

CHIBA RESEARCH

Highlights of Innovative and Collaborative Research

2019



REACHING NEW HORIZONS

Welcome to the third issue of *CHIBA RESEARCH*, a publication that showcases the diverse and innovative work being undertaken at the Institute for Global Prominent Research (IGPR), Chiba University.

The institute was established in 2016, with the ambitious goal of becoming a global hub for top-class research in fields as far-reaching as neutrino astronomy, the science of plant-based medicine, three-dimensional holography, and the creation of a fair, egalitarian society.

The institute is an exciting initiative at Chiba University. It was set up to nurture key research projects being conducted at the university that are deemed to be of special significance. This issue introduces the twenty-two innovative projects currently underway at IGPR. All of these projects were selected by an advisory board that included external experts.

Three of these projects have been singled out as being of top importance – Toshinori Nakayama's work on finding unconventional vaccines that are administered via the mouth, nose or other mucosal system through which most pathogens enter the body (see page 6); Takashige Omatsu's research into spiral-shaped laser beams that exhibit left- and right-handedness and can be used to create helical nanostructures (see page 10); and Shigeru Yoshida's use of chost-like elementary particles known as neutrinos to explore the high-energy Universe (see page 8).

We trust you will become as enthusiastic as we are about this fresh initiative, and we look forward to presenting more of the latest findings from these projects over the coming years.

Guided by its motto “Always aim higher,” **CHIBA UNIVERSITY** strives to nurture globally minded students who have broad outlooks. The university values academic diversity and actively conducts leading-edge fundamental and applied research.

Chiba University was founded as a national university in Japan in 1949, when Chiba Normal School, established in 1874, merged with Chiba Medical College and several other educational institutions.

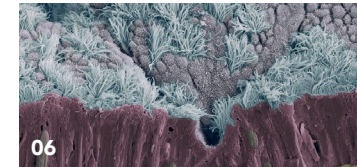
Currently composed of 10 faculties and 13 graduate schools, Chiba University is one of Japan’s largest national universities, having about 11,000 undergraduate students, 3,500 graduate students and 3,500 faculty members on 4 campuses located near Tokyo. The main campus at Nishi-Chiba occupies an area of almost 400,000 square meters (100 acres) and is conveniently located between Tokyo Station (about 40 minutes by train) and Narita International Airport. The 850-bed University Hospital, a core hospital for the region, is adjacent to the School of Medicine on the Inohana campus.



CHIBA UNIVERSITY

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Top Research Program

MUCOSAL IMMUNOLOGY AND THERAPEUTICS

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CHIRAL MATERIALS SCIENCE USING LIGHT TO ESTABLISH

Using Light to Establish a New Field of Chiral Materials

MUCOSAL IMMUNOLOGY AND THERAPEUTICS

FIGHTING PATHOGENS AT THEIR POINT OF ENTRY

Research Keywords: Immunology, Mucosal Immunity, Allergy

The mucous membranes that line many of the tracts and structures in the body are the first lines of defense against foreign invaders. Equipped with a powerful and highly specialized immune system, these mucosal sentinels protect the surfaces and, by extension, the body interior, against the threat of gastrointestinal, respiratory and sexually transmitted infections, as well as cancer, allergies and more.

If these immune cells let their guard down, pathogens such as bacteria and viruses can invade. On the other hand, if they are overly vigilant, hyper-reactive conditions like asthma or autoimmune inflammatory bowel disease can take hold. Getting the balance right is the goal of the International Center of Excellence in Mucosal Immunology and Innovative Allergy Therapeutics.

Launched as a joint initiative between Chiba University and the University of California, San Diego, in 2016, the center aims to harness the power of the mucosal immune system to develop the next generation of preventive vaccines against infectious, allergic and inflammatory diseases.

Most vaccines in use today are administered by injection. But since most infectious agents enter the body at mucosal surfaces, vaccinating through the nose, mouth, or some other mucosal route could provide more protection. Since transmission often occurs at these sites, boosting the body's ability to block that transmission could stop an infection or autoimmune reaction at its source.

"While existing injectable vaccines are able to prevent serious conditions from developing, they are not effective enough to defend against infection," notes program director, Toshinori Nakayama.

FROM BASIC RESEARCH TO CLINICAL APPLICATIONS

Before new treatments can be developed, however, much more needs to be learned about the molecular architecture of the mucosal immune system. That is why the International Center of Excellence is focusing on basic research while simultaneously advancing clinical applications. It is also strengthening ties between researchers and industry in the hope of translating its discoveries into therapies for patients. To this end, Nakayama is building a robust pipeline of talented scientists who can move research findings seamlessly from the lab bench to the hospital bedside.

"The research system we are creating is unprecedented," says Nakayama, who is also vice president of Chiba University and dean of the Graduate School of Medicine and the Faculty of Medicine. Projects at the International Center of Excellence fall into three categories: Hiroshi Kiyono is studying the basic mechanisms of mucosal immunology in response to microbial infections and assorted diseases; Nakayama and colleagues, including Atsushi Onodera, Motoko Kimura and Osamu Ohara, are focusing on allergic reactions and novel treatments that target the mucosa; and Hiroshi Nakajima, Yoshitaka Okamoto and Naoki Shimojo belong to the clinical research team that is developing new vaccines and adjuvants for pathogens endemic to Japan and around the world.

Chiba has initially committed US\$2 million over five years to this alliance. Together with a matching contribution from UC San Diego, the project will facilitate joint research and exchanges between investigators and students on both sides of the Pacific.

MUCOUS MEMBRANE IN THE AIRWAY

Mucous coat layered with tiny hairlike cilia.

Immune cells in the mucous membrane protect the body against invasion by pathogens such as bacteria and viruses, but they are too vigilant they can cause disease.

Vaccines that directly target the mucosal surface could provide more protection than a typical injection.

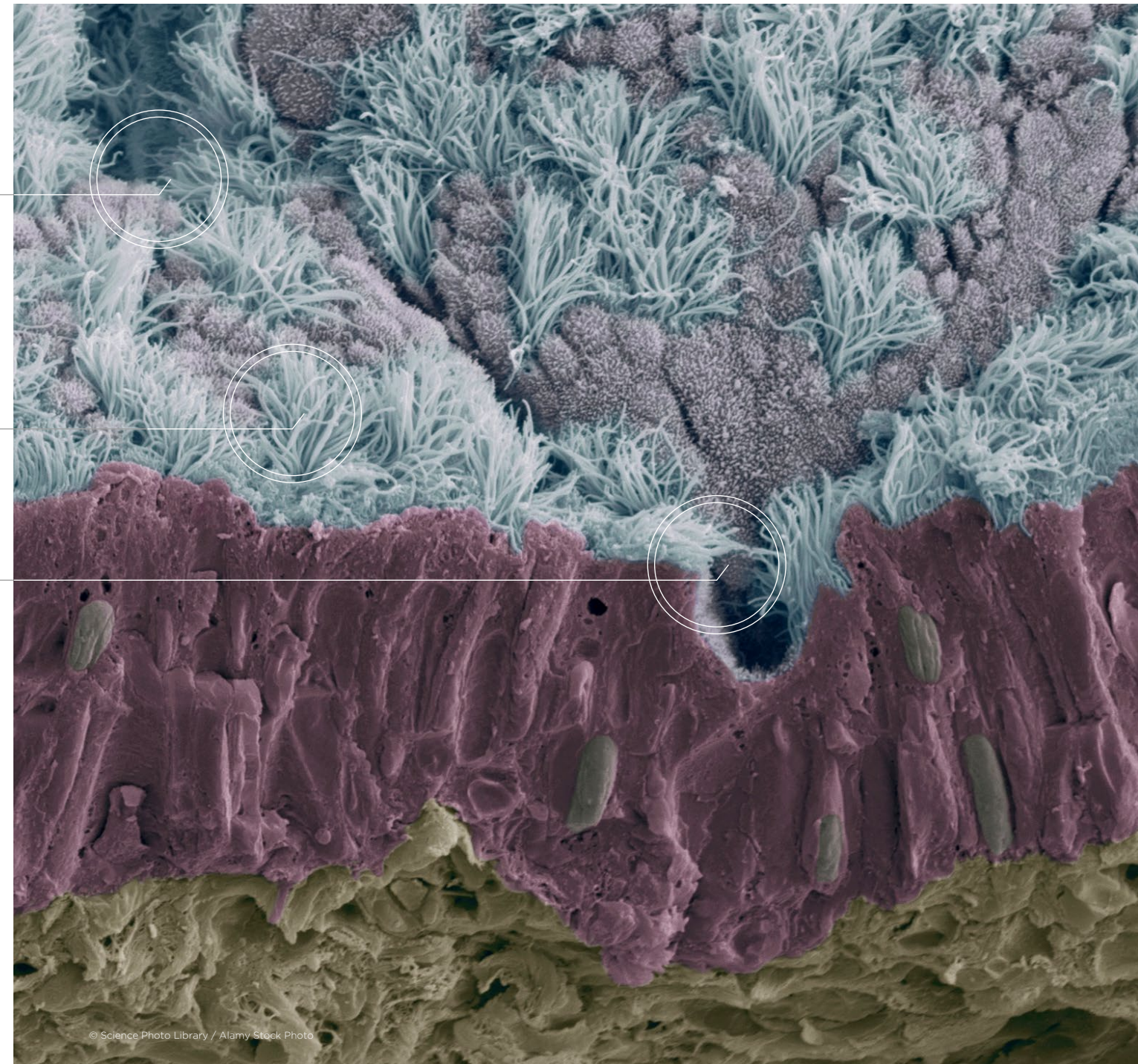
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Atsushi ONODERA	Akira SUTO
Yosuke KURASHIMA	Ryo NASU

—Vaccines that induce immune responses at mucosal membranes of the intestines, lungs and other organs could help prevent deadly infections.



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INTERNATIONAL CENTER FOR HADRON ASTROPHYSICS

REVEALING HIDDEN MESSAGES FROM THE COSMOS

Research Keywords:

Neutrino Astronomy, Cosmic Rays, South Pole, Elementary Particle Experiment

—From a remarkable observatory buried deep in the south polar ice, Chiba University astrophysicists are helping to explore the origins of the Universe.

Humans have been observing the stars for tens of thousands of years, first with our eyes, then with optical telescopes, and more recently using devices that can detect light at the extremes of the electromagnetic spectrum far beyond the visible range. Yet despite phenomenal progress in astronomy over the past half century, much of the Universe remains completely hidden from view, obscured by other matter, other radiation sources, and light's interaction with the interstellar medium. Now, scientists are on the verge of being able to peer into some of the most mysterious corners of the cosmos using not light but neutrinos — near-massless subatomic particles that travel close to the speed of light across the Universe without being deflected by magnetic fields or absorbed by matter.

The International Center for Hadron Astrophysics (ICEHAP) led by Shigeru Yoshida is part of the global collaboration responsible for managing the IceCube Neutrino Observatory deep in the ice at the South Pole's Amundsen-Scott station. "One of the longest standing puzzles in astrophysics is the origin of high-energy cosmic rays and neutrinos," says Yoshida. "The new windows to our Universe opened by neutrino observations, combined with powerful computer simulations

of cosmic plasma, have great potential to finally resolve this mystery."

THE ICECUBE COLLABORATION

Neutrinos are the most abundant particles in the Universe after photons (light particles). They originate in some of the most violent and least understood cosmological phenomena like supernovas, galactic cores and black holes. After their birth, they travel in straight lines from their source with almost no deflection or absorption, making them ideal messengers from the heart of these mysterious astronomical objects. But these same properties also make them exceedingly difficult to detect. The IceCube collaboration, involving 300 physicists from 48 institutions in 12 countries, has gone to extreme lengths to detect these ghost-like, high-energy particles.

The IceCube observatory is a cubic kilometer of crystal-clear ice, deep below South Pole Station — the only place on Earth where such large volumes of clear, pure and stable ice can be found along with the infrastructure needed to support scientific research. By suspending thousands of delicate photodetectors on strings in a network of vertical holes drilled through the ice, physicists can capture the rare explosion of energy that occurs when a neutrino collides with an oxygen

or hydrogen nucleus. Of the trillion, trillion neutrinos that pass through IceCube every day, the facility records just a few hundred collisions from high-energy neutrinos — a minute fraction of the neutrino flux but more than enough to stimulate some very exciting research. "We are proud of having been key players in the discovery of high-energy cosmic neutrinos, which astrophysicists have been dreaming about for more than 30 years," says Yoshida talking about his team members in ICEHAP.

Another important contribution of ICEHAP to understanding the high-energy Universe is its supercomputer-based massive numerical simulation program for deep investigation of the physical mechanisms behind high neutrino production. "Through our simulations we are helping to uncover the hidden messages carried by these neutrinos and to reveal the physical mechanism by which high-energy cosmic rays are accelerated at their source," says Yoshida.

In 2018, the IceCube collaboration has finally discovered that a special type of galaxy, TXS 0506+056, is a birthplace of cosmic neutrinos. This achievement was selected as one of the top breakthroughs by *Science*. It clearly shows the steps being taken forward.



Amundsen-Scott station in Antarctica.

Two towers receive information from 5,160 light-detecting sensors buried 2,500 meters beneath the South Pole.

The IceCube Neutrino Observatory, at the South Pole's Amundsen-Scott station. The International Center for Hadron Astrophysics is part of the global collaboration constructing IceCube.



Neutrinos are subatomic particles that typically pass freely through matter. Other particles cannot penetrate the Earth, so below the 'Dark Sector' near the South Pole, free from every other interference, it is quiet enough for the neutrinos to be detected.

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CHIRAL MATERIALS SCIENCE

USING LIGHT TO ESTABLISH A NEW FIELD OF CHIRAL MATERIALS

Research Keywords: Applied Optics, Optical Vortex, Chirality

—Understanding the universal property of chirality could lead to new materials and technologies for photonics and other applications.

Of the many mysteries still to be unraveled in the natural sciences, one of the most compelling is the origin and power of chirality — the property of a molecule or object that has two mirror-image forms — like our left and right hands.

Chirality is universal in biology, chemistry and physics. It critically affects the biochemical processes underpinning life, is a vital aspect of drug discovery, and crops up in particle physics. Light can have chiral properties that affect how it interacts with matter. But how can the power of chirality be harnessed and controlled? And what new discoveries and technologies might this give rise to? These are some of the questions Takashige Omatsu and his team are asking.

Light beams can be chiral when they are imparted with so-called helical wavefronts, that is, polarity that rotates either left or right. “We can use ‘optical vortices’ to twist the physical properties of metals, semiconductors and organic materials on the nanoscale to create chiral nanostructures with unique features,” says Omatsu. “Our goal is to establish chiral photonic materials as an original research field and to pioneer new technologies such as chiral plasmonics and metasurfaces for nanoscale chiral chemical reactors, chiral-selective imagers and chiral sensors,” he explains.

LIGHT CORKSCREWS

Omatsu’s team focuses on the interaction between helical light and materials, and the physical properties and potential uses of such modified materials. The electromagnetic field of helical light rotates as the light moves through space. When this field interacts with conductive materials like metals, nanoscale corkscrew-like variations in physical properties can be

inscribed on the material’s surface. The modified surface can then react differently to left- and right-handed chiral molecules or helical light, giving rise to a range of interesting possibilities for chemical sensing, synthesis and imaging.

“We can use helical light to create nanostructures such as twisted needles, twisted reliefs and twisted fibers,” says Omatsu.

“We have also found that the same process can polymerize fullerene — a well-known functional organic molecule that is normally not conductive. This causes fullerene to form a novel conductive metallic phase, which could be used as the basis for fabricating electronic devices without metals and semiconductors.”

Omatsu believes ‘nanovortices’ will one day be used for nanoscale precision control of light polarization, electron orbital motion and the aggregation of chiral molecules. “Our research will lead to materials for next-generation photonics and electronics, and new applications in chemical synthesis, pharmacy, biology and medicine,” he says. “It might also allow us one day to answer the scientific mystery: ‘Why does handedness exist in nature?’” Omatsu has collaborated with many Japanese and international researchers, and is always looking for students and early career researchers. “Our research center brings together physicists, chemists, biologists and even medical doctors, and we frequently have brainstorming meetings to think up ideas for new projects,” he says. “Several international researchers work here. There is a wonderful diversity of backgrounds and expertise.”

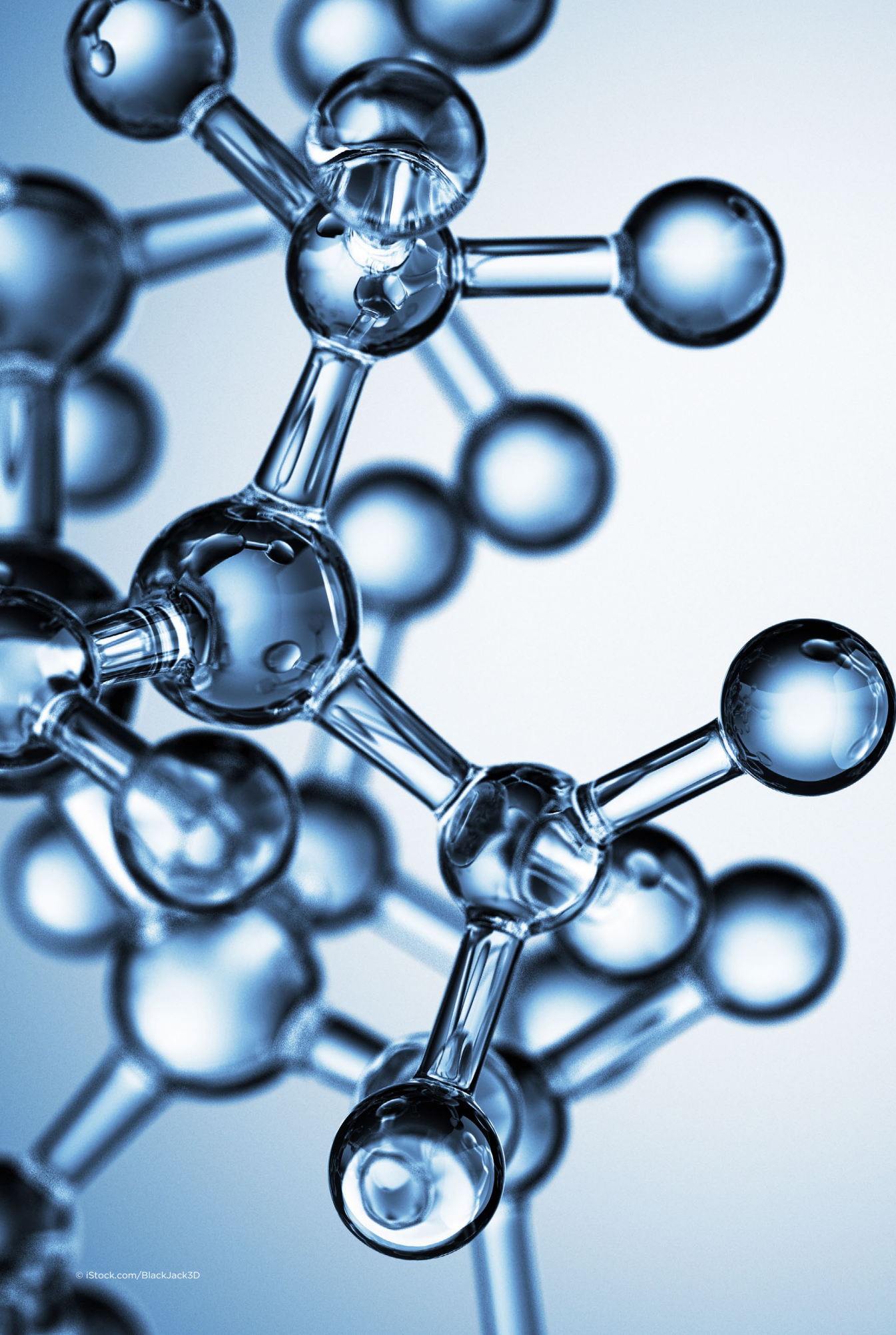
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Medical and Pharmaceutical Sciences

PHYTOCHEMICAL PLANT MOLECULAR SCIENCES

Unlocking the Potential of Phytochemicals

CANCER EPIGENOME CENTER

A Different Approach to Fighting Cancer

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Drug Delivery Systems

PHYTOCHEMICAL PLANT MOLECULAR SCIENCES

UNLOCKING THE POTENTIAL OF PHYTOCHEMICALS

Research Keywords: Plant Molecular Science, Phytochemical, Gene

—Advanced genetic and genomic techniques are transforming our understanding of how phytochemicals can improve human health.



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Since ancient times, people have used the natural compounds in plants, known as phytochemicals, for medicinal and nutritional use. Now, scientists at Chiba University are using advanced genetic and genomic techniques to verify how phytochemicals are generated in plants, how they can be manipulated to optimize certain plant groups, and how they may help tackle lifestyle- and aging-related diseases. Plants naturally generate chemicals for various purposes, including for attracting pollinators and defending themselves. These specialized metabolites allow plants to colonize specific niches in the food chain, adapt to new environments and evolve to survive potential stressors. Crucially, phytochemicals also exhibit properties that can help treat human diseases. Examples in modern medicine include morphine, the antimalarial drug artemisinin and chemotherapy agents derived from taxanes.

ENLISTING PHYTOCHEMICALS TO FIGHT DISEASE

Kazuki Saito, who leads the Phytochemical Plant Molecular Sciences program, says that because phytochemicals display considerable natural diversity, they have huge potential to fight disease. “Although phytochemicals have been used in pharmaceuticals and ancient remedies for many years, it is only now, with the advent of next-generation DNA sequencing, that we can really begin to understand how they work and unlock their full potential,” says Saito. The program consists of three collaborative research groups, each working on a specific theme.

One group is focusing on the genomics of medicinal plants and food crops with the key aim of revealing the genomic principles of phytochemical production. Employing state-of-the-art technologies, the researchers identify and clarify the roles of unknown genes, as well as investigate plant metabolism. In 2016, Saito’s team assembled a draft genome for licorice (*Glycyrrhiza uralensis*), which is used worldwide as a natural sweetener and a medicinal component. They identified several components known to play a positive role in human health within the plant, while pinpointing key genes, the manipulation of which could lead to crop improvements.

The second team is identifying novel phytochemicals and active products in a wide variety of plants, searching for drug components to tackle diseases such as cancer, dementia and diabetes. As well as isolating and analyzing promising molecules, the

group conducts animal trials to assess the pharmaceutical potential of molecules. In particular, they have extensively investigated Lycopodium alkaloids (LAs), molecules found in the vascular plant Lycopodiaceae, which may help to treat Alzheimer’s disease and schizophrenia.

The third group is investigating how plants respond to different environmental stresses by growing plants in different artificial environments and monitoring their responses to change.

“Our aim is to optimize plants so that they produce high-quality phytochemicals that we can harvest for use in medicines and functional foods,” explains Saito. “Our insights will enable us to grow rare plants more successfully and will also inform agricultural practices for commercial crops in the future.” While the group is focusing on phytochemicals, it also conducts wide-ranging interdisciplinary studies and hence welcomes researchers and students with backgrounds in chemistry, horticulture, genetics and pharmacy who are interested in this exciting and rapidly developing area of research.

CANCER EPIGENOME CENTER

A DIFFERENT APPROACH TO FIGHTING CANCER

Research Keywords: Cancer, Epigenome, Inhibitor

—A new center aims to combat cancer by rewriting the epigenetic modifications harbored by tumor cells.

Cancer is thought of as a genetic disease, with mutations to a cell’s DNA causing a normal cell to give birth to a malignant tumor. Yet epigenetic alterations, which leave the DNA sequence intact, can be just as important in a cell’s transformation to cancer. Even though epigenetic regulation through mechanisms such as methyl tags and histone modifications does not alter the DNA sequence, it can chemically modify the genome to signal which genes should be turned on and off. When tumor-suppressor genes are silenced or oncogenes are activated in this way, many different forms of cancer can result.

Fortunately for medicine, epigenetic alterations are not permanent. They can be undone to prevent or reverse cancer, leaving a cell with its entire complement of normal DNA intact.

This is exactly what researchers at the Cancer Epigenome Center are striving to do. Led by Atsushi Kaneda, the center is seeking to understand the various epigenetic drivers that contribute to different types of cancer and then develop new drugs that overturn these effects.

“We will explain key epigenomic aberrations and their molecular causes,” says Kaneda. “And then, taking advantage of small molecules that bind to DNA in a sequence-specific manner, we will develop drugs that can rewrite the accumulated epigenomic aberrations or prevent them accumulating in targeted genomic regions.”

UNRAVELING MOLECULAR MECHANISMS

Kaneda points to ongoing investigations of gastric cancer as an example of this strategy in action. Patients with this cancer exhibit different levels of DNA methylation in their tumor cells, depending on the pathogen responsible for the disease. The cancer-causing bacterium *Helicobacter pylori* is one source of irregular methylation, infection with Epstein Barr virus is another. Both seem to have profound epigenetic impacts on stomach cells, leading to the silencing of many tumor suppressors.

Kaneda and his colleagues are using clinical samples and cell experiments to unravel the molecular mechanisms that induce hyperactive methylation patterns following infection with these pathogenic agents. They ultimately hope to stop the process in its tracks. Similar projects are ongoing to combat colorectal cancers — which Chiba researchers have shown can be categorized into three types, depending on methylation levels — as well as blood cancers and other types of tumor. With an eye to developing novel therapeutics, chemists at the Cancer Epigenome Center are working on new methods to efficiently synthesize molecules that can act on epigenetic aberrations. One such group of molecules is the pyrroleimidazole polyamides. These molecules can bind to DNA at specific sites in the genome, and when coupled to an epigenetic inhibitor they can prevent methylation-based gene silencing. Kaneda hopes to deploy the molecules to edit the epigenome at targeted regions to regulate tumor formation.

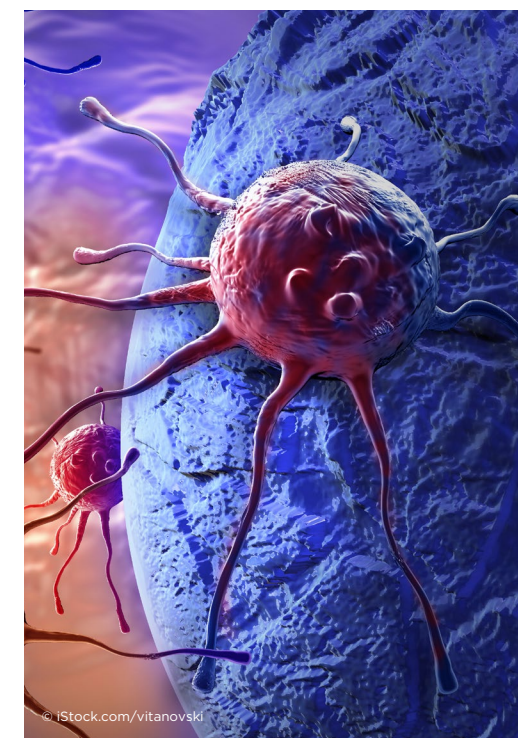
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The Cancer Epigenome Center includes researchers from a wide range of backgrounds and specialties. This multidisciplinary team approach, says Kaneda, is essential for turning the center’s discoveries into clinically meaningful treatments and diagnostic tools. “We will help determine the mechanisms of cancers and develop new cancer drugs through collaborating with experts in medicine, physics and pharmacy,” he says.



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INTEGRATED RESEARCH CENTER ON
REGENERATIVE SYSTEMS AND DISEASES

STEEPED IN STEM CELLS

Research Keywords: Hematopoietic Stem Cells, iPS Cells, Platelets

—New cell therapies, drugs and disease insights should flow from a coordinated approach to stem cell research.

Stem cells have the remarkable capacity to both self-renew and give rise to many types of more specialized cells in the body, which explains their great therapeutic potential in regenerative medicine. But that is not the only reason stem cells have become such a hotbed of scientific inquiry — these cellular transformers are also an invaluable research tool for probing the disease mechanisms that underpin cancer, aging and a host of other health problems.

At the Integrated Research Center on Regenerative Systems and Diseases, Chiba University scientists are advancing both these avenues of stem cell research. Some researchers are focused on developing new kinds of therapies based on stem cells, while others are gaining important insights into disease biology. However, they all share the common goal of improving the lives of patients using stem cells as their tool. The center, which opened in 2016, is divided into three main research groups. The first is dedicated to using stem

cells found in the blood and brain to better understand disease and normal development; the second focuses on reprogramming tissue biopsies taken from patients to make disease-specific stem cells for drug screening; and the third is developing stem cell therapies for treating diabetes, heart disease and other disorders.

Center director, Atsushi Iwama, says their work covers a wide spectrum, from basic to clinical research. Yet despite different researchers adopting different approaches, they all work in a collaborative manner, holding regular group meetings and retreats where new data are discussed and new alliances forged.

COLLABORATIVE PARTNERSHIPS AROUND THE WORLD

The Integrated Research Center is also looking further afield to create a cross-disciplinary research network that spans the globe. It has already formed partnerships

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with other leading stem cell research groups in Japan, Singapore and the United States, and it hopes to build more international connections in the future.

One of those partnerships is with Kyoto University's Center for iPS Cell Research and Application, where Koji Eto has worked for years developing a protocol for making platelets from reprogrammed stem cells. Last year, Chiba University recruited Eto to join its new center. And while Eto will maintain a lab in Kyoto, where he plans to run the first human trial of platelets derived from stem cells, he hopes to expand the study to include patients needing transfusions at Chiba University Hospital. Other notable members of the Integrated Research Center on Regenerative Systems and Diseases include Koutaro Yokote, a leading expert on a form of progeria known as Werner syndrome, and Chiaki Nakaseko, a world leader on a rare plasma cell disorder called POEMS syndrome.

Yokote is making stem cells from patients with Werner syndrome to better understand the disease and find new drugs, while Nakaseko is focused on developing new kinds of transplantation therapies from stem cells derived from bone marrow. These and many other world-renowned investigators make the new Chiba center an ideal place to work and train the next generation of scientists. "We hope to recruit many young people interested in stem cell research and clinical translation," Iwama says.

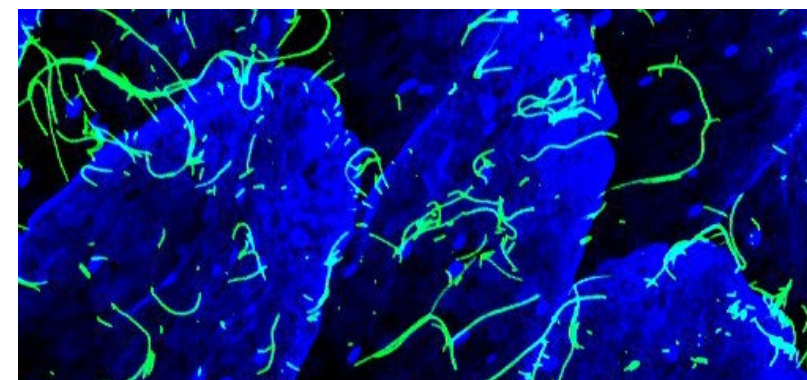
¹⁾ Prof. Iwama has moved from Chiba University on October 1st, 2018.

MEDICAL MYCOLOGY RESEARCH CENTER

MANIPULATING MICROBES FOR HUMAN HEALTH

Research Keywords: Infection and Immunity, Microbiota, Superorganism

—Detailed investigations of host–microbe interactions could yield new therapies against infectious agents and autoimmune diseases.



The human body is made up of a staggering 30 trillion cells or so. But just as numerous, if not more so, are the several hundred trillions of microbial co-inhabitants that team in and on us. These commensal bacteria and fungi are essential to our well-being, and a distortion in the microbial balance can trigger a wide range of disorders, from acne to obesity. Only recently, however, have scientists come to appreciate just how critical this collection of microbiota is for determining human health and disease. They are also becoming excited about the prospect of how manipulating this microbial ecosystem could form the basis for the next generation of life-saving therapeutics. Led by Mitsutoshi Yoneyama, researchers at the Medical Mycology Research Center have launched a comprehensive research effort to dissect the intricacies of host–microbe interactions in the skin, lung, intestines and bone marrow. "Dysregulation of host–microbe interactions can give rise to a wide variety of human disorders, including opportunistic infections, allergies and autoimmune disease," explains

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studying molecular interactions in different host–microbial systems. One, led by Shinobu Saijo and Yuumi Nakamura-Matsuoka, is focused on fungal infections in the skin of mice and humans; another, led by Koichi Hirose and Tomohiro Tamachi, is investigating the microbes — both good and bad — that reside in the respiratory tract. A third group, which includes Yoshiyuki Goto, is concentrating on the gut microbiome and how opportunistic intestinal infections gain a foothold; while the fourth, led by Akiko Takaya, is working on more basic mechanisms of immunological memory in response to microbial invaders. "Results obtained from our projects will help efforts to create innovative new therapeutics against infectious diseases and will eventually lead to improvements in human health," says Yoneyama, whose own research focuses on the mechanisms of innate antiviral immunity. To assist all these research projects, investigators from each group have access to the Japanese government's network of core facilities — a resource known as the Joint Usage/Research Center, which is staffed by specialized researchers and technicians who can run state-of-the-art experiments, including with fungi and other microbes. A bioinformatics unit at Chiba led by Hiroki Takahashi helps with computational analyses.

Yoneyama. "It is hence crucial to understand how hosts and commensal microbes communicate as a superorganism."

Creating a superorganism is an apt metaphor for what Yoneyama is trying to achieve because, through the melding of minds from across Chiba and around the world, the center can make a far greater impact than any individual scientist working independently. At Chiba University, the investigators come from the Graduate School of Medicine and the Graduate School of Pharmaceutical Sciences, while external collaborators are based in the United States, Germany and elsewhere in Japan. These scholars, together with others from around the world, convene each November at the Medical Mycology Research Center for the annual Global Network Forum on Infection and Immunity.

EXPLORING HOST–MICROBE INTERACTIONS

The team that Yoneyama has put together is roughly divided into four groups, each

MEDICINE FOR IMMUNE RELATED RARE DISEASES

INNOVATIVE APPROACH OFFERS HOPE FOR INTRACTABLE PROBLEMS

Research Keywords: Rare Disease, Intractable Cancer, iPSC Cell

—The ReDenim network is developing therapies to treat rare and intractable diseases.



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Scientists at Chiba University have a long track record of excellence in clinical research, particularly for investigations in patients with immune-related diseases. And Chiba University researchers have made a number of important breakthroughs in basic immunology and disease biology. However, connecting these two areas, a field known as translational research, has often been less successful.

That is a problem that Shinichiro Motohashi wants to fix. Motohashi leads Chiba's Research and Development Network of Innovative Medicine for Immune Related Rare and Intractable Diseases — ReDenim. The network is aiming to provide the clinical support and resources needed to take discoveries from the lab to the clinic. In particular, ReDenim has singled out two disease areas for which there are currently no good treatment options — deadly forms of cancer, such as head and neck tumors; and rare diseases that each afflict fewer than 50,000 people in Japan, but collectively affect about 10 percent of the population.

TWO-PRONGED APPROACH

Motohashi and Daiju Sakurai belong to the tumor immunity team, which intends to capitalize on Chiba University's expertise in developing cell-based immunotherapies. Their approach uses tumor-destroying natural killer T-cells to search for combination therapies that can further modulate the tumor immune microenvironment in a favorable way. They also intend to identify biomarkers that can predict how individual patients will respond to these treatments. Led by Sonoko Misawa, the rare-disease team, including Masayuki Kuroda, Kotaro Suzuki and Kiyoshi Hirahara, is using immunomodulating drugs and gene therapies to address neurological syndromes, enzyme deficiencies, inflammatory conditions and recalcitrant fungal infections. Kuroda is also working with the cancer team to develop a transgenic fat cell technology that has therapeutic applications for both tumors and the rare metabolism disorders he is studying. Importantly, both teams will share research experiences, technology platforms and manufacturing facilities. "Sharing the know-how to treat each disease within the network will accelerate drug development," says Motohashi. And the two teams will also have access to support units at the university's Core Clinical Research Hospital, a designation granted to Chiba University under Japan's Medical Care Act in recognition of its ability to apply basic science toward therapeutic applications.

This support includes consultation services on issues such as intellectual property, project management, clinical trial design

and other steps needed to fulfill the promise of translational medicine. "Our ultimate goal is to form a therapeutic cluster that can be applied to a wide variety of rare and intractable diseases," Motohashi says. He can even foresee a day when the infrastructure created through ReDenim could be used to develop new therapies for common diseases, such as diabetes or lung cancer.

Judging by the progress they have made so far, Motohashi and his coworkers are well on their way to fulfilling their dream, and their potential is widely recognized. ReDenim has already forged collaborations with some of the world's leading experts in cancer immunotherapy and rare diseases, and is working with Japanese drug companies to partner on additional research projects.

CENTER OF EXCELLENCE FOR END OF LIFE CARE

PUTTING THE CARE BACK INTO END-OF-LIFE CARE

Research Keywords: Clinical Nursing Science, End of life care, Super-aged Death-ridden Era

—A new research program recognizes that care for the dying is an important issue for both public and professionals alike in a rapidly aging society like Japan.

Japan is teetering on the precipice of a demographic crisis. Already, people over the age of 65 make up more than one quarter of the country's population. And the fraction of elderly people is only expected to rise in the years ahead — it is predicted that in 2060 two out of every five people in Japan will be senior citizens, putting huge logistical and financial strains on the country's long-term care systems. The Center of Excellence for End of Life Care is trying to ease the impact of this skewed demographic by fostering cooperation between the public and the professionals who assist the elderly. The goal, says Center Director Mariko Masujima, is to develop a coordinated research strategy that ensures all older Japanese people can live out their final years in a comfortable and dignified manner with their wishes and aims fulfilled.

"We have to encourage people in our society to talk more openly about their own end-of-life care," she says. Only then will those facing imminent or distant death have the best quality of life in the time they have left — regardless of diagnosis, health condition or age.

The new center is housed within the Chiba Graduate School of Nursing, the oldest school of its kind in the country. It includes members from a wide range of interdisciplinary backgrounds, such as ethicists, engineers, health economists and doctors. These scientists are working together in four large research groups.

PREPARING FOR LATER LIFE

The first group is focusing on helping the elderly prepare for what lies ahead. In one project, they have developed a web-based education tool, which uses a range of animated scenarios to make users think about common end-of-life problems, such as a health emergency or the loss of cognitive functions. A prototype of the tool received favorable reviews in a small feasibility study and the team is now adding new features and functionality to make it more user-friendly.

A second group at the new Center of Excellence is developing a technological surveillance system that deploys remote sensors to detect physical activity among older residents in long-term care facilities. "By tracking changes of vital signs and physical activity in the elderly, the sensors serve as a tool both for research and for end-of-life care," explains Masujima. "They can help nurses and care workers pick up on discomfort that frail, older residents might not be able to express themselves." The system will soon be deployed for pilot testing.

The third research group is focusing on global outreach and has already established links with researchers in Thailand, Taiwan, South Korea, Northern Ireland and elsewhere in Japan, while the fourth group is developing educational materials — for both the public and for other healthcare professionals.

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"Students need a chance to think more about end-of-life issues," Masujima says. "Unfortunately, our healthcare education focuses almost entirely on treating the living, but we also need to care for the dying." The new center hopes to make that a priority in the face of such a rapidly aging society.



GLYCOMEDICINE RESEARCH CENTER

SUGAR SCIENCE'S IMMUNOTHERAPY PLAY

Research Keywords: Immunology, Biochemistry, Glycobiology

—By bridging the gap between glycoscience and medicine, major advances in immunology and drug development are imminent.

Lymphocytes are the body's warrior cells. They circulate through the bloodstream and arrive at sites in the body such as the spleen and lymph nodes, where they combat harmful bacteria, viruses and even cancer cells. Sugars, or glycans, are integral to this migratory process called lymphocyte homing, which is of intense interest to researchers. These scientists hope to target glycans to find new immunotherapies and drugs for autoimmune diseases.

"We now know that glycans — chains of sugar molecules that have diverse functions in our bodies — play an essential role in lymphocyte homing," says Hiroto Kawashima, a professor at Chiba University's Graduate School of Pharmaceutical Sciences, Laboratory of Microbiology and Immunology.

"These glycans are found on the surface of endothelial cells in lymph nodes," he explains. "Thanks to glycans, lymphocytes recognize and bind to the surface of those cells." Lymph nodes activate lymphocytes to fight disease.

In a study published in *Nature Immunology* in 2005, Kawashima and his colleagues in Japan and the United States showed that

glycans produced by two enzymes — N-acetylglucosamine-6-O-sulfotransferase 1 (GlcNAc6ST-1) and GlcNAc6ST-2 — are essential for the binding of lymphocytes, and consequently play a vital role in controlling lymphocyte homing in mice. After working on this study at California's Burnham Institute, Kawashima returned to Japan in 2005, bringing with him the 'knockout' mice (deficient in the two key enzymes) he had developed. At Chiba he has used these to continue hunting for new antibodies that target glycans.

GLYCOMEDICINE TAKES OFF

Today, the expanding fields of glycoscience (the study of glycans) and glycomedicine (combining glycoscience and medicine) are leading to breakthroughs in drug development and diagnostics for autoimmune diseases.

Chiba University's Glycomedicine Research Center, which opened in August 2017, marks a shift towards accelerating such breakthroughs in Japan.

"Many researchers here at Chiba University have been working independently on

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glycans," Kawashima says. "Some specialize in biological functions, while others focus on synthesis or analyze glycan structures. The idea is to bring all of these researchers together, build new collaborations and understand the function of glycans across many biological phenomena."

The new centre has plans to collaborate with teams both nationally, for example, at the Glycomedicine Technology Research Center and the National Institute of Advanced Industrial Science and Technology (AIST), and internationally.

Already, Kawashima has developed antibodies that will specifically bind to the building blocks of glycans and disable them in studies published in *The Journal of Biological Chemistry* in 2010 and 2015. This could halt the dysfunctions involved in autoimmune disease, in which the immune system is overreacting.

"Usually, it's very difficult to generate monoclonal antibodies against carbohydrates," says Kawashima. This difficulty in producing clones of these antibodies is because carbohydrate antigens are not generally very antigenic. "To get around this problem, we immunized knockout mice with cells expressing the missing sugar chains, which are highly prone to stimulating the production of antibodies." The next step will be to further investigate and identify new ideas for drug development and to collaborate with pharmaceutical companies to bring them to market.

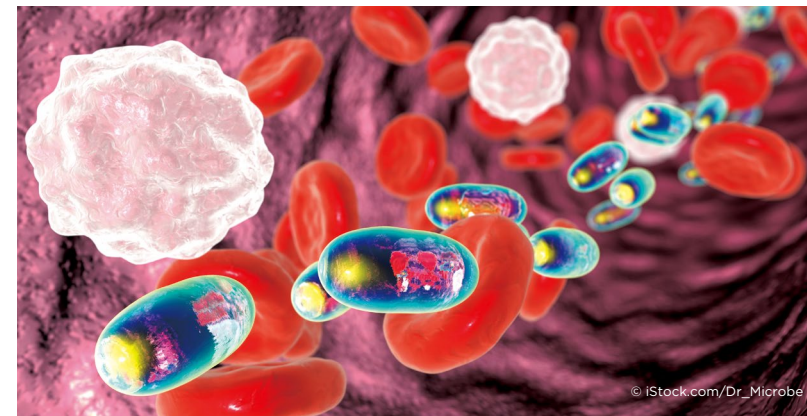
"Right now, there are lots of antibody drugs," says Kawashima. These immunotherapies target issues such as rheumatoid arthritis and cancer, but, he says, new advances are limited by a shortage of molecules to target. "Glycans have unexplored potential, so this is an exciting time to be looking into developing new candidate drugs based on glycoscience."

LABORATORY OF DDS DESIGN AND DRUG DISPOSITION

BIG HOPES FOR NANOTECHNOLOGY BASED DRUG DELIVERY SYSTEMS

Research Keywords: Drug Delivery, Nanobio, Vaccine

—Drug delivery systems that nanocarriers could enhance the effectiveness of therapies ranging from genetics-based cancer treatments Alzheimer's medicines.



Drug delivery systems that nanocarriers could enhance the effectiveness of therapies ranging from genetics-based cancer treatments to Alzheimer's medicines.

Personalised medicine — tailoring medical treatments to individual needs — may no longer be far-off.

Developments in nanocarriers have progressed rapidly, promising targeted delivery and release of nucleic acid-based drugs (NABDs), an emerging class of therapeutics designed to target diseases at the genetic level.

A BREAKTHROUGH MOLECULE

In 2013, Akita's group reported on SS-cleavable Proton-Activated Lipid-like Material (ssPalm), a molecule designed and tested over five years that showed promise for drug delivery.

The molecule itself consists of two main components: One, tertiary amines, are activated in response to an acidic environment, such as the endosome compartment inside the cells of plants and animals. These activat-

ed amines enable membrane destabilisation. The other, a disulfide bond (SS) that can be cleaved in a reducing environment such as in the cytoplasmic material inside cells, triggers the release of NABDs in specific cells.

In proof-of-concept studies in mice in 2016, the researchers showed that lipid-based nanoparticles, formed using ssPalm, enabled efficient delivery to the liver of a genetic treatment that uses small interfering RNA. They have since gone on to develop second-generation ssPalm, which uses Vitamin E as a waterproofing scaffold (ssPalmE). One of the biggest challenges for cancer therapeutics researchers, Akita explains, will be "to develop DNA- and RNA-based vaccines that could target unique genetic changes in individual cancers." The hope is that the versatility of ssPalm could help maximise drug efficacy while reducing side effects. For example, in mouse studies performed in 2018, Akita's group demonstrated that a plasmid DNA-encapsulating lipid nanoparticle (ssPalmE-LNP) induced anti-tumour effects. They

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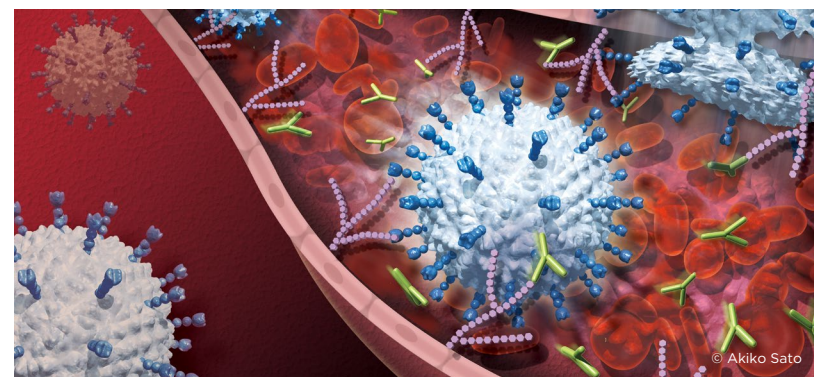
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Humanities and Social Sciences

CHIBA STUDIES ON GLOBAL FAIR SOCIETY

Forging a Fairer World

**SMALL AREA ESTIMATION AND
ITS APPLICATION**

Improving Datasets Using
Small Area Estimation

**MULTI-PERSPECTIVE UNDERSTANDING
COGNITIVE BEHAVIOUR GROUP**

Predicting Human Behaviour

**TRANSLATIONAL RESEARCH PROGRAM
OF PSYCHIATRY AND PSYCHOLOGY**

Cognitive Behavioural Therapy
Comes of Age in Japan

CHIBA STUDIES ON GLOBAL FAIR SOCIETY

FORGING A FAIRER WORLD

Research Keywords: Global Welfare Society, Multidisciplinary Social Science, Fairness

—A multidisciplinary team of researchers looks at how to create a fair society — on a global scale.



With globalization comes the need to ensure that people from all cultures, countries and backgrounds are treated fairly and equally. The drive to create a just global society requires solid foundations in all countries, backed by informed government policies and strong support networks at local, regional and national levels. Much previous research into justice and social change has been dominated by studies of Western societies, but the rapid changes experienced by Asian countries in recent decades have spawned a growing field of research focused on building fair societies in Asia.

Researchers in law, politics, economics and social sciences have recently established the Chiba Studies on Global Fair Society project, with the aim of creating an interdisciplinary research base to inform future local, national and international policies. Lead researcher on the project, Jiro Mizushima, says the key concept is fairness. “We define fairness as the basic element of justice,” he explains. “In fact, we argue that it exceeds justice in most cases. At the same time, we embrace values such as equality and liberty.”

Mizushima, whose research interests lie in welfare state reform in Europe, says the project aims to go beyond the traditional discussion of equality — it seeks to construct new principles that value diversity among people in a global society.

HOW DO WE ACHIEVE A FAIR SOCIETY?

The project consists of four interrelated research groups and a further six teams working to publicize the findings to a wide audience. Their focus is on challenging and overcoming unfair practices on all scales, investigating issues such as gender inequality, widening income gaps, migration, and the collapse of regional and marginal communities, both in Japan and around the world. The key aims of the project are to investigate the development, transformation and limitations of existing welfare state models and to provide empirical evidence for how a fair society can be achieved in the 21st century. Mizushima has spent considerable time researching aspects of the welfare state in the Netherlands, including how it has responded to social challenges such as global economic fluctuations and an aging population. “Fairness has been the core of legal and political philosophy since ancient times, and so another of our teams is examining equality and fairness from a historical perspective, comparing political, economic and legal standpoints over time,” he says. “Another group will analyze the meaning of fairness in the 21st century, providing us with fundamental guidelines to underpin our program.” The team plans to form networks of academics across the globe. To this end, they have hosted five highly successful international symposiums. “Many of our members are involved in local and national policymaking committees, and they are key to informing policy makers of our work,” says Mizushima.

The project welcomes those interested in all aspects of social science, from law and politics to sociology and economics. Students and researchers alike will receive training from scholars in their own field and other program members, allowing them to broaden their research interests.

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SMALL AREA ESTIMATION AND ITS APPLICATION

IMPROVING DATASETS USING SMALL AREA ESTIMATION

Research Keywords: Economic Statistics, Bayesian Statistics, Small Area Estimation

—Statistical techniques can improve the accuracy and scope of limited information, saving time and money.

Collecting comprehensive data on populations is not always possible, or even the best use of resources. Surveys can be expensive and time-consuming, so improving the accuracy of data with “small area problems” can stretch data resources further. “Small area problems happen when an estimator, such as sample mean for a small area, becomes very unstable because of small sample sizes,” explains Associate Professor Genya Kobayashi, who is part of a new Chiba project called Small Area Estimation and Its Application to the Analyses of Poverty, Public Health and Disaster. His group is focused on overcoming such issues by developing small area estimation (SAE) techniques that borrow statistical strength from supplementary data.

OVERCOMING INEQUITY AND PUBLIC HEALTH INSIGHTS

While the applications of SAE are broad, “small area problems arise particularly within official statistics on which governments make important political decisions. Hence, small area estimation techniques could lead to more effective policy making,” notes Kobayashi. An example crops up in the monthly Family Income and Expenditure Survey (FIES) conducted by Japan’s Statistics Bureau. Although FIES provides the latest information on household income and expenditure, at a small area level, such as a city level, the sample size of FIES becomes so small that direct estimators are unstable and can’t grasp detailed trends. But FIES, says Kobayashi, can borrow statistical strength from data in the National

Survey of Family Income and Expenditure (NSFIE). The sample sizes in the NSFIE are much larger than in the FIES and thus more reliable, but because the survey is time consuming and costly, it’s only carried out every five years. The FIES and the NSFIE collect area-level aggregated data, so Kobayashi’s group used the Fay-Herriot, a mixed regression model routinely used in SAE. However, when data is in other formats more appropriate SAE models must be developed. Recently, for example, Kobayashi’s group has been working to improve an income map of Japan based on the Statistic Bureau’s Housing and Land Survey (HLS). Using a new statistical model that accounts for the grouped data format of the HLS and additional data from the Population Census, they measurably reduced the uncertainty of the HLS’s income estimates. SAE’s scope isn’t limited to stabilizing data, adds Kobayashi. SAE techniques can add information. For example, the HLS model could also infer income in areas where data is missing. Using a mixture modeling approach, the team recently estimated the distribution of land prices around train stations in and around Tokyo by making inferences across areas. Contributing to public health discussions, in 2018 Kobayashi collaborated on a paper that used a spatial Poisson regression model to look the links between access to clean water and dropping mortality rates in the early 1900s. Kobayashi and collaborators at the Tokyo Institute of Technology and Duke University in the United States looked at death rates in Tokyo in 1930 against a

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dataset of taps. The group found that access to clean water accounted for 41.3 percent of the improvement in Tokyo’s crude death rate between 1921 and 1937. This paper adds to discussions on the relative importance of nutrition and clean water on mortality. Kobayashi hopes that everyone from policy makers to businesses will soon come to the group to add a finer resolution to their datasets.



MULTI-PERSPECTIVE UNDERSTANDING COGNITIVE BEHAVIOUR GROUP

PREDICTING HUMAN BEHAVIOUR

Research Keywords: Experimental Psychology, Cognitive Science, Data Mining

—Understanding the mind's influence on what we perceive may help researchers model human behaviour to create better smart devices.

As computers become more powerful, nuanced modelling of human decisions is becoming possible. At the same time, new technologies are also bringing fresh tools and disciplines to researchers at Chiba University studying the hidden relationships between behaviour and phenomena, ranging from the physiological to the physical. “With the help of environmental engineers and using deep learning and virtual reality techniques we can expect big developments in the cognitive sciences,” says Professor Makoto Ichikawa, part a diverse group known as the Multiperspective Understanding of Cognitive Behaviour (MUCB) Group.

Ichikawa and his colleagues have been examining the reactions of individuals during a digitally created fire event in a virtual reality environment. While psychologists often use methods such as questionnaires to understand reactions and decisions, Ichikawa's colleagues are also able to use virtual reality scenarios to study biological parameters – such as blood pressure, heart rate and pupil dilation – in real-time. At the same time, they can also record reactions

related to changes in room temperature and humidity. Virtual reality, says Ichikawa, can reveal the effects of situational elements such as illumination, luminance, noise and space on physiological reactions, ranging from metabolism to circadian rhythm. These developments, he says, are not only exciting to psychologists, but will also provide the basis for creating more believable digital worlds. Ichikawa's work is being complemented by mathematicians, such as findings published in 2016 by Chiba University computer scientists. In their paper, they proposed a new method for predicting pedestrian dynamics. Using a technique from geostatistics called ‘kriging’ the researchers were able to predict trajectories up to 10 steps ahead more than 80 per cent of the time. This, they say, could lead to exciting developments in navigation, group-behaviour analysis and abnormal-behaviour detection.

THE COMMON FATE INFLUENCE

To accurately model human behaviour, it's also important to also understand the mind's

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effect on perception. For example, while sitting in a stationary car, some may have felt like they have moved backwards if a neighbouring vehicle creeps forward. This sense of ‘induced motion’ is an optical illusion created in the mind.

In a recent paper published in the journal Perception, Ichikawa and his colleagues examined why one part of a visual illusion (concentric circles) appeared to be moving with or against another part of the illusion. They found that whether the parts of the image appeared to moved together or in opposition is linked to a person's thoughts on the connection between the parts.

In some configurations, the two parts appeared to be moving in opposite directions. As in the car example, if one object appears to be accelerating away from another, the stationary or slower parts may seem to be moving in the opposite direction.

However, a recognition of a common fate, which is an appreciation for the linked nature of the parts, may encourage participants to see the elements move together. The researchers suggest this stems from a principle from the German Gestalt school of psychology that seeks to explain how our brains create order in the world.

The common fate principle suggests that because logical patterns tend to take precedence over individual elements in how we see the world, a flock of birds, for example, may seem to be moving as one.

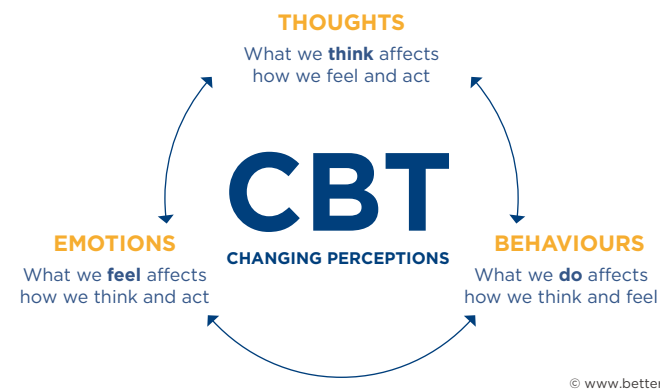
All of these findings, Ichikawa says, will have important ramifications for how we display motion, and group and individual dynamics, on digital devices, in cinematography and in virtual reality.

TRANSLATIONAL RESEARCH PROGRAM OF PSYCHIATRY AND PSYCHOLOGY

COGNITIVE BEHAVIOURAL THERAPY COMES OF AGE IN JAPAN

Research Keywords: Psychiatry, Psychology, Cognitive Behavioral Therapy

—Better access to mental health care in schools, at work and online could help people of all age groups suffering from anxiety, depression and other related conditions.



Major efforts are underway to help treat and prevent anxiety-related disorders in Japan —where as many as one in four people experience mental health problems during their lifetime.

Social Anxiety Disorder (social phobia), one of the most prevalent, is characterised by an intense fear of social situations. In some cases, social phobia can lead to addiction, depression or suicidal behaviour. Many doctors, legislators and patients now recognise cognitive behavioural therapy (CBT) as an effective treatment for social phobia. By changing negative patterns of thinking and behavior, CBT can help children overcome anxiety and the fear of uncertainty, adolescents better manage depression and irritability, and adults deal with a host of stressful life experiences.

A LEADING CENTRE FOR CBT RESEARCH AND EDUCATION

We are now actively trying to increase the number of CBT experts in Japan,” says Eiji

Shimizu of Chiba University's Research Center for Child Mental Development and Chiba University Hospital's Cognitive Behavioral Therapy Center. “However, CBT resources in Japan are still relatively scarce.” Chiba University and its affiliated hospital are spearheading efforts to address this. The Chiba Improving Access to Psychological Therapies (Chiba-IAPT) program, adapted from a UK model, became the first post-qualification training course of its kind in 2010.

“It's important to tailor treatments to reflect not only cultural differences, but also personal differences,” Shimizu adds. His team are developing new tailored interventions, such as internet-based CBT (iCBT), which are low-cost, easy to use, and provide optional anonymity. In 2017, his group released a study protocol for iCBT on patients with persistent insomnia. They have also produced a simplified, five-minute program that can be used to help reduce depressive symptoms. As part of his wider research, Shimizu

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contributed to the first study that visualised changes in brain activity during psychotherapy in 2015. Using functional magnetic resonance imaging (fMRI), the results indicated that the left posterior parietal cortex plays a vital role in cognitive restructuring — a process used in CBT that enables people to challenge existing beliefs.

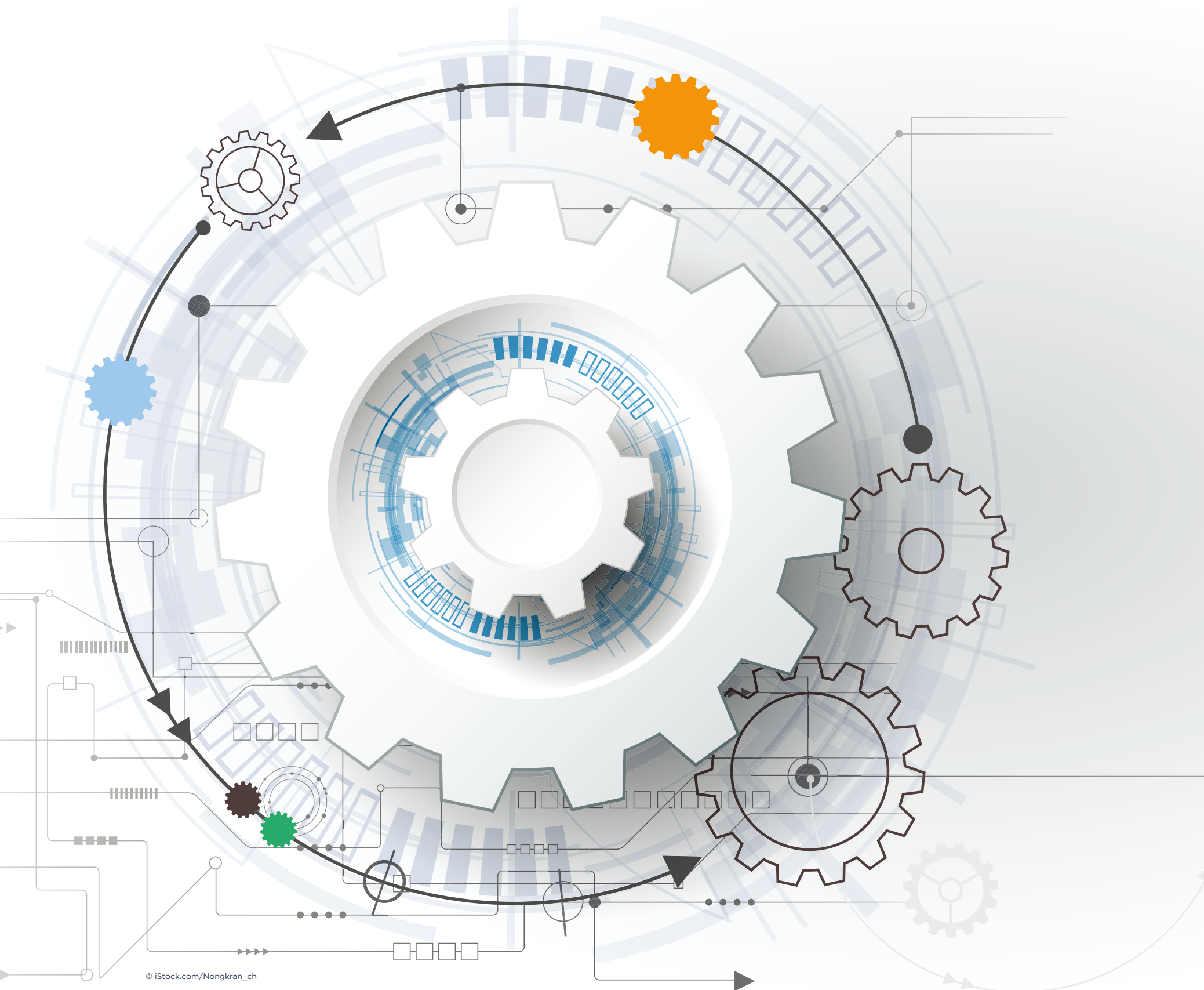
In 2016, Shimizu and his colleagues showed that CBT can help reduce social anxiety for patients ineffectively treated with antidepressants.

In recognition of the growing need for professional CBT care, at the end of 2018 the Japanese government began to certify licensed psychologists. The national health insurance system has been updated to cover doctor-administered CBT for patients with depressive disorders, anxiety disorders and bulimia nervosa.

There are also moves to introduce CBT-based anxiety prevention programs in Japanese elementary schools. A 2018 study, designed by Yuko Urao and supervised by Shimizu, examined the effectiveness of an anxiety prevention program named Journey of the Brave, targeted at children aged 10–12 years. Consisting of ten 45-minute sessions held during school hours, the program involved deepening understandings of anxiety, monitoring feelings, and developing assertiveness skills to reduce social stress.

While further follow-up studies are planned, preliminary results indicate that the program can help children manage their anxiety levels. “Our hope is that in ten years' time, all children in Japan will have access to this program,” Shimizu says.





Science and Engineering

NEXT-GENERATION THREE-DIMENSIONAL DISPLAY AND MEASUREMENT

Future Images —More than Meets the Eye

MULTIMODAL MEDICAL ENGINEERING

Toward Image-Based Disease Diagnostics

HIGH-EFFICIENCY ENERGY CONVERSION

Toward a Zero-Emission Society

CENTER FOR INNOVATIVE MICROWAVE REMOTE SENSING

The Next Wave in Remote Sensing

IMAGING SCIENCE AND TECHNOLOGY FOR MATERIAL APPEARANCE

Realness in Digital Images

INSECTS-INSPIRED BIG INNOVATION

Looking to Nature to Revolutionize Flight

SOFT MOLECULAR ACTIVATION FOR INTELLIGENT MATERIALS

Catalyzing the Future of Smart Materials

NEXT-GENERATION THREE-DIMENSIONAL DISPLAY AND MEASUREMENT

FUTURE IMAGES MORE THAN MEETS THE EYE

Research Keywords: Computer Holography, Volumetric Display, High Performance Computing

—Advances in three-dimensional image display and measurement techniques have applications in multiple fields, from medicine to communication and entertainment.

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Technologies based on three-dimensional (3D) image displays and holography may conjure up visions of science fiction, but the Next-generation Three-dimensional Display and Measurement program aims to make these advanced tools part of everyday life. Holograms create true three-dimensional images, which allow the viewer to see an object from all angles. They are created using coherent light sources such as lasers, which can store the complex light interference patterns required to accurately recreate an entire 3D object in full color. However, the main drawback of holography is the immense computational burden of producing high-quality holograms, not to mention creating moving 3D video images in real time.

Leader of the 3D program, Tomoyoshi Shimobaba says his team is developing ultrafast algorithms and dedicated computers for holography to create the world's first real-time holographic 3D display system.

"These dedicated computers will have a computational speed three or four orders of magnitude higher than the household computers of today," adds Tomoyoshi Ito, advisor on the project. "Based on this dedicated technology, we will investigate holographic projection, digital holographic microscopy and ultrarapid

holographic imaging techniques." Among the team's recent successes is a small, inexpensive, zoomable holographic projection system, suitable for use in classrooms, medical applications and entertainment products. Shimobaba's team refined mathematical image manipulation techniques to ensure a high-resolution, non-grainy holographic image even when zooming in and out. The researchers are further developing algorithms that can reduce 'speckle noise' in reconstructed images to avoid degradation in image quality.

ONE IMAGE, MULTIPLE VIEWS

Another aim is to reconstruct large 3D images with a large viewing angle — something that is difficult to realize using current technologies.

"We are also developing accurate holographic measurement systems, which will be invaluable in medical science because they allow researchers to image and measure samples in 3D alongside visualizing moving phenomena in real time," explains Shimobaba.

In another exciting field of research, the team is exploring a form of 3D image creation called volumetric displays — the difference being that, while holograms can only be seen clearly by a few people at a time, volumetric displays can be viewed by multiple people from different viewpoints. And, in an even more challenging concept, they are trying to create multi-viewpoint images with plural information appearing in specific directions. In other words, one person standing at one place will see one piece of information, while another standing

somewhere else will see completely different information.

"Our volumetric display simultaneously provides several observers with different information," explains Shimobaba. "This very exciting feature is quite new, and we are considering new applications for using it, such as developing multi-language signage for the Tokyo Olympics in 2020," he says. Such 3D displays may benefit from advanced aerial projection techniques, also under development by Shimobaba's team. "Networking is the key to our success," says Shimobaba. "Many students who have graduated from our laboratory move on to conduct research in academia or in private companies, and we continue to work with them. In this way, we expand our project and build fruitful working relationships across academia and industry."

MULTIMODAL MEDICAL ENGINEERING

TOWARD IMAGE-BASED DISEASE DIAGNOSTICS

Research Keywords: Medical Engineering, Physical Measurement, Multimodality

—Novel, high-precision imaging techniques are being used to provide non-invasive disease diagnosis and guide future treatments.

Non-invasive, precise diagnosis of diseases using advanced medical imaging technologies could one day replace traditional techniques based on biopsy and dissection. With this prospect in mind, researchers at the Multimodal Medical Engineering program are combining medical and engineering expertise to create novel, noninvasive imaging-based methods for diagnosing and treating disease.

The program uses various scanning techniques, or 'modalities', including computerized tomography, magnetic resonance imaging (MRI) and ultrasound, to analyze cellular and organ variations caused by different diseases.

The program's goal is to develop highly precise, non-invasive imaging methods, while boosting existing imaging techniques to improve resolution and enable more-detailed tissue analysis, says program leader Hideaki Haneishi.

"Many current disease diagnostics, particularly for cancer, involve highly invasive, unpleasant procedures to clarify the type and stage of the disease," explains Haneishi. "We are investigating, for example, the development of a system to diagnose breast cancer using very-high-frequency ultrasound." Rather than physically sampling and dissecting lymph nodes from potentially cancerous tissue, his team has shown that it is possible to analyse cell characteristics of lymph nodes using ultrasound. Their technique highlights metastasis positive and negative cells in lymph nodes, enabling rapid, painless diagnosis. Haneishi and his team are also devising ways to combine data from two or more modalities. For example, in 2016 they developed an image

registration method that transforms two data sets into one coordinated system using MRI and pathological images of brain tumors.

"If we can establish the technology for registering two kinds of images, then MRI features that are strongly related to the pathological features of tumors can be highlighted. This may eventually allow us to diagnose using only MRI," says Haneishi. "Determining the relationships between different data sets helps us build up detailed pictures of what is going on inside the body, not only for diagnosis but also to improve our understanding of disease development," he adds.

NOVEL OPTICAL PROBES

Alongside conventional imaging techniques, the researchers are also exploring novel optical probes. One example involves a method for monitoring microcirculation — the flow of red blood cells — in the body. The probe comprises multicolored light-emitting diodes (LEDs). As the LED light is scattered through the tissue, it is partly absorbed by molecules in the red blood cells, generating a clear, detailed picture of the cells and their microcirculatory network.

Building on previous work, the team hopes to use this probe to estimate features such as the oxygen saturation of each blood vessel in areas around suspected tumors in real time. This could aid diagnosis and further our understanding of vascular behavior in and around tumors. "Ultimately, we would like to build on these imaging techniques and use machine learning and artificial intelligence technologies to relate measured signals and diagnoses, to develop a comprehensive under-

Members

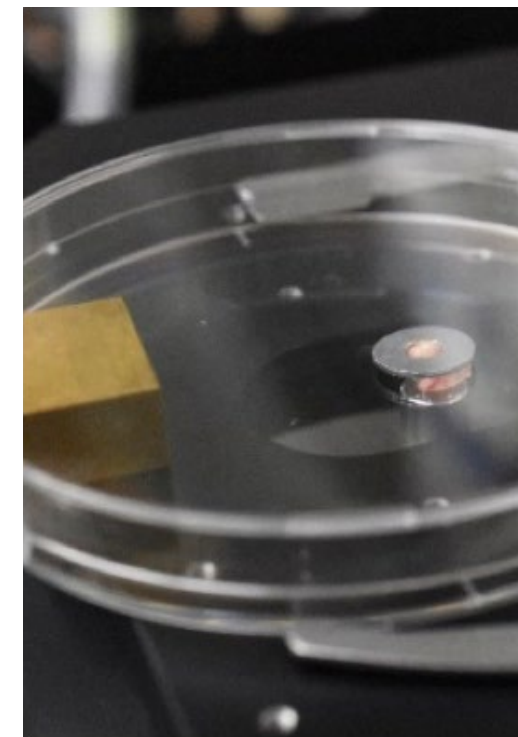
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Ryoichi NAKAMURA	Hiroki SUYARI

standing of different diseases," says Haneishi. The Multimodal Medical Engineering program has access to highly specialized equipment and technologies that can help realize researchers' ideas.

"We welcome engineers and medical researchers who wish to work at the cutting-edge of research and development with direct clinical applications," says Haneishi.



HIGH-EFFICIENCY ENERGY CONVERSION

TOWARD A
ZERO-EMISSION SOCIETY

Research Keywords: Fuel Cell, Photocatalyst for Water Splitting, Organic Nanoarchitecture

—*The future of clean energy production lies in perfecting the nanoscale details of fuel cell components to create an innovative carbon-neutral energy system.*

The race is on to find ways to replace our reliance on fossil fuels with clean, sustainable methods of generating power. Current solar and hydrogen technologies are not yet efficient enough to produce energy on a large scale. With this in mind, researchers from the High-Efficiency Energy Conversion program aim to improve current solar and hydrogen fuel cells, while finding ways to reduce the pollutants already in the environment. “We hope to develop efficient energy conversion systems that don’t emit carbon dioxide and pollutants,” says Nagahiro Hoshi, lead researcher on the program. “We will create a system that generates power fueled by sunlight and water. To do this, we must perfect the structures of the nanomaterials used to make solar and hydrogen fuel cells to optimize their ability to harness energy.” Hoshi’s team works with various nanostructures, including nanoparticles, single-crystal surfaces and organic nanoassemblies, to build devices that can capture as much energy as possible without wastage.

ENHANCING ENERGY CONVERSION

The surface structures of catalysts used in solar cells and hydrogen fuel cells can have a remarkable impact on conversion efficiency. For example, the orientation of atoms on a solar cell’s surface significantly affects the distribution of light across the cell. One way of enhancing a solar cell is to coat its surface with a dye. The dye’s atomic make-up contributes to the cell’s ability to generate electric current when exposed to light, providing it is adsorbed onto an appropriate surface. The researchers recently explored the effects of using a zinc porphyrin (ZnP) dye on single-crystal titanium dioxide (TiO₂) substrate surfaces. They trialed three different TiO₂ substrates and found that their surface structures significantly altered the ability of the ZnP dye to generate an electric current efficiently. In fact, one of the ZnP TiO₂ substrates had an incident photon-to-current conversion efficiency 13 times higher than one of the others.

Members

Nagahiro HOSHI

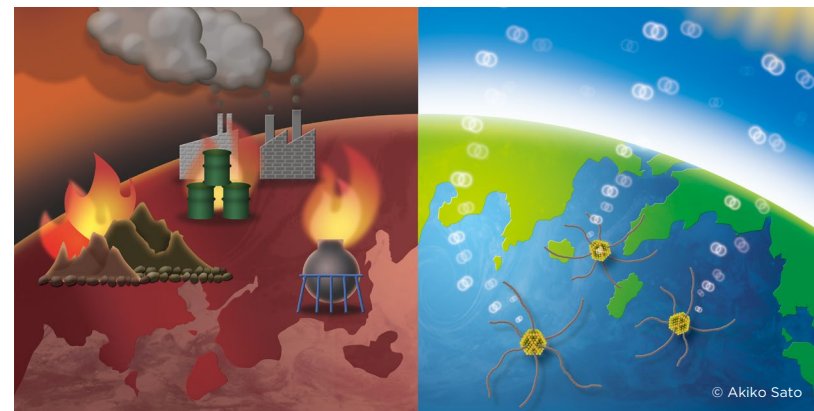
Professor, Graduate School of Engineering

Masashi NAKAMURA Yasuo IZUMI
Shiki YAGAI Takashi KOJIMA

Hoshi attributes the high conversion efficiency on this substrate to the bent configuration of the adsorbed porphyrin ring, which results in a shorter distance between the ring and surface. Such attention to detail in terms of nanoscale surface structures will generate the breakthroughs needed to create highly efficient, scalable and cost-effective solar power.

At present, hydrogen is mainly manufactured by using heat and pressure to separate it from natural gases. But since this manufacturing process also creates large amounts of carbon dioxide, scientists are exploring ways to generate hydrogen from water instead. When burned, hydrogen releases only water and steam, and it has the potential to fuel all kinds of systems. Hoshi’s team has developed a hydrogen-based method that could transform excess carbon dioxide into usable fuel.

“We are researching photocatalysts capable of decomposing pollutants such as carbon oxides, ammonia and waste oil,” says Hoshi. “We have had recent success in investigating the photocatalytic conversion of carbon dioxide into methane — the reaction pressure needed to reduce the carbon dioxide was created using hydrogen gas.” To help realize this vision of a zero-emission society, Hoshi and his team welcome collaborations with researchers and private companies interested in this burgeoning field of nanotechnology.



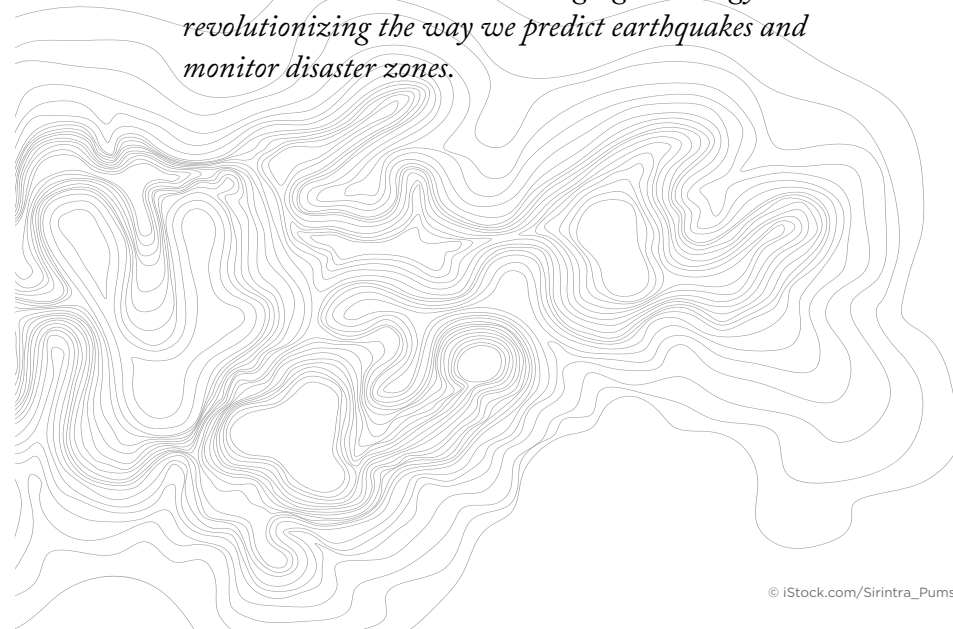
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CENTER FOR INNOVATIVE MICROWAVE REMOTE SENSING

THE NEXT WAVE
IN REMOTE SENSING

Research Keywords: Microwave Remote Sensing, Synthetic Aperture Radar, Environment and Disaster Monitoring

—*Microsatellites and remote imaging technology are revolutionizing the way we predict earthquakes and monitor disaster zones.*



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The Microwave Remote Sensing Laboratory is far more than a laboratory. It is an experimental aerospace workshop where world experts in remote sensing collaborate with mechanical and aerospace engineers to construct state-of-the-art microsatellites and airborne sensors. The research team specializes in microwave-radar technology for detecting ground movements and earthquake predictors as part of a new generation of remote sensing technologies. “Microwave radiation is particularly useful for remote sensing because it penetrates cloud, haze and fog, allowing us to observe the Earth’s surface from space,” explains Josaphat Tetuko Sri Sumantyo who leads this research project. The core area in this research project is the development of synthetic aperture radars (SARs) for microwave remote sensing to monitor land deformation. SAR emits a microwave signal in the direction of the target and then detects microwaves scattered from the target. By comparing SAR images obtained before and after a change such as

an earthquake or a landslide, researchers can determine how much the land has moved. The research team has a well-developed research-and-development program with 15 researchers, 25 students and facilities for designing, manufacturing, calibrating and operating SAR for both aircraft and microsatellite applications.

ADVANCED AEROSPACE FACILITIES

“Our facilities include an anechoic chamber for calibrating sensors, a satellite-ground communication system, and microsatellite calibration and measurement systems. We also have a simulator for designing microwave circuits and antennas, along with a suite of manufacturing equipment,” says Sri Sumantyo. “We even have our own 6-meter experimental unmanned aerial vehicle, the JX-1, which we developed in this laboratory.” They have already developed SAR sensors for circularly polarized (CP) microwave radiation in the L, C and X bands, which

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have been deployed on both large and small aircraft, as well as on the JX-1. The CP-SAR sensor is the first of its kind, utilizing interference between left- and right-handed circularly polarized light to obtain precise information about the Earth’s surface in a compact, lightweight and inexpensive sensor. We have developed several techniques based on SAR imaging to monitor infrastructure and areas affected by disasters such as forest fires, landslides, subsidence and volcanic eruptions,” says Sri Sumantyo.

Engineers in this team are developing two novel microsatellites. One is equipped with radio occultation and electron density temperature probe sensors for measuring the atmospheric signatures thought to precede earthquakes, while the other is a CP-SAR satellite with lightweight gold-coated mesh antenna. These satellites are poised to take the lab’s research beyond the stratosphere. “Our microsatellite program is very exciting for future SAR sensor applications and planetary exploration,” says Sri Sumantyo. “We eventually aim to have five microsatellites in orbit, which will provide real-time monitoring for global disaster mitigation and research.” The team has strong collaborations with Japanese and overseas research institutions and industry — it has more than 50 agreements with research and industry partners throughout the world. The group also encourages short- and long-stay programs under various government programs, through which more than 500 students and researchers from many different countries have worked at the lab.

IMAGING SCIENCE AND TECHNOLOGY FOR MATERIAL APPEARANCE

REALNESS IN DIGITAL IMAGES

Research Keywords: Texture Engineering, Environmental Texture, Real-Time Processing

—Understanding how the human brain interprets images could underpin the future of internet shopping, cosmetics, digital fabrication and even non-invasive medicine.



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When internet purchases arrive and seem nothing like their picture, it can be a disappointing experience for shoppers. So, while big e-commerce players are increasingly investing in technologies to help personalize products or shop via phone or virtual reality headset, a significant stumbling block is rendering realistic, digitally produced images. “To achieve a realistic rendering of something, we also need to deeply consider human perception,” explains Keita Hirai, a member of the Imaging Science and Technology for Material Appearance group at Chiba University’s Graduate School of Engineering. How we perceive a material, he says, can also be linked to cognition, not just physical phenomena.

To examine the complex effect of the mind’s eye, Chiba University have drawn from a diverse range of researchers, including engineers, psychologists, and medical and cognitive scientists.

Recently, Hirai’s team developed a new system for texture evaluation, and through participant feedback have devised a set of algorithms that can produce more realistic digital representations of patinas and colours overlaid onto textured fabrics in digital images. The aim, he says, is to one day digitally simulate photo-real fabric appearance via a smart device. Hirai points out that this will not only be helpful to internet shoppers, but that these algorithms could also find applications in rapidly advancing digital fabrication techniques, such as printing digital patinas onto fabrics or objects, and manufacturing representative digitally-designed 3D products. In fact, the group aims to contribute to industries as diverse as cosmetics and medicine.

Filtered through the brain

Among the work done by the diverse group is a study examining texture. Viewers, suggest the researchers, often see the broad design of patinas printed on fabric, but some textures contribute to a blurring out of finer details. In contrast, high-resolution digital images with very accurate representations of the same material seem unnaturally sharp. To explore this, the researchers developed different ‘blurriness’ filters linked to material qualities and fine-tuned them by asking participants in their experiment to rate the naturalness of the images. Another group found that our perception of colour is affected by our understanding of its dimensionality. The same viewer looking at the same image saw colours differently depending on whether they interpreted the image as two dimensional or three dimensional. Viewing images with one eye or both, and whether the image or the viewer’s head was moving, also affected how natural the image seemed. This work, says Hirai, is important for better smart device production. “A more informed colour management system, for example, may help realize more accurate colour reproduction between different devices: displays, cameras and printers,” he explains.

Hirai says the group’s work will influence the most cutting-edge imaging technology, such as the omni-directional 3D camera systems and virtual reality headsets coming from technology giants such as Sony, Panasonic, Canon and Nikon. While he also mentions cosmetics and automotive painting, one team have already had some

remarkable success in one crucial, but quite unique area — medical diagnostics. These researchers have carefully studied the optical properties of haemoglobin in skin using images taken on a simple DSLR camera. Incredibly, they found they could measure both the heart rate and its variability with 99 percent accuracy. This opens the door to everything from non-invasive medical diagnosis to a better understanding of physical exertion using a simple smartphone app.

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INSECTS-INSPIRED BIG INNOVATION

LOOKING TO NATURE TO REVOLUTIONIZE FLIGHT

Research Keywords: Bioinspired Engineering, Biological flight, Drone

—The beating wings of insects hold the secrets to controlled low-speed flight and Micro Aerial Vehicles.

Inspired by the fascinating flying ability of insects and humming birds, Chiba University’s Biomechanical Engineering Laboratory has been conducting pioneering research on beating-wing flight for more than 20 years. Headed by Professor Hao Liu, the lab is on the verge of revolutionizing the very concept of flight itself.

“Insects have this amazing ability to hover and execute highly controlled flight in both still air and turbulent wind gusts,” says Liu. “Scientists once knew very little about how insects generate aerodynamic force in turbulent environments, and even less about how they are able to maintain such agile control in flight.”

BIOLOGY INSPIRES MICRO AIR VEHICLES

Conventional flight is based on the uninterrupted flow of air over the curved upper and lower surfaces of a wing, which causes a ‘suction’ effect that lifts the wing upward. “Fixed wings need smooth airflow to generate lift,” explains Liu. “Turbulence over the wing can lead to disaster. Our first major breakthrough in unravelling the mystery of insect flight was that most flying insects in fact generate most of their lift force by creating a vortex on the leading edge of the flapping wing. It’s a completely different principle of flight to conventional flight.” It all started in 1996 with Liu’s development of the first computational fluid dynamics simulation for insect flight, which led to the discovery of the universal leading-edge vortex mechanism in insect and bird flight. To delve deeper, the laboratory installed an

ultra-low-speed wind tunnel capable of airflow as slow as half a metre a second. They use it to observe and analyse the flight of live birds and insects such as moths, beetles and dragonflies, as well as micro air vehicles (MAVs), very small drones with potential uses in disaster relief and covert operations. “Using high-speed imaging and particle image velocimetry data, we were able to create a computer model of an insect and its flight mechanism, and from there we made an experimental robot insect that actually flew. That was another pioneering breakthrough,” says Liu.

“Our research brings together biology, engineering, computational physics, biorobotics and neuroscience, and we collaborate with the likes of Cambridge and the University of London on some really interesting international, cooperative projects. Chiba is definitely a world leader in this area with a strong interdisciplinary team and world-class facilities.”

The lab’s research now focuses on developing insect-inspired flight systems, which he expects to lead to big developments in the design of insect- and bird-size MAVs. “For example, we think it’s wing flexibility that gives insects much of their resilience to wind gusts, but we are also seeing that insects use their body much more than we thought to control direction and movement, both actively and passively. This is completely different to the conventional wing-based control used by planes today and has the potential to revolutionize flight control strategies in general,” says Liu. “Ultimately we want to develop an insect-inspired autonomous drone that is far

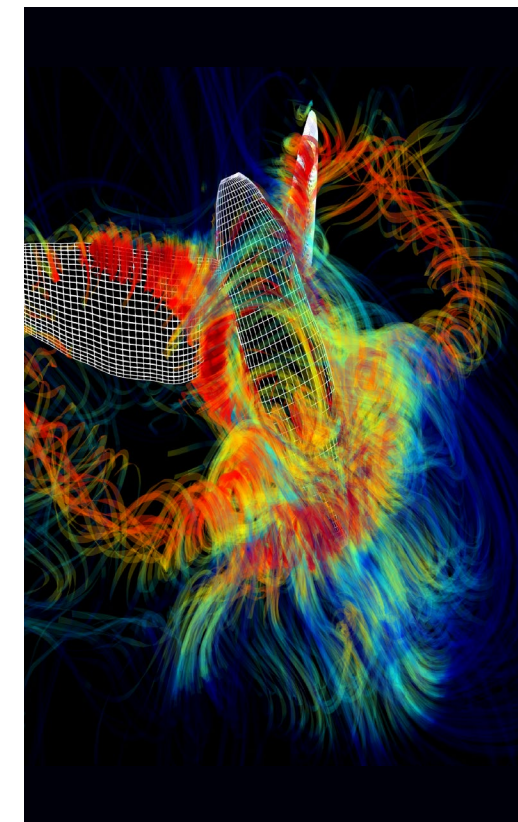
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more reliable and agile than anything based on today’s rotor-based technology. We hope that this will also lead to a new mechanism of flight with potentially much broader applications. In the meantime, we continue to collaborate on the development of advanced, flapping MAVs, as well as help improve the reliability of rotor-based drones by introducing flexible wing technology.”



CATALYZING THE FUTURE OF SMART MATERIALS

Research Keywords: Synthetic Chemistry, Catalytic Reaction, Iodine Bond

—Catalysts developed from soft iodine, graphene and metal complexes could transform smart material technologies.

The very idea of materials that change their shape or function as required sparks the imagination. Smart materials are impressive artificial molecules, often inspired by naturally occurring chemicals, which have the potential to revolutionize design. They undergo changes that are reversible and repeatable, meaning they can function as molecular switches, valves and sensors. Other smart materials include shape-memory alloys that return to their original shape after bending, metal-bearing polymers that can switch from insulator to conductor and drug-delivery systems that slowly release pharmaceuticals where and when they are needed.

Researchers at the Soft Molecular Activation for Intelligent Materials program are leading investigations into catalysts made from soft molecules that could one day transform smart material design. Lead researcher Takayoshi Arai says the program is focused on developing powerful catalysts to create novel smart materials using three catalyst types. “Firstly, soft halogen

catalysts, predominantly using iodine, can be used to develop highly targeted medications,” he explains. “A second type is ‘soft π -electron’ using carbon nanotubes and graphene, which would provide a unique reaction sphere for catalysis. The third type, ‘soft metal’ catalysts allow us to introduce soft elements such as gold and copper into target molecules.”

NEW CATALYST DESIGN

Arai says one of the main goals of the program is to create new asymmetric catalysts, which are used to generate large numbers of very specific molecules. Most biological molecules are chiral, meaning they exist in one of two mirror-image forms called enantiomers. Many drugs and smart materials use just one specific enantiomer, and so catalysts are needed to direct the chemical reactions toward forming the correct enantiomer. For example, iodine has been used to help synthesize specific enantiomers of cyclic

Members

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Professor, Graduate School of Science

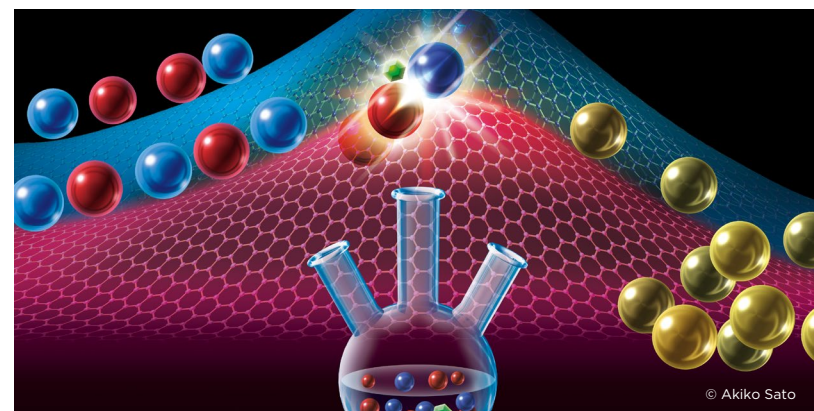
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Yasushi ARANO	Takeshi MURATA
Masami ISHIBASHI	Midori ARAI
Takuya HASHIMOTO	

and ring-shaped molecules. “We are lucky that Chiba prefecture in Japan is one of the world’s leading producers of iodine,” says Arai. “In fact, the Chiba Iodine Resource Innovation Center (CIRIC) has opened at Chiba University in July, 2018. A key goal of our program is to perfect iodine-based soft molecular activation.”

Recent success for Arai’s team includes the development of an aminoiminophenoxycopper carboxylate catalyst that can trigger high yields of O-cyclized molecules. These can, in turn, be used to generate a particular chiral compound that is invaluable for use in antimicrobial and antiosteoporotic compounds.

“A crucial part of our research is designing catalysts that can be reused multiple times, thereby creating cost-effective, sustainable methods for generating useful compounds,” says Arai. His team recently designed a recyclable catalyst made from a zinc-polymeric ligand complex. The polymeric ligand allows the catalyst to be separated from the final product by a simple filtration process, meaning it can be reused — indeed, poly-Zn remained a stable and active catalyst for creating iodine-based ring-shaped molecules more than five times.

“By introducing soft elements to target molecules, our research will facilitate the development of smart materials with smooth and rapid responses,” says Arai. “We welcome anyone interested in research at the forefront of iodine-related soft molecular activation chemistry to come and work in this diverse and challenging field at Chiba.”



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INSTITUTE FOR GLOBAL PROMINENT RESEARCH

To accelerate innovative research beyond the borders of academic disciplines, the IGPR was founded as a core institution at Chiba University in 2016. Aiming at fostering seeds and delivering the fruits to the world, IGPR has been actively supporting research projects with potential impact as a global hub for top-class research.

The institute is also focused on developing young human resources who will lead new research fields in the next generation. Currently, IGPR is supporting more than 20 research projects in diverse areas such as neutrino astronomy and the interdisciplinary science for the End-of-Life Care.

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URL : igpr.chiba-u.jp/global

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MESSAGE FROM THE DIRECTOR OF IGPR

"
...to enhance
prominent
international research
projects of Chiba
University
and
support young
researchers who lead
the fields in the next
generation."
"

It is my great pleasure to have the third issue of *CHIBA RESEARCH* available here for you. All of the research projects introduced in this issue have been carried out with the support from the Institute for Global Prominent Research (IGPR), a university-wide organization of Chiba University. The IGPR was established in 2016, with the goal to enhance prominent international research projects of Chiba University and support young researchers who lead the fields in the next generation. This is an original attempt in that research resources are brought together from all sources throughout the university, and a variety of research fields are comprehensively supported. This approach is possible because Chiba University is a multidisciplinary university and cannot be found in any of the colleges or universities in Japan.

The year 2018 was the third year for the support programs by the IGPR, and it was also a time for us to recognize that each project "seed" had been germinated and grown enough to bear some fruits.

In June 2018, Professor Toshinori Nakayama and his team elucidated the mechanism of "tissue fibrosis", hardening of tissues around trachea that occurs in severe cases of asthma, by identifying a new immune cell population. As inhaled steroid therapy is ineffective to fibrotic tissues, Professor Nakayama's achievement is expected to lead to a new treatment for intractable respiratory diseases for which no radical treatment has been developed so far.

In November, Professor Tomoyoshi Ito and his team succeeded in developing a special purpose computer for holography. This was a result of over 25 years of study in high-speed computer for 3D holography and our press release gained broader attention from the media both in Japan and overseas.

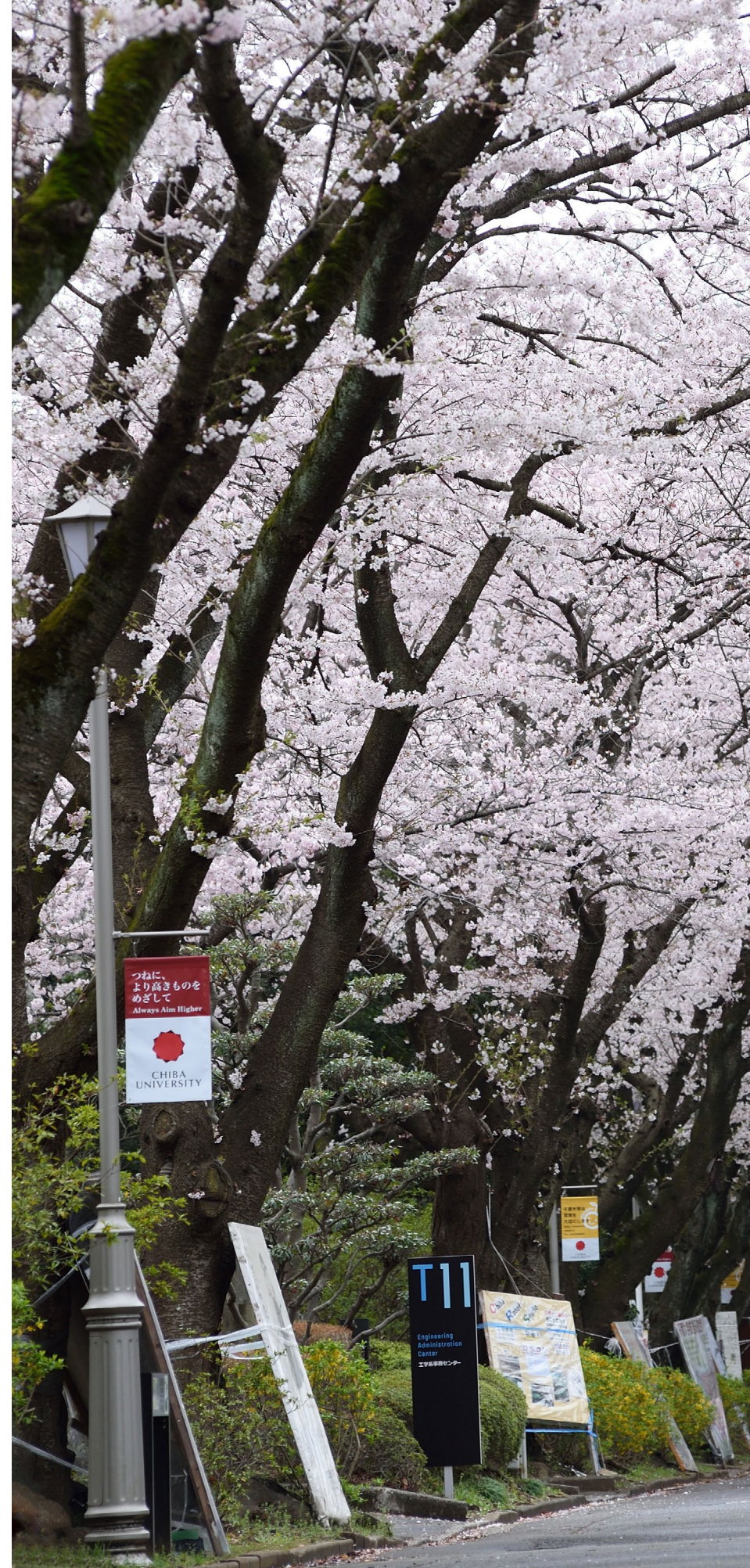
In December, the international science magazine *Science* selected the research outcome of the International Center for Hadron Astrophysics led by Professor Shigeru Yoshida as a Breakthrough of the Year 2018. The Japanese scientists whose studies were selected for this honor include Dr. Shinya Yamanaka (2007 for iPS cell research) and JAXA's Hayabusa team (2011). We can see how honorable this selection is.

In the last year, the research projects were covered by a total of about 90 media in and outside of Japan. The number of symposiums by the research projects reached about 20. As a measure to develop the next generation of researcher, the IGPR also organized a symposium for young researchers from a wide range of fields. It served as an opportunity for about 80 researchers to brush up skills for communicating their studies quickly and effectively to the people having different majors.

Through the IGPR to promote the world prominent research projects, Chiba University continues our efforts to further contribute to society. I strongly hope that this issue of *CHIBA RESEARCH* can help you to have deeper appreciation of Chiba University's front edge research activities.



Takeshi Tokuhisa
Director, IGPR and
President of Chiba University



ABOUT THIS MAGAZINE

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WHERE IS CHIBA UNIVERSITY?

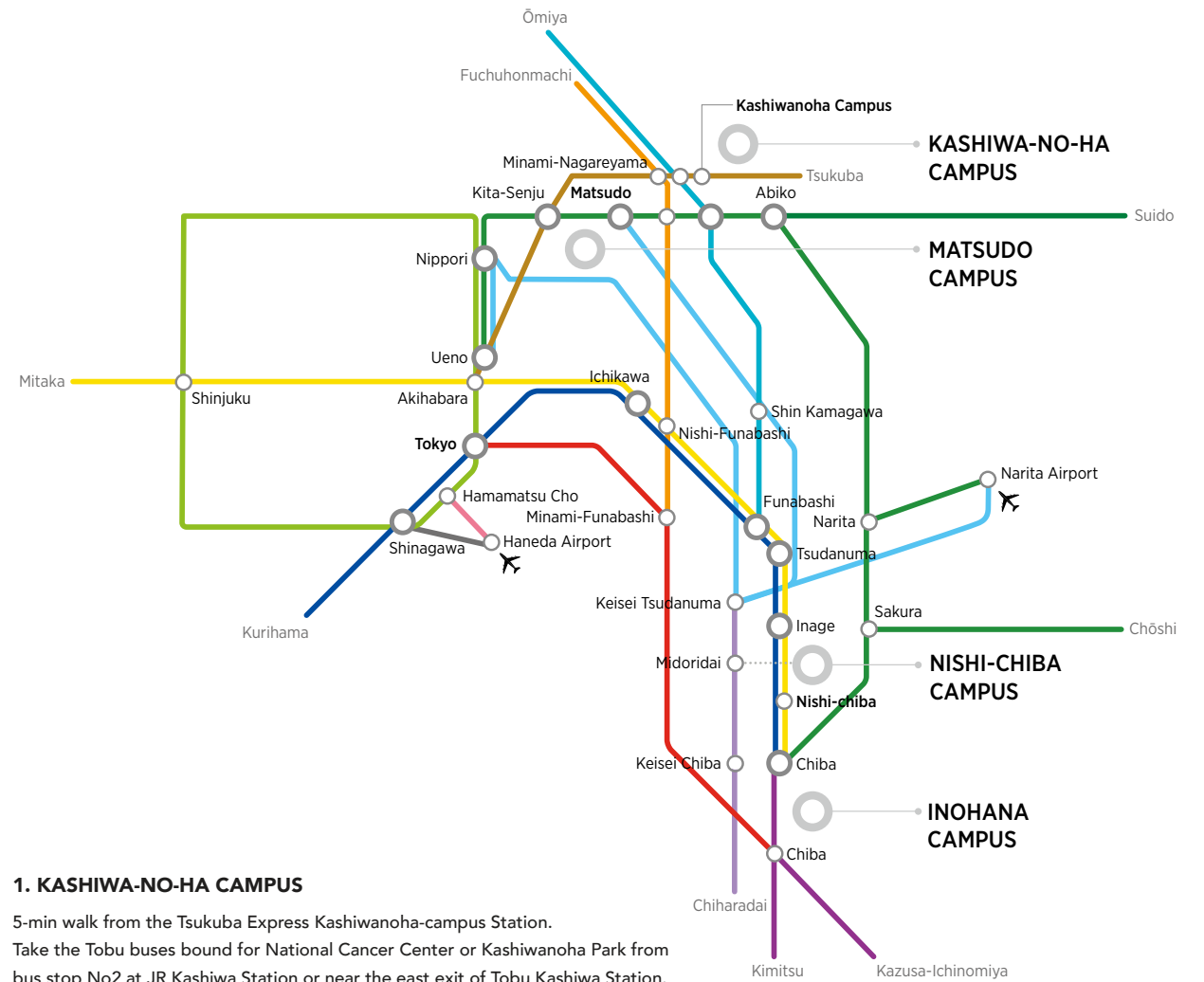
CHIBA Prefecture is located at the east edge of the South Kanto region. It has a population of approximately 6 million, the 6th largest among the 47 prefectures in Japan. Chiba is the center of Keiyo Industrial Area and has the well-developed industry. The three sides of the prefecture are surrounded by the sea, which helps Chiba's growth in the seafood industry as well.

Chiba University has 4 campuses in Chiba Prefecture.

Nishichiba Campus (Main Campus) is located between Narita International Airport and Tokyo Station. It takes about 30 to 40 minutes by train to Tokyo Station and also Narita International Airport.



PUBLIC TRANSPORT TO CHIBA



1. KASHIWA-NO-HA CAMPUS

5-min walk from the Tsukuba Express Kashiwanoha-campus Station.
Take the Tobu buses bound for National Cancer Center or Kashiwanoha Park from bus stop No2 at JR Kashiwa Station or near the east exit of Tobu Kashiwa Station.

2. MATSUDO CAMPUS

10-min walk from Matsudo Station
(JR Joban line, Tokyo Metro Chiyoda Line, Shin-Keisei Line)

3. NISHI-CHIBA CAMPUS

2-min walk from JR Nishi-Chiba Station to the South Gate of Nishi-Chiba Campus
7-min walk from Keisei Midoridai Station to the Center Gate of Nishi-Chiba- Campus
10-min walk from Chiba Monorail Tendai Station to the North Gate

4. INOHANA CAMPUS

After arriving Chiba Station (JR) a bus stop can be found in front of east exit 7 (this bus can also be taken if you get off at Keisei Chiba Station). Take buses bound for Chiba University Hospital or Minami-Yahagi and get off at the School of Medicine Entrance bus stop, or, to get to the university hospital, get off the bus at the Chiba University Hospital stop.

- Tsukuba Express Line
- Yamanote Line
- Sōbu Line [Local Train]
- Sōbu Line [Rapid Service]
- Keisei Line
- Yamanote Line
- Joban Line [Rapid Service] Narita Line
- Musashino Line
- Keiyo Line
- Tokyo Monorail
- Keikyu Airport Line
- Uchibo/Sotobo Line
- Tobu Urban Park Line



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