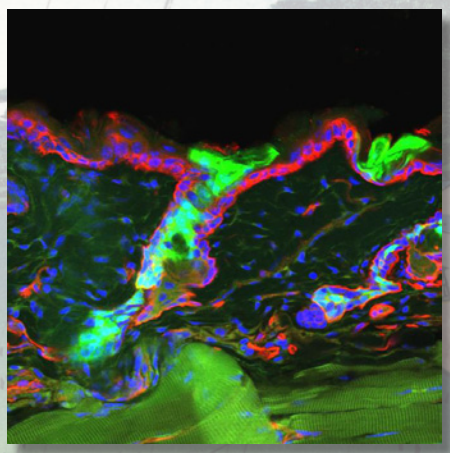
TOKYO MEDICAL AND DENTAL UNIVERSITY

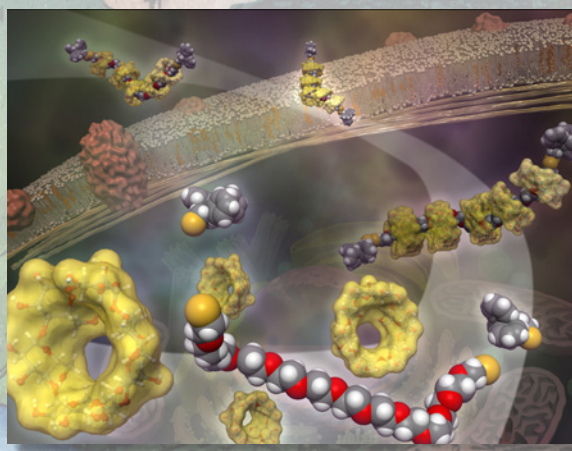
TMDU

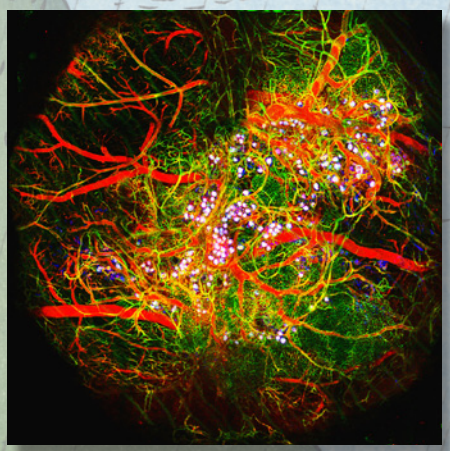
TMDU
東京医科歯科大学

Research Activities 2019



TMDU—Committed to pioneering medical research





TMDU: Did you know...?

University Ranking by Subject

	Medicine	Dentistry
National Rank	3	1
World Rank	51-100	10

SOURCE: QS World University Ranking by Subject 2019

World's Best Small Universities

Ranked #1 in Japan and #15 in the World

SOURCE: Times Higher Education World's Best Small Universities 2018

University Hospitals Promoting Our Research

	Beds	Outpatients Per Year
Medical Hospital	753	555,861
Dental Hospital	60	421,853

International Students

	No. of Int'l.Students	No. of Countries
Graduate Schools	331*	38

* About 19% of graduate school students are **International Students**

Contents

Message from the President

Tokyo Medical and Dental University (TMDU), located in the Ochanomizu/Yushima district in central Tokyo, is one of the most prominent medical research institutions in the world. Since its establishment in 1928 as the first National School of Dentistry in Japan, it has grown into a comprehensive medical university by expanding its research base into medicine and nursing. We have approximately 3,000 students in our graduate and undergraduate schools, which include the Graduate School of Medical and Dental Sciences, Graduate School of Health Care Sciences, Faculty of Medicine, and Faculty of Dentistry. We provide excellent learning opportunities to our students under the TMDU Vision, "Cultivating Professionals with Knowledge and Humanity, thereby Contributing to People's Well-being."

TMDU has two university hospitals on campus, one for medicine and one for dentistry. The medical hospital is the most popular teaching hospital among medical interns in Japan and plays an important role in clinical medicine. The dental hospital treats the highest number of patients with oral disease in the country. We also have two research institutes, the Medical Research Institute and the Institute of Biomaterials and Bioengineering, where researchers collaborate with industries to develop practical clinical applications for the benefit of society.

In 2018, we reorganized how research is done at TMDU in order to achieve groundbreaking innovations and practical applications that go beyond each research area. As a result, we launched the "Organ and Tissue Neogenesis Consortium," which will extend the scope of regenerative medicine to include the generation of new organs and tissues. Our hope is that this consortium will play a central role in boosting international recognition of this field by promoting collaboration among industry, academia and government both in Japan and overseas. Next, we established two other groups to enhance collaboration with industry, with financial support from the Ministry of Education, Culture, Sports, Science and Technology: the Medical Innovation Consortium to advance precision medicine, genomic medicine and novel devices, and the Institute of Open Innovation. Also in 2018, we launched the Cultivating Unit for Innovating Medical Scientist, which selects excellent young researchers in various research fields at TMDU in an aim to encourage the next generation to pursue cutting-edge research.

Beginning in April 2018, we have activated two graduate programs to achieve higher levels of consolidated research. The first one is the "Medical Sciences Program for Preemptive Medicine," a graduate program for integrated preemptive medical and dental health care science to train specialists in the comprehensive analysis of medical big data, utilizing technologies such as IoT, AI and robotics. The second program, "Master of Public Health in Global Health (MPH) Course," aims to develop specialists capable of solving urgent world health issues using diverse programs, including international lectures, case studies, and field trips for overseas work.

TMDU is committed to fostering innovative research exchange at a global level. For instance, in 2018 we hosted a joint research symposium for TMDU, the University of California, San Diego (UCSD) and the University of Southern California (USC), which featured world-class experts from an array of medical and dental research fields. The exchange of ideas and knowledge created invaluable links between our universities and we expect to strengthen them in the future through a wide variety of active exchanges of students, professionals and research experiences.

In this booklet, we highlight outstanding examples of state-of-the-art research activities at TMDU, which are in a continuous state of evolution and refinement. Although these activities represent only a fraction of the research underway at our university, I am confident that these highlights will give you an idea of the exciting opportunities available here for collaboration and study, open to researchers and students worldwide.

TMDU's research vision: To strengthen the core and support the evolution of medical and dental research while aiming toward the future

At Tokyo Medical and Dental University (TMDU), the medical and dental departments have been trendsetters in research and education. TMDU also embraces two research-specific labs: the Medical Research Institute, which pursues the etiopathology of intractable diseases, including cancer, and the Institute of Biomaterials and Bioengineering, which develops materials and devices for treating patients.

Our Medical Hospital boasts the highest percentage in Japan of matching applicants with their desired clinical training. Moreover, many of our faculty members there are involved in the clinical care of patients and are conducting basic research to address clinical problems—a system not widely seen in many other countries. The Dental Hospital has the largest number of patients in Japan, which plays a vital role in revealing important areas for medical and dental research—for example, the relationship between oral bacteria and dementia.

One of TMDU's highlights is preemptive medicine, in which our extensive data collected from patient samples of breath, sweat and tears can be used to evaluate a patient's condition. Precision medicine, which uses genome information, is another field of interest, as it promises to uncover the most suitable therapy for an individual patient.

In 2018, we established the "Organ and Tissue Neogenesis Consortium" by integrating solid research activities from various areas involved in regenerative medicine, where TMDU's strengths lie (see TMDU Research NEWS, pp. 6-7). Moreover, we launched a new training program for outstanding young researchers, called "Cultivating Unit for Innovating Medical Scientist," in which our researchers will work in untapped fields under the guidance of top-flight scientists invited from around the world.

Along with these innovative research opportunities, TMDU continues to ensure intensive lessons and interactions for students, thanks to our high faculty-to-student ratio, which allows faculty members to conduct their own research while also training the next generation of researchers. The TMDU campus is also open to foreign students; in fact, about 19 percent of our graduate students come from abroad, one of the highest percentages at any post-graduate institution in Japan.

TMDU has been building international collaborative partnerships all around the world in both research and education. This booklet highlights the latest scientific research from TMDU. We hope our readers find it fascinating and come away inspired to build collaborative relations with TMDU researchers.

Prominent Researcher

Discovering the breast cancer gene and contributing to diagnosis and treatment

Yoshio Miki

Professor of Molecular Genetics at TMDU

Prof. Miki discovered BRCA1, the gene that causes Hereditary Breast and Ovarian Cancer (HBOC) syndrome.

After graduating from university, Prof. Miki worked as a surgeon at the Hyogo College of Medicine. In 1989, he moved to the Cancer Institute at Japanese Foundation For Cancer Research (JFCR) and joined an ongoing project to isolate the causative gene behind familial adenomatous polyposis.

Following that project's success, he became a research fellow at the University of Utah, where, in 1994, he succeeded in isolating BRCA1. He returned to JFCR the following year and has been a professor at TMDU since 2002.

Following the isolation of BRCA1, a British group discovered BRCA2 in 1995. Today BRCA1/2 testing is used for pre-symptomatic diagnosis and definitive diagnosis of HBOC. Since 2018, TMDU Medical Hospital has offered outpatient treatment of HBOC. Prof. Miki's discovery has contributed enormously to the genomic therapy of breast and ovarian cancer.

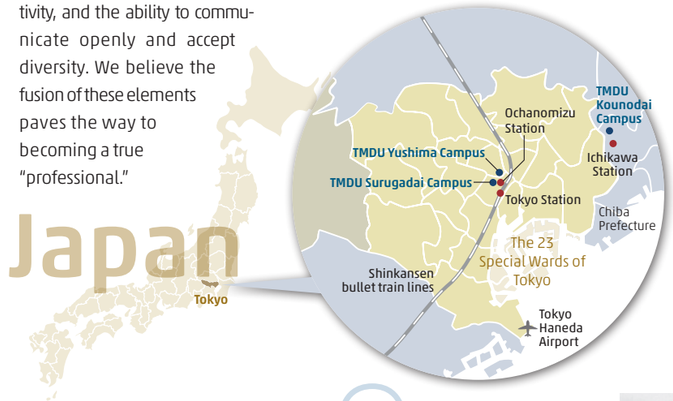
As researchers around the world sought to elucidate the function of BRCA1/2, it was discovered that BRCA1/2, which normally functions to repair DNA double-strand breaks, causes the onset of HBOC when mutated. Following this discovery, drugs have been developed with the strategy of "synthetic lethality," which involves killing cancer cells by inhibiting another DNA-repair function. This therapy is now starting to be adopted worldwide.

Meanwhile, Prof. Miki continues to promote the elucidation of the function of BRCA1/2 with the aim of advancing diagnosis and treatment of sporadic breast and ovarian cancer. For the future of cancer genome research, he believes it is important to promote cooperation among researchers worldwide so as to share genome databases of various populations and analyze them using artificial intelligence. The differences and universal features that can be found in genomes can help spur understanding and discovery.

Prof. Miki has also been making great efforts to apply his clinical experience to basic research. He believes that it is not possible to discover new things through reasoning alone. For him, intuition plays an important role in understanding situations that cannot be explained by theory. These are the key factors that have enabled Prof. Miki to achieve his research success.

Standing at the sacred birthplace of scholarship in Japan

Tokyo Medical and Dental University was established as a national medical and dental educational institution on October 12, 1928. Currently, TMDU is located in the Yushima / Shoheizaka area of Tokyo, which is considered sacred ground for scholarship and learning in Japan. As Japan's only comprehensive medical university and graduate school, TMDU has provided advanced medical treatment through a fusion of the medical and dental fields. It has worked to cultivate professionals with knowledge and humanity, thereby contributing to human health and the well-being of society. The "knowledge" referred to here includes learning, technology, and self-identity, while "humanity" means culture, sensitivity, and the ability to communicate openly and accept diversity. We believe the fusion of these elements paves the way to becoming a true "professional."



Today, TMDU is still located in Ochanomizu / Yushima district where its predecessor, the Tokyo National School of Dentistry, had moved in 1930, two years after its founding. TMDU has become known as one of the most excellent research universities in Japan.

TOKYO - The past and present

This landscape shows a view of Ochanomizu, where TMDU is located today. The buildings on the right-hand side, Yushima Seido and Shoheizaka School, were the center of scholarship since the 17th century, the Edo Period in Japan. Mt. Fuji can be seen in the far distance.

1800s

View of the Eastern Capital, Edo-Ochanomizu (woodblock by Shotei Hokuju)

1928

The Tokyo National School of Dentistry, the predecessor of TMDU, was established at Hitotsubashi.

2019

Present-day Ochanomizu, showing the same view as in the above woodblock. Ochanomizu Station is at the left and the TMDU Main Campus is at the right, with the Kanda River flowing between them.

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Inauguration of the Organ and Tissue Neogenesis Consortium

From early on, the Tokyo Medical and Dental University has been engaged in regenerative medicine research in areas such as immune cells, the oral cavity, the knee joint and the intestinal tract. Furthermore, in order to provide high-quality regenerative medicine to our patients, we have also focused our efforts on the research and development of innovative detection technologies for pathogenic microbes and gene mutations in tumorigenesis.

Based on our extensive experience and achievements in regenerative medicine research, in September 2017, we established the Organ and Tissue Neogenesis Consortium. With the underlying concept of "from Regeneration to Neogenesis," we are creating a new paradigm of "neogenetic medicine" that has advanced from traditional regenerative medicine. We aim to establish an international research center for "neogenetic medicine" with the cooperation of public institutions, leading researchers from both home and abroad, and private companies.

The Consortium is made of nine units that span different departments and laboratories of our university, and has the following three features.

1) Focus on unique target organs

Regenerative medicine research up until now has targeted organs that do not regenerate once they become dysfunctional, such as the heart and nerves. Our university has, however, conducted numerous studies on organs that are inherently highly capable of regeneration, such as the intestines, liver, and hair roots. Through this Consortium, we will focus on research to develop beyond our past achievements with the aim of creating organs for transplantation.

2) Organoid research

Regenerative medicine to date has mostly used disaggregated cells or cell sheets, but we will go further by incorporating organ generation. To be more specific, we are trying to realize regenerative medicine that uses three-dimensional mini-organs called "organoids."

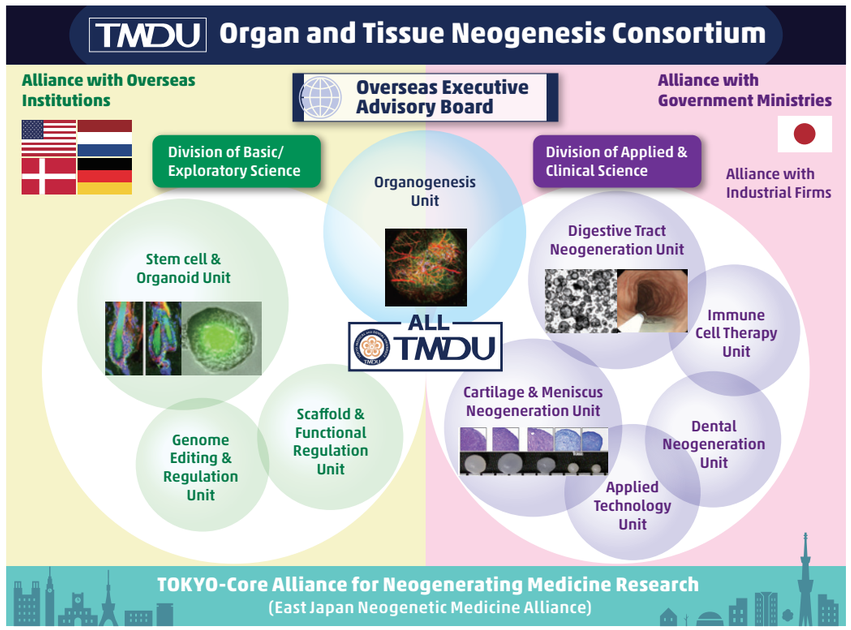
3) Fostering next generation researchers

We believe this is crucial for the establishment of the new academic field of neogenetic medicine. We seek to provide the next generation researchers with suitable environment and research program.

The ultimate goal of this Consortium is to benefit as many patients as possible with the fruits of "neogenetic medicine." In order to pursue basic research and achieve the practical application of research findings, the cooperation and support of companies and government ministries and agencies is indispensable. With strong dedication, we will do our best to meet your expectations. We sincerely seek your cooperation and support for this cause.

Tomohiro Morio

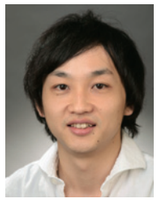
Director,
Organ and Tissue Neogenesis Consortium



The Organ and Tissue Neogenesis Consortium is made up of nine research units. The collaborations within and among the units and their cooperation with research institutes and corporation or companies taking part in the Consortium will not only further this area of research, but is also anticipated to become the place for fostering internationally sought-after human resources.

Introducing the Units

Organogenesis Unit



Takanori Takebe

Professor, Cluster of Advanced Multidisciplinary Research

Create organoids from human stem cells towards transplantation therapy and drug discovery

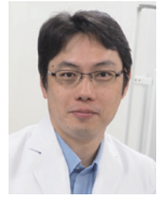
Stem cell & Organoid Unit

Emi Nishimura

Professor, Department of Stem Cell Biology

Contributing to the realization of health and longevity by controlling stem cells to elucidate the aging and regeneration of organs

Digestive Tract Neogeneration Unit



Ryuichi Okamoto

Professor, Center for Stem Cell & Regenerative Medicine

Preserving the health of the whole body through the creation of digestive organs, such as intestinal epithelial organoids

Genome Editing & Regulation Unit

Fumitoshi Ishino

Professor, Department of Epigenetics

Creating disease models using genome editing technology, and developing mRNA drugs

Cartilage & Meniscus Neogeneration Unit

Ichiro Sekiya

Professor, Center for Stem Cell and Regenerative Medicine

Developing new therapies, such as the regeneration of cartilage and meniscus using stem cells

Scaffold & Functional Regulation Unit

Akio Kishida

Professor, Department of Material-based Medical Engineering

Assisting the field of organ and tissue neogenesis with unprecedented biomaterials

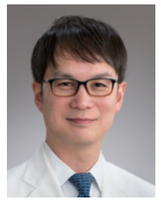
Immune Cell Therapy Unit

Tomohiro Morio

Professor, Department of Pediatrics and Developmental Biology

Developing immune cell therapies and strengthening and creating immune functions, such as the controlling of organ engraftment

Dental Neogeneration Unit



Takanori Iwata

Professor, Department of Periodontology

Hard and soft tissue regeneration with stem cell and cell sheet technology

Applied Technology Unit

Norio Shimizu

Associate Professor, Center for Stem Cell and Regenerative Medicine

Ensuring microbial safety in regenerative medicine, and developing comprehensive and rapid microbial testing systems

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Self-organization of vascularized organoids allows enhanced survival of islet transplants for use in diabetes therapy

Takanori Takebe

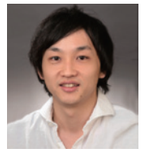
Professor of Organogenesis Unit at TMDU

Q You are aiming to achieve clinical transplantation of tissue fragments. Please explain what this is.

A: Tissue-based therapies are hailed as the next-generation treatment for organ dysfunction. They generally involve the harvesting of tissues, rather than whole organs, from donors. Much of the enthusiasm for this research has been driven by the partial success of pancreatic islet transplantation, which was initially described nearly 20 years ago. A related approach, stem cell-based tissue engineering, aims to provide transplantable tissue without requiring an organ donor. However, both approaches are limited by a lack of success in ensuring efficient formation of new blood vessels, a process known as vascularization. The timely establishment of tissue vascularization within engineered tissue is necessary to ensure its survival and proper functionality *in vitro*, as well as to achieve successful tissue engraftment within the patient's body, followed by appropriate performance of its expected function *in vivo*.

Intravital imaging of vascularized islet transplant

Our image was selected as the cover art for the May 8, 2018 issue of *Cell Reports*.



Dr. Takebe is a Professor at TMDU and Associate Director of the Center for Stem Cell and Organoid Medicine (CuSTOM) at the Cincinnati Children's Hospital Medical Center. He serves on the Board of Directors at the International Society of Stem Cell Research (ISSCR) and has received numerous awards, including the NYSCF Robertson Investigator Award. His lab investigates the mechanisms of human organogenesis, and develops mini-organ technologies from human stem cells - namely organ bud-based approaches. He is applying iPSC-liver buds into drug discovery studies as well as transplant applications for patients with a rare congenital metabolic disorder. His work will ultimately expand the clinical applications to diseases like liver cirrhosis.

Q You recently assessed the use of self-organizing cultures in the growth of pancreatic islets for the treatment of diabetes. What made you focus on this disease and what did you discover?

A: A well-known example of clinical transplantation of tissue fragments involves pancreatic islet transplantation, which promotes insulin independence in patients with severe type 1 diabetes. An important limitation of this method is that transplanted islets have a disappointingly low engraftment rate because these islets lose vasculature during the isolation process. This lack of vasculature induces necrosis, reducing the treatment efficacy. Therefore, rapid establishment of vascular networks is critical for successful engraftment of transplanted islets. Thus far, transplant vascularization generally requires at least a week: rapidly introducing vasculature into transplanted tissue remains challenging.

Q You used a particular technique in your investigation of self-organizing cultures: self-condensation of tissue fragments. Can you explain why this was necessary and what it achieved?

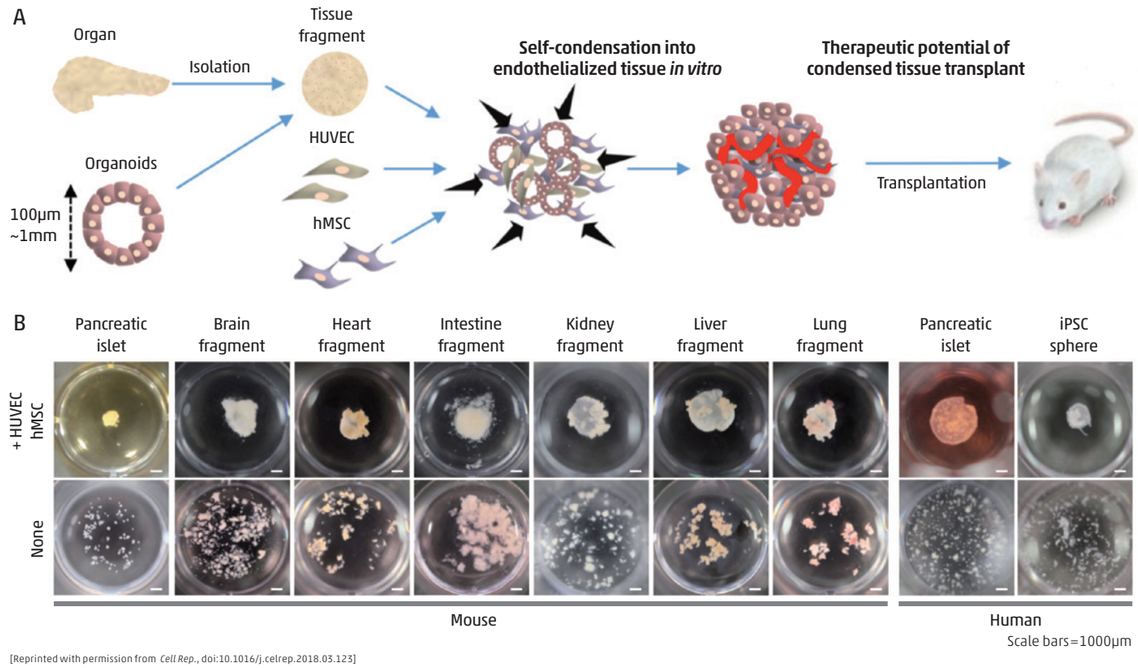
A: Recently, we developed a dynamic self-condensation approach to develop tissue organoids from dissociated organ progenitor cells (early descendants of stem cells that retain the ability to become a broad, but not unlimited, variety of cell types), together with stromal vascular and mesenchymal progenitors. Although we achieved rapid blood vessel induction in tissue organoids generated from single, dissociated cells in suspension, it was not clear whether tissue fragments, such as islets, could also be adapted to follow this self-condensation principle. In the current publication, we showed multiple types of tissue fragments can self-organize three-dimensional tissue structures with developing vascular networks by following the self-condensation culture approach. This method not merely enables an increased scale for self-condensation, but allows for integrating supportive lineages, such as endothelial lineages. Moreover, this method uses primary pancreatic tissues, which are preferable to MIN6 cells used in prior studies that were isolated from an insulinoma of a transgenic mouse expressing the SV40 T antigen in pancreatic islet beta cells. Given that recently evolving organoid-based approaches generally omit vasculature, our methodology can support building additional complexity into engineered tissues or organoids. By enabling the construction of complex and heterotypic structures, this self-condensation principle will aid in disease modeling and drug discovery, and ultimately in regenerative medicine applications.

Q What are the clinical implications of your findings?

A: The primary challenges of islet transplantation are treating patients using a minimal number of donors and achieving stable and long-term glycemic control after transplantation. In diabetic mice, the approach that my colleagues and I have tested showed dramatic improvement of survival rates. These findings were supported by improved islet engraftment rates, insulin secretion function, and glucose responsiveness. One day, we expect that transplantation of vascularized islets into patients with type 1 diabetes may promote long-term insulin independence. Of note, this method might reduce the number of donors required to treat a single patient, which would increase the capacity of the medical community to manage this disease. We hope that success in the treatment of patients with diabetes might entice researchers in other fields to use this approach with complex tissues involved in other diseases, so that we can deliver curative therapies to a broad number of patients with a variety of genetic and lifestyle or environmental pathologies.

Cell Rep., doi:10.1016/j.celrep.2018.03.123

Generation of complex and vascularized tissue grown from various tissue fragments



Scale bars=1000μm

[Reprinted with permission from *Cell Rep.*, doi:10.1016/j.celrep.2018.03.123]

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Studying hair follicle loss as a model of age-related organ decline

Emi Nishimura

Professor of Stem Cell Biology at TMDU

Q Your research uses hair follicles as a model to study the mechanisms of tissue aging. Why did you choose hair follicles as a model system?

A: In mammals, most organs undergo a process called atrophy, where they become smaller (miniaturize) or thinner with age, and generally show reduced function and ability to regenerate over time. Also, if you look closely at aged organs, there is often obvious tissue damage. The hair follicle can be thought of as a "mini-organ" of the skin—like larger organs, it has its own stem-cell system to sustain cellular and tissue turnover. The hair follicle controls hair regrowth and, as we age, miniaturization of hair follicles leads to balding. Because of the relative simplicity of the hair follicle and the obvious physical manifestation of aging follicles, it is a good model system for studying the mechanisms of tissue aging.

Q You published a paper in *Science* on the mechanism of hair follicle aging. Can you explain the background and main findings of this research?

A: Stem cells, which renew themselves and also generate functionally differentiated cells, are important for adult tissue regeneration, and changes in stem cells are recognized as one of the hallmarks of aging. Hair follicle stem cells (HFSCs) generate all cell types needed for hair growth and are located in the hair follicle itself. However, we had not known what happens to aged HFSCs or what role stem-cell aging plays in the overall organ-aging process. In our study published in *Science*, we showed that DNA damage triggers a response in HFSCs that causes stepwise miniaturization of hair follicles, leading to hair loss. More specifically, DNA-damage response in HFSCs leads to the breakdown of type XVII collagen (or COL17A1), which is needed for HFSC maintenance. Instead of producing cell types that contribute to hair growth, those stressed HFSCs exclusively differentiate into terminally differentiated epidermal keratinocytes and are pushed to the skin surface and eliminated. With the other cell types being poorly produced, the hair follicles gradually become smaller until they disappear, resulting in hair loss.

Q Most of your work was carried out in mice—how can you be sure that it also reflects what happens in humans?

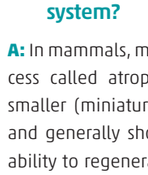
A: After defining the mechanism in mice, we decided to look at scalp tissue samples from women ranging from 22 to 70 years old. By staining these tissue sections with special markers for HFSCs such as COL17A1 and for DNA-damage response, we saw similar DNA-damage response in HFSCs, HFSC depletion and hair follicle miniaturization in tissues from the older women, confirming that our findings in mice are translatable to humans.

Q Your research involved both local and international collaboration. How does this fit into the overall goals of TMDU?

A: TMDU's vision emphasizes cutting-edge translational research that contributes to the health and well-being of society. Collaborating with other leaders in the field helps us achieve the goal of carrying out basic research with clinical applicability.

Q What are the clinical implications and future directions of your work?

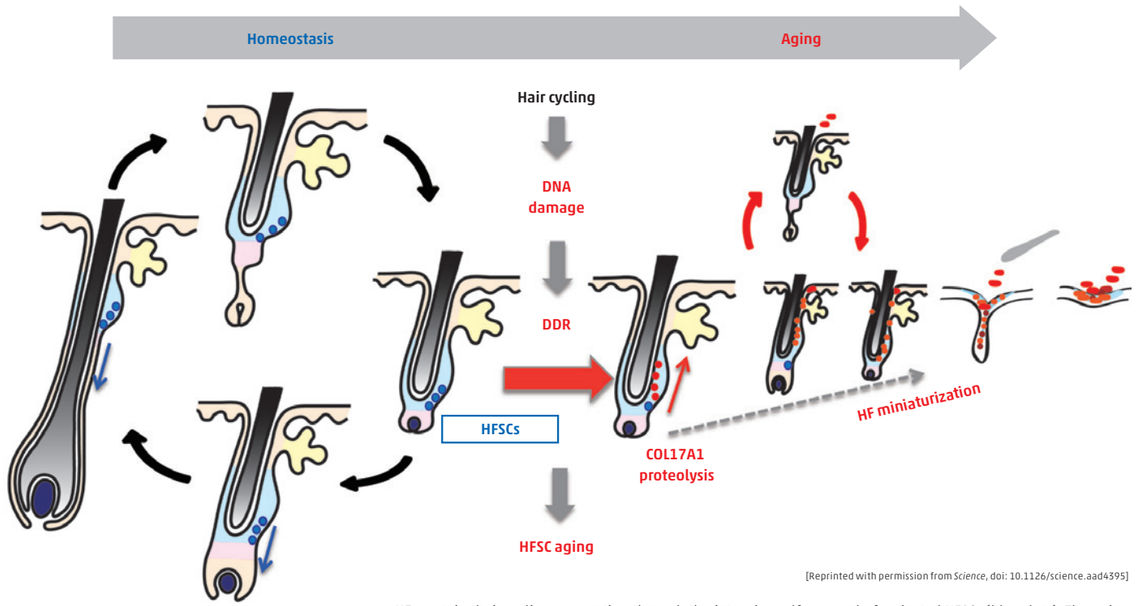
A: Our research uncovered several factors that are critical to the process of organ aging. First, we showed that DNA-damage response in stem cells is tightly linked to epithelial organ aging. Secondly, hair follicle aging could be prevented by controlling the expression of COL17A1, the type XVII collagen needed for maintenance of HFSCs. If levels of COL17A1 were maintained, we could prevent HFSCs from differentiating into epidermal keratinocytes. Age-related organ decline is expected to become an increasingly important health issue given the aging population. The hair follicle aging process is a good model of organ and tissue shrinkage and provides us with vital information for examining the functional decline of other organs. Understanding the key steps in the organ aging process provides exciting new avenues for the development of therapies that apply these processes to prevent and treat aging-associated diseases.



Dr. Nishimura obtained her MD in 1994 and did her Dermatology residency at Kyoto University Hospital. She then obtained her PhD at Kyoto University and did her postdoctoral training at the Dana Farber Cancer Institute, Harvard Medical School. She then started her own group as an Associate Professor at Hokkaido University in 2004, and became a Professor at Kanazawa University the following year. Her laboratory moved to TMDU in 2009. She is currently a Professor at the Medical Research Institute of TMDU. She identified melanocyte stem cells in 2002 and revealed that the exhaustion or depletion of stem cells in hair follicles underlies the graying and thinning of hair in aging. Her group is currently focusing on epidermal stem cell aging and the mechanisms of skin homeostasis, aging-associated decline of the skin, and cancer development.

Science, doi: 10.1126/science.aad4395

The mechanism of hair follicle aging and associated hair loss



[Reprinted with permission from *Science*, doi: 10.1126/science.aad4395]

HFs sustain their cyclic regeneration through the intensive self-renewal of activated HFSCs (blue dots). The aging of HFSCs is triggered by DNA-damage response (DDR)-induced COL17A1 proteolysis. Once aged HFSCs (red dots) are activated during the hair cycle, they leave the niche and terminally differentiate into epidermal keratinocytes and are then eliminated from the skin surface. HF, hair follicle; HFSC, hair follicle stem cell.

TMDU Research NEWS

TMDU,UCSD and USC held joint symposium

In September 2018, TMDU hosted the "1st TMDU-UCSD-USC Joint Symposium," providing the three universities with a vital opportunity to deepen relationships and exchange cutting-edge information and experience regarding medical and dental research.

The first symposium featured the research theme, "Frontiers in Liver Research and Global Medicine." After opening remarks from TMDU President Yasuyuki Yoshizawa, three speakers from each university gave lectures on the research theme.

The nine speakers were all well-known, active researchers in their respective fields of liver research: from UCSD, Vice Chancellor David Brenner, Health Sciences, Assistant Vice Chancellor Mounir Soliman, Health Sciences, and Associate Prof. Tatiana Kisseleva, Department of Surgery; from USC, Prof. Hidekazu Tsukamoto, Department of Pathology, Associate Prof. Kinji Asahina, Department of Pathology, and Associate Prof. Keigo Machida, Department of Molecular Microbiology and Immunology; and from TMDU, Prof. Hiroshi Nishina, Department of Developmental and Regenerative Biology, Prof. Shinji Tanaka, Department of Molecular Oncology, and Associate Prof. Sei Kakinuma, Department of Liver Disease Control.

Some 100 participants enjoyed the lectures and participated in question and answer sessions. The symposium concluded with remarks by Vice Chancellor David Brenner from Health Sciences, UCSD.

TMDU looks forward to continuing a wide variety of exchanges with UCSD and USC in the future.

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Out with the old, in with the new: Stem cell therapy for inflammatory bowel disease (IBD)

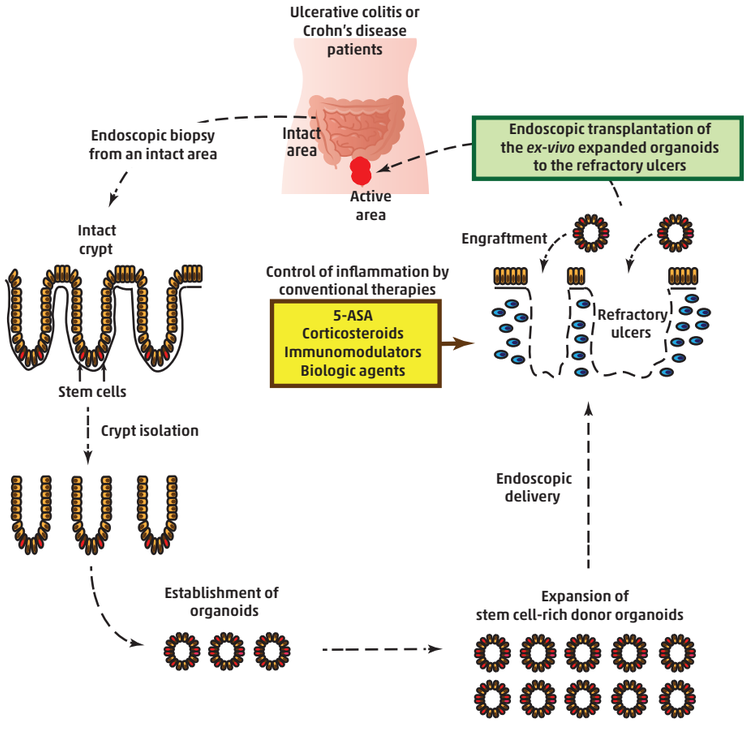
Ryuichi Okamoto

Professor of Stem Cell and Regenerative Medicine at TMDU

Q You work at the Center for Stem Cell and Regenerative Medicine at TMDU. Can you explain what regenerative medicine is?

A: Regenerative medicine refers to the repair or replacement of diseased cells, tissues, or organs in order to restore normal function. One way to achieve this is by transplanting stem cells, which are cells that continuously renew themselves and can differentiate into specialized cell types. I work on inflammatory bowel diseases (IBDs) such as Crohn's disease and ulcerative colitis, which result in damage to the intestinal epithelium (the gut lining). We are looking at ways to remove this damage and regenerate the normal structure through 'mucosal healing'. We aim to restore the important functions of the gut lining as a mucosal barrier with a role in nutrient absorption, hormone secretion, and immune system regulation. Such treatment contrasts with conventional therapies, which try to reduce inflammation but have limited benefits and are not successful in all patients.

Regenerative medicine for inflammatory bowel disease (IBD)



Dr. Okamoto received his MD and PhD from TMDU in 2004, after which he became a Research Fellow in the Japan Society for the Promotion of Science. In 2007, he became an Associate Professor at TMDU. Since 2013, he has been a Professor at the Center for Stem Cell and Regenerative Medicine at TMDU.

Q Can you provide us with background on stem cells and further elaborate on their importance in regenerative medicine?

A: Stem cells have been known to exist in the intestinal epithelium since the 1970s. However, the identification of proteins expressed by intestinal stem cells, which can be used as markers to locate the stem cells, was only achieved fairly recently. This has enabled the culture of intestinal stem cells to be refined. They can now be grown in the lab, using suitable growth media and the support of an underlying extracellular matrix, to create a three-dimensional mini-organ, as the TMDU research team headed by Prof. Tetsuya Nakamura reported in an earlier study (*Nat. Med.*, doi: 10.1038/nm.2695). Transplantation of healthy mini-organs to damaged intestines has been achieved in animal models of disease. Stem cells are important to regenerative medicine because they enable lesions to be replaced with healthy tissue.

Q Is your current work based on intestinal stem-cell therapy?

A: Yes, we are working on a form of therapy for IBD patients who have ulcers that do not respond to current treatments. We are developing a method known as autologous transplantation in which biopsies of healthy areas of the patient's own intestinal epithelium taken during an endoscopy will be grown in the lab to extract intestinal stem cells. These cells will then be expanded and enriched using our previously established culture techniques. Once we have enough healthy cells for a mini-organ, this can be endoscopically delivered to an ulcerous site in the patient's gut for repair. The benefits of this include the fact that the mini-organs will not invoke an immune response because they derive from the patient's own cells, so there should be no barrier to achieving tissue regeneration. However, we first need to maximize the efficiency of this technique, and ensure that the mini-organs can be delivered safely without introducing new problems, such as the development of tumors.

Q What does the future hold for patients with IBD?

A: The intestine is made up of multiple cell types, including those of the inner surface of organs and those that line the inside of blood vessels, as well as muscle, nerve, and immune cells. Future work is likely to more accurately reconstruct the three-dimensional culture of mini-organs based on these different cell types. This could eventually lead to the transplantation of the intestine as an entire organ to repair or renew severely damaged lengths of intestine in patients with IBD. Because many of these cell types are involved in disease pathology, stem cells deriving from bone marrow have also been used in the treatment of IBD. So far, this has met with varying levels of success, suggesting further optimization is needed. It is also possible that a combination of cell therapies may improve the clinical outcome. In the future, patients may receive treatment that is better suited to the extent of their disease and the pathologic changes that have occurred.

Digestion., doi:10.1159/000438663

Innovative Researcher

IBD, and beyond: Extracellular matrix dictates cell fate transition during inflammation

Shiro Yui

Assistant Professor, Center for Stem Cell and Regenerative Medicine at TMDU

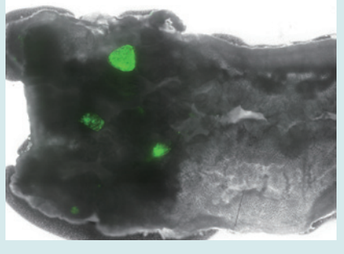
Inflammatory bowel disease (IBD) is a chronic inflammatory disorder in the human gut. In one subset of IBD, patients have to be treated lifelong for lasting distressing symptoms such as bloody stool, abdominal pain and weight loss. IBD is even life-threatening in the case of severe inflammation or cancer. Medical care of IBD has improved in the past 20 years, but further improvement is necessary. Prolonged inflammation seen in IBD indicates that cell regeneration is impaired. We need to understand the process of regeneration of intestinal epithelial cells (IECs) to understand IBD.

My research was initiated with the invention of the primary culture system of IECs in 2009 at TMDU under the supervision of Prof. Mamoru Watanabe and Prof. Tetsuya Nakamura. In the system, Collagen Type I gel is used as extracellular scaffold, and IECs are formed into a spheroid that we named "TMDU sphere." We originally reported epithelial regeneration after transplantation of TMDU spheres, which showed the feasibility of cell-based therapy for IBD. Recently, the unique character of the TMDU sphere was finally identified. In the course of intensive analysis over nine years, the similarity to fetal enterospheres developed by Prof. Kim Jensen at University of Copenhagen was discovered. This provided a novel insight for understanding the system of 'fetalization' in IECs, which is indispensable for regeneration, and illustrates a useful scheme for understanding how inflammation induces regeneration.

Drawing on the intersectional research community of physicians and basic biologists, and through the international ties between TMDU and University of Copenhagen, I will expand my research to investigate IBD in a more scientific manner. Our goal is to improve clinical achievements in various types of inflammatory disorders beyond IBD.

Nat. Med., doi: 10.1038/nm.2695
Cell Stem Cell, doi: 10.1016/j.stem.2017.11.001

Murine TMDU sphere (green) transplanted in colon



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Immune checkpoints in T cell-mediated tissue inflammation

Miyuki Azuma

Professor of Molecular Immunology at TMDU

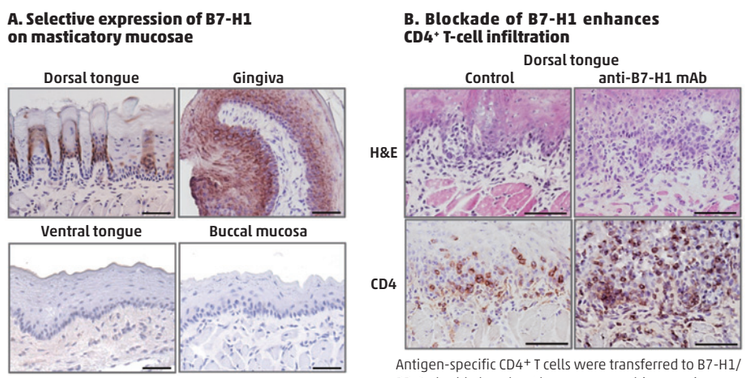
Q You are exploring the regulation of immune responses through specific immune checkpoints. Please explain what this is.

A: Immune checkpoints help to regulate the immune system. This is important to prevent the development of autoimmunity, which is when the immune system erroneously attacks the body's own healthy cells instead of invading pathogens or tumors. This regulation is achieved by requiring a second signal for full immune system activation, or by inhibiting activity because the target is recognized as a normal part of the body. In cancer, immune checkpoints are often manipulated to suppress anti-tumor immune responses, allowing the tumor to grow in an unrestricted manner. Additionally, immune checkpoints can also be important in cases of chronic inflammation, in helping to avoid excessive damage to the area surrounding the affected tissue.

Q You recently investigated the expression of co-inhibitory molecules on masticatory mucosae in the mouth. What made you focus on this process, and what did you discover?

A: Masticatory mucosae (the layers of tissues covering the gums, top of the tongue, and hard portion of the roof of the mouth) are specialized oral mucosae for mastication (crushing and digesting foods), as well as protection from environmental damage. Our initial interest in masticatory mucosae arose from histological studies of tissues and cells expressing B7-H1 (also known as PD-L1), which is a ligand (binding partner) for PD-1, an important inhibitory receptor in T cells. We found that masticatory mucosae, but not other oral mucosae or mucosal surfaces of other organs, showed stable expression of B7-H1.

B7-H1 (PD-L1), a ligand of immune checkpoint receptor PD-1 expressed on masticatory mucosae, negatively regulates T cell-mediated tissue inflammation



Scale bars = 50μm

Antigen-specific CD4+ T cells were transferred to B7-H1/PD-1-double knockout bone marrow chimera mice.

[Reprinted with permission from *Mucosal Immunol.*, doi:10.1038/mi.2016.89]

Q You performed antigen stimulation through mucosal surfaces in your investigation of immunity in masticatory mucosae. Can you explain what aspect of the immune response was discovered by using this technique in masticatory mucosae?

A: We knew that B7-H1 expressed on antigen-presenting cells or tumor cells could interact with PD-1 and inhibit T-cell activation, and that the presence of B7-H1 in tissues could regulate the activation of T cells. However, we did not know how B7-H1 expression was regulated in oral mucosae or how B7-H1 functioned in the oral cavity. The oral mucosae receive external stimuli through the mucosal surface and internal stimuli through immune cells, such as infiltrating T cells and macrophages. Antigen stimulation studies, combined with the use of unique TCR-transgenic mice, allowed us to determine how B7-H1 functions: We learned that keratinocyte/epithelial cell-associated B7-H1 interacts with PD-1 that is expressed on antigen-primed, tissue-infiltrating CD4+ T cells to provide negative regulatory signals.

Q What are the clinical implications of your findings?

A: The induction of B7-H1 expression in masticatory mucosae appears to be important in the prevention of excess immune responses in chronically inflamed tissue and in homeostasis in the mouth.

Dr. Azuma completed dental and graduate school at TMDU, where she received her DDS and PhD. She performed postdoctoral research in the Department of Immunology at DNAX Research Institute in Palo Alto, CA, USA and continued her career as an Assistant Professor of Immunology at Juntendo University School of Medicine, and as a Research Associate in the Department of Immunology at National Children's Medical Research Center in Tokyo. She returned to TMDU as a Professor of Molecular Immunology in 2000.

Mucosal Immunol., doi:10.1038/mi.2016.89

Controlling multipotent stem cell differentiation with molecularly-tuned movable surfaces

Nobuhiko Yui

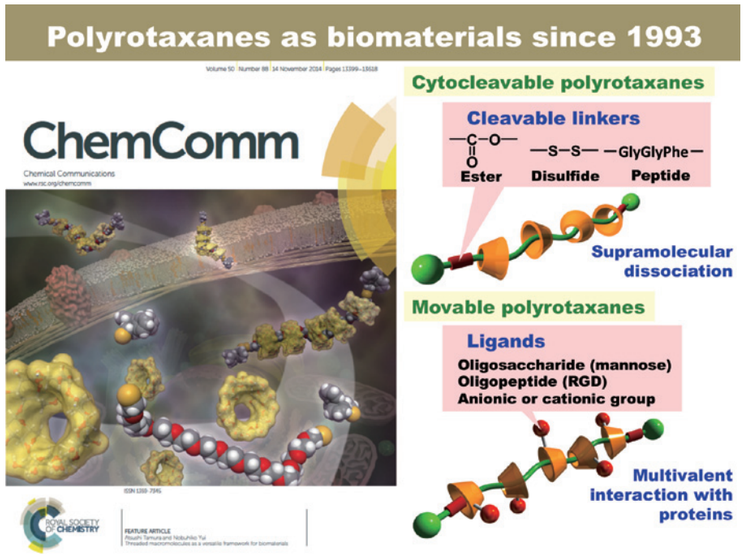
Professor of Organic Biomaterials at TMDU

Q What are multipotent mesenchymal stem cells, and how can they be used to improve human health?

A: Mesenchymal stem cells (MSCs) are "multipotent" because they can differentiate into so many cell types, depending on the environment in which they find themselves. Clinical studies are currently underway to see if injecting mesenchymal stem cells can help treat conditions like osteoarthritis, Crohn's disease, or multiple sclerosis by allowing the body to repair itself. In our research, we looked for ways to culture MSCs so that they differentiate into the desired cell types.

Q What are some of the novel methods TMDU researchers have developed to control the differentiation of these stem cells?

A: One of the most important signals that controls the fate of stem cells is the molecular mobility of the surfaces to which they attach. MSCs that adhere to less mobile surfaces tend to spread out by creating actin fibers, and become osteogenic, bone-forming cells. In contrast, MSCs on highly mobile surfaces are more likely to become muscle or fat cells. Here, we have developed a process of culturing stem cells on polyrotaxane (PRX), a novel supramolecular polymer whose surface mobility can be easily tuned owing to its interlocking molecular assembly.



Cover art of the Nov. 14, 2014 issue of *Chemical Communications*

Dr. Yui started his academic career at Tokyo Women's Medical University as an Assistant Research Professor after completing his PhD at Sophia University in 1985. He then joined the Japan Advanced Institute of Science and Technology (JAIST) in 1993 as an Associate Professor and became a Professor in 1998. Since 2011 he has been a Professor at TMDU as well as Professor Emeritus at JAIST. He now serves as President of the Japanese Society for Biomaterials.

Q Please tell us more about the unique properties of the PRX polymer.

A: PRX has many excellent features. By changing the amount of α-cyclodextrin threaded on a linear polyethylene glycol chain, we can alter its physical properties, including its molecular mobility. Stiffness of materials have been known to affect cell fate. However, the stiffness at the interface with the body is not so precisely controlled when implanted in the body. A main accomplishment of our research is to utilize the controlled molecular mobility of supramolecular PRX at the interface with cells in order to explore a wide range of applications using stem cells, including tissue regeneration and repair.

Q What are the broader applications of your research?

A: Stem cell differentiation is controlled by the cytoskeleton – the internal scaffold responsible for the cell's shape – which changes as the cells are grown on artificial materials. We hypothesize that the Rho family of small GTPases that control cytoskeletal organization is universally modulated in cells via altering the surface molecular mobility of PRX. The signaling cascade can easily reach every part of a cell, and has important implications not only for tissue engineering, but also for treating diseases such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis.

Adv. Healthc. Mater., doi:10.1002/adhm.201400173

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Physiological and environmental biosensing for preemptive and preventive medicine

Koji Toma

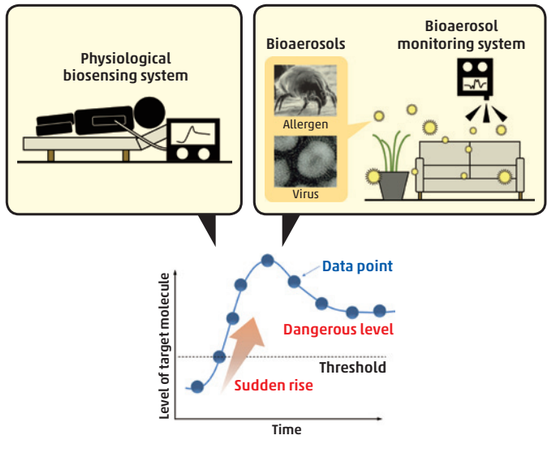
Assistant Professor of Biomedical Devices and Instrumentation at TMDU

After working at AIT Austrian Institute of Technology as a research fellow and obtaining my PhD from the University of Natural Resources and Life Sciences, Vienna, Austria in 2012, I worked at Forschungszentrum Jülich in Germany as a postdoctoral fellow and Humboldt research fellow. In 2014, I started my academic career as an Assistant Professor of Biomedical Devices and Instrumentation at TMDU.

My current research focuses on biosensors for medical applications, in particular preemptive and preventive medicine. A biosensor is a sensor device especially designed for selective detection of chemical or biological substances by utilizing biologically derived materials, for example, antibodies, enzymes and receptors. In preemptive and preventive medicine, the temporal information of a target molecule is important to accurately understand the risk and status of diseases. However, biosensors are not always good at continuous sensing – for example, immunosensors, which exploit antibodies to capture antigens. This deficit exists because those biologically derived materials have been denatured in a harsh environment, such as in a low or high pH solution, in order to regenerate a biosensor for subsequent measurement.

In my current research, I am aiming to overcome such obstacles and develop biosensors that can be used repeatedly for physiological and environmental biosensing. The outcome of this research will pave the way for a novel technique that helps to predict and eliminate the risk of disease development by notifying users of a sudden rise in disease-related biomarker levels in their bodies or a high bioaerosol level in their residential environments.

Reusable biosensors for monitoring physiological status and bioaerosol level in the environment



Predict and eliminate the risk of disease development from 2D (concentration & temporal) information of target chemical or biological molecules.

Identification of therapeutic targets for nephrogenic diabetes insipidus

Fumiaki Ando

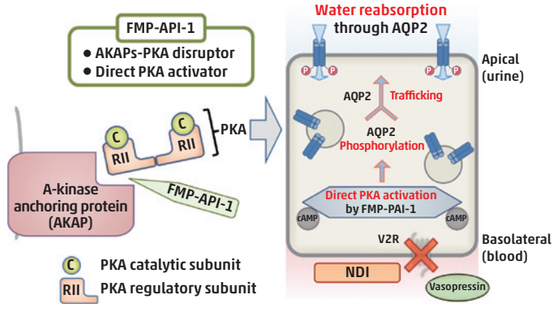
Specially Appointed Assistant Professor of Nephrology at TMDU

After graduating from TMDU in 2008, I accumulated five years of clinical experience as a physician. I started my research career in 2013 and received a PhD in 2017. I was then assigned to become the Specially Appointed Assistant Professor of Nephrology and was also elected to the Candidates of Innovating Medical Scientist at TMDU. One of the goals of our laboratory's research is to develop a definitive treatment for congenital nephrogenic diabetes insipidus (NDI).

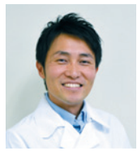
Congenital NDI is characterized by defective urine-concentrating ability. Daytime polyuria with nocturia significantly reduces a patient's quality of life. In healthy patients, in response to dehydration, the antidiuretic hormone vasopressin binds to the vasopressin type 2 receptor (V2R) in renal collecting ducts and increases water reabsorption by rapid translocation of aquaporin-2 (AQP2) water channels to apical plasma membranes. Most cases of congenital NDI are caused by mutations to V2R that cause a loss of function, resulting in unresponsiveness to vasopressin.

We found novel therapeutic molecules of congenital NDI that can activate AQP2 by bypassing defective V2R signaling. The classic calcium-signal transducer, Wnt5a, activated AQP2 through calcineurin (*Nat. Commun.*, doi: 10.1038/ncomms13636). Screening for calcineurin activators is a potential therapeutic strategy for the treatment of congenital NDI. In renal collecting ducts, calcineurin is co-localized with A-kinase anchoring proteins (AKAPs). AKAPs regulate the intracellular distribution and substrate specificity of protein kinase A (PKA). We next focused on the inhibition of AKAPs binding to PKA and found that AKAPs-PKA disruptors activated PKA and AQP2 to the same extent as vasopressin (*Nat. Commun.*, doi: 10.1038/s41467-018-03771-2). AKAPs-PKA disruptors are a potential novel category of therapeutic drugs for congenital NDI and other PKA-related diseases. We are now developing more potent compounds that will be effective in specific target issues.

AKAPs-PKA disruptors activate PKA and AQP2



Zirconia ceramics: promising restorative material offers strength and aesthetics



Masanao Inokoshi

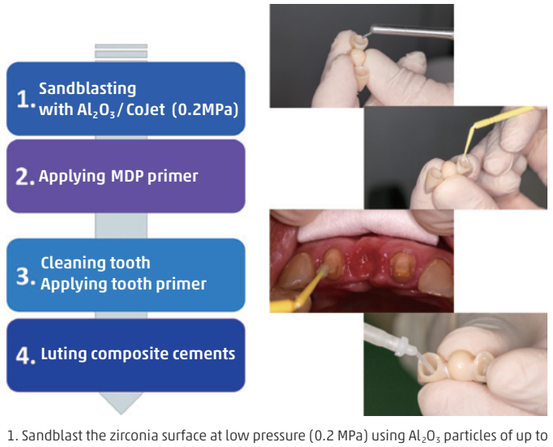
Assistant Professor of Department of Gerodontology and Oral Rehabilitation at TMDU

After I obtained my DDS degree in 2006, I started my first PhD training at TMDU. In 2010, I won a Flemish scholarship for Japanese students and moved to the University of Leuven (KU Leuven) in Belgium to conduct my second PhD training. In Leuven, I studied under Prof. Bart Van Meerbeek who is head of the KU Leuven BIOMAT research cluster. I obtained my second PhD in 2014 from KU Leuven.

At KU Leuven BIOMAT, my research topic was dental zirconia ceramics. Zirconia ceramics have become increasingly popular in dentistry, thanks to their aesthetic and biocompatible properties as compared to conventional metal-based restorations. Although zirconia has been applied in dentistry, scientific background for zirconia is still lacking. Previously, we focused on the resistance to aging and the bonding strategy of zirconia ceramics. We clarified that zirconia is aging-resistant as a dental restorative material. Regarding bonding strategies for zirconia ceramics, combined mechanical (alumina sandblasting) and chemical (MDP containing primer application) pre-treatments are important to obtain durable bonding to zirconia. Our paper, published in the *Journal of Dental Research*, is the first to report on having conducted meta-analysis regarding bonding efficacy to dental zirconia (*J. Dent. Res.*, doi: 10.1177/0022034514524228).

More recently, highly translucent zirconia is booming in dentistry. Compared to conventional zirconia ceramics, highly translucent zirconia is more aesthetically pleasing and can be used in full-zirconia restorations. Now we are focusing on this new material to clarify its properties. We are striving to create novel aesthetic, strong and aging-resistant highly translucent zirconia ceramics, as well.

Procedure to obtain durable bonding to zirconia



1. Sandblast the zirconia surface at low pressure (0.2 MPa) using Al_2O_3 particles of up to 50 μm in size; alternatively tribochemically silica sandblast/coat (CoJet, 3M ESPE) using silica-coated Al_2O_3 particles of up to 50 μm in size. 2. Apply MDP-containing primer to the sandblasted surface. 3. Clean tooth and apply tooth primer if necessary. 4. Apply luting composite cements and light-cure them using light-curing unit.

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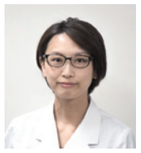
Therapeutic targets in chronic active EBV infection



Mayumi Yoshimori

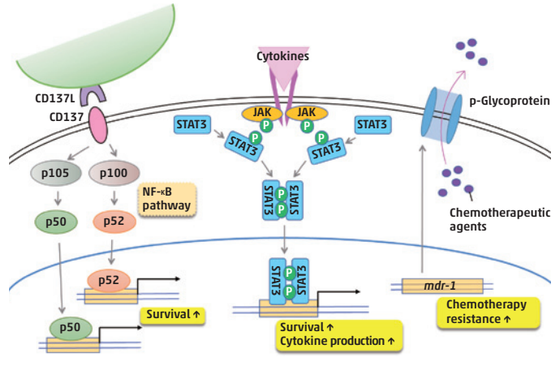
Specially Appointed Assistant Professor of Laboratory Molecular Genetics of Hematology at TMDU

After graduating from TMDU, I worked as a medical technologist for five years. In 2017, I decided to become a medical researcher and started my career in my present position. My research subject has been clarifying the molecular mechanisms of the development of chronic active Epstein-Barr virus infection (CAEBV).

EBV is a common virus. Once EBV infects human beings, it cannot be eradicated and latently infects B cells throughout the lifespan. However, EBV genome is also positive in some T- or NK-cell neoplasms. CAEBV is one of them with a poor prognosis. The mechanisms of the development of CAEBV have not been clarified and the only current curative strategy is hematopoietic stem cell transplantation. CAEBV has a marked geographic bias for East Asia, suggesting a genetic context for disease development. However, CAEBV certainly exists in Western countries, too. As Japanese researchers, we feel responsible for addressing and elucidating the issues of CAEBV.

During the graduate course, we demonstrated that *in vitro* infection of EBV in T cells upregulated the CD137 expression and promoted the survival of infected cells (*PLoS One*, doi: 10.1371/journal.pone.0112564). We also found that EBV infection of T cells enhanced P-glycoprotein expression in the infected cells, contributing to CAEBV's resistance to chemotherapy (*Cancer Med.*, doi: 10.1002/cam4.494). Our recent studies have revealed that constitutively activated STAT3 promoted cell survival and cytokine production, which had been suppressed by the effect of ruxolitinib (*Oncotarget*, doi: 10.18632/oncotarget.25780). Based on these findings, we are now planning to initiate clinical trials of ruxolitinib for CAEBV.

Suggested molecular mechanisms of CAEBV development

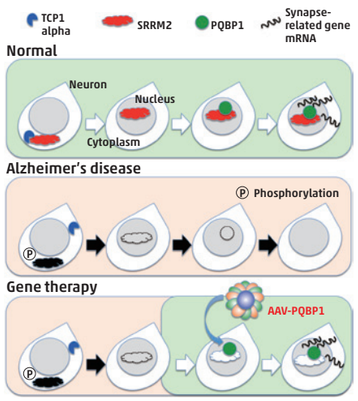


Rethinking the amyloid plaque: PQBP1 rescues Alzheimer's disease pathology

Extracellular aggregation of beta-amyloid peptide is a hallmark of the Alzheimer's disease (AD) brain; however, Phase III trials have found that beta-amyloid removal does not improve memory or cognition. Attention has therefore shifted to investigating pre-aggregation changes. One such change is the phosphorylation of the protein serine/arginine repetitive matrix 2 (SRRM2), which has been studied in work involving TMDU researchers led by Hitoshi Okazawa. Using mouse models and post mortem AD brains, they confirmed that phosphorylation of SRRM2 occurs before extracellular beta-amyloid aggregation, and that this prevents translocalization of SRRM2 from the cytoplasm to the nucleus. This deficiency of nuclear SRRM2 causes a downregulation of polyglutamine binding protein 1 (PQBP1), a causative gene for intellectual disability. Remarkably, PQBP1 supplementation resulted in recovering altered synapse morphology in the cerebral cortex and reversing cognitive impairment in AD model mice. These results indicate, for the first time, the importance of PQBP1 for synaptic and cognitive functioning in AD, which is important for the development of new therapeutics for the treatment of AD.

Mol. Psychiatry, doi:10.1038/s41380-018-0253-8

Theory of gene therapy by AAV-PQBP



In the Alzheimer's disease state, the amounts of nuclear scaffold protein SRRM2 and the synapse-gene regulator PQBP1 are decreased. By increasing PQBP1 in neurons, the expression of synapse genes is recovered and cognitive defects improve in Alzheimer's disease model mice.

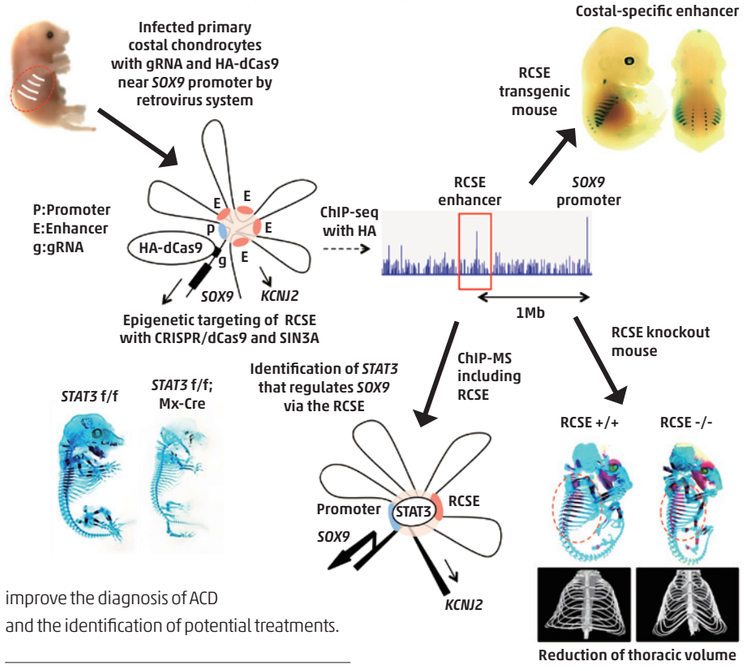
Cut-and-paste tool spots distant enhancer of cartilage genes

Patients with the congenital skeletal disorder acampomelic campomelic dysplasia (ACD) have mutations in their *SOX9* gene, which encodes a transcription factor protein that controls cartilage development. Some ACD patients have DNA changes located far away from *SOX9*, hinting at the existence of important but distant regulatory elements of *SOX9* expression.

A research team led by Hiroshi Asahara from TMDU used a range of techniques based on the precise gene editing tool known as CRISPR/Cas9 to closely investigate this upstream region. An enhancer of *SOX9* was identified within a DNA sequence that is highly conserved among different mammalian species and whose inhibition by the CRISPR/Cas9 tool reduced *SOX9* expression. Moreover, the enhancer (named as Rib Cage Specific Enhancer, RCSE in this study) functioned specifically in cartilage, and mice lacking this region in their genome had symptoms similar to ACD patients.

Incorporating CRISPR/Cas9 into a strategy to identify proteins associated with gene regulation complexes, the team showed that the STAT3 protein binds to the enhancer to assist its regulation of *SOX9*. These techniques could help improve the diagnosis of ACD and the identification of potential treatments.

***SOX9* enhancer for cartilage expression found responsible for ACD**



Dev. Cell, doi:10.1016/j.devcel.2018.07.024

[Reprinted with permission from *Dev. Cell*, doi:10.1016/j.devcel.2018.07.024]

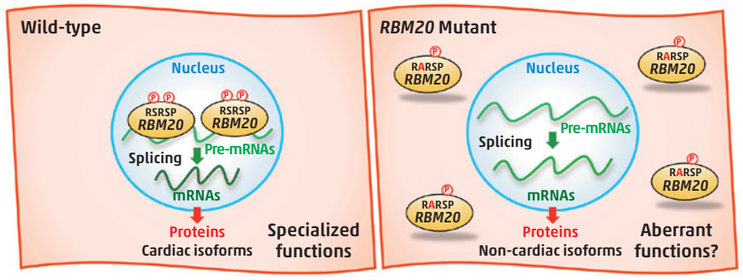
Cut it out: New research reveals key to regulation of *TTN* splicing in the heart

Dilated cardiomyopathy (DCM) is a disease in which the heart becomes enlarged and no longer pumps blood effectively. An inherited form of DCM (autosomal-dominant familial DCM) is linked to mutations in the RSRSP stretch of the gene *RBM20*. Understanding the functional deficits caused by the *RBM20* mutations is important for developing new DCM treatments. RBM20 regulates splicing of *TTN*, the gene encoding the largest known protein, titin, which is important for heart muscle function. Patients with DCM caused by *RBM20* mutations predominantly produce aberrant titin isoforms.

An international research team, led by Akinori Kimura and Hidehito Kuroyanagi from TMDU, showed for the first time that phosphorylation of the two serine residues in the RSRSP stretch was essential for nuclear localization, which allows RBM20 to interact with *TTN* pre-mRNA. They generated an *Rbm20*^{S637A} knock-in mouse, mimicking an un-phosphorylatable mutation found in a well-studied case of DCM. These mice exhibited aberrant titin isoform generation in the heart and developed DCM. Identification of the mechanism for nuclear localization of RBM20 will help guide efforts toward developing therapeutics for DCM patients.

Sci. Rep., doi:10.1038/s41598-018-26624-w

Missense mutations in the RSRSP stretch disrupt normal functions of RBM20.



(Left) In the wild-type, the two serine residues in the RSRSP stretch are phosphorylated and the RBM20 protein is localized in the nucleus, where RBM20 regulates alternative pre-mRNA splicing of its target genes so that cardiac isoforms of mRNAs are produced. (Right) In the *RBM20* missense mutant with a substitution in the RSRSP stretch, the mutant RBM20 proteins are no longer imported into the nucleus. Pre-mRNAs of the RBM20-target genes are processed into non-cardiac isoforms of mRNAs, which are then translated into non-cardiac protein isoforms, which may lack specialized functions and/or exert aberrant functions. The mutant RBM20 proteins retained in the cytoplasm may also exert aberrant functions.

[Modified from *Front. Mol. Biosci.*, doi: 10.3389/fmolb.2018.00105]

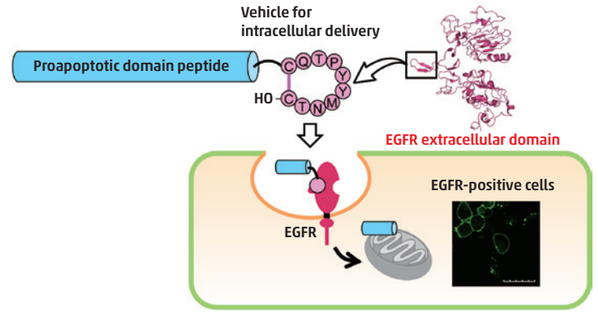
Targeting and treating EGFR-expressing cancer cells using peptides

Numerous types of cancer cells are known to overexpress the EGFR – epidermal growth factor receptor – therefore, targeting the EGFR can provide an efficient method for intracellularly delivering cargo, through a process known as endocytosis. CQTPYYMNTC is a cyclic peptide that mimics the dimerization arm of EGFR and can be used as a targeting moiety to promote cell uptake. Hirokazu Tamamura and coworkers from TMDU have shown that CQTPYYMNTC can be used to facilitate the cell internalization of $[KLAKLAK]_2$, a peptide that induces cell death but shows poor membrane permeability and cancer-cell specificity.

CQTPYYMNTC-mediated endocytosis was successfully demonstrated in EGFR-positive cell lines, and the key role of EGFR was supported by siRNA knockdown in A549 cells. The therapeutic potential of targeting using the peptide loop was demonstrated by treating EGFR-expressing cells with CQTPYYMNTC conjugated to $[KLAKLAK]_2$ through a cleavable linker. The peptide conjugate was shown to affect the viability of EGFR-expressing cells and to induce cell death, highlighting the potential of the system for both cancer-cell targeting and therapeutic delivery.

Bioconjug. Chem., doi:10.1021/acs.bioconjchem.8b00250

Mechanism of treating a cancer cell with a cyclic peptide



A cyclic decapeptide, which mimics the dimerization arm of the EGF receptor (EGFR), was previously found to be captured into cells. The authors have found the promising potential of this peptide as an intracellular delivery vehicle directed to EGFR-positive cells. The cellular uptake of the conjugated peptide, which was composed of the cyclic peptide, the proapoptotic domain peptide and a linker cleavable with a protease, was evaluated by treatment of EGFR-positive cells. Significant suppression of proliferation by the conjugated peptide was shown in a cell-viability assay.

[Reprinted with permission from *Bioconjug. Chem.*, doi:10.1021/acs.bioconjchem.8b00250]

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Iridium oxide micro pH sensor distinguishes active from arrested dental caries

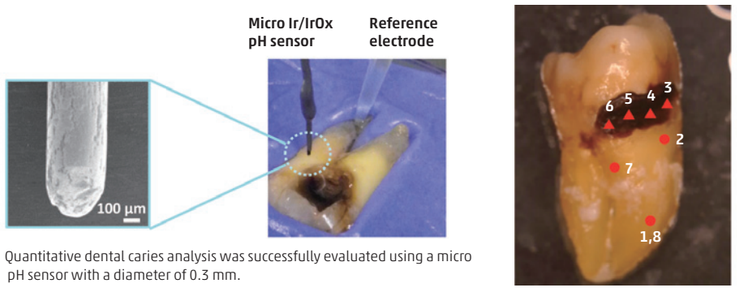
Dentists usually distinguish between active and arrested caries by visual inspection facilitated by a dental explorer, or radiography. However, these approaches risk damage to teeth or necessitate exposure to radiation, and successful diagnosis requires expertise. Bacteria interacting with carbohydrate on the tooth surface produce acid, and previous studies have shown that tooth pH could be diagnostically useful. However, available pH measuring devices have not been clinically convenient.

To address this, TMDU researchers, led by Yuji Miyahara and Miyuki Tabata, constructed a micro pH sensor from thin wires of iridium oxide. With spatial resolution of 0.3 mm, this device was able to measure the pH of active and arrested caries on extracted human teeth. Active (lowest pH) and arrested (low pH) caries were easily distinguished from each other and from healthy teeth on the basis of validated and reliable pH measurements. The categorization correlated highly with that of a dentist visually inspecting the teeth.

The use of a novel iridium oxide pH probe could aid in the diagnosis of hard-to-reach caries without the need for probing or X-rays.

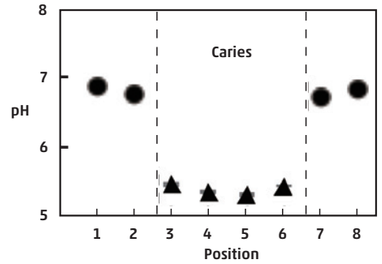
Anal. Chem., doi:10.1021/acs.analchem.8b00867

Quantitative analysis of caries activity using micro Ir/IrOx pH sensor



Quantitative dental caries analysis was successfully evaluated using a micro pH sensor with a diameter of 0.3 mm.

High spatial resolution pH mapping



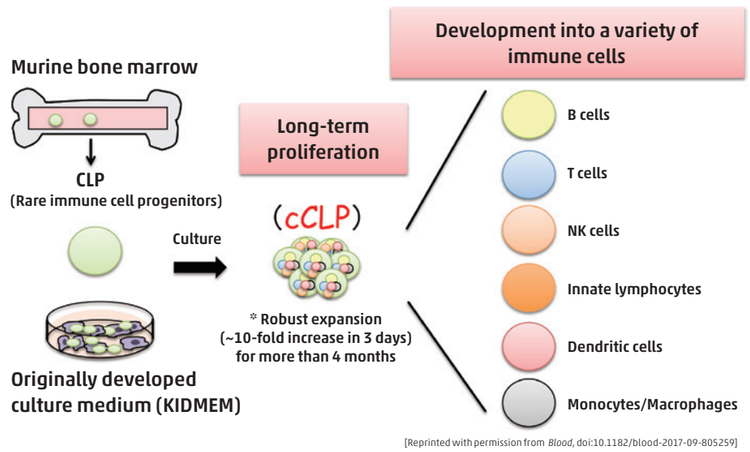
[Reprinted with permission from *Anal. Chem.*, doi:10.1021/acs.analchem.8b00867]

Breakthrough method for production of undifferentiated lymphoid progenitor cells

Stable cell lines that will proliferate over a long time are essential tools for almost all fields of disease research, yet maintaining a non-genetically-modified progenitor cell line (cells that are precursors to other cell types) has proven almost impossible. Common lymphoid progenitors (CLPs), which give rise to all subsets of lymphoid cells, have never been maintained as an unmodified cell line with stable differentiation potential. To address this, an international research team led by TMDU's Yohei Kawano has isolated uncommitted CLPs from mouse bone marrow and cultured them with a helper-cell line. Using a step-wise optimization process, they developed a specialized growth medium, named KIDMEM, that would support the long-term expansion of CLPs. More than half of the resulting CLP clones could be induced to differentiate into all tested lymphoid cells, and some myeloid cells, both *in vitro* and *in vivo*. Successful introduction of gene-expression vectors suggested that more advanced methods of targeted gene expression may also be possible. The ability to obtain large numbers of progenitor cells presents exciting new possibilities in the study of lymphocyte generation from CLPs.

Blood, doi:10.1182/blood-2017-09-805259

A simple, rapid and safe method for the robust expansion of hematopoietic progenitors, "cCLPs (cultured CLPs)"



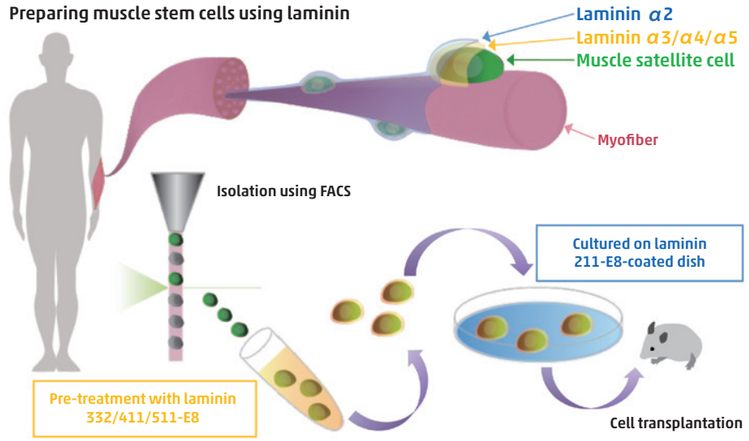
[Reprinted with permission from *Blood*, doi:10.1182/blood-2017-09-805259]

In vitro laminin treatment helps stem cells retain muscle regeneration ability

Satellite cells constitute muscle stem cells that might be useful in the treatment of Duchenne muscular dystrophy. However, these cells lose their natural stemness when they are transferred to an *in vitro* setting, hence there are limitations in using these cells in potential therapies. To solve this problem, Kana Ishii, Chihiro Akazawa and other experts from TMDU investigated the ability of laminin, a prominent extracellular matrix protein that exists in satellite cell niches within muscle, to retain the stemness of satellite cells *in vitro*. Notably, treatment with LM-E8, a fragment of laminin, promoted satellite cell growth such that stemness was retained. This was due to modified JNK and p38 signaling pathways, both of which control differentiation of satellite cells. When transferred to injured muscle tissue, satellite cells grown with LM-E8 increased the regeneration of muscle fibers, compared to regeneration using satellite cells grown without LM-E8. This method for growing satellite cells that retain their muscle regeneration capabilities may be effective as a therapy for patients with Duchenne muscular dystrophy.

Stem Cell Reports, doi: 10.1016/j.stemcr.2017.12.013

Preparing muscle stem cells using laminin



[Reprinted with permission from *Stem Cell Reports*, doi: 10.1016/j.stemcr.2017.12.013]

Prostate cancer-secreted hsa-miR-940 induces osteoblastic-type bone metastasis

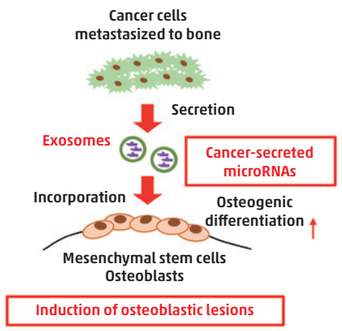
Prostate cancer, one of the most prevalent cancers in men globally, frequently metastasizes to bone. Bone metastases originating from prostate cancer are usually osteoblastic (bone-forming) in nature, and often associated with severe pain and other issues, such as pathological fractures. However, the mechanisms underlying the osteoblastic phenotype induced by prostate cancer are not fully understood.

MicroRNAs (miRNAs) transfer among cells via exosomes for intercellular communication and can modify the tumor microenvironment when secreted by cancer cells. Shingo Sato, Kyoko Hashimoto, *et al.* screened exosomal miRNAs secreted by a variety of human cancer cell lines and identified hsa-miR-940 released from prostate cancer cell lines as an osteotropic factor.

In vitro, hsa-miR-940 significantly promoted osteogenic differentiation of human mesenchymal stem cells by targeting two genes, *ARHGAP1* and *FAM134A*. Remarkably, even a breast cancer cell line, which usually induces an osteolytic (bone-resorbing) phenotype, produced widespread osteoblastic lesions in a bone metastasis mouse model when engineered to overexpress miR-940. The study suggests that hsa-miR-940 secreted from prostate cancer cells in the bone metastatic microenvironment promotes osteogenesis of mesenchymal stem cells to induce osteoblastic-type bone metastasis.

Proc. Natl. Acad. Sci. U. S. A.,
doi: 10.1073/pnas.1717363115

Osteoblastic bone metastasis induced by cancer-secreted microRNAs (miRNAs)



In the bone metastatic microenvironment, the crosstalk between metastasized cancer cells and the surrounding bone cells is critical for the formation of the osteoblastic or osteolytic phenotype. miRNAs are transferred between cells via exosomes and influence the phenotype of their recipient cells. The present study demonstrated that cancer-secreted miRNAs induced osteoblastic-type bone metastasis through promoting osteogenesis of mesenchymal stem cells.

Please contact us »» uraoffice.adm@tmd.ac.jp

Sharing expertise and groundbreaking research around the world

Our international exchange activities in research and education are based in three centers, in Ghana, Thailand and Chile. We further promote educational collaboration with Harvard Medical School, Imperial College London and Australian National University. We also have 107 affiliated schools in 32 countries.

Students join in an oversea program at UZ Leuven, Belgium.

International Faculty Development Course (IFDC) was held to introduce TMDU dental expertise to other countries, in Thailand.

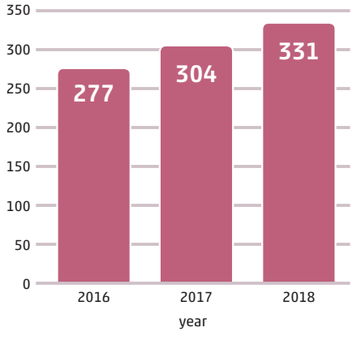
Researchers study infectious diseases at Ghana TMDU Research Collaboration Center.

● Our international collaboration centers
■ Our representative international education partners

Students participate in an exchange program with Australian National University.

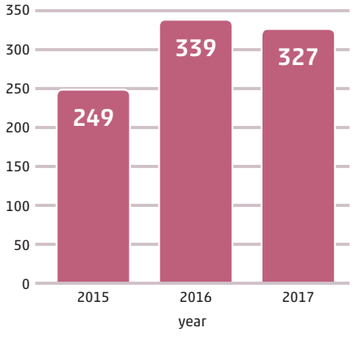
At TMDU's Latin American Collaborative Research Center in Chile, doctors from TMDU and Clinica Las Condes work on a project to prevent neoplasia of the colon and rectum.

International Students



International students comprise about 19% of TMDU's postgraduate student body. May, 2018

Students Sent Overseas



About 22% of eligible students study abroad. March, 2017

International students prepare traditional Japanese sushi-roll, called *eho-maki*.

The students enjoyed *setsubun*, a seasonal event, and wore *kimono*, Japan's traditional clothing.

In the summer, they played a watermelon-splitting game, called *suikawari*.

TMDU's medical students pursue clinical training in the United States at Harvard Medical School.

How do you like life at TMDU?

Kathryn Siongco (Philippines)

TMDU cultivates an environment suitable for the academic implementation of scientific endeavors among professionals from diverse backgrounds. This setting enabled me to progress in my graduate studies. I was able to develop ways to support the application of research in an atmosphere that also helps an individual development of proficiency in academia. The education offered provides assurance towards precise accumulation of knowledge and skills pertinent in dealing with the needs of the society.

Peerapong Wamasing (Thailand)

TMDU is not only one of the world's top-ranking universities where you can gain academic experience and knowledge, it also offers good opportunities to explore Japanese culture and traditions through various activities. As a foreign student, I can say that the foreign student support unit will help you with any problems. Studying and working at TMDU has been one of the greatest experiences in my life.

Studying abroad, the acquisition of a new language, and engaging in a new life environment could all be challenges but each one brings a lifetime of benefits. TMDU offers multiple opportunities, ranging from scholarships to the acquisition of high-level research skills. At TMDU, I received a high-quality education, training from supreme scientists, and the chance to unlock my inner potential. In addition, I was able to experience the rich culture of Japan, acquire a third language and exchange my culture with many international colleagues.

Hind Al-Busani (Yemen)

Main campus of TMDU (Ochanomizu / Yushima District)

Cultivating professionals with knowledge and humanity, thereby contributing to people's well-being

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