Kyoto University
2020 Spring

KYOTO U Research News

Thinking glocally, acting responsibly

What does it mean to be an internationally-oriented university?

For a large institution, internationalization is more than simply learning English or other languages. What sort of faculty and staff we hire, what sort of pedagogy we pursue, what cultures permeate the classrooms and lecture halls: many, many factors meld to form the campus environment.

There are also financial concerns: how do we extend opportunities to learn and pursue research to those who lack independent means of doing so? For those with sufficient ambition and ability, there are always solutions. The university must find the ways to these answers, and make them equitably available.

At Kyoto University we encourage self-thinking, self-study, and self-responsibility. Those who choose to learn with us must come prepared: to inquire, to ask, and to doggedly pursue the root of knowledge.

As I approach the close of my term as president this fall, I see a great many challenges that my successors will face as we forge ahead: changing needs and expectations of incoming students, evolving relations and partnerships with other institutions in Japan and overseas, and an ever-shifting role for the university to play in society, as an institution nurturing future leaders and expanding the boundaries of science and scholarship.

As information and communication technologies enable us to connect with each other everywhere, we must think both locally and globally, or *glocally*, and act responsibly in order to pursue harmonious coexistence within the human and ecological communities on this planet.

Join us as we once again seek to redefine our mission, reach beyond our borders and our preconceptions, and meaningfully connect with a world of constant change.

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

In keeping with the lead story on bioethics, a woman in *ukiyo-é* style reflects on her image (and her makeup) against a background of a modern laboratory. Based on the Utamaro woodblock print, *Sugatami Shichinin Keshô*. (Trais/Fujiwara)

Into the human unknown

What we understand about ourselves constantly expands, but a fundamental question remains: instead of using data gathered from other animals, what if medical science were based purely on knowledge of human biology? A new institute seeks an answer.

At the heart of pharmacology are mountains of data based on animal tests. These are invaluable, having made drug treatments and therapies possible where once existed only despair. But taking these results and then assuming that they also apply to humans requires a leap of faith and even more careful testing, leading in part to the enormous expenses and time required to produce new treatments. And even then these are not lacking in harmful side effects.

The difficulty is that gathering equivalent data directly from humans has been impossible. Kyoto University's **Institute for the Advanced Study of Human Biology** — ASHBi — takes this puzzle as its starting point, seeking to redefine the scientific basis of medicine in human terms. We sat in on a recent conversation including the institute director, **Mitinori Saitou** (center right), chief ethicist, **Misao Fujita** (center left), veteran KyotoU scholar of ethics, **Carl Becker** (far right), and guest moderator and ethicist at RIKEN, **Douglas Sipp**.

Into the human unknown

Defining 'human'

Sipp: Because the mission of ASHBi is finding ways to study human biology using new technologies, an important question for researchers, philosophers, or ethicists is: what makes humans unique? What are the traits that represent that line separating humans from all other species?

Saitou: When I started working on germ cells, the cells that create eggs and sperm, I was interested in the mechanism of why only the germ cell lineage can transmit our genetic information and create new organisms. In an extreme sense it was investigating the mechanism of immortality. Then I started thinking about the purpose of medicine itself. In essence it is to make an immortal human being. That is what made me interested in germ cell biology. After we succeeded in making sperm and oocytes — egg cells — from human induced pluripotent stem or *iPS* cells, clinicians started to get interested in the possibility of making offspring from them. But that is still very challenging and raises many ethical issues. For example, if you were born from a skin cell using this technology, how would this change your perception of your 'self'?

Becker: We used to imagine that tool making and communication are what made you human. Now we know that other species make tools. So that leaves the communication. Of course, other species do communicate, but not about specific plans, for example, "meet me at the station at 9:00 am." That's distinctly human and becomes critical if you forget where the station is, or what time it is.

The other major distinction that prominent KyotoU primatologists **Juichi Yamagiwa**, **Tetsuro Matsuzawa**, and others have noted is our ability to simulate the future. We as a species have developed the abilities not only to discuss our problems, but to simulate and anticipate different possible futures depending on what we do today. That's basically what ethics is about. If you know what future you want to choose, then you know what's permissible by and large with a lot of grey areas to be negotiated. If you haven't chosen what future you want yet, you have no way to get there.

Douglas Sipp studies regulatory policy and ethics relating to stem cell research and regenerative medicine. Originally from the United States, since 2002 he has worked at RIKEN — Japan's largest network of research institutes — and also serves as visiting professor at Keio University School of Medicine. He has authored more than 70 peer-reviewed publications and serves on many international committees and working groups.

Public opinion and iPS cell technologies

Sipp: The ethical issues surrounding artificial *gametogenesis*, the creation of sperm and eggs in the lab — which could potentially be used in novel forms of human reproduction — open up lots of new questions that are being asked here in Japan and around the world. At what stage is the Japanese public right now?

"Training a new generation of bioethicists is the most important thing we can do."

Misao Fujita is professor of iPS cell ethics at KyotoU's Center of iPS Cell Research and Application — CiRA — and is now also professor of bioethics at ASHBi. As an undergrad, Fujita majored in clinical psychology at Tsukuba University — where she first met Carl Becker — and began her foray into bioethics. After serving as assistant professor at the University of Tokyo's Department of Biomedical Ethics, she moved to CiRA to study the ethical issues surrounding iPS cell research. With the increasing possibility of producing germ cells with iPS cells thanks to Saitou's research, Fujita is keen on exploring the ethics behind this new technology.

Fujita: I am not sure if they know that we theoretically could create gametes and embryos — and even babies — from iPS cells. When I conducted a questionnaire about gametogenesis, we provided detailed information explaining the technology first, then asked about their attitudes. Most respondents were very surprised about the technology's applications in reproduction: they mostly thought of iPS cells as tools in basic research and therapy.

Animal models for human medicine

Becker: Western research increasingly acknowledges that mice are not very useful. There are some things they can teach us, but millions of mice are raised and exterminated for things that are not useful, and when we bring the results into human trials we find out later that all of that research was not helpful.

Saitou: Ten or twenty years ago, the key model systems for mammals were mice, the most advanced models we had. However, even at that time I was already realizing the limitations of the animals. A very obvious example is in our field of germ cell specification. The precursors of both sperm and egg are formed very differently in mice compared to other organisms. The moment we started researching the development of human embryonic stem cells is when we started to really investigate the basic mechanisms of human development. People were struggling to figure out why there is such a difference between human and mouse stem cells.

Legal questions and fresh blood for bioethics

Sipp: Since ASHBi will be looking very closely at the generation of *gametes* — egg and sperm — how is the Japanese government handling this? They appear to be treating this as a strictly research activity.

Fujita: Yes. The problem is that there are many ethical guidelines for basic research in creating gametes and dealing with human embryos. In clinical settings, though, there are no laws or regulations. And that is a concern to many in government. Recently, the health ministry released a notice about needing to create new laws regarding the editing of human embryos.

Sipp: What might be a way that Japan could address this new set of technologies that are appearing one after another?

Fujita: Training a new generation of bioethicists is the most important thing we can do. There are very few young researchers in this field.

Into the human unknown

"There are many talented new researchers looking for positions. I welcome them to ASHBi."

Mitinori Saitou has spent decades extensively investigating the genetic and epigenetic mechanisms that determine the development of germ cells, the cells fundamental to all life. Using iPS cells, he has recently succeeded in generating human primordial germ cell-like cells, or PGCLCs, which are responsible for producing sperm and oocytes. He is the recipient of numerous prestigious awards including the Takeda Prize for Medical Science and The International Society for Stem Cell Research Momentum Award.

As director of the newly formed institute ASHBi, Saitou is committed to leading an international and interdisciplinary effort to define a human basis for the future of medicine. ASHBi was selected in 2018 to be part of the Japanese government-sponsored *World Premier International Research Center Initiative*, or WPI program, joining an extensive network of ground-breaking institutes across the country, including the University's first WPI institute iCeMS — the Institute for Integrated Cell-Material Sciences — which was founded in 2007.

wpi
World Premier International Research Center Initiative

ASHBi
WPI Kyoto University

ashbi.kyoto-u.ac.jp

Whenever I go to a conference, the participants are mostly the same familiar faces.

Sipp: How are you attracting younger people to your research group in ASHBi?

Fujita: We are recruiting graduate students first, along with postdocs. Another concern is English. Most social scientists in Japan do not read or speak English. We have difficulty keeping up with global developments, because everything moves so quickly. I also need to improve my own language skills together with a new crop of bioethicists.

Sipp: One thing that is interesting about the ethics community is how diverse the backgrounds are. You find some people who are essentially clinicians or medical doctors or sometimes research scientists. You also get philosophers, legal scholars, social scientists: they all come together, bringing different perspectives.

Fujita: Yes, my research team is quite diverse. We now have someone who specializes in research analysis, philosophers who specialize in policies, and even nurses and administrators. We are also working with other universities constantly.

Becker: Your team is quite multi-disciplinary. It's a good example of something which is often very hard to do in Japan.

Saitou: That is very important and a really fortunate aspect for ASHBi, especially in the context of science in Japan. Japanese are not really good at communicating frankly among different disciplines. I think this may be a cultural thing. Japan is very isolated and is mostly composed of similar kinds of people. Nonetheless, we are in a period where traditional bioscience academics really need to fuse with different disciplines, because we have so much information and data to share.

Sipp: How do you think you can break that bottleneck and bridge the different disciplines and thoughts?

Saitou: While it's difficult to organize and bring people together, I think what is necessary is for people to work together in a close environment, like this building we are in now. It stimulates conversation. For example, for over a year now we have been holding periodic meetings with our mathematical group. Every two weeks or so, pure mathematicians and pure biologists come together and discuss common topics we can work on. This allows us to gradually understand the language of our respective topics. I'm already thinking of biological questions as mathematical ones, and visa-versa from my mathematics collogues.

Becker: You also collaborate with Cambridge University and other foreign institutes and teams: a good incentive to broaden your perspective.

Saitou: Yes, we have overseas PIs based at McGill in Canada, EMBL in Germany, and also Cambridge, with many other collaborative projects underway.

Fujita: How is the training of younger researchers at ASHBi going so far? We've had a few seminars and workshops that feature their work.

Saitou: One of the current problems in Japanese science is that there are very few places where early career researchers can freely concentrate and work on their science. So, one of the reasons why I wanted to be involved in the WPI initiative is to create such opportunities for young researchers. There are many talented new researchers looking for positions, but not in Japan. I welcome them to ASHBi.

The search for a philosophy of human biology

Sipp: So, we've looked at the scientific, ethical, legal, and policy sides of ASHBi's research effort. What other big challenges or questions are there for the institute?

Saitou: One thing that has become evident is the necessity of having better understanding of bioethics, especially when we start investigating the core concept of ASHBi: *What is it to be human as a biological entity?* This question is being dealt with globally, and to progress in human biology, we really need to take special care in how we move forward.

Becker: ASHBi is a good way for a younger generation of researchers become knowledgeable in bioethics.

Saitou: Yes. A friend who is a gynecologist — and pushes me to pursue applications of my research— tells me that what is important is the philosophical reasoning to justify the birth of humans from non-reproductive, *somatic* cells. Moreover, the reasoning should be written or referenced within **Kitarô Nishida**'s Kyoto School of philosophical thinking. I have little knowledge of philosophy let alone Nishida's work; his writings are very difficult for me to understand. Yet Nishida is strongly rooted in the university and in the city of Kyoto, and had unique thoughts on life. I feel that understanding his work is going to be vital for us.

Becker: Nishida is great, not because his philosophy is eternal, but because he tried to reach what German philosophers and psychologists in the early 20th century were doing, except

from a Japanese perspective. This is the reason why Dr Fujita can be great. Not because she will create an eternal philosophy, but because she will know what is happening in science both in Japan and in other parts of the world. She can be a bridge between different ways of looking at things. Nishida is great but you don't need to read him.

Saitou (laughing)**:** Yes, I bought one book and I couldn't understand what he was trying to say.

Becker: Nishida was trying to make Western science understandable in a Japanese philosophic framework. He didn't succeed in some ways. But the effort to make and use new technologies, whether it's gene editing or humans from somatic cells, needs to be translated in a way that the Japanese people, and people of the world, can understand.

Saitou: Yes, that's what I'm also learning. Philosophy itself has a very deep background originally from European countries, and Nishida was one of the first people who interpreted what they said into Japanese culture. Nonetheless, very few scientists understand the history of German philosophy. People at KyotoU might know who Nishida is or at least have heard of him. But if we are to have a research group dedicated to ethics and philosophy we are obligated to have frequent discussions like we do with the mathematicians.

Becker: The goal of Nishida was not to create a unique philosophy. It was to make the cutting-edge science of the early 20th century acceptable to a Japanese world. Therefore, there's a similar goal for ethics and philosophy here in ASHBi, to make the cutting-edge science of the 21st century understandable and acceptable to today's Japanese.

Saitou: Can I ask a question? What was the general theme of European philosophy in the 19th and early 20th centuries? Were they competing with pure scientists?

Becker: I don't think so. Especially if we look at Kant, Hegel, Marx and then psychologists like Wundt, Alzheimer, and Kraepelin — who Nishida was looking at — they were trying to understand how history, society, and humans moved. They used and studied cutting-edge technology, in those days it was looking at light, or biology, like Mendel's genetics. They were looking at what they knew about genetics and science to try and model history and society. What we know today is much more advanced, and we must develop a new understanding of human society and history.

Saitou: Is that your understanding of the role of philosophy in the current climate?

Becker: That was its role in 19th century Germany. But Nishida did not follow Hegel and Marx; he did not try to interpret history. He looked at *Zen no Kenkyû* and *Basho no Ronri*, and for Nishida the big problems were not society and history. He didn't need to discuss society because Chinese philosophy already did that. Nishida felt that German logic and German truth or 'goodness' are very different from Japanese logic and Japanese truth. So, he asked how can I as Nishida understand German truth and German logic as a Japanese?

Saitou: Would it lead to the creation of unique identity or values on a new style of life? Like humans made from somatic cells?

Becker: Well in Nishida's case, his arguments about *Zen no Kenkyû* or *Basho no Ronri* are an antithesis to German thinking. He says that's not the only way to understand good; we in Japan have a different way to understand good. There is a *Basho no Ronri* which is different for us. Similarly, even if the Germans or the Europeans all say, "this is our stand on animal experimentation," you can say, "we as Japanese take a different stance."

Sipp: The important thing is to be able to articulate that, so that other people can understand that it is a rational argument.

Becker: Exactly.

Saitou: It is important to make a series of general international rules. But if everything is similar it is neither interesting nor appropriate to individual cultures.

Becker: You can't take American-style informed consent or IVF practices, and use them in a Japanese hospital. You can't expect these to be immediately accepted by everybody in Japan.

Fujita: With the example of informed consent, I do agree that what works for one country may not work for another, because of cultural differences. But I don't think many people refuse the concept of informed consent itself. We would agree to the concept of respect for autonomy. I think there is some variance among cultural values, but at the same time

Carl Becker is specially-appointed professor of policy science at the University’s Medical School. His research focuses on medical ethics at the end of life, psycho-social support for terminal patients, and burnout of medical staff. Arriving in Japan 45 years ago, Becker was originally impressed with the way that Japanese dealt with end-of-life issues in Hawaii, and wanted to see it firsthand in Kyoto. He began his study on the ethical issues of death and dying at KyotoU’s Faculty of Letters, and moved to the School of Human and Environmental Studies in 1992 to study bioethics.

we should follow and remember that we also have the same shared values in an international setting.

Becker: So, the challenge then, both for Nishida and for Saitou is figuring out how to adapt those universal values to be suitable to the Japanese culture today.

Saitou: And somehow at the same time to create something original from our viewpoint and then influence the rest of the world.

Sipp: Looks like you’re off to a great start both on the scientific side and the ethics side.

Saitou: It is a great challenge.

Sipp: Thank you. It was interesting hearing about the philosophy of science and looking back at a transformative time in biology and physics. Now we’re seeing very similar transformations in fundamental concepts in science, like the idea of the genome. What we used to think were clear boundaries between human and nonhuman are starting to get fuzzier. These are areas that your labs are now looking at from different angles, both scientifically and ethically.

Cutting edge

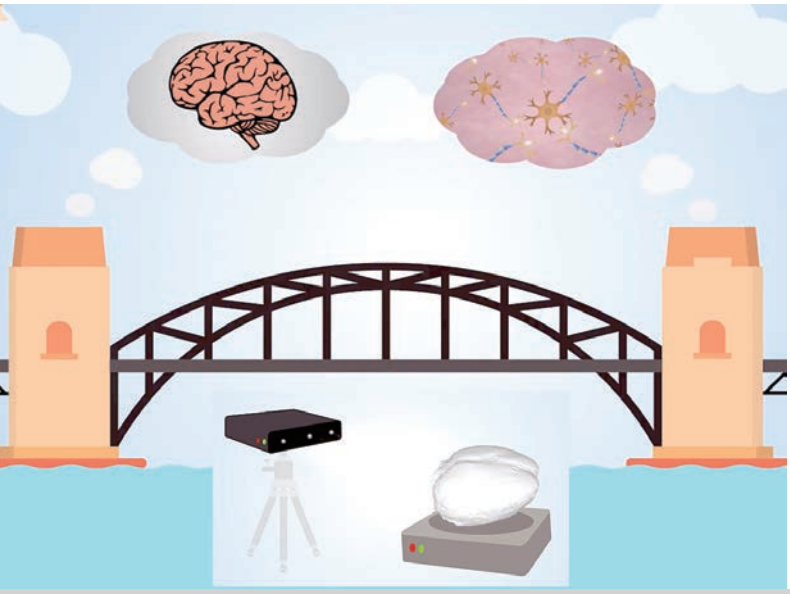
www.kyoto-u.ac.jp/cutting-edge/

This second section features a sampling of the latest scholarship from KyotoU, covering a broad range of fields of inquiry from brain science and genetics to animal cognition, cancer therapies, and developmental biology.

Bridging the scales of the brain

Significant recent advances now allow researchers to view the body's dynamic systems in unprecedented detail, but a significant drawback is that these technologies typically only work at specific spatial resolutions. A device designed to monitor the interactions of a million cells cannot be simply 'refocused' to monitor a single cell, for which a different instrument would be required.

"If we hope to observe dynamically moving architectures, the trade-off between resolution and recordable viewing angles needs to be resolved," states Masanori Shimono of the School of Medicine and the Hakubi Center for Advanced Research.



"To solve this, we combined MRI data with 3D scanning technology to study the brain from macro-scale structures all the way down to individual neurons."

3D scanners are commonly used in engineering, but less so in wet, bio-physiological experiments. It has typically been thought that the technology is not as easily applicable to wet, soft surfaces.

In a video report published in *JoVE*, Shimono's team began by scanning mice with an MRI to collect brain data. The surfaces of the mice brains were then analyzed with a structured-light 3D scanner. The two data sets were combined and evaluated together.

"Interestingly, the gap distances between the two datasets was around 55 μm, which is fairly close to the typical spatial scale of neuronal distributions," states Shimono. "At the same time, we confirmed that we can record electrical signals from brain slices."

The study not only bridges two spatial scales, but also the fields of medicine and engineering. Shimono hopes that the new protocol will be utilized extensively by researchers in both fields, in order to better understand how the brain works, stating that having a micro and macroscopic view of the brain can provide insight into the neuronal basis of mental disorders and other pathologies.

"When we first purchased our 3D scanner system, the vendor told us that they could not guarantee it would work on wet surfaces like the brain. The procedure to reach our current accuracy level was challenging, but there is still room for improvement." ■

An overactive cerebellum causes issues across the brain

Consider the cerebellum: the part of your brain tucked into the lower backside of your skull. Also known as the 'little brain', it plays a key role in regulating voluntary movement such as balance, motor learning, and speech.

Recent studies indicate that the cerebellum is also involved in higher-order brain functions including visual response, emotion, and motor planning. And now, a KyotoU team has found another link, this time to depressive behavior.

Writing in *Cell Reports*, the research team found that in rats, acute cerebellar inflammation puts the structure in an overexcited state, resulting in the animal developing a temporary decrease in motivation and sociability.

Team leader and Hakubi scholar Gen Ohtsuki explains that the investigation began in an effort to understand how the brain's immune system can change its activity.

"Even though we now know more about the cerebellum's role in higher brain functions, the detailed signal transduction machinery has remained a mystery. So we conducted a series of experiments in which we activated immune cells in the cerebellum."

The brain's immune cells, or *microglia*, respond to

Why fruit flies eat practically anything

Despite the name, fruit flies eat more than just fruit.

Writing in *Cell Reports*, a team of scientists describe how the insects' diverse diet stems from a flexible response to carbohydrates, lending insight into how humans also evolved to have such diverse palates.

The fruit fly, *Drosophila melanogaster*, may be considered a nuisance, but to scientists these minuscule pests are giants in the study of genetics, having provided deep insight into how genes function in our bodies. As with fruit flies, omnivorous humans are known as 'nutritional generalists'.

Some close genetic cousins of the fruit fly, however, are 'nutritional specialists', only feeding on specific plant varieties. Many questions remain as to how some organisms — even within the same genetic family — vary so widely in feeding habits.

"Understanding molecular mechanisms in nutritional generalists and specialists can help us uncover how organisms adapt to variable nutritional environments," explain Kaori Watanabe and Yukako Hattori of the Graduate School of Biostudies, who led the study.

The team began by examining whether larvae of generalists and specialists could adapt to three experimental diets: high protein, high carbohydrate, and 'medium' protein-carbohydrate. As expected, generalist flies — including the common fruit fly — grew under all diets. Larvae of specialists, on the other hand, could not survive under carbohydrate-rich conditions.

These specialists are known to eat and reproduce only on specific fruits or flowers, and examining the nutritional profiles of their native diets showed that their intake is low on carbohydrates. This led the team to hypothesize that the difference between the flies lies in the genetic pathways that control their response to carbohydrates.

"The 'TGF-β/Activin signaling' pathway regulates the body's response to carbohydrates. In the generalists, the flexibility of this pathway maintains metabolic homeostasis under different diets," say Watanabe and Hattori.

In contrast, the specialists' response resulted in reduced adaptation, suggesting that the generalists retained robust, carbohydrate-responsive systems through genome-environment interactions, whereas specialists lost them in consistently low-carbohydrate environments. ■

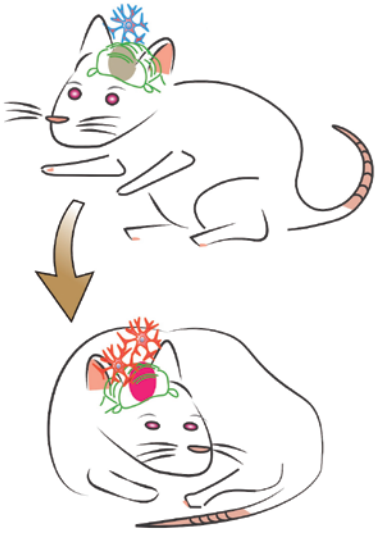
bacteria and viruses to mitigate the intruders. This response results in inflammation. Utilizing electrophysiological techniques, the team found that microglia caused neurons to fire at an increased rate, a phenomenon known as *intrinsic-plasticity*. This in turn caused the cerebellum to go into a state of 'hyper-excitement'.

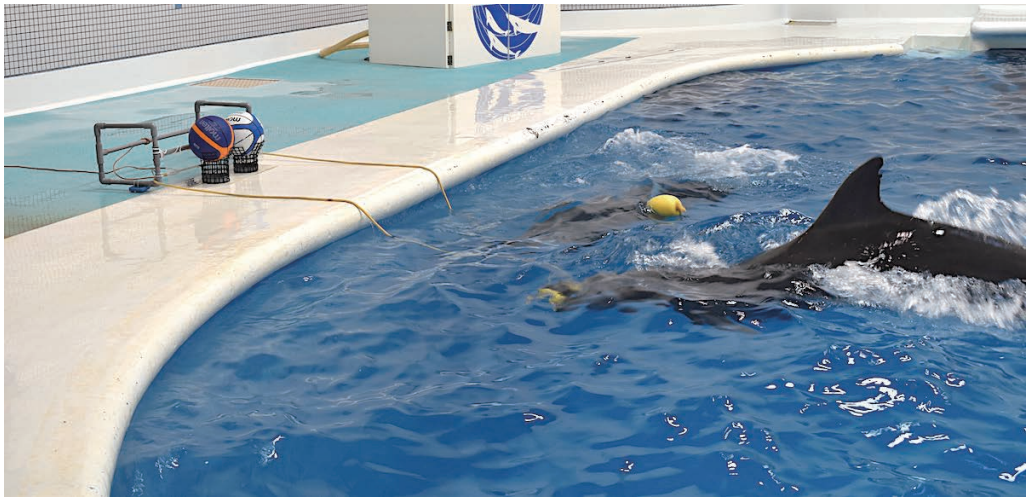
The team succeeded in demonstrating that this immune-triggered response changed behavior. Rats induced with acute cerebellar inflammation showed a dramatic decrease in sociability, free-searching, and motivation.

"These are 'depression-like' behaviors. Once the inflammation subsided, they were back to normal," Ohtsuki continues.

The team is encouraged by their results, but states that further investigation is needed.

"Excessive immune activity in the brain can induce behavioral pathology, and we expect it to be involved in other mental and cognitive disorders such as dementia. But to understand anything about these pathological mechanisms we need to combine these results with additional data such as genetic risk factors," concludes Ohtsuki. ■





Lend me a flipper

Cooperation is a key trait for any social species. From hunting to breeding to child rearing, cooperative behaviors have allowed many animals — including humans — to survive and thrive. As we better understand the details on how animals work together, many researchers have been focusing on the degree of cooperation and cognitive abilities required for each shared activity.

Dolphins are well known to socialize in 'fission-fusion' groups — pods — that merge and split over time. Earlier studies have suggested that dolphins may understand each other's roles in cooperative tasks, but due to the complex mechanics of conventional experiments, it was difficult to determine how this behavior was characterized.

Now a research group from KyotoU's Primate Research Institute, Kindai University, and Kagoshima City Aquarium have written in *PeerJ* about a study that greatly simplifies previous experimental conditions.

"We wanted to find out how bottlenose dolphins coordinate their cooperative behavior. Our setup was the so called 'Hirata task', where two dolphins pull on opposite ends of a rope simultaneously to receive a reward," explains first author Chisato Yamamoto.

The Hirata task, also known as the cooperative pulling paradigm, has been used to demonstrate that a significant number of animals — including chimpanzees, dogs, and elephants — have cooperative abilities.

And it appears dolphins are just as cooperative. In the test, an 'initiator' was first sent in the direction of the task, and then after a few seconds a 'follower'. The team observed that the initiator waited for its partner to reach the task, and that the follower would coordinate its swimming speed to match the initiator.

"Seeing behavior coordination has previously been observed in chimpanzees and orangutans," continues Yamamoto, "but dolphins appear to be more flexible in their coordination, capable of changing their actions depending on where their partners are."

Team leader Masaki Tomonaga explains that this coordination is likely rooted in the dolphins' patterns of affiliative behavior, a method of social interaction that functions to reinforce social bonds within a group.

"Synchronized swimming in is one of these affiliative behaviors. How social characteristics influence cooperative systems may be one of the important questions that will reveal the evolution of cooperation in mammals." ■

Using a ch
cancer figh

KyotoU researchers have developed a new 'tumor-on-a-chip' device that can better mimic the environment inside the body, paving the way for improved screening of potential cancer-fighting drugs.

The path to drug discovery is never easy. Scientists and clinicians can go through tens-of-thousands of potential compounds for years and find just a handful of viable candidates, only to then have all of them fail at the clinical test stage.

"Potential compounds are tested using animal models and cells cultured in a dish. However, those results frequently do not transfer over to human biology,"

The little a
lived in the

Study of a 700,000-year-old fossilized bone indicate that a close relative of the most abundant seabird species in the North Atlantic — the modern dovekie, or 'little auk' — used to thrive in the Pacific Ocean and Japan.

Seabirds are top predators in the marine ecosystem, and their distributions are shaped by numerous environmental factors in the ocean. As such, extensive scientific inquiries have been conducted on how seabirds respond to fluctuating oceanic environments in ecologic and geologic timescales.

"The North Pacific has been one of the most intently investigated regions, but the fossil record of seabirds in the Pleistocene Epoch, about 2.6 to 0.01 million years ago,

ip to find better ting drugs

explains Yuji Nashimoto formally of the Graduate School of Engineering and now at Tohoku University.

"Further, cells on a dish lack the three-dimensional structure and blood vessels — or vasculature — to keep them alive. So we came up with a a device that solves these issues."

The device, as described in the journal *Biomaterials*, is the size of a coin with a 1 mm well at its center. This well is flanked by a series of 100 μm 'microposts'. In use, a three-dimensional culture of tumor cells is first placed in the well, and then cells that construct blood vessels are placed along the microposts. Over a few days the vessels grow and attach to the culture.

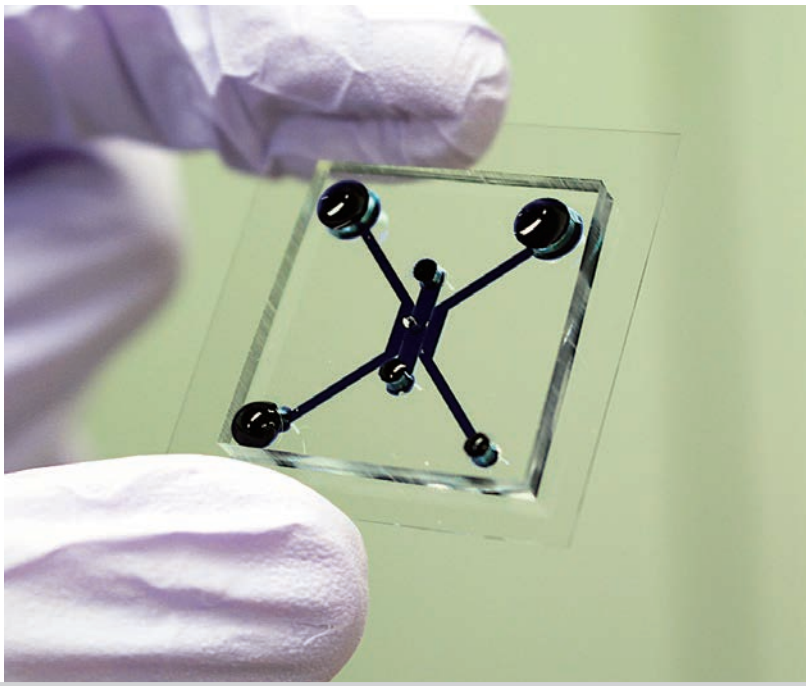
"This 'perfusable vasculature' allows us to administer nutrients and drugs into the system to mimic the environment in the body," continues Nashimoto, the study's first author.

"This allows us to have a clearer picture of the effectiveness of cancer treating compounds."

Fortunately the device worked as expected, revealing the interesting result that the drug being tested was more effective under static conditions than when nutrients were flowing through the tumor cells. Ryuji Yokokawa, who led the team, explains that the unexpected results demonstrate the need to consider the balance between the proliferation of tumor cells and the efficacy of drugs under particular nutrient flow conditions.

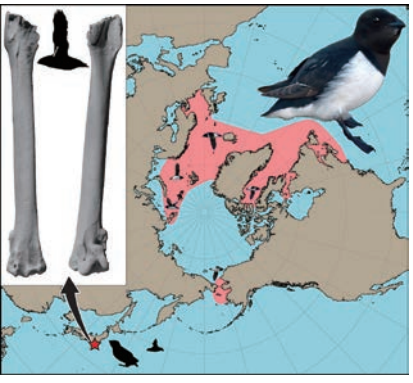
"We hypothesize that at low doses the benefit of the nutrient flow outweighs the effect of the anti-tumor drug. It proves the importance of blood flow in the vasculature when screening for drugs."

He concludes by saying, "Due to its size and utility, we hope this new device can expedite tests on countless numbers of potential new drugs. While many questions remain, we are happy to have shown that this device can be vital for reaching the next step." ■



uks that Pacific

has been scarce," states Junya Watanabe of the Graduate School of Science.



"This has led to a frustrating lack of information from this critical time period concerning the origin of modern seabird communities."

In recent years, Watanabe and his team have been investigating seabird fossils from several locations in Chiba and Tokyo prefectures, gaining new insight into the Pleistocene seabird community in the region.

The group had been successful in identifying 17 fossils representing at least nine species of birds: three species of ducks, a loon, an albatross, a shearwater, a cormorant, an extinct penguin-like seabird called a mancalline auk, and a dovekie. Most of these species can be found in the region today; however, the presence of a dovekie was completely unexpected.

Watanabe, first author of the study, explains his findings published in the *Journal of Vertebrate Paleontology*.

"At first it confused us that the fossil didn't match any of the Pacific auks, but once we compared it with Atlantic ones, the similarity with the modern dovekie was apparent. It is not clear whether the present fossil is from the same species or a very close cousin, but we are positive that it at least comes from the same lineage."

Dovekies today are mostly restricted to the North Atlantic and Arctic oceans, with rare sightings in Japan considered accidental visits. Given the unlikeliness of such accidental visitors having been preserved as fossils, the new findings suggest that dovekies were once fairly common in Japan and the Pacific.

The question of why dovekies are so rare in the North Pacific today remains unexplained, however, and awaits investigation of further fossil materials. ■

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

Reconstructing the clock of human development

KyotoU researchers have successfully reconstituted a human 'segmentation clock' — a key focus of embryonic development research — using induced *pluripotent stem cells*, or iPSCs.

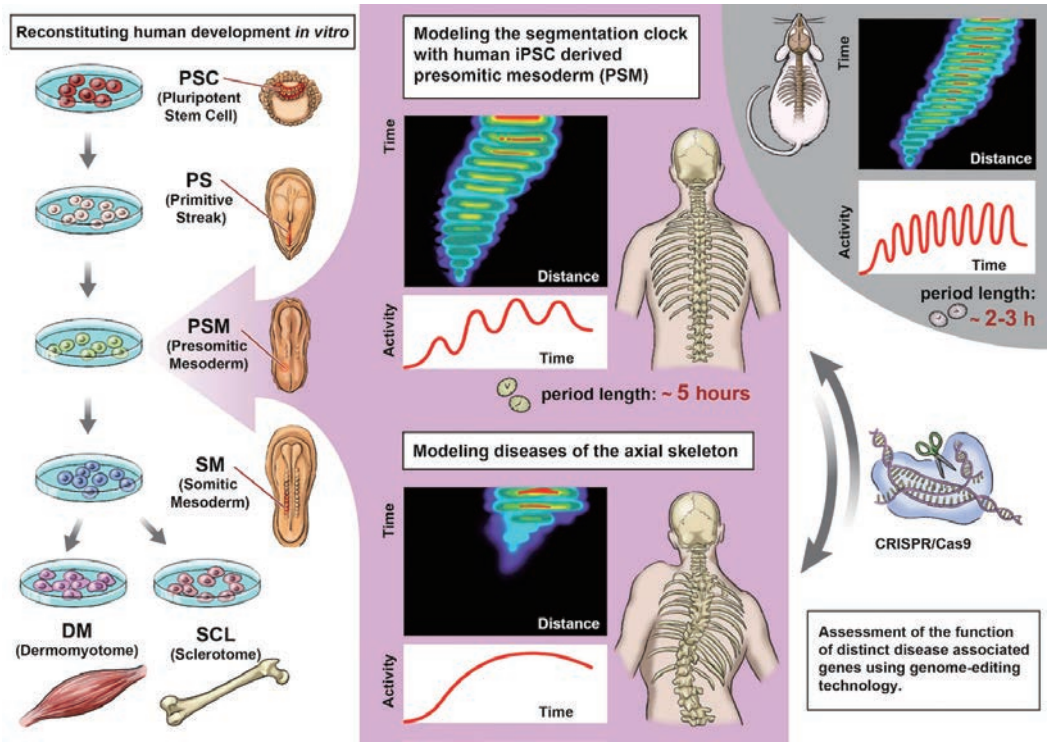
From the first division of a fertilized egg, a complex network of proteins and genes push-and-pull on each other to construct the pattern of cells that form our organs. Like the pendulum on a clock, each swing and pulse needs to carefully align, to maintain the rhythm that forms life.

Much of our understanding of early human development is exceedingly limited, however, due to the lack of experimental models that can accurately reproduce these complex biological processes.

"For example, about 20 days after fertilization the human embryo develops segments called *somites*, which determines the basic pattern of the body," explains team leader Cantas Alev from the Institute for the Advanced Study of Human Biology, ASHBi.

"Somites eventually contribute to the formation of the vertebrae and ribs."

The emergence of somites is determined by the segmentation clock, a genetic oscillator that controls and guides their emergence. Almost nothing is known about how this clock develops in humans.



In their paper published in *Nature*, the team consisting of members from ASHBi, KyotoU's Center for iPS Cell and Research Application — CiRA — and RIKEN describes how they used human iPS cells to form the 'pre-somitic mesoderm', the precursor cells of somites.

"Studying the genes that were being expressed in a rhythmic pattern revealed the novel genetic components of the 'segmentation clock' we were looking for," Alev continues.

And the team also replicated a second hallmark of the segmentation clock, a 'wave' of expression. Using gene-editing technology, they then assessed the function of the key genes related to spine deformation.

As expected, mutations in these genes dramatically altered aspects of the segmentation clock including synchronization and oscillation. They then went further by generating iPS cells from patients with known genetic defects, identified relevant mutations, and corrected them.

The study demonstrates how iPS cells can be used to accurately recapitulate distinct aspects of human embryonic development and other complex biological processes.

"Like many developmental biologists I am fascinated by embryos and embryonic development," says Alev.

"The elegance and beauty by how complex organs and tissues are formed from very simple initial structures is astounding. I hope to reconstruct and analyze many other aspects of embryonic development, and expand our still limited understanding of human and non-human development." ■

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 the forefronts of research, overseas offices and labs, and student life.

Science with industry:

KyotoU venture bringing light to patients' eyes

"Ten years ago I returned to Kyoto University to start clinical research."

Hanako Ikeda, a practicing ophthalmologist, divides her time between the lab and treating patients, but what brought her into the front lines of clinical studies was a casual lunch with an old colleague and a strong desire to treat patients with glaucoma.

"Akira Kakizuka and I were talking about our respective research and he mentioned these small molecules his lab had been developing, which he called *Kyoto University Substances*, or KUS, which can control ATP production in cells."

ATP — *adenosine triphosphate* — is the fuel that powers the cells in our bodies.

"It goes without saying that our eyes are important to us. But beyond being figurative 'windows to the soul' they are also in a very real sense windows into the brain. The eyes are the only part of the central nervous system we can directly study and treat."

When Ikeda first started seeing patients, she come across many whose eye conditions had varying degrees of treatability. Some maladies, such as retinal degeneration, where the cells in the eyes die, resist any form of treatment.

"There are many causes for this cell death, including a lack of energy for the cells to function, or to put it another way, decreased ATP production. So there I was, presented with compounds that can control ATP concentration in cells. I resolved to bring KUS onto the market to treat these patients."

Ikeda floated the idea with pharma firm reps in the hopes of receiving funding. But all she got were rejections, based on a belief that such research would take too long to bear fruit. The usual public funding sources were also out of the question, as they wouldn't last long enough to cover clinical trials.

"Thankfully, we succeeded in securing backing from the University's then newly-formed incubator, KYOTO-iCAP, as well as the Japanese government's medical funder AMED, allowing us to begin trials in 2016. Since then our work has received greater recognition and support has grown."

With the first phases of clinical trials now concluded successfully, the final, phase 3 trials are set to begin in 2020. Ikeda still faces a few years of hard work before a product goes to market, but she can now feel that the endeavor, and a potential treatment for patients, might be a bit closer to the light at the end of the tunnel.

For more see www.kyoto-drug.com/en/

News from overseas centers

Washington North American Center

On 20 November 2019, the Center hosted a celebration commemorating the first anniversary since its establishment, joined in Washington DC by more than 80 individuals and institutions that have supported the Center's efforts, including strong showings from the University's Washington DC alumni and the New York Rakuyu-Kai alumni association, as well as old, new, and prospective partner organizations.

KyotoU's third overseas office, the Center is working to enhance the University's presence and support for academic and student exchange activities in North America. The first year saw an intensive push to expand and solidify networks of communication with universities, academic institutions, and alumni associations in the region.

KyotoU president Juichi Yamagiwa's welcome remarks were followed by speeches by Japan's ambassador Shinsuke Sugiyama, Yoshiaki Nishimura of Sumitomo Riko Company Ltd and vice-president of the KyotoU Kanae-Kai, Sachiko Kuno, president and CEO of the S&R Foundation, and Frank Jannuzi, president of the Mansfield Foundation. The speakers expressed their wide-ranging encouragement for the future activities of the Center.

Center director Nathan Badenoch provided an overview of the Center's activities during its first year, including the signing of new student exchange agreements with three universities and prospects for three more in progress. The Center also develops new concepts for interdisciplinary collaborative research with partners.

President Yamagiwa's stimulating keynote address provoked discussion of Japanese perceptions of nature and human evolution. Participants expressed deep appreciation for the president's intellectual leadership. Kayo Inaba, executive vice-president for gender equality, international affairs, and public relations brought the ceremony to a close with thoughts on the importance of a regional presence in promoting internationalization.

Moving into its second year of operation, the Center will continue to function as a "window" to North America, serving as a hub to deepen cooperative relationships while enhancing internationalization efforts in the region.


North America


Africa

Addis Ababa Africa Office

KyotoU marked an important milestone in August 2019 with the official opening of its Africa office — KUAO — in the Ethiopian capital, where Addis Ababa University (AAU) and its Institute of Ethiopian Studies (IES) are generously acting as hosts. Located on the Sidist Kilo main campus, the KUAO space is at the entrance of the well-known Museum of Ethnography at IES, a popular tourist attraction. The office seeks to facilitate collaborative research between Japanese and African students and scholars. KUAO will also support courses in Japanese language and culture at AAU, encouraging Ethiopian students interested in studying in Kyoto.

ASEAN

www.oc.kyoto-u.ac.jp/en/

Europe

Heidelberg European Center

In October 2019, KyotoU concluded strategic partnership agreements with the Universities of Bordeaux and Vienna. Then in January 2020, European Center director Yasuyuki Kono paid them his first official visits, discussing efforts to deepen collaboration based on these strategic partnerships. (Pictured during a signing ceremony are Kono and Vienna vice-rector Jean-Robert Tyran.)

Joint activities with Bordeaux will focus on three themes: African studies, health and aging, and sustainable cities. The European Center has especially high expectations for African studies, given the opportunities presented by the newly established KUAO, forming a unique triangular network connecting Europe, Africa, and Asia, with KyotoU at its head.

KyotoU and the University of Vienna will continue their long-standing collaboration in fields such as law and cognitive biology, with interest growing in new areas stemming from recent joint events such as a 2019 humanities workshop.

Financial support for joint activities, provided by KyotoU and respective strategic partners, will include seed funding to enhance the mobility and exchange of researchers and students, as well as subsidies for workshops, seminars and summer school programs. Through these efforts, the Center anticipates that these strategic partnerships will strengthen and expand ties with institutions across Europe.

Bangkok ASEAN Center

The Japan-ASEAN Science, Technology and Innovation Platform — JASTIP, jastip.org/en — is a particularly notable international interdisciplinary project initiated by KyotoU. ASEAN Center and JASTIP staff together promote active dialog among scientists, policy makers, administrators, and members of the private sector and general public, to support multilateral projects on energy and the environment, bio-resources and biodiversity, and disaster prevention. These are in turn authorized and advanced by the ASEAN secretariat, successfully integrating researchers with non-academic stakeholders from all member states.

During the recent 8th JASTIP symposium held 17–19 January in Hanoi (pictured), representatives from the JASTIP team presented their achievements and evaluation process for the five-year project, while executives from sci/tech-related ministries and companies, together with KyotoU alumni demonstrated that the cooperation toward social implementation was both productive and promising. Participants from Japan and ASEAN showed great interest in continuing the project, agreeing to focus on high-priority goals, research fields, and young talent capacity development as well as utilizing research administrators to further strengthen ASEAN–Japan ties.

Together with friends in Benin, Muratsu has founded an NGO providing free vocational training to socially and economically disadvantaged girls.

Muratsu's installation *If it touches you, you will die*, depicting the deity Kubito.

Evoking the 'reality' of a distant land

Ran Muratsu (5th Year, 5-year integrated doctorate, Graduate School of Asian and African Area Studies)

The screen fills with women in bright pink dresses, moving together in rhythm. Possessed by the snake god, they form a circle into which no one else may enter. But one youth makes his way in and joins the dance.

Ran Muratsu elaborates on this scene from her documentary film Tohossou: "The young man has what we might call an intellectual disability, and I often saw him being teased. But in this ceremony the women, possessed by a divinity, were showing him respect. It made me wonder what kind of being he really was."

Muratsu's field work takes her to the Republic of Benin in West Africa, where she studies the lives of the people and their natural surroundings. Vodun traditions portrayed in *Tohossou* — and other indigenous beliefs — are deeply rooted in their lives.

Even as an undergrad, Muratsu's insatiable curiosity led her clear across the Eurasian continent. After seven years working for a Japanese firm, she joined the Japan Overseas Cooperation Volunteers and was dispatched to Benin.

"In different cultures, people imagine different things," she explains. "I wanted to engage with the rich imaginative powers of the people of Benin, so I chose the path of research in the hope of learning more about this society, where religion permeates all aspects of daily life."

At the heart of anthropological research is ethnography: in-depth observations and documentation of peoples' customs and ways of life.

"With a video camera in hand, I listen to people's stories and record life in their communities."

As Muratsu's research has progressed, she has come to understand that the Vodun deity Tohossou is sometimes born in human form, and that children with physical and intellectual disabilities are often seen to be this deity incarnate. The film that resulted from her work received an encouragement award at the Tokyo Documentary Film Festival 2018.

"I want to create works that immerse audiences in the reality of local peoples," Muratsu says. Expanding the scope of ethnography, she is testing a variety of methods to express 'reality', including novels co-created with locals, and art installations.

"Reality is something that grows around us based on our perceptions of our environment," she explains. "I hope to create works that 'transmit' local peoples' lives as genuine experiences."

Sitting for this interview in Benin — over a shaky, internet audio connection — Muratsu's clear vision shines through, her strong voice filled with passion for exploring the potentials of anthropology and brimming with the strength to turn her camera's probing gaze onto the lives of peoples far away.

Muratsu with her host-mother in Benin, whom she visits once or twice a year. "The people open their hearts to you only if you learn to speak, eat, and live together with them."

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

Dark Blue New Sounds Orchestra

Title: Take the "A" Train
Composer: Billy Strayhorn

Most likely you've heard Take the "A" Train — one of the best-known works in the repertoire of the Duke Ellington Orchestra — at least once. The cheerful melody and rich solos that are the whole point of jazz music make this an approachable work even for newcomers to the genre.

Faculty of Medicine Photography Club
Mako Otsuki (3rd Year, Faculty of Medicine)

Orange street lamps illuminate the city at night. A cobblestone street lined with stone buildings bustles with gentlemen in hats and carrying walking sticks, accompanied by elegantly dressed ladies. Talk and laughter fills the air of a pub. This sort of scene came to mind when I heard this piece of music. I wanted a photograph where light contrasts with the darkness of night, so I chose this one, which I took at a Christmas market in Germany.

Taking your hand, leading you into the light.
Even in the cold winter's air our joined hands feel warm.
I hold up a pair of tickets, looking at you intently.
He and she, you and I,
—No one else can know. Your expression belongs just to us.
The winter cold drags on.
But just for this moment, we stand in the light.

Yu Aoba (2nd Year, Faculty of Integrated Human Studies)

Winter is a difficult season for me. It's cold. But also thanks to this forbidding weather, the time we spend with others is especially appreciated. Those moments when we can believe that everyone is connected to someone else more than make up for the trials of the season. It's not so bad after all. But it's still cold.

facebook.com/Kyoto.Univ.E

@KyotoU_News

@kyotouniversity

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