NATIONAL INSTITUTE FOR MATERIALS SCIENCE

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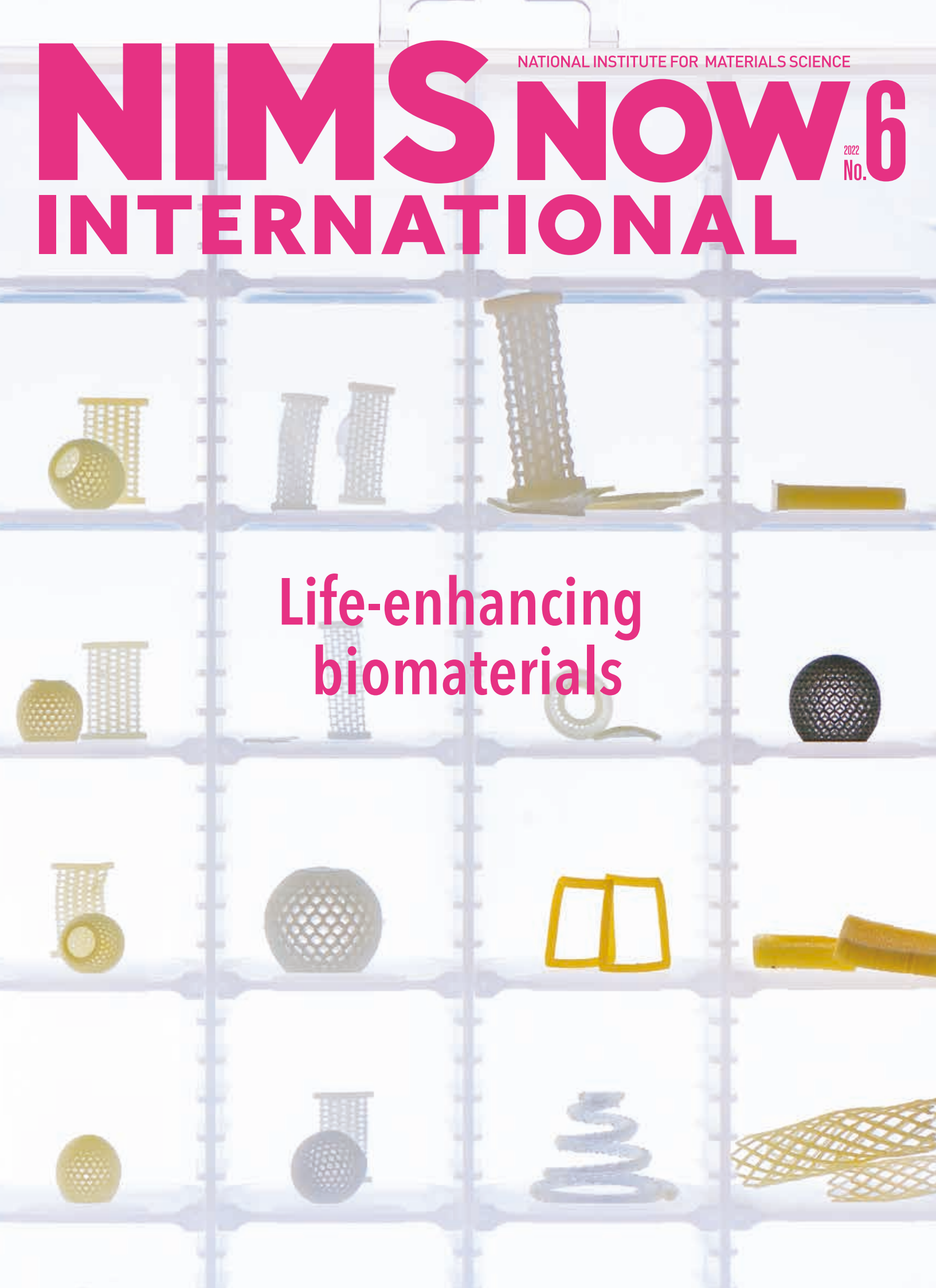
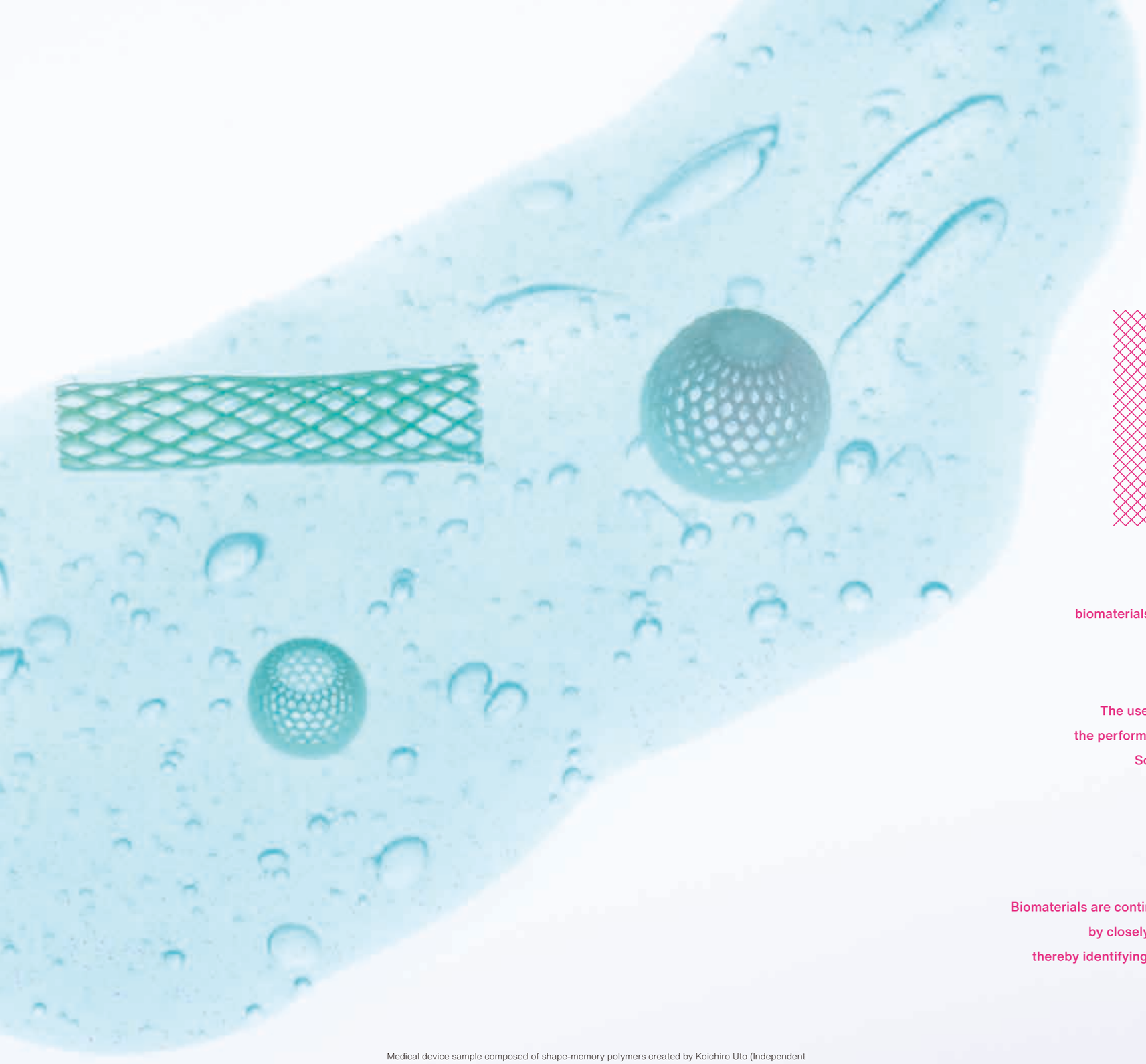


Life-enhancing biomaterials



Medical device sample composed of shape-memory polymers created by Koichiro Uto (Independent Scientist at NIMS) using 4D printing technology*. Uto—who has been engaged in mechanobiological research—has been working to find ways of stimulating the body's healing ability by applying mechanical forces to cells and tissues rather than relying on drugs.

* Four-dimensional printing is used to create a three-dimensional object capable of changing its shape in response to an environmental stimulus. The fourth dimension is the time-dependent shape change after printing.

Life-enhancing biomaterials

We live with physical materials. In particular, biomaterials designed to support our biological functions are in direct contact with our bodies. Contact lenses are worn to correct vision and artificial bones and pacemakers are completely integrated into human bodies.

The use of biomaterials has contributed immensely to medical advancement by enhancing the performance of medical products and increasing the number of medical treatment options. Some biomaterial-based drugs are used to selectively target disease-affected areas, reducing the stress on a patient's body. Research is underway to regenerate damaged body parts by culturing cells from scratch and transplanting them to the affected areas. Biomaterials also have been used to promote the growth of cultured cells.

Biomaterials are continuing to evolve. Scientists are pursuing a new approach to developing biomaterials by closely observing the relationship between individual cells and materials applied to them, thereby identifying cell-material interactions that could be used to produce desirable medical effects.

NIMS has been researching biocompatible materials with the goal of developing next-generation medical treatments.

Introduction

Saving lives with biomaterials

Biomaterials have evolved significantly over the past several decades and have developed into a major branch of materials science. Mitsuhiro Ebara has engaged in many research projects with medical doctors in an effort to develop practical biomaterials. We asked Ebara about the history of biomaterials R&D and NIMS' vision for next-generation biomaterials.

Shift from the use of existing materials to the development of optimum materials

Humans have dealt with various medical problems since ancient times. Records indicate that ancient Egyptians sutured wounds using plant fiber and ancient Mayans used seashells to replace lost teeth.

Many of the materials used in medical applications were initially developed for non-medical purposes. The use of existing materials in medicine rapidly became more common after the First and Second World Wars. The first artificial blood vessels are said to have been made of a tough, shred-resistant parachute material and the first contact lenses are believed to have been created using a warplane windshield material after it was observed that people's eyes did not develop inflammation when they came in contact with tiny windshield fragments.

The practice of using existing materials for medical purposes eventually declined and scientists began developing medical materials from scratch in pursuit of more effective medical treatments.

"Biomaterials are materials that come in contact with the human body either internally or externally," Ebara said. "Many medical innovations and quality of life improvements have been achieved using them."

Biomaterials have been used in a wide range of medical, cosmetic and hair care products, including stents used to open narrowed blood vessels, artificial joints and blood and urine test kits.

Three generations of biomaterials

Materials scientists began developing biomaterials for medical applications to meet the needs of medical doctors, such as the need for suitable artificial organ materials.

The human body's defense mechanisms protect it from invasive foreign objects. An implanted artificial organ sometimes induces blood coagulation when the body recognizes it as a foreign material. The early objective of biomaterials research was therefore to develop biocompatible materials, such as antithrombogenic materials. One of the most successful examples of this endeavor is the MPC polymers developed by Kazuhiko Ishihara, a 2022 NIMS Award winner (see p. 14). These polymers have been regarded as the highest performance antithrombogenic material available and have been used as a coating material for many different medical products.

"Biomaterials have traditionally been classified as first, second or third generation to reflect their level of technological advancement," Ebara said. "The MPC polymers are regarded as first generation due to their biocompatibility."

Second-generation biomaterials—including polymeric nanocapsules used in drug delivery systems—were designed to effectively interact with the human body. A patient using a drug delivery system is administered drug-containing capsules which travel to a target site in his/her body where they are subjected to biological reactions, releasing the drugs. Another example of a second-generation biomaterial is cell sheets, a regenerative medical technology developed by Teruo Okano, another 2022 NIMS Award winner (see p. 13). When cell sheets composed of cells cultured in vitro are transplanted to a target site in the body, they interact with extracellular matrices, producing desired effects.

Third-generation biomaterials are designed to exhibit more advanced functions by themselves contributing to the treatment of disease.

"Developing these materials requires more precise design made possible by advances in polymeric synthesis, molecular biology and genetic engineering techniques," Ebara said. "I'm developing anti-inflammatory plastics capable of suppressing the inflammation response of immune cells, although further research is still needed."

"I want to clarify that different generations of biomaterials are not independent from each other," Ebara added. "Although first-generation biomaterials were designed to be biocompatible, all other biomaterials, including those of later generations with more advanced functions, also need to be biocompatible."

Vision for fourth-generation biomaterials

NIMS has been researching a wide range of biomaterials, including those with first-, second- and third-generation properties composed of various materials (e.g., metals, ceramics and polymers). Artificial bones made of a ceramic material developed by NIMS are already in commercial use.

The importance of biomaterials has increased due to the COVID-19 pandemic. To meet this increased demand, NIMS is preparing to found a new research center scheduled to begin operating in April 2023. The center is expected to facilitate collaboration between biomaterials and polymer researchers. Synergy between researchers with different backgrounds—including areas of research, diseases focused on and the nature of their research (e.g., basic or applied)—is expected to produce innovation.

Ebara—part of this collaboration—is enthusiastic about producing fourth-generation biomaterials.

"I have seen clear changes in medical treatments in recent years," Ebara said. "For example, the main players in pharmaceuticals are shifting from low-molecular compounds to the biomolecules found in antibody drugs."

In fact, COVID-19 vaccines are made of mRNA, a biomolecule produced by DNA transcription. Similarly, some of the latest cancer treatments involve the administration of patients' own cells. These new medical technologies are not without problems, however.

"In addition to their high prices, antibody drugs have some problems," Ebara said. "Patients develop antibodies against these drugs after the first administration, requiring a long interval between the first and second administrations. Side effects are also common. New technologies (i.e., fourth-generation biomaterials) are needed to overcome these problems."

Ebara believes that bioadaptivity is the key to develop such technologies.

"The concept behind first-generation biomaterials was to develop materials undetectable by the body," Ebara said. "However, foreign materials cannot deceive the body forever. The concept behind fourth-generation biomaterials therefore should be materials that are mutually responsive and capable of coexisting with the body. For example, a fetus could be seen by a pregnant woman's body as a foreign entity due to its different genetic composition, but her immune system never rejects it. Similarly, intestinal bacteria is not subject to immunological rejection. It's my dream to achieve this type of coexistence between materials and the body."

A hypothetical fourth-generation biomaterial designed to regenerate damaged tissues in the body could work using the following mechanism: 1) the material first induces cells to repair damaged tissues, 2) the damage-repairing cells then release enzymes which either alter the material's mechanical properties or break it down into its constituents and 3) the altered material or its constituents act as drugs. If this type of mutual communication between cells and materials can be achieved, this mechanism can be applied to various medical fields, including vaccine development and biosensors, bringing revolutionary change to medicine.

Delivering advanced medical treatments across the globe

Ebara has been working closely with medical doctors on his biomaterials R&D with the goal of delivering advanced medical treatments to patients around the world. He is looking forward to working with other polymer specialists at the new research center to achieve this goal.

"As you probably know, plastic pollution is a serious environmental issue," Ebara said. "Television news programs often show images of discarded plastics in unexpected places, such as the summits of mountains and remote islands. In addition to the severity of plastic pollution, these images made me realize that plastics have been thoroughly distributed to every corner of the world. This could mean that cheap plastics (i.e., polymers) could likewise be used very effectively to create medical technologies that could be delivered all over the world. The polymer researchers joining the new research center have different perspectives from biologists and have very advanced polymeric synthesis skills. I look forward to working with them to develop medical technologies that can be delivered to patients around the world. I also hope to produce research results that contribute to the development of next-generation medical treatments and build NIMS' reputation as a premier biomaterials R&D organization." NIMS' new research center is expected to promote the development of life-enhancing biomaterials.

(by Kumi Yamada)

Mitsuhiro Ebara

Group Leader
Smart Polymers Group
Polymers and Biomaterials Field
Research Center for Functional Materials

Biomaterials: key to revolutionizing medical treatments

We spotlight four young NIMS researchers engaged in biomaterials development.
They have already made significant achievements using their unique and diverse research experiences.

Round-table discussion
among young researchers

Research experience before joining NIMS

Nishiguchi: When I was a graduate researcher, we created various types of miniature, three-dimensional biological organs in test tubes. These tiny organs were useful in assessing the effectiveness of drugs targeted to specific organs. Their growth process was supported by cell-adhesive biomaterials. After graduation, I spent two years in Germany as a postdoctoral materials science researcher. To engage in more practical research on medical biomaterials, I joined NIMS in 2017. I'm currently engaged in both basic and applied research projects, including the development of medical adhesives capable of closing surgical wounds and preventing postoperative complications.

Yoshitomi: I'm currently developing a cancer drug that can be administered locally and a material that can be used to mark target surgery sites in the body. Although I researched biomaterials in graduate school, my research focus shifted to plants when I was with my previous employer. However, I rediscovered my interest in medical materials and joined NIMS in 2020 to resume my biomaterials research.

Uto: Since joining NIMS as a postdoctoral researcher in 2010, I have been researching and developing shape-memory polymers. My recent research focus has been mechanobiology: the study of mechanisms by which cells and other biological systems respond to mechanical forces. Using this approach, I have been developing biomaterials capable of manipulating cells and other biological systems. This project was inspired by my participation in the FIRST program—a program that funds world-leading innovative R&D on science and technology—under the guidance of Professor Teruo Okano, a 2022 NIMS Award winner (see p. 13). In this program, Okano's group was responsible for deriving cardiomyocytes (heart muscle cells) from stem cells, while our group was tasked with developing a material capable of selectively extracting cardiomyocytes from the various types of cells that differentiate from stem cells. This was the first time I studied cells and I was fascinated to find that their functions can be controlled using polymers. This experience inspired me to develop materials with biological applications.

Yamamoto: Like Dr. Uto, I had no experience studying biological materials—such as cells and proteins—as a college student. My research focus then was the synthesis of photodegradable organic compounds. These compounds have a variety of industrial and medical applications when combined with biomaterials, including organic thin film transistors and phototherapeutic technologies. In 2011, I worked at NIMS as a student research intern for two months. This was when my academic advisor at the time and Dr. Jun Nakanishi—leader of the NIMS research group of which I'm currently a member—conducted joint biomaterials research using a photodegradable molecule I had synthesized. After the internship, I worked as a postdoctoral researcher first at NIMS and then at the University of Tokyo, where my research involved the use of the CRISPR/Cas9 genome editing technology, which captured a great deal of public attention when its discoverers won the Nobel Prize. I resumed my research at NIMS this April. In line with my group's research goals, I'm developing protein-immobilized nanoparticle conjugates as anticancer drugs. I'm also seeking to carry out research in a direction never attempted before at NIMS by leveraging my diverse research experience.

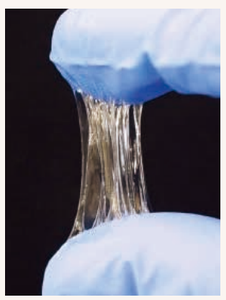

Akihiro Nishiguchi

Biomaterial research at NIMS ❶

Hotmelt tissue adhesive that can prevent postoperative adhesion

Akihiro Nishiguchi

Medical adhesives need to be easy to handle during surgery and capable of closing wounds. Although there are several types of medical postoperative barriers including film and double-syringe liquid adhesives, film types are weak in bonding strength and liquid adhesives are often difficult to mix homogeneously. To resolve these issues, Akihiro Nishiguchi focused on a hotmelt adhesive composed of gelatin derived from porcine tendons. This adhesive is a sol (a colloidal solution in a liquid state) at higher temperatures that transforms into a gel as it cools below its sol-gel transition temperature. The adhesive is applied to a wound in a sol state to fill the gap and becomes a gel as it cools, tightly sealing the wound. Although tendon-derived gelatin shows higher sol-gel transition temperature than skin-derived gelatin, its sol-gel transition temperature was still low. To sufficiently improve its transition temperature, Nishiguchi incorporated UPy groups* into it and controlled the degree of substitution. As a result, the hotmelt adhesive is now able to transform into a gel when it cools to body temperature. Moreover, because the adhesive property loses once it transforms into a gel, it doesn't cause adhesion (i.e., the binding of wounded tissue to neighboring tissue/organs). Other advantages of this adhesive include its single-syringe form—making it easier to handle than double-syringe liquid adhesives— and no needs of reoperation due to its ability to degrade under physiological conditions and be absorbed by the body after wound healing.



* UPy group: ureidopyrimidinone group

In-depth understanding of cellular mechanisms

Nishiguchi: As I said earlier, I have been conducting both basic and applied research. In the basic research, I have been studying hydrogels intended for regenerative medical applications. Hydrogels are composed of crosslinked polymers with three-dimensional network structures containing water. I aim to regenerate damaged tissues by encapsulating cells in hydrogels and injecting them into damaged tissue. The injected cells express biological functions in the body using the hydrogels as a scaffold. The hydrogels gradually degrade and finally disappear after the surgical wounds heal. I'm currently investigating the cellular response to changes in the nano-/micro-spaces within hydrogels in which cells are encapsulated. I'm also studying the cells' response to hydrogels capable of altering cells' physical properties. My experiments have produced interesting results, although it's still too early to reveal them in detail. I just began collaborating with Dr. Uto to further investigate these results.

Uto: The data Dr. Nishiguchi showed me indicated very interesting cellular phenomena. I had a hunch that a mechanobiology approach could be a viable option for in-depth investigation of the mechanisms behind these phenomena. Mechanobiology is a field of science based on the work of Professor Donald Ingber, a 2022 NIMS Award winner (see p. 15) well-known for the development of organ-on-a-chip technology, among other work. Mechanobiology has been applied to orthodontic treatments, for example. A force is applied to dental tissue using a specialized device to regulate the activities of osteoblasts and osteoclasts in the tissue, correcting the alignment of teeth. As illustrated by this example, cell behavior can be changed by applying force to them or otherwise altering their mechanical properties. A primary goal of mechanobiology research is to identify the mechanisms behind cellular phenomena at the molecular level. Dr. Nishiguchi observed cellular phenomena specific to the hydrogel design. I believe that understanding the mechanisms behind these phenomena will promote the development of new biomaterials.

Yamamoto: I see. Dr. Nishiguchi developed the hydrogel material and Dr. Uto is evaluating its mechanobiological effects. I think a cell manipulation technique (e.g., the CRISPR/Cas9 genome editing technique) would be helpful if incorporated into this investigation. The genome editing technique has many advantages and is very effective in disabling specific genes. This technique can be a powerful tool in identifying the genes responsible for specific cellular phenomena and functions. In this technique, 1) a specific cellular gene is first disrupt, 2) a mechanical force is then applied to the treated cells and a phenotype or function exhibited by them is observed, 3) these steps are repeated while disabling different genes and 4) the collected data is then analyzed to identify the gene responsible for the observed phenotype or cellular function.

Nishiguchi: In addition to the genome editing technique, analytical techniques have also advanced dramatically. The spatial resolution of microscopes has improved, moving from the tissue to the single cellular level and now to the molecular level. It's important to actively utilize these emerging material evaluation technologies. For example, suppose that I encapsulate and culture 100 cells in hydrogels and measure their average gene expression levels. The average value itself does not indicate the variability between cells—100 cells with similar gene expression levels will yield the same average value as a combination of 10 cells with high expression levels and 90 cells with low expression levels. I want to use the variability information to optimize my hydrogel design strategy. Technologies that enable analysis of individual cells can be very useful, and I intend to actively introduce them into my research.

Collaborative research vital to achieving medical applications

Yoshitomi: Joint research with medical doctors affiliated with university medical departments is very helpful in achieving medical applications for research projects, selecting the types of diseases on which to focus and ensuring that your research is on the right track. The research lab I worked in as a graduate student actively collaborated with the department of medicine at the same university. One faculty member in the department was a gastroenterologist who once gave me a tour of a clinical facility where cancer patients were treated using photodynamic therapy (PDT). The PDT procedure involves 1) administration of a photosensitizer to a patient via an intravenous infusion, allowing cancerous tissues to absorb it and 2) red laser irradiation which selectively kills these tissues. While PDT is minimally invasive, it also has a problem: due to the systemic administration of the photosensitizer, patients suffer from photosensitivity for extended periods of time after PDT treatment. Nurses at the clinical facility have to be constantly vigilant to avoid exposing patients to light of an intensity that could trigger photosensitivity by dimming the hallway lighting below a specific lux level. A 75-year-old male patient I met had to spend the first two weeks after treatment in a dark room and another month in a patient room without going outside. In addition to the stress of PDT treatment itself, long confinement after the treatment is very difficult, especially for elderly patients who are more susceptible to complications like dementia and delirium. Thus, my current research focus originated from the desire to overcome this disadvantage of PDT treatment.

Nishiguchi: Biomaterials should be practical and useful to patients. It is therefore important for biomaterials researchers to study the needs of medical facilities. Dr. Yoshitomi is fortunate to have had the rare opportunity to work closely with medical doctors—for most of us, finding collaborators with professional medical expertise relevant to our areas of research is very difficult. I collect information relevant to my research by attending scientific meetings specialized in medicine. I also feel that publishing one's own research is important. My research on medical adhesives was published this May in the form of a press release. I received positive responses from many people and have finally begun collaborating with medical doctors.

Uto: When I participated in a research meeting hosted by the Japan Agency for Medical Research and Development (AMED), I met many scientists specialized in medicine and biology. I learned that most of them don't have access to proper materials needed to investigate biological phenomena of interest or to create tools with specific functions. Materials scientists are able to develop and provide the materials these scientists need once we understand their specific requirements. In this way, we can support Japan's medical research. I have been conducting joint research with medical doctors and biologists, giving me the chance to learn about the fundamental and applied aspects of medicine and biology.

Yamamoto: I have been gathering information relevant to my research through direct communication with other researchers. Although research publications and textbooks

Biomaterial research at NIMS ❷

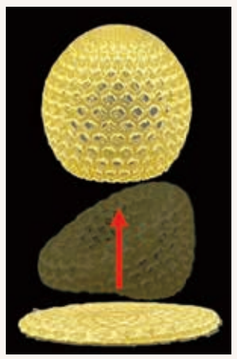
Investigating biological phenomena using functional shape-memory polymers

Koichiro Uto

Crosslinked PCL* is a well-known biodegradable shape-memory polymer (SMP). Koichiro Uto has synthesized many types of PCLs with different functions (e.g., a polymer capable of memorizing multiple shapes and reversible shape change) by making various modifications, such as altering the number of branches in a PCL and its polymeric chain length and using different crosslinking techniques. One of his outstanding accomplishments is the development of an advanced temperature-responsive PCL-based SMP. While most existing temperature-responsive SMPs require a temperature difference of about 10°C to change their shapes, Uto's PCL can reshape itself within a temperature difference of only 4–5°C—the smallest difference ever reported.

Uto has been using this PCL-based SMP in biological research. He developed a cell culture dish with fine grooves on its surface made of the PCL. These grooves are present at 32°C or lower temperatures and disappear when the temperature increases to 37°C, allowing cells to be cultured while being subjected to the presence and absence of the grooves. These cells have been used to study the impact of mechano-structural cues on them, among other investigations. Uto has also been conducting other research projects using SMPs, including investigating the relationship between materials' geometric structures and functions, known as mechanical metamaterials.

*PCL…Poly(ε-caprolactone)



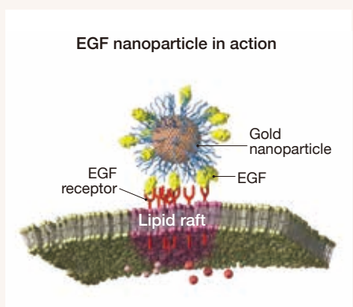
Biomaterial research at NIMS ❸

Development of protein-immobilized nanoparticle conjugates as anticancer drugs

Shota Yamamoto

An epidermal growth factor (EGF) induces cell proliferation upon binding to its receptor (Epidermal growth factor receptor; EGFR) that exists on a cell membrane. The application of gold nanoparticles with EGFs immobilized to their surfaces (i.e., EGF nanoparticles) has been found to be effective in apoptotic activities to cancer cells although how they induce it had been unknown. Shota Yamamoto investigated the mechanism behind this unique phenomenon. He identified an essential role of membrane rafts, cholesterol- and sphingolipid-enriched membrane nano-domains on plasma membrane, in the apoptosis processes, evoked by EGF nanoparticles.

Yamamoto believes that EGF nanoparticles can be used a new anti-cancer drug. His experiments found that EGF nanoparticles can induce apoptosis only in cancer cells with a high EGFR expression; on the other hand, normal cells do not exhibit pro-apoptotic activity. He plans to the unique apoptotic activity of EGF immobilized on nanoparticles using various nanomaterial for the application of cancer therapy.



are a useful source of information, it's difficult to reproduce the experiments described in them because the subtle tricks used by the authors are rarely included. I find information gathered through direct conversations to be much more useful. I therefore actively engage in discussion with senior researchers and researchers with expertise that differs from mine right here at NIMS. This convenient accessibility to other scientists is a major advantage of NIMS.

Growing interest in highly functional biomaterials

Yoshitomi: The recent practical introduction of mRNA-based COVID-19 vaccines really surprised me. Messenger RNA is inherently unstable and decomposes quickly after being injected into the body. This problem was resolved using drug delivery technology: the mRNA was coated with a lipid layer, allowing it to be delivered to target cells. Steady basic research efforts made this technology readily available when it was urgently needed. These new vaccines signify that biomaterials research could contribute to the development of technologies capable of helping people around the world, making me feel proud of my profession and motivating me to develop beneficial technologies.

Yamamoto: Our group has been conducting fundamental research to investigate the relationship between the application of mechanical forces to cells and subsequent cellular function. Steady, continuous basic research efforts may potentially provide more technological options in times of emergency. Moreover, latest research conducted elsewhere include the development of hydrogels composed of a combination of biopolymers (e.g., proteins) and synthetic polymers through an interdisciplinary approach. Because biopolymers and synthetic polymers behave differently, combining them enables the development of materials with a wider range of functions. In addition, these materials can be highly biocompatible when they contain proteins—abundant cellular components. More diverse biomaterials may potentially be created using a broad perspective.

Nishiguchi: Developing biocompatible materials is a key mission for biomaterials scientists. The human body reacts to biomaterials introduced into it no matter how safe they are. This is why NIMS plans to put significant effort into the development of bioadaptive materials for medical applications (i.e., materials which, when administered to a patient, interact with his/her body, producing desired medical effects).

Uto: Dr. Nishiguchi and I have been working to develop hydrogels that are adaptive rather than chemically stable and culturing cells in them. The hydrogel is required to respond to cell-secreted enzymes and cell-generated forces to degrade and undergo structural remodeling to allow the cultured cells to exhibit their physiological cellular functions. Achieving this requires the hydrogel to be conducive to proper cellular activities and mutually responsive to cells.

Yoshitomi: mRNA vaccines are known to rarely cause various side effects. Biomaterial researchers need to study these and find their solutions.

Pursuing dreams at NIMS

Yoshitomi: I have dream to create biomaterials capable of revolutionizing medical treatments ever since I started my research. My desire to achieve this goal has become stronger since I joined NIMS. When I conducted research that involved both biology and materials science at my previous place of employment, the material evaluation equipment I needed to use was unavailable and I had to borrow it from companies. I greatly appreciate the research environment at NIMS, which enables us to perform all necessary tasks ourselves, including synthesizing and analyzing materials and animal testing.

Nishiguchi: That's right. When I previously brought a newly developed biomaterial to medical department faculty members to ask their opinions about the prospects for its medical application, they were unable to comment because animal testing had yet to be conducted. It's very convenient that NIMS is equipped with all of the facilities we need, including animal testing labs.

Uto: In addition to its well-equipped facilities, NIMS allows me to learn about various types of materials from its other researchers with different expertise, broadening my perspective. In fact, I'm currently carrying out joint research with other researchers specialized in spintronics and structural materials. Although this project is still in its early stages, we have discovered some new potential applications for shape-memory polymers, such as making them exhibit elastocaloric effects and mechanical metamaterial properties. These findings made me realize that the components of a biomaterial we have developed may have applications beyond medicine.

Yamamoto: I've gained experience in various areas of research since college, including organic synthesis, biomaterials and genome editing. Through these experiences, I have been able to broaden my perspective by learning the advantages and disadvantages of different field, which I think is very valuable. I'm currently conducting biomaterials research again at NIMS using its resource-rich research environment. I look forward to using my diverse experience to steadily produce results.

Nishiguchi: NIMS will launch a new center next year to promote biomaterials research. I expect that this initiative will encourage materials researchers in biological fields to work together more closely and start many collaborative projects. Although NIMS has developed a number of biomaterials that have been put into practical use, they were either inorganic materials or inorganic-organic composites. Polymeric materials researchers hope to achieve the same success so that we can live up to the expectations of our supporters. I look forward to many challenges ahead and to absorbing new information with a sense of curiosity.

(by Akiko Ikeda)

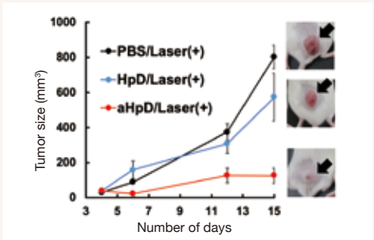
Biomaterial research at NIMS 4

Locally administered photodynamic therapy with reduced side effects using adhesive photosensitizer

Toru Yoshitomi

Photodynamic therapy (PDT) has been used to treat cancer in a minimally invasive manner. A cancer patient is systemically administered a photosensitizing drug, allowing cancer cells to absorb it. These cells are then irradiated with laser light, activating the absorbed drug and killing them. A major disadvantage of PDT is that treated patients are required to avoid exposure to light for more than a month in order to prevent them from developing inflammation in the skin and eyes due to residual photosensitization. This forces PDT recipients to refrain from indoor/outdoor activities, including working, for extended periods of time.

To address this problem, Toru Yoshitomi designed and developed an adhesive photosensitizer, aHpD, by modifying a porphyrin photosensitizer with positively charged polymers. The aHpD photosensitizer is able to adhere to negatively charged cell surfaces and extracellular matrices for nearly a week. Yoshitomi confirmed through animal experiments that aHpD exhibits excellent anticancer properties without increasing skin phototoxicity in test animals. He is also pursuing other uses for aHpD by leveraging its ability to adhere to tissues, including the marking of target surgery sites.



Comparison of tumor treatment effectiveness between the aHpD photosensitizer Yoshitomi developed (red), a conventional photosensitizer (blue) and the untreated group (black). The aHpD treatment exhibited the highest anticancer activity.

NIMS AWARD
NATIONAL INSTITUTE FOR MATERIALS SCIENCE

Interview with NIMS Award winners

The NIMS Award is bestowed annually on researchers who have made outstanding achievements in materials science.
We interviewed this year's three NIMS Award winners, whose work contributed to the development of innovative medical technologies.

Research Summary

Prof. Teruo Okano

Professor Okano invented the world's first temperature-responsive cell culture dish with its surface coated with a temperature responsive (smart) polymeric material controlled by nanometers level in thickness. Because the cell adhesiveness of the nano-controlled polymeric surface diminishes with decreasing temperature, a cell sheet grown in this dish at 37°C can be easily removed from it under 32°C without the use of enzymes simply by lowering the temperature. Okano has proposed the concept of cell sheet engineering and achieved first-in-human clinical in regenerative therapy. In particular, his notable achievements include transplanting cultured muscle cell sheets into the heart of a patient with severe cardiac deterioration, which led to a significant recovery and enabled the patient to walk again without using an artificial heart. His other medical achievements include corneal and periodontal regeneration and preventing the esophagus from constricting due to surgical removal of esophageal cancer. Expectations are high for Okano to continue developing novel cutting-edge medical technologies.

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Prof. Kazuhiko Ishihara

Professor Ishihara contributed to the synthesis of the 2-methacryloyloxyethyl phosphorylcholine(MPC) polymer—a biomimetic polymer inspired by cell membrane surface structure and functions. At first, he developed a precious method for the synthesis of MPC and its effective purification process of it. The MPC can polymerize with other functional monomers by conventional polymerization methods. He has demonstrated that the MPC polymer can prevent protein adsorption significantly, and following immune reactions, blood coagulation, tissue reactions, and bacterial infection. He also verified that the performance of medical devices for long-term implantation improves significantly when they are coated with MPC polymers.

See page 14

Prof. Donald E. Ingber

Inspired by the similarity between biological cells and tensegrity architecture, Prof. Ingber proposed the "cellular tensegrity model", where cell structure is stabilized by balancing tensile and contractile forces through establishment of an internal prestress. He has demonstrated that cellular life and death are regulated by mechanical forces through geometrical control of cells using micropatterning technology. He also created organ-on-a-chip technology to recapitulate cell and tissue deformation during breathing and pulsation. With that, he applied it for drug discovery and personalized medicine using these miniaturized organ mimics instead of experimental animals.

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Regenerating failed organs and tissues using cell sheets

Teruo Okano

Professor Emeritus, Tokyo Women's Medical University
Professor and Director, Cell Sheet Tissue Engineering Center, University of Utah

Professor Okano earned his Ph.D. from Waseda University in 1979. After working as an assistant researcher at Tokyo Women's Medical University (TWMU), he moved to the University of Utah as a research assistant professor in 1984. He returned to TWMU as an associate professor (1988) and later as a full professor (1994). He became the Director of TWMU's Institute of Biomedical Engineering in 1999 and established the Division of Advanced Biomedical Engineering and Science in 2001. In 2008, he founded and became a Director of the TWMU–Waseda University Joint Institution for Advanced Biomedical Sciences (TWIns). After retiring from TWMU in 2014, Okano continued his research endeavors, establishing and becoming the Director of the Cell Sheet Tissue Engineering Center at the University of Utah in 2016. He has since been conducting research there.

—How did you come up with the idea of coating cell culture dishes with a temperature-responsive polymeric material?

When I was a graduate student at Waseda University, my research focus was polymer chemistry. During my doctoral program there, I had strong interest for the foreign material recognition of living system. I learned about the research on artificial organs and biomaterials being conducted at TWMU's Institute of Biomedical Engineering. I was so intrigued by these projects that I persuaded the TWMU researchers to let me join them. Following this research experience, I enrolled in the College of Pharmacy at the University of Utah in the United States, where I carried out research on drug delivery systems (DDSs) and temperature-responsive hydrogels. A few years later, my former advisor and colleagues at TWMU invited me to return, and I accepted. I developed the technique for growing cell sheets while at TWMU.

The basal side of surfaces of cell sheets are covered with adhesive proteins. Because of these surface proteins, they can be easily attached to target areas of tissues and organs in the human body via transplantation. Cells grown in cell culture dishes were previously separated from the dishes using enzymes. However, these enzymes break down the adhesive surface proteins and also intercellular proteins. I worked to address this problem and eventually came up with the idea of using a temperature-responsive polymer instead of enzymes to detach cultured cells from the dishes. This polymer is hydrophobic at temperatures above 32°C and becomes hydrophilic at lower temperatures. I coated cell culture dishes with this polymer using electron beam irradiation. Cell sheets adhere to hydrophobic surfaces at 37°C but can be easily detached from hydrophilic surfaces at 20°C. Taking advantage of this property, we cultured cells at about 37°C in the polymer coated dishes and simply cooled the dishes to about 20°C before harvesting fully grown cell sheets. This was the first-generation temperature-responsive cell culture dish I developed. I then developed a technique for forming thin irreversible coating films with various nanostructures (i.e., smart surfaces) using polymers with different designs. I worked to optimize these nanostructures to facilitate the growth and harvesting of cell sheets made of different types of cells through repeated cell culture assays and separability evaluations. As a result, I developed the second-generation temperature-responsive cell culture dish with optimized structures and cell sheet production techniques. This represents an example of a successful interdisciplinary approach between cell biology and surface science.

—What do you think is the significance of materials science in advanced medicine, including cell-based medical treatments and biopharmaceuticals?

Foreign body reactions that occur at the cellular, tissue and systemic levels are a serious issue in various medical fields (e.g., medical treatment and diagnosis and disease prevention). Developing biomaterials capable of preventing these reactions from occurring is indispensable. Expectations are growing for the development of innovative medical diagnostic and treatment technologies, such as implantable artificial organs and sensors. However, these technologies require materials able to function within the human body over a moderate to long period of time. Like as semiconductors are required for computers, I believe that biomaterials will continue to be a necessity for making breakthroughs in advanced medicine.

—What types of research environments and frameworks do you think are needed for Japan to develop innovative medical technologies?

Medical research in Japan has traditionally been conducted in a discipline-specific manner. Developing breakthrough biotechnologies and medical techniques will require a combination of science and engineering. The importance of collaboration between medical scientists and engineers has already been recognized, and I believe that even closer collaboration will be vital to the development of better and more advanced medical technologies. Japan needs to reform its current R&D and educational systems to make them more conducive to interdisciplinary approaches. I actually put this philosophy into practice by establishing the TWMU–Waseda University Joint Institution for Advanced Biomedical Sciences (TWIns) in 2008. Constructing proper interdisciplinary frameworks will promote more creative, challenging research projects.

—What are your future research plans?

To put the world's first cell sheet-based regenerative medicine into practice and achieve its widespread use, we need to organize a balanced collaborative framework involving not only an R&D team but also a clinical research team, a regulatory science team and a team responsible for creating new industries. I intend to work with these teams to create a regenerative medical center capable of treating diseases that are currently incurable. My ultimate goal is to make regenerative medicine—which can potentially be used to fundamentally cure many medical conditions—accessible to everyone as an alternative to conventional drug-based symptomatic treatments. Using the cell sheet technology, I hope to help ease the pain of patients suffering from serious diseases and disorders around the world.

Overcoming foreign body reactions using biomimetic polymers

Kazuhiko Ishihara

Specially Appointed Professor, Graduate School of Engineering, Osaka University
Emeritus Professor, The University of Tokyo

Professor Ishihara earned his Ph.D. from Waseda University in 1984. After working as a researcher at the Sagami Chemical Research Center, he began conducting MPC polymer R&D at the Tokyo Medical and Dental University in 1987. He then assumed a position first as an associate professor (1998) and later as a full professor (2000) at the University of Tokyo, School of Engineering. He assumed his current positions in 2021.

– What was your motivation for developing a technique for mass-producing the monomeric components of MPC polymers?

I began conducting MPC polymer research soon after joining the Tokyo Medical and Dental University in 1987. I focused on a type of MPC polymer designed to mimic the structures of a cell membrane. Although some reports on MPC polymers was already available at the time, no one had really tried to use them as functional polymers. I considered due to a quite small amount of the MPC polymers obtained and low purity to evaluate the functionality. Despite this problem, my interest in MPC polymers remained keen as I was encouraged by the fact that phospholipid molecules—which were similar in structure to the MPC polymer I was focusing on—were beginning to be used in drug formulation and because I had been deeply interested in the structures and functions of cell membranes since I was a college student. I also had a hunch that the MPC polymer could potentially be used as a blood-compatible material. To address the mass production problem of the MPC polymers, I first attempted to develop a technique for synthesizing high-purity MPC.

About three months into this endeavor, I succeeded in synthesizing the MPC in a flask at a purity higher than 98% in the form of white crystals. I then moved on to another challenge: achieving medical application of MPC polymers by ensuring their stable supply and quality control. I tried to find a Japanese pharmaceutical manufacturer willing to undertake these tasks. However, due to the absence of a market for this very new material, my efforts were unsuccessful.

After some time had passed, I gave a speech about the MPC polymers at an international scientific conference. A researcher from a British startup company was very impressed by the performance of MPC polymers and asked me on the spot to supply two tons of the MPC within five years. I immediately resumed negotiations with domestic chemical manufacturers and entered into a contract with one. This company and I collaboratively designed a production plant while taking various issues into account, including restrictions on the types of reagents and solvents that can be used in industrial-scale production and waste gas treatment. The plant began operating in 1999 and was eventually able to produce several tons of monomers annually.

– What aspects of designing MPC polymers did you find particularly important?

When I manually synthesized MPC polymers in the lab, I was able to prepare only small amounts of them due to the limited amount of monomer available. It was therefore important for me to be able to evaluate the performance of synthesized MPC polymers using only these small amounts. I also wanted them to be easy to synthesize and apply to medical devices. To meet these conditions, I designed them to be suitable for coating the components of common medical devices by ensuring that they are stable and safe under the conditions in which the devices are used. For example, one of the MPC polymers I designed is compatible with relatively safe solvents (e.g., ethanol) at a polymer concentration of approximately 0.5 wt% (i.e., a 1000 mL solution contains 5 g of polymer).

Because the use of each type of biomaterial is generally limited to only a few specific purposes, many types of biomaterials with different functions are needed to meet a wide range of applications. However, because preparing many types of functional polymers is industrially impractical, more versatile polymers with universal designs are needed. MPC polymers are very versatile because different physical properties (e.g., hydration property and lubricity) can be imparted to them through molecular design. In addition, base materials (e.g., silicone rubber) can be surface modified with MPC polymers in several different ways (e.g., graft polymerization of MPC from the surface or reacting with MPC polymers to the surface of a base material) depending on the conditions under which they are used. MPC polymers have been a global standard since being adopted as a contact lens material in the UK more than 25 years ago. These polymers have also been used in coronary stents, flow diverter device, and artificial lungs. In Japan, they have been clinically used as implantable artificial heart, and also artificial hip joint.

– What is your R&D philosophy? Do you have any expectations for NIMS?

Basic scientific research is vital to the development of medical technologies that can be used to help patients recover from various medical conditions. In addition, it is important for scientists to perform medical materials R&D while keeping in mind the specific conditions under which target materials are used and how long they need to last. Researchers, therefore, need to spend time at the medical facilities where the materials will actually be used so that they can identify the specific issues that need to be addressed.

Some overseas countries have systematically compiled large amounts of accurate scientific data from both basic and clinical research conducted by various organizations. By contrast, Japan has many obstacles that prevent scientific data from being aggregated efficiently. For example, many Japanese private companies are reluctant to publicize their data in order to protect their intellectual property. These issues need to be addressed. I carefully select joint research projects after determining whether collaboration can achieve common goals.

It takes an extremely long time to achieve the clinical application of a biomaterial after it is developed. In fact, it took me 24 years to achieve the clinical use of MPC polymer-integrated artificial hip joints after I succeeded in synthesizing the monomeric components of MPC polymers in a flask. I imagine that professional researchers at NIMS are in a favorable position to carry out longer-term research projects and collaborative research with private companies. Using these advantages, I hope that NIMS will grow into Japan's premier biomaterials research facility.

Clarifying the relationship between cells and "force" and developing organ chips

Donald E. Ingber

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Wyss Institute for Biologically Inspired Engineering at Harvard University, USA
Judah Folkman Professor of Vascular Biology, Harvard Medical School and Boston Children's Hospital, USA
Hansjörg Wyss Professor of Bioinspired Engineering, Harvard John A. Paulson School of Engineering and Applied Sciences, USA

Professor Ingber earned his combined M.D. and Ph.D. in cell biology at the Yale School of Medicine and Yale Graduate School of Arts and Sciences in 1984. He then worked as a researcher at Harvard Medical School and Boston Children's Hospital. He became a professor at Harvard Medical School in 1999 and was also appointed as Professor of Bioengineering at the Harvard School of Engineering and Applied Sciences in 2008. In 2009, he was appointed as a Founding Director of the Wyss Institute for Biologically Inspired Engineering at Harvard University. He has been active in the industrial sector as well, founding seven startup companies in addition to working as a professor and researcher at the Wyss Institute.

– Can you explain how you first noticed the similarity between cells and tensegrity architecture?

The architect, R. Buckminster Fuller, who has been one of my inspirations, once said "Nature has no separate departments of physics, chemistry, biology, or art". I have been lucky in my career to have been trained with this spirit in mind from the time I was young.

One day, while I majored in science as an undergraduate at Yale College, I saw students carrying sculptures of geodesic polyhedra that looked much like viruses and molecules. They were made in a sculpture class entitled, "Three Dimensional Design". I became eager to take his class, but the professor was curious about the reason. I explained that I studied science and that life at the molecular level is essentially "Three Dimensional Design." He welcomed my idea and allowed me to take the course.

One day, he asked us to bring wood dowels and high-tension fishing line and build structures that hold themselves self-stable in 3D without allowing the sticks to touch each other. When one student eventually built such a structure, he explained that this building system is known as a tensegrity. Tensegrity structures depend on continuous tension, local compression, and establishment of a tensile prestress for their stability.

He pressed down on the sculpture, and it responded by changing its shape and flattening. When he released his hand, the sculpture leapt off the ground. This reminded me of living cells, which I had cultured for the first time that very same week, and they had behaved in a similar manner. This is when I first thought that cells also might use tensegrity to structure themselves, but at the molecular level.

– After discovering that cells have a tensegrity structure, what kind of research did you pursue?

My research on cell tensegrity suggested that the forces applied to cells when they are deformed may control key functions of living cells, such as growth and differentiation. However, biologists believed the primary regulator of cell proliferation to be binding of soluble molecules to cell surface growth factor receptors and insoluble extracellular matrix (ECM) adhesion molecules to other surface receptors, called 'integrins'. To demonstrate the concept that mechanical forces could control cell behavior by altering cell shape, we setup collaborative research with George Whitesides at Harvard, who had developed an inexpensive alternative to manufacture computer microchips called 'microcontact printing'.

We microcontact printed arrays of cell-sized adhesive islands of different sizes and shapes surrounded by non-adhesive regions, which we coated with a high density of ECM molecules. Depending on the sizes of the adhesive regions, cells formed a flat 'pancake' shape, a 'cupcake' form, or appeared round like a golf ball-on-a-tee. In all case, the cells contacted the same high density of ECM proteins and bound the same amount of soluble growth factors, thereby we could manipulate cell shape independently of both soluble growth factors and changes in ECM molecular density.

What was exciting was that we found that cell shape distortion did in fact control cell growth as well as a form of programmed cell death, known as 'apoptosis'. The spherical cells on the tiny islands switched on a suicide program, whereas cells that spread to a moderate degree were induced to 'differentiate' and express specialized functions of the organ from which they were derived (e.g., liver cells secreted high levels of blood proteins as they do in the body) and spread cells grew. The two Science articles we published describing these findings are now cited over 7,500 times collectively.

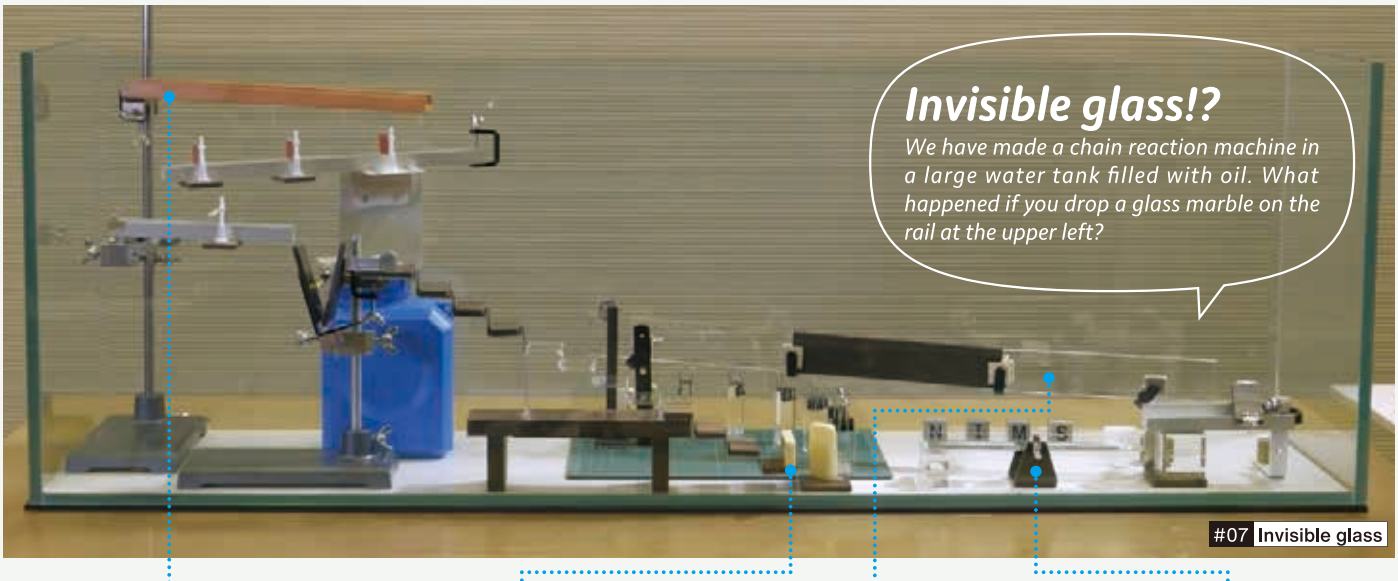
– How did you move on to the organ-on-a-chip study from that study?

My collaboration with the Whitesides lab on soft lithography progressed to include fabrication of microfluidic systems, which were beginning to miniaturize all sorts of analytical and diagnostic instrumentation. In the late 1990s, we started to culture cells under fluid flow within these devices. A few years later in the mid 2000s, I heard Shuichi Takayama, who used to work as a postdoc between Whitesides lab and my own and became a young professor at U. Michigan, talk about a 'Lung on a chip' at a small meeting. He showed early results of testing a microfluidic device with a hollow channel the same size as the small airways of the lung, and when he flowed fluid droplets through it to mimic mucus plugs the device made a sound that was virtually identical to the 'crackle' sound that I was taught to listen for through a stethescope when I listened to the lung of a patient as a medical student. I was impressed!

When the student that did that work - Dan Huh- applied to my lab for a postdoctoral fellow position, I suggested to him that we build a real lung living lung-on-a-chip that would be lined by lung living cells interfaced with capillary vessel cells and replicate the air-liquid interface and mechanical breathing motions of lung because I was confident that mechanical forces are so important for biological function. And that is precisely what we did.

A Message to Future Scientists

— YouTube video clips by NIMS and EUPHRATES —




Drop a glass marble...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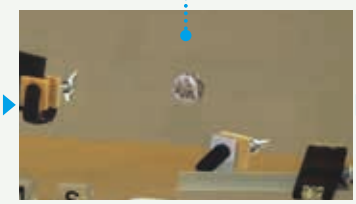

Invisible rail??


Invisible seesaw???

What is “A Message to Future Scientists” ?

“A Message to Future Scientists” is a YouTube video clip series created jointly by NIMS and EUPHRATES Ltd. (a group of specializing in creative work, including NHK’s educational TV programs). We have added an English subtitle option to these clips.

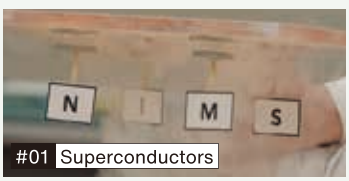
This scientific video series has been popular in Japan with a cumulative view count exceeding 7 million. These clips demonstrate the various intriguing scientific phenomena and unique materials NIMS has developed using fascinating images that are also entertaining and beautiful.

An English subtitle option makes it accessible to a broader global audience with an interest in science. We hope you enjoy it!

"A Message to Future Scirntists" video clips

List of “A Message to Future Scientists” video clips

We have released 16 video clips so far.



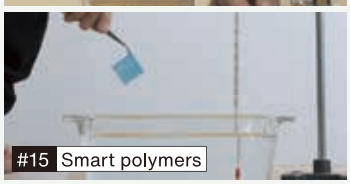


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photo by Michihito Ishikawa editorial design by Barbazio Inc.
on the cover: medical device sample composed of shape-memory polymers (see p.2 and 8)

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