

Taking the Next Step from Regeneration to Neogenesis

Organ and Tissue Neogenesis Consortium Launched

In September 2017, based on the key concept of “taking the next step from regeneration to neogenesis,” TMDU established the Organ and Tissue Neogenesis Consortium consisting of nine multidisciplinary units that transcend the boundaries of traditional divisions and labs. Dr. Yasuyuki Yoshizawa, TMDU President, and Dr. Mamoru Watanabe, Executive Director and Executive Vice President responsible for Innovative Research and Collaboration, explained the background to the establishment of the consortium. Further, the unit leaders discussed how they intend to cultivate regenerative medicine, a field in which TMDU excels, in order to create a new paradigm of “organ and tissue neogenesis.”

Consortium established
Reinforcing TMDU's strengths
symbolized by the five petals of
a plum blossom

Yoshizawa: TMDU's predecessor, Tokyo National School of Dentistry, was established in 1928. The school was later renamed Tokyo Medical and Dental College, and then finally, in 1951, it was reorganized as Tokyo Medical and Dental University under Japan's new educational system. At that time three organizations were established, the Faculty of Medicine and the Faculty of Dentistry, the Research Institute for Dental Materials, which was the predecessor of the present-day Institute of Biomaterials and Bioengineering. Two more followed, the College of Liberal Arts and Sciences in 1965 and the Medical Research Institute in 1973. These five organizations are symbolized by the five petals of a plum blossom (TMDU's official symbol), representing each organization's concerted efforts to heal people, thereby enabling their lives to blossom. Now, after a long history of informal collaboration between these five organizations, the university has decided to create an overarching system to more effectively coordinate their respective strengths.

My first task upon becoming TMDU President was to implement an academic field-based system. Since TMDU is a relatively small medical university, we have combined those elements of education, research, and clinical practice to reinforce effective and ideal cooperation among all five organizations. The consortium takes this a step further. We have established the Institute of Research, led by Dr. Mamoru Watanabe, Executive Vice President of Innovative Research and Collaboration, and Dr. Akinori Kimura, Executive Senior Vice President of Research, Accredita-

tion and Evaluation, to strengthen the research capabilities of TMDU as a whole.

Research fields in which TMDU excels include regenerative medicine, intractable immune diseases, and genomic medicine. We will promote multidisciplinary research by leveraging the strengths of each field. Our first initiative is in the field of “organ and tissue neogenesis.” Although this is usually considered a facet of regenerative medicine, we call it “organ and tissue neogenesis” to express our ambition to pioneer a new academic field



Yasuyuki Yoshizawa
President
TMDU



Mamoru Watanabe
Executive Director and Executive Vice President
Innovative Research and Collaboration



that transcends regenerative medicine. This was the context in which we established the Organ and Tissue Neogenesis Consortium.

Watanabe: Let me discuss the Organ and Tissue Neogenesis Consortium. The consortium has three characteristics. Firstly, the research targets: Conventionally, regenerative medicine focuses on organs that do not regenerate once destroyed, such as the heart and the nervous system. In contrast, TMDU has conducted numerous research projects targeting organs with high regenerative capacity, such as the intestines, the liver, and the hair roots. Our concept of “taking the next step from re-

generation to neogenesis” envisions the creation of organs, taking regenerative medicine a step further. Secondly, the research methodology: Whereas regenerative medicine typically uses cell sheets or separated cells, we also tackle the creation of organs. We are working to realize “organoid medicine” through production of three-dimensional miniaturized organs. Thirdly, an emphasis on fostering next-generation researchers in an effort to pioneer a new discipline: We have invited young researchers working overseas to return to TMDU to take on leading roles in the consortium. They include Professor Takanori Takebe from Cincinnati Children's Hos-

pital Medical Center and Assistant Professor Shiro Yui from the University of Copenhagen.

Characteristics of the units
From basic to clinical research with
a view to organ production

Yoshizawa: Now I would like to address some questions to the leaders of the units. Professor Ichiya Sekiya of the Center for Stem Cell and Regenerative Medicine is spearheading TMDU's research into regenerative medicine. How do you propose to take the next step from regeneration to neogenesis?

Sekiya: I first used cells for treatment of cartilage in 2008. At that time, al-

though there were guidelines for treatment using human stem cells, safety criteria were vague and so we had to inch our way forward. But the clinical application of iPS cells and their transplantation to patients was a watershed. There has subsequently been further progress and the transplantation of iPS cells manipulated in various ways in advance is already underway.

Our innovative concept of “organ and tissue neogenesis” has an important bearing on the future of regenerative medicine and it is significant that TMDU is a pioneer. We aim to develop a new treatment for knee osteoarthritis involving simultaneous regeneration of joint cartilage and the meniscus.

Yui: I moved from the University of Copenhagen to TMDU in October 2017. I had studied gastroenterology at TMDU graduate school where I was involved in development of unique intestinal epithelial cells cultured using collagen fibers, which are known as “TMDU cells.” As a result of their transplantation into mice, we found that they can be used for treatment of intestinal inflammation.

As TMDU cells can serve as a model for inflamed intestinal epithelium, I think they will also be useful for development of new markers specific to such diseases as ulcerative colitis. By pioneering the application of TMDU cells to other organs and cancer cells, I want to enhance their versatility, expanding their application field to include various diseases and organs, and use them for personalized medicine, thus maximizing the utility of TMDU cells. Although TMDU is highly regarded overseas, awareness of TMDU cells is still low. TMDU should publicize the attributes of these eponymous cells that it has developed.

Nishimura: Our lab has been doing research on hair follicle stem cells and melanocyte stem cells. The objectives are to prevent loss of stem cells due to aging or disease, and furthermore to prevent loss of mini-organs or organ dysfunction by preserving remaining tissue stem cells and then increasing their number. This is the research approach promoted by the Stem Cell &



Professor
Ichiro Sekiya
Unit C2: Cartilage & Meniscus Neogeneration

Organoid Unit. For example, niche cells are known to play an important role in stem cell maintenance and self-renewal, but as one ages, the number of molecules maintaining stem cells decreases or stem cells themselves are lost. This mechanism has become clearer and we are trying to develop a method of controlling cells by utilizing it.

Okamoto: Our lab is working on the world’s first treatment using organoids for intestinal epithelia. The use of organoids is a key objective of this consortium and it is our lab’s mission to accomplish this. Through our research we want to demonstrate the effectiveness of organoid medicine and share the technology with researchers not only within the consortium but also around the world. Dr. Yui has already clarified the fundamental technology in the basic research he mentioned earlier. On the assumption that the research outcomes will be applied in the treatment of patients, we are accumulating cell technology to enhance safety and effectiveness.

Watanabe: Dr. Sekiya and Dr. Nishimura bring both clinical and research experience to this work. With regard to intestinal epithelium cells,

basic research by Dr. Yui and clinical studies by Dr. Okamoto are connected seamlessly, constituting a vital strength of TMDU.

Takebe: I used to be very clinically oriented. In fact, my original ambition was to become a surgeon and I was considering studying transplantation therapy in the U.S. Although I am pursuing basic research, what motivates me to continue this work is my determination to achieve results within 10 years that can lead to the saving of even a single patient. Otherwise, I may quit. Having set myself milestones, one every three years, I am advancing step by step. Some six years have passed since I started this research. The next three to four years will be devoted to research that benefits the prognosis of patients based on the outcomes of the basic research done so far. The “neogenesis” concept fits my research perfectly.

The current mainstream approach in medical research follows a reductive path from organs to cells and molecules. In contrast, our approach is “reverse reductionism.” In the case of the liver, by paying attention to those factors, besides hepatocytes, that enable the liver to function while also taking cells that play supportive roles into consideration, we have been doing research that augments our understanding of the organ. In this consortium, we are taking our research to a higher level by envisioning simultaneous regeneration of multiple organs, including the bile ducts, the pancreas, and tubular organs such as the duodenum, all of which are intimately related to the functions of the liver.

Fortunately, TMDU has many excellent intestine researchers conducting research with a view to practical applications. Thanks to the efforts of the doctors here today, we have a good chance of creating a new paradigm. This is a thrilling prospect.



Professor
Takanori Takebe
Organogenesis Unit

Fostering next-generation researchers
An environment where young researchers can actively transcend the limits of their disciplines

Watanabe: TMDU is also committed to fostering young researchers. We have established the Next Generation Researchers Development Unit* objective is to nurture highly capable individuals of the caliber of Dr. Takebe and Dr. Yui by providing research funding to selected young researchers.

Takebe: From the perspective of young researchers benefiting from this research funding, communication plays a vital role in helping them develop their capabilities. Also essential for young researchers are opportunities for discussion that transcend the conventional limits of departments, divisions, or specialties. I recently had an opportunity to discuss matters of mutual interest with Dr. Okamoto. It would certainly be desirable to create mechanisms encouraging labs in related fields to engage in fruitful cooperation, for example, by setting up a reading circle for researchers from different labs. In fact, this consortium is triggering such initiatives. As



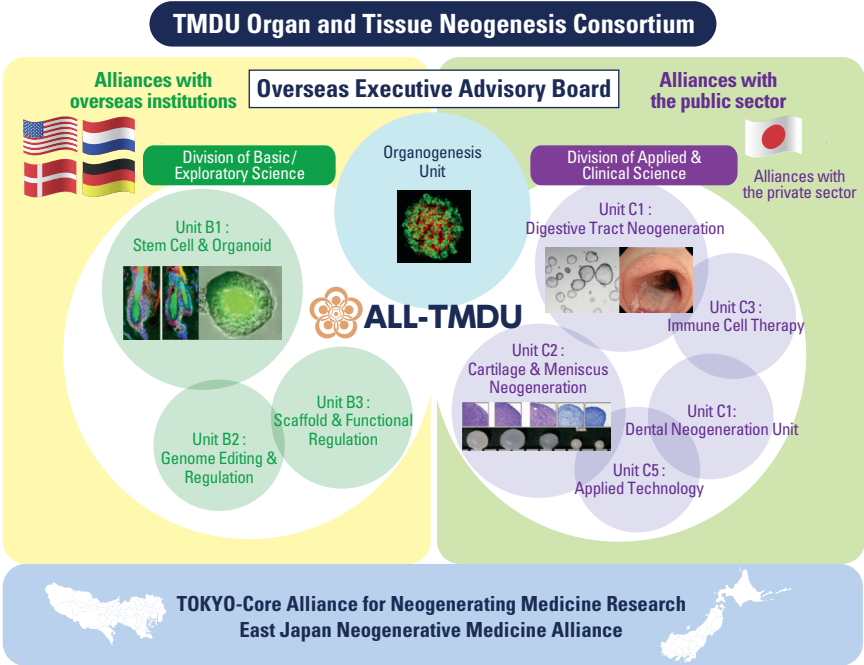
Professor
Emi Nishimura
Unit B1: Stem Cell & Organoid

a young researcher, I am eager to participate and contribute to their success.

Yui: I also think it is vital to cultivate an environment where many people can be involved in one’s research. Young researchers need to publicize their research themes in Japan and overseas in order to secure funding. In regard to TMDU cells, we need to communicate the value of our research far and wide so as to broaden their application field to include more diseases and organs rather than only focusing on a single disease. So the recent symposium on neogenerative medicine was a welcome opportunity.

Yoshizawa: In addition to supporting young researchers, research funding is also necessary for mid-career researchers within the framework of research expenditure. Young researchers who are receiving substantial funding are expected to rapidly establish their career trajectories.

Okamoto: I agree. But TMDU’s labs have become invigorated and are yielding good results, not least because of the participation of Dr. Takebe and Dr. Yui as well as excellent graduate students. While mid-career researchers should make efforts to secure funding, I



The Organ and Tissue Neogenesis Consortium consists of nine research units. In addition to promoting collaborative research involving individual units, multiple units, and other participating research institutions and companies, the consortium is also expected to foster the development of talented personnel who will play an active role internationally.

am also convinced of the need to communicate the attractiveness of research to undergraduate students and high-school students, who will be the next generation of researchers.

Watanabe: This consortium is also promoting industry-academia-government collaboration with a particular emphasis on collaboration with industry. Dr. Sekiya has been working with the private sector and we welcome his advice.

Industry-academia-government collaboration
Systematic support for industry-academia-government collaboration so researchers can concentrate on research

Sekiya: In recent years when applying for funding from the Japan Agency for Medical Research and Development (AMED), AMED requires that TMDU and the private-sector partner submit a joint research agreement clarifying the exit strategy. To ensure research outcomes are useful in practice, over and above doing excellent research and presenting great papers, it is necessary to target medicine that will be beneficial and practical with an eye to future inclusion in insurance coverage and commercialization. Although researchers previously tended to accumulate know-how while working alone, nowadays the know-how needs to be shared to secure substantial research funding because practical application of research outcomes is required. With this in mind, TMDU has already held two seminars in which Dr. Tetsuro Watabe and I discussed how best to set about securing sufficient research funding. We spoke about all the difficulties we had encountered and how we dealt with them. I would like other researchers to learn from our experience.

Yoshizawa: Recognizing that the university should systematically support researchers, TMDU is establishing a



Professor
Ryuichi Okamoto
Unit C1: Digestive Tract Neogeneration

system for that purpose. No doubt you have encountered difficulties in pursuing your research but the Open Innovation Institute will take care of miscellaneous tasks from now on.

Nishimura: Hair was not originally a particular interest of mine. Having suffered from atopic dermatitis as a child, I wanted to understand the mechanism of that disease and eventually became a dermatologist. In clinical practice, I came to recognize various issues and social needs. While searching for stem cells and endeavoring to elucidate their mechanism, I gravitated to my research theme, namely, graying hair and hair loss, which obviously could lead to commercial opportunities.

Yoshizawa: To date, collaboration with companies has largely been driven by individual researchers' personal connections. I want to make the open innovation system function officially and effectively to facilitate collaboration between the university and companies.

Watanabe: This consortium not only views collaboration as taking place within TMDU only but also emphasizes creating alliances with AMED and the Ministry of Education, Culture, Sports, Science and Technology, the Ministry



Assistant Professor
Shiro Yui
Unit C1: Digestive Tract Neogeneration

of Health, Labour and Welfare, and other governmental organizations. The field of neogenerative medicine and regenerative medicine is complicated, involving numerous technologies. Therefore within the open innovation system we have established an affiliate program that a company can join for a modest fee. Our objective is to tell the world about TMDU. We are also considering alliances with overseas institutions and also alliances with organizations nearby in Tokyo or East Japan. Starting with organ and tissue neogenesis, our initiative will expand its scope to include genomic medicine and intractable immune diseases.

Yoshizawa: I agree with you. It is often said that TMDU's considerable brand power is largely untapped and consequently our strengths have not gained the appropriate recognition they deserve. By launching this consortium and enhancing our organizational power so that we can compete effectively in the academic field, I believe TMDU's capabilities as a formidable contender on the global stage will be communicated. I greatly appreciate your cooperation in these endeavors.

Organ and Tissue Neogenesis Consortium Unit introduction

"Organ and Tissue Neogenesis Consortium" established in September 2017 consists of nine research units focusing on the research field that Tokyo Medical and Dental University has advantages. From re-regenerative medicine to neo-generative medicine, introduce what each unit aims and research contents.

Organogenesis Unit
Create organoids from human stem cells towards transplantation therapy and drug discovery
Professor Takanori Takebe
Cluster of Advanced Multidisciplinary Research, Institute of Research

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Stem cell & Organoid Unit
Contributing to the realization of health and longevity by controlling stem cells to elucidate the aging and regeneration of organs
Professor Emi Nishimura
Department of Stem Cell Biology, Medical Research Institute

2

Digestive Tract Neogeneration Unit
Preserving the health of the whole body through the creation of digestive organs, such as intestinal epithelial organoids
Professor Ryuichi Okamoto
Center for Stem Cell and Regenerative Medicine, Institute of Research

3

Genome Editing & Regulation Unit
Creating disease models using genome editing technology, and developing mRNA drugs
Professor Fumitoshi Ishino
Department of Epigenetics, Medical Research Institute

4

Cartilage & Meniscus Neogeneration Unit
Developing new therapies, such as the regeneration of cartilage and meniscus using stem cells
Professor Ichiro Sekiya
Center for Stem Cell and Regenerative Medicine, Institute of Research

5

Scaffold & Functional Regulation Unit
Assisting the field of organ and tissue neogenesis with unprecedented biomaterials
Professor Akio Kishida
Department of Material-Based Medical Engineering, Institute of Biomaterials and Bioengineering

6

Immune Cell Therapy Unit
Developing immune cell therapies and strengthening and creating immune functions, such as the controlling of organ engraftment
Professor Tomohiro Morio
Department of Pediatrics and Developmental Biology, Graduate School of Medical and Dental Sciences

7

Dental Neogeneration Unit
Hard and soft tissue regeneration with stem cell and cell sheet technology
Professor Takanori Iwata
Department of Periodontology, Graduate School of Medical and Dental Sciences

8

Applied Technology Unit
Ensuring microbial safety in regenerative medicine, and developing comprehensive and rapid microbial testing systems
Associate Professor Norio Shimizu
Center for Stem Cell and Regenerative Medicine, Institute of Research

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