Kyoto University
2019 Spring

KYOTO U
Research News

On the occasion of Tasuku Honjo's Nobel Prize

The streets of Stockholm are cold in December. As president, I was fortunate to join Tasuku Honjo there and attend the ceremony and banquet. It was both an immense honor and an unforgettable experience.

Walking the cobbled lanes and seeing the holiday lights and decorations, I felt the immense sense of history and tradition surrounding the prize, which Alfred Nobel established in 1895, two years before the founding of our University.

Nobel laureates have shaped popular thought and understanding of the world far beyond their own fields of study. It is remarkable to feel this power in Stockholm, where Marie Curie and Alfred Einstein also trod the paving stones. And Japan's first laureate, Hideki Yukawa, who had been an undergraduate and then later full professor in Kyoto, inspired our war-ravaged nation when he received the physics prize in 1949.

Yukawa's message to Japan and the world was that science should represent the best that humanity has to offer: that science's outcomes must further peace and the betterment of life on the planet, in line with Nobel's vision for the prizes.

Dr Honjo joins Shinya Yamanaka as our second, active medicine laureate among the research faculty. Both continue to be leaders in their fields, seeking to improve the lives of patients worldwide through diligent pursuit of knowledge in basic science.

In March 2018, Kyoto University implemented a policy of not accepting research funding from military sources. Life on this planet is too precious and too fragile to be placed in any more jeopardy than it currently faces. We will do our utmost to imbue our graduates and researchers with this guiding principle, as well as a desire for harmonious coexistence with all life and the natural environment.

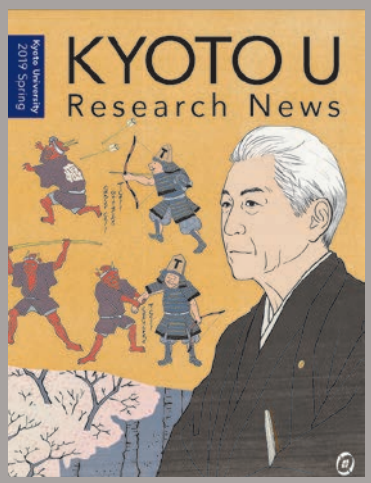
Juichi Yamagiwa, President

Contents

Editorial team
KURN Editorial Board, assisted by the Offices of Public Relations, Research Administration (KURA), and International Strategy (iSO-KU)

Publisher: TRAIS K.K.

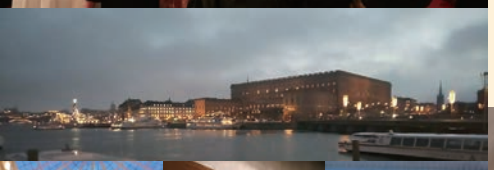
Contact: Kyoto University, Japan
+81 75.753.7531
ku-info@mail2.adm.kyoto-u.ac.jp



On the cover
An *ukiyo-e* (traditional woodblock print) style design, featuring Nobel laureate Tasuku Honjo in his ceremonial garb, an *oni-taiji* themed depiction of T-cells battling ogre-like cancer cells (read clockwise from upper-right), and a scene of the medical school campus in spring. Can you recognize some notable KyotoU figures among the cherry-viewing crowd? (Trais/Fujiwara)

© Nobel Media AB/Nanaka Adachi

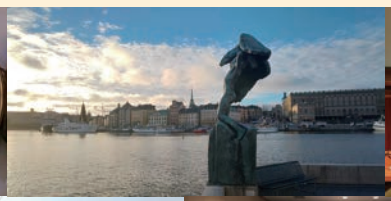
On the cover:
Nobel Prize 2018

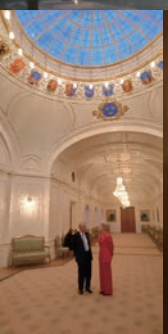


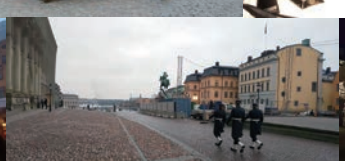
Congratulations, Honjo-sensei!

Join us in this special issue as we celebrate the *2018 Nobel Prize in Physiology or Medicine*, awarded jointly to **Tasuku Honjo**, distinguished professor of Kyoto University, and **James P Allison**, of the University of Texas, "for their discovery of cancer therapy by inhibition of negative immune regulation."

This spring issue's first section follows Honjo from the announcement of the prize in early October, to his attendance at 'Nobel week' in Stockholm in early December, and then to his return to Kyoto later that month. Interspersed are discussions he had with prominent KyotoU scholars and an introduction to the science behind PD-1 and cancer immunotherapy.







Congratulations, Honjo-sensei!

The announcement

Monday 1 October 2018, shortly past 18.30. With a bevy of news trucks parked outside the Clock Tower in anticipation, the live stream from Stockholm broke the news of Honjo and Allison's joint award. A few minutes later, Honjo, President Juichi Yamagiwa, and ExecVP/Provost Nagahiro Minato sat down in front of the amassed reporters and cameras for their first press conference.

The most indelible image of the evening, first released by the Nobel Foundation, was of Honjo surrounded by celebrating lab members. The photograph — taken at the behest of Stockholm using Honjo's own phone — captured the global flavor of his research team.

The following morning, Honjo was back at the Clock Tower for more in a continuing round of interviews, congratulatory phone calls, and a more personal press conference together with his wife Shigeko.

The interim

October and November. The initial excitement of the announcement was followed by two frenzied months, during which Honjo made government courtesy calls in Tokyo, gave numerous television interviews, and started into his preparations for the trip to Sweden, all while continuing his typically non-stop schedule of research meetings and appearances.

Nobel week

Wednesday 5 December, early morning. Dr and Mrs Honjo arrived at Kansai International Airport, where a room full of reporters queried him on his final thoughts before departure. Ending weeks of speculation, he announced his intention to donate a majority of his prize money to a fund to support early career researchers.

The Honjos, accompanied by University support staff, then boarded a flight en route first to Helsinki.

Same day, late evening. As soon as the Honjos' Finnair plane parked at the gate at Stockholm's Arlanda Airport, the Swedish government's attaché assigned

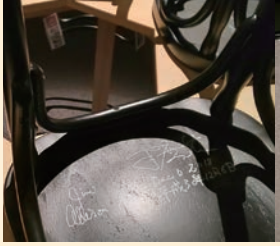
Defining 'Kyotoness' in the research environment

"I have an unusual boast," says Honjo wryly, "for there are not many in Japan who have been on the payroll of all three universities of Tokyo, Osaka, and Kyoto."

These experiences, together with time spent in the United States, have given him a unique perspective in understanding what makes Kyoto a special place for a researcher.

In an historic salon room at the Grand Hôtel, overlooking Stockholm harbor, Honjo managed to take a short break from his hectic Nobel week schedule to sit down on Sunday afternoon with two colleagues, Drs Yamagiwa and Minato, respectively the President and the Executive Vice President for research/Provost. Yamagiwa is a preeminent primatologist, and Minato, in addition to being a leading immunologist, is a long-time collaborator of Honjo's.

"Throughout my career, I have been fortunate to be able to learn from others, without having to study everything from the basics myself. This 'ear-training' served me well at all


to Honjo boarded to whisk them past the crowds and entry procedures. Within minutes they were in their black, chauffeured Nobel vehicle, on their way to downtown Stockholm.

Meanwhile a jostling crowd of Japanese reporters and news cameras were waiting on the edges of the red carpet in front of the Grand Hôtel, craning to catch a glimpse of the new laureate as he stepped out of the car. Nobel week had begun.

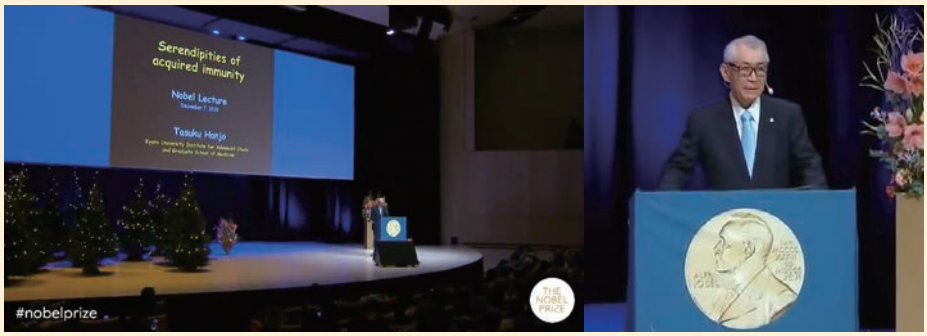
Thursday 6 December, morning. Laureates, accompanied by their families and guests, gathered at the nearby Nobel Museum for a half-day of informal welcoming into the traditions of the institution, as well as an opportunity to sign one of the café chairs. Honjo donated a framed, four-character saying, written in his own hand, reading: *yû-shi kyô-sei*, or "Without ambition, nothing is acheived".

The highlight of the afternoon was a joint press conference at the Nobel Forum, during which Honjo and Allison's discussions of their research and consequences for cancer treatment were interspersed with lighter moments about their personal lives.

Friday 7 December. Honjo had stated before departing from Japan that he was particularly looking forward to his official Nobel lecture, and this moment came on Friday afternoon at the immense Aula Medica of the Karolinska Institutet. Speaking to a capacity crowd of medical students, young scientists, and ordinary citizens inspired by his work, Honjo delivered a passionate account of his decades-long quest to unravel the mysteries of the body's immune system. Mixing descriptions of the scientific processes with anecdotes about his life and numerous collaborators, he painted a picture of the immense complexity that exists in all our bodies, ending on the note that we have evolution to thank for the intricate systems that maintain our health. The hour-long speech was widely praised as being one of the best on record by any laureate.

Saturday and Sunday 8–9 December. With the hard work under his belt, Honjo could now concentrate on many other, lighter activities, while preparing for Monday's ceremony and banquet.

Saturday started with a Japanese press interview, followed by a reception and press conference hosted by the Japanese ambassador to Sweden and including a courtesy visit with the Swedish minister for science. In the evening, all the



three universities, and when I returned to Kyoto, I realized that the environment of the medical school was particularly open to sharing knowledge."

"For example in immunology," says Honjo, "I was a total newcomer. Dr Minato helped me understand what was what."

Minato laughs at Honjo's unexpected show of modesty. "Our field was really not very rigorous until Dr Honjo appeared. It was interesting, and there was a great deal of fascinating work going on, but a solid, molecular and genetic foundation for the processes we were observing had yet to be established.

"Dr Honjo arrived and immediately began asking pointed questions. It quickly dawned on the younger faculty that we needed more knowledge about the scientific foundations, and he pointed the way for us."

It is an enlightening moment, demonstrating how cross-seeding of

Congratulations, Honjo-sensei!

laureates and their families and guests joined members of the Swedish royal family for a gala Nobel concert at the Stockholm Concert Hall, which would then become the venue for Monday's award ceremony.

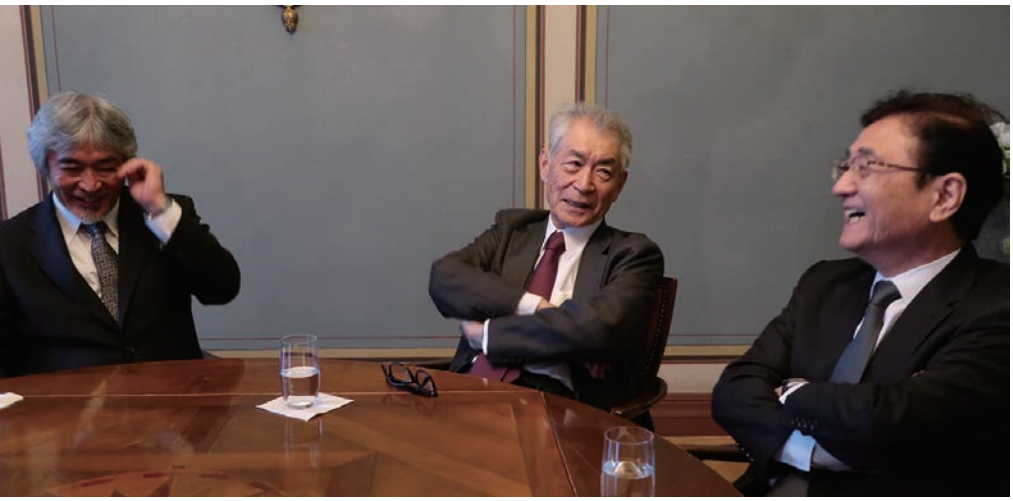
Sunday was punctuated with meetings such as with KyotoU's Yamagiwa and Minato (see below), and an emotional event where Honjo and Allison met with cancer survivors whose lives had been saved thanks to the two scholars' research. After many hugs and

moist eyes, Honjo spoke to Swedish television crews covering the event of how much it means to him to see the positive effects of what he had achieved.

Later in the afternoon there was some short time for a family outing, to see the historic sailing vessel *Vasa*. While the museum housing the immense, preserved ship is open to the public, only visiting heads of state and Nobel laureates are allowed to actual go onboard.

Monday 10 December. The long-anticipated day of greatest pomp and circumstance began quietly with a rehearsal in the morning, followed by elaborate dressing — and for the ladies, hairdressing — associated with Japanese traditional formal wear. Honjo's black *haori hakama*, emblazoned with his family crest, was noted in the Swedish media as being a breath of fresh air amongst an "ocean of tuxedoes". The weather, which had been largely grey up to that point, suddenly brightened as the winter sun lightened the sky and the city.

At the ceremony itself, where Honjo and his Nobel peers received certificates and medals from the Swedish monarch, King Carl XVI Gustaf, the assembled were treated to an enlightening musical rendition of how Honjo and Allison's discoveries released the 'brakes' on the body's immune system, first with a solo violin playing a melody from Bizet's *Carmen*



experiences and knowledge can lead to new and unexpected outcomes.

"What makes Kyoto a special place for you, as a researcher?" probes Yamagiwa.

"The quiet, peaceful atmosphere," says Honjo, "and the freedom to pursue your curiosity. For years we didn't know what PD-1 did, but we did have a feeling it must be important.

"When all the pieces came into place, the link to cancer became obvious to us, thanks to having had the time to discover this and a lack of constraints. Kyoto made this possible for us."


© Nobel Media AB/Alexander Mahmoud

Suite, followed by the full orchestra, illustrating newly found vigor in a fight against cancer cells.

Laureates and guests then followed the King and royal family to the vast Blue Hall of the historic Stadshus, where they leisurely consumed a banquet dinner interspersed with music and dance performances and endless conversations around the long tables. With much fanfare, Honjo had the honor of delivering a final speech (see below), marking the end of the meal and the beginning of further festivities that would continue throughout the night, concurrent to Swedish observation of the festival of St Lucia.

Tuesday and Wednesday 11–12 December. Following such a long day and night, most laureates chose not schedule anything immediately

Honjo's speech at the Nobel banquet

"Your Majesties, your Royal highnesses, excellencies, dear laureates, ladies and gentlemen,

On behalf of [fellow laureate] Professor Jim Allison and myself, I wish to express our heartful appreciation to the Nobel Assembly of the Karolinska Institute and the Nobel Foundation.

Cancer has been the number one cause of death during the last half-century. The trend is getting even worse as the average life span increases.

The concept of cancer immunotherapy was theoretically proposed by the Australian Nobel laureate Sir Frank Macfarlane Burnet over sixty years ago, and since then, a large number of people have tried to apply it, but without success. This was probably because their efforts focused on pushing the accelerators of the immune system. Jim and I independently discovered that the reactivation of the immune system by blocking two major negative regulators, CTLA4 and PD-1, can cure a significant portion of cancer patients. Fortunately, our experiments in mouse models were successfully applied to humans. As a result, Jim and I have experienced many occasions that have made us feel well rewarded, such as meeting cancer patients who say their lives were saved by our therapies.

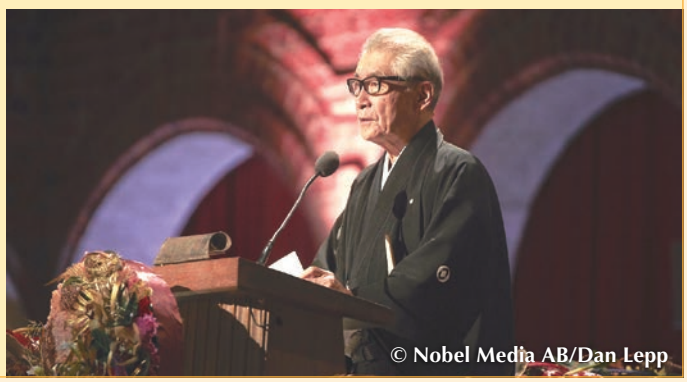
Cancer immunotherapy is possible because we have a highly sophisticated immune system called 'acquired immunity', which can catch small changes in tumor cells. How could we develop such a sophisticated immune recognition system that employs gene rearrangement? The genetic rearrangement mechanism must have developed accidentally — probably about five hundred million years ago, when vertebrates evolved. Thereafter, it must have persisted through natural selection due to the advantage of surviving infectious diseases.

Considering that the chance of such mutation and selection must be unbelievably low, we human beings are all very fortunate.

Jim and I both know that the development of our discovery is just beginning, as currently only 20 to 30 percent of patients respond to the immunotherapy. Andy Coghlan and Dan Chen described our discovery as the cancer equivalent of penicillin, which gave rise to a whole generation of antibiotics that changed medicine, and consigned most previously fatal infections to history. We encourage many more scientists to join us in our efforts to keep improving cancer immunotherapy. We sincerely hope this treatment will reach far and wide so that everybody on our planet can benefit from this evolutionary gift for healthy life.

Jim and I acknowledge that we were selected for this highest of all scientific honors. We accept the distinction with our deepest gratitude for the great institutions that have supported our work, for our many devoted and skilled coworkers, without whom our achievements would have been impossible, and, finally, for Alfred Nobel for his wisdom to institute the prize and the people of Sweden for a fantastic Nobel Week.

Thank you."


© Nobel Media AB/Dan Lepp

Congratulations, Honjo-sensei!

afterward, but Honjo was active as always, attending a luncheon at the Japanese ambassador's residence and then being joined by chemistry laureate Frances Arnold for an open discussion at the Swedish parliament, where young legislators with a science and health policy bent asked the two luminaries for their opinions on promoting science education and improving public health.

A second session of dressing and hairdressing followed, ahead of an evening's banquet as guests of the royal house, in the stately palace just across the channel from the Grand Hôtel.

Then on Wednesday morning Honjo and Allison paid a final visit to Karolinska, this time for an informal session with

young researchers, who peppered the two with deep and probing scientific questions, often bringing out the humor in the two men. The afternoon saw all the laureates reunited at the Concert Hall, this time for a recording of the annual "Nobel Minds" program for the BBC and Swedish national television.

Thursday 13 December. The final day was back to grey skies, as the Honjos paid farewell to the hotel staff and made their way to the Nobel Foundation. Here, as tradition dictates, Honjo sat in Alfred Nobel's chair to sign a book of laureates, remarking that the experience of being in that place, as with Einstein and Yukawa and many more before him, left a deep impression on him. Taking a wreath then to Nobel's grave,

the Honjos sped off to Arlanda and the voyage home.

The return

Friday 14 December. The initial mass of reporters in Stockholm had dwindled to a handful by the end of Nobel week, but upon setting foot in Osaka, Honjo was quickly reminded of the baited breath with which the news media were still following his movements. Displaying the Nobel medal for the first time to the press gathered outside the arrivals area at KIX, Honjo renewed his determination to continue supporting younger colleagues, advancing his field, and promoting basic research across the nation.

Driven by curiosity

Nowhere else in Asia can you find a single university with two Nobel laureates active among its research faculty. Curious as to what might result from a discussion between the two scientists — Dr Honjo and Shinya Yamanaka, the director of the Center for iPS Cell Research and Application, CiRA, and the 2012 Nobel laureate in medicine — ExecVP/Provost Minato suggested that an open discussion would be good for students, and a special event was arranged for 27 December 2018 in the historic Memorial Auditorium on the med school campus. An excerpt follows.

Minato: In closing, we all have different reasons for being researchers, but what motivates you? What is your approach to devoting your life to science?

Honjo: Research has always been a joy for me; I can't recall a moment when I've suffered so much that I wanted to stop doing it.

Nonetheless there comes a moment when anyone seeks deeper meaning in life, whether to make money, or to pursue something for love. In that sense, the life of a researcher isn't for everyone. It's not something you can just stumble into. If you find yourself asking "what should I do?" then that's not the right mindset.

To be a scientist, you need a constant drive of curiosity and the motivation to pursue the answers on your own. As children, everyone has the potential to become anything. As you then grow up, you learn your likes and limits, and a vision of yourself takes shape.

I chose the study of immunology. I wish you all the best as you seek to find what is your lifelong motivation.

What is PD-1, and why a Nobel prize for it?

Understanding how the immune system can be coaxed to fight cancer

Cancer is caused by irregular division and proliferation of our own cells. Normally, the immune system identifies and eliminates such anomalies, but under some circumstances these cells evade natural defenses and grow to the point of threatening essential body functions.

Surgery, radiation, and chemotherapy are established methods of cancer combat, and even the idea of recruiting the immune system in the fight isn't new. As stated in his banquet speech, Honjo gives credit for the concept to a 1960 medicine laureate. For decades it just wasn't clear how to actually make this work.

The immune system is the body's way to find and eliminate harmful, foreign elements, such as invasive bacteria and viruses. Specialized 'T' cells are the system's infantry, carrying receptors on their surfaces for detecting unwanted outsiders.

However, an intricate balance must be maintained so that the body doesn't attack itself. When this occurs, such as is suspected in the case of dangerous allergic reactions, the result can be swift and fatal.

In 1992, Tasuku Honjo discovered PD-1, a protein on the surface of T-cells. While not immediately sure of its function, years of diligent experiments led him and his team to a realization that the protein acts as a 'brake' on the T-cell, stopping it from causing an immune response. Eventually they recognized further that blocking PD-1 could activate the immune system to attack cancer.

One of the ways cancer cells avoid being detected by our immune system is by blocking the PD-1 receptor with another receptor, PD-L1. When PD-L1 on a cancer cells binds with PD-1 on a T-cell, it steps on the 'brake', protecting the cancer.

The immune system is tricked into thinking that the cancer is a normal part of the body.

So by stopping these receptors from binding, Honjo developed a way to release the brake, freeing the immune system to fight the abnormal cells.

22 years after the discovery of PD-1, a cancer drug based on Honjo's finding was first approved for use in Japan, sending a shockwave through the world of cancer treatment.

But as is often the case in science, these few answers generated even more questions, and Honjo states frequently that he cannot retire, because "there is still so much that we simply don't know."

Yamanaka: Dr Honjo puts it very well. You must enjoy what you are doing in order to be a scientist.

I began my career as an orthopedic surgeon, something I wanted to be from a young age. But I soon realized that I wasn't very good at it, so I tried my hand at research.

In one of my first experiments I had to test a drug that would raise the blood pressure of a mouse. Surprisingly, the blood pressure fell! But what most astonished me was my own reaction: I was excited by this unexpected result.

This experience galvanized my idea of becoming a researcher; I simply followed the questions and results that interested me. I then went to the United States to study arteriosclerosis, but when the gene I was focusing on was linked to cancer, I became fascinated with cancer research. Cancer then led me to stem cells.

I was always simply pursuing my curiosity. Dr Honjo and I have followed different, but equally valid paths. The common threads are that we both have immense curiosity and the motivation to try to find answers to the unexpected.

Cutting edge

www.kyoto-u.ac.jp/cutting-edge/

This second section features a sampling of some of the latest scholarship from KyotoU, covering a broad range of fields of inquiry from medical science and robotics to sociology and economics.

New gears in your sleep clock

A long-studied factor controlling human sleep cycles actually has two forms, one that keeps a key protein stable and another that promotes its degradation.

From the heart and lungs that propel our blood, to our rumbling stomachs at lunch time and feeling of tiredness in the evening, our bodies keep steady rhythms day in and day out.

This 'circadian clock' is a series of tightly controlled cycles of specific amounts of proteins that make us either sleepy or wakeful. It has recently attracted public attention with the 2017 Nobel Prize for Physiology or Medicine, but numerous aspects of the clock's functions and how it regulates our health remain a mystery.

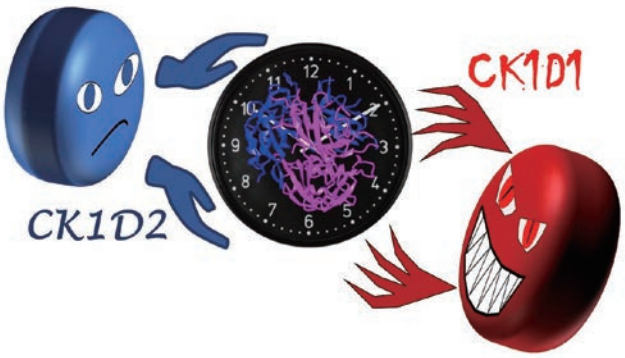
One of the first circadian rhythm sleep disorders to be discovered was Familial Advanced Sleep Phase Syndrome, or FASPS. Patients with this condition fall asleep early in the evening, around 7 pm, and wake up early in the morning, around 3 am, and are thus unable to adjust to standard cycles without undergoing treatment.

"FASPS is characterized by a mutation in the gene that codes for a protein essential for the circadian clock, called Period 2, or PER2," explains corresponding author Jean-Michel Fustin from KyotoU's Graduate School of Pharmaceutical Science.

"The stability of the PER2 protein is a key factor in determining how fast your circadian clock ticks."

In FASPS patients, PER2 is unstable, resulting in a sped-up clock. This is due to a mutation that changes one amino acid in the protein from a serine to a glycine.

"The stability of PER2 is regulated by the phosphorylation of several critical amino acids — a common way proteins are regulated in the body. This process is conducted by other proteins called kinases," continues Fustin. "We knew of a kinase that could destabilize PER2 — Casein kinase 1 delta, or CK1D — but we couldn't find one that could stabilize it by phosphorylating the serine that is mutated in FASPS patients."



Writing in PNAS, Fustin and his collaborators explain that the stabilizing kinase was within the Ck1d gene itself all along. Their findings show that in addition to destabilizing PER2, Ck1d has another form, one that does the exact opposite.

While structurally very similar, these two kinase forms are named CK1D1 and CK1D2.

"The opposite activity of CK1D2 was completely unexpected. These two versions of this kinase can be likened to the kind Dr Jekyll — CK1D2 — and the destroyer Mr Hyde — CK1D1," states Fustin. "While in many cases the same gene can code for different proteins, such a stark difference in function is rare."

"Circadian clock mechanisms can be found in bacteria, insects, plants, and vertebrates. Understanding these fundamental mechanisms allows us to understand our relationship with the rhythmic environment," concludes co-corresponding author Hitoshi Okamura. "Our discoveries indicate that the circadian clock can be adjusted between these kinases, and provides new targets for the treatment of circadian disorders."

What does the koala genome tell us about the taste of eucalyptus?

Koalas have long captured people's hearts and minds thanks to their cuddly features and seemingly relaxed demeanor.

Now, in a collaborative study by the Koala Genome Consortium — involving 54 scientists at 29 institutions, including KyotoU — researchers have successfully sequenced the entire koala genome, uncovering much that has been unknown about these mesmerizing marsupials.

Past studies have revealed many unique features of the koala's morphology, physiology and ecology. However, little

Meet ERICA. She wants to listen to you

We've all tried talking with devices, and in some cases they talk back. But it's a far cry from having a conversation with a real person.

Now a research team from Kyoto University, Osaka University, and the Advanced Telecommunications Research Institute, or ATR, have significantly upgraded the interaction system for conversational android ERICA, giving her even greater dialogue skills.

ERICA is an android created by Hiroshi Ishiguro of Osaka University and ATR, specifically designed for natural conversation through incorporation of human-like facial expressions and gestures. The research team demonstrated the updates during a symposium at the National Museum of Emerging Science in Tokyo.

"When we talk to one another, it's never a simple back and forward progression of information," states Tatsuya Kawahara of KyotoU's Graduate School of Informatics, an expert in speech and audio processing.

"Listening is active. We express agreement by nodding or saying 'uh-huh' to maintain the momentum of conversation. This is called 'backchanneling', and is something we wanted to implement with ERICA."

The team also focused on developing a system for 'attentive listening'. This is when a listener asks for elaboration, or repeats the last word of the speaker's sentence, allowing for more engaging dialogue.

Deploying a series of distance sensors, facial recognition cameras, and microphone arrays, the team began collecting data on parameters necessary for a fluid dialog between ERICA and a human subject.

"We looked at three qualities when studying backchanneling," continues Kawahara. "These were: timing — when a response happens; lexical form — what is being said; and prosody, or how the response happens."

Responses were generated through machine learning using a counseling dialogue corpus, resulting in dramatically improved engagement. Testing in five-minute sessions with a human subject, ERICA demonstrated significantly more dynamic speaking skills, including backchanneling, partial repeats, and statement assessments.

"Making a human-like conversational robot is a major challenge," states Kawahara. "This project reveals how much complexity there is in listening, which we might consider mundane. We are getting closer to a day where a robot can pass a Total Turing Test."

was known about the animal's genome. With this study published in *Nature Genetics*, the koala is now the fourth marsupial species to have its genome sequenced, providing further understanding of the genetic background of its biology, and establishing a high-quality genomic reference for marsupial mammals.

The consortium sequenced over 3.4 billion base pairs and 26,000 genes in the koala genome. With this new data, Takashi Hayakawa of KyotoU's Primate Research Institute and Don Colgan of the Australian Museum analyzed the evolutionary background of the koala's taste receptor genes relating to its unique adaptation to feed on eucalyptus.

"Initial studies gave us insight into genes related to sensory receptors and detoxification enzymes, and I was curious about the koala's palate," explains Hayakawa. "In all animals, including humans, 'bitterness' is usually a warning sign indicating toxicity. Eucalyptus leaves are toxic to most animals including koalas, and we were interested in how they perceive these leaves."

After analyzing the genome, the duo found that koalas have more bitter taste receptor genes than any other Australian marsupial, and even more than most mammals. This enables the animals to detect toxic metabolites contained in eucalyptus, suggesting koalas can discriminate the toxicity levels of the leaves they ingest.

"Koalas have been shown to demonstrate selectivity in the leaves they consume, avoiding as much of a plant's toxic metabolite as possible," states Hayakawa. "Expansions in the taste receptor gene catalog enable koalas to optimize ingestion of nutrients and avoid plant toxins."

Further analysis also showed that koalas appear to have functional receptors for both sweetness and umami perception, previously not observed in other animals with highly specialized diets.

"A complete genome sequence is the gold standard in understanding any unique biological quality of an animal," concludes Hayakawa. "Knowledge of the koala genome is going to play a pivotal role in the conservation of these animals."

Giant, recently extinct seabird also inhabited Japan

Scientists report that a large, extinct seabird called the spectacled cormorant, *Phalacrocorax perspicillatus* — originally thought to be restricted to Bering Island, far to the north — also resided in Japan nearly 120,000 years ago.

Writing in *The Auk Ornithological Advances*, the team indicates that the species underwent a drastic range contraction or shift, and that specimens found on Bering Island are 'relicts' — remnants of a species that was once more widespread.

The global threat of human activity to species diversity is grave. To correctly assess human-related extinction events, it is imperative to study natural distributions before first contact with humans. This is where archaeological and fossil records play crucial roles.

The spectacled cormorant, a large-bodied seabird first discovered in the 18th century on Bering Island, was later hunted to extinction, following colonization of the island in the early 1800s.

"Before our report, there was no evidence that the cormorant lived outside of Bering Island," explains first author Junya Watanabe of KyotoU's Department of Geology and Mineralogy.

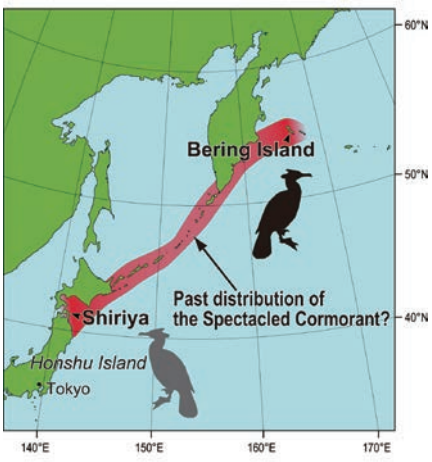
Studying bird fossils recovered from Shiriya, Aomori prefecture, Watanabe and his team identified 13 bones of the spectacled cormorant from upper Pleistocene deposits, formed nearly 120,000 years ago.

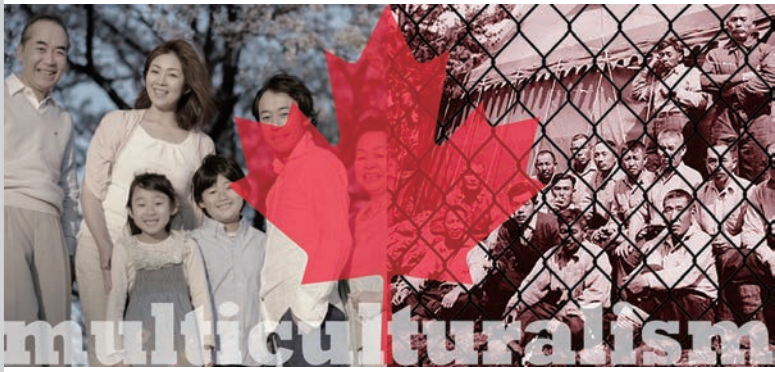
"It became clear that we were seeing a cormorant species much larger than any of the four native species in present-day Japan," states co-author Hiroshige Matsuoka. "At first we thought this might be a new species, but these fossils matched bones of the spectacled cormorant stored at the Smithsonian Institution."

Changes in oceanographic conditions may be responsible for the local disappearance of the species in Japan. Paleoclimate studies show that oceanic food productivity around Shiriya dropped drastically in the Last Glacial Maximum, around 20,000 years ago. This would have seriously affected the cormorant population.

And prehistoric Japanese may have hunted the species, but archaeological evidence of this has not yet come to light. All told, the extinction of the spectacled cormorant may be more complex than previously thought.

"The cormorant was a gigantic animal, its large size thought to have been achieved through adaptation to the island-oriented lifestyle on Bering," adds Watanabe. "But our finding suggests that this might not have been the case; after all, it just resided there as a relict. The biological aspects of these animals deserve much more attention." ■





Japanese in Canada, with mixed feelings

Canada's policies on multiculturalism are often seen as a model for a more inclusive and diverse world. They were designed with the assumption that multiculturalism is good for minorities, and were therefore supported by these groups.

However, in a study published in the journal *OMNES: The Journal of Multicultural Society*, Japanese-Canadians show ambivalence to multiculturalism due to past experiences of incarceration during the Second World War.

Since the 1960s, Japanese-Canadians have been showcased as a 'model minority' due to their high levels of education, professional success, and English language proficiency. They have settled throughout Canada, and have married almost exclusively outside of their communities.

So why the ambivalence towards multiculturalism?

"Younger generations of Japanese-Canadians are supportive of it, but some argue that it is only enacted in superficial ways," explains Lyle De Souza of KyotoU's Institute for Research in Humanities, who led the study.

"But there is lingering trauma from early racism and incarceration."

To study how this trauma distorts the effect of multiculturalism on Japanese-Canadians, De Souza spent several months in Canada conducting interviews with academics, writers, and Japanese-Canadians.

One well-known interviewee featured in the study is animator and filmmaker Jeff Chiba Stearns, whose works include the documentary *One Big Hapa Family*.

Partly as a result of multiculturalism, Japanese-Canadians are more likely to showcase their ethnicity rather than to hide it. According to Chiba Stearns, "As Canada becomes more multicultural, what makes you unique — like your ethnicity — is something you want to have stand out."

These records highlight the value of considering factors such as immigrant identity, voice, political conditions, social environments, and political economy when assessing multiculturalism. Governments must tailor policies to specific minority groups along with state-level initiatives.

De Souza says that these results can help other countries that may need to embrace expanded immigration in order to alleviate declining populations, such as Japan.

"There is much to learn from the experience of Canada," he concludes. "Japan already has many minorities, so it is a mistake to lump them all together as 'non-Japanese' and thereby prevent their unique qualities from enriching the culture." ■

Search for article titles
for paper, author details & more!

Finding success through failure

Learning from failure is a matter of common folk wisdom. But in reality, most loath to fail, as loss of motivation and confidence — and perhaps even lower standing among peers — often result. In spite of everything we know about failure, we know very little about its precise benefits.

Emmanuel Manalo at KyotoU's Graduate of Education and Manu Kapur at ETH Zurich in Switzerland report that, while failure is essential to learning, instances where failure leads to beneficial outcomes and eventual success can be traced to particular circumstances.

Their editorial, published in a special issue of *Thinking Skills and Creativity*, introduces 15 research articles from experts around the world discussing the benefits of failure in a wide range of subjects, from mathematics to science, and robotics to video gaming. Together these reveal how it is possible to cultivate attitudes and competencies that support learning from mistakes.

"We put out an international call for research pertaining to the benefits of failure," explains Manalo. "The 15 papers we selected represent the most robust research clarifying what is necessary for failure to become beneficial in an educational context."

For instance, working in collaboration with Yoshinori Oyama from Chiba University, Manalo reveals in one study that people are more motivated to continue working after failure if they perceive themselves to be close to completion. Moreover, this motivation increases the more clearly the person sees how to complete the task.

Meanwhile a team from Ben-Gurion University in Israel shows that when teachers discuss their failures with colleagues, they only benefit from the discussion if the experience is framed productively. In other words, how failure is interpreted in such conversations makes all the difference.

Manalo states that worldwide, testing and test scores are becoming more important to schools, teachers, and students: to the extent that they lose sight of the very purpose of education, which is to promote learning.

"Failure is essential to learning, but simply saying 'we should learn from failure' or '*ganbatte*' in Japanese is usually not enough," concludes Manalo. "We must actively learn from the experience, and be aware of what to improve."

Until students and educators understand these conditions, failure will continue to be feared and avoided, and people will hesitate due to fear of failing, potentially resulting in missed opportunities for success. ■

Using microcredit to increase rice yield in Bangladesh

In the developing world, access to credit can lead to higher productivity and an increase in living standards, but this access is not universal. Formal financial institutions are reluctant to lend to households with low-incomes or which lack collateral. This is where 'microfinance institutions' — or MFIs — play a role.

MFIs extend small loans, called microcredits, to individual households. While standard microloans tend to be geared toward business and entrepreneurial endeavors, in recent years Bangladesh has made a name for itself internationally by providing microcredits to tenant farmers.

Now, in a collaborative study with institutions in the United States and Bangladesh, a team led by Mohammad Abdul Malek — of KyotoU's

Cutting edge

Graduate School of Agriculture and the Research and Evaluation Division of BRAC — has examined the impact of agricultural microcredits on the livelihood of these farmers.

Writing in the *American Journal of Agricultural Economics*, the researchers analyzed various outcomes of these loans, such as: adoption of high-yield or hybrid rice, overall rice yield, and household income.

"The agricultural microcredit program Borgachashi Unnayan Prakalpa — BCUP — began in 2009 with the primary objective of increasing the credit access of tenant farmers to formal financial institutions," explains Malek. "So we conducted two surveys in 2012 and 2014 to see how households receiving this financing changed over time."

The Bangladesh Bank — the central bank of Bangladesh — started BCUP with a low-interest revolving fund, as part of its financial inclusion strategy. The average loan amount was equal to the production cost of rice for one hectare of land.

The team's results show that BCUP helped increase rice yield as well as overall farm crop income, and additionally the probability of adopting hybrid and higher yield rice. Further, there appeared to be a somewhat positive effect on the cultivation of owned land and livestock ownership.

"BCUP has had a number of positive effects," continues Malek. "We did not find a change in household income, but we noticed that the farmers were able to allocate more time to self-employment activities."

While several studies have examined the role of agricultural credit on the livelihood of farm households, this is the first to examine the impact of a program designed specifically to increase the financial inclusion — in the broader economy — of tenant farmers.

The team hopes to continue their inquiry into the effects of microcredits in order to better inform future policy decisions, while acknowledging that other interventions, in combination with microcredit, may be necessary if the program is to be scaled up in Bangladesh or elsewhere in Asia. ■

Making an eye for you

If you want to build an organ, such as for transplant, you need to think in 3D.

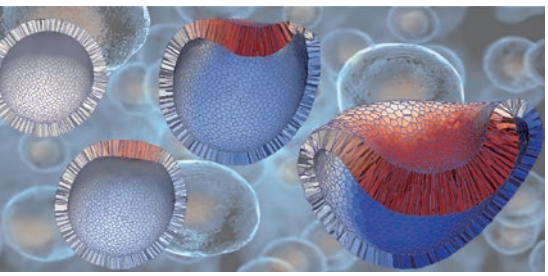
For some time, scientists have used stem cells to grow parts of organs in the lab, but that is a far cry from constructing an actual, fully-formed, functioning, three-dimensional organ.

For students of regenerative medicine and developmental biology, this is why understanding how cells bend and move to form organs and bodily tissue is a hot topic.

And now a team at KyotoU's Institute for Frontier Life and Medical Sciences have gained new understanding of how cells undergoing mechanical strain create the spherical structure of the eye.

Publishing in *Science Advances*, the team has found that individual cells together form a primordial, cup-like structure — an 'optic cup' — by sensing mechanical forces resulting from the deformation of the entire tissue.

"In the past, we succeeded in making the optic cup by culturing embryonic stem — ES — cells. To form a sphere, the tissue first needed to protrude from primordial brain tissue and then invaginate inside," explains first author Satoru Okuda.



"But how individual cells sensed and modulated themselves to form that shape had been unclear."

The team developed a computational simulation that calculates the formation of three-dimensional tissue structures. Using this knowledge and past experimental data, they constructed a virtual precursor-eye and were able to predict the physics driving the sphere-forming cells.

Their findings show that during optic cup formation, a cell differentiation pattern — pushing cells into the cup shape — is generated, causing a portion of the cells to spontaneously fold into the tissue. This force caused by 'self-bending' propagates to the boundary region, where other cells sense the strain.

"The combination of the tissue deformation and the strain on the boundary of the optic cup generates a hinge that further pushes the bending cells," continues Okuda, "leading to the cup-like structure."

"The next step was to verify this prediction using actual ES cells."

Utilizing mouse ES cells in culture, the team applied mechanical strain on specific points and were pleased to detect the calcium responses, mechanical feedback, and cell shape changes they had predicted in the simulations.

These findings reveal a new role for mechanical forces in shaping organs, which is crucial in forming complex tissues, even in a petri dish. The team will continue to investigate these forces, seeking to advance the field of regenerative medicine.

"While our research shows the possibility of controlling the shapes of organs made *in vitro* — using appropriate mechanical stimulation based on prediction — current techniques are still limited," concludes lead scientist Mototsugu Eiraku.

"We hope to improve the predictive accuracy of our simulations and recreate more complicated tissues and organs in the future." ■

Kyoto University spans three campuses in the city of Kyoto, numerous offices, research facilities, and other operations around the country, and dozens of centers, liaison offices, and field stations across the globe. In this third section, learn of some of the latest developments from industry outreach, overseas offices, and student life.

Science with industry:

Microbes are us. But how can we see them?

"And this is the DNA sequencer."

Fumito Maruyama, smiling infectiously, pulls out a device the size of a flip phone and begins to explain how it can help us 'see' the world of microbes.

"We've come a long way since the days when plagues and disease were interpreted as acts of heavenly wrath. But there is still so much to learn."

The palm-sized, USB-powered DNA sequencer is a key part of Maruyama's **suitcase lab**, an innocuous-looking rolling bag housing all the equipment a microbiologist needs for genetic sampling and analysis in the field. We were lucky to catch him just as he was about to embark on another trip to the Pacific coast of South America.

"We're collaborating with government, academia, and industry in Japan and Chile. Together we've founded the MACH — Monitoring of Algae in Chile — project, supported by SATREPS, to understand the microbiological basis of algal blooms, which have a detrimental impact on commercial salmon farming."

Together with Japanese chemical manufacturer Kaneka Corp, Maruyama has developed the suitcase lab to allow anybody to analyze DNA in water samples in the field. These data form a snapshot of the microorganisms in the water: a vital step in predicting and even mitigating dangerous algae.

"By looking at the whole biome — 'holobiome' — of algal blooms and mapping the dynamics of viruses and bacteria, we gain a deeper understanding of how these fragile ecosystems stay in or fall out of balance."

Beyond MACH, Maruyama looks to a future for the suitcase lab as a tool for citizen science or for teaching about the vast, microbiological world. He sees applications in industries such as agriculture and forestry, and after speaking with him it's hard to imagine what *isn't* affected by microbes.

"Humanity has been dealing with microbes since far before the advent of civilization, but we've only just now begun to understand them. Biosphere 2 ran into problems because the designers only had the human environment in mind."

With talks of colonizing Mars and living in space coming ever closer to reality, Maruyama says the time is ripe to study the microbiology and ecology that sustain us. Our survival hinges not on maintaining 'cleanliness', but rather in determining how we must stay in balance with this unseen environment.

For more on MACH see: www.mach-satreps.org/en/

News from overseas centers

North American Center opens in Washington DC

2200 Pennsylvania Avenue NW • Room 4057,
4th Floor East • Washington DC 20337 USA

In October 2018, Kyoto University established its North American Center to promote and deepen educational and research ties with universities and research institutions in the Americas.

Located in central Washington DC, the office will work to enhance the University's contribution to knowledge-creation, technical innovation, and intellectual openness for the betterment of global society.

"A physical presence in Washington is another critical step in the internationalization of Kyoto University, representing a commitment to enhancing partnerships with institutions of academic excellence in North America," explains Nathan Badenoch, Center director, faculty member at the International Strategy Office, and a KyotoU alumnus.

The University has six institutional-level student exchange agreements with American universities and also six in Canada. With this new presence on the East Coast, the Center seeks to facilitate the mobility of students between Japan and North America, including the development of summer courses and short-term programs to increase early-exposure opportunities for students on both sides of the Pacific.

Existing research projects and institutional development underway in faculties and centers across the University will also be supported, based in part on existing MoUs, providing a solid and dynamic foundation from which to expand KyotoU's research engagement across North America.

Director Badenoch (rear, second from left) with East Coast KyotoU alumni

Director Badenoch is an East Coast native, who has since spent more than 15 years in Japan and another eight in Southeast Asia. After his 2006 PhD at KyotoU in Asian and African studies, he worked in Thailand and Laos before returning to Kyoto as a member of the first class of Hakubi scholars in 2010. After this he began teaching, while continuing research at the Center for Southeast Asian Studies. Now this new position has brought him back to the United States to assist in expanding KyotoU's global presence.

The Center has already organized alumni gatherings in Washington and New York City, receiving a warm welcome from East Coast-based graduates. And initial contacts with research and educational partners in the region indicate high hopes for KyotoU's new presence. Now with three Centers worldwide, the University has a better ability than ever to coordinate its global activities, collaborations, exchanges, and knowledge-creation.

The North American Center is supported by the North American team at the International Strategy Office in Kyoto, as well as by Kyoto University staff seconded to Halcyon in Washington under the University's John Mung Program.

Bangkok ASEAN Center

www.oc.kyoto-u.ac.jp/overseas-centers/asean/en/

KyotoU's ASEAN Center received official foreign NGO status from the Thai Ministry of Labour in March 2018, as a result of sustained efforts by Director Mamoru Shibayama and Center staff, with continuous support from regional partners. This approval was a landmark achievement not only for Kyoto University, but also for Japanese academia more broadly in Thailand and the ASEAN region: the first of its kind bestowed upon a Japanese university.

At a commemorative ceremony in Bangkok on 28 September, the attendance of 100 officials and researchers affirmed the significance attached to this achievement. At the same event, KyotoU concluded a MoU with Thailand's National Science and Technology Development Agency, demonstrating the collaborative synergies that are being accelerated by the ASEAN Center.

The new NGO status reflects the commitment on the part of representatives from both countries toward strengthening Japan-ASEAN collaboration in education and research, with the Center playing a central role in catalyzing these connections.

Student mobility is a key factor in ensuring that this momentum accelerates. Approximately 180 students from KyotoU are currently studying in Thailand, while 60 Thai students come to Kyoto annually. The University has developed double-degree programs with the universities of Chulalongkorn, Kasetsart, and Mahidol, and established on-site laboratories in the Vidyasirimedhi Institute of Science and Technology and at Mahidol University.

Growing forces of regionalization such as the ASEAN Economic Community increasingly require the next generation of scientists to cooperate in finding common ground within their heterogeneous perspectives. Expectations are high that the Center's new status will increase the exchange of students and researchers between KyotoU and its partners in Thailand and throughout ASEAN, increasing the reach of mutually beneficial Japan-ASEAN collaboration.

Heidelberg European Center

www.oc.kyoto-u.ac.jp/overseas-centers/eu/en/

As part of its mission to facilitate intellectual exchange on significant social and scientific issues, KyotoU's European Center has supported the planning and organizing of joint symposia with four universities in Sweden (Stockholm University, Uppsala University, KTH Royal Institute of Technology, and Karolinska Institutet), as well as with Bordeaux, Bristol-Heidelberg, UCL, Zurich, and Hamburg. A series of these meetings took place between 2014–2018 in order to deepen intellectual partnerships and foster collaborations by sharing the strengths of each university.

KyotoU hosted the 2nd KyotoU-Universität Hamburg Symposium, 9–11 October 2018, showcasing joint projects in law, sociology, and management begun at the 2017 meeting in Hamburg, as well as new cooperation in ecological research, development studies, climate, and digital transformation in logistics.

In 2019, international workshops with Vienna University and Zurich University are planned to further develop regional relations and encourage reciprocity with these universities.

The European Center's location facilitates KyotoU's follow-through on such symposia and workshops, exploring and designing future research collaboration through continual close communication with counterpart universities, fulfilling its role as a pivotal hub between Kyoto University and partner institutions throughout Europe.

Tea and the taste of *omotenashi*

Shinchakai 'spirit of tea' club

Rika Yokoi (4th Year, Faculty of Integrated Human Studies)

A *mizusashi* (water vessel) by Dr Hisamatsu, featuring the *sadoshin* — way of tea — that he taught the first club members

Using a tea bowl acquired by Dr Hisamatsu to commemorate the club's 20th anniversary

"With tea ceremony, learning the movements is just the beginning. You then start to pay attention to the smallest of details, such as the exact placement of your hands and whether your breathing is in tune with that of your guest." Rika Yokoi's first experience with tea ceremony was in a high school club, and when she enrolled at Kyoto University she joined the Shinchakai.

Rika pays particular attention to timing. "After serving the guest a confection, I pace the tea preparation to match when the guest will finish eating. If the guest needs more time, I slow down."

At the behest of students, assistant professor of philosophy Shinichi Hisamatsu founded Shinchakai in 1941 with help from Urasenke master Tantansai.

Sadô — Japanese tea ceremony — originated from practice of Zen Buddhism. Shinchakai is infused with the Zen thinking of Dr Hisamatsu, including conducting Zen meditation before and after each tea practice.

Rika finds one Hisamatsu episode — related to her by a club alumna — to be unforgettable. One day a student asked the professor how they could afford the cost of the confections and tea for an upcoming ceremony. Hisamatsu replied: "For the confection, go to nearby Mt Yoshida and pick up some chestnuts. And if the tea's too expensive, just serve hot water. What matters is your spirit of hospitality — *omotenashi*."

These words gained special meaning for Rika in her third year, when she was responsible for organizing a ceremony of gratitude by younger students for graduating seniors. Club alumni were also invited. She worked very hard on the choice of temple venue and on assigning roles to everyone.

When the ceremony was over, a thank you note from an alumni guest left an indelible impression on Rika's heart. It included a *tanka*: "A lovely, youthful ceremony, full of freshness."

"Sending a thank you letter is a matter of etiquette, but to also write such a heartfelt poem is wonderful and really moved me. I was so nervous that day and I'm sure I made many mistakes, but in spite of this, the alumni were watching over me with real warmth."

"I hope to continue until I graduate." Rika is currently in her fourth year at the Faculty of Integrated Human Studies. "Even if I can't always be perfect in my club activities and studies, I want to complete them properly." Her major is Christian art history. In her quest to master the 'way of tea', Rika shows boundless curiosity, and in her four years with Shinchakai her heart has filled to overflowing with the feelings of the many people she has encountered and connected with through her spirit of *omotenashi*.

Club members intensely critique each other during practice, from the positions of their fingers to the tempo of their movements

Artwork by Kyoto University students, combined with artistic scenes as glimpsed by researchers.

いろ

Videographer:
Butterfly Studies Club
Taisuke Nomura (2nd Year Master's, Graduate School of Agriculture)

Gentle tranquility and nostalgia exude from the foregoing works. In mid-May, the Japanese Clouded Apollo butterfly begins to dance in the backwoods of Sakyo-ku, on the outskirts of Kyoto. Looking at these butterflies, flittering about the uplands which are largely unchanged for centuries, I feel curiously calm. I wish to protect Japan's traditional landscapes for all time.

こと ば

Yukihiro : The stars… were they beautiful?

Riko : Yes, they were. So beautiful that I wish I could have shown them to you.

Yukihiro : I see… (cries)

Riko : What's the matter?

Yukihiro : It's nothing. Sorry. I'm happy… I really am, but…

Keppeki Theater Troupe
Koshi Takaya (4th Year, Faculty of Letters)
Excerpt from: *Siblings Enraptured*

A man and a woman are reunited at the boundary of life and death. Their words spring forth from the contradictions between meeting and parting, joy and sadness, dreams and reality. The nostalgic strains of the music, with hints of enjoyment and lament, occasionally cherishing a life filled with contradictions, reminded me of this scene.

おと

Shun Fujii (2nd Year Master's, Graduate School of Engineering)

Title: *Cinema Paradiso* medley
Composer: Ennio Morricone

When I first got interested in the saxophone, I listened to many sax CDs. One in particular, featuring the enduringly popular Italian film Cinema Paradiso, captivated me with its hauntingly beautiful, nostalgic melodies.


facebook.com/Kyoto.Univ.E
@KyotoU_News
@kyotouniversity
attacking again
antibody glove
Cancer advances
KYOTO UNIVERSITY
KYOTO JAPAN
FOUNDED 1897
www.kyoto-u.ac.jp/cutting-edge/