose the tumor receives."

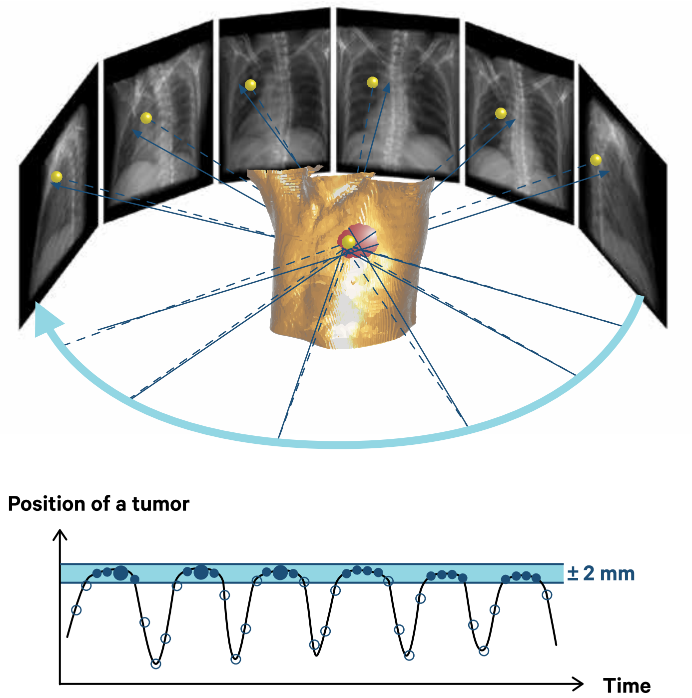
"Hokkaido University has specialized in high-precision four-dimensional tumor tracking, but there is more room for improvement. With the help of a gold marker implanted near the tumor, we aim to more accurately visualize the tumor during treatment."

Reducing "artifacts": a vital next step

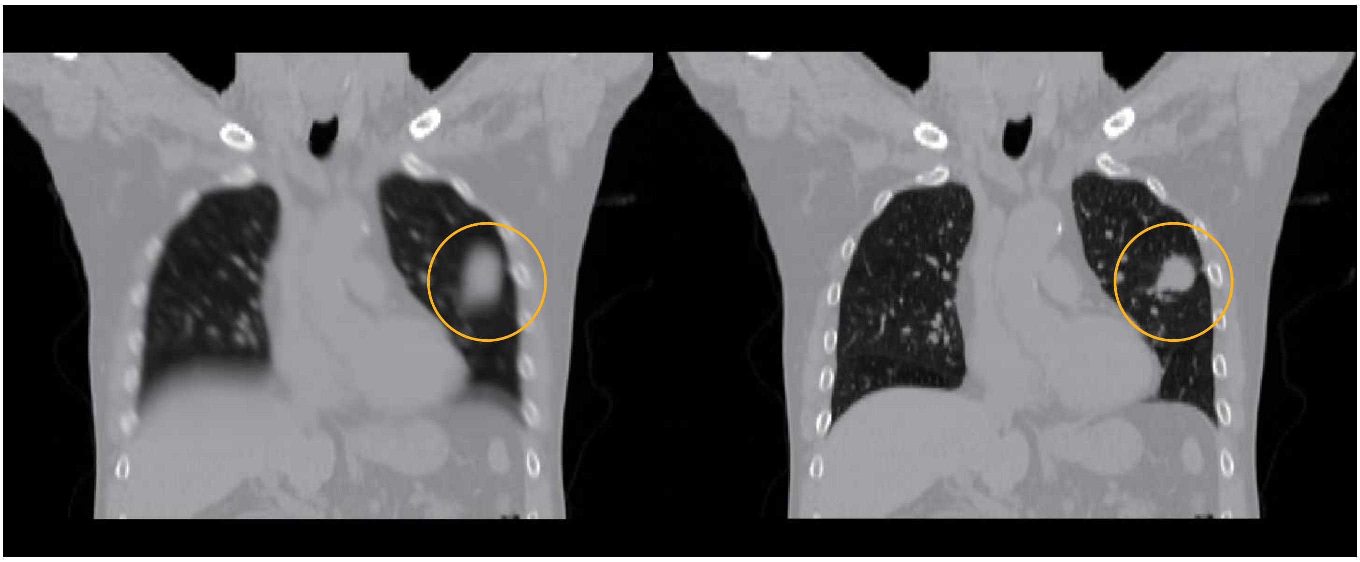
The RAPT system is designed to obtain clear, reconstructed CT images of a tumor by using only images when the gold marker is in a certain position. It also seeks to improve the quality of tumor images by removing "artifacts," which are distortions or fuzziness in images caused by respiratory movements or the presence of metals in the body. Metals, such as dental fillings and implants, can cause lines to appear in an image, which makes identifying the boundary between a tumor and healthy tissues and vital organs more difficult.

"If we have clear images, we can reduce the area of proton beam irradiation and increase the dose the tumor receives to more effectively fight the cancer while further reducing side effects," Shimizu explains.

In the RAPT system, cone beam computed tomography (CBCT), which uses X-rays coming from two directions, is used in the treatment room with the patient lying on the bed. The CBCT device rotates 360 degrees around the patient while irradiating X-rays from two directions, gathering a massive amount of data on the diseased area, with a gold marker inserted near the tumor serving as a reference point.



▲ Imaging procedure of the cone beam computed tomography (CBCT). The patient is exposed to X-ray beams emitting from two axes in order to obtain images of the tumor. Images taken when the gold marker is within the 2 mm-gating window are selected to improve image quality.



▲ An ordinary reconstruction of a tumor image (left), and a four-dimensional reconstruction of a tumor image made with CBCT images when a gold marker is in a certain position (right).

▲ **The Proton Beam Therapy Center (PBTC) building at Hokkaido University's Sapporo campus.**

Hastening treatment decisions

The position of the gold marker is determined by projection images obtained by CBCT. Only the images in which the gold marker is in a certain position — the gating range — will be used for the four-dimensional reconstruction of the tumor. This will then be used to plan the patient's proton therapy. "Currently, we take CT images before the treatment to plan proton therapy, but in the future with the new system we will be able to do it right in the treatment room," he said.

However, a formidable challenge remains before the treatment can become a reality.

Currently, it takes several hours to identify the range of a tumor's border with healthy tissue, based on images taken before the treatment and elaborate computer calculations. Shimizu says that eventually this task will need to be done automatically by artificial intelligence (AI) for the RAPT system to be usable in the treatment room. However, no such technology yet exists. "We will probably end up using technology that somebody else develops because that in itself is a good research topic," Shimizu said. "We are trying to clear hurdles one by one to make this kind of treatment possible in the future." Shimizu is also conducting research to determine whether tumor tracking is possible without the use of a gold marker, which would make the treatment less invasive.

Besides his own research, Shimizu is busy treating patients at the Proton Beam Therapy Center. As a specialist in prostate cancer radiation therapy, Shimizu says he is determined to do the best for every patient who comes to Hokkaido University Hospital. For some, the center is their last resort. "We have treated cancer patients who were declared incurable by other hospitals," he said. "Some were cured. Some were not. But we did our best for all of them."

Shimizu admitted that his research will not generate as much public attention as cancer immunotherapy, which became a hot topic after two scientists were awarded the 2018 Nobel Prize in Physiology or Medicine for their research in that field. "We are simply trying to improve what we have done in proton therapy," Shimizu said. "Doing so may not lead to a major scientific breakthrough, but we will continue to go forward with our research to make proton therapy a better treatment option for cancer patients and improve their post-treatment quality of life."

Dr. Taeko Matsuura

+ Associate Professor of Quantum Science and Engineering at Hokkaido University
+ Medical Physicist

Forecasting biological damage caused by proton therapy

Taeko Matsuura works with medical professionals to make proton therapy more accurate and efficient, rendering expertise from the perspective of a physicist. While developing an algorithm to evaluate the biological effects on tumors and healthy tissues, she ventures into the domain of ultrasonic waves to verify proton beam ranges.

When she was a graduate student conducting research on basic particle theories, Associate Professor Taeko Matsuura's main interests lay in finding "what we would see if we reached the end of the universe" and gleaning a better understanding of spacetime. But some soul-searching while she was a postdoctoral researcher prompted Matsuura to say goodbye to fundamental physics and venture into applied physics in the medical domain, which was also a subject of interest as a student.

Matsuura came to Hokkaido University in 2010 after a stint at the National Cancer Center Hospital East, which was the first hospital-based institution to conduct proton therapy in Japan. Since arriving in Hokkaido, Matsuura has harnessed her expertise in physics to conduct research toward improving proton beam therapy for Hokkaido University's Proton Beam Therapy Center, a facility that opened a few years after her arrival.

"I started with several staff members at a medical physics lab for proton beam therapy, but later like-minded researchers joined me to develop hardware and a simulator to improve the therapy from a physical point of view," Matsuura said. "My priority is to make proton beam therapy more accurate and efficient." She has contributed to realizing effective proton therapy with reduced side effects by developing a method to calculate the appropriate dose for each patient and a simulator to estimate the actual dose delivered. She also developed a device that spreads out a sharp peak of proton beam so it can be delivered to a wider area at once.

Algorithm developed to gauge biological effects

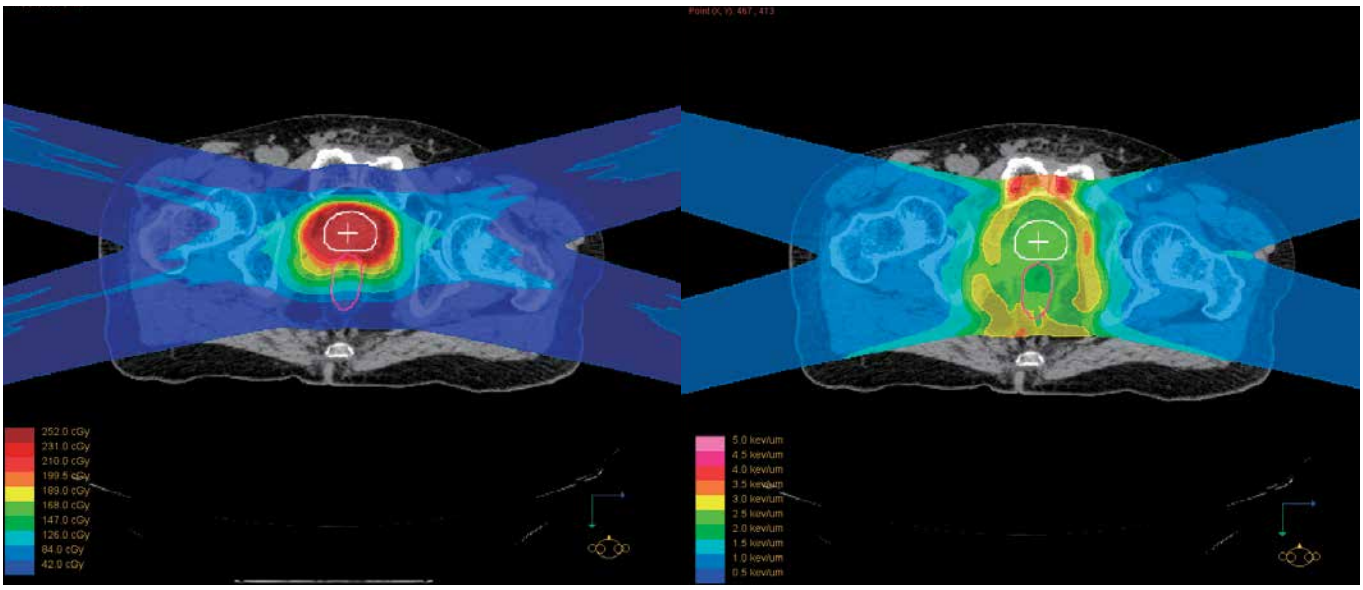
Now Matsuura is tackling one of the hottest topics in proton beam therapy: evaluating and assessing the biological effects of proton beams. "Calculated dose distribution is not the same as the actual biological damage done to the tumor and adjacent healthy tissues," Matsuura explained. "Biological damage is done off the path of a proton beam, and we sometimes find that healthy tissues or an organ a few millimeters beyond where the beam was supposed to stop have been damaged."

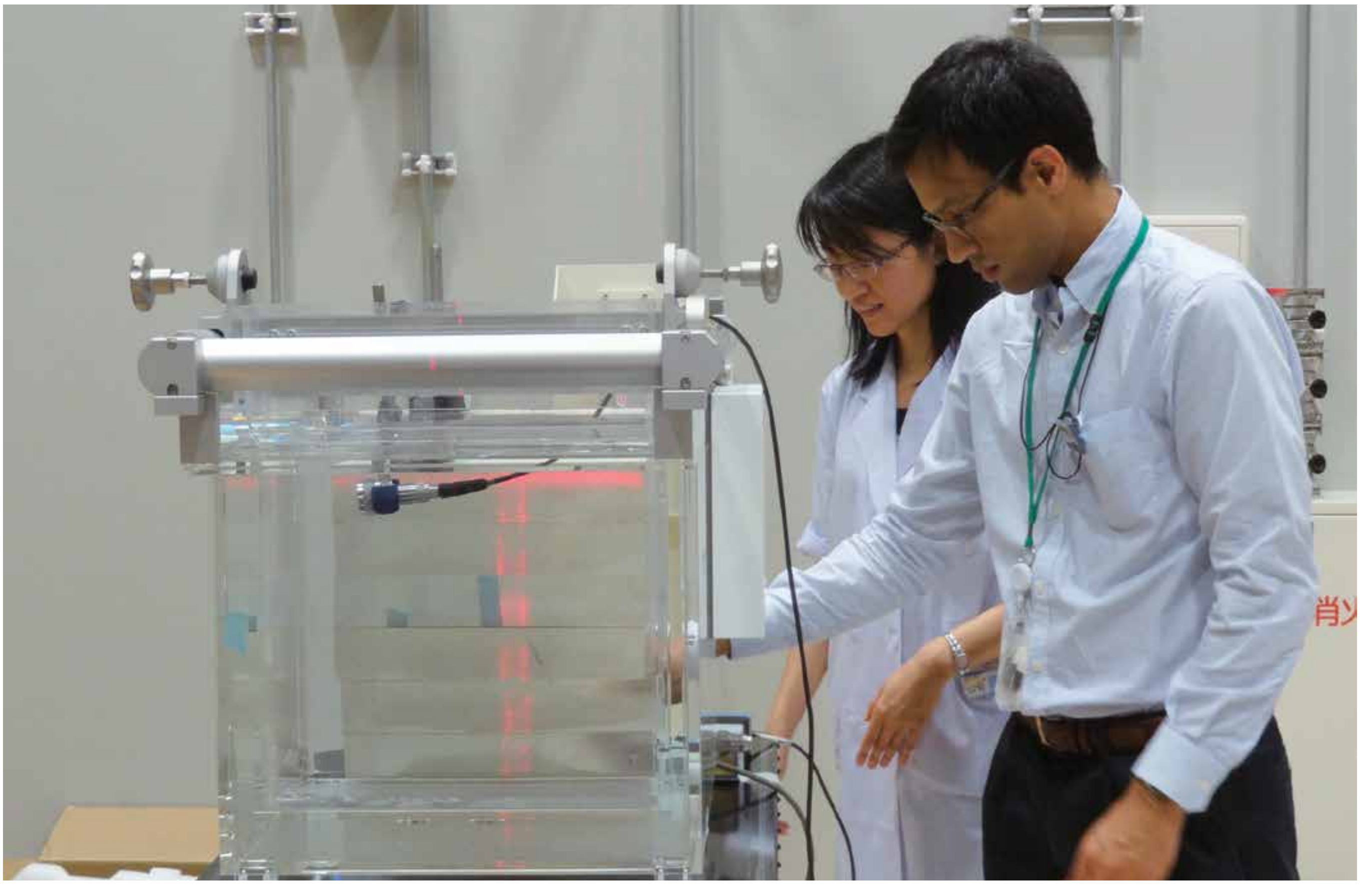
To gauge the actual biological damage, Matsuura and her team developed a novel calculation algorithm for linear energy transfer (LET), the amount of energy that protons transfer to tissues. Biological damage is proportional to LET: The higher the LET, the greater the damage.

The algorithm Matsuura's team developed is called the "Dual-LET kernel model" and enables a quick and accurate calculation of LET. "We can calculate LET in a few minutes, which makes it possible to use the model in a clinical routine," Matsuura said. This development represents a leap forward in LET calculation. The conventional Monte Carlo simulation takes more than 10 hours to complete the calculation and another available algorithm, called the "Single-LET kernel model," has been dismissed as impractical because of its extreme inaccuracy.

Calculating LET is necessary not only to reduce side effects, but also for killing the tumor effectively. "Even though the same dose is given, the magnitude of LET varies. If LET is low, damage is done to only sporadic areas, failing to break strands of the DNA double helix of cancerous cells and thus failing to kill them," Matsuura said. "If that occurs, cancerous cells can quickly recover

▾ **The physical dose distribution of a proton beam (left) is not the same as LET distribution which represents the actual biological damage (right). The team's Dual-LET kernel model enables quick calculation of LET while delivering accurate results.**





▲ Researchers conducting preliminary experiments to measure shock waves.

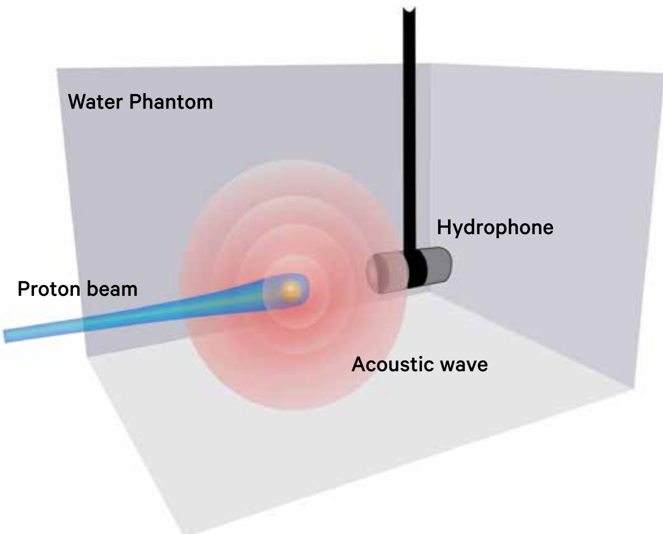
and proliferate again." She hopes the algorithm will eventually be used in clinical routines, but several hurdles remain, such as issues in legality and cost. Matsuura said these problems will be addressed gradually.

Ultrasonic waves used to verify proton beam range

Looking ahead, Matsuura is involved in developing a real-time verification method for a proton beam range by using ultrasonic waves. She has teamed up with a Turkish expert in ultrasonic waves who is a researcher at the university as part of the university's Global Institution for Collaborative Research and Education (GI-CoRE) project.

"At present, we can't see exactly where proton beams are delivered to a patient lying on the treatment room bed right in front of us," Matsuura said. "Ultrasonic waves could be a solution for finding the exact range of proton beams."

When proton beams are delivered to a spherical metal marker embedded in a tumor, it generates a single frequency (resonance) acoustic wave, or a shock wave from a pulsed ion beam. This acoustic wave could be used to verify the proton beam's range, or to pinpoint in real-time where the beam reached the Bragg Peak in relation to the gold marker, according to Matsuura's research plan. Although full-fledged research has yet to start, Matsuura has high hopes that the method will become an indispensable tool in the treatment room in the future. "If we are able to know instantly where and when the beam reaches its Bragg Peak, we will all have peace of mind about the treatment, enabling us to provide better care to patients," Matsuura said. ●



▲ A conceptual drawing showing a device to measure shock waves from proton beams hitting a target.

Voices from Stanford

Since its foundation in 2014, the Hokkaido University Global Station for Quantum Medical Science and Engineering (GSQ) has been conducting extensive collaborations with Stanford University's Radiation Oncology Department. Divided into the Hokkaido University Unit headed by Dr. Hiroki Shirato and the Stanford University Unit headed by Dr. Quynh-Thu Le, doctors and researchers from both institutions work together in the fields of medical physics, clinical science, and radiation biology, devising and conducting joint-experiments and sharing research data and results to further expand the understanding and application of radiotherapy.

Dr. Le and her colleague at Stanford, Dr. Lei Xing, shared their thoughts on the GSQ collaboration in this article.

"The Stanford and HU teams understand the importance of being on the same page to creatively motivate and bounce ideas off each other."

The collaborations with faculty and students from Hokkaido University (HU) have been very fruitful and mutually beneficial, as the two teams have similar mindsets and research and clinical goals, but somewhat different skills and experience. For example, the team members from HU have abundant experience in proton therapy; coupled with the availability of the state-of-the-art proton therapy system at HU, this greatly benefited our group from Stanford University. With access to in-depth knowledge and proton therapy equipment, we were able to accomplish several important research projects that would have otherwise been impossible, including several biological and clinical research projects outside of proton therapy, that have resulted in a number of impactful joint publications.

Currently, there are several ongoing projects within the GSQ that are very promising. The development of proton acoustic imaging in particular is both scientifically interesting and clinically important because it could help identify "in vivo range verification"; a critical step to minimize the final uncertainty in proton dose delivery.

In practice, proton therapy has been a treatment modality of increasing interest in radiation oncology, as it delivers maximal doses of radiation to a tumor within a narrow region defined by the Bragg peak — the point where protons moving through matter release the most energy before coming to rest. However, uncertainties in predicting the location of the Bragg peak in human tumors can adversely impact treatment accuracy, leading to either under-dosing the tumor or over-dosing the surrounding healthy tissues.

Our collaboration is addressing this challenge to provide a clinically practical solution to this bottleneck problem in proton therapy. We are actively working on developing both time-of-flight (TOF) and time-reversal (TR) protoacoustic imaging techniques, which use sound waves to estimate the Bragg peak position. These techniques will provide critical tools for the quality assurance of proton therapy independent of tumor size, shape or location within the body, and will lead to enhanced patient survival while minimizing treatment toxicity.

The Stanford team is internationally known for our expertise and creativity in medical imaging, treatment planning, and radiation biology. Our knowledge in these fields have been extremely valuable in moving collaborative research with

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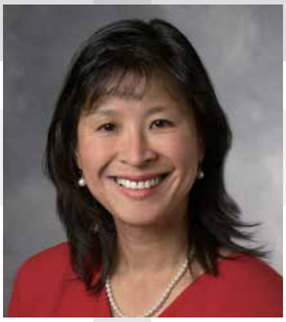


In addition to leading the Stanford University Unit of the GSQ, Dr. Quynh-Thu Le has been the Co-Director of Stanford Cancer Institute's Radiation Biology Program since 2004, and the Chair of Stanford's Department of Radiation Oncology since 2011. Her expertise focuses on head and neck cancer, and she has participated extensively both in clinical and laboratory fieldwork.

Dr. Lei Xing is another member of the Stanford University Unit of the GSQ, working within the medical physics division. After earning his Ph.D. in Physics from Johns Hopkins University, he continued his research in the fields of medical imaging, AI, and their potential uses in oncology. He has been the Director of Stanford's Radiation Physics Division since 2010.

HU forward. Trainees and students from both institutions have benefited greatly through active participation in these collaborations. They get to know not only each other and the faculty members, but also themselves. They learn to assess their own skills, knowledge, efficiency and reactions to requests and critiques. They also learn to re-evaluate their critical thinking and decision-making skills through their first-hand experience in computational and hands-on physics and/or biological experiments.

The biggest challenge presented during the collaborative process with HU has perhaps been the lack of real-time two-way communications due to the geographical separation of the two institutions. The Stanford and HU teams understand the importance of being on the same page to creatively motivate and bounce ideas off each other, brainstorm, and learn from each other throughout the process. To help alleviate the challenges presented by the physical distance, frequent visits of faculty and students have taken place in addition to regular telecom conferences.

While continuing our current projects, we plan to initiate a few new projects related to artificial intelligence in medicine (AIM) and stereotactic body radiosurgery (SBRT). AIM promises to fundamentally transform healthcare, and the tremendous possibilities that AI can bring to medicine have triggered a flood of recent research activities. We plan to utilize newly available deep learning technologies from the engineering fields and develop solutions to improve current clinical practices in radiation therapy. We strongly believe that the collaboration with HU will provide new opportunities for future clinical innovations and breakthroughs. The collaboration regarding SBRT is directly related to patient care and may help the transition of the cutting-edge research being performed in the GSQ from the lab into clinical practice. The Stanford group has extensive experience in SBRT treatment of cancers of the prostate, liver, lung, head and neck, and brain. With effective integration of emerging therapeutics, we will work together to develop individualized SBRT treatment strategies and image guidance tools to advance the management of cancer patients.

“We strongly believe that the collaboration with HU will provide new opportunities for future clinical innovations and breakthroughs.”

Photos provided by the Department of Radiation Oncology, Stanford University

Dr. Yasuhito Onodera

- Lecturer, Faculty of medicine, Hokkaido University
- Specialist of molecular biology and biochemistry

Dr. Jin-Min Nam

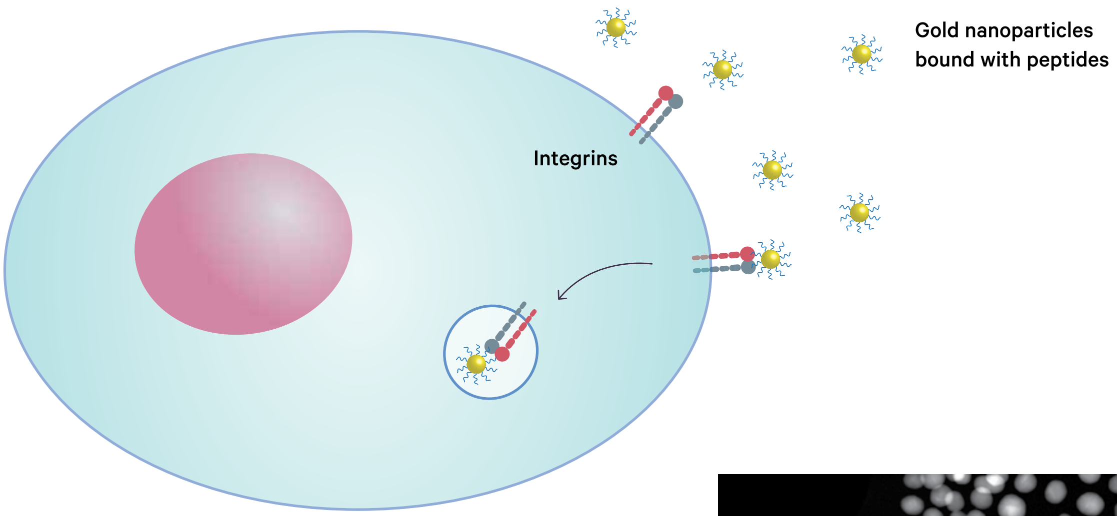
- Lecturer, Global Station for Quantum Medical Science and Engineering, Hokkaido University
- Specialist of molecular biology and radiation biology

Dr. Ping Hsiu Wu

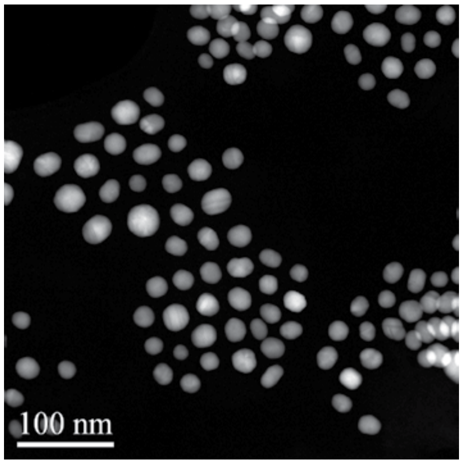
+ Graduate student, Graduate School of Medicine, Hokkaido University
+ Former radiation oncologist at VGHKS hospital, Taiwan

Fighting cancer radioresistance and invasiveness

Jin-Min Nam and her colleagues are tackling with a class of cellular proteins called integrins which are known to enhance cancer radioresistance and invasiveness; a stumbling block in the fight against cancer. To address these problems, they focus on targeting integrins with gold nanoparticles as sensitizers, while unraveling the mechanism behind the radioresistance and increased invasiveness.



▲ **A gold nanoparticle with peptides binds to integrins on the cancer cell surface, and is then incorporated into the cell, where it enhances the effectiveness of radiotherapy. This method exploits a cellular system that circulates integrin molecules between the cell surface and inner cell.**



▲ **A microscopic image of gold nanoparticles bound with peptides. (Ping-Hsiu Wu et al., *International Journal of Nanomedicine*, July 14, 2017)**

"Integrins" might sound unfamiliar to many people, but this class of transmembrane proteins plays an essential role in various biological processes and, in particular, adhering cells to other cells or extracellular material. But some integrins have properties disadvantageous to our fight against cancer because they enhance cancer's radioresistance and invasiveness.

Cancer-facilitating integrins are one common theme being examined by an international team of researchers at Hokkaido University as they strive to prevent the metastasis of cancers and enhance the effectiveness of radiation therapy. Their current focus is two-pronged: targeting integrins with gold nanoparticles as sensitizers and identifying the mechanism behind radioresistance and increased invasiveness. The research projects involve Senior Assistant Professor Jin-Min Nam from South Korea; Senior Assistant Professor Yasuhito Onodera from Japan; and Ping-Hsiu Wu, a medical doctor from Taiwan currently affiliated with Hokkaido University's Department of Radiation Medicine.

Use of gold nanoparticles effective

"We are trying to find ways to enhance the effectiveness of radiation therapy, and, in this research, we focus on gold nanoparticles as sensitizers," Nam said. Although radiation therapy is one of the three major cancer-fighting treatments, it can trigger invasive recurrence and metastasis when a cancer cell survives the therapy. Researchers are urgently trying to unravel this acute problem. In recent years, gold nanoparticles have attracted attention as possible clinical agents for enhancing the effect of radiation therapy in various cancers.

Nam explained the team's achievements in layman's terms. "A peptide attached on the surface of a gold nanoparticle helps it bind with integrins, which will then be able to enter the cancer cells," Nam explained, adding that their research was based on cultured breast cancer cells. "It is important that we target certain types of integrins that are expressed specifically in invasive breast cancer cells. By doing so, we can accumulate gold nanoparticles inside of the invasive cancer cells efficiently." The peptide they attach to a gold nanoparticle is part of another protein called fibronectin, which is known to bind with integrins. "We also found that radiation therapy together with gold colloid (a suspension consisting of nanoparticles in fluid) in cancer cells suppresses their invasiveness."

Nam said using gold nanoparticles as sensitizers in radiation therapy enables a reduced dose to be irradiated in the body, thereby reducing side effects.

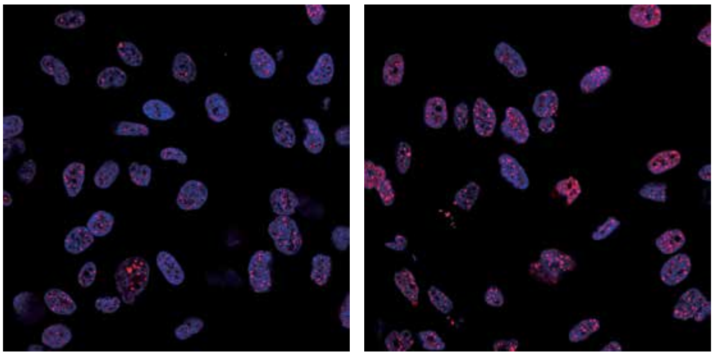
Wu provided research ideas from the viewpoint of a medical doctor. "In the past decade or so, there have been a lot of studies on sensitizers using rats, but none have been used for clinical research because they were not proven effective enough," Wu said. "We are using gold nanoparticles in cultured cells, but eventually we'd like to use the sensitizer for clinical purposes and make it more cost effective."

Nam admits there are many unanswered questions regarding the use of gold nanoparticles as sensitizers for radiation therapy. For example, mystery shrouds its mechanism for suppressing radioresistance and invasiveness of cancer cells, but she cited one theory that gold nanoparticles facilitate ionization, affecting the production of reactive oxygen species (ROS), a type of unstable molecule that contains oxygen and easily reacts with other molecules, including DNA. Nam plans to study this mechanism and conduct further research to find out if gold nanoparticles are also effective in proton therapy.

Distribution of mitochondria key

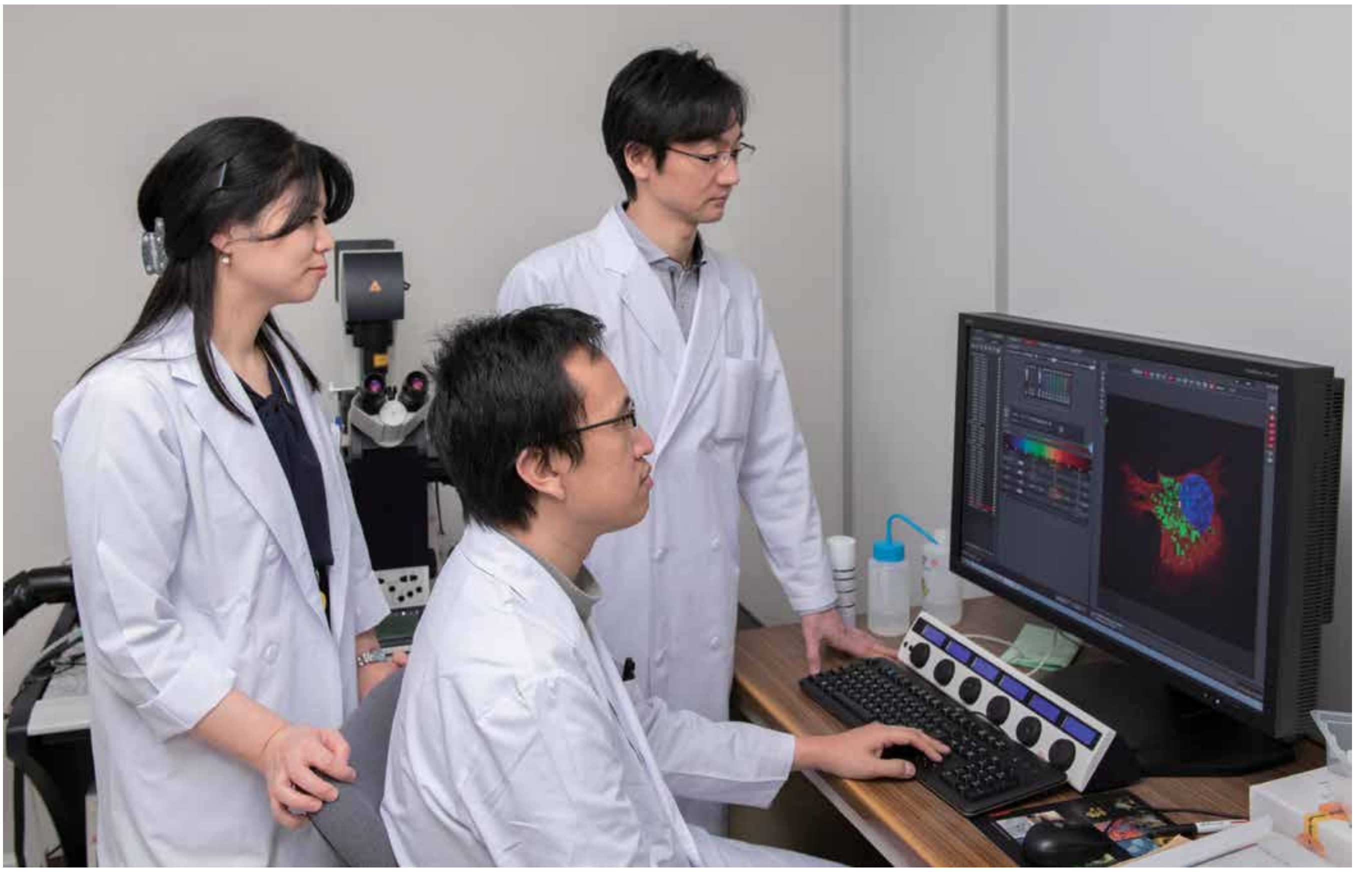
Reactive oxygen species, or ROS, are known to increase in many cancerous cells, making cancers invasive and more aggressive. But if excessive ROS are produced inside cancer cells, it is harmful to the tumors themselves and the cells can die. In other words, ROS are a "double-edged sword" for tumors.

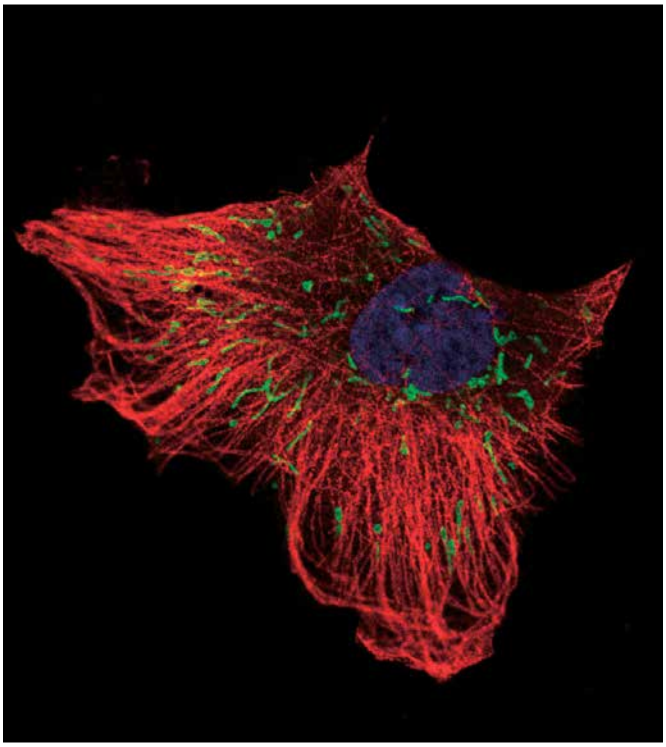
Onodera's research examined the distribution of mitochondria in a cancer cell and the amount of ROS to unravel

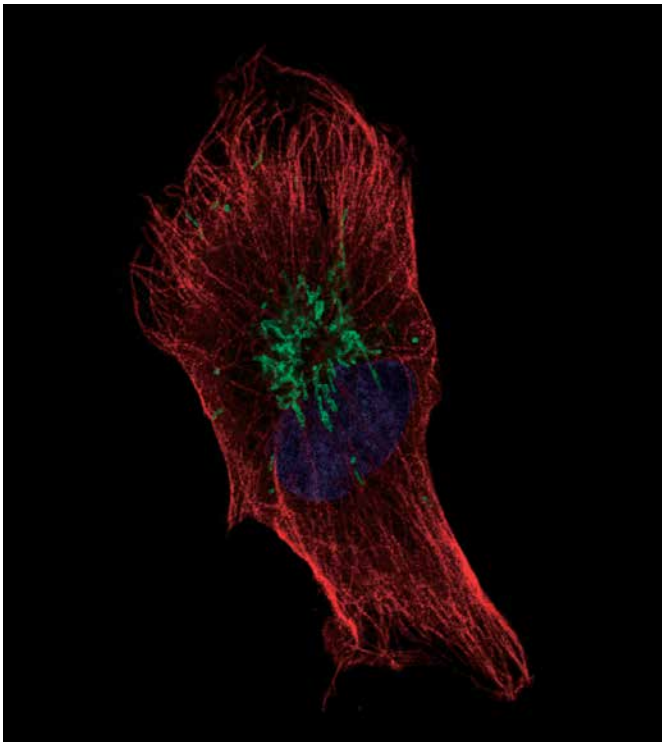


▲ **DNA damage (red) following irradiation increased in the cells treated with gold nanoparticles (right), compared with parental cells (left). Red: γ-H2AX; Blue: DAPI (nucleus). (Ping-Hsiu Wu et al., *International Journal of Nanomedicine*, July 14, 2017)**

> "Using gold nanoparticles as sensitizers enables a reduced dose to be irradiated in the body, thereby reducing side effects."







▲ Dispersed mitochondria (green, left) aggregated near the nucleus when a pathway controlling integrin recycling was disrupted (right) in a cancer cell, leading to excessive production of reactive oxygen species. (Onodera Y., et al., *Nature Communications*, July 11. 2018)

the mechanism of radioresistance in invasive cancers. Mitochondria are organelles found in large numbers in most cells and responsible for energy production. They also are known to produce ROS.

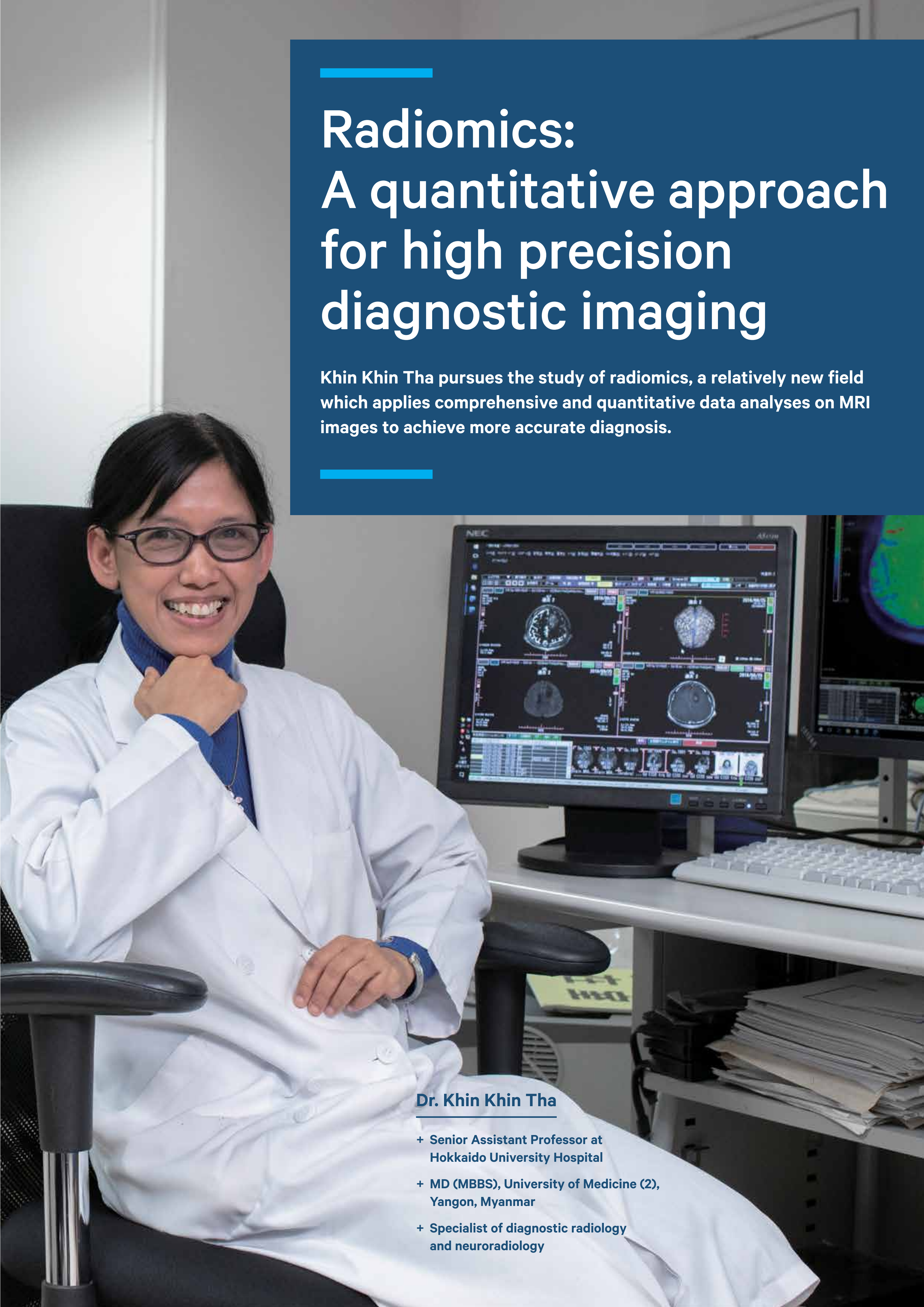
"Many researchers are interested in the fact that cancer cells become more sensitive to radiation when the function of integrins is inhibited," said Onodera, who has been studying integrin recycling, in which the proteins circulate between the cell surface and inner cell. "So we decided to examine the mechanism behind it."

According to their study, a procedure to inhibit integrin recycling resulted in an accumulation of mitochondria at the center of a cancer cell, leading to an excessive production of ROS. Before integrins were blocked, smaller amounts of ROS were found and mitochondria were scattered inside the cell, which enables the cancer cell to utilize ROS for their invasiveness. The production of large amounts of ROS, on the other hand, sensitizes the cancer cells to radiation and suppresses their invasiveness, the researchers found. "We discovered that the distribution of mitochondria in cancerous cells and the amount of ROS production affect cancer invasion and radioresistance. Our data also suggests that the integrin signaling is essential for mitochondria distribution," Onodera said.

"We can create a situation in which mitochondria accumulate near the nucleus, and thus increase the amount of ROS, which causes the cancer cells to destroy themselves."

The three young researchers' ultimate goal is for the results of their research to be used in clinical routines in the form of drugs or treatment methods, they said, so that in the future cancer can be conquered.

> "Cancer cells become more sensitive to radiation when the function of integrins is inhibited."



Radiomics: A quantitative approach for high precision diagnostic imaging

Khin Khin Tha pursues the study of radiomics, a relatively new field which applies comprehensive and quantitative data analyses on MRI images to achieve more accurate diagnosis.

Dr. Khin Khin Tha

+ Senior Assistant Professor at Hokkaido University Hospital
+ MD (MBBS), University of Medicine (2), Yangon, Myanmar
+ Specialist of diagnostic radiology and neuroradiology

Since its debut in the late 1970s, magnetic resonance imaging (MRI) has helped doctors diagnose everything from sprained ankles to cancer in millions of patients. While computed tomography (CT) scans can provide images quickly and are highly suited for identifying bone fractures and calcification, and positron emission tomography (PET) scans are capable of visualizing metabolic processes within the body, the MRI scan's non-invasive nature and lack of radiation exposure can make it the ideal choice for patients who require multiple scans. The MRI also provides finer anatomical details than both the CT scan and the PET scan, making it the superior choice in helping doctors diagnose patients with certain diseases.

However, for all the information an MRI can provide, there are still weak spots when it comes to the analytical appraisal of the scan. Radiologist Khin Khin Tha of Hokkaido University Hospital's Department of Diagnostic and Interventional Radiology explains, "Until now, radiologists have tended to evaluate MRI results with our eyes instead of measurements. This is a fast and reliable method of analysis for radiologists working on the clinical side but is sometimes inadequate for research purposes when exact data is necessary, as a visual-only analysis can carry the risk of results being influenced by the radiologist's bias." After receiving her Ph. D in radiology at Hokkaido University in 2005, Tha has focused her research on applying quantitative analysis to MRI scans, as opposed to the commonly used and accepted visual analysis techniques. After meeting with a group of Stanford researchers, in 2015 she began working in what she describes as her "dream field": the newly developed field of radiomics.

▲ Dr.Tha with an MRI unit (top) and the image reading room (bottom).

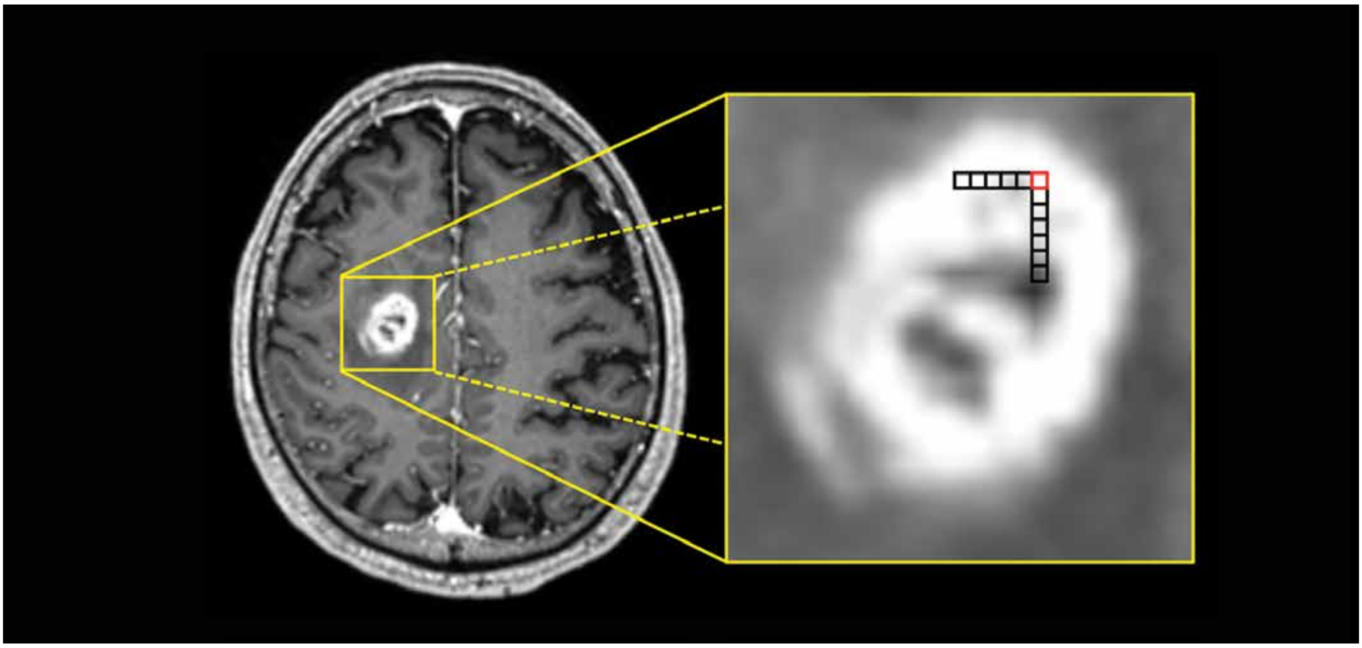
A new method for accurate diagnosis

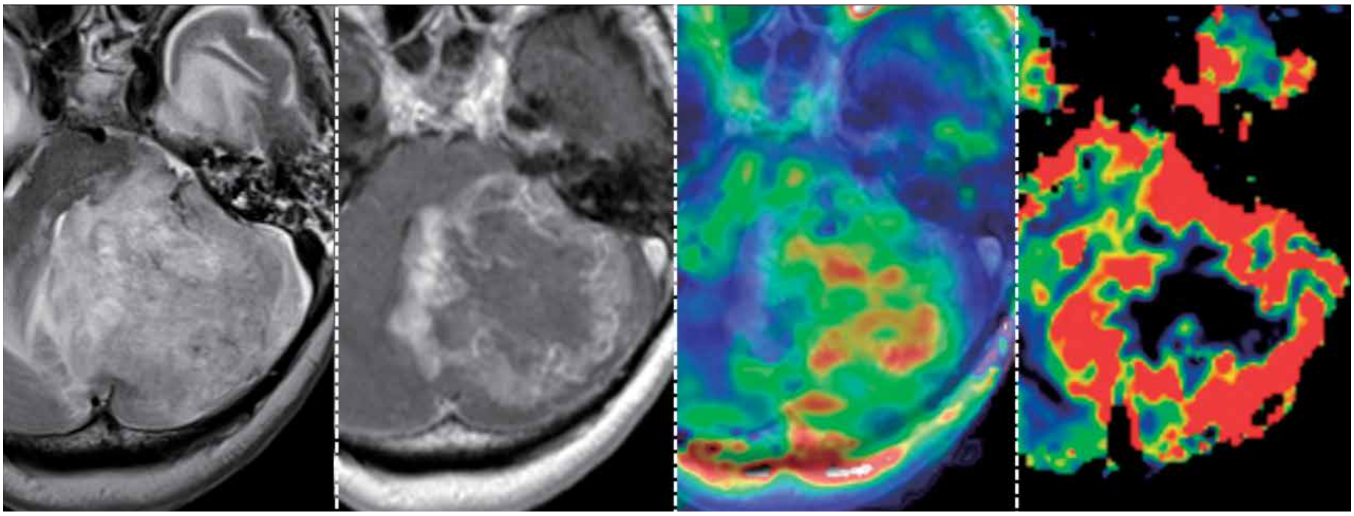
Developed about 10 years ago, radiomics is a technique that combines image and comprehensive data processing. It allows radiologists to obtain large amounts of quantitative data from an MRI image that are impossible to gather through a purely visual inspection of an MRI scan. Radiologists upload the MRI results into a system that analyzes the images and cross-references them within a large database of other related tumors, providing comprehensive information on the tumor's quantitative features, such as signal intensity characteristics, surface area, texture, and volume. For cancer patients suffering from glioblastoma, the most common and usually aggressive type of brain cancer found mainly in adults, MRI scans conducted utilizing radiomic techniques were able to help radiologists identify substantial differences in features within the same tumor that had visually appeared to be homogeneous on a standard scan. "Before radiomics, radiologists were satisfied with their visual assessment because they believed their own eyes," Tha explains. "However, through radiomics, we are able to breakdown and comprehensively analyze different parts of a tumor without performing an invasive biopsy."

Without using radiomic techniques, the only way to accurately assess certain features of a glioblastoma tumor was to extract a section of the tumor itself for analysis. With radiomics, doctors can fully characterize a tumor by obtaining data regarding the intensity, shape, and texture of the full tumor from just an MRI scan, providing vital information about the tumor's aggressiveness and helping doctors create individualized treatment plans for the patient. This is especially important due to a phenomenon known as intra-tumor heterogeneity, in which diverse

"Before radiomics, radiologists were satisfied with their visual assessment because they believed their own eyes."

▾ **A standard MRI scan of a glioblastoma tumor (left). By applying radiomic analytics to the scan, the image can be broken into individual voxels (right), which can independently verify specific quantitative features of the tumor, helping doctors better understand its inner-complexities. This data can then be used to obtain a comprehensive view of the entire tumor, a feat which was previously impossible using only visual analysis methods.**





▲ Different MRI datasets (from left to right, a T2-weighted image, a contrast-enhanced T1-weighted image, a mean diffusion kurtosis image, and a cerebral blood volume image) of a glioblastoma showing intratumor heterogeneity. The signal intensity on T2-weighted image, degree of contrast enhancement, mean diffusional kurtosis (which reflects tissue complexity at the microstructural level), and cerebral blood volume all vary greatly within the tumor.

types of cancer cells behave differently within the same tumor, providing a severe roadblock to effective treatment methods. Due to this phenomenon, even a physical biopsy is sometimes not enough to fully understand the characteristics of a glioblastoma tumor, as the biopsied section may not have been representative of the tumor as a whole. Radiomics helps solve this issue by giving radiologists and doctors nearly all the information they need to assess the tumor, in best-case scenarios down to its genetic sub-type, and deliver an accurate prognosis and treatment regimen.

A global team effort

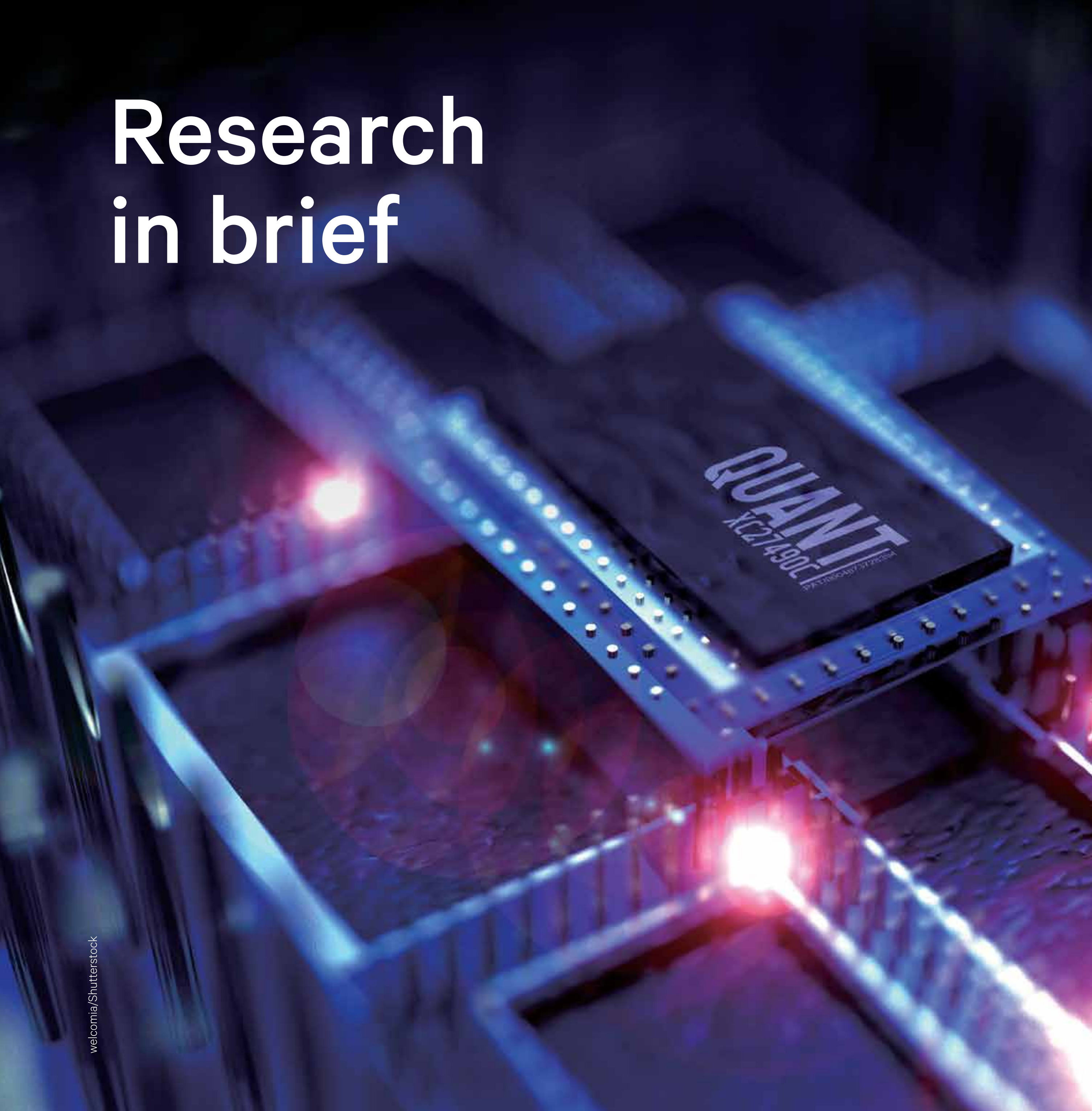
In its current state, radiomics is a true team effort, requiring a collaboration of radiologists, computer scientists, clinicians, and biologists to derive the required results. Due to the necessity of this inter-disciplinary collaboration, it can sometimes be challenging to obtain the necessary expertise to advance research forward. Through the GI-CoRE program, Hokkaido University partnered with Stanford University, creating a mutually beneficial research environment where both universities are able to take advantage of shared knowledge and resources. Together, this collaboration has published three research papers on applying radiomics to glioblastoma patients, with the results indicating that survival prognosis was better when radiomic techniques were used in assessing a patient's tumor compared to using only conventional prognostic measurements and techniques.

Still, despite the promising results that radiomic analysis offers, there are still a multitude of challenges that must be overcome before the technology can gain widespread use. While the ultimate goal is to be able to have the MRI system itself conduct the processes necessary to obtain a radiomics report, in its current state radiologists must undertake additional image processing steps in order to receive the fully comprehensive data, which can take time. However, according to Tha, the main obstacle researchers are facing now comes down to data. "A large amount of data is needed to carry out a radiomic report," she says. "However, currently this data is not always available due to differences in collection and treatment methods and a lack of standardization, not only between methodologies but also between the MRI scanning equipment itself. For my research on glioblastoma, there were also issues in data collection due to the relative rarity of the disease and different intervention practices between hospitals, with some hospitals intervening with aggressive treatments earlier than others."

Forging ahead in the field of radiomics

As more research is conducted, Tha hopes that one day radiomic assessment will be the standard in MRI-based cancer screenings, with machines completely capable of carrying out complex data analysis utilizing advanced AI technology under the guidance of a single operator. She also envisions a future where these techniques are applied to other diseases affecting not only the brain, but also different parts of the body. "We have already applied AI radiomic techniques to identify triple-negative breast cancers, which have the worst prognosis out of all breast cancer types. In addition, we are currently working on studies to use radiomics to help identify MRI features of Parkinson's disease which would allow for a speedier diagnosis. Still, more work needs to be done, especially collaborative work, in order to gather the amount of data needed to implement radiomics on a wide-scale." ●

Research in brief



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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.

CONTACT

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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.

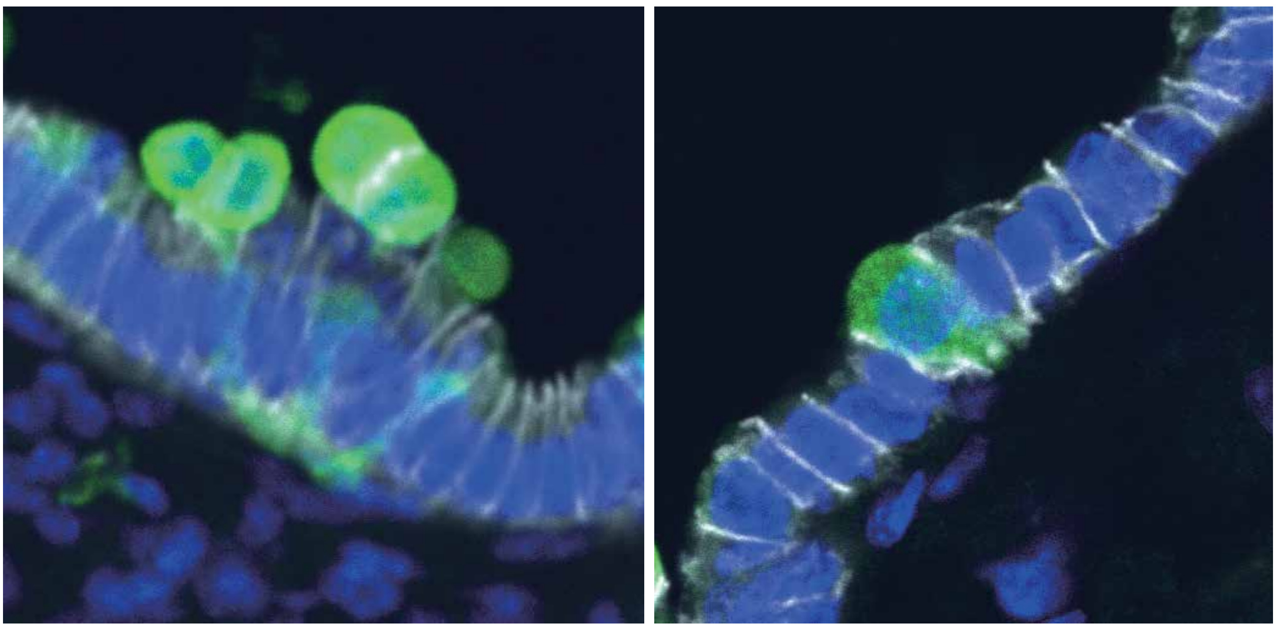
Feeding the Ras mice high-fat diets, which resulted in severe obesity, suppressed the defense mechanism and therefore increased the number of Ras-transformed cells remaining in the tissue. This suppression was seen in the intestine and pancreas, but not in the lungs. Furthermore, a month later the Ras-transformed 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.

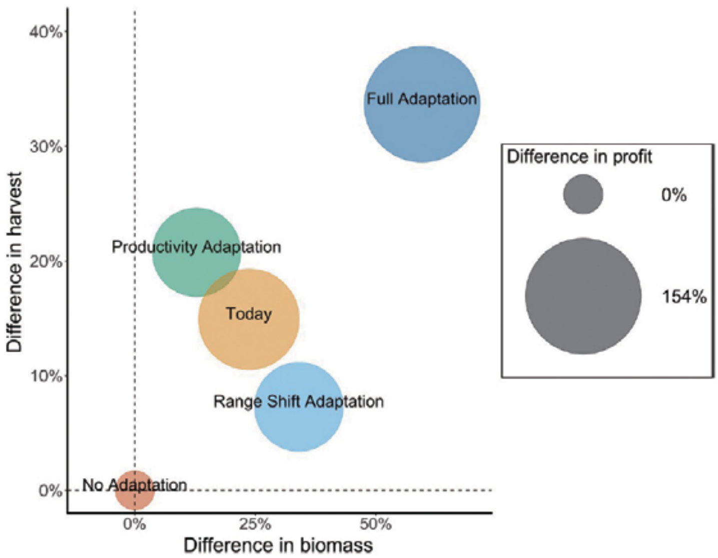
This is because, under what has been determined as the best management scenario, some major fish and shellfish stocks that are commercially harvested, broadly referred to as fisheries, will grow and become more profitable, offsetting the many others projected to shrink or even disappear. On a global 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 @zorandim / 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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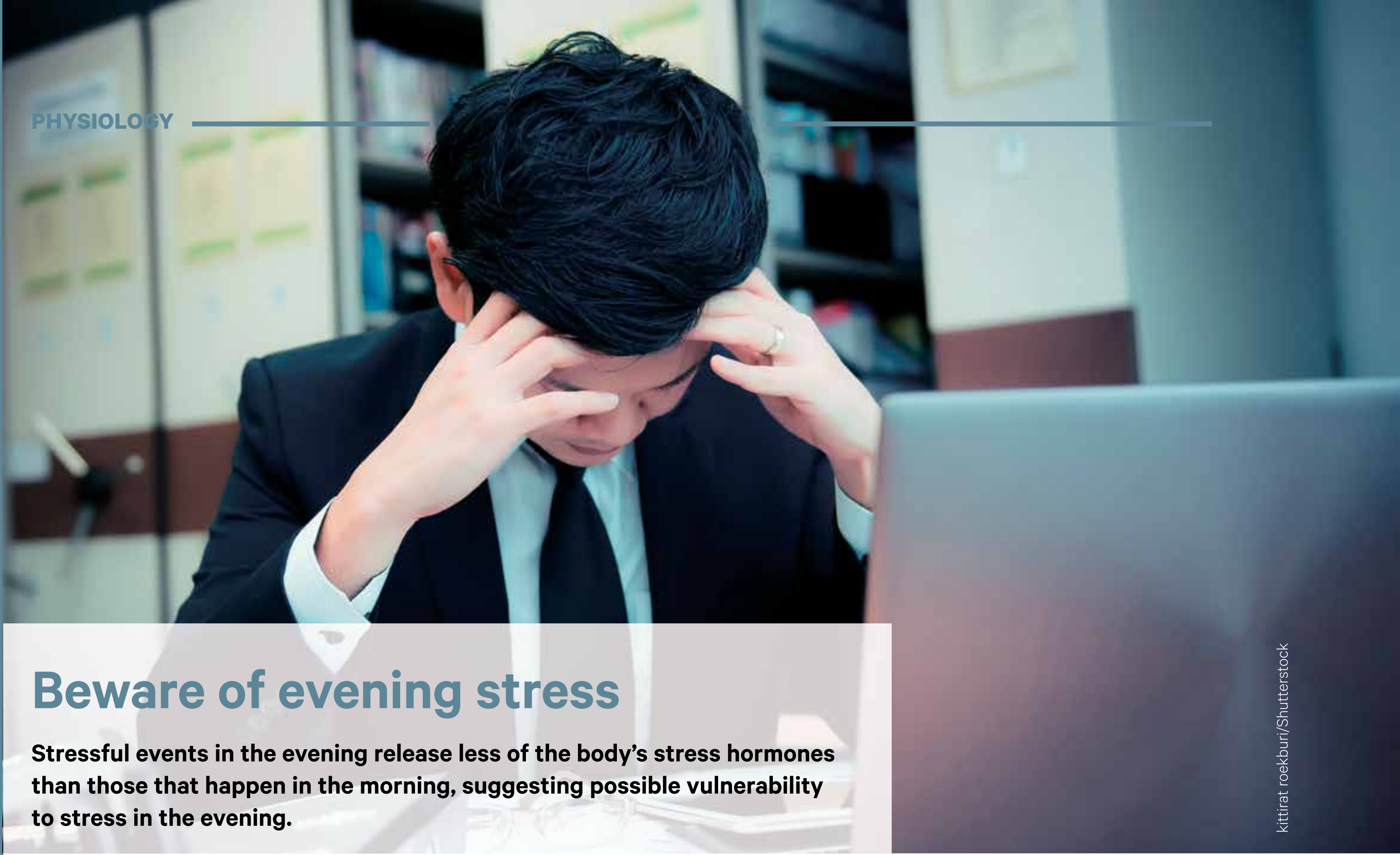

Beware of evening stress

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

Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science (JSPS) (16K01723) and scholarship donations from Yotsuba Milk Products Co., Ltd.

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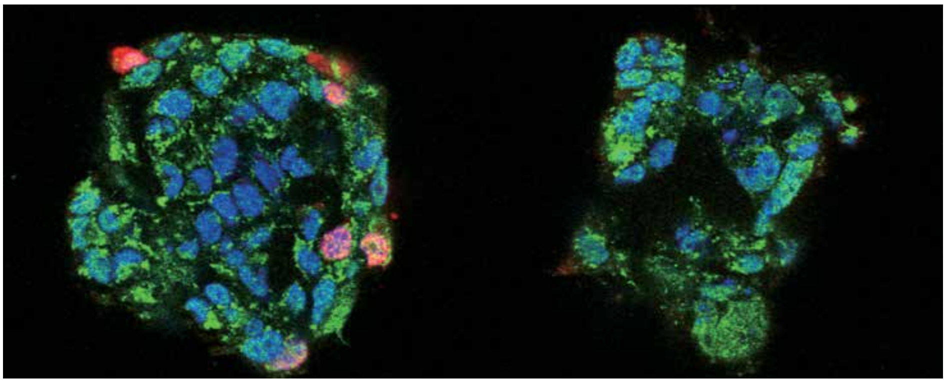
Key molecule for flu infection identified

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.

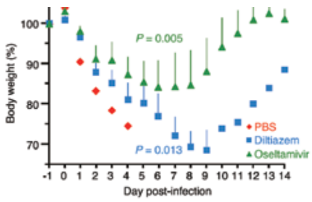
In the latest study published in *Cell Host & Microbe*, the same team has discovered that the Ca2+ channel, a transmembrane protein that allows Ca2+ to move across the cell membrane, is the key receptor molecule for IAV infections. Furthermore, treating human cells with calcium channel blockers (CCBs),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

FUNDING
ImPACT Program of Council for Science, Technology and Innovation (Cabinet Office, Government of Japan), KAKENHI (No.16H02211), JST PRESTO (JPMJPR1668), JST ERATO (JPMJER1601), and JST CREST (JPMJCR1673).

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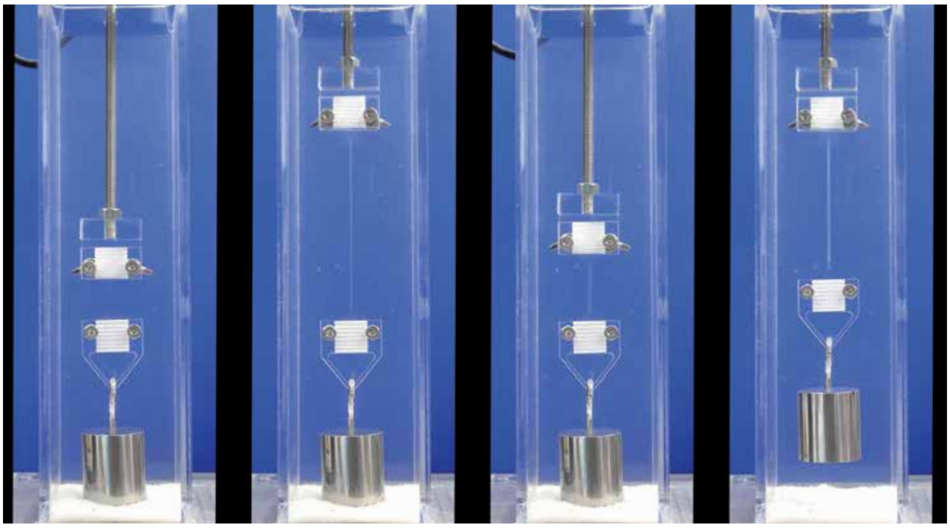
Self-growing materials that strengthen in response to force

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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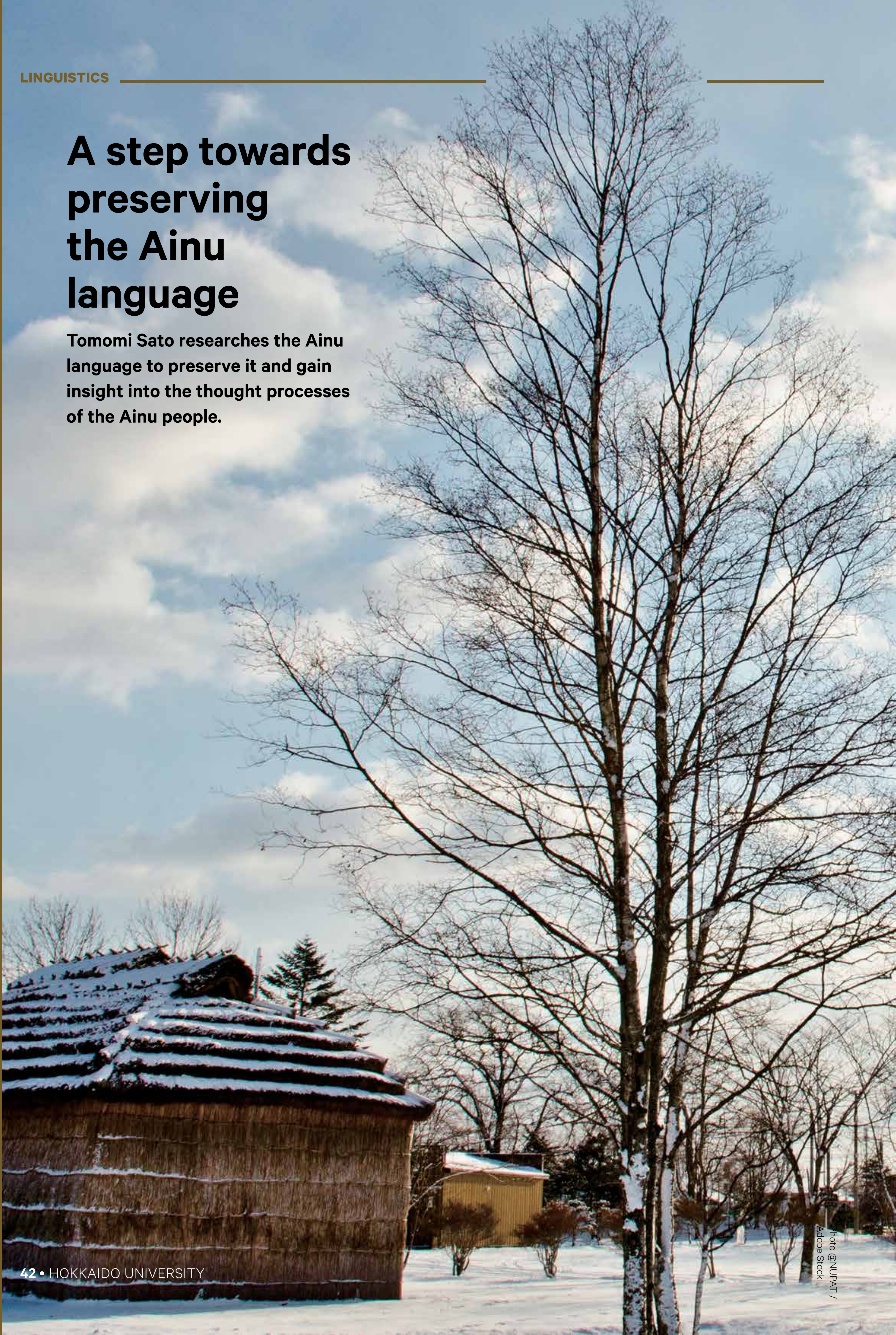

A step towards preserving the Ainu language

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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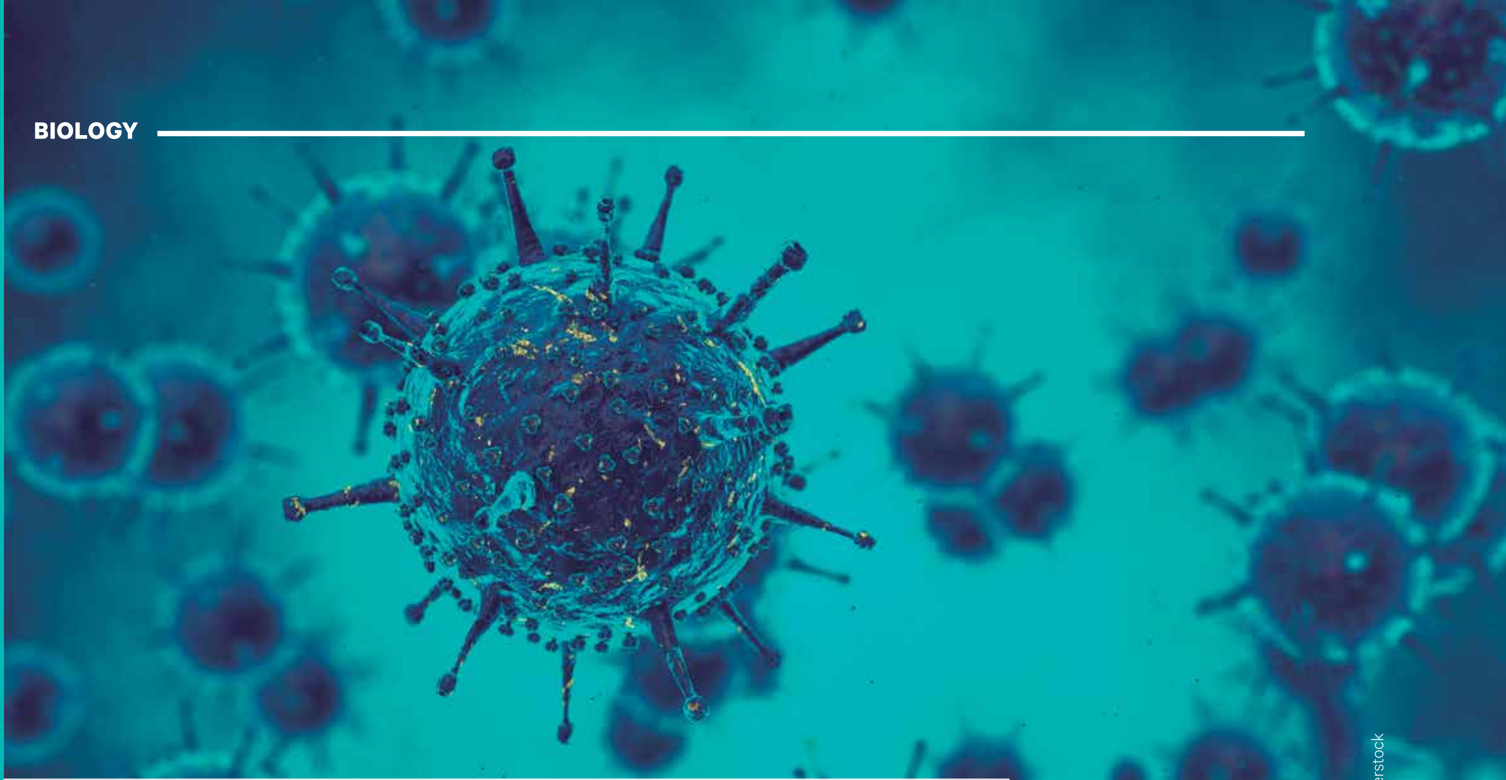

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Engineering a cancer-fighting virus

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

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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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 anti-cancer 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.

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.

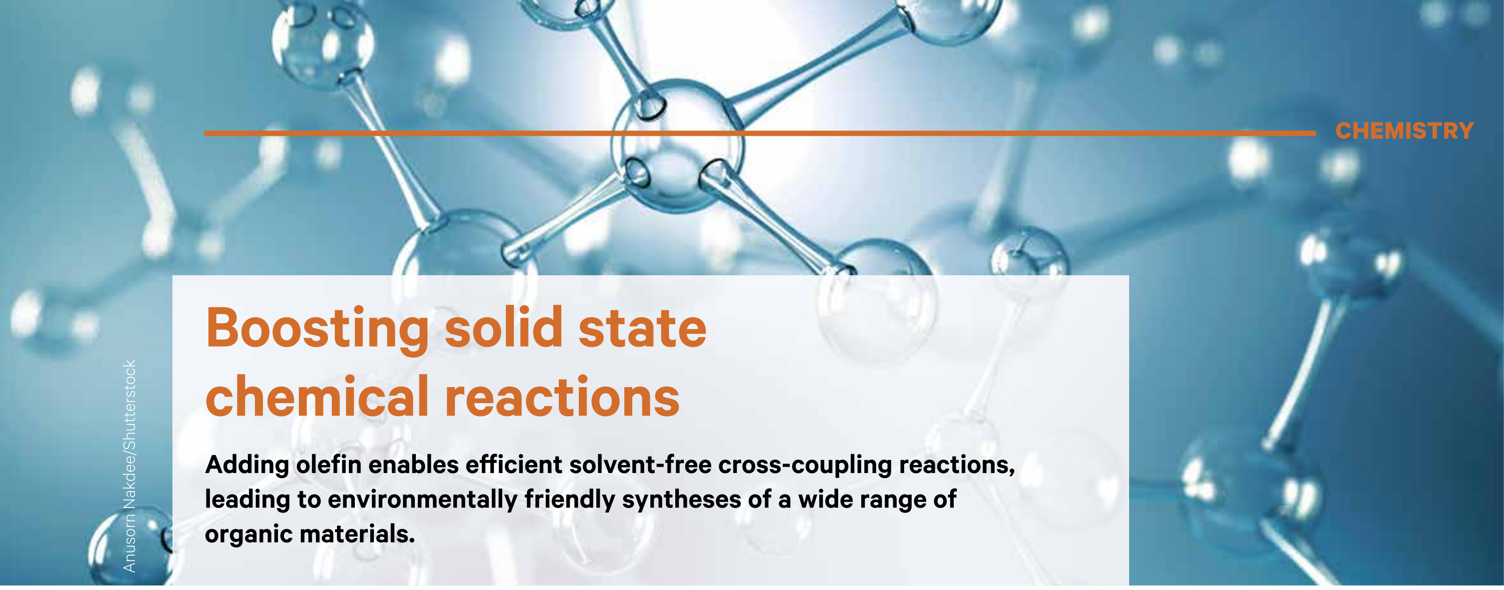
Finding new chemical reactions is indispensable for generating advanced materials and chemicals as well as reducing energy consumption and environmental burdens. So far, such development requires a trial-and-error approach which tends to be time-consuming, laborious, expensive, and inefficient. The new 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
Institute for Chemical Reaction Design and Discovery
HOKKAIDO UNIVERSITY

ICReDD members at Hokkaido University gathered to prepare for the international kick-off meeting.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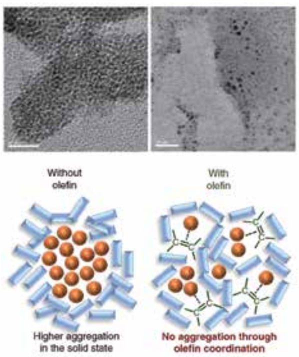
Boosting solid state chemical reactions

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



▲ 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)

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." ●

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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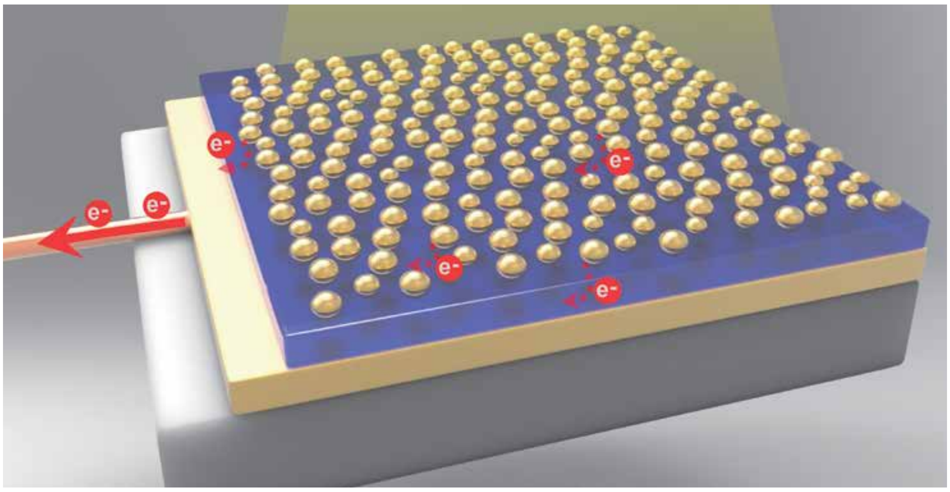
Golden sandwich soars photoelectron conversion efficiency

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.

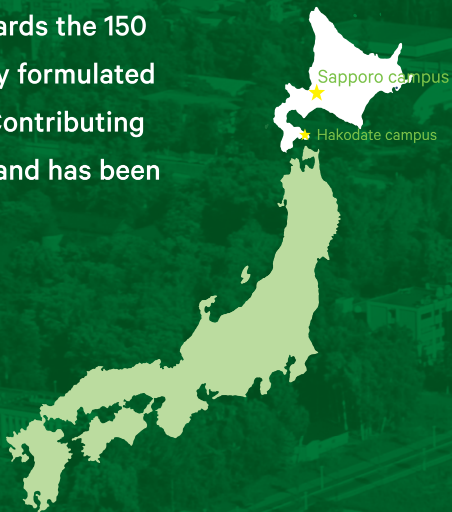
The rubber used for the tires was developed by the Bridgestone corporation based on the double network gel technology devised by Professor Jian Ping Gong's laboratory at Hokkaido University. The technology integrates two different kind of polymers, one rigid and brittle and the other flexible and stretchable, 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.

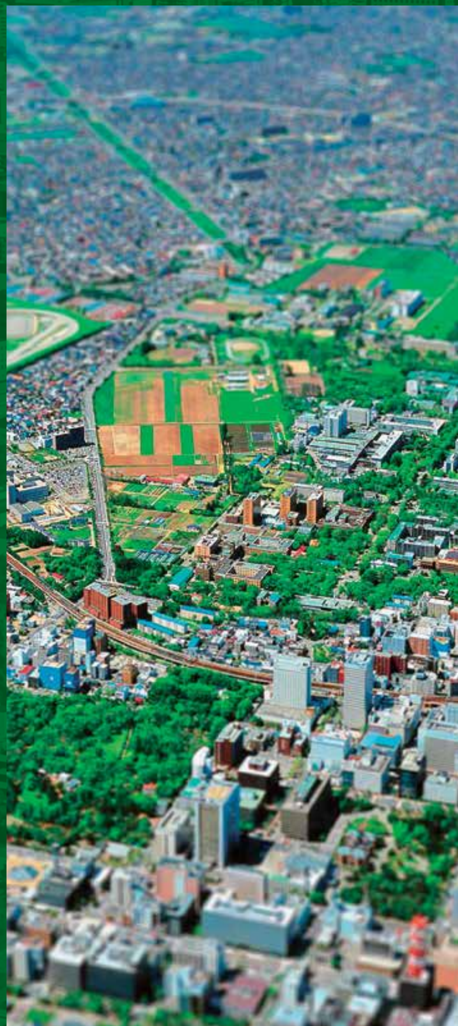
The novel polymers developed in this program could have a widespread ripple effect throughout the polymer industry in the future.

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.

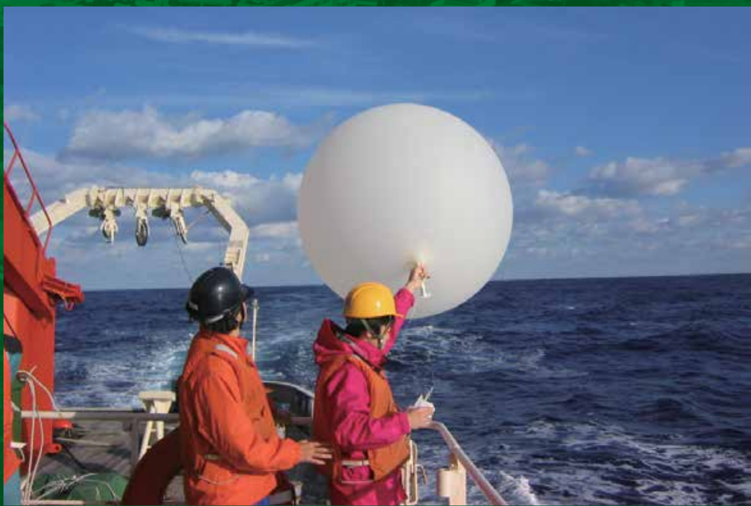


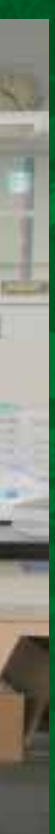


Contributing towards the **resolution** of **global** issues

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

RANKING

6th
in Japan
THE Japan University Rankings 2018

32nd
in Asia
QS Asia University Rankings 2018

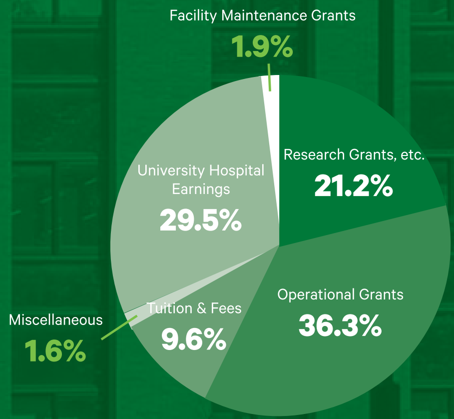
90th
World's Most
Innovative University
Reuters 2018

3,974
faculty&staff

24
Research centers and institutions

REVENUE

¥98,366m
revenue in 2018



Be ambitious.
Inazo Nitobe

HOKKAIDO UNIVERSITY

TOP GLOBAL UNIVERSITY JAPAN

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