TOKYO MEDICAL AND DENTAL UNIVERSITY

TMDU

Research Activities 2016

TMDU – Committed to pioneering medical research

Contents

TMDU Quick Facts

University Ranking by Subject

	Medicine	Dentistry
National Rank	4	1
World Rank	101-150	6

SOURCE: QS World University Ranking by Subject 2015

University Ranking by Faculty / Students

Ranked #1 in Japan and #11 in the World

	Students	Faculty Staff
Graduate	1,492	747
Undergraduate	1,494	

SOURCE: QS World University Ranking 2015

World's Best Small Universities

Ranked #1 in Japan and #12 in the World

SOURCE: Times Higher Education World's Best Small Universities 2016

University Hospitals Promoting Our Research

	Beds	Outpatients Per Year
Medical Hospital	763	575,000
Dental Hospital	60	450,000 *

* Ranked #1 among dental hospitals in Japan

International Students

	No. of Intl.Students	No. of Countries
Graduate Schools	203*	36

* Ranked #1 among medical graduate schools in Japan

Message from the President

President

吉澤靖之

Yasuyuki Yoshizawa

Since the Tokyo Medical and Dental University (TMDU) was established in 1928 as the first national dental school in Japan, TMDU has grown into a comprehensive medical university by expanding into medicine and nursing, and has become one of the most influential medical research institutions in the world. TMDU is currently located in the Ochanomizu / Yushima district in central Tokyo, which has long been considered the traditional birthplace of scholarship in Japan since the 17th century.

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 foster our students under the TMDU Vision, "Cultivating Professionals with Knowledge and Humanity, thereby Contributing to People's Well-being".

On our campus we have two university hospitals, 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 accepts the highest number of patients with oral disease in the country. A large number of patients visiting our hospitals give us strong motivation and the opportunity for medical and dental research in order to understand and treat intractable diseases. For example, our research on regenerative medicine originates from clinical needs arising at these hospitals, as will be explained later in detail in our Features of TMDU Research section. In addition, with an eye on the Tokyo 2020 Olympic and Paralympic Games, we have established the Sports Science Organization to provide integrated care for athletes and apply our scientific knowledge to public health, and have invited a gold medalist in the hammer throw at the 2004 Athens Olympics to serve as a professor in the organization.

In addition to our schools and university hospitals, we have two research institutes, the Medical Research Institute and the Institute of Biomaterials and Bioengineering. Researchers there collaborate with industry to develop practical clinical applications for the benefit of society. In 2015, we also launched two venture companies involved in innovative medical instruments (endoscopic surgery robot) and drug development (heteroduplex oligonucleotide). We promote such translational research in order to link basic research with clinically applicable products. We are also conducting collaborative investigations and education at our overseas research centers in Thailand, Ghana and Chile.

In this brochure, we highlight typical 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 nevertheless confident that these highlights will give you an idea of the exciting opportunities available here at TMDU for collaboration and study open to researchers and students worldwide.

Interview with Ikuo Morita, Executive Director

Medical and Dental Science – serving patients and society

Ikuo Morita
Executive Director /
Vice President of Research and
International Cooperation at TMDU

Unique and ongoing results in genome and regenerative medicine

—— What are the distinctive characteristics of TMDU research?

Dr. Morita: Our research is goal oriented, based on both medical and dental science. Of course, considering a thesis is important, however, we are focused more on the benefit for patients, which can come from new medical methods, medicines, and devices.

Unlike other medical and dental science schools, we incorporate two unique institutes, the Medical Research Institute and the Institute of Biomaterials and Bioengineering, where researchers study in collaboration with our Faculty of Medicine and Faculty of Dentistry.

—— Which fields of study are emphasized at TMDU?

Dr. Morita: First, I would like to highlight the genome research that is conducted mainly at the Medical Research Institute. There, we focus on cancer, developmental anomalies, and cerebroneuropathies, such as Alzheimer's disease. We are practicing personalized medicine and preemptive medicine by analyzing genomes, including epigenomes, and comparing genomic data with clinical data provided by our Medical Hospital. Recent accomplishments include the discovery of a gene causing Scirrhous stomach cancer, and a study based on proteome analysis and system biology, which proved that a phosphorylated protein is seen at the early stages of Alzheimer's disease. Both of these lead to personalized preventive medicine and treatment.

As for preemptive medicine, successful collaborative research with Sony Corp. on the interpretation of genomic information has made us start a new business providing information about the risk of cancer and lifestyle diseases based on genome analysis data—a "Genome and Health Information Service".

Another highlight is regenerative medicine, which is mainly implemented by clinical researchers in the Faculty of Medicine. TMDU stands among the great research institutes in regenerative medicine in Japan, which include the Center for iPS Cell Research and Application at Kyoto University directed by Professor Shinya Yamanaka. TMDU is one of the leading institutes in Eastern Japan. TMDU's main approach is to use autologous stem cells from patients, not iPS Cells. Notably, the treatment of an extruded injured meniscus by transplantation of synovial stem cells has already been under clinical trial. Also, regeneration of large intestine epithelium cells will be under the trial within one year, offering great hope for the treatment of ulcerative colitis and Crohn's disease, which unfortunately lack effective treatments. Other professors are researching stem cells' quality maintenance and standardization, alongside the above trials.

In addition, researchers are studying the mechanism of the generation of gray hair and hair loss, which could lead to the development of preventive approaches and could be considered a kind of regenerative medicine, even though it does not utilize stem cells.

Dental university pursues collaborative medical and engineering research

—— TMDU was established as Tokyo National School of Dentistry in 1928, and the Faculty of Medicine was launched later. Is the tradition of the dental university affecting current research activities?

Dr. Morita: Of course. The Faculty of Dentistry has developed the materials for regeneration and repair of teeth with the collaboration of the Institute of Biomaterials and Bioengineering and medical companies. These materials include dental adhesive and titanium alloy wires for braces that are currently used for dental treatments. They also have developed a technique for sintering a powder of hydroxyapatite—a major component of bones and teeth—and making artificial bones and teeth roots for practical use.

Even in the Faculty of Medicine, basic research on bones and other hard tissues such as teeth is broadly conducted and many related medical departments exist, including Orthopaedic Surgery.

The combination of the traditions of dental science and regenerative medicine has started bringing great results. One of them is a technique for regeneration of alveolar bone. Alveolar bones can disappear due to periodontal disease, and this might complicate dental implants. With this new technique, however, cultured mesenchymal stem cells from a pulled tooth can be transformed into a membrane and applied to the remaining alveolar bones so that they regenerate. The culturing substrate has been developed in collaboration with Dai Nippon Printing Co., Ltd. Trials on rats have shown the efficacy of this method and efforts are underway to pursue human trials.

—— What kinds of materials are being studied in the Institute of Biomaterials and Bioengineering?

Dr. Morita: One of the goals of this institute is to develop biocompatible materials, so researchers are utilizing all sorts of materials, such as metals, organic materials and inorganic materials. They are also researching the sensors required to monitor a human body's status, and are developing assisting robots for surgery.

The research that brings engineering techniques to medical study is largely applied, not only in this institute. For example, our Urology team has developed a 3-D Head Mount Display for surgeons in collaboration with Sony Corp. The display device is a modified gaming headset that provides images from an endoscope, which means the surgeon does not need to view images on a standard monitor. This can resolve the operator's usual problem of having to watch both his hands and the monitor simultaneously, and therefore can improve surgery processes. The Head Mount Display went on the market in 2013 and has been approved for sale in Europe and the United States. Currently, this newly developed display is being used in all urology surgeries at TMDU and by other departments and hospitals.

Successful alliances between academia and industry provide models for other universities

—— It is necessary to collaborate with industry in order to market new medical methods, medicine and devices, isn't it?

Dr. Morita: People may not know, but TMDU is actually highly regarded as a leader in building academic-industrial alliances and as an excellent model of this approach.

In order to develop academic-industrial alliance systems, both defensive and offensive approaches are required: "Defensive" includes, for example, creating regulations concerning bioethics and conflicts-of-interest, while "offensive" includes intellectual property strategy, policy advocacy, and strategies for attracting the attention of industry. TMDU, primarily led by the Research Center for Industry Alliances, proactively provides information to companies, launches new ventures, and holds seminars to educate its own professors about regulations and intellectual property strategy.

We also have established an organization called medU-net (Japanese Association of Medical University Network for Technology Transfer). More than 80 academic institutions, such as medical universities, as well as more than 85 companies seeking information about research results, have participated in medU-net. MedU-net plays an effective role as a platform between industry and academia and provides the opportunity to share the TMDU-grown system of academia-industry collaboration. Moreover, through medU-net, TMDU itself can initiate relationships with companies.

The above efforts resulted in substantial collaborative research with companies and 788 contracts between industry and TMDU in FY 2014. By overcoming the inherent difficulties, venture companies that produce nucleic acid medicine and robots have been established, and in FY 2015 TMDU's total income from patent licensing and lump-sum payments from new ventures will place it among the highest ranked of all Japanese universities.

—— We have heard about your vigorous activities to provide materials to researchers and companies, both domestic and international. Please tell us more.

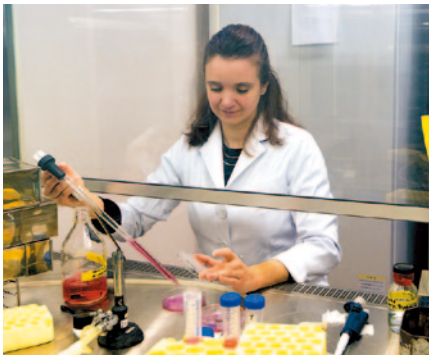
Dr. Morita: TMDU owns a "Mice Key Bank" with more than 100 kinds of experimental mice. Also, many of our researchers own unique antibodies. With material transfer agreements (MTA), this research material is available upon request to outside researchers. In addition, an undocumented MTA is also available to provide material within three days for 28 research institutes from Japan, Europe and the United States, such as Stanford University.

—— TMDU is not only conducting high-level basic research but also making efforts to collaborate with industry so as to achieve results that benefit patients. What is its main direction for the future?

Dr. Morita: We would like to promote globalization of research with the goal of improving research abilities and creating superior outcomes.

TMDU is the top medical university in Japan in terms of the number of accepted international students. We also have international institutes in Chile, Thailand, and Ghana, and 30 – 40 % of our current students have studied in one of those international institutes, or at Harvard Medical School in Massachusetts or Imperial College London.

Unfortunately, however, international collaborative research efforts are few. So our Research Administration Division is actively promoting the idea by providing our research scientists with information about outside researchers and their study results. I hope this brochure will be a good step in promoting new international relations and a robust network among researchers around the world.



International researcher

From research to clinic: Medical Hospital

From clinic to research: Dental Hospital

Novel oligonucleotide based on DNA/RNA heteroduplex structures: Opening a new horizon for human gene therapy

Takanori Yokota

Professor of Neurology and Neurological Science at TMDU

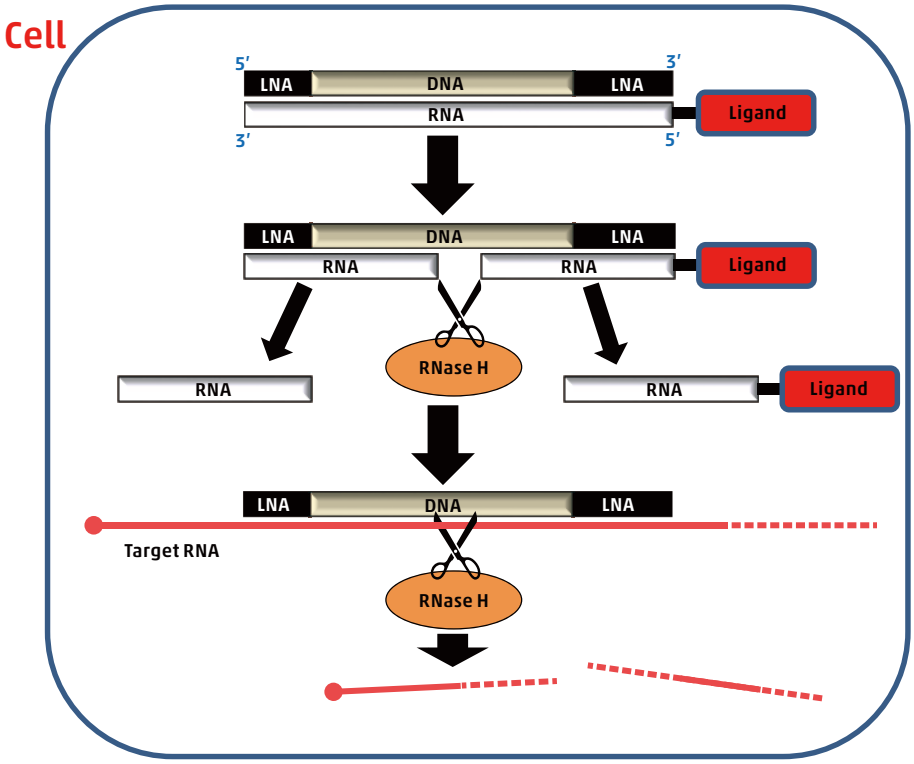
Dr. Yokota received his MD from TMDU. His postdoctoral research was performed in several institutes including Tokyo Metropolitan Neurological Hospital and Sanford-Burnham Medical Research Institute in the United States. He returned to TMDU as a Junior Associate Professor of Neurology in 2000, became an Associate Professor of Neurology and Neurological Science in 2004, and assumed his present post in 2009.

A brand-new oligonucleotide drug, heteroduplex oligonucleotide

Two major types of RNA targeting oligonucleotide drugs are currently being developed as therapeutic platforms for the reduction of target gene expression: short interfering RNA (siRNA) and RNase H dependent antisense oligonucleotides (ASO). Although the design of oligonucleotides has progressed considerably, methods that further increase the potency of oligonucleotide drugs and improve their safety and tolerability are highly desirable, as with any medical products. The insufficient delivery and poor cellular uptake of oligonucleotides, and their inefficient access to target RNA, are major impediments to their use in *in vivo* gene silencing.

I developed a novel short DNA/RNA heteroduplex oligonucleotide (HDO). This HDO has a structure different from the double-stranded RNA used for siRNA and from the single-stranded DNA used for ASO, and also different functional molecular mechanisms from siRNA or ASO in cells. HDO is composed of DNA/locked nucleic acid (LNA) gapmer as ASO and its complementary RNA (cRNA). When α-tocopherol (vitamin E) is conjugated to cRNA of HDO, α-tocopherol can improve the delivery of HDO to the liver, and the gapmer DNA strand is activated by its release from HDO due to cleavage of cRNA by cellular nuclease (Fig.1).

Fig. 1. Molecular mechanism of HDO in cells



Unique structure enables high efficacy with less adverse effect

When α-tocopherol (Toc) as a drug delivery moiety is conjugated to ASO directly without any linker (Fig.2), its silencing effect is reduced because conjugated lipid interferes with the mechanisms of ASO. On the other hand, Toc-HDO is significantly more potent at reducing the target messenger RNA compared to the parent ASO (Fig.2). I measured the Effective Dose 50 (ED_{50})

–the dose required for a 50% reduction of the target gene. Toc-HDO targeting *Apolipoprotein B* (*ApoB*) mRNA (ED_{50}, 0.038 mg/kg) was 22.2 times more potent than the parent ASO (ED_{50}, 0.841 mg/kg) in mouse liver. In addition to lowering *ApoB* mRNA, the Toc-HDO reduced serum low-density lipoprotein (LDL)–cholesterol. Moreover, the pharmacological effects lasted more than one month at a 0.75 mg/kg of Toc-HDO injection only, not at ASO injection.

A significant improvement in activity was also observed when targeting another gene in the liver. In addition, the Toc-HDO using another chemically modified nucleic acid instead of LNA in the wing portion of the DNA strand showed a similarly enhanced potency. This HDO technique can be applied to any ASOs that have been previously reported. Furthermore, the high potency of the suppression of the target messenger RNA was observed not only in rodents but also in non-human primates.

Mipomersen, the first oligonucleotide drug, was approved by the U.S. FDA, but not by the EU, due to liver toxicity. A reduction in liver dysfunction was observed when using high potency Toc-HDO, probably because much smaller doses of nucleotide were administered, than when using the parent ASO with the same silencing effect. These results suggest that DNA/RNA heteroduplex structures can be the basis for a novel class of oligonucleotide drugs, opening a new horizon for human gene therapy.

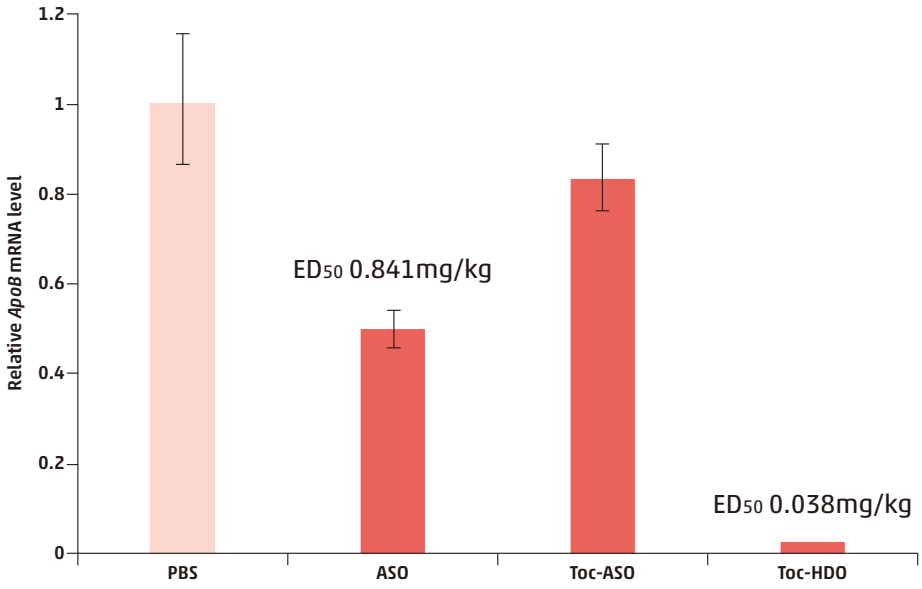


Fig. 2. High efficacy of the Toc-HDO

When Toc-HDO that targets mouse *Apolipoprotein B* (*ApoB*) mRNA was intravenously injected into mice, it produced a greater reduction of *ApoB* mRNA compared with an equivalent dose of the parent ASO without α-tocopherol, or with α-tocopherol that is directly conjugated to ASO.

From lab to clinical use

To commercialize this highly promising HDO technology, a start-up company named Rena Therapeutics Inc. was established in January, 2015 as the fourth venture company launched by TMDU. Its mission is to address unmet medical needs by creating a novel class of nucleic acid medicine with unique and effective drug delivery systems and chemical modifications. On April 20, 2015, six million Japanese yen Series A financing from Innovation Network Corporation of Japan, DBJ Capital Co., Ltd. and KSP Inc. was completed and Rena's research and development operations kicked into gear. The company name "RENA" is an acronym for Renaissance of Nucleic Acid, reflecting the company's mission to revive nucleic acid medicine through research and development of this HDO technology, especially pursuing practical clinical applications.

TMDU and co-patent holder Osaka University granted the exclusive license of the HDO patent family to Rena, and Rena will make this HDO technology applicable to nucleic acid medicine as quickly as possible through cooperation with biotech and pharmaceutical companies. Its revenue model comprises three parts: 1. The research and development of HDO seeds and pipelines up to the preclinical or early clinical stage, and licensing to pharmaceutical companies; 2. The creation of co-development project (s) of HDO technology with partner companies as collaborative research or alliances; and, 3. The licensing and sub-licensing of the HDO patent family and related Rena patents to outside companies.

Although Rena's first important role will be to cross a deep "Death Valley" where many obstacles are expected, this HDO technology has such strong competitive advantages for drug delivery that we see more than enough potential to cross through the valley. For the next few years, Rena plans to focus on developing delivery modifications of HDO technology to develop it for drug pipelines. Through these research, clinical and business development activities, TMDU and Rena hope to increase HDO technology's potential further so as to enter clinical trials as early as possible.

DNA/RNA heteroduplex oligonucleotide for highly efficient gene silencing,
Nature Communications, 6:7969 doi: 10.1038/ncomms 8969.

Innovative cloning-free CRISPR/Cas9 system: Efficiently creating targeted model mice

Kohichi Tanaka

Professor of Molecular Neuroscience at TMDU

Dr. Tanaka received his MD and PhD from Niigata University. His postdoctoral research was performed with the Neural Network Team at RIKEN. He became a section chief of Neurodegenerative Diseases at the National Institute of Neuroscience in 1993 and assumed his present post at TMDU in 1998.

Genetic engineering in mice

The mouse has become the most commonly used animal in the biological and medical sciences because its genome can be specifically modified with one-nucleotide precision. Recent advances in genomic microarray and next generation sequencing technologies have identified many genetic variants associated with common and complex human diseases. To determine whether these variants are causal for specific human diseases, we need to investigate their biological functions. One possible approach to address this is the use of mouse models that incorporate the identified genetic variants. Although traditional gene targeting in embryonic stem (ES) cells is suitable for carrying any desired genetic modifications, it is laborious and time-consuming.

The development of engineered zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and, most recently, clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR-associated endonucleases (Cas) is revolutionizing genetic engineering in mice. These technologies depend on the cell processes triggered by the DNA double strand break (DSB) in specific DNA sequences (Fig.1). The non-homologous end-joining (NHEJ) pathway, which repairs DNA damage in the absence of template DNA, results in the introduction of random insertions or deletions that disrupt gene function. In contrast to NHEJ, homology-directed repair (HDR) uses a DNA donor template that is homologous to the DSB site to achieve precise recombination. These methods provide exciting and groundbreaking opportunities, enabling direct and rapid gene targeting in fertilized mouse eggs, with no need for ES cells. Using *in vivo* genome editing, genetically engineered mice can be created in months rather than years.

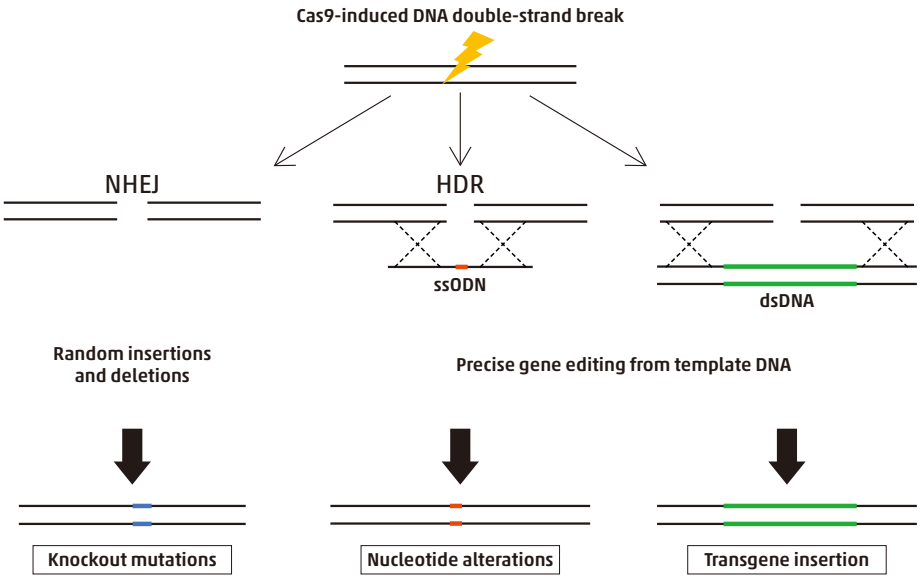


Fig. 1. Cas9-induced genome editing

Cas9 induces double-strand (ds) DNA breaks. Then, DNA is repaired by either non-homologous end joining (NHEJ) or homology-directed repair (HDR). NHEJ results in the introduction of random insertions or deletions that may disrupt gene function. HDR with exogenous 'repair templates', such as single-stranded donor oligonucleotides (ssODN) or ds DNA, can lead to the introduction of precise nucleotide substitutions or transgene insertion. Dashed lines indicate homologous recombination.

Cloning-free CRISPR/Cas system

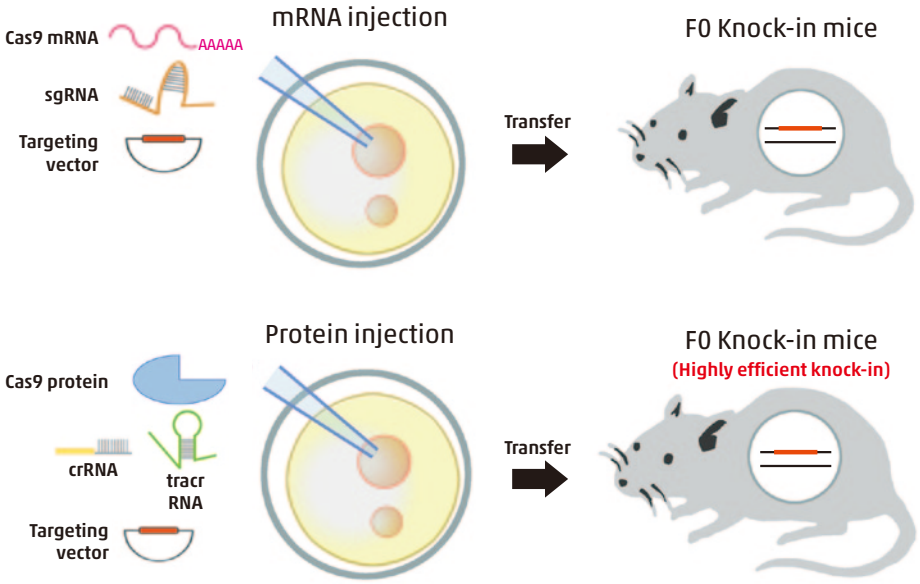
In contrast to ZFNs and TALENs, the most recent CRISPR/Cas system is remarkably

simple and efficient. Consequently, a flood of studies using CRISPR/Cas-mediated *in vivo* genome editing have reported the production of knockout mice and knock-in mice that carry single nucleotide substitutions using oligo DNA donors. Yet there has been only one report of the successful production of knock-in mice that carry reporter gene cassettes, which are essential tools for analyzing complex tissues, such as brain, *in vivo*. In that case, the reported efficacy of the targeted insertion of the reporter gene was only about 10%. Moreover, since founder F0 mice are often mosaic, transmission of the targeted allele to the next F1 generation is not guaranteed. The low success rates and the mosaicism of gene-cassette carrying knock-in mice limit the applicability of CRISPR/Cas-mediated *in vivo* genome editing.

The CRISPR/Cas system was initially reported as an adaptive immune system in bacteria, consisting of three components, including Cas9 nuclease and two small RNAs—the CRISPR RNA (crRNA), which guides the Cas9 complex to the target sequence, and trans-activating crRNA (tracrRNA), which binds to crRNA and forms a ribonucleoprotein complex with Cas9 nuclease. When it was harnessed as a genome editing tool, the dual-crRNA:tracrRNA was engineered as a chimeric single guide RNA (sgRNA). The CRISPR/Cas system consisting of two components - Cas9 nuclease and sgRNA - became the standard approach in the field of genome editing due to its enhanced convenience and robust targeting. However, it is still unknown whether the commonly used sgRNA works more efficiently than the dual-crRNA:tracrRNA, especially for the production of knock-in mice that carry reporter gene cassettes.

I have now overcome this issue by developing an innovative, highly efficient CRISPR/Cas system (Fig.2), which resulted in the targeted insertion of a long gene cassette, including enhanced green fluorescent protein (EGFP), into the mouse genome in fertilized eggs with efficiency of up to approximately 50%. I reproduced the natural state of the CRISPR/Cas system, which consists of three components: Cas9 protein, chemically synthesized crRNA, and tracrRNA, instead of the commonly used two-component system consisting of Cas9 mRNA and sgRNA. This has led to extremely high efficiency in several respects. First, the direct delivery of Cas9 protein, chemically synthesized crRNA and tracrRNA, and targeting vector into the pronuclei of zygotes allowed for the highly efficient generation of knock-in mice carrying gene cassettes in the endogenous gene. Second, the CRISPR/Cas vector construction and in vitro RNA transcription could be omitted by using commercially available Cas9 protein and chemically synthesized crRNA and tracrRNA, leading to a cloning-free CRISPR/Cas system. Third, the Cas9 protein-RNA complex was rapidly degraded in embryos, thus reducing the likelihood of off-target effects and mosaicism. Thus, the cloning-free CRISPR/Cas system further provides highly convenient and accurate gene modification, and its successful transmission to the next generation.

Fig. 2. Cloning-free CRISPR/Cas9 system



The application for the cloning-free CRISPR/Cas9 system

This improved CRISPR/Cas system will be useful for a variety of applications, including the creation of humanized mice for the modeling of genetic diseases, drug metabolisms, immunity, and infectious diseases. Further, accurate targeted insertion will improve the safety of gene therapy in human patients in the future. Taken together, our streamlined cloning-free CRISPR/Cas-mediated *in vivo* genome editing system provides highly efficient and extremely convenient one-step generation of knockout and knock-in animals, leading to the acceleration of *in vivo* functional genomic research.

Cloning-free CRISPR/Cas system facilitates functional cassette knock-in mice, *Genome Biol*, doi: 10.1186/s13059-015-0653-x.

Regenerative medicine for inflammatory bowel disease

Mamoru Watanabe
Vice President of TMDU
Professor of Gastroenterology and Hepatology at TMDU

Q You are well along in research involving colon epithelial stem cells. Please explain briefly.

A: We succeeded in establishing our own method (called the TMDU-method) to maintain and efficiently expand mice colonic epithelial stem cells *in vitro*. By using the TMDU-method, we also succeeded in preparing a large number of colonic epithelial stem cells starting from a single cell, and regenerated damaged colonic mucosa by *in vivo* transplantation of those *ex vivo* expanded stem cells. We are now ready to expand *human* colonic epithelial stem cells *in vitro* by using endoscopic biopsy specimens as the starting material.

Q What brought you to this research? Did it have anything to do with TMDU's perceived strengths?

A: "Mucosal healing" (MH) has recently become the most important goal of treatment of inflammatory bowel disease (IBD). However, up to 40% of IBD patients currently fail to achieve MH. Therefore, a new therapeutic approach—such as regenerative medicine—is urgently needed. TMDU has long been the world's leading institution in the treatment of IBD, and enteroscopy techniques. In 2012, we started running the Advanced Clinical Center for Inflammatory Bowel Diseases (ACCIBD), which is dedicated solely to the treatment of IBD. Since then, an increasing number of newly diagnosed IBD patients are rushing to our clinical center. Through the treatment of these patients, we have become quite sure that a new therapeutic approach is needed to improve the prognosis and treatment of refractory patients.

Dr. Watanabe completed his medical and graduate school at Keio University, where he received his MD and PhD. He performed postdoctoral research at Harvard Medical School in Boston, Massachusetts. He became an Instructor at Keio University Hospital in 1992, then an Associate Professor in 1996. He joined TMDU as a Professor and Chairman of the Department of Gastroenterology and Hepatology in 2000. He became the Vice President of TMDU in 2016.

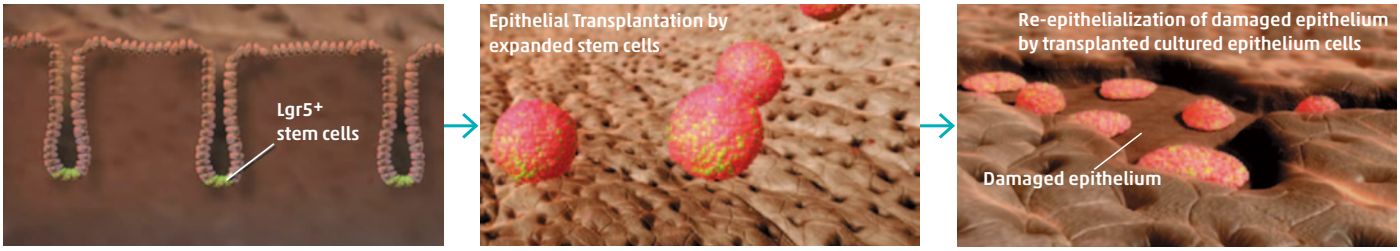
Q Stem cells, like the iPS and ES, have made headlines in regenerative medicine in recent years. Meanwhile, you are focused on epithelial cells. Why?

A: We always start thinking from the bedside, not from the bench. We know that pluripotent cells, such as iPS cells and ES cells, surely have great scientific, as well as therapeutic, potential. However, to use those cells in clinical applications, we may need to clear various technical as well as ethical problems, which may take many years to solve. In the meantime, why not use adult tissue stem cells? They have low risk of tumorigenicity and do not require time for differentiation. Moreover, we already have a method for preparing the required number of donor stem cells from a small piece of mucosal tissue. This will make it possible to establish and provide stem cell-based regenerative therapy for IBD patients in a minimum period of time.

Q You have been successful in culturing small intestine epithelial cells *in vitro* and transplanting them to the colon, too. In this case, transplanted cells showed the properties of small intestine cells even months later. What might this accomplishment mean?

A: Firstly, it provides an important scientific message that adult somatic stem cells can maintain their identities even in an orthotopic environment. This indicates that those stem cell identities are tightly programmed in the cell - intrinsically - and may not be easily affected by extrinsic signals. Future studies may reveal the mechanism behind how such a tight identity can be maintained in each stem cell. Secondly, from a therapeutic point of view, the data guarantees the therapeutic potential of *ex vivo* cultured small intestinal stem cells. Thus, the data open a way to use stem cell transplantation to treat refractory small intestinal ulcers that may appear in Crohn's disease, Behcet's disease, radiation enteritis or NSAID-induced enteropathy.

Colonic stem cell culture and stem cell transplantation to damaged epithelium



Q How do you expect your research to develop in the future? What about the possibility of a joint study with international researchers?

A: Currently, we are doing our best to apply our stem cell culture method and transplantation technique to treat refractory ulcers of IBD patients. There still remain plenty of technical problems and regulatory issues that need to be solved, but we now feel quite confident that we are very close to reaching our goal. Also, we are running several basic research projects to find the answer to questions raised in such areas as stem cell biology, mucosal immunology and gastrointestinal oncology. We definitely welcome joint studies with international researchers to share both scientific and therapeutic interests in various areas.

Functional engraftment of colon epithelium expanded *in vitro* from a single adult Lgr5+ stem cell, *Nat. Med.*, doi: 10.1038/nm.2695.
Transplantation of expanded fetal intestinal progenitors contributes to colon regeneration after injury, *Cell Stem Cell*, doi: 10.1016/j.stem.2013.09.015.
Small intestinal stem cell identity is maintained with functional Paneth cells in heterotopically grafted epithelium onto the colon, *Genes Dev.*, doi: 10.1101/gad.245233.114.

Innovative Researchers

Stem cell aging study for tissue regeneration

Emi Nishimura
Professor of Stem Cell Biology at TMDU

Diffuse hair loss radially extends with aging. Shown is a 28-month-old wild-type mouse (C57BL/6N).

In aging societies, it is crucial to understand the mechanisms of physiological aging and the basis for aging-associated diseases. Stem cell systems play fundamental roles in the homeostatic maintenance of many tissues and organs. I did my dermatology residency at Kyoto University Hospital and earned my Ph.D. at Kyoto University, studying melanocyte (pigment cell) development. We subsequently identified melanocyte stem cells as reservoirs for melanocytes in skin and hair follicles (*Nature*, doi: 10.1038/416854a), and then revealed that aging-associated depletion of the population results in graying hair (*Science*, doi: 10.1126/science. 1099593). The study clearly indicated that the aging of stem cells is a key to understanding tissue and organ aging.

Since establishing my own research team as a Professor at Kanazawa University in 2006 and then at TMDU in 2009, we started working on the niche microenvironment of stem cells and have revealed that hair follicle stem cells function as "niche cells" for melanocyte stem cells (*Cell Stem Cell*, doi: 10.1016/j.stem.2010.11.029). We also have found the existence of a "stemness checkpoint", which determines the fate of somatic stem cells, namely whether stem cells stay in an immature state as stem cells or commit to differentiation, during aging and under genomic stress (*Cell*, doi: 10.1016/j.cell. 2009.03.037).

More recently, we have been focusing on the *in vivo* cellular dynamics and exact changes that occur in somatic stem cells during aging and the eventual fate of those stem cells in tissues and organs. Our approach has revealed the existence of a "stem cell-centric aging program" that governs tissue aging characterized by miniaturization of hair follicle, the mini-organ to grow hair and hair loss (senescent alopecia) (*Science*, doi: 10.1126/science.aad4395). This helps explain why and how organs in our bodies become smaller (miniaturize) and/or thinner, with associated functional decline, due to aging. We are devising new strategies for tissue regeneration and rejuvenation by focusing on somatic stem cells. We welcome international collaboration to realize the therapeutic potential in this area.

Genomics in cancer research leads to improved prognoses and new therapies

Shumpei Ishikawa
Professor of Genomic Pathology at TMDU

Q **Research is gaining ground for genome analysis as an approach to discovering genes that are responsible for diseases. Which particular diseases are you currently focusing on?**

A: We are working on any intractable diseases that have no effective therapeutics. Diffuse-type gastric cancer is one such disease, with a strong impact on public health in Japan. It is usually said that cancer is a disease for elderly people, but diffuse-type gastric carcinoma is common at relatively younger ages, so its effect on economic activity is significant. Genome sequencing is a powerful approach for profiling somatic mutations, but in addition to simple cancer cell abnormality, we also focus on multicellular complex systems like cancer-stromal interaction and cancer immunology. We are taking a data-science approach, gathering a large amount of genomic data, which can lead to the understanding of disease systems and identification of therapeutic targets and biomarkers.

Q **What is the key to identifying the responsible gene among many suspected genes?**

A: In cancer genome analysis, two type of somatic mutations are observed: mutations of driver genes, which are important for cancer development and progression, and passenger gene mutations, which are stochastically incorporated into the cancer genome and are not important for the cancer cell. To discover a small number of true driver gene mutations among a large number of background candidate mutations, we collect genome sequencing data from many cases and focus on the mutation density and distribution within genes. In particular, the mutation positions in relation to the protein structure and the amino acid substitution pattern are important. Knowledge and experience of bioinformatics and structural biology are needed. It is also necessary to validate the biological significance of our data-based findings by combining them with laboratory experiments.

Q **Any comment on how the responsible gene RHOA you have newly discovered might contribute to medical treatment?**

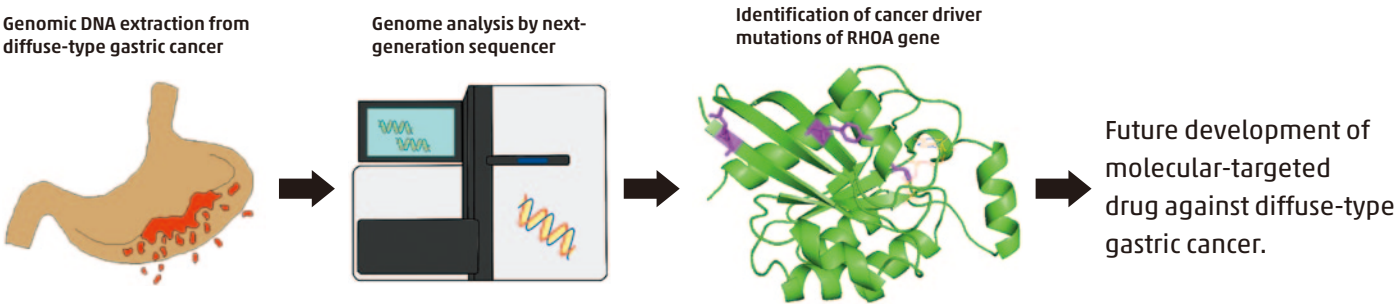
A: Diffuse-type gastric cancer has a poor prognosis because currently there are no therapeutics available. Our research shows that mutant RHOA is a driver mutation that is indispensable for the disease phenotype of diffuse-type gastric cancer. It is possible that a molecular-targeted drug can be successfully developed for mutant RHOA. With current drug design technology, only limited protein families, such as the kinase family, can be targeted, and these are called "druggable proteins". Mutant RHOA is not a typical "druggable" protein, so further knowledge of its exact biochemical mechanism is needed in order to discover a "druggable" point. New drug development technologies, such as simulation of protein-drug interaction and DDS (Drug Delivery Systems) for nucleic acid drugs will be also necessary.

Q **You also serve TMDU as a member of the Bioresource Research Center. Please describe your work there.**

A: In this Center, we collect and deposit clinical materials from TMDU hospital patients with their informed consent. I am working on the development of a standardized processing protocol for disease tissue used in genomics research. Unlike the case of peripheral blood, the preservation and nucleic acid extraction protocols vary for disease tissue, and could differ depending on disease type and locus. The differences in sample-by-sample and inter-facility bioresource quality has proven to be a significant problem for genomics re-

Dr. Ishikawa graduated from the Faculty of Medicine at the University of Tokyo in 2000, and received his PhD degree in Pathology. He performed postdoctoral research in the Genome Science Division of the Research Center for Advanced Science and Technology at the University of Tokyo. He became an Associate Professor in the Department of Pathology there, and joined TMDU as a Professor of Genomic Pathology in 2013.

Genome sequencing and therapeutic target discovery for diffuse-type gastric cancer



search, and a standardized process is necessary to address this issue.

Q How will your research project develop in the future? Is there the possibility of a joint study with foreign researchers?

A: I am eager to collaborate in research on cancer genomics and immunogenomics using Bioresource Research Center materials. In particular, oral cancer is strong area of TMDU and excellent research resources exists. As to international collaboration, we are now conducting research with Indian groups about functional genomics screening for Indian anti-tumor natural products. In addition to disease research and clinical diagnosis, genomics could be applied to microbe metagenomics, functional genomics screening, and synthetic biology, which are among our strong interests. Also, genome science has an important role in social and medical infrastructure, so I would like to contribute to Japanese society by contributing to the creation of national policy in this area.

Recurrent gain-of-function mutations of RHOA in diffuse-type gastric carcinoma, *Nat Genet.* ,doi: 10.1038/ng.2984.

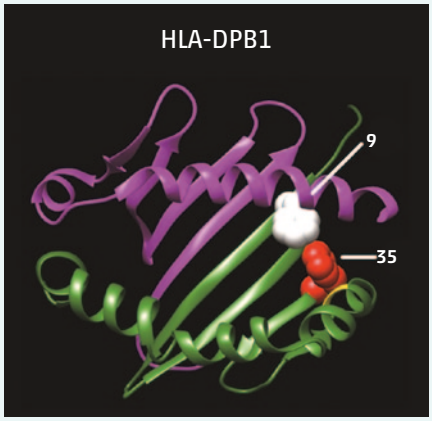
Innovative Researchers

Big Data and Statistical Genetics

Yukinori Okada
Junior Associate Professor of Human Genetics and Disease Diversity at TMDU

A major challenge in human genetics is to devise a systematic strategy to integrate disease genome Big Data with diverse datasets to provide insight into disease pathogenesis and to guide drug discovery. After two years of experience as a post-doctoral researcher at Harvard Medical School, I started my career as a tenure-track faculty member at TMDU. The research theme of our group is to empirically prove that *in silico* approaches based on Statistical Genetics can contribute to this challenge. We constructed an *in silico* bioinformatics pipeline to systematically integrate the identified rheumatoid arthritis (RA)-risk genetic loci with a variety of biological, medical, and epidemiological databases. We demonstrated that RA-risk genetic loci are significantly enriched with genes that are the target of therapies currently approved for RA treatment. Our analysis further suggested that drugs approved for other disease indications may be repurposed for the treatment of RA (e.g., CDK4/CDK6 inhibitors currently used for treating cancer).

A visionary project applying a cognitive computing system to disease genome Big Data has also been launched to develop a path to drug discovery. We have recently developed a novel genetic analytical framework named "HLA imputation method", which can computationally estimate high-resolution HLA gene polymorphisms. Comprehensive HLA gene analysis by the HLA imputation method successfully elucidated



HLA-DPB1 amino acid positions with Graves' disease risk.

risk biomarkers that contribute to both the onset and development of autoimmune diseases, such as Graves' disease. Together, our studies provide empirical evidence that Statistical Genetics can provide important information for human diseases, including novel therapeutic targets and drug discovery, in the era of Big Data (*Nature*, doi:10.1038/nature12873).

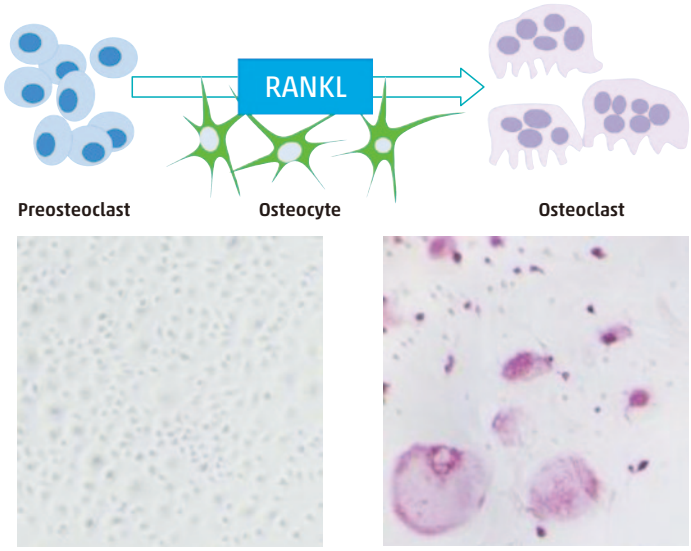
Bone biology
~Beyond the boundaries~

Tomoki Nakashima
Professor of Cell Signaling at TMDU

Q You are conducting research on bone metabolism. Concerning hard tissues, which particular studies are drawing attention, or leading the way, internationally? Of those studies, which are you most interested in and possibly working on?

A: Bone is constantly renewed by the balanced action of bone formation and bone resorption, both of which mainly occur at the bone surface. This restructuring process, called "bone remodeling", is important not only for normal bone mass and strength, but also for mineral homeostasis and haematopoiesis. An imbalance of bone remodeling is linked to various bone diseases. Furthermore, bone traditionally has been regarded as a part of the skeletal and locomotor system, but recent studies suggest that the skeletal system regulates systemic biological functions based on the inseparable link between the bone system and other systems, such as the endocrine system. This systemic network is called the "osteonetwork".

Using a genetic approach in mice, we established a new method for the isolation of high purity osteocytes. We demonstrated that osteocytes embedded within the bone matrix are the commander cells at the initiation of bone remodeling, through regulation of osteoclastogenesis (1). Furthermore, we recently reported that the semaphorin molecule Sema3A has a crucial role in the regulation of bone remodeling. Sema3A that is derived from osteoblast lineage cells, including osteocytes, inhibits osteoclast differentiation and promotes osteoblast differentiation synchronously to increase bone mass. These studies provide a scientific basis for future therapeutic approaches to bone diseases (2) .



***In vitro* osteoclastogenesis was remarkably induced by osteocytes**

Q TMDU is known for scores of milestone R&D results in dentistry. How is your research related to this tradition?

A: TMDU is a distinguished institute and known as a world center for the study of hard tissue biology for tooth and bone diseases. So, research and medicine at TMDU is critical for the future welfare of the human race, and is of particular importance in Japan, the world's most rapidly aging society.

Q What do you expect from your future projects?

A: We have been studying the mechanism of bone remodeling, intracellular signal transduction and the source of RANKL in the context of osteoclastogenesis. Our recent studies have identified the molecules mediating the communication among cells in bone (3) . A molecular-level understanding of the osteonetwork will provide a novel framework for understanding the bone and systemic systems as well as a molecular basis for developing new strategies against various diseases.

Dr. Nakashima graduated from the Graduate School of Pharmaceutical Science, Nagasaki University. In 2002, he joined the Penninger laboratory at the University of Toronto as a postdoctoral fellow. In 2006, he joined the Takayanagi laboratory at TMDU as an Assistant Professor. In 2013, he became a Principal Investigator at the Graduate School of Medical and Dental Sciences at TMDU.

1) Evidence for osteocyte regulation of bone homeostasis through RANKL expression, *Nat Med.*, doi:10.1038/nm.2452.
2) Osteoprotection by semaphorin3A, *Nature.*, doi: 10.1038/nature11000.
3) New insights into osteoclastogenic signaling mechanisms, *Trends Endocrinol Metab.*, doi: 10.1016/j.tem.2012.05.005.

Robotics in clinical medicine: A robot that performs endoscopic surgery

Kenji Kawashima
Professor of Biomechanics at TMDU

Q Please explain briefly about the EMARO surgical robot.

A: EMARO is an endoscope-holding robot that is driven by pneumatics. It controls the endoscope by sensing vertical and horizontal movements of the surgeon's head, through a gyroscope that the surgeon wears on his forehead. The endoscope has freedom of movement in four directions: forward and backward (for insertion and removal), up and down, left and right, and rotation. The surgeon directs this motion by controlled movements of his head and by operating switches with his feet. The operation is activated only while the foot switch is pressed.

Pneumatic drivers make it possible for the robot to move gently and smoothly. Moreover, the pneumatic approach makes it possible to create a compact and lightweight design; sufficient power can be obtained by injecting or extracting air through a cylinder no larger than a standard syringe—about 10 mm in diameter.

The operating surgeon can receive clear endoscopic images without the shaking of the camera, resulting in more precise surgeries. Also, EMARO, taking the role of a scopist, can be useful in smaller hospitals that have fewer doctors, allowing more patients to undergo laparoscopic surgery.

Dr. Kawashima received his doctoral degree in Engineering from the Department of Control Engineering at the Tokyo Institute of Technology in 1997. From 1997 to 2000, he worked as a research assistant at Tokyo Metropolitan College of Technology. He then worked as an associate professor in the Precision and Intelligence Laboratory at Tokyo Institute of Technology. Since April 2013, he has been a professor at the Institute of Biomaterials and Bioengineering at TMDU.

EMARO

Q In which ways did TMDU's unique resources contribute to EMARO development?

A: One strength of TMDU is that it has a technology institution within it—the Institute of Biomaterials and Bioengineering, where I belong. EMARO has developed with the effective advice and major support of medical doctors in TMDU's Research Center for Minimally Invasive Medicine and Dentistry. EMARO has been used in the Medical Hospital at TMDU.

Q A venture firm has been formed to handle marketing of the robot. Why and how?

A: Tight cooperation between TMDU and Tokyo Tech (Tokyo Institute of Technology) generated the success of EMARO. As medical robots present a risk in terms of profitability for big companies, a venture company has emerged from both universities, supported by the government funding with the mission of developing the EMARO system.

Q What is the outlook for your robot development project?

A: EMARO is the first in a series of surgical assist robots that will use ultra-precision pneumatic manipulation technology. Development is now underway for a surgical robot system that uses the pneumatic drive design and incorporates forceps.

http://www.titech.ac.jp/english/news/2015/031929.html

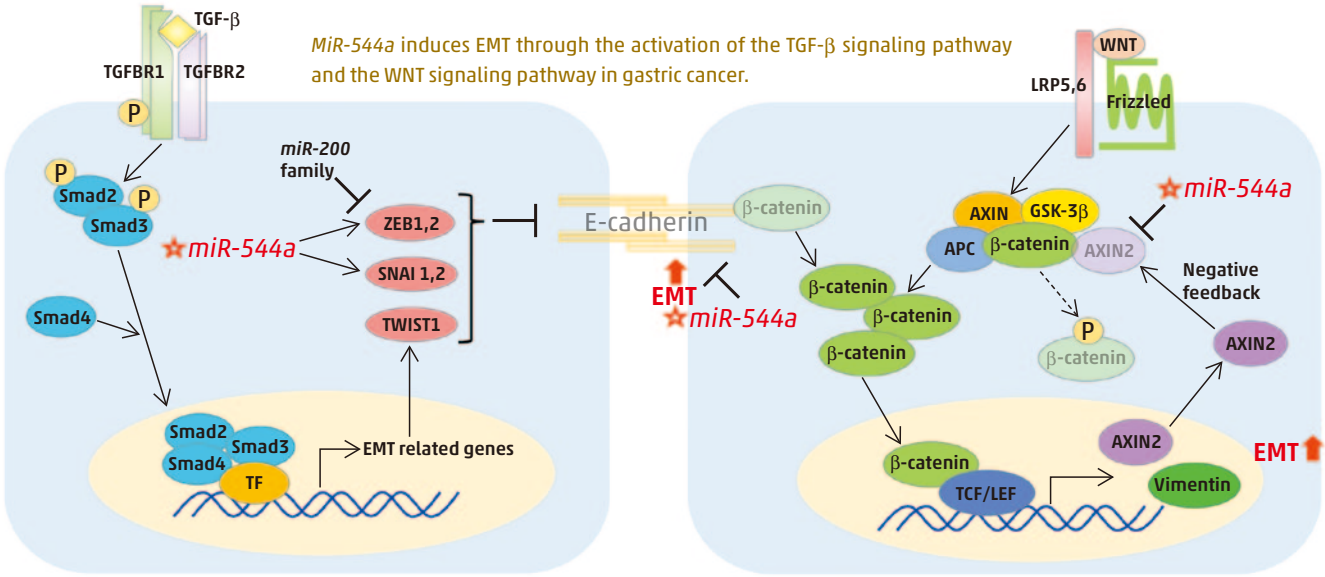
New tumor suppressor microRNA, *miR-544a*, identified; possible therapeutic target for gastric cancer

The epithelial-mesenchymal transition (EMT) contributes to cancer progression, as well as normal organ development, wound healing, and organ fibrosis. We established a cell-based reporter system for identifying EMT-inducing microRNAs (miRNAs) with a gastric cancer cell line, MKN1, transfected with a reporter construct that contained a promoter sequence of *VIM* in the 5′ upstream region of the TurboRFP reporter gene. Function-based screening using this reporter system was performed with a 328 miRNA library, and resulted in the identification of *miR-544a* as an EMT-inducing miRNA. Although *miR-544a* is already known to be involved in the regulation of *CDH1*, the mechanism by which EMT occurs remains poorly understood.

We demonstrated that overexpression of *miR-544a* induces *VIM*, *SNAI1* and *ZEB1* expression, and reduces *CDH1* expression, resulting in an EMT phenotype. In addition, we found that *CDH1* and *AXIN2*, which are related to the degradation and the translocation of β-catenin, are direct targets of *miR-544a*. Subsequently, the reduction of *CDH1* and *AXIN2* by *miR-544a* induced the nuclear import of β-catenin, suggesting that *miR-544a* may activate the WNT signaling pathway through the stabilization of β-catenin in the nucleus. Our findings raise the possibility that inhibition of *miR-544a* may be a therapeutic target for treating metastatic gastric cancer.

Carcinogenesis, doi: 10.1093/carcin/bgv106.

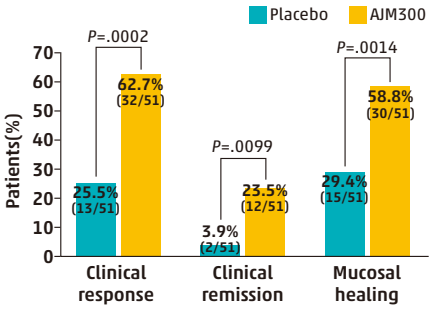
MiR-544a induces EMT through the activation of the TGF-β signaling pathway and the WNT signaling pathway in gastric cancer.



TMDU clinical center wins world recognition as center of excellence in treatment of inflammatory bowel disease

The number of patients with inflammatory bowel disease (IBD) is rapidly growing in Japan. Professor Mamoru Watanabe, chief of the Gastroenterology Department at TMDU, has served as the chairperson of Japan's national IBD research group since 2007. To provide excellent care to patients with IBD, TMDU established the Advanced Clinical Center for IBD in 2012. During the past 3 years, it has accepted almost 1,000 newly referred patients, and has become one of the largest IBD centers in Japan. Innovative procedures are incorporated into daily clinical practice there. For example, more than 200 small intestinal endoscopies are performed annually, and their usefulness in the management of Crohn's disease has been reported (1).

Based on this foundation in IBD research, Professor Watanabe led a nationwide study of patients with moderately active ulcerative colitis to examine the efficacy and safety of an oral α4-integrin antagonist (AJM300), which blocks lymphocyte recruit-



Proportion of patients with a clinical response, in clinical remission, and with mucosal healing at week 8 of treatment with AJM300 or placebo. The patients in the AJM300 group demonstrated a higher rate of improvement compared with those in the placebo group in every outcome.

ment to the gut from the systemic lymphoid tissues. The drug showed a remarkable clinical efficacy (2) .

Through these activities, the TMDU IBD center has played a leading role in clinical as well as basic research in IBD, and is recognized as a center of excellence for IBD in the world.

1) *Gastroenterology,* doi: 10.1053/j.gastro.2014. 04. 008.

2) *Gastroenterology*, doi: 10.1053/j.gastro.2015.08. 044.

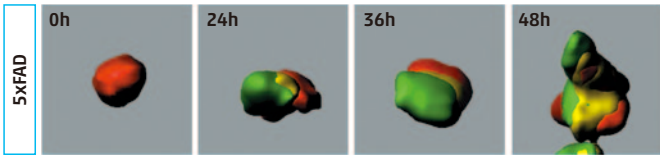
Fasting to activate macroautophagy not enough to cure Alzheimer's disease

Macroautophagy has been considered a protective mechanism in neurons against various types of neurodegenerative diseases. Activation of macroautophagy by rapamycin or fasting is hypothesized as a therapeutic approach to neurodegeneration, although it is not settled whether autophagy is, in fact, activated in the brain by fasting or not. On the other hand, in Alzheimer's disease, the autophagosome is suggested as a place for generating beta-amyloid, which accumulates both outside and inside neurons. The questions of the role of autophagy in Alzheimer's disease and whether fasting induces autophagy are not yet solved.

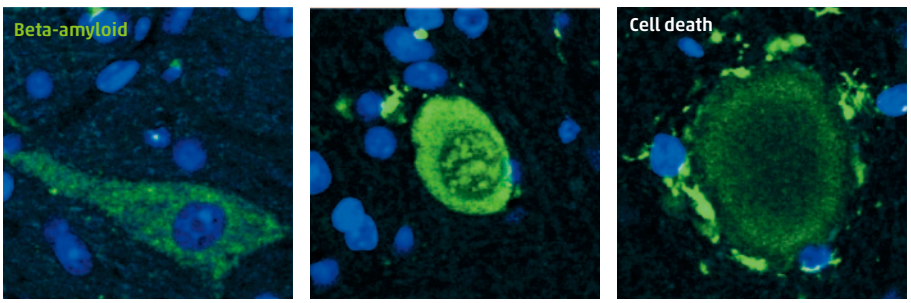
By using the fluorescent marker protein of macroautophagy and fluorescent beta-amyloid, we directly observed the dynamics of autophagy and the degradation of beta-amyloid in the mice models of Alzheimer's disease. The results showed that macroautophagy is actually activated in the brain as in other organs after fasting, but surprisingly revealed that fasting increased the accumulation of intracellular beta-amyloid in neurons. We expect that this was probably the result of starvation-enhanced endocytosis of extracellular beta-amyloid and the impaired function of macroautophagy in the Alzheimer's disease brain. Thus, our experimental results caution that exaggerated calorie restriction might lead to the progression of Alzheimer's disease, even in patients who are overweight, unless they have diabetes and related disorders.

Sci. Rep., doi:10.1038/srep12115.

Beta-amyloid clearance is insufficient and leads to cell death

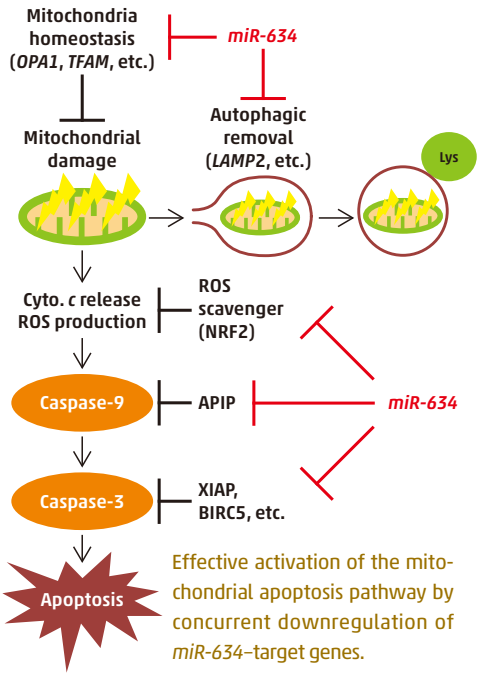


Red : beta-amyloid
Green : autophagosome in neurons



Macroautophagy is activated by fasting, and the activation is more prominent in the mice models of Alzheimer's disease. With Alzheimer's disease, however, associated endocytosis increases the uptake of beta-amyloid and the starvation-induced autophagy is insufficient to degrade the toxic substance in neurons.

MiR-634 enhances chemotherapy-induced cytotoxicity



Effective activation of the mitochondrial apoptosis pathway by concurrent downregulation of *miR-634*-target genes.

Some tumor-suppressing miRNAs target multiple oncogenes concurrently and therefore may be useful as cancer therapeutic agents. Further, such miRNAs may be useful to address chemotherapeutic resistance in cancer, which remains a primary clinical challenge in need of solutions. Thus, cytoprotective processes upregulated in cancer cells that are resistant to chemotherapy are a logical target for investigation. Here, we report that overexpression of *miR-634* activates the mitochondrial apoptotic pathway by direct concurrent targeting of genes associated with mitochondrial homeostasis, antiapoptosis, antioxidant ability, and autophagy. In particular, we show how enforced expression of *miR-634* enhanced chemotherapy-induced cytotoxicity in a model of esophageal squamous cell carcinoma, where resistance to chemotherapy remains clinically problematic. Our findings illustrate how reversing *miR-634*-mediated cytoprotective processes may offer a broadly useful approach to improving cancer therapy.

Cancer Res., doi: 10.1158/0008-5472.CAN-15-0257

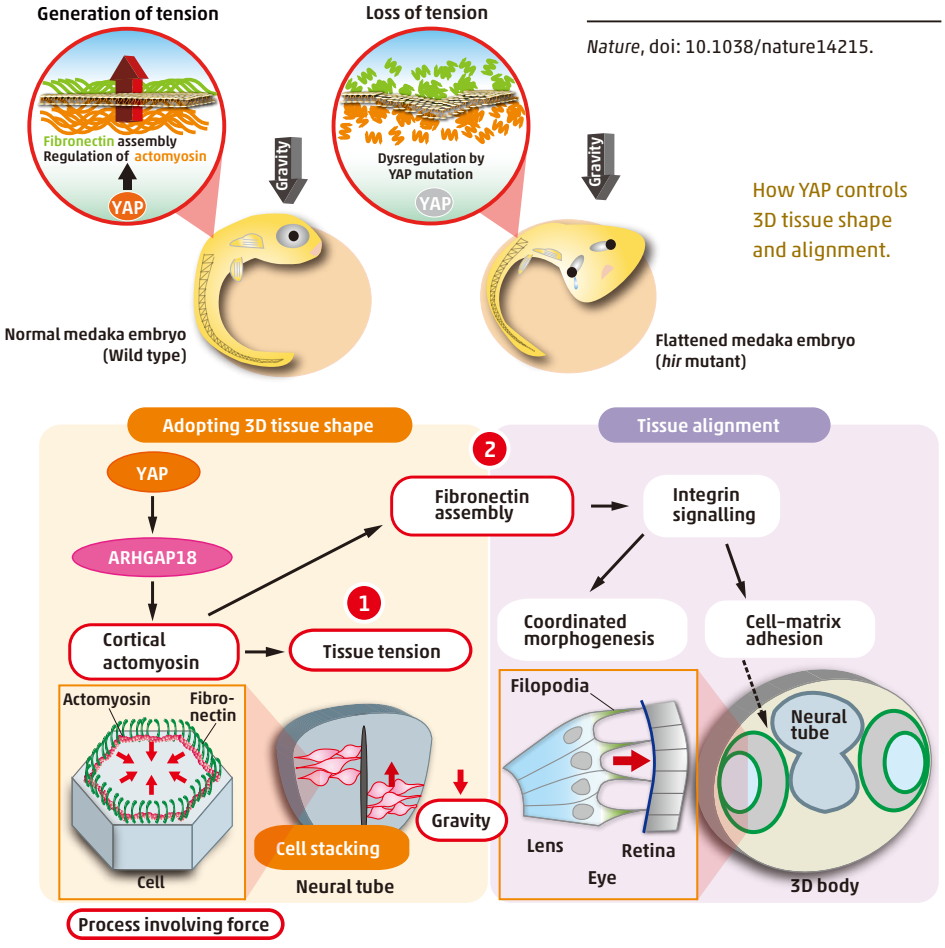
Solving a 100-year-old mystery: Discovery of a flat medaka mutant shows how 3D body morphogenesis happens in opposition to gravity

A century ago, Sir D'Arcy Wentworth Thompson, a British mathematical biologist, postulated that terrestrial animal body shapes are conditioned by gravity. However, there has been no animal model directly demonstrating how the mechano-morphogenetic processes are coordinated to generate a body shape in opposition to the force of gravity. A unique medaka (*Oryzias latipes*) mutant, *hirame* (*hir*), which means flatfish in Japanese, was isolated using a phenotype-driven mutagenesis screen for mutations that affect organogenesis in medaka embryos.

Due to mutation of the transcriptional co-activator YAP, *hir* embryos are sensitive to deformation by gravity and exhibit a markedly flattened body. Actomyosin-mediated tissue tension and fibronectin fibril formation are abnormal in *hir* embryos, leading to tissue flattening and tissue misalignment, both of which contribute to the flattened body. The YAP-knockdown human 3D spheroid also exhibits collapse upon exposure to external forces, which is reminiscent of the *hir* phenotype.

Together, these findings reveal a novel mechanism behind gravitational resistance in the 3D morphogenesis of a variety of animals, including fish and humans. This was discovered in a multi-institutional research project spearheaded by TMDU Professor Hiroshi Nishina's group, Institute of Science and Technology Austria Professor Carl-Philipp Heisenberg's team, and Makoto Furutani-Seiki's lab from the University of Bath in the UK.

Nature, doi: 10.1038/nature14215.



How YAP controls 3D tissue shape and alignment.

TMDU collaborates with Chile to improve its screening system for colorectal cancer

In Chile, mortality from colorectal cancer (CRC) has increased rapidly. To help address this, TMDU was invited to supervise a new project for screening, based on TMDU's history of collaboration with Chile since 1968. In 2009, the Ministry of Health of Chile, Clinica Las Condes, and TMDU signed a collaboration agreement for CRC screening. TMDU has continuously dispatched several experts in pathology, endoscopy and research, to construct a new national system of CRC screening in Chile.

A project for CRC screening named "PRENEC" was initiated in 2012 after intensive support from TMDU. From June 2012 to July 2014, a total of 10,575 asymptomatic participants were enrolled in PRENEC. Screening detected 107 cases of CRC, amounting to 1.01% of all participants, whereas the detection rate by the previous screening system in Chile was 0.2%. Other indicators also showed the higher quality of the new CRC screening system. Furthermore, most of the CRCs detected in PRENEC were early intramucosal cancers without risks of metastasis, and these lesions were treated successfully by endoscopy.

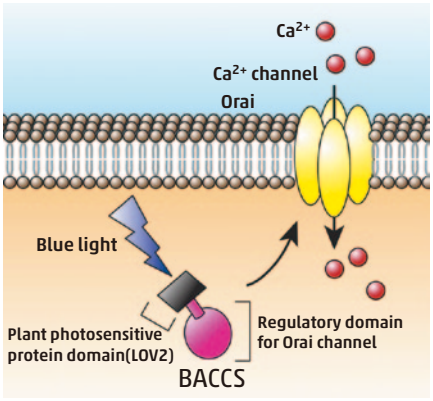
Cancer, doi: 10.1002/cncr.29715.

Colonoscopy training of Chilean doctors by TMDU researcher.

Light control of intracellular Ca^{2+} signals by a genetically encoded protein, BACCS

Ca^{2+} signals are tightly regulated in time and space, controlling a wide variety of cell functions from cell division to cell death. Both direct observation and manipulation of Ca^{2+} signals in living cells would be straightforward and effective approaches for investigating the roles of Ca^{2+} signals. Although sophisticated genetically encoded Ca^{2+} indicators have been developed to visualize the fluctuations of intracellular Ca^{2+} signals, efficient genetically encoded Ca^{2+}-controlling tools have been eagerly awaited. We have engineered a blue light-activated Ca^{2+} channel switch (BACCS), which is composed of a plant photosensitive protein —LOV2 domain— and a regulator of human or *Drosophila* Ca^{2+}-selective Orai ion channels. The *Drosophila* BACCS, combined with *Drosophila* Orai, is a highly efficient Ca^{2+} photoswitch with a large dynamic range in mammalian cells. We also generated BACCS mutants, which exhibit fast and slow recovery of intracellular Ca^{2+}. With BACCSs, we used light to successfully control NFAT-mediated gene expression in cultured cells and electrophysiological responses in the mouse olfactory system. Thus, BACCS will be a useful optogenetic tool for controlling a wide variety of Ca^{2+}-dependent cellular events, both *in vitro* and *in vivo*.

Nat Commun, doi: 10.1038/ncomms9021.



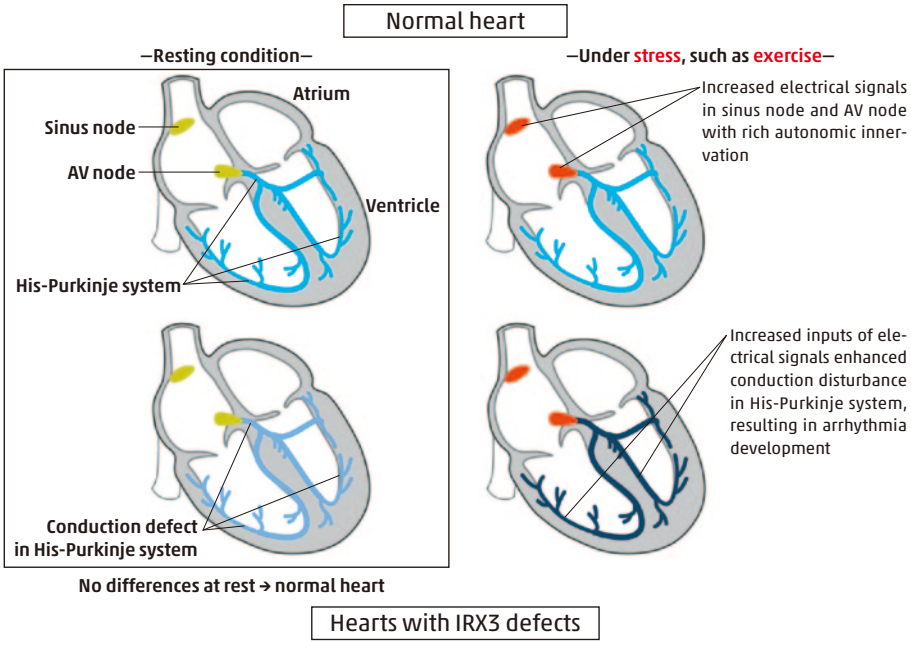
Schematic representation of BACCS. Blue light induces a conformational change of LOV2, which allows interaction between BACCS and Orai, resulting in an influx of extracellular Ca^{2+}.

Discovery of novel gene mutations associated with lethal arrhythmias that occur during exercise

The His-Purkinje system is a newly developed system in birds and mammals, which improves cardiac function by providing rapid and retrograde propagation of electrical signals in the ventricle. The His-Purkinje system is known to play an important role in the development of lethal arrhythmias and sudden deaths. The underlying mechanism, however, remains unknown.

Irx3/IRX3 is a transcription factor present only in the His-Purkinje system in the heart. It is key to determining the fast and reverse propagation of electrical signals in the ventricle. We found that genetic defects in Irx3/IRX3 were associated with lethal arrhythmias and sudden deaths in both mice and humans, particularly when they occurred during exercise. Sudden death related to exercise occurs in roughly one out of 10,000 individuals with normal hearts. Some genetic diseases, such as long QT syndrome and arrhythmogenic right ventricular cardiomyopathy, are implicated as the cause of sudden death related to exercise. Our data add the genetic dysfunction of Irx3/IRX3, a transcription factor specifically expressed in the His-Purkinje system, as a possible cause of sudden death related to exercise.

Eur. Heart J., doi:10.1093/eurheartj/ehv449.



The possible mechanism of exercise-related arrhythmias associated with *IRX3* genetic defects. *Upper:* normal hearts. *Lower:* hearts with *IRX3* defects. *Left:* resting condition. *Right:* under stress, such as exercise. In the resting condition, the functions of the heart with *IRX3* genetic defects (lower left) cannot be distinguished from those of the normal heart. Under stress, such as exercise, increased inputs of electrical signals into the His-Purkinje system manifest as a conduction disturbance, resulting in the development of arrhythmias.

Join us in pursuing new horizons

TMDU pursues numerous research themes that would be excellent opportunities for international collaboration. Several are highlighted here. If you are interested in learning more about them, please contact us.

Development of nuclear receptor ligands and their clinical application

Hiroyuki Kagechika
Professor, Department of
Organic and Medicinal Chemistry

Nuclear receptors elicit the transcriptional activities by binding to specific ligands. We have developed various novel ligands for specific nuclear receptors, such as retinoid (RARs and RXRs), vitamin D (VDR), androgen (AR), and progesterone receptors (PR). In particular, our synthetic retinoids have demonstrated RAR or RXR selectivity, including Am80 (tamibarotene), which was approved as a drug for acute promyelocytic leukemia in Japan. These compounds would be useful as chemical tools for elucidation of nuclear receptors, and also for clinical use in the fields of cancer, autoimmune diseases, neurodegenerative diseases, and metabolic syndromes.

Exploring oral mucosal immune responses to develop safe and effective immunotherapy

Miyuki Azuma
Professor, Department of
Molecular Immunology

The sublingual mucosa has long been used as a route for sublingual immunotherapy (SLIT), which induces tolerance against allergens. However, the actual contribution of sublingual mucosal dendritic cells (DCs) has not been clarified. Our group has been studying DCs at several oral mucosal sites after antigen application. Recently, we have found that repeated topical antigen painting on the sublingual mucosa resulted in a unique distribution of characteristic DCs, leading to efficient induction of allergen-specific immune tolerance (*Vaccine*, doi: 10.1016/j.vaccine.2014.08.013). To induce such a tolerogenic situation in the sublingual mucosa does not require specific allergens. We would like to extend this finding and to develop a novel SLIT, which is safer and more economical. We welcome collaborative research.

Novel sources of mononuclear phagocytes shed light on new therapeutic applications

Toshiaki Ohteki
Professor, Department of
Biodefense Research

Mononuclear phagocytes include dendritic cells (DCs) and monocytes/macrophages. DCs have crucial functions in the induction of tolerance under steady-state conditions, and of innate and adaptive immunity following infection. On the other hand, monocytes and monocyte-derived macrophages cause a variety of inflammatory disorders, including metabolic syndromes and tumor development. Our group recently discovered novel sources of DCs in mice and monocytes/macrophage progenitors in humans that generate no other hematopoietic cells. Our discoveries will provide insights into mononuclear phagocyte differentiation pathways and new therapeutic applications that target progenitors for infectious diseases, cancers and metabolic syndromes.

Combatting nonalcoholic steatohepatitis (NASH)

Yoshihiro Ogawa
Professor, Department of
Molecular Endocrinology and Metabolism

Nonalcoholic steatohepatitis (NASH) is closely associated with the progression to liver cirrhosis and hepatocellular carcinoma. There are numerous unmet medical needs for NASH. Recently, we have identified a unique histological feature in the liver of NASH mice and patients, termed "hepatic crown-like structure (hCLS)", where macrophages aggregate to surround dead hepatocytes with large lipid droplets. Our data suggest that the hCLS serves as an origin of hepatic inflammation and fibrosis during the progression from simple steatosis to NASH. This helps us elucidate the pathogenesis of NASH, pursue specific biomarkers, and evaluate potential therapeutic strategies.

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QR

Molecular and cellular bases of primary immunodeficiencies (PIDs)

Tomohiro Morio
Professor, Department of
Pediatrics and Developmental Biology

Our team has been working on deconstructing the pathogenesis of primary immunodeficiencies (PIDs), especially focusing on the molecular basis of antibody deficiency and of PIDs that are prone to develop malignancy. Our team is also leading in the clinical field, with the largest number of PID patients and hematopoietic cell transplantation cases in Japan. Recent topics of research include the characterization of signals that control survival and differentiation of dendritic cells, and of signals that govern development of B cells. This research project focuses on novel gene products that we have recently identified as responsible for these processes (data unpublished). We are also endeavoring to develop novel technologies to detect multiple pathogens, and new systems to detect gene mutations in rare cell populations.

Regulation of body fluid homeostasis in health and disease

Shinichi Uchida
Professor, Department of Nephrology

Our interest is focused on understanding the kidney's function in regulating body fluid homeostasis, and the pathophysiological mechanisms causing human diseases when that regulation is disrupted. Recent achievements include the discovery of a novel signal cascade –WNK kinase signaling– that controls blood pressure and electrolyte homeostasis. We are now trying to develop drugs to modulate WNK signaling. We are also experts on AQP water channels and CLC chloride channels, both of which are important drug targets for certain human diseases. We are working in close collaboration with leading researchers at Harvard University, NIH, Washington University, and other labs around the world. We welcome further collaborative research.

SHH signaling in craniofacial development

Sachiko Iseki
Professor, Department of
Molecular Craniofacial Embryology

The sonic hedgehog protein (SHH) transduces its signal through the primary cilium and is involved in variety of biological processes, including craniofacial development. Loss of the SHH gene, loss of cilium function and alteration in cilium structure are each associated with congenital disorders in which a cleft lip and/or palate (CLP) is one of the major phenotypes. In this collaborative study, the ways SHH signaling and the primary cilium are involved in craniofacial development will be investigated by paying particular attention to CLP.

Physiological and pathological roles of a novel autophagy pathway

Shigeomi Shimizu
Professor, Department of
Pathological Cell Biology

Autophagy is a fundamental cellular process that degrades subcellular constituents. It has been believed that Atg5 and Atg7 are essential for autophagy, but we recently discovered that mammalian cells also have an alternative type of autophagy that is independent of Atg5 and Atg7. This alternative autophagy is required for mitochondrial elimination during erythrocyte maturation. It also functions in various other physiological events, and its disruption causes various diseases, including neurodegenerative diseases, cancer, and etc. Our research focuses on identifying other diseases that are caused by the failure of this alternative autophagy, in order to elucidate the molecular mechanisms of such diseases, and to develop small therapeutic compounds for these diseases.

Sharing expertise and groundbreaking research around the world

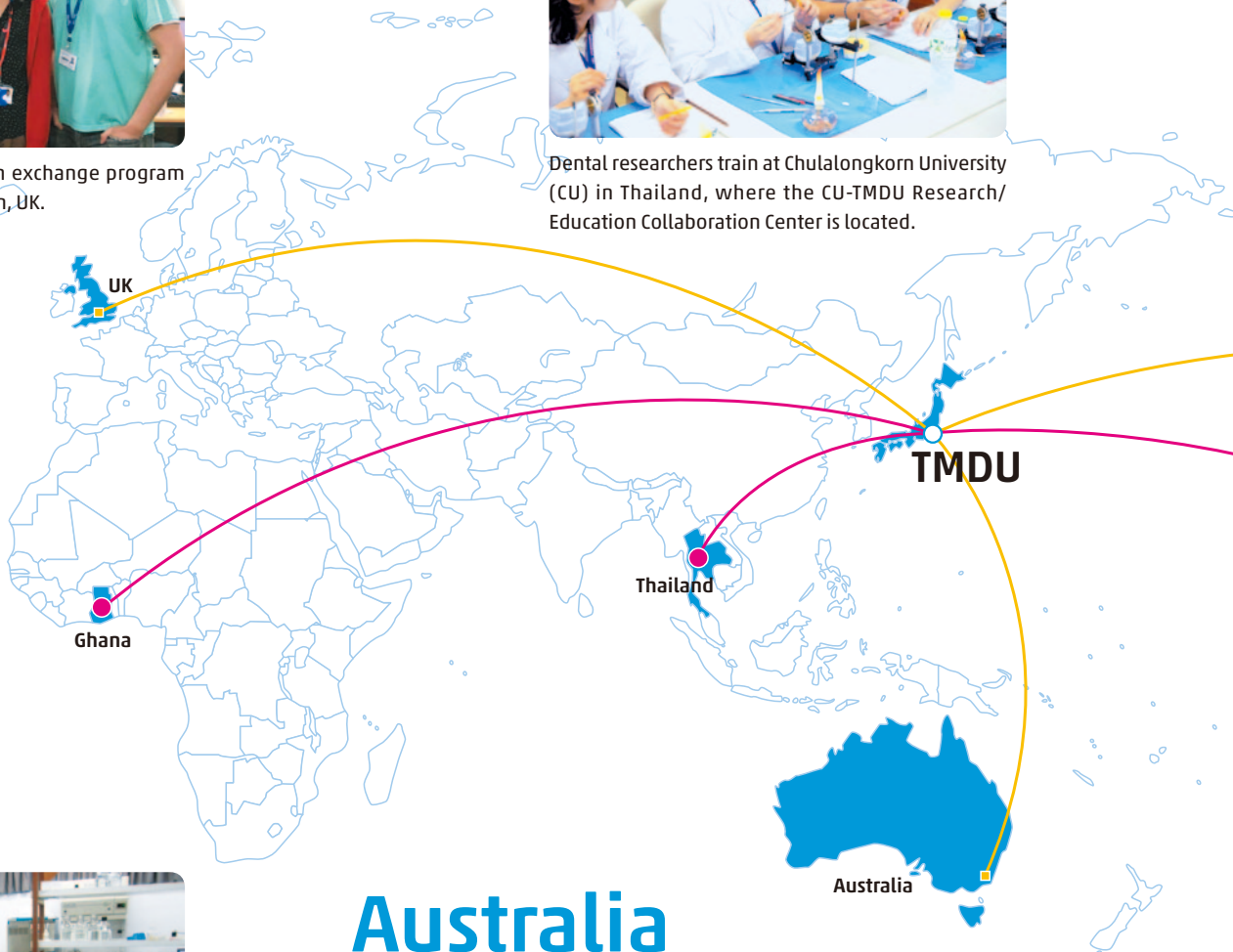
Our international exchange activities in research and education are based in three centers, in Ghana, Thailand and Chile. We further promote educational collaboration with Harvard Medical School, Imperial College London and Australian National University.
We also affiliate with 85 other schools in 27 countries.

UK

Students participate in an exchange program at Imperial College London, UK.

Thailand

Dental researchers train at Chulalongkorn University (CU) in Thailand, where the CU-TMDU Research/ Education Collaboration Center is located.



Ghana

Researchers study infectious diseases at Ghana-TMDU Research Collaboration Center.

Australia

International students participate in exchange program with Australian National University.

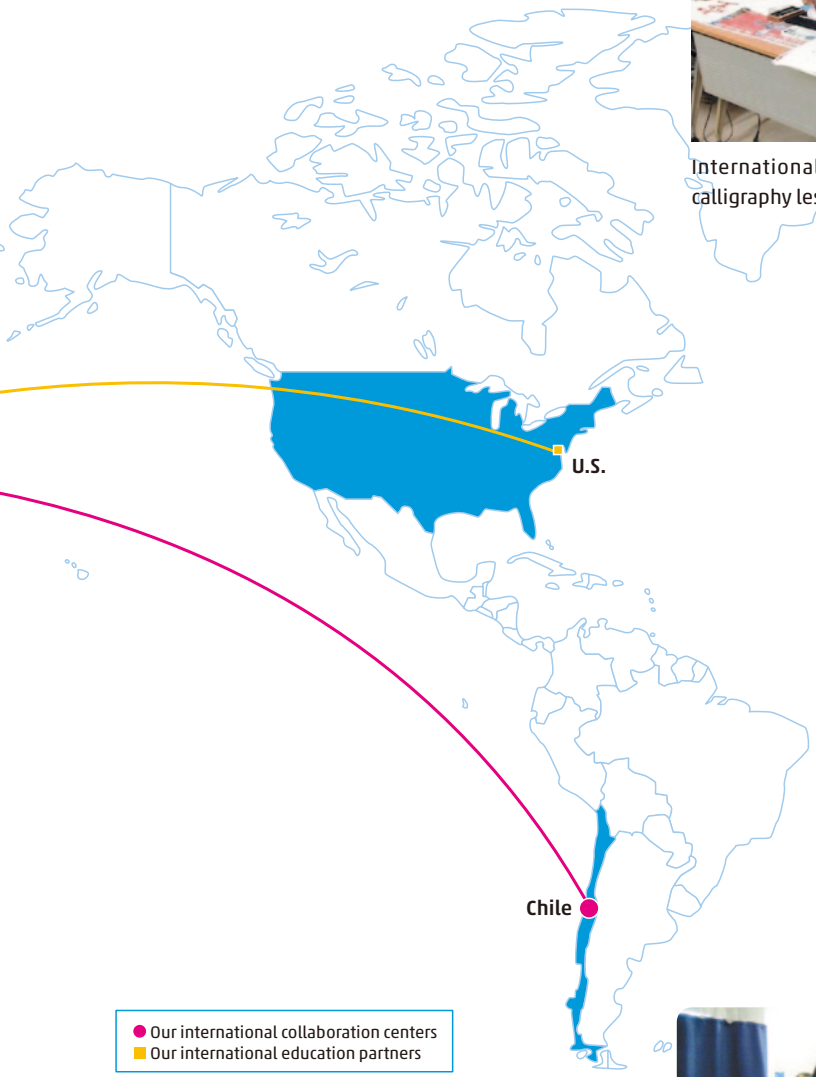
International researchers celebrate the new year with “Mochi-Tsuki” (rice pounding), a Japanese custom.

Students celebrate Children’s Day holiday in the Japanese way.

Students visit a shrine in Tokyo for Tanabata, the star festival in July.

International students take Japanese calligraphy lesson.

Participants in the International Summer Program learn about medical and dental sciences.



U.S.

TMDU’s medical students experience clinical training at Harvard Medical School’s affiliated hospital in Boston, Massachusetts.

Chile

In Chile, where TMDU's Latin American Collaborative Research Center is located, doctors of TMDU and Clinica Las Condes work on a project to prevent neoplasia of the colon and rectum.

Main campus of TMDU (Ochanomizu / Yushima District)

TMDU Research Activities 2016

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

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