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NARA INSTITUTE of SCIENCE and TECHNOLOGY

RESEARCH HIGHLIGHTS 2016

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A NEW VISION

Blurring the edges of possibility in augmented reality **p18**

BUDDING IDEAS

Exploring a biological clock that controls flower growth and underpins our food supply **p52**

A CUT ABOVE?

Why diamonds and pencils are created equal to one atomic explorer **p57**

NAIST®

The history of NAIST

NAIST was founded in 1991 as a Japanese national university consisting solely of graduate schools in three integrated areas: information science, biological sciences and materials science. At present, about 1,000 students — 19% from overseas — are supervised by roughly 200 NAIST faculty.

With its cutting-edge facilities and a 5 to 1 student-to-faculty ratio, NAIST's world-leading education and research are a direct result of its rich, global environment and supportive infrastructure. Moreover, the outstanding achievements of NAIST's faculty and students are shared worldwide through patents, licenses, spin-off companies, and active exchange with overseas partners.

NAIST has quickly established itself as a world-class education and research center where young science and technology researchers become tomorrow's global leaders.

Aims & Scope

NAIST Research Highlights showcases the most promising and important research achievements of each laboratory at NAIST and presents their current research and core technologies to the public. The publication distills highly technical research papers into short, easy-to-understand articles that appeal to a global audience of both specialists and non-specialists. *NAIST Research Highlights* aims to inform readers of the latest developments in NAIST's pioneering research, and to stimulate new and existing international collaborations. Digital versions of each issue can be accessed online at: http://ipw.naist.jp/iri/naura/en/highlight.html

NAURA

NAURA (NAIST URA team) publishes *NAIST Research Highlights* under the auspices of the "Program for Promoting the Enhancement of Research Universities", which is funded by Japan's Ministry of Education, Culture, Sports, Science and Technology (MEXT). Through this program, NAIST further supports its cutting-edge research while expanding into new interdisciplinary fields in science and technology toward becoming a globally recognized education and research center.

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NAURA (NAIST URA Team)

Institute for Research Initiatives
Nara Institute of Science and Technology
8916-5 Takayama-cho, Ikoma, Nara
630-0192, JAPAN
E-mail: naura@rsc.naist.jp

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For further information on the research published in *NAIST Research Highlights* or to arrange an interview with a faculty, please contact:

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University Research Administrators

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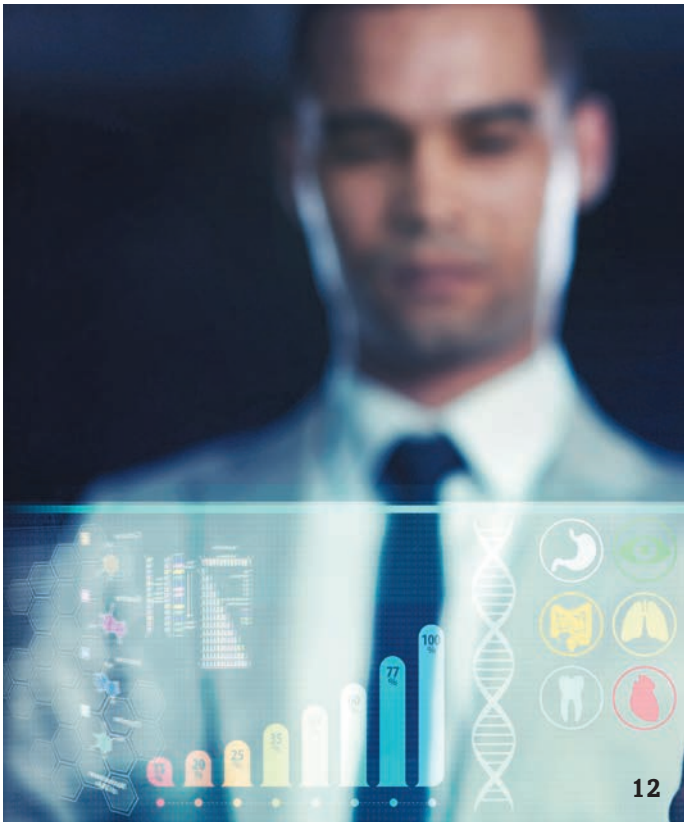

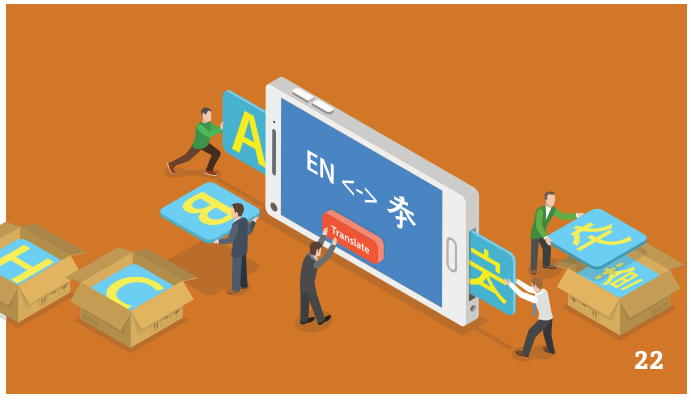

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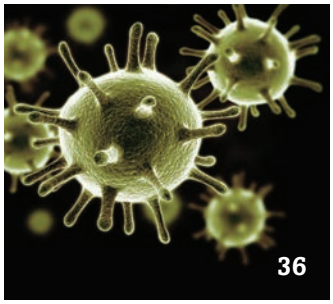

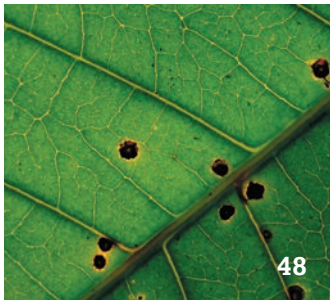

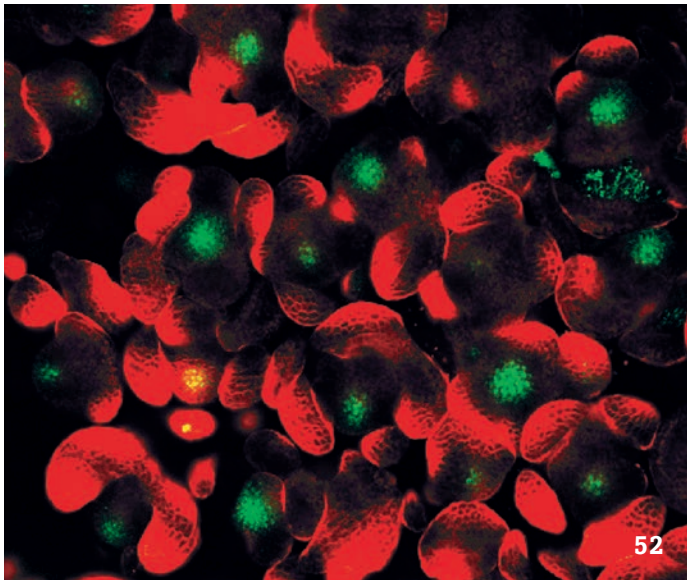

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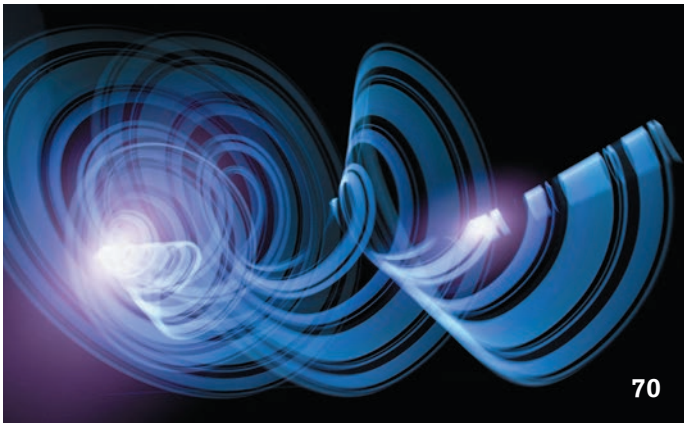
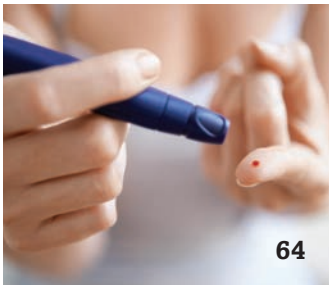
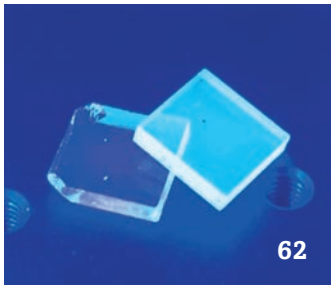






Nurturing discovery

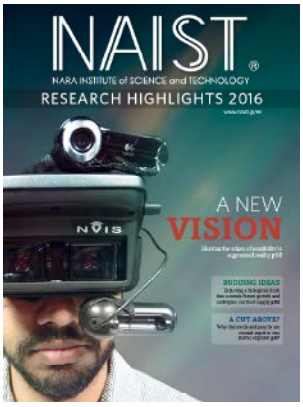
Welcome to NAIST Research Highlights 2016. This publication provides an overview of the work and people of one of Japan's leading research bodies, the Nara Institute of Science and Technology. In these pages we present a view of the institute's achievements in three different formats. **Research Highlights** are short features that cover recent extraordinary advances and breakthroughs: from the development of an implantable continuous glucose monitoring device with potential for diabetics (p64); to the discovery of a scintillator with possible security and medical applications (p62).

Five longer **Impact** profiles explore some of our research achieving significant applied outcomes, such as the work of the Functional Genomics and Medicine Laboratory (p33). Under Yasumasa Ishida's leadership, this lab is at the forefront of investigations of the PD-1 gene that controls aspects of the body's T-cell immune response.

Our Augmented Human Communication Laboratory, headed by Satoshi Nakamura, is using big data to develop software capable of seamless speech translation (p22).

Of course, at the heart of such outcomes are our researchers. Each year NAIST attracts more leaders in scientific fields. And here, in a series of six longer **Features**, we spotlight the careers of some of the latest international stars to join our ranks. They include Chistian Sandor, a leader in augmented reality (p18), and parasitic plant specialist, Satoko Yoshida (p40), who will lead our new Plant Symbiosis Laboratory.

We look forward to nurturing their important work and the careers of all our researchers in the atmosphere of cutting-edge discovery that will continue to be fostered at NAIST.



On the cover

By coming up with a fast way to calibrate actual and virtual realities, NAIST researchers are one step closer to their goal of producing the ultimate display.

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NAIST Graduate Schools

NAIST graduate education and research programs aim to be at the world-leading edge of research in science and technology, specifically in the core fields of information, biological and materials sciences. They actively engage in cross-disciplinary studies to explore and seek solutions in the most challenging areas.

Information Science

The core focus of the Graduate School of Information Science is on communication between society, people and computers, as well as the computing infrastructure for the big-data era that will support sustainable growth and societal development well into the future. Our world-class faculty, staff and curriculum contribute to the cultivation of researchers and engineers who will be leaders in tomorrow's universally connected society.

Computer Science
- Computing Architecture
- Dependable System
- Ubiquitous Computing Systems
- Mobile Computing
- Software Engineering
- Software Design and Analysis
- Internet Engineering
- Internet Architecture and Systems

Media Informatics
- Computational Linguistics
- Augmented Human Communication
- Network Systems
- Vision and Media Computing
- Interactive Media Design
- Optical Media Interface
- Ambient Intelligence
- Social Computing

Applied Informatics
- Robotics
- Intelligent System Control
- Large-scale Systems Management
- Mathematical Informatics
- Imaging-based Computational Biomedicine
- Computational Systems Biology
- Robotics Vision

Biological Sciences

The ultimate goal of research in the Graduate School of Biological Sciences is to uncover various structures and functions of microorganisms, plants and animals at the molecular and cellular levels, and to clarify principles of the basic phenomena of life and biological diversity. Based on highly advanced basic research, we provide research and development that benefits human well-being, through which we train researchers to play active roles in the global community.

Plant Biology
- Intercellular Communications
- Plant Cell Function
- Plant Developmental Signaling
- Plant Metabolic Regulation
- Plant Growth Regulation
- Plant Morphological Dynamics
- Plant Stem Cell Regulation and Floral Patterning
- Plant Immunity
- Plant Symbiosis
- Plant Developmental Biology

Biomedical Science
- Molecular Signal Transduction
- Functional Genomics and Medicine
- Molecular and Cell Genetics
- Tumor Cell Biology
- Molecular Immunobiology
- Applied Immunology
- Molecular Medicine and Cell Biology
- Developmental Biomedical Science

Systems Biology
- Microbial Molecular Genetics
- Systems Microbiology
- Cell Signaling
- Applied Stress Microbiology
- Structural Biology
- Membrane Molecular Biology
- Gene Regulation Research
- Systems Neurobiology and Medicine

Materials Science

The main research area in the Graduate School of Materials Science is photonic nanoscience, which seeks to understand the mechanisms of materials on the electron, atomic and molecular levels from the perspective of 'seeing with light', 'creating with light' and 'transmitting with light'. Researchers aim to create new materials, structures and functions. We systematically educate students to become excellent leaders in research and development fields in global society.

Organic Materials
- Advanced Polymer Science
- Synthetic Organic Chemistry
- Photonic Molecular Science
- Photofunctional Organic Chemistry
- Nanomaterials and Polymer Chemistry
- Functional Polymer Science
- Ecomaterial Science
- Advanced Functional Materials

Device Materials
- Photonic Device Science
- Information Device Science
- Sensing Device
- Organic Electronics
- Mesoscopic Materials Science
- Intelligent Materials Science
- Sensory Materials and Devices

Quantum Materials
- Quantum Materials Science
- Surface Materials Science
- Bio-Process Engineering
- Nanostructure Magnetism
- Complex Molecular Systems
- Green Nano Systems

As of April 1, 2016

Biological Materials
- Biomimetic Materials Science
- Supramolecular Science
- Biocompatible Materials Science

- Nanostructure Magnetism
- Complex Molecular Systems
- Green Nano Systems

Information Science


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IMPACT

Internet Architecture and Systems Laboratory & ITC | Professor Kazutoshi Fujikawa

A beacon of hope in an emergency

RESEARCHERS ARE BUILDING A RELIABLE COMMUNICATION INFRASTRUCTURE USING SATELLITE SYSTEMS FOR USE IN DISASTERS

At 2:46 pm on 11 March 2011, a magnitude 9 earthquake hit 70 kilometres off Japan's eastern shore, precipitating one of the world's most devastating and costly natural disasters.

Within minutes, the North Pacific Ocean had risen and was threatening Japan's eastern coastline. At 3:18, a swell of eight-metre waves struck the city of Ofunato. At 3:26, 8.5-metre waves were recorded in the Port of Miyako, almost 100 kilometres to the north and at 3:51 waves taller than a three-storey building, higher than 9.3 metres, inundated Soma city, more than 200 kilometres to the south.

The hour and five minutes it took for the tsunami to reach its maximum height was about the same amount of time it would have taken emergency workers to set up a satellite communication system. Kazutoshi Fujikawa and his team at NAIST's Internet Architecture and Systems Laboratory, have since reduced that time to about 15 seconds, in a project that looks certain to save many lives.

Fujikawa also leads the Information Initiative Center, which manages and operates an advanced network infrastructure and computer system for students and researchers at NAIST, known as Mandara. The system connects more than 4,000 terminals and is one of the fastest campus networks in the world.

Unlike many researchers in Japan studying satellite communication, Fujikawa is more interested in its applications than in theoretical analysis. "We want to design useful communication infrastructure by using satellite systems in the case of a disaster," he explains. Natural disasters can cause comprehensive breakdowns in existing mobile, landline and internet telecommunications infrastructure. These failures can delay emergency responses and rescue efforts, leading to preventable losses of life.

Decentralized Wi-Fi routers can open up channels of communication during a disaster, but only within a radius of 100 metres. Some researchers have even suggested using low-flying aircraft to serve as emergency Wi-Fi access points, but they also have limited coverage. Satellite communication networks cover a much wider range, from entire countries or regions to the whole Earth. But, these systems can take up to 3 hours to set up and require 1.3 seconds to transmit information between users, via space — a delay that is impossible to eliminate.

Fujikawa's group has applied network management and operation techniques to seamlessly switch, within seconds, from the regular telecommunication network to the satellite network. In their system, a dish known as a very small aperture terminal (VSAT) is used to send and receive information from an orbiting satellite.

The VSAT system weighs less than 60 kilograms, and fits in a box about 1 cubic metre in size. In a recent trial, Fujikawa hitched the VSAT system to a hybrid car to allow users to transmit information while on the move, as would be required during a disaster response operation. To realize the network, they partnered with satellite communications provider Japan Radio Company (JRC) and satellite operator JSAT.

Fujikawa's team has also since incorporated drones equipped with Wi-Fi access points to their network for emergency reconnaissance

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and rescue. People who are injured or trapped can connect to the drone's Wi-Fi service using their mobile phones, which then records their position. When the drone returns to the car (see image, right), this information is sent via satellite for processing to pinpoint the exact location of stricken individuals.

Fujikawa's team is now working to implement various configurations of the network so that it can be used in real disaster situations. "Our aim is to provide communications infrastructure in an emergency, which can be used as ordinary internet," he says.

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The Japan Disaster Medical Assistance Team (DMAT) tested the system in a 2015 training drill on 1 September, the anniversary of the Great Kanto earthquake of 1923 that killed almost 150,000 people. This date is now used each year to mark Japan's Disaster Prevention Day, during which nationwide safety drills are held. A VSAT system was fixed aboard the Izumo-class helicopter destroyer ship in Yokosuka, south of Tokyo, to transmit messages between a stationary DMAT team and the hybrid car.

Although the high cost of the system might prove prohibitive to its adoption by the government on a national scale, individual hospitals across Japan are already using the system to prepare themselves for the next big disaster. VSAT transceivers have been set up on the rooftops of four hospitals: Yonemuri Hospital, on Japan's south-western tip; Iwate Medical University, in the far north; and, in between, the National Disaster Medical Center and Osaka National Hospital.

These systems will allow rescue teams to get immediate assistance from doctors for treating critical injuries when the usual lines of communication have broken down.

Fujikawa plans to further test the satellite communication system for transmission delays and to assess its geographic reach.

More information about the group's research can be found at http://isw3.naist.jp/Contents/Research/cs-08-en.html
Researcher: Kazutoshi Fujikawa

Intelligent System Control Laboratory | Professor Kenji Sugimoto

Robotics

Smart systems

Rolling forward to meet society's needs

Robotic wheelchairs detect, adapt and immediately respond to users' intentions

"After a brief training period, the wheelchair could deduce the intended destination, more than 80% of the time."

Fully automated wheelchair navigation systems have been in use for some time and can easily transport users to predefined locations. But, what happens when a user decides to take a last-moment detour to the kitchen for a midnight snack or navigate a hallway where a pet has inconveniently decided to take a nap? Existing systems falter in such instances.

Recognizing the gap between available technologies and the needs of wheelchair users, the Japan Society for the Promotion of Science provided researchers at NAIST and the University of Technology Sydney with an International Joint Research Grant for the "development of mobility assistance shared control strategies for increased autonomy." The collaborative project has resulted in a sensor-laden wheelchair designed to guide users' movements through their surrounding environments.

The wheelchair represents an amalgam of assistive inventions, including touch-recognition algorithms originally developed for a robotic hand at NAIST, which allow wheelchairs to 'sense' user intentions as they navigate through complex real-world environments.

Leading the Japanese side of the international collaboration has been Takamitsu Matsubara, of NAIST'S Intelligent System Control Laboratory. Matsubara's

other projects include the development of several technologies in artificial intelligence and motor control for humanoid robots, and these have made significant contributions to the wheelchair project. Just as an artificial robot hand trying to use an unknown object must examine its properties, the wheelchair's sensors continuously probe the proximity of nearby walls and furniture, providing a sensitive rendering of its precise relationship to surrounding objects and surfaces.

In a more recent development, Matsubara has realized that while his robotic hand would probably be fully operational all the time, the wheelchair had to navigate only when needed. In response, the team has explored the development of algorithms that would allow the user to stay in control for as long as desired, both to foster his or her sense of control over the environment and to maintain mental and motor skills.

Exerting a little control goes a long way. An experimental trial showed that after a brief training period, the wheelchair could deduce the intended destination more than 80% of the time using only its knowledge of current location and recent joystick movements. If the direction seems wrong to the user — or if some time on a sunny porch beckons instead of a shower — a simple movement of the joystick can immediately alter the robot's calculation of intended destination.

A paper detailing the technologies used in the project to allow assistive wheelchairs to sense user intentions as they navigate through complex real-world environments was presented at the IEEE RO-MAN2015 conference[1], where it was recognized by the Robotics Society of Japan and the Korea Robotics Society with the Distinguished Interdisciplinary Research Award. The award recognizes, Matsubara says, that the technology the team is developing may allow wheelchair users to express human desire and intent in the near future.

Reference

1. Matsubara, T., Miro, J. V., Tanaka, D., Poon, J. & Sugimoto, K. Sequential intention estimation of a mobility aid user for intelligent navigational assistance. *Proceedings of the 24th IEEE International Symposium on Robot and Human Interactive Communication (RO-MAN2015)* (2016).

The intelligent wheelchair developed by NAIST and the University of Technology Sydney.

More information about the group's research can be found at http://isw3.naist.jp/Contents/Research/ai-02-en.html
Researcher: Takamitsu Matsubara

IMPACT

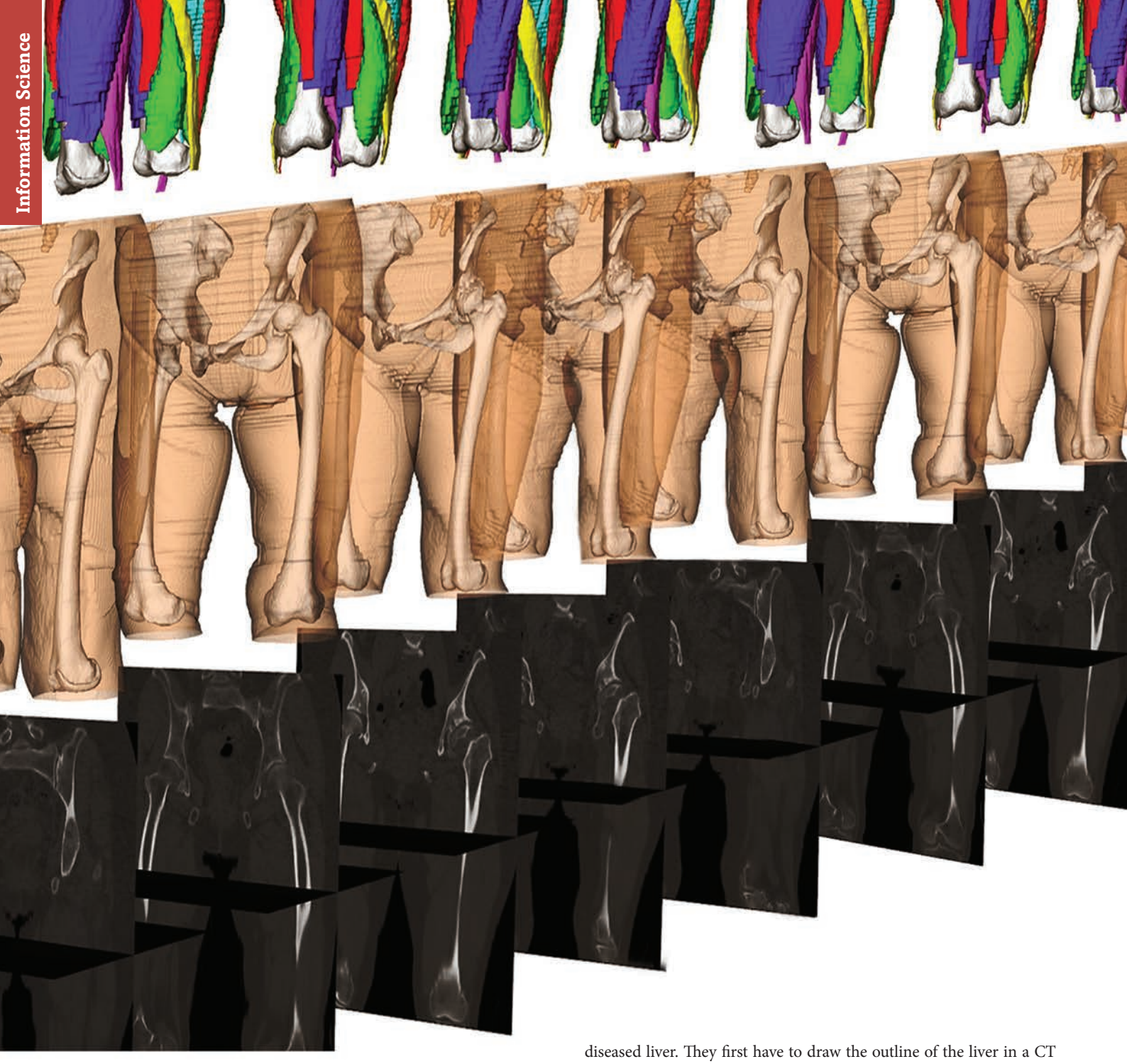
Imaging-based Computational Biomedicine Laboratory | Professor Yoshinobu Sato

Teaching human anatomy to intelligent machines

RESEARCHERS ARE DEVELOPING MEDICAL IMAGE ANALYSIS SOFTWARE FOR IMPROVED DIAGNOSIS, RECOVERY AND REHABILITATIVE CARE

Google has revolutionized the way we navigate our world by using raw satellite images to build powerful, interactive maps of almost every city and town. Now computer scientists, Yoshinobu Sato and Yoshito Otake, are doing much the same thing for the human body. Their team at NAIST's Imaging-based Computational Biomedicine laboratory is using raw CT, MRI and X-ray images to develop some of the most advanced anatomical maps available of bones, muscles and abdominal organs. These could soon be used as tools to train medical students, improve the accuracy of diagnosis and surgery and speed up patient recovery.

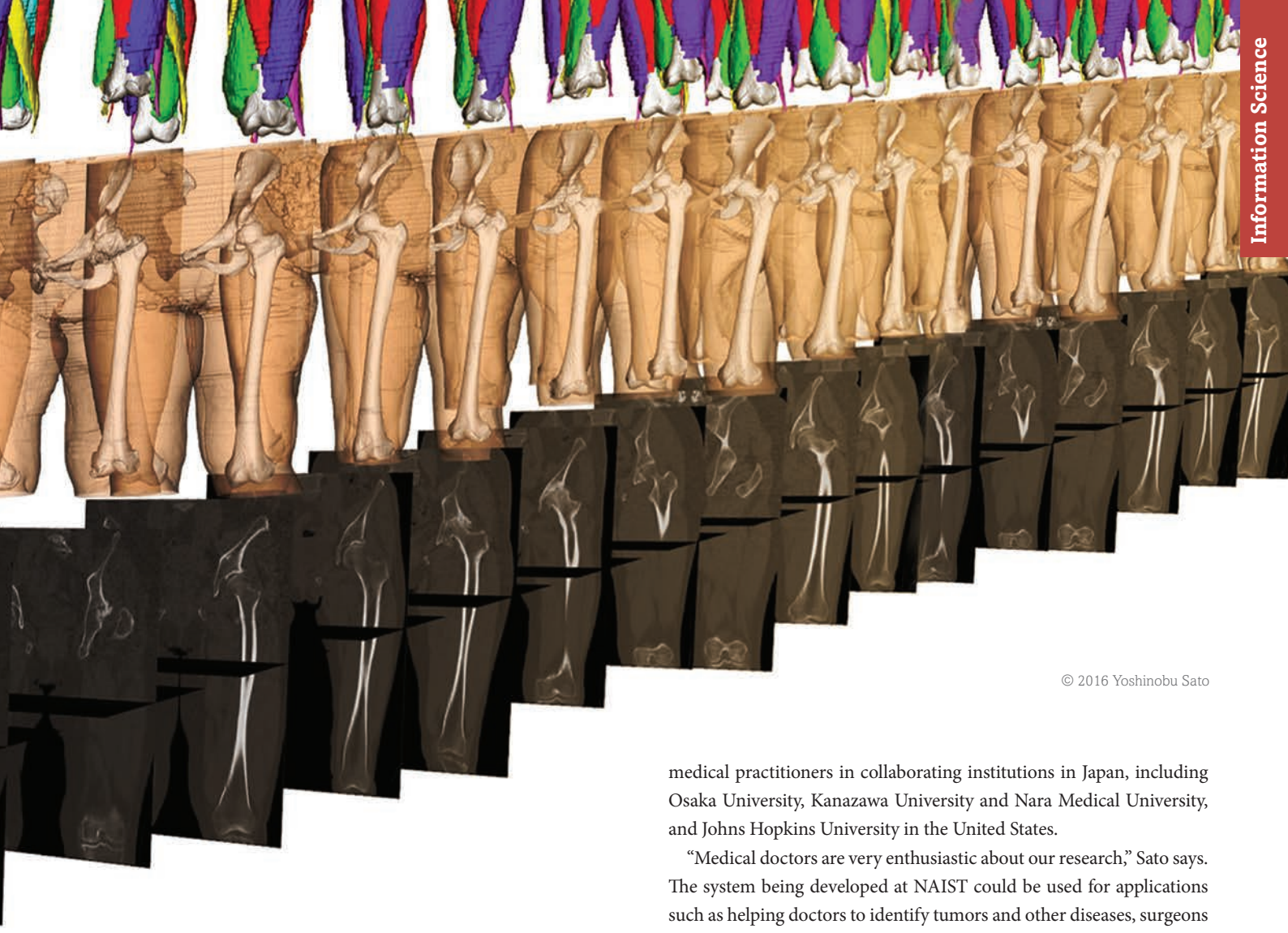
"We want to harness the power of computers for real clinical care," says Sato, the laboratory's head, who has 20 years' experience in this field. "The fun part about our job is developing systems that will really help patients get better," adds Otake, a specialist in X-ray image analysis.



Doctors often diagnose diseases by using machinery — such as CT and MRI equipment — that creates images using electromagnetic radiation to scan internal structures that are hidden to the naked eye. To make the most of these tools they need to spend years learning how to accurately interpret the sliced, black-and-white representations of interconnecting tissues and organs that they produce. Sato and Otake are now teaching computers to read these scanned images with similar or even higher degrees of accuracy. "For computers to understand medical images, they need to understand human anatomy," Sato explains.

Current image analysis software requires a lot of manual input. Imagine, for example, a doctor treating a patient suspected of having a diseased liver. They first have to draw the outline of the liver in a CT scan for the system to calculate its characteristics. Sato and Otake want to automate the entire process, and in the case of the liver, are using large image databases — known as 'medical big data' — to train computers to recognize the shape of this and the rest of the body's organs. The artificial intelligence system then gradually learns to predict the location of the liver, as well as other features of interest such as mass, tissue damage and any potentially cancerous growths.

To recognize multiple organs and tissues, the system employs a technique that would be familiar to lovers of jigsaw puzzles, Sato explains. It begins by identifying the easier sections, such as the skin and bones, before moving on to the more ambiguous regions of the muscles. "Basically our algorithm implements common sense," Sato says. This strategy creates a more accurate depiction of multiple organs as they appear in the context of the body. Sato compared the strategy to current state-



of-art techniques and found that the pancreas, aorta and inferior vena cava were more accurately defined using the hierarchical approach of the system developed by him and Otake.

The NAIST researchers' technique is also extremely versatile and can be used to describe many different bodily organs using a wide range of image formats, including images enhanced with contrast agents, such as dyes. By analysing X-ray imagery in real-time, the system could be brought into the operating room, and could be used to observe muscles in motion. "We are trying to combine image analysis with simulations to eventually be able to predict biomechanical function," Otake says.

> **"We are trying to combine image analysis with simulations to eventually be able to predict biomechanical function."**

The team plans to extend its application to the entire body and eventually to all diseased states and wants to improve the system's robustness by using larger databases of thousands of images.

Sato and Otake hope to bring their systems to clinical practise within the next five to 10 years. To achieve this, they are working closely with medical practitioners in collaborating institutions in Japan, including Osaka University, Kanazawa University and Nara Medical University, and Johns Hopkins University in the United States.

"Medical doctors are very enthusiastic about our research," Sato says. The system being developed at NAIST could be used for applications such as helping doctors to identify tumors and other diseases, surgeons to develop more accurate surgical plans and technicians to design implants more suited to a patient's personal bone shape and structure. The large database of knowledge embedded in the systems could also be used to teach medical students. Sato and Otake have already begun testing the technology for the construction and preoperative planning of knee, hip and arm implants.

Prior to total hip replacement surgery, experienced surgeons have to develop preoperative plans in which they identify the size, three-dimensional position and orientation of an implant using CT scans of a patient. Sato fed these previously generated plans to an automated system, and then tested the system's ability to generate pre-operative plans for new patients. The system effectively reproduced the plans of experienced surgeons in 40 cases.

Ultimately, Sato and Otake's research will lead to quicker and easier recoveries for patients as well as saving lives. "Our research will ultimately help to make surgery more accurate, precise and safe," Otake says.

More information about the group's research can be found at http://isw3.naist.jp/Contents/Research/ai-05-en.html
Researcher: Yoshinobu Sato

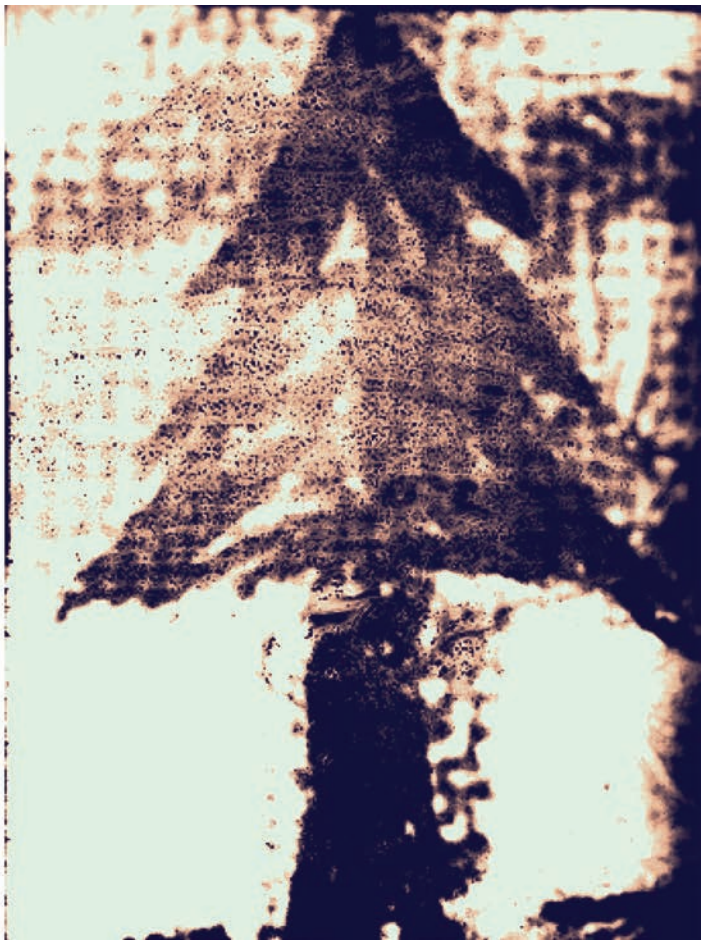
Optical Media Interface Laboratory | Professor Yasuhiro Mukaigawa

Imaging technology

A penetrating gaze

Vizualization of hidden features in objects such as paintings is improved by a sophisticated image processing technique

“Our method could also be applied to medical imaging to look inside the human body.”



Multi-frequency illumination can reveal hidden internal features of materials and objects, such as earlier artworks (right) that have been painted over (left).

Recently developed techniques such as X-ray fluorescence (XRF) and infrared reflectography (IRR) have given researchers a previously unimagined ability to look below the surface of paintings and other objects. They have, for example, found lost, obscured art, forgotten artists' signatures and multiple layers of paint beneath famous works of art such as the *Mona Lisa*.

Now, NAIST researchers have developed a non-contact method that allows them to see through the surface of translucent objects to visualize hidden layers[1]. Their technique makes it possible to sequentially unveil the history of objects such as paintings without the potential damaging effect of XRF and with more clarity than IRR. This next-evolution of depth-penetrating visualization has been developed by Yasuhiro Mukaigawa, who heads NAIST's Optical Media Interface Laboratory, Osaka University's Kenichiro Tanaka and colleagues.

"The structure inside a translucent object is often invisible due to overlying material. However, by removing the light-scattering effect of the upper layers, we can visualize a clear image of the internal structure," Mukaigawa explains. "The problem is, the appearance we normally observe is the visual 'sum' of all internal layers, and separating these layers as images is usually impossible."

The team began with a theoretical analysis of the problem. As light penetrates a material, it is progressively scattered by the matter until it can penetrate no deeper. This scattered light can then re-emerge from the surface, but is re-scattered on its way back out.

The researchers modelled this process as a series of depth-dependent 'point spread functions', and in doing so realized they could recover the deeper images by illuminating the material with a checkerboard pattern and processing the obtained images.

"We project a checkerboard pattern on to the material and scan the pattern pitch from small to large," Mukaigawa says. "We can then separate the internal layers corresponding to each pitch using some slightly complicated, but straightforward, computation."

The researchers used their 'multi-frequency illumination' technique to reveal with remarkable clarity hidden paintings and even the signed name of an artist whose work had been painted over.

This imaging technique also forms the basis for a document-scanning system that can filter out the appearance of the wrong side when scanning double-sided prints. Historical artwork and archiving, however, are not the only potential application of this technique. "Our method could also be applied to medical imaging to look inside the human body," Mukaigawa says.

Reference

1. Tanaka, K., Mukaigawa, Y., Kubo, H., Matsushita, Y. & Yagi, Y. Recovering inner slices of translucent objects by multi-frequency illumination. *Proceedings 28th IEEE Conference on Computer Vision and Pattern Recognition* 5464–5472 (2015).

More information about the group's research can be found at http://isw3.naist.jp/Contents/Research/mi-06-en.html
Researcher: Yasuhiro Mukaigawa

Christian Sandor

Blurring the edges of reality

Science fiction and real family hardship inspire this shining star of augmented reality

Ask Christian Sandor to summarise his research in one sentence and he will tell you he wants to build a holodeck. Star Trek fans will know, of course, that he's talking about the fictional virtual reality simulator that first appeared in the landmark sci-fi television series during the 1980s!

Sandor is now a 40-year-old computer science associate professor in NAIST's Graduate School of Information Science. But at heart, he's still a kid with a dream and he believes his vision can best be served in his new Nara laboratory base.

"There are really no limits to the research you can do at NAIST. It's the ultimate freedom," Sandor explains. "If someone offered me a place at Cambridge or Stanford University I wouldn't go. This is definitely the best place for my work."

Sandor is a leading light internationally in augmented reality, where technology aims to enhance our perceptions of real-world experiences. Inspired as much by science fiction as his studies, he's determined to bring his childhood dreams to life.

"When I was growing up, I watched a lot of *Star Trek*," Sandor admits. "I loved the holodeck room where you can experience anything you want, from a sandy beach to a historical setting, and everything feels completely real."

Sandor began his PhD in 2001 at the Technical University of Munich in Germany. As he began experiencing augmented reality with leading scientists such as Professor Gudrun Klinker, who is known for exploring links between augmented reality and wearable and ubiquitous computing, he realised his childhood

© TedX Adelaide

ambitions were already coming to life. “Professor Gudrun Klinker was actually making this idea happen, which was very inspiring for me,” Sandor recalls. “It was a very important juncture in my career.”

In 2004, Professor Steven Feiner, who directs the Computer Graphics and User Interfaces Laboratory at Columbia University, agreed to be Sandor’s associate PhD supervisor.

“Professor Feiner is a pioneer of this field,” Sandor says. “He’s mentored me a lot since then. I discuss every job offer with him.”

After completing his PhD in the United States, Sandor went to work at the Tokyo research headquarters of Canon, the Japanese multinational that specialises in imaging and optical technology. “At that time, Canon were by far the industry leaders in this area so I spent 2 years in Japan as a researcher,” Sandor says.

He then moved to the other side of the world, to Australia, where he founded the Magic Vision Lab at the University of South Australia in the city of Adelaide.

Industry collaborations on cutting-edge technology with multinational giants, Samsung and Google, followed. Despite substantial career success, however, Sandor still felt he could achieve more in a different research environment and in 2014 accepted an opportunity to work alongside Hirokazu Kato, heading up NAIST’s Interactive Media Design Laboratory. The institute’s drawcards were reduced teaching obligations, strong funding levels and atmosphere of intellectual freedom.

“When I was in Australia, I was teaching 12 hours a week. Now, I teach 12 hours a year,” Sandor says, explaining the appeal of the NAIST model. “This is fantastic because I have so much more time to do research. No professor I talk to, whether from America, Europe or China, can believe this.”

Sandor also appreciates NAIST’s financial resources. “I think in my first year, I spent more than [I did] in 6 years in Australia,” he says. “There is a continuous stream of funds from the university so you’re not completely dependent on government grants, and industry sponsorship.

“It means I could just sit in my office and have crazy ideas, if I wanted to. Very few places offer that opportunity.”

Sandor heads a team working on refining the augmented reality experience to make it indistinguishable from actual reality. “The two most important senses to get right are vision and touch,” he says. “A major problem for all augmented reality products is establishing a realistic depth of field. All the headset displays that are currently available suffer from this problem.”

In the real world, when an eye refocuses beyond an object it will become blurry, he explains. However, in the virtual world, all objects remain in focus. “So just by refocusing your eye you can immediately tell what is virtual and not virtual,” Sandor says. “Our lab now has a prototype that means when a person refocuses, the computer graphics will react accordingly. So I think we are leading in this area of research.” (See "Keeping it real in the virtual world" on page 18.)

Sandor’s team is also making progress in touch, a sensory area that offers even greater challenges when replicating the human experience. “We have a room-sized robot that we can use to experiment with touching large-scale virtual objects in a 3 × 3 × 2 metre workspace,” he says. “I don’t think any other research group has achieved that yet.”

As a teacher, Sandor is very comfortable with NAIST’s pedagogic model. “I do project work with my PhD and master’s students, which I prefer to the classical classroom teaching style. I actually don’t think that [traditional] model works very well,” he says. “Hands-on work is better than one-way communication.”

Throughout his career, Sandor has been inspired by his father, who escaped from communist Hungary in 1956, and created a prosperous life in Germany. “He had nothing,” Sandor explains. “But within 10 years he was a millionaire in Germany. That was inspiring for me. The idea that if you work hard you can achieve anything.

“My ultimate goal is for people [to] experience a world like in the movie *The Matrix*; a world where digital information and real things are blended together, so it’s not clear any more what’s digital and reality.”

More information about the group's research can be found at http://isw3.naist.jp/Contents/Research/mi-05-en.html
Researcher: Christian Sandor

Interactive Media Design Laboratory | Professor Hirokazu Kato

Augmented reality

Keeping it real in the virtual world

Tracking eye movements allows fast calibration of augmented reality displays

The eye-imaging camera automatically keeps the head-mounted display calibrated.

To appreciate how computer-made virtual realities are merging with our real-world experiences, we can look to pilots viewing heads-up displays of flight-paths or Google Glass users looking through web-based data at real scenes around them.

NAIST has much bigger ambitions than these. Combining actual and virtual realities, however, requires calibration systems to match the movements of a user with their view of the virtual objects with which they are interacting. Christian Sandor and colleagues at NAIST's Interactive Media Design Laboratory have helped develop a greatly improved calibration technique that can be performed simply, quickly and needs to be done only once[1].

"My mission in life is to build the ultimate display," says Sandor, describing his work on augmented reality systems in which virtual objects merge with the real world around us. He wants to build systems that allow users to be able to manipulate and feel computer-generated objects that can be examined and altered remotely. This could be useful for designers, doctors, city planners and anyone who needs to interact with objects and information not directly before them in the real world.

"The applications are literally endless," says Sandor, as he talks of concepts now found only in science fiction. To advance to more sophisticated options the current calibration procedures need to be greatly simplified. Many of the most advanced systems require the virtual images to be viewed through a headset. Sandor explains that putting on a headset and moving your head around to calibrate before each use is acceptable for a laboratory environment but not for general application.

His NAIST team, in collaboration with colleagues in Japan, Germany and the United States, has integrated an eye-tracking system into their augmented reality headset (see image). This means that after an initial calibration, the system automatically recalibrates each time it is put on.

> **"My mission in life is to build the ultimate display."**

Significant challenges remain before the eye-tracking calibration process can be incorporated into commercial applications. Some of these concern improving the accuracy and resolution of the calibration. Ironically, however, to make the user's experience ever more lifelike some challenges involve recreating the limitations of real life. "For example, we want to make graphics that get blurred like real objects do when users refocus their eyes," explains Sandor. To address such challenges, his work towards the ultimate display continues.

Reference

1. Moser, K., Itoh, Y., Oshima, K., Swan, J. E., Klinker, G. & Sandor, C. Subjective evaluation of a semi-automatic optical see-through head-mounted display calibration technique. *IEEE Transactions on Visualization and Computer Graphics*, **21**, 491-500, March 2015

To read more about the career of Christian Sandor, one of NAIST's newest researchers, see* Blurring the edges of reality *on page 18.

More information about the group's research can be found at http://isw3.naist.jp/Contents/Research/mi-05-en.html
Researcher: Christian Sandor

IMPACT

Augmented Human Communication Laboratory | Professor Satoshi Nakamura

Statistics to remove language barriers

BIG DATA AND ALGORITHMS ARE HELPING TO MAKE SIMULTANEOUS SPEECH-TO-SPEECH TRANSLATION A REALITY

Researchers in NAIST's Augmented Human Communication (AHC) Laboratory are pushing technological and international boundaries to boost the speed and accuracy with which computers convert spoken words from one language to another.

"We are aiming to beat the human interpreter with our speech-to-speech simultaneous translation," explains AHC Laboratory director, Satoshi Nakamura, one of the world's leading speech recognition and translation technology developers. AHC is a NAIST Super Research Group; established in 2011 with the broad agenda to 'go beyond the communication barrier' and examine 'next generation big data analytics'. The two areas are closely linked, says Nakamura, with big data increasingly being incorporated into the most effective and accurate translation systems.

> **"We are working on knowledge acquisition from the web and knowledge acquisition from the human being."**

Speech-to-speech translation is a three-step process. The initial speech recognition must first be performed as accurately as possible by the computer. Then the computer must translate what has been said into the target language, via a process known as machine translation. Finally, the computer synthesises the translated words into speech recognisable by the end-user.

Nakamura says the prospect of being able to have one's words translated automatically into another person's language has long been a dream for humankind. It's an area of strong government and industry interest across the world. In the United States, the Defense Advanced Research Projects Agency (DARPA) has been investigating speech-to-speech translation for use by defence personnel, while the European Union has been looking at it for use in its multilingual parliament. Separately, Microsoft has been working at speech and text translation for use as part of applications such as Skype.

Nakamura has been at the forefront of the field since he received his bachelor's degree from the Kyoto Institute of Technology in 1981 and joined the Sharp Corporation to help create a voice-activated word processor. "I was very much attracted to the study of the human perception or human understanding by computer," he explains. He was soon seconded from Sharp to be part of Japan's first national speech translation project, the Advanced Telecommunications Research Institute International (ATR). He received his PhD on that research from Kyoto University.

At the time, machine translation was largely a rules-based process, revolving around guidelines devised by linguists who set out what should happen when one language was translated into another. However, Nakamura was among the global research leaders to drive the shift in the early 21st century from the handcrafted rules-based model to the modern statistics-based model.

The statistical model has little need for linguistics and instead focuses on a corpus — or huge databank — of parallel sentences in each language, which is analysed to guide translations. "Once we collect a huge amount of data, the computer can determine the rules automatically," Nakamura

says. Putting this into practice in 2007, Nakamura and his colleagues created the world's first network-based speech-to-speech translation service for 3G mobile phones — the NTT Docomo 905i — at ATR. And in 2010, they created VoiceTra for the iPhone at Japan's National Institute of Information and Communications Technology (NICT). Both are designed to cater for travel-related translation, relatively short sentences of between two people at most, and have been accessed many millions of times. These applications, however, are limited by the need for translations to be done on a sentence-by-sentence basis to prevent misunderstandings. This significantly slows the process, as the translation of each sentence cannot begin until the previous one has been completed.

At NAIST's AHC Laboratory, researchers are now working to look for ways of overcoming this delay. They're looking to have the technology break up the sentences it 'hears' and, using algorithms, determine the probability of what the sentence will mean when complete, to come up with the most accurate translation.

At the same time, the accuracy of any translation is dependent on the size of the databanks of the original and target languages. To increase the size and scope of the language data stored, the AHC lab has an ambitious plan to be able to include information drawn from the internet. This is being done as part of the NAIST Big Data Project. "We are working on knowledge acquisition from the web and knowledge acquisition from the human being," Nakamura says. "And trying to determine how we can generalise the knowledge in order to use this knowledge to improve speech translation quality."

Prior to Nakamura's 2011 move to NAIST, he was a leader in international efforts to engineer compatible international networked translation systems. This is to ensure that the massive language databanks being created can be accessed internationally and enable multilingual translation of as many as possible of the world's more than 6,000 languages. He has helped devise standardized international communication protocols as part of the Universal Speech Translation Advanced Research (U-STAR) Consortium.

"It is very important to extend the speech-to-speech technology to various countries and their languages," Nakamura observes. This entails ongoing work with NICT and equivalent organisations in countries across Asia and the rest of the world.

Nakamura says he is now approaching one of his original research goals, to determine how human beings, and therefore computers, can understand speech.

"The interesting thing is that there are a lot of differences between the cultures and languages," he notes, "but all of these factors can be considered in speech-to-speech translation."

More information about the group's research can be found at http://isw3.naist.jp/Contents/Research/mi-02-en.html
Researcher: Satoshi Nakamura

Internet Engineering Laboratory | Professor Suguru Yamaguchi

Cyber behaviour

Eyes open to online security

An internet web user's gaze is linked to their likelihood of falling prey to online phishing scams

By tracking eye movements during online activities, NAIST researchers have identified the browsing habits that could be putting users at risk of online fraud[1]. The findings have the potential to plug one of the largest gaps in web security — user behaviour.

Online businesses invest heavily in securing websites for users. Financial institutions, for example, rely on extremely high levels of security for online banking. Such systems are generally resistant to hacking attacks. But organizations remain largely powerless to prevent users from being deceived by so-called 'phishing' scams that directly target their clients.

A typical phishing attack occurs when a user is directed to a bogus website that is a carbon-copy of a legitimate site and duped into entering login details, which can then be used by criminals. Although a phishing attempt can be easily identified by confirming the legitimacy of the web address before entering any personal details, it remains one of the most prevalent and successful of online scamming methods.

Eye tracking shows that when presented with a web page, expert web users spend most of their time evaluating the address bar. Novice users focus, instead, on page elements such as logos.

Youki Kadobayashi from NAIST's Internet Engineering Laboratory and project colleagues, Daisuke Miyamoto, from the University of Tokyo, and Gregory Blanc from Telecom SudParis drew on cognitive psychology insights to explore whether users display tell-tale signs that they might be susceptible to such attacks. Their investigation was conducted as part of the international NECOMA project, a cyber-defense research collaboration between the European Union (EU) and Japan. And, in a rare arrangement, it was supported by the EU's main instrument for research funding, the Horizon 2020 program (formerly the FP7 — Seventh Framework Programme for Research and Technological Development).

"Even experienced users can be at risk," Miyamoto explains. "When told that there has been suspicious activity on an online account, users' primary focus is on logging into the account to check for theft, not evaluating whether the notification itself is a potential phishing attack."

The research team set up a series of experiments to investigate whether the movement of a user's gaze around a web page could be used to flag browsing behavior that was putting them at risk of phishing. Using a software application that tracked eye movements via the computer's camera, the researchers were able to generate 'heat maps' of a user's gaze (see image) that told much about their level of security risk.

"We found that novices do not look at the address bar and do not have rigorous criteria for evaluating phishing," Miyamoto says. "This system could be used to warn users when they are not being wary enough, without being intrusive or blocking potentially legitimate websites."

The researchers are now developing a browser extension that interacts with eye-tracking devices to monitor user activity and phishing risk.

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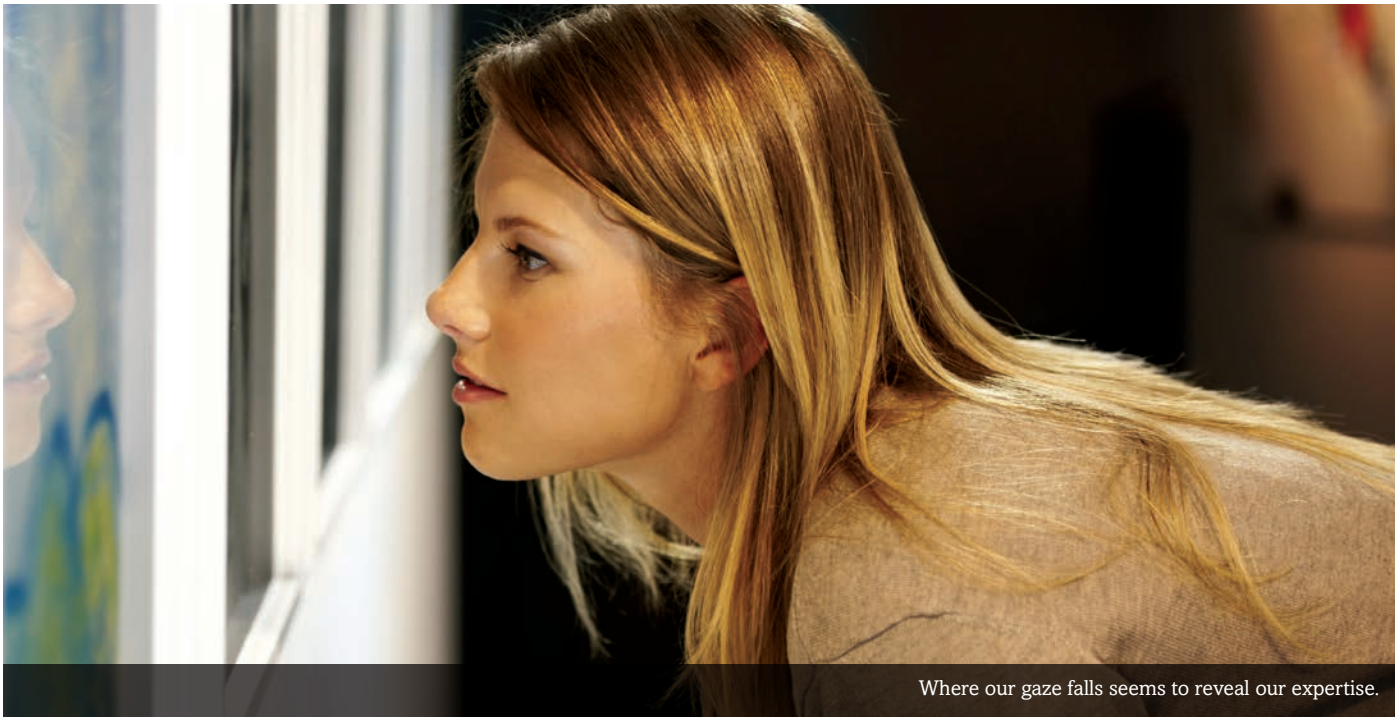
More information about the group's research can be found at http://isw3.naist.jp/Contents/Research/cs-07-en.html
Researcher: Youki Kadobayashi



Where our gaze falls seems to reveal our expertise.

Informatics

More to viewing art than meets the eye

Artists may extract visual information from different and deeper features in paintings than art novices

What do our eyes do when we look at a painting? Research suggests the answer depends on the viewers' expertise, a finding with surprisingly wide-ranging implications[1]. Differences in the way people look at a work of art could hold clues to the processes going on within a viewer's brain. The insights gained by NAIST scientists studying this issue may be applied to many other situations when the way we view a scene is influenced by our expertise and experience.

Naoko Koide is now part of the research team in Kazushi Ikeda's Mathematical Informatics Laboratory at NAIST. But her first degree was in fine art and she is intrigued by how people view art . . . literally. "Naoko wondered why and how artists and art novices were different," Ikeda explains. "She joined my lab to study the differences using neuroscientific methods." The NAIST team tackled the challenge along with co-workers at the National Institute of Information and Communications Technology, in Osaka, and Kyushu Institute of Technology, in Fukuoka.

The researchers used a commercial eye-tracking system based on infrared cameras that record where a subject's gaze is focused at time intervals of 100 milliseconds. The subjects were six art students with a high level of artistic ability and experience, and eight novices with no art expertise. To prevent any influence from depictions of obvious real-life objects, they viewed a variety of abstract paintings. Digitized versions of the paintings were used to classify the most obvious and striking aspects of each. The gaze of the art student 'experts' was found to be more widely focused on the paintings as a whole, compared to the novices who focused more on the obvious features.

"Our results suggest artists may extract visual information from paintings based on high-level features," Ikeda says.

By this he means that the artists' knowledge and experience leads them to look beyond the most obvious visual stimuli in a painting and pay more attention to deeper details.

"Artists are an example of experts," he adds, and so they may reveal insights into the behavior of many kinds of experts. Ikeda is now investigating other activities in which visual attention is crucial, such as driving a vehicle.

It may eventually become feasible to detect whether or not someone has specific expertise or experience just by monitoring their gaze. How we look at things, it seems, may reveal secrets about what we know.

Reference

1. Koide, N., Kubo, T., Nishida, S., Shibata, T. & Ikeda, K. Art expertise reduces influence of visual salience on fixation in viewing abstract paintings. *PLOS One* **10,** e0117696 (2015).

More information about the group's research can be found at http://isw3.naist.jp/Contents/Research/ai-04-en.html
Researcher: Kazushi Ikeda

Ubiquitous Computing Systems Laboratory | Professor Keiichi Yasumoto

Yutaka Arakawa

Embedded in life

The iPhone changed everything for this ambitious inventor who is using information to tweak human behaviour

As a child, computer scientist Yutaka Arakawa spent a lot of time making things in a "secret lab space", where he tinkered with a soldering iron creating electronic gadgets.

It was a portent of things to come. "In my mind, I'm not a true scientist," he says of the direction his professional life has taken. "But an engineer with academic knowledge."

Arakawa spent the first 12 years of his science career at Tokyo's Keio University, where he gained his PhD in engineering and moved swiftly up the ranks to become an assistant professor.

"In the early part of my career, I was researching the high-speed broadband network, and how the network could work more efficiently," Arakawa recalls, describing it as an "interesting but heavy" research field.

"It required a massive budget and lots of cooperation with companies. If you proposed an improved method, then the process would need to be standardized before it could be distributed," he says, explaining that because there were many researchers working together, the contribution of each became diluted.

"I felt this kind of research was good for the company, but bad for young researchers."

In his spare time, Arakawa was developing applications and websites for fun. And soon his desire to make an individual contribution to the fast-developing digital communications industry became overwhelming.

During his PhD studies, the young scientist had been working as a software engineer at a technology company. But after several years, Arakawa realised that as fast as he could develop a new idea, his commercial competitors would catch up. "Technologies evolved every year, so it was exciting, but I felt unstable," he says. "Any small technical advantage was soon used by other companies.

"At this point I received some good advice. My PhD supervisor, Naoaki Yamanaka, a professor at Keio University, encouraged me to keep exploring novel technology in an academic position. He told me to find a great technical advantage for establishing a strong commercial company," Arakawa says.

He knew Yamanaka was right and in 2006 Arakawa accepted an assistant professor position at Keio where he began exploring new technology that could help him establish his own company in the field of computer networks. "It was not easy. In two years I couldn't find an idea," he says. "Then the iPhone came along, and I decided to change my research topic drastically from computer networks to smartphone technology!"

Arakawa began exploring ubiquitous computing systems — where sensors and wireless networks are incorporated directly into our lives via the world around us, and everyday items have embedded microprocessing technology.

"This decision changed my life. I succeeded in getting a new position with Kyushu University [in Fukuoka], in 2009," he says. "I found the new research topics interesting and had many

good ideas. In 2011, I won an international scholarship to study in France and Germany for 15 months."

Soon after returning to Japan in 2013, Arakawa joined the cutting-edge Ubiquitous Computing Systems Laboratory at NAIST and he's become passionate about developing sensors that allow people to increase their self-awareness.

"To understand a human by using various sensors is very interesting to me. And I love wearables," he explains. "It is so exciting to create a new service that can be installed into any user's smartphone or gadget to give them a new experience."

For scientists such as Arakawa, whose work must keep pace with heavily resourced global IT companies, finding the right research environment is key. "Creativity, implementation and speed are the important points. In our field, Apple and Google are very powerful leaders. They have lots of money, and stimulating work environments," Arakawa says. "Therefore, we must propose novel and creative ideas to match them, and also create a productive workplace with excellent facilities.

"In my lab at NAIST we are lucky. Researchers have big budgets, and are encouraged to explore innovative research topics. We have created a good, collaborative atmosphere where students stay late, chat and forge friendships, while working on breakthrough science."

Arakawa's team is made up of scientists whose skills complement one another. "In Japan, one professor generally manages one laboratory. But at NAIST, the professor teams up with an associate professor and two assistant professors to manage one laboratory," he says. "All of them work together for one goal without question. Only a few universities in Japan have this style, and it's one of the reasons I wanted to work here."

Arakawa says that this style of collaboration helps move his research forward more quickly. "For example, I'm not good at analysing the data from my work. So in the past, my research has stopped when I no longer have the skills to take an idea further," he says. "Now, I can collaborate with my assistant professor who is an expert in data mining. This leads to new knowledge that we can use to propose a new research application."

Arakawa is now close to preparing his first product for market, a small sensor board that he has been developing for the past decade. And his research focus is shifting towards the next step for his field — computational intervention. (See "Playing with urban sensing" on page 30.)

"This is when our behaviour is changed by information," he says explaining that a simple example is a recently launched location-based mobile game called Ingress. "Participants move in the real world based on the information from the internet. The game tells players to visit places in order to get points, so it encourages exploration and exercise."

To Arakawa, such an intervention is the beginning of a deeper conversation: "We start considering how we can evoke changes in human behaviour, and encourage behaviours that are more sustainable for society."

More information about the group's research can be found at http://isw3.naist.jp/Contents/Research/cs-03-en.html
Researcher: Yutaka Arakawa

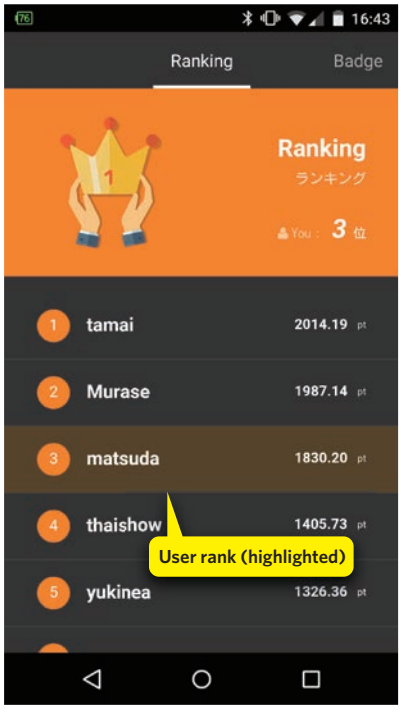
Ubiquitous Computing Systems Laboratory | Professor Keiichi Yasumoto

Ubiquitous computing

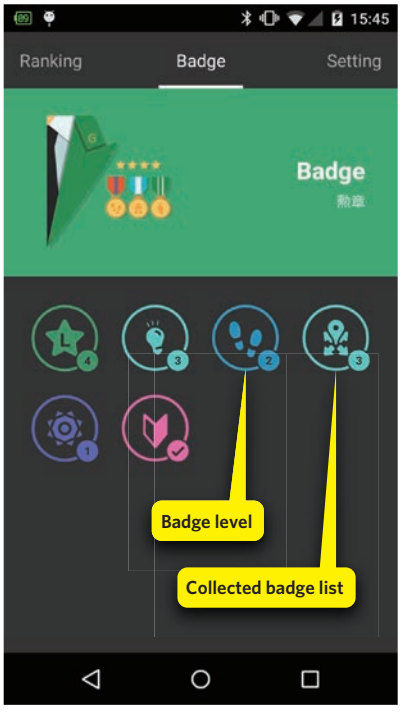
Playing with urban sensing

Using crowds to collect data is an invaluable resource for planning and public health, and these researchers want to make it fun

Ranking system



Badge system



Badges and rankings from a smartphone app that 'collects' the brightness of street lamps.

Researchers working on urban planning, environmental monitoring and public health issues have turned to crowds of people with smartphone, to collect and analyze data on a scale beyond anything previously possible.

It's called 'participatory sensing' and because it relies on volunteers' willingness to submit accurate, up-to-date information, incentives are needed to maintain continued user involvement.

Money is one obvious lure, but with research budgets typically limited, two NAIST information technology experts have applied game play techniques to motivate engagement. "I want to make sensing more fun by introducing gamification," explains Yutaka Arakawa from NAIST's Ubiquitous Computing Systems Laboratory.

In an invited commentary in the *Journal of Information Processing*, Arakawa and colleague Yuki Matsuda liken the problem of encouraging participatory sensing to sailing[1]. The yacht could be fitted with an engine, but the gasoline to run it would be expensive. Gamification, they argue, provides a natural

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energy source — the wind in the sails, as the metaphor goes — although the moving yacht must continuously resist the "splashing waves" of disinterest and dissatisfaction from users.

The authors discuss two gamification experiences from their own participatory sensing research that deal with these "splashing waves". In one study, Arakawa and colleagues asked participants to report various features of the surrounding environment with photographic or textual explanations; using points, titles and rankings to keep people immersed in the task at hand. The other, from Matsuda and a collaborator, called for participants to collect information on the brightness of street lamps, integrating badges, rankings and maps to provide similar incentives for involvement.

In these two instances, the gamification elements worked "so-so," Arakawa admits. "There are many issues that should be improved." But generating more fun and value for participants is not easy. "The balance of game and sensing is a difficult issue," he says. But it's not insurmountable. Arakawa points to the community-based traffic and navigation app Waze, which is wildly successful with more than 50 million drivers worldwide uploading information such as the price of gas or location of accidents. He expects many more similar platforms to trickle into our lives.

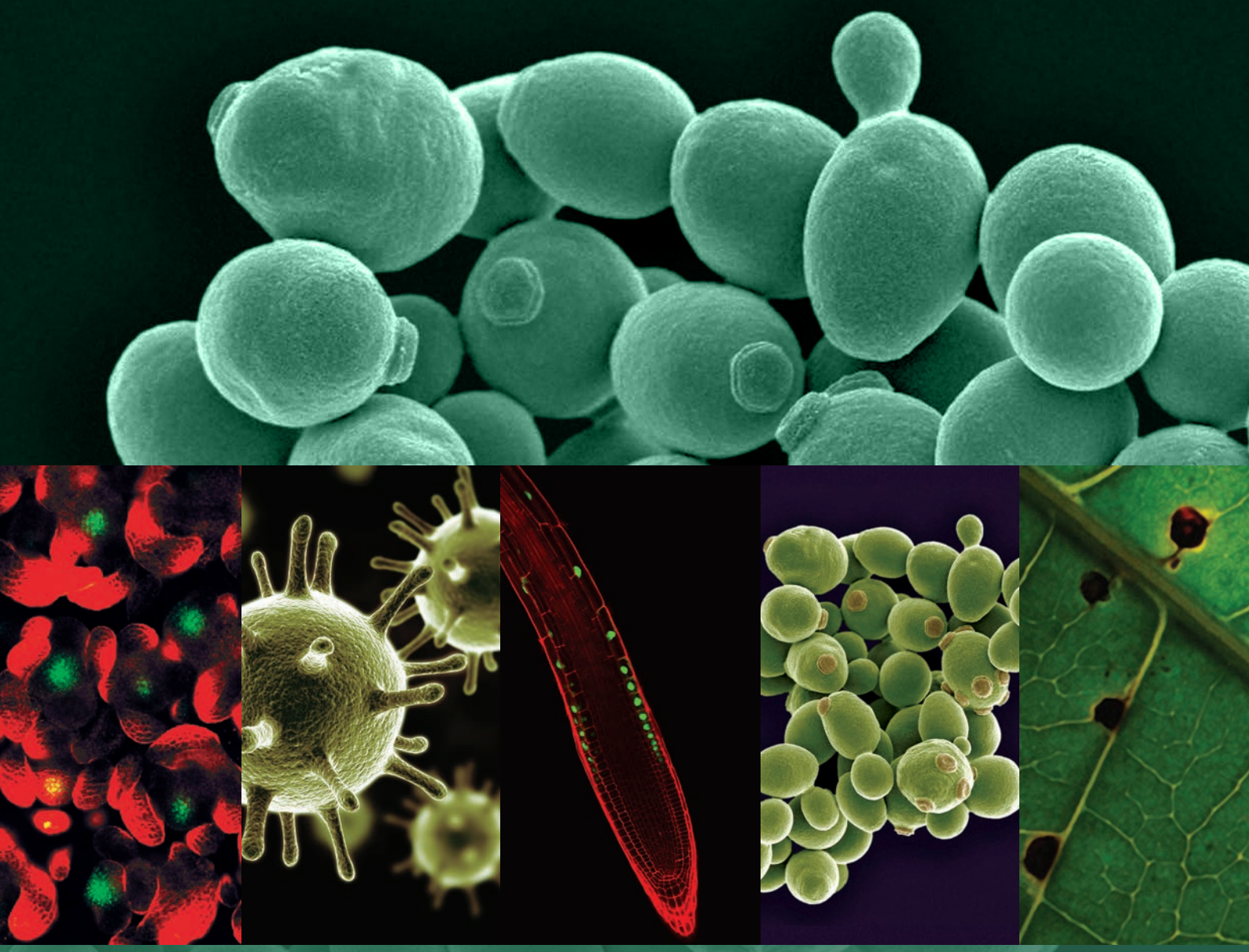
"Various human activities promoted by gamification would be helpful for our future," Arakawa says. "If we successfully introduce 'fun' into various social problems, I expect that gamification will be one of the most important ingredients for a smart and sustainable society."

Reference

1. Arakawa, Y. & Matsuda, Y. Gamification mechanism for enhancing a participatory urban sensing: survey and practical results. *Journal of Information Processing* **24**, 31–38 (2016).

To read about the inspiration behind the work of Yutaka Arakawa, another of NAIST's newest researchers, see* Embedded in life *p28.

More information about the group's research can be found at http://isw3.naist.jp/Contents/Research/cs-03-en.html
Researcher: Yutaka Arakawa



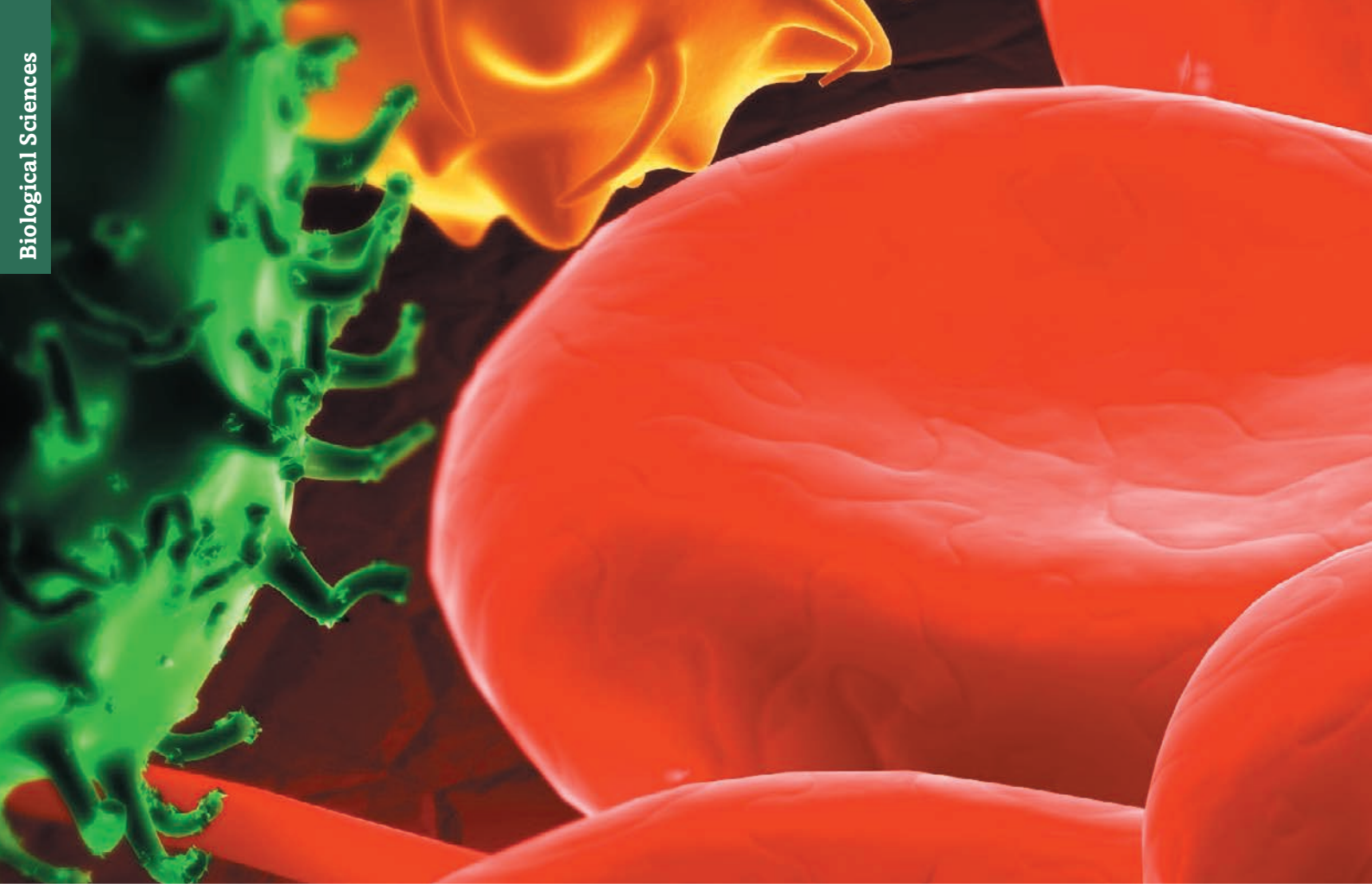
Biological Sciences

IMPACT

Functional Genomics and Medicine Laboratory | Associate Professor Yasumasa Ishida

Search for a sense of self in immunity

NEW RESEARCH AIMS TO ANSWER ONE OF MEDICINE'S BIGGEST QUESTIONS: HOW DO THE BODY'S IMMUNE CELLS DETERMINE WHAT IS SELF AND WHAT IS NOT?



The immune system's ability to identify what to tolerate and what to attack is a puzzle that has gripped laboratories worldwide for decades. At NAIST, the Functional Genomics and Medicine Laboratory, led by Yasumasa Ishida, is at the forefront of this research with new investigations of the PD-1 gene that effectively switches parts of the body's T-cell immune response on and off.

This work has the potential to transform medicine, from transplants and the treatment of autoimmune diseases and cancers, to vaccines and chronic disorders. "No one doubts that PD-1 plays some kind of pivotal roles in 'self–nonself' discrimination by T cells," Ishida explains. "We are trying to elucidate its real physiological functions to better explain its role in cancer and other diseases and so enable more effective and less-damaging treatments."

> **"PD-1 appears to be protecting cancer cells from attack by the immune system. Is PD-1 on our side, or on the side of cancer cells?"**

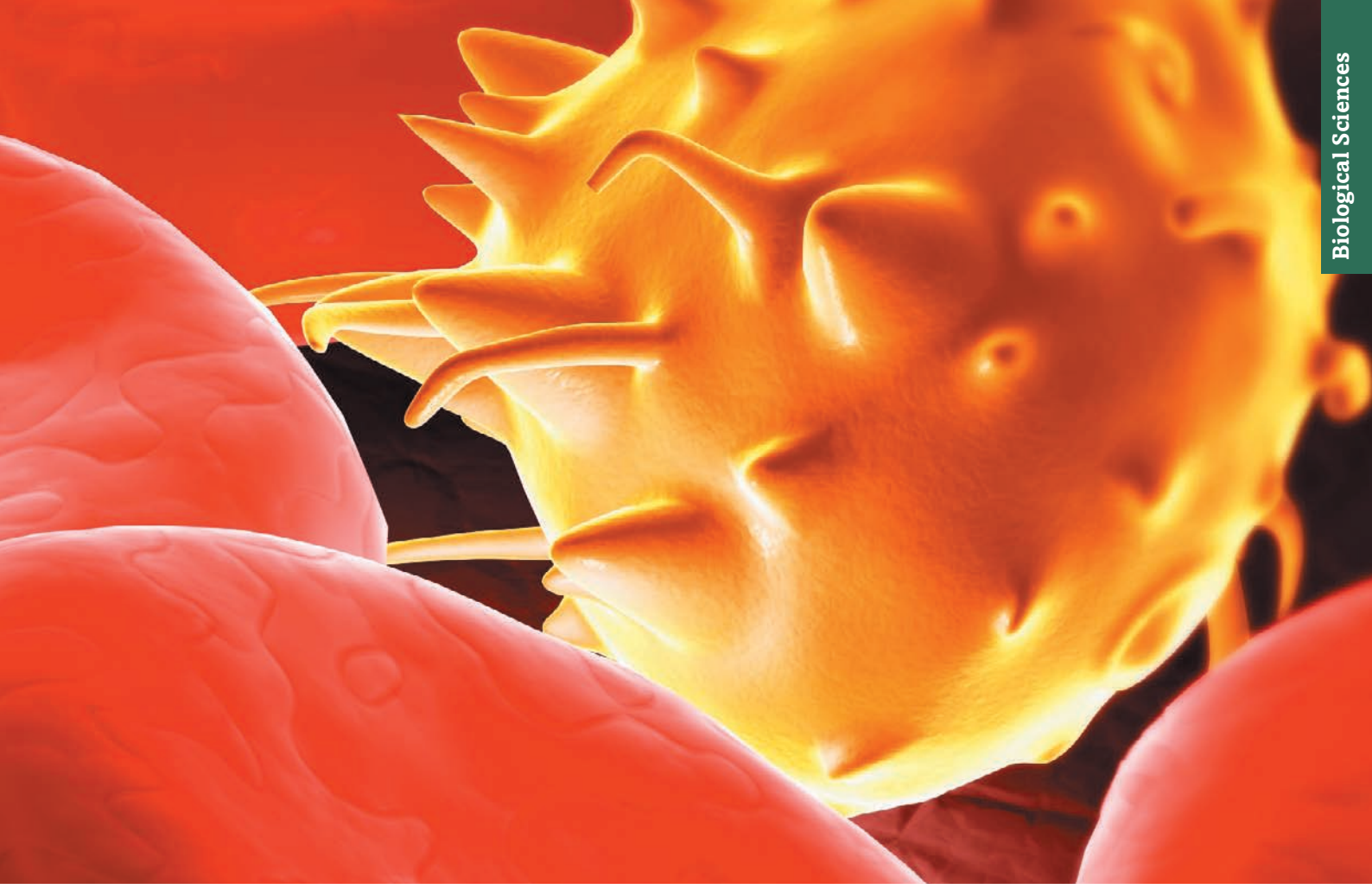
It was Ishida who first identified the PD-1 gene, in 1991 when he was an assistant professor at Kyoto University, under the supervision of Tasuku Honjo. At the time, there was a global race to find the genes that caused cells to undergo 'programmed cell death' as part of normal development. This happens on a large scale to immature T cells in the thymus, as part of the body's effort to weed out ineffective or overaggressive immune cells.

Ishida's interest in immune research was sparked during his medical training, when he became fascinated by the mechanisms behind graft rejection in transplant patients. "I wondered why the same human tissues are rejected by our immune system and I strongly wished to understand the molecular mechanisms with which our T lymphocytes – the conductor of the immunity orchestra — could distinguish 'self' from 'nonself'," Ishida says.

At Kyoto he used the then relatively new genetic analysis technique, subtractive hybridization, to try to determine what gene or genes in T cells were being expressed when the cell deaths occurred. His work identified the single gene that he labelled the PD-1 gene, for programmed death. However, not long afterwards it was found that the expression of this gene, also called *PDCD1*, did not induce cell death but instead stopped the immune response of T cells.

Expression of the gene creates the signalling protein, PD-1, that forms a receptor on the surface of the T cell. When this receptor is linked with one of its ligands — PD-L1 or PD-L2 — it triggers inactivation of the cell's immune response, stopping it from destroying cells it would otherwise attack.

In the case of melanoma, renal, lung and blood cancers, and potentially many others, the tumours appear to use PD-1 signalling to stop the



immune system attacking them. Recent breakthrough immunotherapies block the PD-1 signal, using a PD-1 or PD-L1 antibody to prevent the cancer cells triggering PD-1 activation, and allowing the body's T cells to attack tumours. When successful, the altered T cells become serial killers and even a small number can wipe out a large tumour.

These new immunotherapies have been led by PD-1 antibody drug, nivolumab — which has been approved since 2014 and 2015 by the US Food and Drug Administration for use as a targeted therapy to treat melanoma and certain lung and kidney cancers. Nivolumab has been yielding outstanding results in people with metastatic cancers that haven't responded to other treatments. In many cases it has been shown to cause aggressive tumours to shrink rapidly before disappearing. The benefits appear to be long-lasting, without the need for ongoing intense treatment.

Alongside this, there is a mounting body of research from the United States, Australia and India suggesting that PD-1 might also be central to chronic conditions such as HIV, hepatitis, tuberculosis and malaria. Further evidence indicates that PD-1 also plays critical roles in the regulation of autoimmunity, transplantation immunity, allergy and immune privilege.

In addition to cancer immunotherapies, pharmaceutical companies are looking into the development of new PD-1-related drugs for the treatment of autoimmune conditions such as rheumatoid arthritis; using the stimulation of PD-1 to prevent the immune system from attacking the normal host cells.

"PD-1 appears to be protecting cancer cells from attack by the immune system. Is PD-1 on our side, or on the side of cancer cells?" Ishida asks. "Why do almost all of the 'bad guys' — cancer cells, chronically virus-infected cells, *Mycobacterium tuberculosis*, malaria parasites, and more — target PD-1 for their long-term survival in our body? These are the remaining unanswered questions."

At the NAIST Functional Genomics and Medicine laboratory, Ishida and his colleagues are now focussed on creating a coherent explanation of how the PD-1 gene influences the immune system. Their hypothesis is that the gene plays a pivotal role in how the body distinguishes between what is self and what is foreign. To test this, the lab is using functional genomics to further investigate when and why the PD-1 gene is expressed and what impact this has on the body over time.

These questions have personal significance for Ishida. He explains: "I am obliged to carry out this project because explanation of the molecular mechanisms involved in self–nonself discrimination by the immune system was the ultimate goal for me from the very beginning of my career as a scientist."

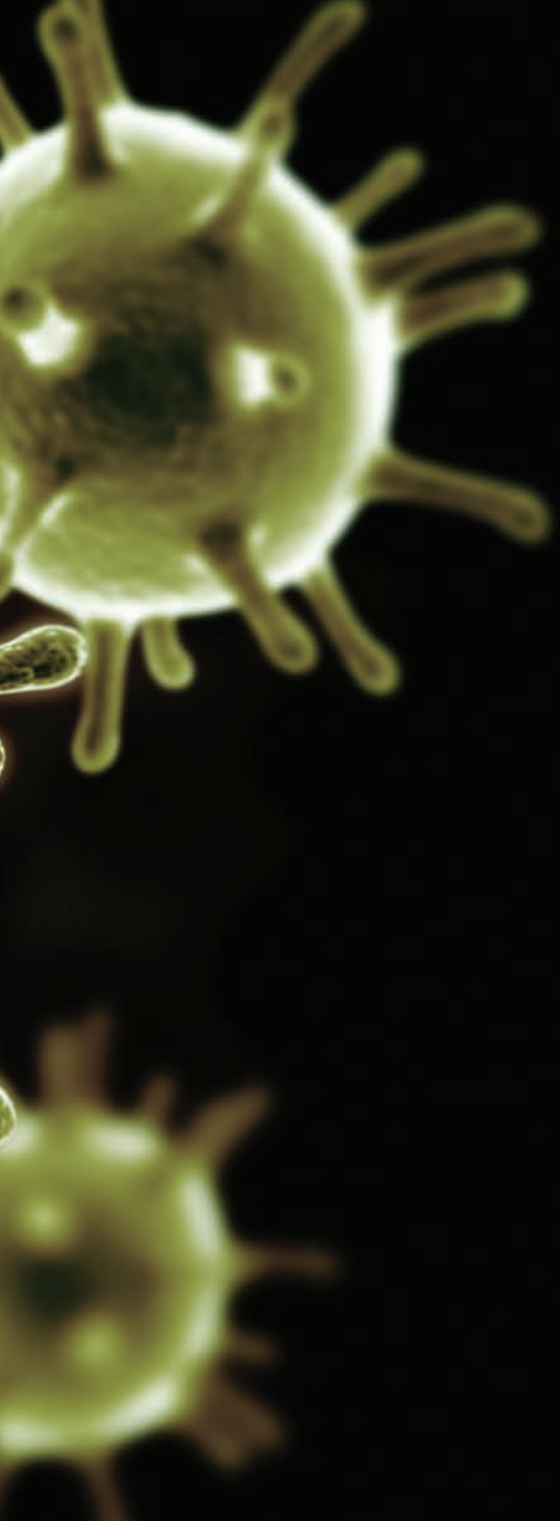
More information about the group's research can be found at http://bsw3.naist.jp/eng/courses/courses211.html
Researcher: Yasumasa Ishida

Molecular Immunobiology Laboratory | Professor Taro Kawai

Molecular immunity

On the pathway to successful therapies

Molecules that trigger innate immunity could be potential targets for new antiviral drugs



> **"By understanding the molecular mechanisms and signalling processes that lead to the production of IFN, we can find ways of boosting the body's natural immunity."**

When a person is infected by a virus or other pathogen, the immune system must be activated quickly for it to detect invading cells and prevent the infection spreading. Researchers at NAIST are investigating this response, focusing on the role of individual proteins and lipids and how they aid the work of innate immune receptors[1].

It is the job of innate immune receptors, including RIG-I-like receptors (RLRs), to sense pathogen replication within cells and trigger the production of the body's protective agents, such as type 1 interferon (IFN). Taro Kawai from NAIST's Molecular Immunobiology Laboratory and colleagues are investigating the molecules responsible for triggering and regulating innate immune responses, with the goal of developing new antiviral and anticancer therapies.

"By understanding the molecular mechanisms and signalling processes that lead to the production of IFN, we can find ways of boosting the body's natural immunity in the face of illness," Kawai explains. In 2013, he and his co-workers uncovered the role of a lipid called phosphatidylinositol-5-phosphate (Ptdlns5P), which plays a key part in activating IFN production[2]. They found that levels of Ptdlns5P, which is produced from a kinase called PIKfyve, increase rapidly upon viral infection. Ptdlns5P then directly binds to the transcription factor IRF3 and its associated kinase TBK1. This in turn activates the signalling pathway that induces IFN.

Knocking down PIKfyve resulted in decreased Ptdlns5P and IFN levels, leading to a rise in viral replication. Perhaps most importantly, the researchers found that when they added an artificial version of the lipid, called C8-Ptdlns5P, to a vaccine, they were able to significantly boost immune responses in mice. "Ptdlns5p might be a good target for the design of vaccines against viruses like Influenza A," Kawai says. "Further in-depth analysis of C8-Ptdlns5P will tell us more."

Kawai's other recent work includes the discovery of a protein crucial to the correct functioning of RIG-I-mediated innate immunity. Kawai's team believes that the significance of the protein, known as MEX3C, means it could be targeted for inactivation by evolving viruses[3].

Although RLRs help protect the body against invading pathogens, a carefully balanced regulatory system is needed to mediate their behavior and prevent the development of excess inflammation and autoimmunity. Kawai is working to pinpoint the key players in this regulatory system, and his findings may one day guide the treatment of inflammatory diseases such as multiple sclerosis. He hopes that in future it will be possible to enhance natural innate immunity via designed therapies inspired by such research.

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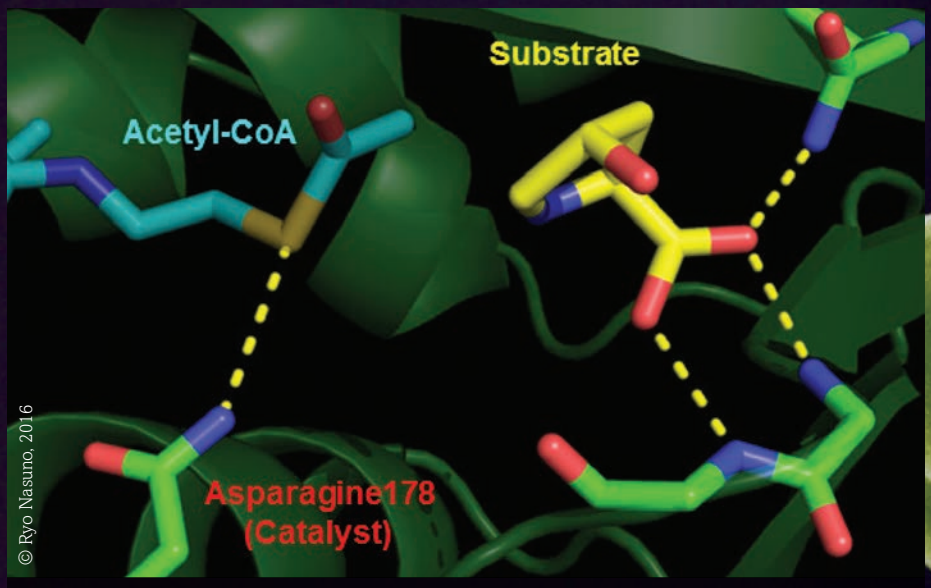
3. Kuniyoshi, K., Takeuchi, O., Pandey, S., Satoh, T., Iwasaki, H., Akira, S. & Kawai, T. Pivotal role of RNA-binding E3 ubiquitin ligase MEX3C in RIG-I–mediated antiviral innate immunity. *PNAS* **111,** 5646–5651 (2014).

More information about the group's research can be found at http://bsw3.naist.jp/eng/courses/courses209.html
Researcher: Taro Kawai



Using structure-based molecular design, NAIST researchers have created the thermostable yeast protein Mpr1 that could increase tolerance to heat stress of industrial yeasts.

Molecular design

Brewing a heat-loving yeast species

The crystal structure of a protein is helping generate yeast strains with increased stress tolerance

> "The support of a multi-disciplinary team at NAIST enabled us to visualise Mpr1 in atomic-level detail."

Yeasts have been used for centuries for industrial applications such as food production and there is much potential in developing strains capable of withstanding heat shock, freezing temperatures and ethanol treatment. NAIST scientists have been exploring the structure and function of individual molecules within yeast species and using their results to generate more robust modern strains.

Recently, Hiroshi Takagi, head of NAIST's Applied Stress Microbiology Laboratory, and co-workers have been examining an unusual yeast protein from the Gen5-related N-acetyltransferase (or GNAT) superfamily called Mpr1, homologs of which are found in most species of yeast and fungi.

They have established that in *Saccharomyces cerevisiae* — a yeast species that's been used for centuries in wine and bread making and brewing — Mpr1 reduces levels of reactive oxygen species in cells via the conversion of an imino acid known as P5C, and this lends a degree of protection from environmental stresses.

Mpr1 also appears to mediate a metabolism process that results in the creation of nitric oxide, another aid to increased tolerance.

In 2013, Takagi and his team successfully visualized the crystal structure of Mpr1 and its complex with substrate cis-4-hydroxy-L-proline (CHOP) in high resolution for the first time[1]. Their findings have since allowed the team to work on Mpr1 mutant forms of yeast with higher heat tolerance.

"It took considerable time and repeated attempts to achieve crystallization of Mpr1 at a high enough quality to determine its structure," explains Ryo Nasuno, Takagi's graduate student. "The support of a multi-disciplinary team at NAIST enabled us to visualise Mpr1 in atomic-level detail."

The researchers found that, while Mpr1 shared a folding structure with other GNAT proteins, it exhibited a unique reaction mechanism. The team was surprised to discover that Mpr1 uses one of its own amino acid residues, Asn178, as a catalyst — a unique feature. A further amino acid, Asn135, plays a critical role in substrate recognition and directly binds Mpr1 to CHOP.

"We then examined the roles of Asn135 and Asn178 in more depth by creating mutant forms of Mpr1," Nasuno says. "Making these amino acid substitutions had a knock-on effect on levels of P5C. These insights helped us learn how to manipulate yeast cells' reaction to heat stress."

Takagi and his team have recently designed Mpr1 mutants with higher thermostability based on the crystal structure of Mpr12. They also hope to breed new industrial yeast strains with the ability to support fermentation at higher temperatures. Their insights into the antioxidative properties of yeast mediated by Mpr1 could also help with the development of anti-fungal drugs.

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More information about the group's research can be found at http://bsw3.naist.jp/eng/courses/courses305.html
Researchers: Ryo Nasuno and Hiroshi Takagi

FEATURE

Plant Symbiosis Laboratory | Associate Professor Satoko Yoshida

Satoko Yoshida

Planting seeds of wisdom

A career spent looking for answers in the natural world continues on a prestigious path

While she was at high school, Satoko Yoshida began noticing that her biology textbook was sometimes short on facts. More than a decade later, she's about to join NAIST's Graduate School of Biological Sciences as a tenure track associate professor and it's fitting that she's chosen an institute with a reputation for rewriting text books.

"I remember that some of the descriptions in my books were ambiguous," Yoshida recalls. "For example, one text read: 'The presence of a flowering hormone is expected, but hasn't been found.'" In 2007, the late NAIST plant molecular geneticist, Ko Shimamoto, found the first such hormone, a protein known as florigen Hd3a, which induces flowering in rice.

"Until that point I believed that textbooks must contain only facts," Yoshida says. "But then my high school teacher pointed out that information had changed even since the book was written."

Yoshida — a plant biologist with particular expertise in molecular biology, genetics and genome biology — specialises in parasitic plants. Fascinated by the diversity and flexibility of botanical structures, she has focused her research on plant symbiosis: the phenomenon of organisms living in close association with each other, often to the detriment of one but benefit to the other.

"I have always been interested in plant science, but my current research field is entirely a coincidence," Yoshida says. After finishing her PhD on leaf senescence at the University of Tokyo, she felt that her research area was becoming crowded.

"I was working on *Arabidopsis* and at that time the research field was becoming more competitive," she says, referring to the flowering plant *Arabidopsis* that is used as a model system in botanical genetics. Yoshida shifted her attentions to the species *Lotus japonicus* and plant symbiosis, when she accepted a postdoc position at The Sainsbury Laboratory in the United Kingdom. She became fascinated by inter-organism interactions and fortunately her path crossed with that of molecular biologist, Ken Shirasu, who specialised in the area. At the time he was a group leader in the Sainsbury lab and he went on to become Yoshida's mentor for the next decade.

After leaving the United Kingdom, Shirasu became a group director at the Japanese research institute, RIKEN, and encouraged Yoshida to join him. Within a decade she had become a senior research scientist at RIKEN's Center for Sustainable Resource Science. "Ken invited me into the world of parasitic plants. He supported me for almost 10 years in RIKEN," Yoshida says of her long-time mentor. "He taught me how big the agricultural problem of parasitic plants is and explained how only a few laboratories are working on the molecular biology of parasitic plants. He let me work freely as I liked."

The parasitic plants that Yoshida is currently studying include *Striga* spp, some of which are major agricultural pests, and *Phtheirospermum japonicum*. (See *Exploring the secrets of parasitic plants* p42). Because some species of *Striga* cause twisted growth and discolouration in the plants they infect, the group has the common name of witchweed.

"We are trying to understand the molecular mechanisms of plant parasitism; how they recognise host plants, develop the invasion organ and connect compatible vasculatures between plants," Yoshida says. "We are also working on how to make host plants resistant, in order to prevent parasitic weeds from taking over."

In recent years, Yoshida and her team have been working on plant models to identify the genes that regulate parasitism. "We can now identify mutated genes by a process of forward genetic screening," she explains. "During the last few decades, mutation identification has become easier and can be done in a shorter time. You used to only be able to do it in model species. But now, because sequencing techniques have improved dramatically, any plants can be sequenced."

Yoshida hopes that future analysis of plants at the molecular level will lead to breakthrough developments in scientists' understanding of plant diversity. After a decade working at RIKEN, Yoshida will this year move to NAIST and is excited about what this will mean to the next stage of her career.

"NAIST scientists and the facilities are some of the best in the world. I think that if you gather top-class professors in the same building then this synergy will increase the quality of science output," Yoshida says. "People with diverse skills and expertise have a very positive effect on the progress of research."

Having worked closely with mentors for much of her career, Yoshida understands the importance of close professional relationships between professors and students. "The students at NAIST are very motivated and high calibre, which makes it an attractive place to work for me," she says. "Because there are no undergraduate courses, all students actively decide to come to NAIST. So that focus on science discovery and education is decisive and clear."

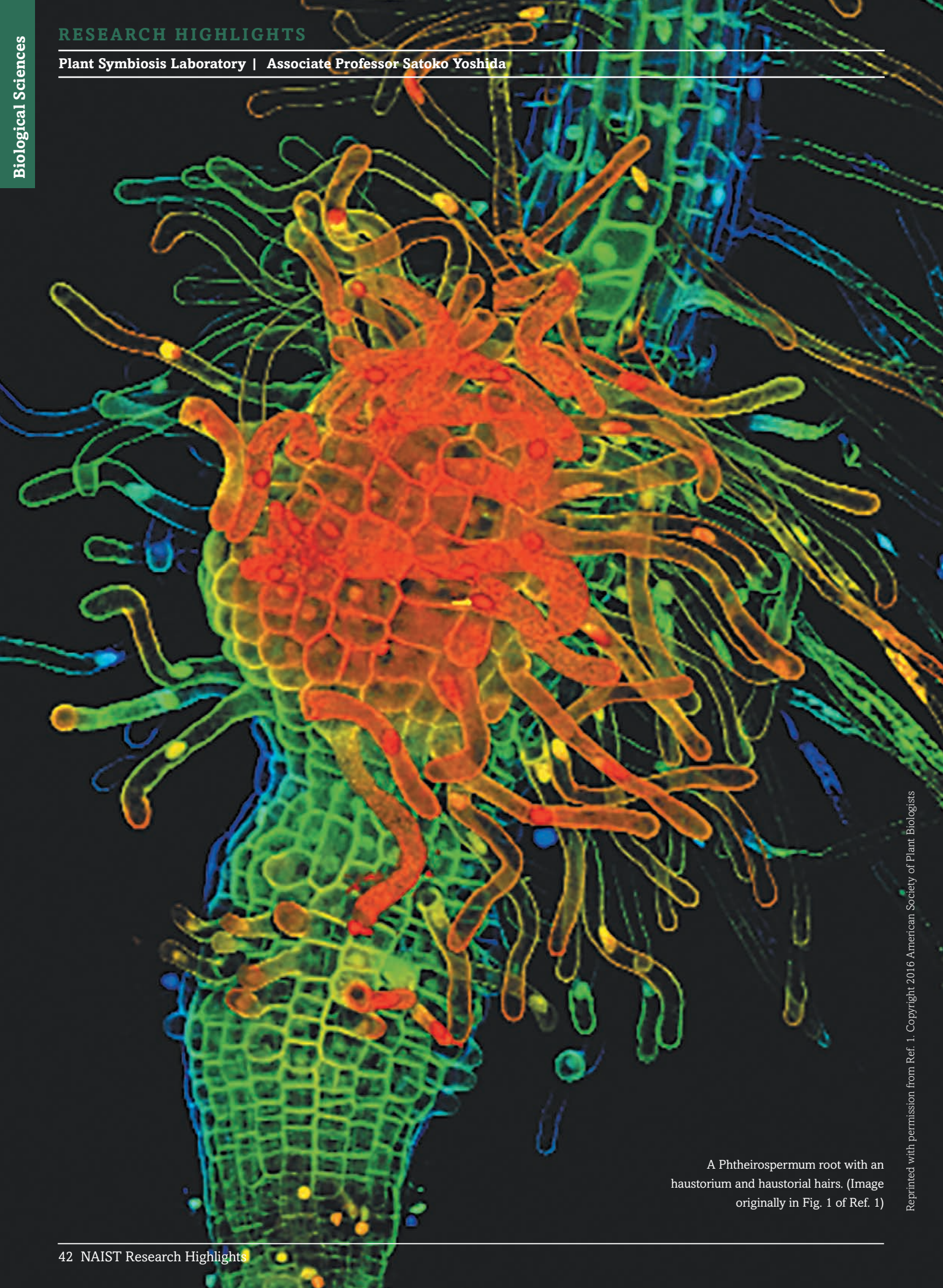
Yoshida believes that scientists need to remain fresh to the challenge of pushing the boundaries of research throughout their careers. She points out that many subject areas require decades of exploration before yielding results.

In 1966 for example, Yoshida explains, researchers identified a class of compounds known as strigolactones, secreted from the root systems of certain weeds that were found to germinate the seeds of parasitic plants and stimulate the growth of symbiotic fungi. But that wasn't the end of the story for this compound's role, she points out. More recently, researchers have discovered that it also plays an important part in regulating plant growth above the ground.

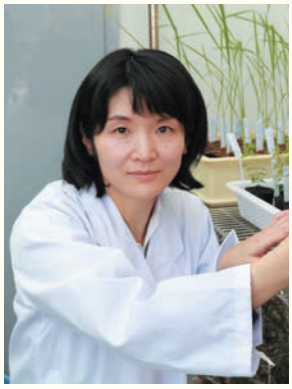
"There are definitely still more answers like this to be found," Yoshida says, "so that's why it's very important that scientists maintain their curiosity, keep asking questions and making a big effort."

More information about the group's research can be found at http://bsw3.naist.jp/eng/courses/courses113.html
Researcher: Satoko Yoshida

Plant Symbiosis Laboratory | Associate Professor Satoko Yoshida



A Phtheirospermum root with an haustorium and haustorial hairs. (Image originally in Fig. 1 of Ref. 1)



Parasitic plants

Exploring the secrets of parasitic plants

Mutants expected to reveal key steps in plant parasitism as part of new research

Researchers are using a model plant to explore the physiology and genetics of one of the world's worst agricultural pests, *Striga,* in the hope of finding a way to control it.

Striga is a parasitic weed genus that afflicts sorghum, maize, and rice crops across Africa and Asia. Nine years ago, plant geneticist Satoko Yoshida joined a project in Ken Shirasu's Plant Immunity Research Group at the Japanese research institute RIKEN to study the pest. "It's quite a high impact weed," explains Yoshida, who this year joins NAIST to start up the Plant Symbiosis Laboratory to continue her work. "The estimated annual loss could be several billion dollars. It was listed as one of the world's seven worst agricultural pests in a 2010 *Science* paper."

Striga is an obligate parasite, which makes it difficult to work with in the lab. "We decided we needed a model plant," Yoshida says. Accordingly, she tested ten different species in search of an ideal candidate. "Some of the mountain plants just didn't germinate, or they germinated and died, or it took forever to get seeds."

Yoshida eventually settled on *Phtheirospermum japonicum* as a model species to investigate how these parasites work and how to control them. Parasitic plants such as *Phtheirospermum* and *Striga* detect chemicals released by their host's roots and respond by forming a specialized organ called an haustorium. Hairs on the haustorium help it adhere to a hosts' root before it invades to connect with the hosts' internal transport network.

To understand haustorium formation, Yoshida's RIKEN team chemically mutagenized *Phtheirospermum* seeds, grew them into plants, and then exposed the mutants to an haustorium-inducing chemical[1]. Most formed haustoria, but a few mutations did not. The team recovered one mutant that formed elongated haustoria, two mutants lacking haustorial hairs, and a mutant that didn't form haustoria at all.

"The mutants without haustorial hairs have been easy to work with, while the one that doesn't form haustoria has been a bit more difficult," Yoshida says. Analysis of the haustorial-hair mutants revealed that haustorial hair development is controlled by the same genetic program controlling root hairs and demonstrated that haustorial hairs are important for maintaining physical contact with the host root.

"Nobody has ever made a mutant with parasitic plants," Yoshida says. Next, the team will use whole-genome sequencing to identify the mutated genes.

At NAIST, Yoshida will lead a team of researchers trying to understand how these plants prey on others. She hopes it will eventually be possible to find the master genes controlling haustorium formation. "If we can find the genes that switch haustoria on and off, it may help us combat these parasitic weeds," she says.

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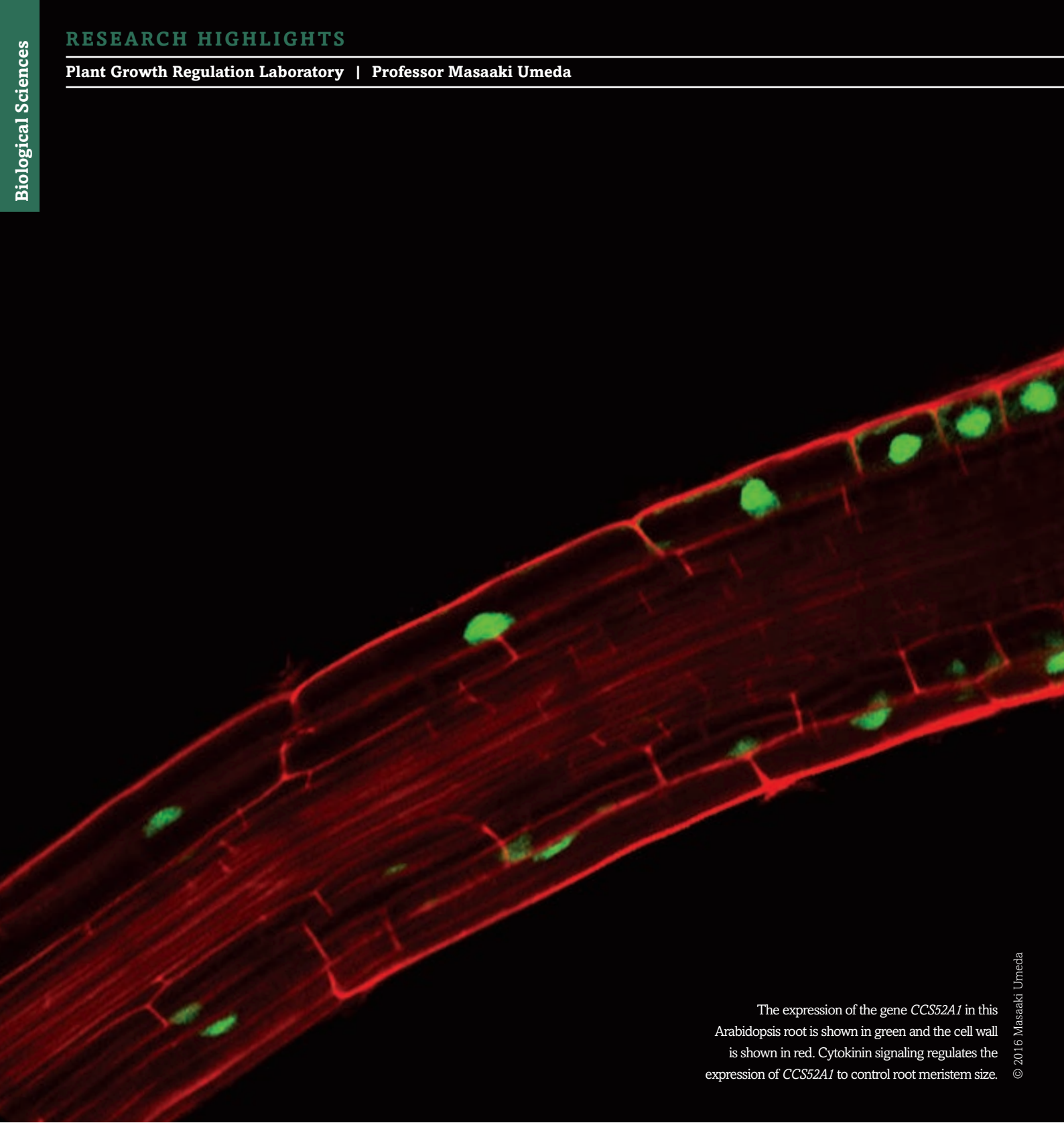
**** To read more about the work of Satoko Yoshida, one of the new international researchers to join NAIST, see "Planting seeds of wisdom" on page 40.***

More information about the group's research can be found at http://bsw3.naist.jp/eng/courses/courses113.html
Researcher: Satoko Yoshida

Plant Growth Regulation Laboratory | Professor Masaaki Umeda

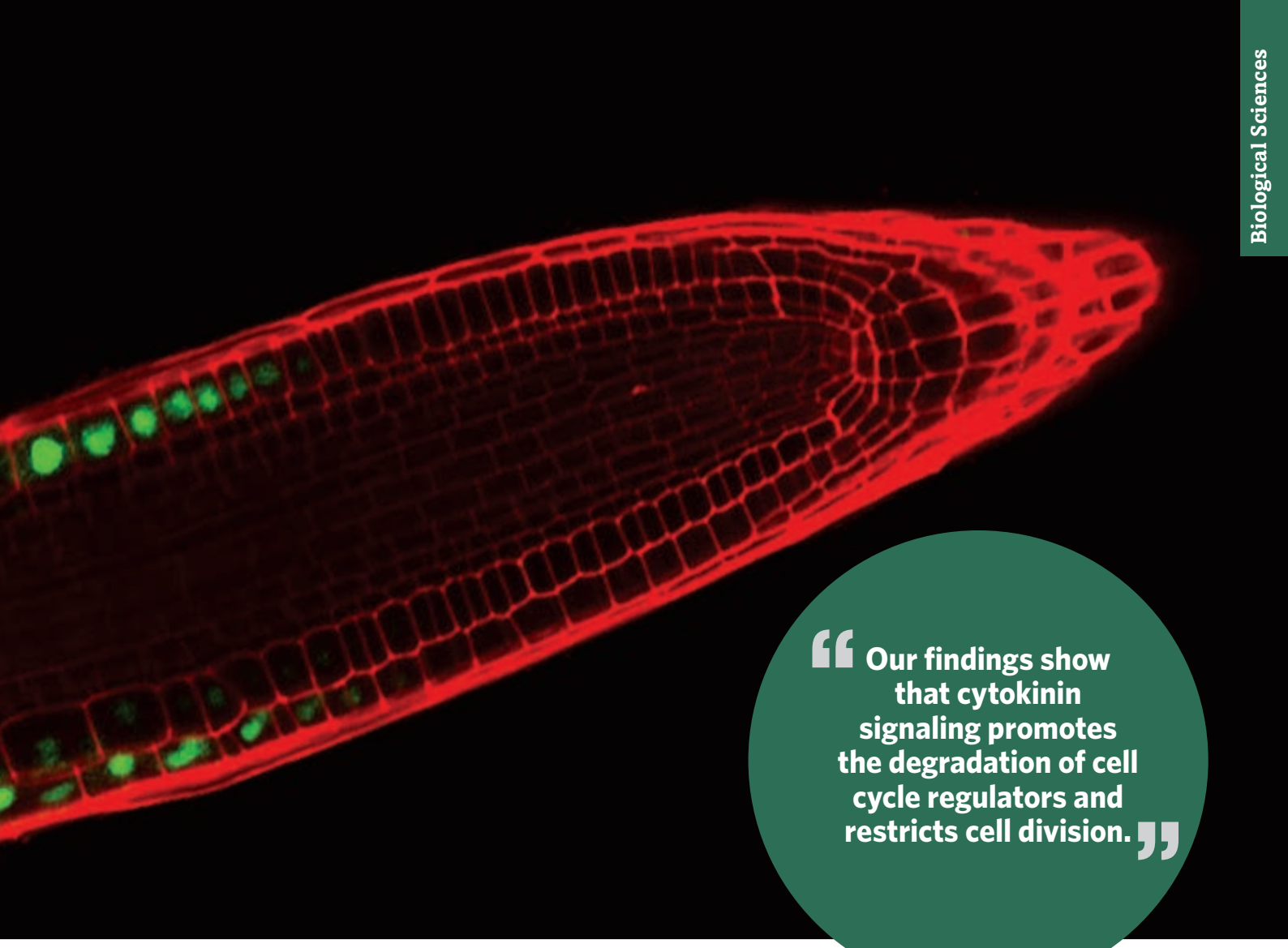


The expression of the gene *CCS52A1* in this Arabidopsis root is shown in green and the cell wall is shown in red. Cytokinin signaling regulates the expression of *CCS52A1* to control root meristem size.

Plant hormones

Getting to the root of what lies beneath

The hormone cytokinin halts cell division to control root growth



> **“Our findings show that cytokinin signaling promotes the degradation of cell cycle regulators and restricts cell division.”**

A plant’s roots play an essential role in keeping it alive and flourishing, with the cells inside elongating root tips exploiting finely tuned hormonal signaling networks to control root growth.

Now researchers at NAIST have pinpointed the function of one type of plant hormone — cytokinin — involved in this elaborate regulatory cross-talk. They have found that cytokinin not only shuts down the signalling of another hormone involved in cell proliferation, it also causes cells to stop dividing while continuing to duplicate the DNA in the cell nucleus.

This is an essential process for root cell differentiation, explains plant biologist, Naoki Takahashi, an assistant professor at NAIST’s Plant Growth Regulation Laboratory. “It was elusive how plant hormones regulate cell cycle progression in roots,” he explains. “Our findings show that cytokinin signaling promotes the degradation of cell cycle regulators and restricts cell division.”

A team led by the laboratory’s head Masaaki Umeda and Takahashi used the weed thale cress (*Arabidopsis thaliana*) to study hormonal action in the root’s transition zone — between the meristem, where cells actively divide, and the elongation zone, where cells expand and take on more defined roles.

They showed that cytokinin, through an intermediary regulatory protein, induced the expression of the gene called *CCS52A1*. This encodes an activator of an enzyme that controls root meristem size. Specifically, this enzyme — known as an E3 ubiquitin ligase — degrades certain regulators of cell division, causing the cell division cycle to cease. This pathway is notably distinct from the way in which cytokinin counteracts the activity of another hormone called auxin to halt cell division. The researchers reported their findings in the prestigious journal *Current Biology*[1].

The dual nature of cytokinin signalling is unlikely to be restricted to just *Arabidopsis* or related plant species, Takahashi notes. “Most of the genes involved in root growth regulation are highly conserved between plant species,” he says, “suggesting that similar mechanisms controlling root growth exist in other plant species.”

Takahashi anticipates that a better understanding of cytokinin’s roles in root growth will prove useful in crop breeding and other agricultural applications. “We may be able to control the speed of root growth by changing the activity of cytokinin signalling, so that root growth may not be arrested, even in stressful environmental conditions,” he says. This, he adds, would lead to an “increase in the yield of crops and plant biomass.”

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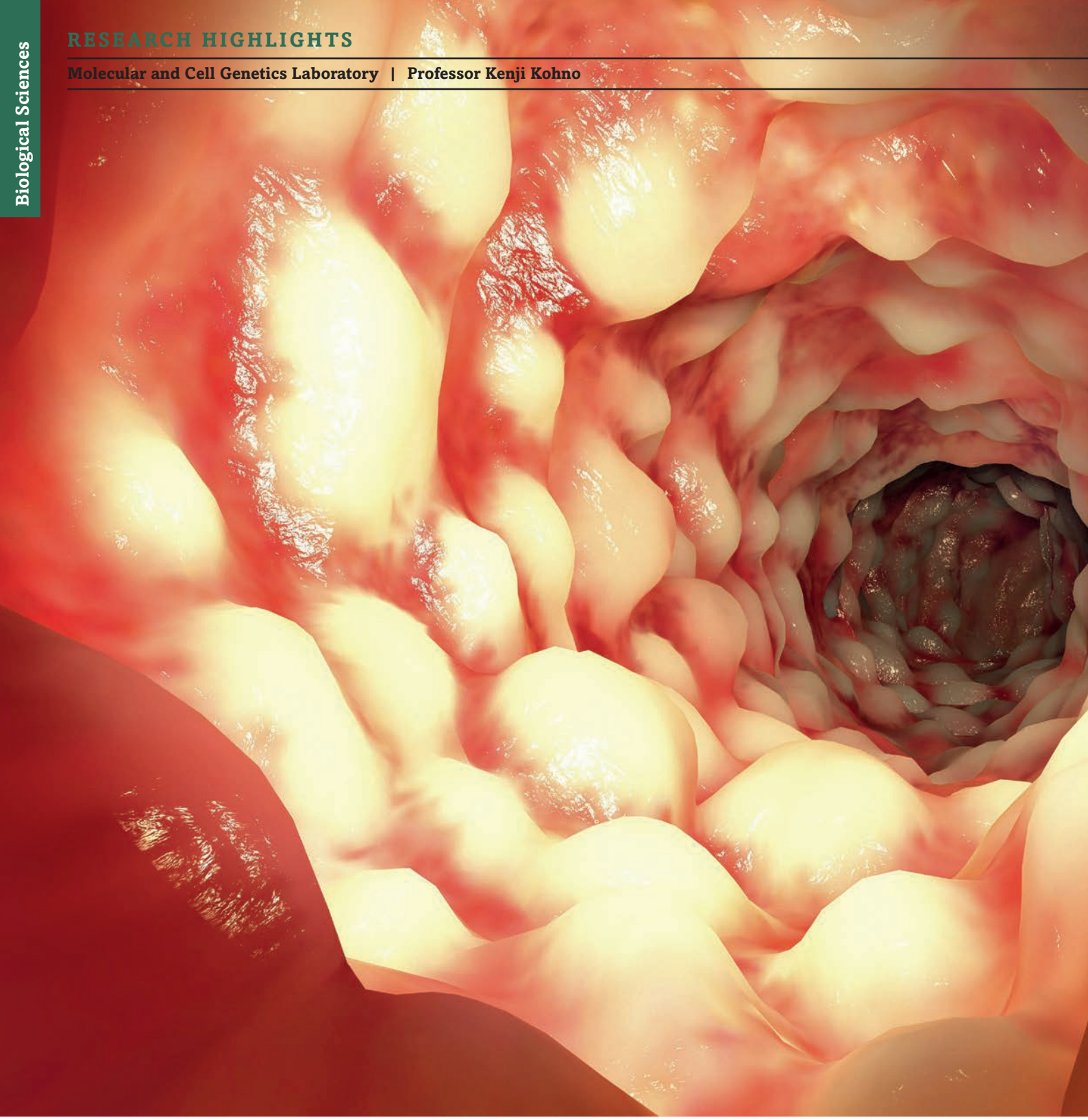
More information about the group's research can be found at http://bsw3.naist.jp/eng/courses/courses105.html
Researchers: Naoki Takahashi and Masaaki Umeda

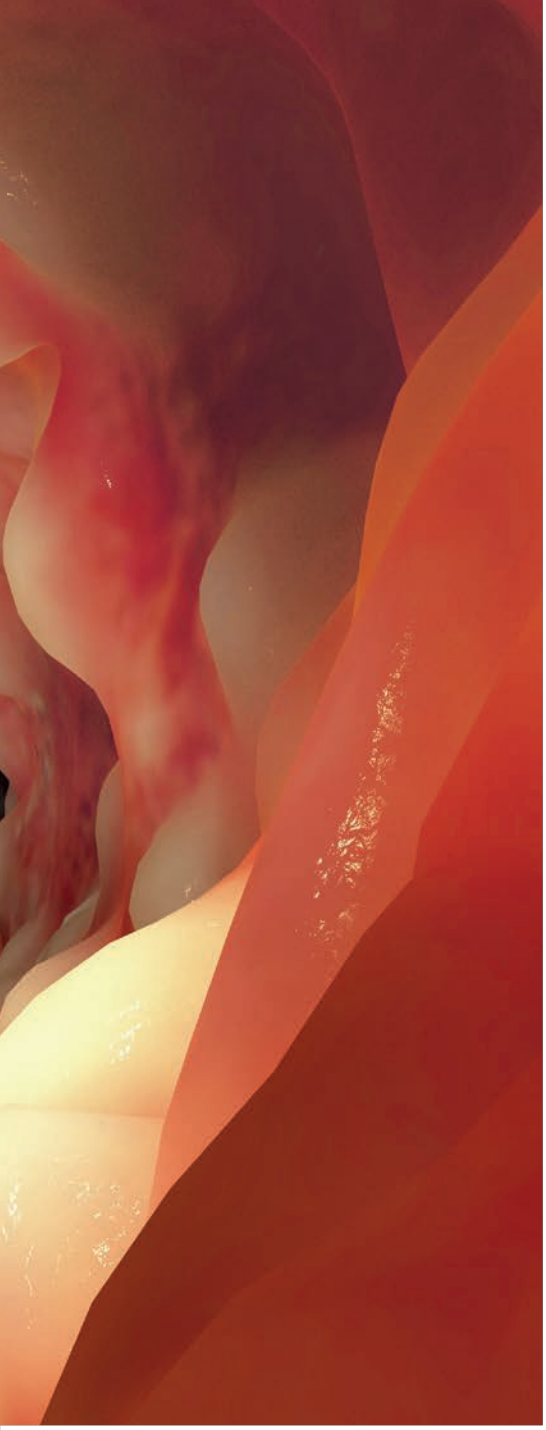
Molecular and Cell Genetics Laboratory | Professor Kenji Kohno

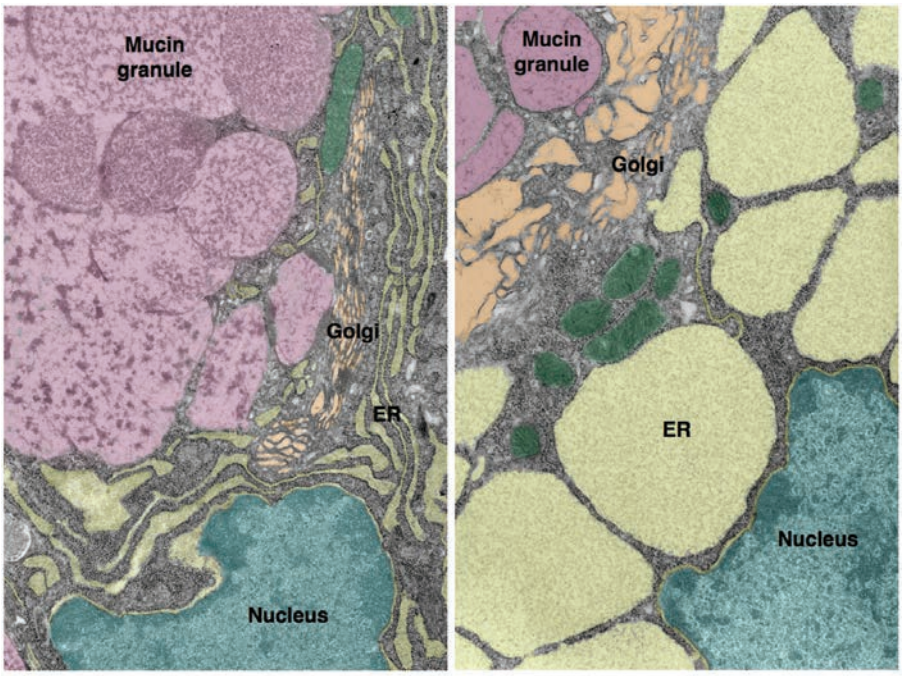


Genetics

Inflammatory disease study yields knockout results

Research provides insight into how a protein might help protect against bowel disease





Slides showing the effect of the stress sensor IRE1β on regulation of mucin production in digestive tract cells. Main: An artistic image of an endoscope of an intestine affected by Chrohn's disease.

"Finding the location of cells expressing IRE1β and identifying the relationship between IRE1β and mucin production are breakthroughs in our understanding of IRE1β function."

The occurrence rates of digestive tract disorders known collectively as inflammatory bowel diseases (IBDs) appear to have been rising in Western countries for about 70 years, and the reasons remain unclear.

IBDs, of which the most common forms are Crohn's disease and ulcerative colitis, are autoimmune disorders that cause the body's immune system to attack the colon and small intestine of the digestive tract[1]. NAIST researchers have been using gene knockout mice to explore the function and physiological significance to IBD of a poorly understood stress sensor known as inositol-requiring enzyme 1β (IRE1β), which is expressed selectively in the mammalian digestive tract. This is involved in activating a process called the unfolded protein response (UPR), although researchers don't know how.

"There are several stress sensors in the UPR pathway, but among these IRE1β is one of the least understood," explains Akio Tsuru, from NAIST's Molecular and Cell Genetics Laboratory. "Previous studies suggested that IRE1β plays a role in preventing intestinal bowel disease, but the mechanism behind this function is completely unknown."

The correct topology — shape, geometry and orientation — of proteins is vital for cells to function correctly. Newly synthesized proteins pass into the endoplasmic reticulum (ER), a specialized cellular subunit that folds and modifies them to their required topology. If, however, the influx of proteins to the ER exceeds its capacity, unfolded or misfolded proteins accumulate and ER stress results. Activating the UPR is an important way that cells respond and if the UPR is unable to deal with the stressed conditions, then apoptotic (programmed) cell death is initiated.

"The UPR is now a popular area of research because of the links between ER stress and many other diseases as well, such as Parkinson's," says Tsuru. "Our study has revealed that IRE1β located in the ER of goblet cells in the digestive tract regulate and optimize mucin [the main component of mucus] production. It enables the efficient secretion of mucin, which protects the digestive tract surface from intestinal bowel disease.

"Finding the location of cells expressing IRE1β and identifying the relationship between IRE1β and mucin production are breakthroughs in our understanding of IRE1β function."

Reference

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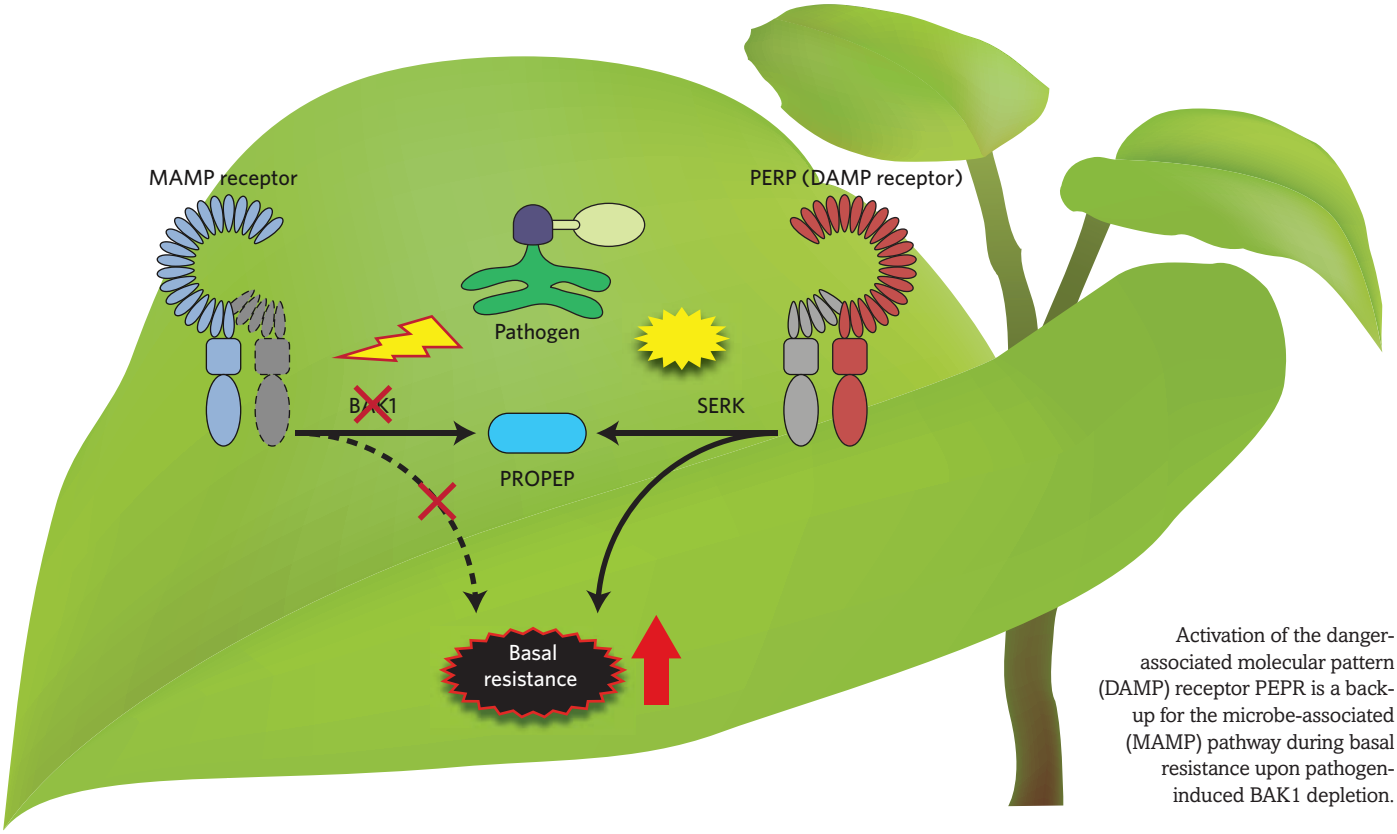
More information about the group's research can be found at http://bsw3.naist.jp/eng/courses/courses207.html
Researchers: Akio Tsuru and Kenji Kohno

Plant Immunity Laboratory | Associate Professor Yusuke Saijo

Plant immunity

Decrypting plant defense signals

A genetic approach sheds new light on danger-associated defense mechanisms in plants



Activation of the danger-associated molecular pattern (DAMP) receptor PEPR is a back-up for the microbe-associated (MAMP) pathway during basal resistance upon pathogen-induced BAK1 depletion.

Reliable food production hinges on the ability of plants and animals to fight infections by recognizing and responding to microbes. New research from NAIST provides insight into the mechanisms controlling basal resistance in plants, paving the way for the development of next-generation sustainable disease-resistant crops[1].

Plant immunity involves cell membrane-localized receptors that detect and recognize microbe-specific molecular signatures, such as bacterial flagellin and fungal chitin. Evidence suggests that the membrane-bound receptor kinase BAK1, serving as a co-receptor for these pattern-recognition receptors, plays a pivotal role in the resulting immune response. Its perturbation occurs during pathogen infection, which is typically perceived by the plant, but the underlying mechanisms remain unclear. Other receptors sense danger-associated molecular patterns originating from pathogen-infected plants, which elicits an immune response. Specifically, the detection of elicitor-active Pep portions by so-called PEPR receptors produces a similar response to microbe-associated patterns. However, the mechanism that activates this immunity is also unknown.

To fill this knowledge gap, Yusuke Saijo and colleagues from NAIST's Plant Immunity Laboratory used a genetic approach to assess the contribution of BAK1 to PEPR-mediated immunity.

Many researchers had previously assumed that microbe and danger-associated receptors worked in parallel. But, Saijo's team envisioned a layered structure involving functional interactions between different receptors. "This helped us hypothesize a model in which danger-induced PEPR signaling acts as a back-up when BAK1-dependent microbe-associated receptors become dysfunctional upon BAK1 disruption," Saijo explains.

The researchers discovered that PEPR, which was initially considered as a simple BAK1-dependent receptor, retained its function better without a co-receptor, validating its role as a back-up (see image). To their surprise, mutant plants devoid of BAK1 exhibited an increase in Pep peptide-induced growth inhibition; a proxy for defense activation.

Furthermore, Saijo's team demonstrated that a PEPR ligand precursor acted as a danger-associated protein presenting increased production that was released in correlation with pathogen virulence and host cell death. They showed that infection by the fungal pathogen *Colletotrichum higginsianum* resulted in BAK1 depletion in Arabidopsis plants and PEPR participated in anti-fungal resistance. "This dramatic decrease in BAK1 accumulation during the fungal infection was also an unexpected but important finding," Saijo says.

The researchers are currently evaluating the role of BAK1 in balancing salicylic acid and jasmonic acid hormone-based defense responses in the PEPR pathway, an important trade-off between these antagonistic hormones. To generate new disease-resistant crops, they are also investigating the PEPR-mediated immunity against *Colletotrichum* fungi, which affect a wide host range and cause enormous agricultural yield losses.

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More information about the group's research can be found at http://bsw3.naist.jp/eng/courses/courses111.html
Researcher: Yusuke Saijo

Toshiro Ito

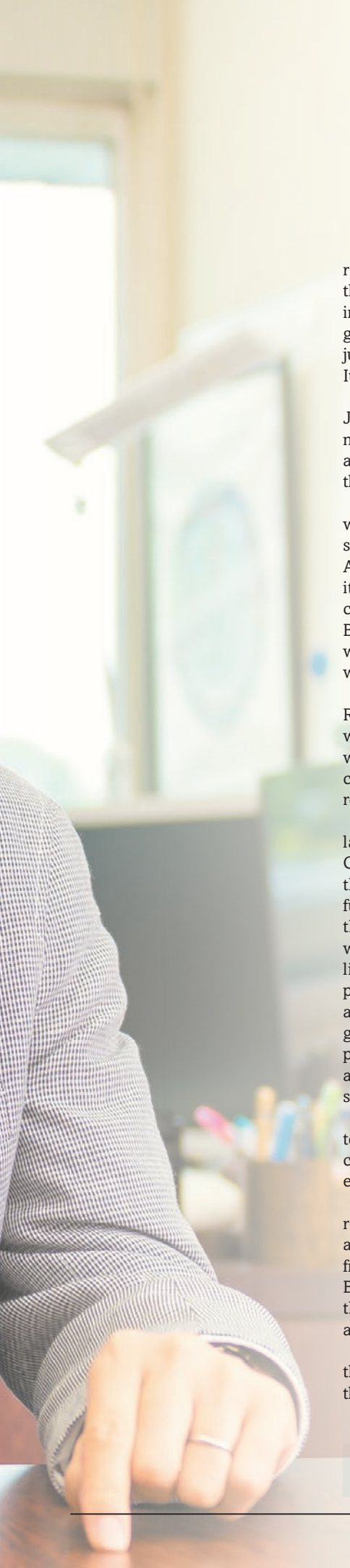
Exploring the fundamentals of plant growth

A renowned plant geneticist's move to NAIST continues a tradition and marks a return home

For Toshiro Ito, the chance to join NAIST's biological sciences faculty meant returning to his roots.

This internationally respected plant geneticist was born in Japan and completed his undergraduate, master's and PhD studies here, but had been living abroad, mostly in the United States, since taking up a postdoctoral position with the prestigious California Institute of Technology in 1997. There, Ito had risen through the ranks to become a senior principal investigator, before relocating to Singapore in 2005 to lead the Plant Systems Biology Group at Temasek Life Sciences Laboratory.

His most recent move has been to NAIST, for the opportunity to step into a senior role left vacant by one of Japan's leading plant



researchers. At NAIST, Ito will be picking up the mantle of Ko Shimamoto who passed away in 2013. This well-regarded professor of plant genetics was in Singapore to deliver a seminar just months before he died, and his visit inspired Ito to move to Nara.

"He was one of the greatest plant scientists in Japan in recent times. He died six months after I met him, and I inherited his laboratory," Ito says, acknowledging that he has large shoes to fill in the new role.

Ito also had other heartfelt reasons for wanting to return to his country of birth. "My sons are 13 and 11, and were born in America. After that, we moved to Singapore where is it always hot," Ito explains. "My memories of childhood in Japan are about the four seasons. But my children have never had a cold winter! I want them to enjoy spring, summer, autumn and winter, and have nature close by."

Ito opened NAIST's new Plant Stem Cell Regulation and Flora Patterning Laboratory, where research areas covered by major projects will include the developmental coordination of cells to produce flowers and the environmental response and acclimation of plants.

"Plants have really robust structures. The largest living thing on Earth is a sequoia in California that has been growing for two thousand years," Ito says, explaining that the fundamentals of plant life are ubiquitous, from the largest species to the smallest. "In my lab, we work with *Arabidopsis*, tiny plants with a lifespan of six weeks. They are genetically predetermined to terminate their own growth and save the nutrients to build the next generation of flowers. We are looking at the powerful molecular mechanisms behind this activity." (See "The timer that controls flower size" on page 52.)

Ito's team is also studying how plants adapt to their environments and hopes this research could be useful in the future for managing the effects of climate change on natural habitats.

"Plants have no brains, but they can still remember environmental change and respond accordingly," he explains. "If you move a plant from a cold climate to a very hot one, it will die. But if you incubate the plant before moving it, then it can get used to the higher temperature and adapt.

"Once we understand the mechanism behind this, we can manipulate genes and make plants that are more resistant to severe conditions."

Ito wasn't always as interested in plants. He began his career researching animal development: "I discovered I needed to kill hundreds of mice and I didn't like that, so I changed to plants."

For Ito, joining NAIST felt like a natural transition. In his field of research, he had visited the campus many times and become familiar with the faculty staff. "Due to its small size, the atmosphere is very friendly. It also means that it's easy to get things done. Things can be changed quickly to suit your work needs without any hassle," he says.

Since joining the team, Ito has enjoyed the relaxed style of collaboration, and says it's unlike anything he's experienced in Singapore or America. "Recently we went on a faculty retreat to the hot springs," he says. "Some of our faculty members are more than 60 years old, but they still stayed up until 2 am drinking sake, and talking about education, research and the future of NAIST. Spending time together like this enables us to develop a strong bond, and build up trust."

Ito is looking forward to following, and perhaps being involved in, the next big breakthroughs in the biological sciences. "Biology has changed rapidly in the past 15 years," he says. "While I want to be a pioneer in my field, I also accept we need to nurture the next generation who will be responsible for making the next scientific leaps."

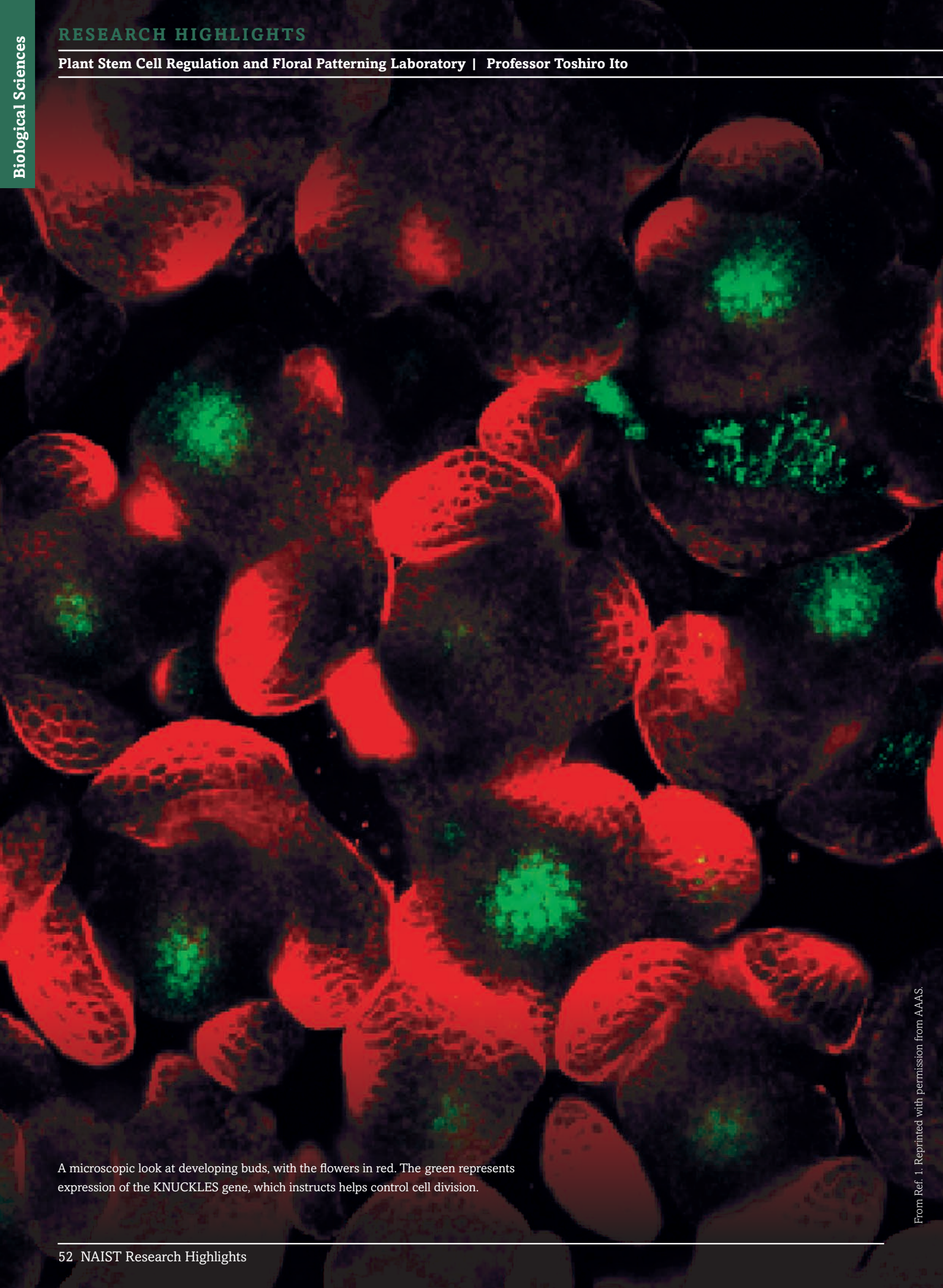
Ito will be bringing his own traditions to NAIST, which include a firm emphasis on hard work. His strong sense of self-discipline was instilled in him by his PhD supervisor at Kyoto University.

"I remember that I came in one morning and found a note on my desk," Ito recalls. "It was a piece of writing by [the eminent molecular biologist] James Watson from 1984, which said: 'I'm not interested in people who won't work 10 hours a day and be there on Saturday and Sunday, because someone will be. In this world, there are clever people who never seem to study and still get good grades in exams. You do not see that in science.'"

For Ito, the quote underlined the importance of working hard to achieve his goals: "It was simple advice but sometimes you forget it. Nowadays we can't force students to work 10-hour days, or weekends. But we can still remind ourselves that success will be rooted in our work. It's the basis for great science."

More information about the group's research can be found at http://bsw3.naist.jp/eng/courses/courses112.html
Researcher: Toshiro Ito

Plant Stem Cell Regulation and Floral Patterning Laboratory | Professor Toshiro Ito



A microscopic look at developing buds, with the flowers in red. The green represents expression of the KNUCKLES gene, which instructs helps control cell division.

From Ref. 1. Reprinted with permission from AAAS.

Plant genes

The timer that controls flower size

A biological clock triggers a key event in flower development

Plants grow by the continuous division of small groups of cells, called meristems, at the tips of shoots and roots. Some meristems divide indefinitely, but those that form flowers terminate according to specific genetic programs. They divide a specific number of times before completely differentiating into floral organs.

NAIST researchers have now revealed a biological timer that determines when cell divisions are switched off in flower buds[1].

Continuous growth of above-ground meristems is maintained by the *WUSCHEL* gene. In floral meristems, *WUSCHEL* is repressed by another gene, *KNUCKLES*, which sets the meristem on the path to termination. *KNUCKLES* is switched on by *AGAMOUS*, the same gene that promotes reproductive organ development, although *KNUCKLES* isn't activated until 2 days later.

"The timing of *KNUCKLES* induction is really key to the balance between proliferation and differentiation," explains Toshiro Ito, head of NAIST's Plant Cell Regulation and Floral Patterning Laboratory, who led the study. Flowers develop extra organs if *KNUCKLES* is switched on too late and not enough if it is switched on too early.

Ito's team showed that *KNUCKLES* is activated after a certain number of cell divisions rather than a specific period of time. When they used drug treatments to accelerate or inhibit cell divisions, *KNUCKLES* was activated either earlier or later.

KNUCKLES expression is epigenetically controlled; it is normally repressed by a chemical modification of a specific lysine residue of the histone H3 protein — a process known as methylation — that blocks transcription. Methylation is maintained by Polycomb-group (PcG) proteins and the team showed that these are responsible for the delay between *AGAMOUS* and *KNUCKLES*. "Once *AGAMOUS* is induced, it binds to *KNUCKLES* and causes the eviction of Polycomb," Ito explains.

Without PcG to maintain the histone methylation, the bio-timer starts ticking. Cell divisions dilute the repressive histone modification and *KNUCKLES* is eventually activated.

The team showed that attaching the Polycomb binding sites from *KNUCKLES* to a ubiquitously expressed fluorescent reporter was enough to switch it off. "It was a result we expected, but, at the same time, it worked beautifully, so we were excited," Ito says. They then designed an artificial protein to mimic *AGAMOUS* by targeting Polycomb sites and evicting the protein. "It worked!" Ito says. "We saw induction of the reporter."

Work continues in Ito's team to unravel the genetic cascade at the heart of floral development. "Flowers are really important for human life as a source of food," he says. "We research flowers and flower development because what we eat, fruits and vegetables, are all products of flowers."

Reference

1. Sun, B., Looi, L.-S., Guo, S., He, Z., Gan, E.-S. *et al.* Timing mechanism dependent on cell division is invoked by Polycomb eviction in plant stem cells. *Science* **343**, 1248559 (2014).

**** Toshiro Ito is another of NAIST's newest professors. To read more about his career, see "Exploring the fundamentals of plant growth" on page 50.***

More information about the group's research can be found at http://bsw3.naist.jp/eng/courses/courses112.html
Researcher: Toshiro Ito

Systems Neurobiology and Medicine Laboratory | Professor Naoyuki Inagaki

Cell growth

A creative flow finds the forces behind cell migration

Insights into the molecular actions that drive cell movements could enhance our understanding of diseases

The correct migration of cells in the body is necessary for normal growth and functioning. Disruption of this 'directional cellular motility' is implicated in many diseases, including immune disorders and cancer. Interdisciplinary research at NAIST aims to enhance our understanding of the molecular mechanisms inherent in cell motility, particularly the forces that propel cells forward.

Directional cellular motility plays a vital role in embryogenesis, neuronal network formation, immune responses and tissue repair. Neurons — nerve cells — contain long, thin, specialized extensions called axons that protrude from their surface and transmit information to other neurons and cells.

At the tips of axons are 'growth cones'; highly sensitive structures that respond rapidly to chemical signals from axon guidance molecules outside the cell and create the driving forces to push the cell forward. Growth cones contain a variety of molecular structures, including dynamic linear polymers called 'actin filaments' (or F-actin). With the signal from axon guidance molecules, F-actin polymers move away from the leading edge of the cell membrane to allow new molecules to take their place. This backwards movement is known as F-actin retrograde flow.

"We believe that the forces required to drive cell motility are generated during F-actin retrograde flow by the coupling of F-actin with substrates outside the cell," explains Naoyuki Inagaki, head of NAIST's Systems Neurobiology and Medicine Laboratory. "We think this is achieved via F-actin linking with cell adhesion molecules on the cell membrane, but the molecular basis of this process remains unclear. Using fluorescent tagging, we traced the movement and behavior of molecules in growth cones to find out more."

Inagaki and his team revealed that the coupling process requires the extra help of two binding molecules; one, called cortactin, acting on F-actin itself, and the other linked to the cell adhesion molecule L1-CAM and known as shootin1[1].

Cortactin is 'caught' by shootin1 and mediates the link between F-actin retrograde flow and L1-CAM. This in turn promotes traction forces for axon outgrowth. The researchers also found that an axon guidance molecule, netrin-1, induces the cortactin-shootin1 interaction. Stimulation with netrin-1 can promote forces for axonal outgrowth.

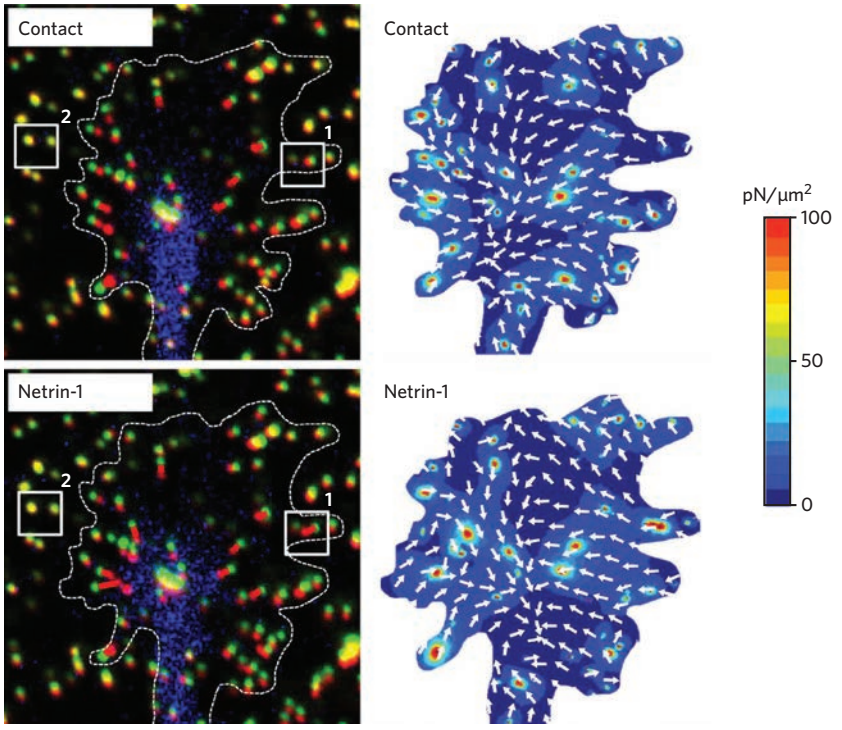
"Without the creative environment at NAIST, which encourages collaborations between disciplines, this kind of project would be very difficult," Inagaki explains.

"We were lucky to work alongside colleagues in Information Science and in Materials Science to create a unique picture of the forces generated by this coupling process."

Inagaki hopes these insights into the interactions between F-actin and L1-CAM will enable further examination of diseases involving axon outgrowth dysfunction.

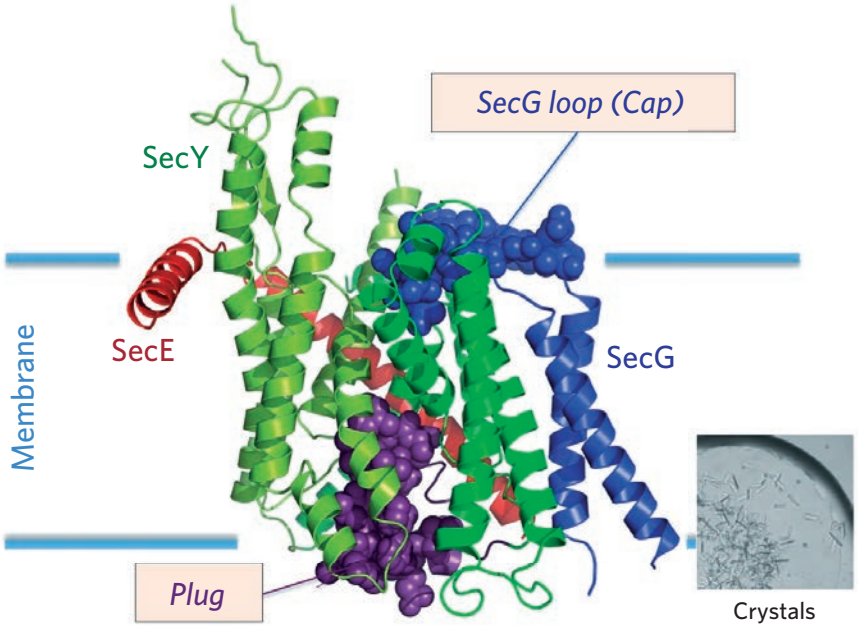
Reference

1. Kubo, Y., Baba, K., Toriyama, M., Minegishi, T., Sugiura, T., Kozawa, S., Ikeda, K. & Inagaki, N. Shootin1–cortactin interaction mediates signal–force transduction for axon outgrowth. *The Journal of Cell Biology* **210,** 663–676 (2015).



Forces generated by molecular interactions in axon growth cones help cells move correctly when required. NAIST researchers have uncovered some of the molecular mechanisms at play in growth cones, and shown how forces can change under stimulation with axon guidance molecule netrin-1.

More information about the group's research can be found at http://bsw3.naist.jp/eng/courses/courses204.html
Researcher: Naoyuki Inagaki



The crystal structure of a bacterial SecYEG complex has been revealed at high resolution for the first time.

Membrane biology

Protein-secretion machinery

The structure of a bacterial protein complex involved in moving proteins through cell membranes is seen in high resolution for the first time

Proteins fulfil many tasks in the body. They need to move in and between cells, passing through membranes without causing structural damage. NAIST researchers are investigating how cell membrane channels, known as 'translocons', open to allow proteins through.

Translocons themselves can be made up of multiple proteins and, although their structure varies, their function in different organisms is the same. In bacteria, translocons have a central protein complex called SecYEG that comprises three components; SecY, SecE and SecG. This undergoes conformational changes from a resting state, to the point where a 'gate' in the translocon opens to allow proteins through. When bacteria invade a host, some secretory proteins cause acute poisoning in host cells. For disease control, it is crucial to understand exactly how translocons function.

Tomoya Tsukazaki of NAIST's Membrane Molecular Biology Laboratory recently led a project that achieved the highest resolution crystal structures of SecYEG to date, both in a resting state and peptide-bound state, which is the first stage before the opening of the channel gate[1].

"SecYEG has several flexible regions, which prevent defect-free crystallization," Tsukazaki explains. "Most SecYEG crystals are poor quality. To overcome this, we had to collect X-ray diffraction data from a dozen SecYEG crystals from the bacteria *Thermus thermophilus* to build up a clear picture at high resolution."

His team's results revealed the hour-glass structure of SecY, which is stabilized from behind by SecE. They also found that the SecG protein contains a loop that covers the cytoplasmic side of the channel. Tsukazaki and his team believe the SecG loop may play a key role inside the cell in blocking the movement of proteins through the translocon. The channel is sealed on the periplasmic side, outside of the cell membrane, by a plug, or 'gate' that opens at a given signal when a protein is ready to pass through (see image).

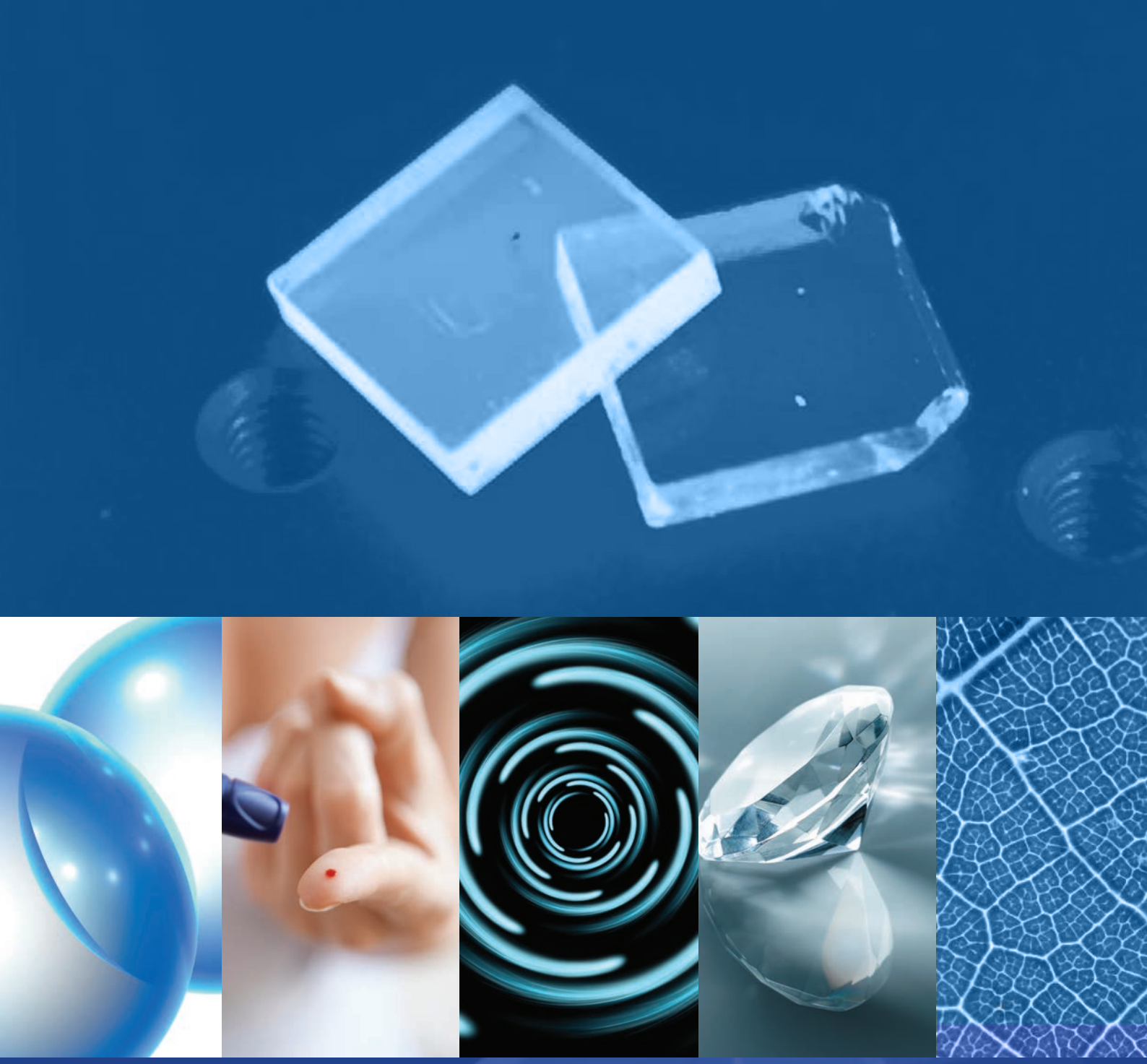
A second stage — the peptide-bound state of SecYEG — was also identified by Tsukazaki's team. Their results indicate that the cytoplasmic side of SecYEG responds to signal peptides changing conformation in preparation for the periplasmic 'gate' to open.

"Bacterial Sec machinery is an essential system," Tsukazaki says. "Perhaps our SecYEG structure will help scientists find new antibiotics to target Sec proteins. We also know that SecYEG interacts with other important proteins in the membrane, forming a larger complex that we hope to determine using X-ray crystallography in future."

Reference

1. Tanaka, Y., Sugano, Y., Takemoto, M., Mori, T., Furukawa, A. *et al.* Crystal structures of SecYEG in lipidic cubic phase elucidate a precise resting and a peptide-bound state. *Cell Reports* **13,** 1561–1568 (2015).

More information about the group's research can be found at http://bsw3.naist.jp/eng/courses/courses309.html
Researcher: Tomoya Tsukazaki



Materials Science

IMPACT

Surface and Materials Science Laboratory | Professor Hiroshi Daimon

Making use of an ultra-small world

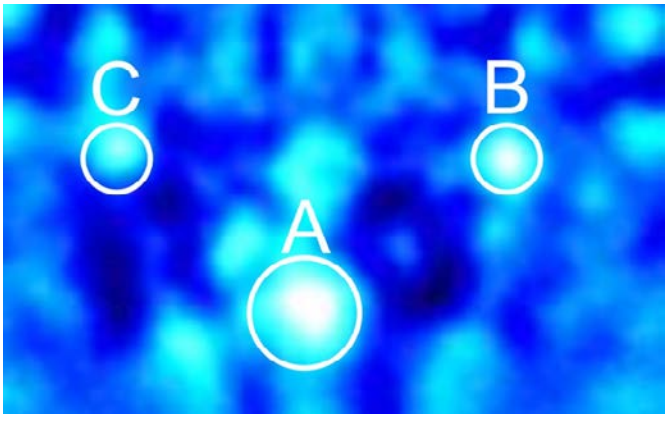
A WEALTH OF MATERIALS AWAITS DISCOVERY BY SCIENTISTS SCRATCHING THE SURFACE OF NANOMETRES

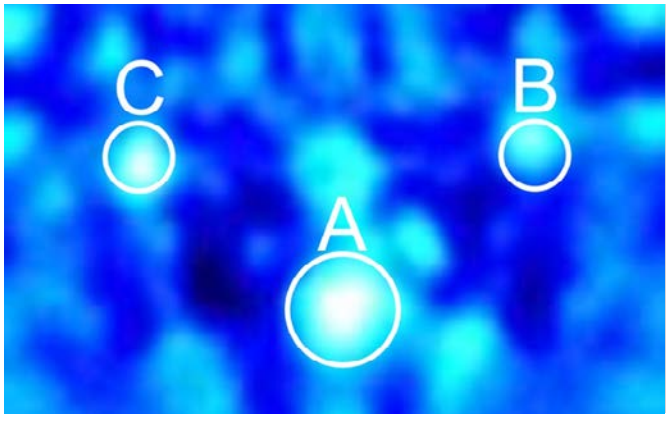
Crystal clear: the difference in the way carbon atoms are arranged distinguishes soft graphite from ultra-hard diamond. Exploring these arrangements has been a life-long passion for NAIST's professor Hiroshi Daimon.

Hiroshi Daimon uses a simple question to draw people into his complex area of research: What's the difference between a diamond and the 'lead' in a pencil? The answer: only the way their carbon atoms are arranged.

The household implement and the object of great desire are constructed from the same atomic components, but being tightly bonded in a cubic structure in the super-hard gemstone and layered in loose sheets of soft graphite in the pencil, their properties and uses are worlds apart.

Daimon, who heads NAIST's Surface and Materials Science Laboratory, is known professionally as a quantum physicist, but describes himself simply as an explorer of atoms. He and his team aim to analyse the structures of atoms in nanomaterials and their electronic properties. A nanometre is one billionth of a metre or about 1/100,000th of the thickness of a sheet of paper. Unusual features emerge when materials are examined below this very tiniest of scales. Iron, for example, loses its magnetic properties, and gold, a non-active metal, becomes chemically active below 1 nanometre. These changes emerge because their atomic arrangements differ from those at the large scale and the resultant altered capabilities can help yield new kinds of materials with diverse applications.





The DIANA device that Professor Daimon and his colleagues developed allows researchers to visualize the positions of atoms within material, such as the three atoms circled in these images. In a viewer, pairs of stereoscopic holograms combine to form a three-dimensional image.

In recent years, for example, nanotubes of carbon have been applied in a wide range of uses, from toughened sporting equipment and body armour to efficient water filters. These lattices of carbon molecules arranged at the nanoscale into tubes resembling the structure of wire mesh are stronger than steel and yet extremely lightweight. They're also a good example of a novel material born from atomic engineering, a discipline that emerged during the late 20th century.

Daimon and collaborators believe research into the properties of surface materials could have similar revolutionary applications. An example is nanodots that change polarity to represent binary digits, offering the possibility of magnetic memory that is much faster and more dense than current technology. Also in their sights are materials found to behave like superconductors, even at room temperature, that could dramatically accelerate computer speeds and help save energy.

To unravel the structure of atoms and determine their relationship with other atoms, Daimon and his collaborators at NAIST use the only one-of-a-kind instrument invented by Daimon; a display-type spherical mirror analyzer known as DIANA. When an atom in a sample material such as a graphene monolayer is irradiated with circularly polarized X-rays, it emits photoelectrons that are reflected off a spherical mirror in the device.

These photoelectrons then converge on an aperture and are projected on a screen. The emission angles of the photoelectrons are preserved in this process and the angular distribution patterns they show are referred to as a hologram. These can reveal the positional relationship of atoms and are extracted into stereoscopic images. Displayed on the DIANA screen, the holograms viewed simultaneously can combine to form a

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three-dimensional image of the atomic structure of the material being examined. Some look like fuzzy dots but they can show the arrangement of the atoms in the target material.

"Other devices can only measure in one direction, but this one can measure in all directions at the same time, making it highly efficient and the best machine for analyzing holograms," Daimon says.

> **"Other devices can only measure in one direction, but this one can measure in all directions at the same time, making it highly efficient and the best machine for analyzing holograms."**

Daimon has been collaborating with researchers such as Toshio Hakoshima, a structural biologist at NAIST, as well as private-sector researchers working on sensors and solar cell technology. Another important collaboration partnership involves the RIKEN SPring-8 synchrotron radiation facility in Harima Science Park, Hyogo Prefecture; the largest facility of its kind in the world. Using as much as 8 gigaelectron volts of power, this synchrotron can accelerate electron beams close to the speed of light while guiding them along a circular route with magnets. While Daimon and his team use the facility for photoelectron spectroscopy, synchrotron radiation produced there can be used to analyse proteins and materials, including impurities, isolated during forensics investigations. Daimon aims to promote his unique research and methods overseas, particularly Europe, which also hosts several good synchrotron radiation facilities.

Daimon likens DIANA to a new kind of microscope that can peer directly into atoms. The technique allows for real-time analysis of the atomic motion of a specific atom in nanomaterials, which plays a key role in its special nanofunction. The fact that no special glasses or other apparatus are needed to view the imagery is an added bonus: to illustrate that, Daimon has demonstrated the holograms on Nintendo 3DS video game consoles, which can render graphics in 3D.

Daimon has been fascinated by the atomic structure of molecules since his early graduate studies at the University of Tokyo, where he focused on developing simpler methods of atomic structure measurement. Apart from Nintendo 3DS demos, one of the most effective ways of communicating his research interests to the public during outreach events is to show people molecular mockups.

"Even kids love atoms, especially building the plastic models of molecules, because you can see the structure directly," says Daimon, who is passionate about getting younger generations interested in scientific research. "You can also show how impurities are working in things like the silicon used in computer chips, and we're researching exactly how that happens with our holography and stereoscopic imagery techniques."

More information about the group's research can be found at http://mswebs.naist.jp/english/courses/1341/
Researcher: Hiroshi Daimon

Takayuki Yanagida

A scintillating career

After great commercial success, a brilliant physicist returns to basic research to shed light on old mysteries

Takayuki Yanagida was torn between two career paths as a 21-year-old undergraduate: join a company and go into business or become a scientist.

He recalls that two people influenced him to pursue the second choice. "I remember learning about Einstein's theory of general relativity and being very inspired," Yanagida says. "At that time, I thought time is something absolute, but Einstein showed me that time is also relativistic; it was totally surprising to me!"

His second source of inspiration was a fellow student. "When I was at university, I'd study during the day, and then, every evening, I would head for the basketball court to play with a friend," Yanagida explains. "In Japan, it's unusual for people to be good at sports and at science, but my friend excelled at both.

"One day he told me he was going to become a scientist, which surprised me because I associated him with the basketball court. Up until that point, I'd never thought of myself at that level. Few people from my hometown of Sendai are even offered a place to study at the University of Tokyo, let alone become scientists. But, I thought, if he can do it… so can I."

A gifted physicist, Yanagida set out early in his career to focus on basic research into the phenomenon of scintillation: the flash of visible light produced as X-rays pass through a transparent material. He pursued a master's and then PhD in astrophysics at the University of Tokyo, during which he used scintillation detectors to observe X-rays emitted from parts of the universe known as 'star-forming regions', to better understand how stars are formed.

"After finishing my PhD, my aim was to find industrial uses for my discoveries," Yanagida says. "In my final thesis I identified compounds that had great potential, and I was keen to work on the applied side of my research."

In 2007, Yanagida joined Tohoku University as a research assistant and concentrated on scintillator materials and scintillation detectors — which, as radiation detectors, have applications in areas as diverse as security and medicine. Soon his work was attracting serious commercial attention.

"I designed quicker and more accurate scintillator detectors that could improve the resolution of X-ray images," he explains. "This technology was bought and developed by many companies. It's now used in security inspection systems in airports."

Moving in 2012 to the Kyushu Institute of Technology to become an associate professor, Yanagida continued to work closely with industry before relocating to NAIST in 2015 to become a professor and head of the Sensing Device Laboratory. Yanagida says his commercial success has taught him to value the importance of basic research. And here, at NAIST, he has been given the support to shift his attention back to pure science and away from researching the practical applications of his work. (To read about a recent success from Yanagida's lab see "Bright future for radiation detection" on page 62.)

"In many universities, there is little time to focus on your research. You have to teach many lessons and spend hours preparing your material," he says, explaining that professors at NAIST are in an enviable position. "At NAIST there are no undergraduate students, so faculty members have more time away from teaching to pursue their own goals. There is far, far less teaching time so I can spend many hours on basic research."

Yanagida now hopes to be able to unlock many of the secrets of scintillators that have evaded scientists for a century. "Scintillators were discovered more than 100 years ago. But even though we use them in many industries — from medicine to security — we still haven't opened that black box to explain exactly how they work," Yanagida explains. "I am doing experiments that I hope will solve the basic process. But this could take another 10 years or more."

In comparison to other research institutions, Yanagida believes that the general setting for the institute in Nara make it an excellent place to settle and focus his attentions. "The NAIST campus has a different atmosphere to other universities," he says. "It is a calm place. The students are older so they mostly study. When students are younger, a university environment can be a little more crowded and noisy."

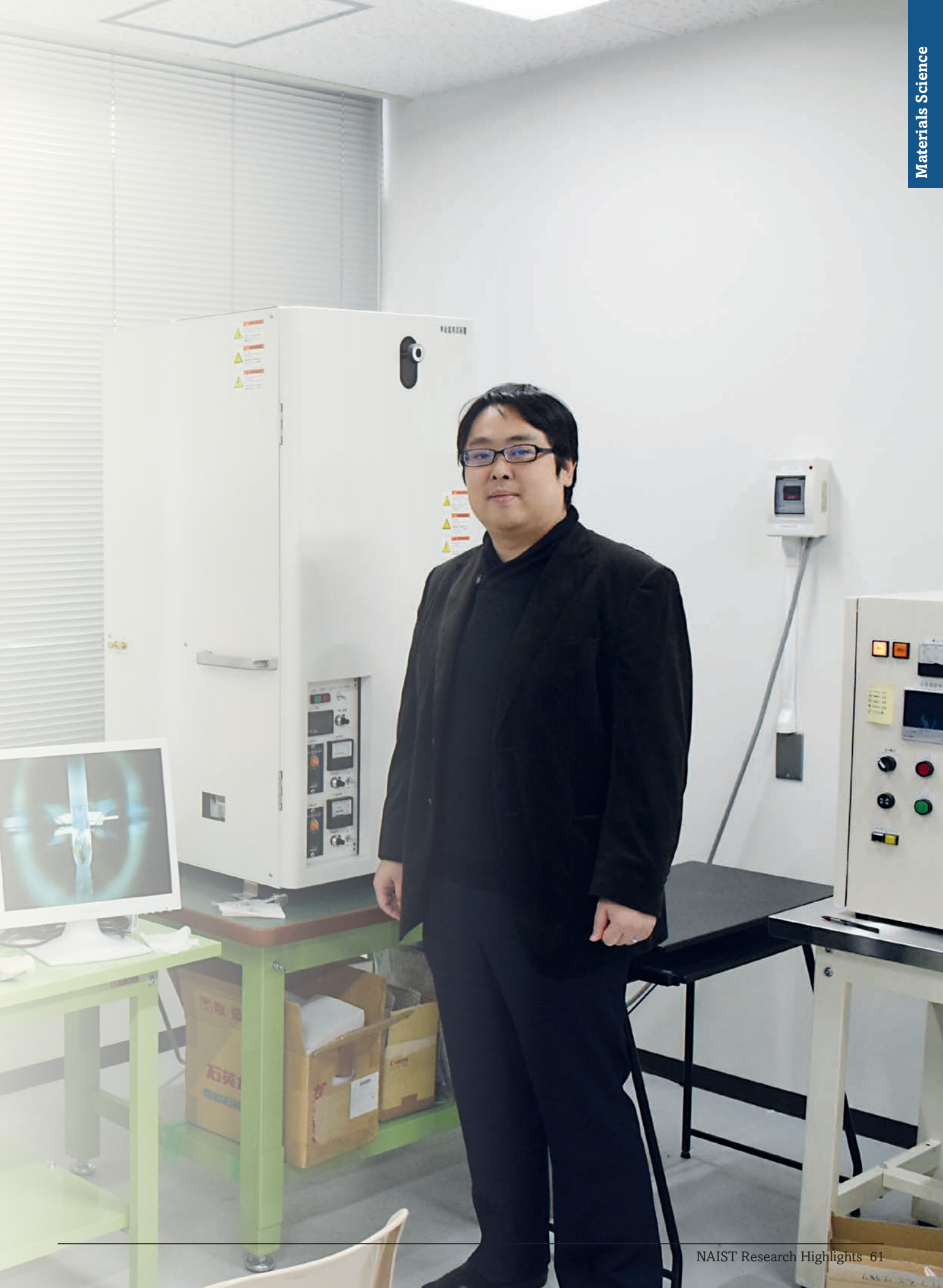
The support of his family, has been crucial for Yanagida. "My secretary is my wife, and has been ever since I worked at Kyushu University," he says. "In fact, she's the reason that I work in materials science, rather than astrophysics."

Two decades ago, after completing his PhD in astrophysics, Yanagida was expecting to find work in his original research field. But then his wife, Satoko, developed leukaemia. "We needed to move to her hometown so she could go to hospital," he says, recalling what turned out to be a serendipitous career move to Tohoku University. "In northern Japan, there's little call for astrophysicists. The biggest university is Tohoku University and they are strong on materials research. So I became a materials scientist."

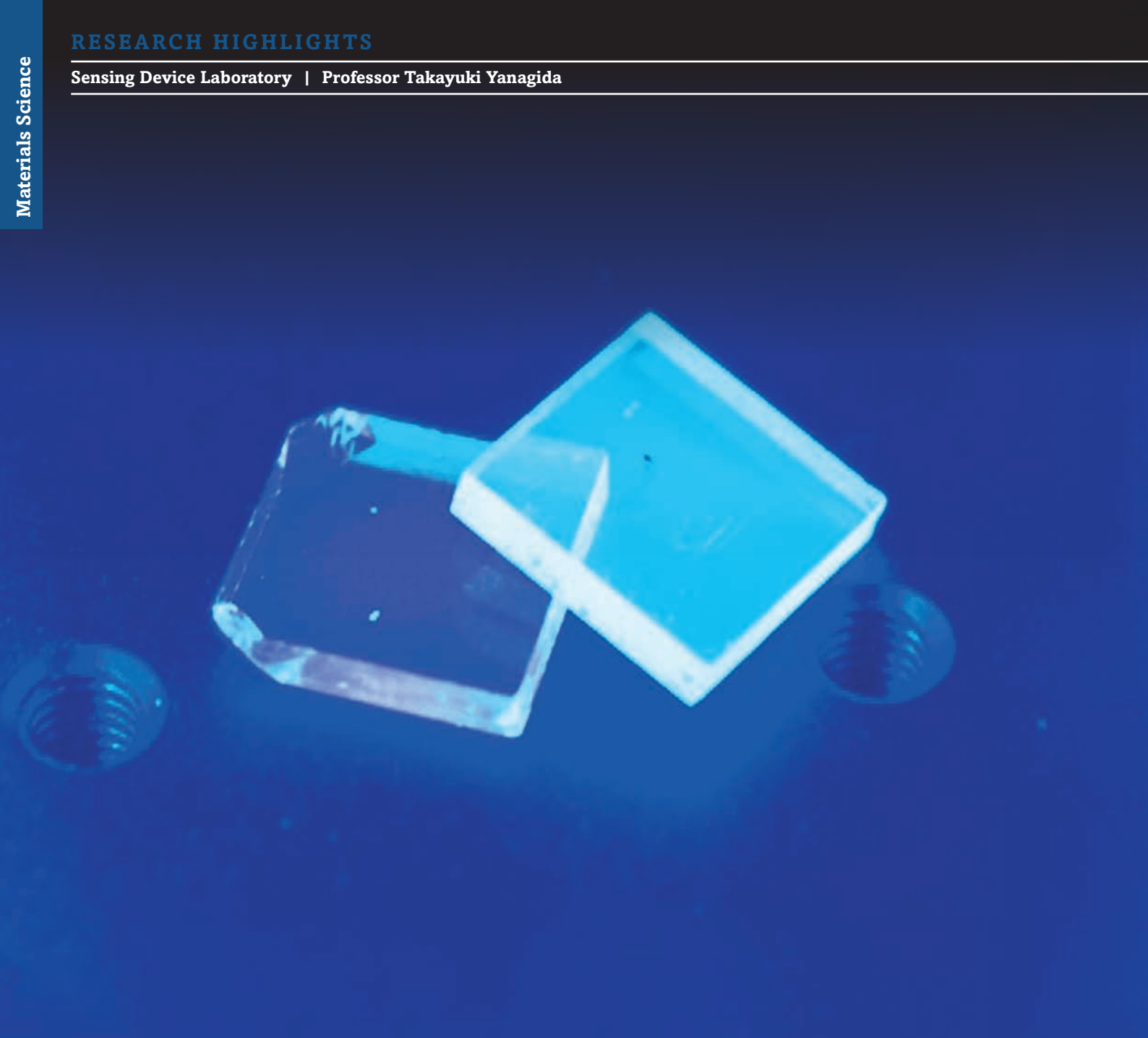
Now the couple have an 11-year-old girl, Shiona, who loves to come and visit Yanagida in his NAIST laboratory, which he joined just under a year ago. "She thinks it is fun to see luminescent materials," he smiles. "I make many of these in my lab, so she comes and checks the colour for me."

More information about the group's research can be found at http://mswebs.naist.jp/english/courses/1989/

Researcher: Takayuki Yanagida



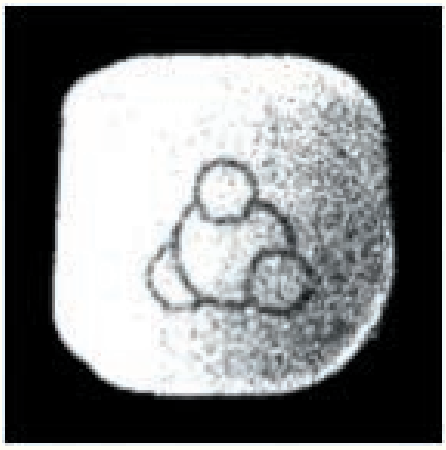
Sensing Device Laboratory | Professor Takayuki Yanagida

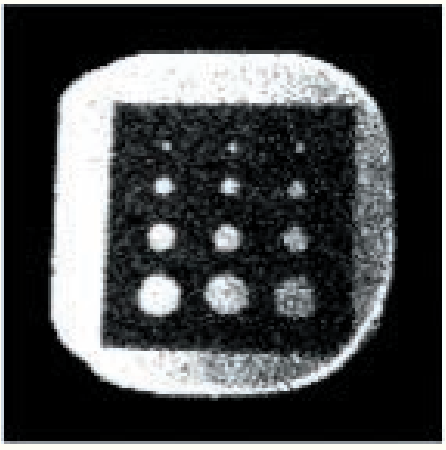


Scintillators

Bright future for radiation detection

New crystalline material shows promise for security and medical applications





The new scintillator can detect complex shapes made from a neutron-blocking material.

NAIST scientists have developed an alternative to the rare gas used to detect radiation in medical imaging, astrophysics and security screening.

This function has routinely been done with low-energy (or 'thermal') neutron detectors fuelled by helium-3. However supply of this gas, which is highly sensitive to neutrons, is extremely limited and demand far outstrips supply.

Takayuki Yanagida and colleagues from NAIST's Sensing Device Laboratory have, however, come up with a readily available alternative: crystals of lithium calcium aluminum hexafluoride ($LiCaAlF_6$) doped with traces of the metal, europium[1]. Energy detecting materials such as this emit light when exposed to thermal neutrons and are known as scintillators.

The materials for this new scintillator include lithium fluoride enriched in lithium-6, a light isotope of the metal that is sensitive to thermal neutrons. When a neutron hits lithium-6, the collision produces two particles: an alpha particle made of two protons and two neutrons and a triton, which contains one proton and two neutrons. These two particles speed through the crystal, and in their wake excite electrons that eventually transfer their energy to the europium ions, which emit photons (measurable particles of light). The researchers found that for every neutron that hits the material, the europium produced about 29,000 photons.

The team then tested the scintillator's ability to image two hidden objects, known as masks. One mask contained a series of holes, while the other had a more complex interlocking ring pattern. The scintillator sat on one side of the mask, while a beam of neutrons fired at it from the other side. Because the neutrons could only pass through holes in the masks, the light emitted by the scintillator formed a sharp shadow image of the objects after about 10 minutes, revealing features smaller than a millimeter in size (see image).

This material, which is now available from Japan-based chemical manufacturer Tokuyama Corporation, offers the second-highest light yield of any commercial scintillator. "One application is security," Yanagida says. "Neutron detectors are required to prevent nuclear terrorism." He and his collaborators have, for example, used the scintillator to develop a security instrument for airports and are also testing it for medical applications that use neutrons to treat disease.

Yanagida has subsequently invented an even more luminous scintillator — a form of cerium-doped gadolinium aluminum gallium oxide, which is also commercially available. He is now developing an improved theoretical model of the scintillation process, which should help to design even more sensitive radiation detectors.

Reference

1. Yanagida, T., Kawaguchi, N., Fujimoto, Y., Fukuda, K., Yokota, Y. *et al.* Basic study of Europium doped LiCaAlF6 scintillator and its capability for thermal neutron imaging application. *Optical Materials* **33**, 1243-1247 (2011).

To read more about the work of Takayuki Yanagida, another of NAIST's newest researchers, see A scintillating career on page 60.

More information about the group's research can be found at http://mswebs.naist.jp/english/courses/1989/
Researchers: Takayuki Yanagida and Go Okada

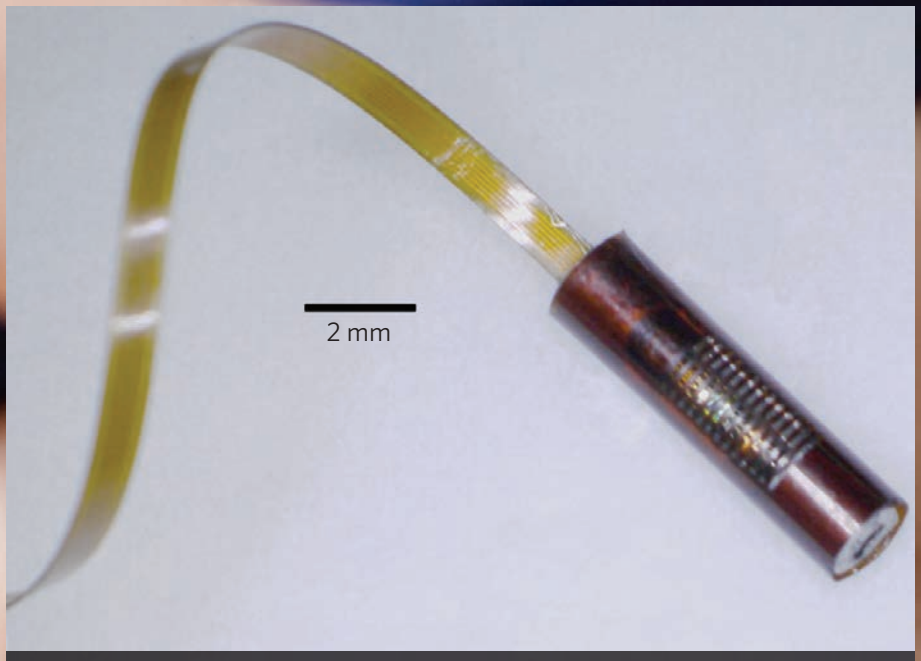
Photonic Device Science Laboratory | Professor Jun Ohta

Photonics

Glucose monitor gets under your skin

An implantable device offers continuous glucose monitoring for diabetes sufferers

“Our sensor has features which are suitable for bioimplantable devices.”



NAIST's new implantable glucose monitoring device promises to make life easier for diabetics.

Diabetes can lead to cardiovascular disease, foot ulcers, serious eye problems and even stroke. People with the condition must regularly take blood samples to check their glucose levels; an effective, but onerous task. In some cases, when it is necessary to take more frequent or even continuous readings, extracting blood samples is simply not feasible.

Now, researchers from NAIST's Photonic Device Science Laboratory have made glucose monitoring easier by designing and testing *in vivo* a small, implantable glucose-sensing device for on-demand or even continuous glucose monitoring[1].

They used hydrogel containing a glucose-responsive fluorescent dye that was illuminated using a light-emitting diode (LED) attached to the gel. The presence of glucose enhanced the fluorescence, which was quantified using a sensor. "Our sensor has features which are suitable for bioimplantable devices, such as those using a small number of control wires. It is minimally invasive, and so there is little risk of infection," explains Takashi Tokuda, who worked on the project. "The CMOS image sensor used in our work uses basically the same mechanism as that used for digital cameras. It consists of a two-dimensional pixel (photosensor) array and sequential readout circuit. In most CMOS image sensors, including ours, the light-sensing circuit in each pixel can detect a very small amount of light."

The pixel sensor array allows the device to operate at multiple sensitivities simultaneously. It was most sensitive at the borders of the pixel array, whereas higher levels of glucose could be measured by analysing the central pixels.

The researchers assessed the device's performance in a rat model and compared the readouts to standard self-monitoring of blood glucose. The animals were injected with specific glucose concentrations and the data read using both approaches. The sensor had to be calibrated as it read glucose from an interstitial medium rather than blood. But once calibrated, it successfully monitored glucose levels over several hours.

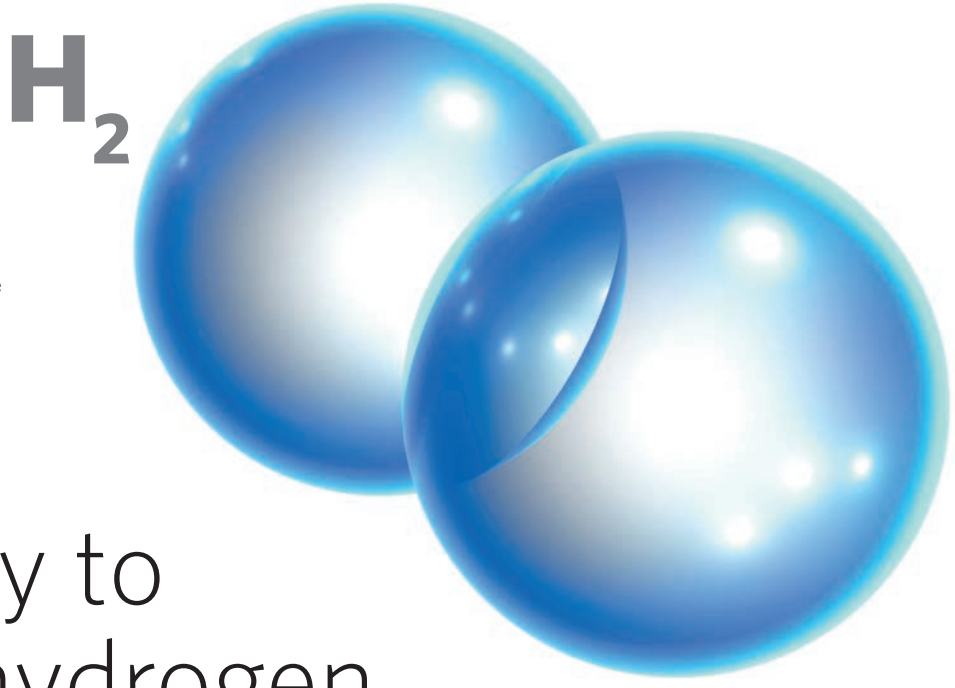
The sensor lagged the blood glucose measurements by 60 minutes, so the researchers modified the device structure, application protocol, hydrogel thickness and sensor placement. They have now reported sensor performance in which the lag time is the same as that for conventional self-monitoring of blood glucose[2].

References

1. Tokuda, T., Takahashi, M., Uejima, K., Masuda, K., Kawamura, T. *et al.* CMOS image sensor-based implantable glucose sensor using glucose-responsive fluorescent hydrogel. *Biomedical Optics Express* **5**, 3859–3870 (2014).

2. Kawamura, T., Masuda, K., Hirai, T., Ohta, Y., Motoyama, M. *et al.* CMOS-based implantable glucose monitoring device with improved performance and reduced invasiveness. *Electronics Letters* **51**, 738–740 (2015).

More information about the group's research can be found at http://mswebs.naist.jp/english/courses/1408/
Researcher: Takashi Tokuda



The nickel-iron active site within a hydrogenase enzyme needs an electron pathway to reversibly split hydrogen gas. New findings show that iron–sulfur clusters can turn this flow on or off.

Electron pathways

A gateway to splitting hydrogen

The discovery of a reaction control switch during a crucial biological reaction brings hope of a fuel cell closer

Hydrogen gas (H_2) is known as 'nature's fuel' because of the role it plays keeping bacteria and other microorganisms alive and plentiful. Through the action of enzymes known as hydrogenases, these microbes can both rip apart and generate H_2 — releasing and storing electrons in the process. Now, a team from NAIST has identified critical electron transfer sites that may help researchers control this activity by switching hydrogenases on or off[1]. It brings the realization of low-cost hydrogen fuel cells, as a lightweight, emission-free energy source, a step closer.

The core activity of hydrogenases occurs within their 'catalytic centres', which contain nickel (Ni) and iron (Fe). These metals reverse the oxidization of H_2 into protons and electrons through electron transfer. Many fuel cells perform this same function by using expensive platinum catalysts. Reproducing the hydrogenase-based biochemical technique within artificial devices, however, would be challenging because H_2 cleavage and creation involves complex, multi-step processes in microbes.

"Even though this chemical reaction is very simple, the mechanism is quite complicated," explains Shun Hirota, from NAIST's Supramolecular Science Laboratory. For example, he notes, one particular enzyme called [NiFe] hydrogenase has at least seven intermediate states that either participate in the reaction or are activated by H_2. "And now we've found another one in the catalytic cycle, making it eight," Hirota says.

To produce H_2, an enzyme's active site needs an external source of electrons. Usually, charges come from a carrier protein that attaches to the outer surface of the hydrogenase. Hirota, in collaboration with Hulin Tai, and colleagues at the University of Hyogo, discovered that a light-generated intermediate known as the 'Ni-L' state plays a vital role in ensuring that electron transfer to the NiFe active site proceeds normally.

> **"The electrons have to pass through the cluster — it's like a gate, the more we know about what is going on in this reaction, the better we can utilize it."**

Hirota says that the light sensitivity of hydrogenases has been established for decades, but the Ni-L state was never considered as part of the catalytic cycle. The team proved it was included by watching infrared vibrations of bonds at the NiFe centre under light and dark conditions. They used laser irradiation to initiate the Ni-L state, and captured it for analysis at 138 kelvin.

Electron transfer to and from the active site is controlled by three iron-sulphur (FeS) clusters located within the small subunit of the enzyme. The researchers' analysis revealed that opening this electron pathway required oxidation of the FeS cluster closest to the NiFe centre: the catalytic reaction stops and the Ni-L state is trapped when the FeS cluster is reduced. "The electrons have to pass through the cluster — it's like a gate," says Hirota. "The more we know about what is going on in this reaction, the better we can utilize it."

Reference

1. Tai, H., Nishikawa, K., Suzuki, M., Higuchi, Y. & Hirota, S. Control of the transition between Ni-C and Ni-SIa states by the redox state of the proximal Fe–S cluster in the catalytic cycle of [NiFe] hydrogenase. *Angewandte Chemie International Edition* **53**, 13817–13820 (2014).

More information about the group's research can be found at http://mswebs.naist.jp/english/courses/1421/

Researchers: Shun Hirota and Hulin Tai

Nano-fabrication

Bleeding-edge science to improve digital memory

A protein found in blood has been used to help create the world's smallest transistor

NAIST researchers have fabricated the smallest transistor to date, forming the possible basis for the next generation in digital memory[1], using ferritin protein molecules to form nanodots in short V-grooves.

Advances in computing performance rely on the incremental downscaling of the individual switching elements on which digital technology is based. The elements are the 'bits' that can be switched to either on or off to give the binary states of 0 and 1, and are realized using electronic semiconductor transistors.

Technological advances in micro- and nano-fabrication techniques have taken the industry to transistor scales below 10 nanometers, but researchers are finding that, at this level, existing fabrication techniques are not reliable enough for commercial production of the next generation of digital memory.

Yukiharu Uraoka and colleagues from NAIST's Information Device Science Laboratory and the National Institute of Advanced Industrial Science and Technology (AIST) — one of Japan's largest public researcher organizations — have used a biological process to create a transistor as small as 4 nanometres. "We have demonstrated the memory operation of a semiconductor device with the shortest channel length in the world, utilizing nanodots fabricated using biotechnology," says Uraoka. "This is a fusion of semiconductor technology and biotechnology that has proved to be very effective for fabricating new functional semiconductor devices."

A semiconductor transistor consists of a junction between two electronic terminals that only conducts electrons when the voltage across it reaches a certain threshold. Typically, a semiconductor material with these properties, such as silicon oxide, is used in the junction. But at sub-10 nanometre scales the semiconducting properties of silicon become unstable.

> **"We have demonstrated the memory operation of a semiconductor device with the shortest channel length in the world."**

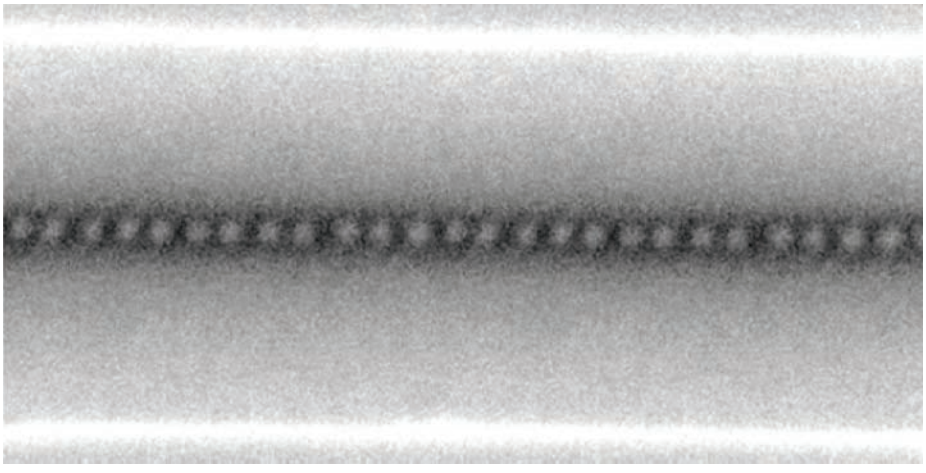
Uraoka's team fabricated a V-groove junction with a nanodot of semiconducting iron oxide 'floating' on a wedge of insulating silicon dioxide in the groove. "By charging or discharging electrons into the nanodot embedded in the gate oxide, the threshold voltage of the junction changes to high or low, corresponding to memory states of 1 or 0," explains Uraoka.

The challenge for the research team was fabricating the nanodots consistently and they came up with an ingenious solution. They used the cage-shaped protein ferritin, which stores iron in the cells of humans and other mammals, to 'biomineralize' a nanodot with predictable and well-defined dimensions. "The nanodot size is uniform because it is designed by DNA," says Uraoka.

"As a memory element, we achieved low-voltage operation and a wide threshold voltage shift, but the technique is also potentially applicable to displays, sensors or energy harvesting devices such as solar cells and thermal transducers."

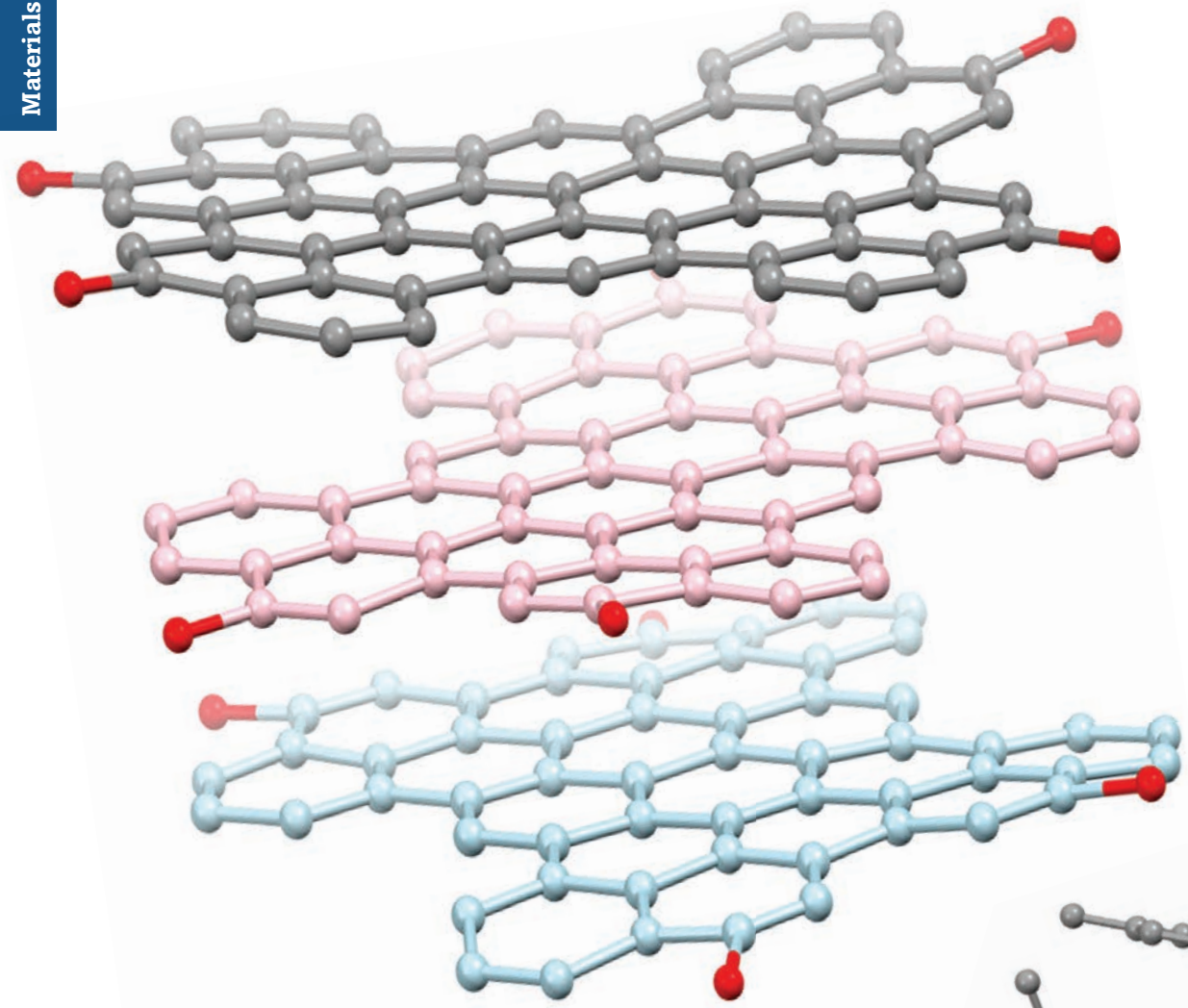
Reference

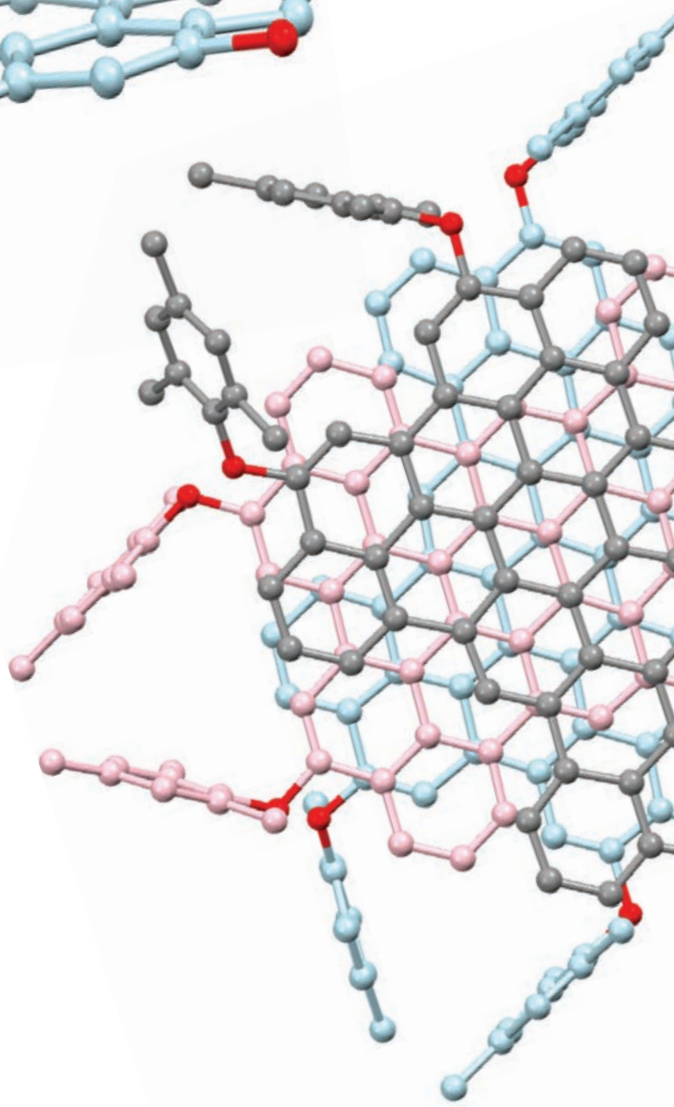
1. Ban, T., Uenuma, M., Migita, S., Okamoto, N., Ishikawa, Y., Yamashita, I. & Uraoka, Y. Ultra-short channel junctionless transistor with a one-dimensional nanodot array floating gate. *Applied Physics Letters* **106**, 253104 (2015).



Iron oxide nanodots can be fabricated in the V-groove of a junction transistor using ferritin protein.

More information about the group's research can be found at http://mswebs.naist.jp/english/courses/1410/
Researcher: Yukiharu Uraoka





Nanotechnology

Stacking the odds in graphene's favour

Eye-catching 2D carbon sheet arrangements can act as stable, multi-charge storage devices for memory applications

Atomically flat graphene sheets are a speedier alternative to silicon transistors, but integrating these materials into confined nanoscale devices is challenging. Now, a NAIST team has discovered how to synthesize graphene into tiny, triple-layered clusters that can release unusually large amounts of electric charge[1].

Graphene sheets are usually isolated by peeling graphite crystals apart layer by layer. Early 'sticky tape'-based methods to do this have been replaced by more efficient liquid-phase exfoliations, but mechanically agitating the atom-thin layers makes it hard to control final product morphologies. Some researchers have been experimenting with bottom-up approaches, such as surface-directed chemistry, that assemble graphene into desired shapes from molecular precursors.

Naoki Aratani, Hiroko Yamada and colleagues from NAIST's Photofunctional Organic Chemistry Laboratory investigated a different bottom-up method based on polycyclic aromatic hydrocarbons (PAHs) — organic molecules containing multiple rings. These compounds, which are found naturally in coal, oil, and gas, resemble graphene networks at truncated, nanoscale dimensions. Synthesizing PAHs with custom frameworks, however, is tricky due to their low solubility and cumbersome structures.

For their nanographene synthesis, the NAIST team targeted the PAH peripentacene. Flat, rectangular, and composed of 14 interlocked benzene rings, this molecule has been identified as a 'missing piece' of the simplest PAHs because it is unstable under standard ambient conditions. Part of the problem is that electrons in peripentacene are delocalized and can exist as reactive free radicals.

> **"When we saw the trimer, we thought, what a beautiful structure."**

To trap peripentacene in a usable form, the researchers turned to a PAH with a central core of four flat aromatic rings surrounded by several other ring systems. By mixing this PAH with the strong oxidizing agent iron chloride, the team removed electrons from the precursor and caused it to spontaneously fuse into a nanographene sheet composed of 56 carbon atoms.

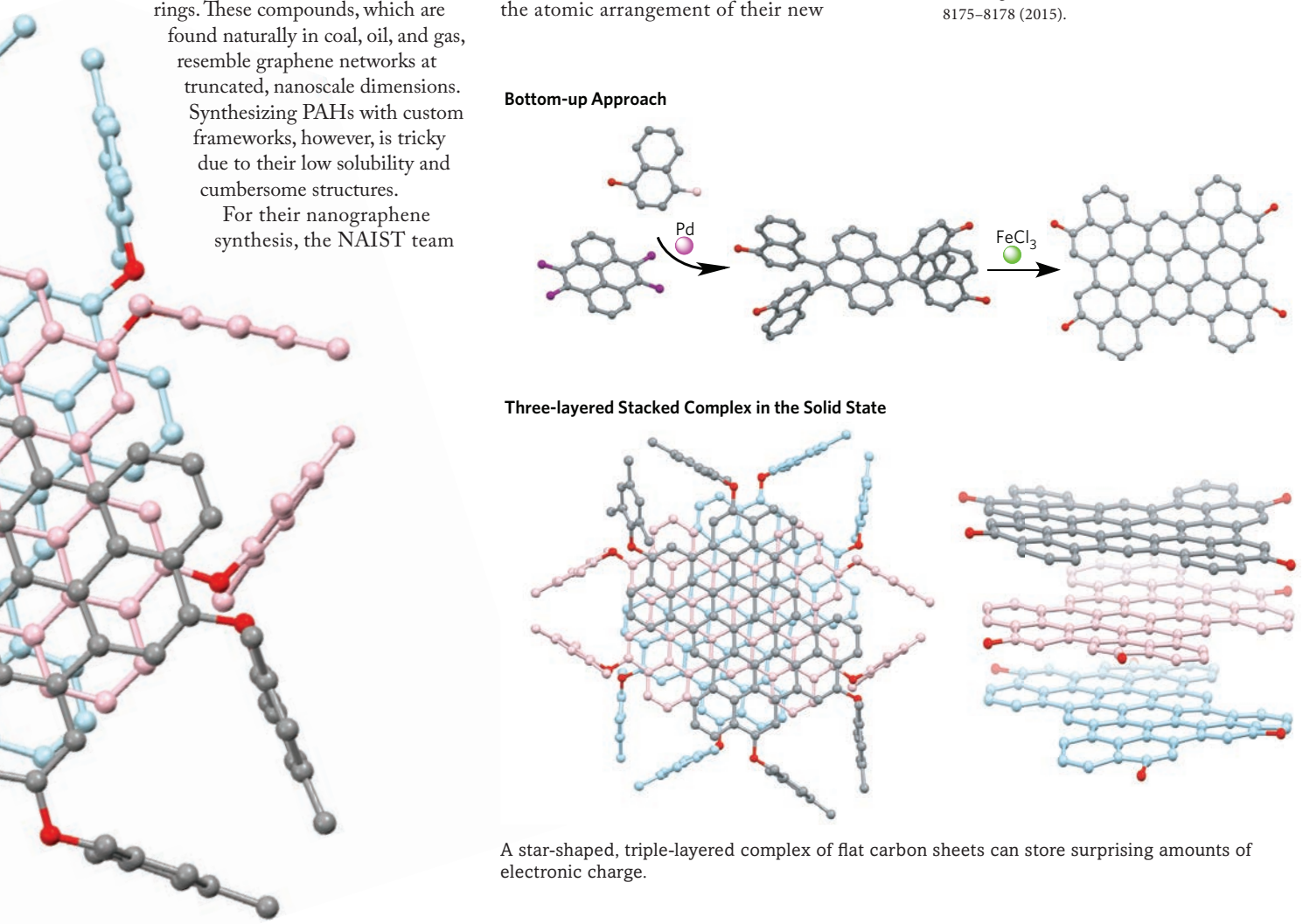
When the team used X-rays to observe the atomic arrangement of their new peripentacene, a curious result was apparent. Instead of a single sheet, their nanographene was identified as a three-layered stacked complex that, when viewed from above, took on a symmetric, star-shaped appearance (see image). "When we saw the trimer, we thought, what a beautiful structure," recalls Aratani.

The nanographene in solution also imparted unique electronic capabilities. Electrochemical measurements revealed the new peripentacene could reversibly release and take in five electrons — one of the largest positive charge storage values ever recorded for an all-carbon organic framework.

"We were so excited by this behaviour," says Aratani. "This multi-charge storage ability makes the peripentacene a nice counterpart to C_{60} buckyballs."

Reference

1. Matsumoto, A., Suzuki, M., Kuzuhara, D., Hayashi, H., Aratani, N. & Yamada, H. Tetrabenzoperipentacene: Stable five-electron donating ability and a discrete triple-layered β-graphite form in the solid state. *Angewandte Chemie International Edition* **54,** 8175–8178 (2015).



A star-shaped, triple-layered complex of flat carbon sheets can store surprising amounts of electronic charge.

More information about the group's research can be found at http://mswebs.naist.jp/english/courses/1432/

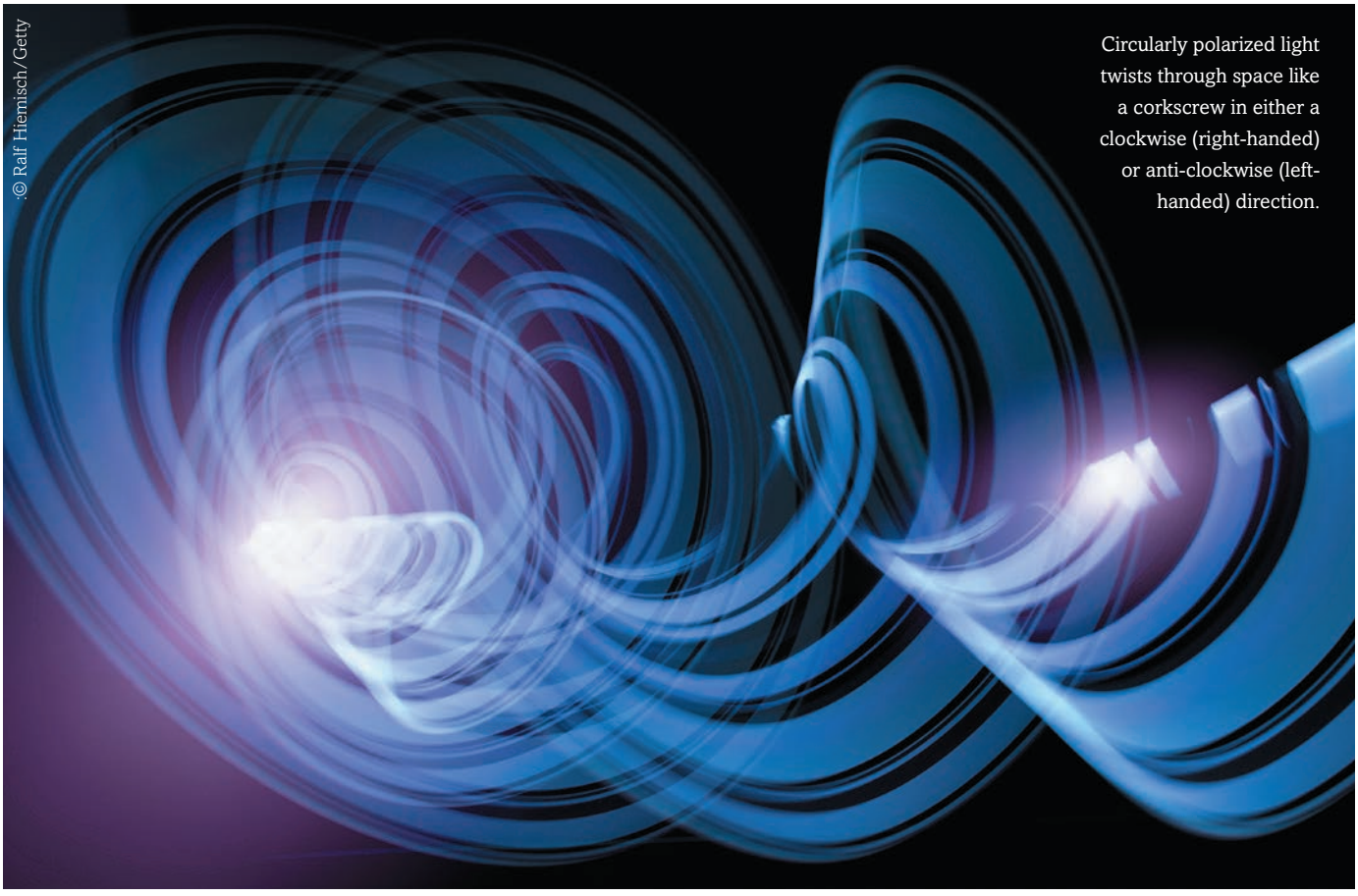
Researchers: Naoki Aratani and Hiroko Yamada

"Sugar and magnets may have little in common, but we found that a sugar film covered with red dye looks to circularly polarized light like a magnet."

Optical phenomena

The sweet lure of light to sugar

A red dye–sugar combination interacts with light in an unexpectedly magnetic way



Circularly polarized light twists through space like a corkscrew in either a clockwise (right-handed) or anti-clockwise (left-handed) direction.

A possible new research focus into optical phenomena and light manipulation has been exposed through the discovery at NAIST of a non-magnetic double-layer film that can interact like magnetic materials with light[1].

Light interacts with materials in a wide range of ways, from complete absorption by some metals to perfect transmission by transparent glass. Some materials — such as the liquid crystal used in computer displays — interact with light in ways that change the orientation of its polarization. However, one of the more scientifically useful light–material interactions is biological.

Most biological molecules, such as proteins for example, come in mirror-image versions with either left- or -right-handed symmetry. This 'chirality' is key to the functionality of many biomolecules; a right-handed version, for example, may be able to combine with other molecules in a way the left-handed form cannot.

Light with a corkscrew-like rotating polarization (see image), known as circular polarization, also interacts differently with left- and right-handed chiral molecules depending on the light's own 'handedness'. This effect is exploited in the spectroscopic measurement of concentrations of specific chiral proteins in biological solutions. Such biological molecules are said to be optically active, and their interaction with circularly polarized light produces an effect called circular dichroism.

"In absorptive chiral molecules, rotation of circular polarization is accompanied by circular dichroism due to the absorption difference between the left- and right-handed circularly polarized light," explains Satoshi Tomita, a researcher in NAIST's Quantum Materials Science Laboratory,

Circularly polarized light can also be manipulated using magnetism. By passing this sort of light through a magnetic field with a particular orientation, it is possible to flip the polarization plane and reverse the light's rotation. Tomita and his NAIST colleagues have discovered that a thin film of glucose topped with rhodamine red dye can achieve this same polarization reversal at the absorption wavelength of the dye. This is the first non-magnetic medium known to do this.

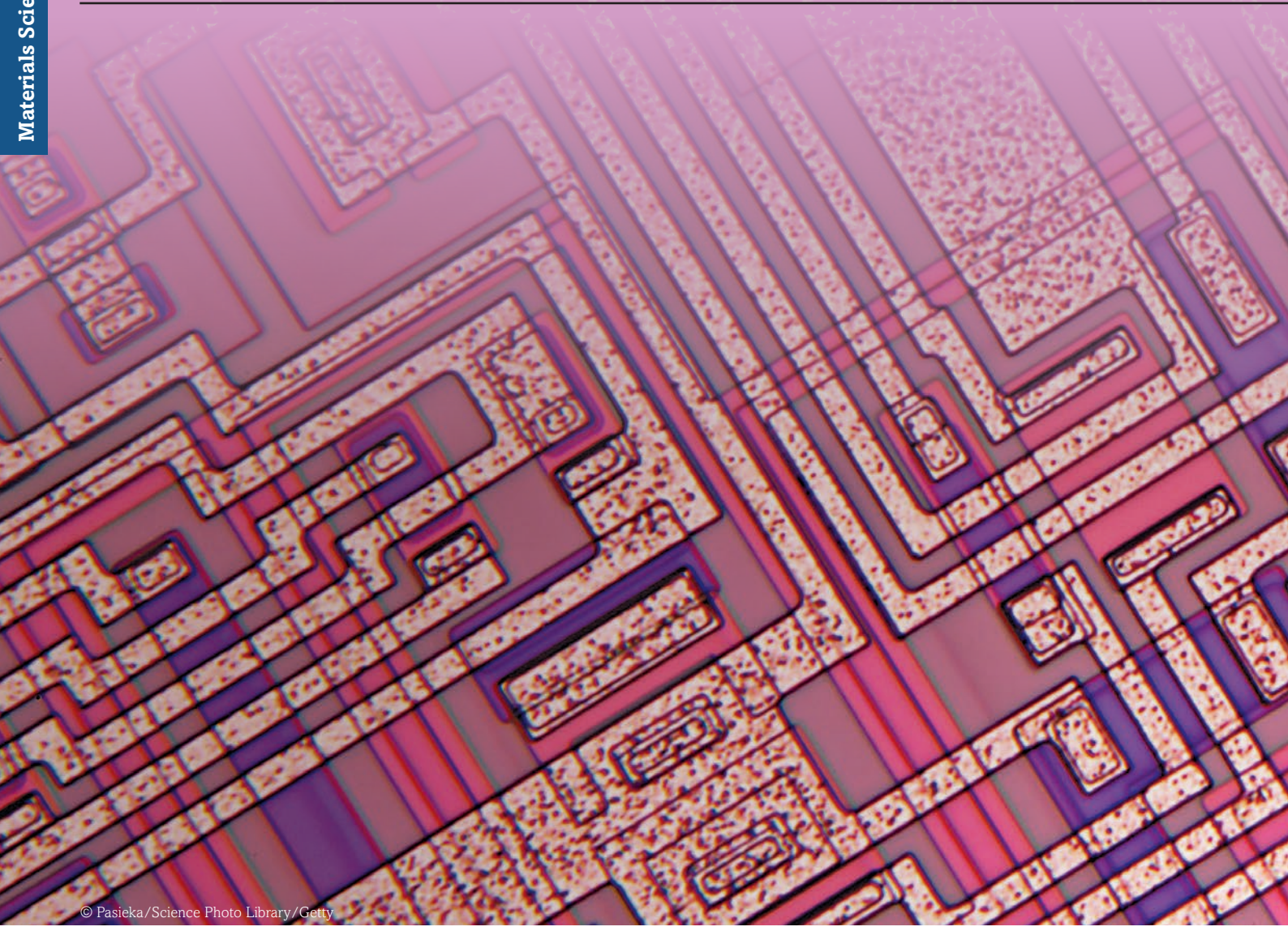
"Sugar and magnets may have little in common, but we found that a sugar film covered with red dye looks to circularly polarized light like a magnet," Tomita says. "Although the origin of the reversal we have discovered is still unclear, the interface between the transparent chiral glucose molecules and the absorptive achiral dye in the double-layer films is essential to this effect. It is a 'chiral meta-interface' that could pave the way for exploring new optical phenomena and could be used as an optical isolator without magnetic fields."

Reference

1. Tomita, S., Kosaka, Y., Yanagi, H. & Sawada, K. Chiral meta-interface: Polarity reversal of ellipticity through double layers consisting of transparent chiral and absorptive achiral media. *Physical Review B* **87**, 041404(R) (2013).

More information about the group's research can be found at http://mswebs.naist.jp/english/courses/1162/
Researchers: Satoshi Tomita and Hisao Yanagi

Photonic Molecular Science Laboratory | Professor Tsuyoshi Kawai



Photonics

Feeding a growing need for shrinking devices

New material could improve processes for sub-microscopic manufacturing

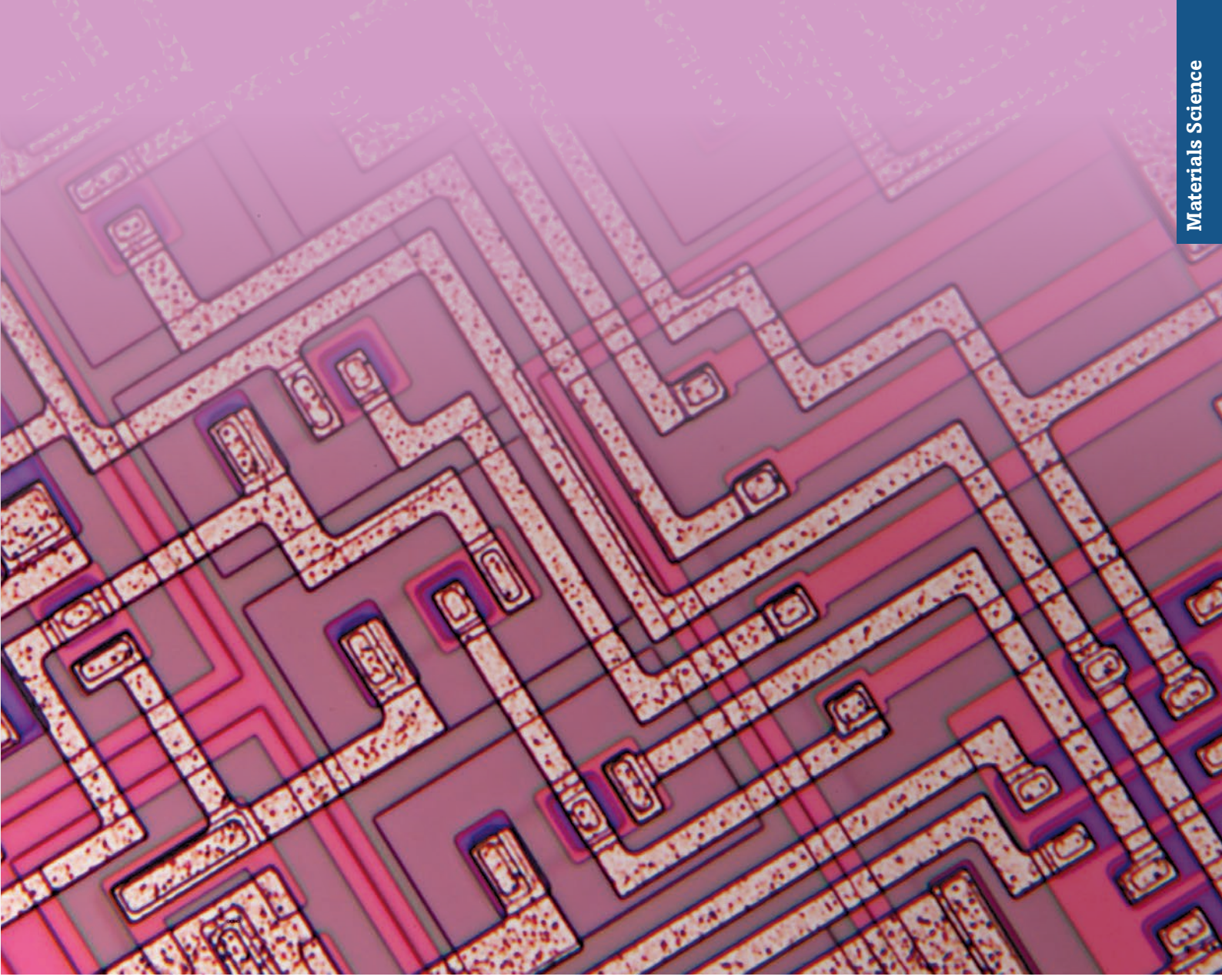
The increasing demand for miniaturization of electronic devices, such as semiconductors and transistors, down to nanoscale dimensions is pushing the capacity of the optical lithography processes used to produce them. There is a strong need for new light-sensitive materials, known as photoresists, that can meet the demands of more advanced micro-photolithographic techniques.

Micro-photolithography is used in the fabrication of super-miniature and highly complex patterns such as those on integrated circuit boards. It allows for patterns that are only a few tens of nanometers in size to be etched or deposited onto photoresists.

Among the critical components of photoresists are photoacid generators (PAGs). These produce the strong acids required to engrave or deposit patterns on to substrates. More efficient PAGs could lead to improvements in the performance of micro-photolithographic processes, but also of rapid prototyping (3D printing) and photocuring systems.

NAIST researchers have been investigating a new type of PAG by irradiating photochromic triangle terarylenes with ultraviolet light, inducing an electrocyclic reaction that produces a closed-ring structure and triggers the release of methanesulfonic acid by the PAG1. By introducing hydrogen atoms and the acid's conjugate base to both sides of the structure a self-contained PAG was formed.

"We had already developed highly effi-



> **This breakthrough could lead to improvements in 3D printing as well as in processes that produce sealants, protective gloves and rubber stoppers for pharmaceuticals.**

cient photo-quantitative compounds based on compounds with a triangle terarylene structure," explains Tsuyoshi Kawai, from NAIST's Photonic Molecular Science Laboratory. "Although this new type of PAG only achieved a quantum yield of 52% during the study, it promises the possibility of super-efficient photoresists in the future with quantum yields close to 100%."

PAGs with higher quantum yields are more efficient at producing photoacids and could lead to better performing photoresists and improvements in photolithographic processes. The PAG developed in the study was also capable of photo-initiating the cationic polymerization of cyclohexene oxide — an epoxy monomer. This could lead to improvements in 3D printing as well as in photocuring processes that produce materials used for such products as sealants, protective gloves and rubber stoppers for pharmaceuticals.

"Although photochromic reactions that lower the pH of photoacids have been reported, they are not able to generate sufficiently strong and reactive acids for cationic polymerization to occur," Kawai says. "Employing the PAG as a phototrigger of cationic polymerization indicates that the new PAG is compatible with photopolymer systems and represents another significant outcome from our research."

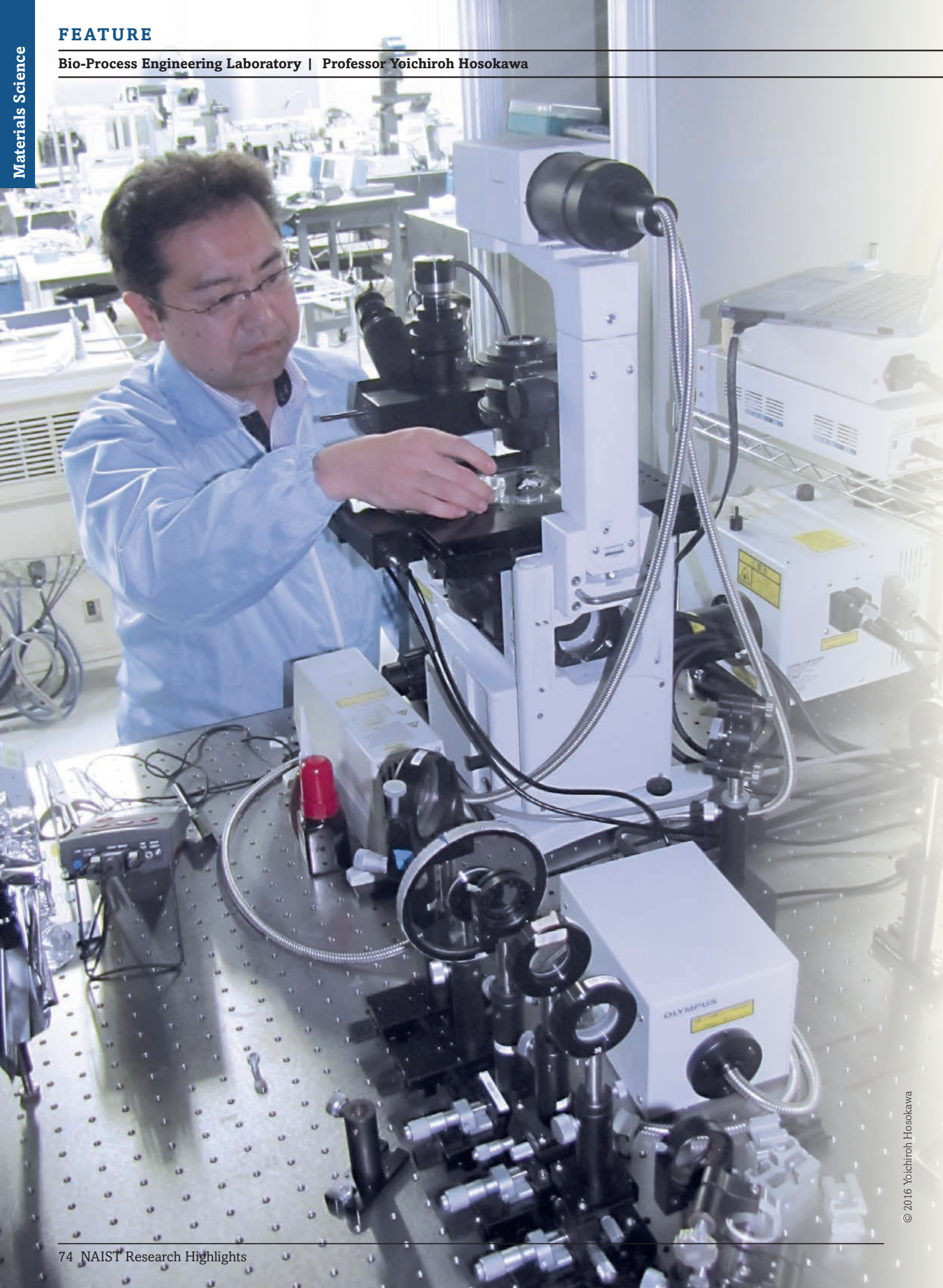
Reference

1. Nakashima T., Tsuchie K., Kanazawa R., Li R., Iijima S., Galangau O., Nakagawa H., Mutoh K., Kobayashi Y, Abe, J. & Kawai T. Self-contained photoacid generator triggered by photocyclization of triangle terarylene backbone. *Journal of the American Chemical Society* **137,** 7023–7026 (2015).

More information about the group's research can be found at http://mswebs.naist.jp/english/courses/1427/
Researcher: Tsuyoshi Kawai

FEATURE

Bio-Process Engineering Laboratory | Professor Yoichiroh Hosokawa



Yoichiroh Hosokawa

Exploring cells with intense light

Physics meets biology in a flash of brilliance as a novel use of lasers opens a bold new field of research

The lab of Yoichiroh Hosokawa provides a fine example of the interdisciplinary and collaborative research approach that has become a hallmark of NAIST in recent years. Its name — the Bio-Process Engineering Laboratory — describes both the physics-based technology at its core and the biological world that is the focus of the lab's research. Its students and young researchers have a range of backgrounds, from physics and chemistry to biology and medicine.

Hosokawa is keen to see the collaborative approach adopted in all directions. "Although I like to apply the most advanced laser-based engineering for biological research, I think that we could also apply biological phenomenon for engineering," he explains. Through such innovative research, he is hoping to foster students who can work creatively beyond orthodox paths of thinking and communicate well with other people with various backgrounds.

Hosokawa embarked on a career based on laser technology in 1995 when he began a master's degree at Osaka University. His supervisor in the university's Department of Applied Physics, Hiroshi Masuhara, who is now retired, told him: "Laser has huge potential, so you won't have trouble finding a job if you can operate advanced laser devices."

But, by the time Hosokawa had earned his PhD, five years later, laser-manufacturing technology had greatly advanced and the devices had become user-friendly and already widely used in many areas. "I had to think of a way to take advantage of my skills," he says. Hosokawa turned his attention to biotechnology, where the use of lasers for cell manipulation had barely been explored.

Even today, laser for many biologists is used as a tool mostly to visualize cells under microscopes. Fluorescent probes are an example. As a result, the weakest possible light is usually considered best, to avoid disturbing the cellular environment. But, what Hosokawa now offers his biological collaborators is the exact opposite: the laser he applies for cell manipulation is more than 1,000 times stronger than lasers used for fluorescent visualization.

"People won't normally do such a crazy thing," he acknowledges. "I know it is reckless, but if we understand the properties of light and cells well and stop just a few steps before going out of control, we can open a new research field."

Hosokawa uses a femtosecond laser, which is usually used for precision cutting of hard materials, such as the silicon substrates for solar cells and glass in liquid crystal displays. Hosokawa repurposeds it for manipulating and measuring cells under the microscope without direct contact.

Because the intense ultrashort laser pulses for just one quadrillionth of a second, it is too short a blast for heat generation, temperature doesn't interfere with the processes of manipulation and measurement. This way, researchers' understanding of cell interactions and their responsiveness is enhanced.

It's a bold approach that wouldn't work without a steady stream of suitable sample material provided by biologists. And so, soon after Hosokawa became a researcher at Osaka University in 2000, he began visiting the laboratories of biologists to seek possible collaborations. Many of them showed interest. "But I was not an expert in cells, so our conversations were very clumsy," he recalls.

Hosokawa says his move to NAIST in 2008, as a research associate professor with Masuhara when he opened a new laboratory here, helped him take a big leap forward. "NAIST is a compact institute with many powerful scientists, and provides a great opportunity to effectively work with top-level researchers from other institutions," he says. "Until then, my network was mostly confined to within Osaka University."

In 2011, he became independent and established his own laboratory within the Graduate School of Materials Science. A breakthrough soon followed as part of a collaboration with Akihiko Ito, a pathologist in Kinki University's Faculty of Medicine in Osaka. Their team developed a new way to investigate cell–cell adhesion strength using the femtosecond laser.

In their method, the laser is focused in the vicinity of targeted cells. The irradiation generates a shockwave and an impulsive force that propagates toward cells in a micron-sized region and breaks the adhesion between them.

Further practical achievements were reported in 2015 as part of a collaboration with Kazusato Oikawa and Mikio Nishimura from the National Institute for Basic Biology in Okazaki. Hosokawa and collaborators studied the mechanism of photosynthesis and succeeded in estimating the adhesion strength in plant cells without breaking cell walls (see "Shedding new light on plants" on page 76).

Hosokawa says NAIST's operational environment suits his current working style. The institute appreciates freedom and appraises performances based purely on research outcomes, unlike many Japanese universities that also require a lot of administrative work and long hours doing paperwork in an office.

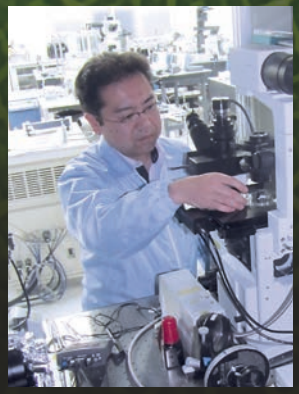
This flexibility is critical for the father of two young boys, because his wife, Chie, is also a busy researcher, at the National Institute of Advanced Industrial Science and Technology in Osaka. When she is travelling for work, Hosokawa leaves his laboratory mid-afternoon to take care of their children at home.

Although they share the same research interests, the couple spend more time talking about their children. "Child-raising is the most difficult thing," Hosokawa says. "As for the limited time, I can't compete with researchers who work 24 hours a day." But he is producing good outcomes. In fact, his performance has been so good that NAIST has recently made him a professor, a promotion that will be effective from April 2016.

More information about the group's research can be found at http://mswebs.naist.jp/english/courses/1447/

Researcher: Yoichiroh Hosokawa

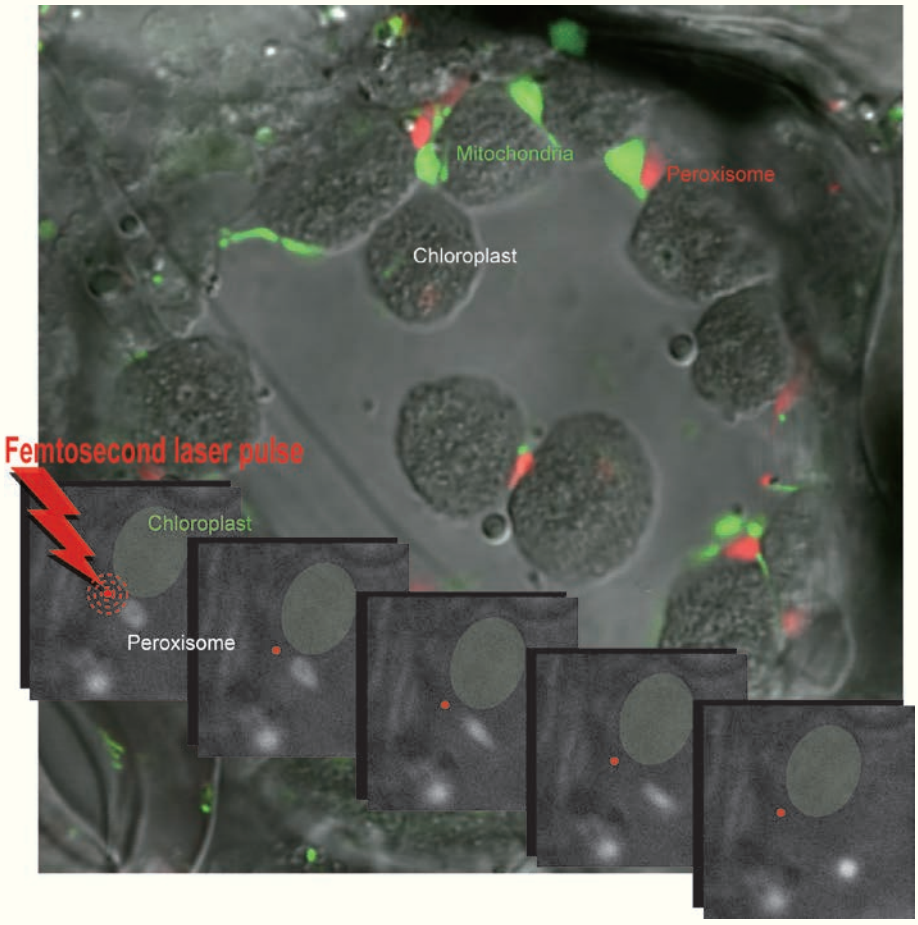
Bio-Process Engineering Laboratory | Professor Yoichiroh Hosokawa



Laser science

Test of strength sheds new light on plants

Ultrashort laser pulses reveal dynamic subcellular interactions during photosynthesis



Peroxisomes co-locating with chloroplasts and mitochondria: a laser pulse breaks the adhesion between chloroplast and peroxisomes.

From the food we eat and clothes we wear, to the fuels we burn, plants underpin most aspects of our lives. Now, a NAIST team has used laser technology to come up with fundamental new insights into how plants photosynthesise — that is, how they use sunlight to transform carbon dioxide and water into glucose[1].

The research team, led by Yoichiroh Hosokawa from NAIST's Laser Nano-Manipulation Science Laboratory, in collaboration with the National Institute for Basic Biology, was interested in how subcellular features inside plant cells interacted during photosynthesis. Using a two-photon excitation laser scanning microscope they observed that in darkness, small structures called peroxisomes, which are responsible for carrying vital metabolites, floated unresponsively in the cellular cytoplasm.

But, when exposed to light the peroxisomes became active. They co-located with chloroplasts, substructures that are key for photosynthesis, and mitochondria, which generate energy, before changing shape and appearing to spread over the surface of the chloroplasts.

The researchers then focussed intense ultrashort laser pulses at the site of contact between peroxisomes and chloroplasts. The laser light caused a mini-explosion — of about 1 micrometre in diameter — at its point of focus and the resulting shockwave broke the adhesion. The strength of the adhesion was estimated from the laser intensity that was required to break it. "Normally this laser is used for metal or semiconductor processing," Hosokawa explains. "Our new idea was to use it to probe plant cells under the microscope. The laser can transmit through the cell wall and focus to a point size smaller than the cell itself.

"So, for the first time we could estimate adhesion strength inside a plant cell without breaking the cell wall and while maintaining physiological conditions."

The data from the experiments suggested that adhesion strength between the subcellular structures increased under light. The researchers believe the adhesion is likely to be involved in ensuring an efficient flow of metabolites between the organelles at the contact site.

They also examined how the quality and wavelength of light modified peroxisome behaviour and found that peroxisome-chloroplast interactions, as well as electron transport processes in chloroplasts, are key to healthy photosynthesis.

"At a practical level, these insights might be useful in agriculture, ultimately to find seeds with excellent crop yield," Hosokawa says. "But, our laser method is not limited to plant biology. It offers a general way to quantify binding strength between of all sorts of different complex integrated micro-objects in biology or technology."

Reference

1 Oikawa, K., Matsunaga, S., Mano,S., Kondo, M. et al. Physical interaction between peroxisomes and chloroplasts elucidated by in situ laser analysis. *Nature Plants* **1**, 15035 (2015)

To read more about the career of Yoichiroh Hosokawa, one of NAIST's newest professors, see "Exploring cells with intense light" on page 74.

More information about the group's research can be found at http://mswebs.naist.jp/english/courses/1447/
Researcher: Yoichiroh Hosokawa

Nanomaterials and Polymer Chemistry Laboratory | Associate Professor Hiroharu Ajiro

Polymer printing

Dissolving obstacles to a superior drug solution

Inkjet printer forms layer-by-layer coating of polymers loaded with an anti-cancer cargo

Layer-by-layer (LbL) assembly has been a superior method used to create thin films and other advanced composite materials, by repeatedly and alternately dipping a substrate in two different chemical solutions. But these dipping and washing cycles can be time consuming and waste a lot of chemicals.

Now, NAIST researchers have used an inkjet printer to deliver droplets of dissolved polymers to build up a biocompatible thin film that releases an anti-cancer drug[1]. Such films could be used to coat the surfaces of medical implants to prevent the body rejecting them, or to improve disease treatments.

> **"This compound, which is difficult to dissolve in water, could be released from the thin films into water."**

Inkjet systems can print alternating layers much more quickly than LbL without the need for washing between each layer. But, it is difficult to print thin films of synthetic polymers in this way because the polymers are typically dissolved in solvents that evaporate during the process, leaving solid residues that clog inkjet printer nozzles.

Hiroharu Ajiro of NAIST's Nanomaterials and Polymer Chemistry Laboratory and colleagues have used a water-soluble polymer to overcome this problem. The polymer is based on a strand of polyethylene glycol (PEG) with long sections of polylactide (PLA) attached to each end.

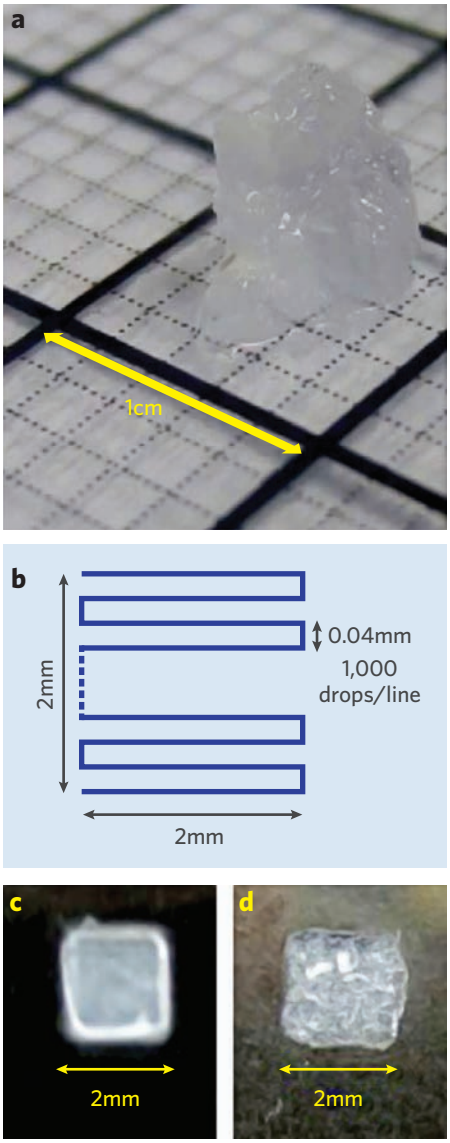
Crucially, PLA can take two different mirror-image forms, depending on how chemical groups are arranged along its polymer backbone. Known as poly(L, L-lactide) (PLLA) and poly(D, D-lactide) (PDLA), these forms can bind together to form a relatively strong 'stereocomplex' (see image). This helps stabilize thin films that contain alternating layers of PLLA and PDLA.

The researchers dissolved separate batches of the PEG-PLLA and PEG-PDLA polymers in a mixture of water and the solvent acetonitrile, which helps stereocomplex formation, and added the anti-cancer drug paclitaxel to each solution. They then loaded the mixtures into an inkjet printer, which could spit out individual liquid droplets containing just 20 picolitres (20 trillionths of a litre). Under computer control, it printed 50,000 droplets of the first mixture in a square pattern onto a glass substrate and added the second mixture on top in the same pattern. Repeating this cycle 1,000 times created a thin film on the glass substrate.

When this was dipped in a saline solution, the film released about 60–70 per cent of its paclitaxel cargo over the course of an hour. "This compound, which is difficult to dissolve in water, could be released from the thin films into water," Ajiro explains. The team now aims to study how the rate of drug release is affected by variables such as changes in the polymers' structures or the number of cycles used to print the layers.

Reference

1. Ajiro, H., Kuroda, A., Kan, K. & Akashi, M. Stereocomplex film using triblock copolymers of polylactide and poly(ethylene glycol) retain paxlitaxel on substrates by an aqueous inkjet system. *Langmuir* **31,** 10583–10589 (2015).



Mixing solutions of the PEG-PLLA and PEG-PDLA polymers forms a gel that is held together by stereocomplex formation.

More information about the group's research can be found at http://mswebs.naist.jp/english/courses/1844/
Researcher: Hiroharu Ajiro

Innovative Research and Education Programs

NAIST constantly strives to renew its research and education programs toward producing science and technology researchers prepared to meet the demands facing tomorrow's global scientific community. These programs are regularly awarded external funding for their wide-ranging benefits.

Program for Promoting the Enhancement of Research Universities (2013–2023)

The Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) launched the Program for Promoting the Enhancement of Research Universities in October 2013, which is a new type of research funding in Japan that aims to enhance research capabilities by utilizing university research administrators (URA) who implement intensive reforms to strengthen the research environment at their respective universities. NAIST is one of 22 universities and research institutions selected to receive support through this program.

NAIST continues to conduct frontier-opening research while expanding into new interdisciplinary fields in science and technology. With the establishment of a university-wide strategic research infrastructure, NAIST endeavors to leverage its abundant resources to attain the new research materials and facilities necessary for next-generation research, to disseminate its achievements and human resources around the globe, and to further expand its global research and education network in order to contribute to the overall advancement of science and technology.

Projects being supported through this program include (1) the Creating New Research Streams Program, which creates new research domains promising a high global profile, (2) the Sustainable Development of Research Capabilities Program, which enhances NAIST's world-class research capabilities, and (3) the Joint International Research Program, which raises the global visibility and standing of NAIST's research capabilities.

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Reforming the research system to enhance NAIST's research capabilities

Top Global University Project (2014–2024)

In October 2014, NAIST was one of 37 universities selected for another prestigious MEXT initiative, the Top Global University Project. For a period of ten years, MEXT will support outstanding universities in their efforts to reform institutional governance and collaborate with top universities worldwide in order to strengthen international competitiveness.

Through the Top Global University Project, NAIST has committed to enhancing its international graduate courses by (1) including a joint degree scheme, (2) developing a new model for graduate education based on top-notch research, (3) reforming institutional governance and strategic agility, (4) creating a campus environment that supports transdisciplinary education and cultural diversity, and (5) reorganizing its three graduate schools into a single entity with a view to establishing new, flexible research groups.

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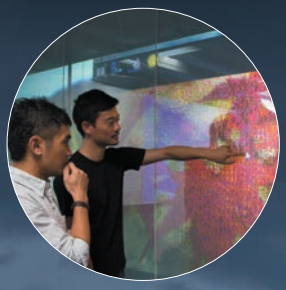


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