Main campus of TMDU (Ochanomizu / Yushima District)

TMDU Research Activities 2018

TMDU

Research Activities 2018

TMDU – Committed to pioneering medical research

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

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http://www.tmd.ac.jp/tmd-research/english/

Contents

TMDU: Did you know...?

University Ranking by Subject

	Medicine	Dentistry
National Rank	4	1
World Rank	101-150	3

SOURCE: QS World University Ranking by Subject 2017

University Ranking by Ratio of Faculty / Students

Ranked #7 in Japan and #11 in the World

	Students	Faculty
Graduate	1,525	734
Undergraduate	1,486	

SOURCE: Times Higher Education Top universities with the best student-to-staff ratio 2018

World's Best Small Universities

Ranked #1 in Japan and #17 in the World

SOURCE: Times Higher Education World's Best Small Universities 2017

University Hospitals Promoting Our Research

	Beds	Outpatients Per Year
Medical Hospital	753	570,969
Dental Hospital	60	436,058*

* Ranked #1 among university dental hospitals in Japan

International Students

	No. of Int'l.Students	No. of Countries
Graduate Schools	304*	39

* Ranked #1 in international enrollment among medical graduate schools in Japan

Message from the President

Since Tokyo Medical and Dental University (TMDU) was established in 1928 as the first national dental school in Japan, it 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 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. Our 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. In addition, with an eye on the Tokyo 2020 Olympic and Paralympic Games, we established the Sports Science Organization to provide integrated care for athletes and apply our scientific knowledge to public health, and have invited a 2004 Olympics gold medalist in the hammer throw to join us as a professor.

We also have two research institutes, the Medical Research Institute and the Institute of Biomaterials and Bioengineering, where researchers collaborate with industries to develop practical clinical applications for the benefit of society. In 2016, we established two centers: the Center for Personalized Medicine for Healthy Aging, which provides preventive medicine based on individual genetic backgrounds to contribute to longevity, and the Institute of Global Affairs/Institute of Education to promote university-wide globalization in the fields of research, education and medical treatment. Furthermore, in April 2017, we established the Institute of Research to reinforce the deep collaboration among our finest researchers in the fields of medicine, dentistry and engineering, thereby promoting ground-breaking innovations and practical applications that go beyond each research area. We are also conducting collaborative investigations and education at our overseas research centers in Thailand, Ghana and Chile.

In order to achieve higher levels of consolidated research, we will activate two plans to reorganize our graduate program, starting in April 2018. First, a new graduate program for integrated preemptive medical and dental health care science will open to train specialists in the comprehensive analysis of medical big data utilizing technologies such as IoT, AI and robotics, in order to provide preventive medicine with higher accuracy. Secondly, our "Global Health Leader Training Course" will develop specialists capable of solving the world's urgent health issues, using diverse programs, including international lectures, case studies, and field trips overseas work.

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 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.

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

Executives discuss TMDU's evolution as a research facility – An interview

Mamoru Watanabe
Executive Director / Executive Vice President, Innovative Research and Collaboration
Akinori Kimura
Executive Senior Vice President of Research, Accreditation and Evaluation

TMDU is in the midst of revising its organization in order to enhance its research potential. Two executives answer questions about current developments and the future at TMDU.

– What are the outstanding features of TMDU?

Watanabe: Tokyo Medical and Dental University is an institution with a dual focus on medicine and dentistry: The medical department is highly esteemed and the dental department ranks third in the UK's QS World University Rankings. TMDU has research-specific labs, among them the Medical Research Institute, which pursues the biological research concerning etiopathology of intractable diseases including cancer, and the Institute of Biomaterials and Bioengineering, which is tasked to develop materials and devices for use in treating patients.

In April 2017, the Institute of Research was inaugurated to realize a vision for integration across all TMDU research areas. By coordinating projects from different groups on our campus, we are tackling challenges in ways that otherwise would be impossible, and thereby discovering how to impact future therapies. (Some of these challenges are introduced later in this booklet.)

TMDU is proud of its affiliated hospitals. The Medical Hospital boasts the largest number of applications for receiving clinical training in Japan. With many of its faculty members involved in clinical duties and basic research at the same time -- a system not widely seen in Europe and the United States -- the staff can find new research themes while treating patients at the hospital, conduct basic research targeting those themes, and address clinical problems.

The hospital includes diagnostic centers focused on refractory cases, including inflammatory bowel diseases, connective tissue diseases and rare neurological disorders. Registered patients come from across the country, a phenomenon that helps us collect a sufficiently large volume of clinical data and samples so as to forward our research effectively.

The Dental Hospital has the largest number of patients in Japan. It has long played a vital role in extracting research themes in both medical and dental fields, uncovering, for example, a relationship between oral bacteria and dementia.

Kimura: Among other facilities that strengthen its research capability, TMDU has the Research Core, which employs the latest lines of analytical and imaging equipment, the Center for Experimental Animals, and the Bioresource Research Center, which collects and analyzes the genome information of clinical samples from our hospitals.

TMDU enjoys a high faculty-to-student ratio, which allows faculty members to spend enough time carrying out their own research while also ensuring intensive lessons and interactions for students.

No less important is that the campus has been opened to foreign students. Currently, about 13 percent of our graduate students come from abroad, one of the highest ratios at any post-graduate course in Japan.

Dr. Kimura

– How are research profits being returned to society?

Watanabe: We're building a system with the aim of shortening the continuous process of growing "seeds," found in labs, into new drugs or therapies. Especially, we are focusing on establishing venture capital arrangements to promote successful alliances between academia and industry, ensuring that research leads to products and services. TMDU has already enjoyed a growth spurt and was named by Reuters as one of the Asia-Pacific region's Most Innovative Universities in 2017, as measured by patent revenue, number of material transfer agreements, and so on.

We see it as another important mission of the university to help Japan continue to develop smoothly as a truly healthy aging society. In fact, TMDU has undertaken diverse social programs, including one to provide genome information we think is necessary to maintain people's health.

– Which research is particularly important to TMDU?

Watanabe: TMDU has scored solid results in regenerative medicine, genome research, and immunology and inflammation. To bolster research skills in these fields, we are restructuring our organization. Part of that effort calls for enlisting top foreign scientists as advisory board members or invited researchers.

Kimura: Among the latest topics of research drawing our special attention is big data in biomedicine, an approach where genome and clinical data are analyzed in an integrated manner for use in preemptive medicine. Precision medicine, which uses genome information, is another field of interest as it promises the most suitable, or customized, therapy for each individual patient.

In addition, as part of medical (dental) engineering, development is accelerating in the area of devices that collect data from breath, sweat and tears in order to examine a patient's condition. The data collected will also support our big data medicine. (For details, see the following pages.)

Watanabe: In 2018, we will launch an ambitious system for training up-and-coming researchers to work in untapped fields, beyond the three domains just mentioned. This new system will enroll about 20 members via competition each year, and they will conduct research at 'Gaia Laboratory', a new research facility. The lab will invite top-flight researchers from abroad to guide the young researchers.

– What about cooperation with overseas institutes?

Watanabe: TMDU has expanded its international joint-degree program, with research hubs previously opened in Ghana, Chile and Thailand. Also, our faculty members frequently visit and teach at overseas universities.

The next step is to expand collaboration with European and U.S. universities in both research and education. We already send many young researchers to leading institutions for about three years to strengthen these relationships.

– Any message for the readers of this booklet?

Watanabe: Are there TMDU faculty members among the Japanese medical researchers or dentists you are aware of? If so, you'll soon be impressed by their record as scientists. If they are from the same field as yours, why not consider joining hands with such researchers?

Kimura: TMDU holds its doors wide open for students and collaborative researchers from around the world. If you want to know more about our education or research system, please contact the URA Office at the address given at the top of this page. TMDU will spare no effort to explore the possibility of building close relations with you.

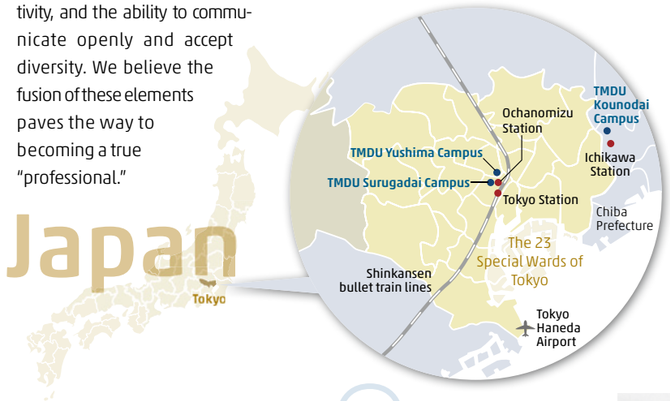
Dr. Watanabe

Promising young researcher joins new division

In September 2017, TMDU established the Division of Advanced Multidisciplinary Research. In this division, the Consortium for Neogenetic Medicine was launched to pursue research in the field of regenerative medicine. TMDU invited Dr. Takanori Takebe to join as professor in the Consortium. In 2013, Dr. Takebe generated a vascularized and functional human liver in a mouse by transplantation of liver buds created from human induced pluripotent stem cells, receiving remarkable attention. He will continue to develop his research at TMDU.

Standing at the sacred birthplace of scholarship in Japan

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



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

TOKYO - The past and present

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

1800s

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

1928

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

2018

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

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Professor Junji Tagami of the Department of Cariology and Operative Dentistry, Graduate School of Medical and Dental Sciences, receives the 2017 IADR Wilmer Souder Award

The International Association for Dental Research (IADR) presented Prof. Junji Tagami of the Department of Cariology and Operative Dentistry, at TMDU's Graduate School of Medical and Dental Sciences, with the 2017 IADR Wilmer Souder Award at the 95th General Session & Exhibition of the IADR held in San Francisco on March 22, 2017.

The Award, founded in 1955, is the oldest of the 17 IADR Distinguished Scientist Awards, which honoring Dr. Wilmer Souder, the father of modern dental materials research, for his motivating force in establishing the Dental Section at the National Bureau of Standards (currently referred to as the National Institute of Standards and Technology). This Award is designed to encourage advancement in dental materials research based on scientific concepts, and is made on the basis of scientific achievement of outstanding quality that is considered to lead to significant advancements in dental service to the public. It is intended to confer the highest honor in the field of dental materials research.

Prof. Tagami is the first Japanese researcher to have received the Wilmer Souder Award since 1999. His fundamental research on the mechanisms of adhesion to tooth tissue has greatly contributed to the development of new bonding approaches, leading to the advancement of adhesive dentistry.

Prof. Tagami (right), with Prof. Jukka Meurmam of University of Helsinki, who was then President of IADR, at the 2017 IADR Wilmer Souder Award ceremony.

Eugen-und-Ilse-Seibold-Preis (Eugen and Ilse Seibold Prize) awarded to Professor Takeshi Tsubata of the Department of Immunology, Medical Research Institute

Prof. Takeshi Tsubata of the Department of Immunology, Medical Research Institute of TMDU was awarded the Eugen-und-Ilse-Seibold-Preis (Eugen and Ilse Seibold Prize) by the Deutsche Forschungsgemeinschaft (German Research Foundation) on Oct. 10, 2017 in Bonn, Germany.

This Prize, named after marine geologist, Prof. Eugen Seibold, and his wife, Ilse Seibold, is awarded once every two years to one Japanese and one German researcher in honor of their long-term successful and dedicated commitment to academic and cultural exchange between the two countries, and for particular achievements in all fields of research. Prof. Tsubata is the first researcher to have received the Prize in the field of Life Science and Medicine. He is honored for an outstanding contribution to "discovering novel aspects of the basic principles of the humoral immune response".

In the normal immune system, antibodies are produced in reaction only to microbes, not to other components, including self-components. Prof. Tsubata's research group has made various advancements and vital contributions to the immunology field, including identification and clarification of the mechanism by which antibodies are produced only to microbes, identification of the signal cascade for inducing the B lymphocytes of suppressive function, and identification of a receptor to prevent autoimmunity via recognizing self-components.

Prizewinners Prof. Tsubata (second from left) and his German counterpart, Prof. Thomas Bock, at the award ceremony with Prof. Katja Becker, Vice President of the German Research Foundation (left) and Dr. Ursula Seibold-Bultmann, daughter of the Seibolds (right).

Large datasets of entire genomes will help identify disease subtypes and optimize treatments

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

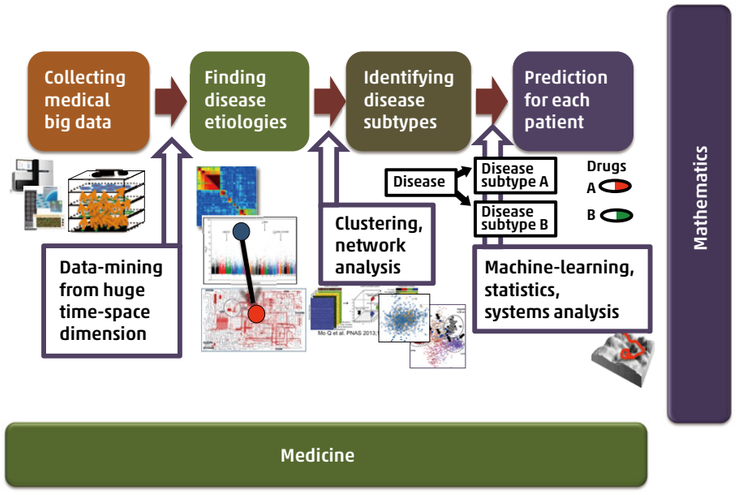
Tatsuhiko Tsunoda

Professor of Medical Science Mathematics at TMDU /
Group Director at the RIKEN Center for Integrative Medical Sciences

Q Your work aims to achieve "precision medicine." Please explain what this is.

A: Ever since scientists started to unravel the secrets of the human genome, a time was predicted when differences in individual genes, lifestyles, and environments could be taken into account when selecting treatment strategies. Precision medicine aims to achieve just that, by optimizing prevention or therapeutic interventions to suit the needs of groups of similar individuals rather than taking a "one size fits all" approach. This is particularly important for cancer therapy, which has traditionally relied on treating the type of cancer based on the location, e.g. tissue, of the tumor in the body. However, tumors within the same region may derive from different mutations and mechanisms. This causes the tumors to respond differently to treatment. "Omics profiling" teases these differences apart, and builds up an outline of patients with respect to differences in their genetics (somatic and germline variations, including copy number and structural variations), gene expression regulations, protein expression changes and modifications, and the production of small molecules and autoantibodies. These outlines not only help us understand disease development and categorize subtypes, but also identify disease "biomarkers" that can be used to predict patient outcomes. Worldwide collaborative efforts between clinicians and scientists have enabled the coordination of such information for a huge number of patients, but this big data requires careful mathematical analysis. To this end, I have proposed a novel bottom-up statistical method that considers the many differences among samples, and can be combined with a top-down analysis for biomarker exploration.

Medical big data analysis



Q You recently carried out a large-scale genetic analysis of liver cancer. What made you focus on this disease and what did you discover?

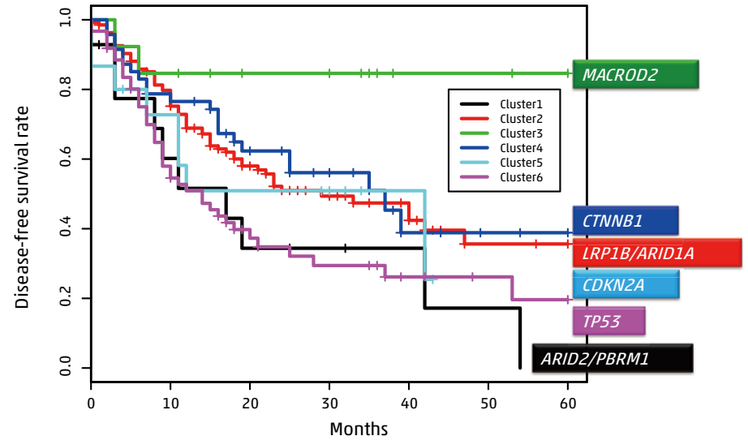
A: As the fifth most common cancer worldwide, liver cancer places a huge burden on public health. It is mainly caused by infections of hepatitis B and C viruses, but its numerous other causes include alcohol intake and exposure to liver carcinogens. Several genes have been identified that are mutated in 30%–60% of liver cancer cases, as well as many that are mutated in a tiny number of cases. However, as with all genetic analysis, the greater the sample size the more statistical punch it can pack. We therefore looked at the entire genomes of 300 Japanese patients with liver cancer, mostly hepatocellular carcinomas. Each mutation that occurs during cancer development leaves its mark on the genome, and these "mutational signatures" have previously been identified in liver cancer patients of other ethnicities. The signatures we detected that associate with hepatocellular carcinoma in Japanese patients did not match those from French or Chinese studies, suggesting that different populations undergo a different set of mutations in their development of cancer. More mutations were found in older patients, and those who smoked or had larger tumors. They were also more common in parts of the genome that replicated themselves late in the cell cycle, possibly because these are less accessible to DNA repair mechanisms. Driver mutations confer a growth advantage on cancer cells, and we identified several new driver genes associated with liver cancer, including those involved in liver metabolism, DNA repair, and DNA chromatin remodeling. We showed that DNA rearrangements in the form of deletions and duplications affected the expression of cancer-related genes, while sections of DNA that do not code for proteins (such as promoters or other regulatory regions) were also repeatedly mutated.

Dr. Tsunoda graduated from the University of Tokyo, where he studied elementary particle physics and computer science. He obtained two PhDs -- in 1995 in Engineering, and in 2007 in Medicine. He started his career as Assistant Professor at Kyoto University in 1995 and then became Research Associate and Assistant Professor at the University of Tokyo. In 2000, he moved to RIKEN, where he continues to lead the Research Group for Medical Science Mathematics, RIKEN Center for Integrative Medical Sciences. He became Professor of Medical Science Mathematics at TMDU in 2015.

Q You used a particular technique in your investigation of mutations across the entire genome. Can you explain why this was necessary and what it achieved?

A: Because our work looked at the entire genomes of patients, it was common for their mutation distributions to be sparse. To overcome this problem, we used a network-based stratification approach that relied on the fact that mutations causing the same disease often occur in genes that are in close proximity and within a network of interactions between proteins. A statistical technique based on the bottom-up approach was used to divide the total population into clusters of patients with mutations in similar network regions. We then used further statistical analyses to compare the length of time that patients within clusters survived without disease recurrence to help understand the biological importance of different mutations and their effects on patient survival.

Liver cancer analysis



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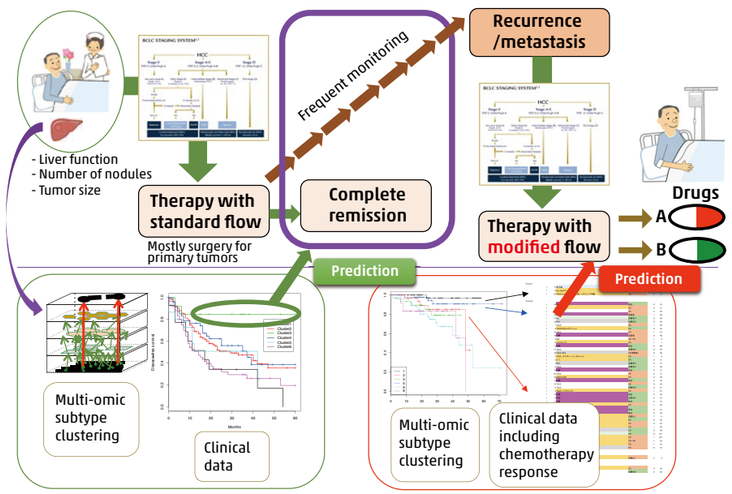
Liver cancer analysis and prediction



Q What are the clinical implications of your findings?

A: Some of the Japanese mutation signatures that we identified, as well as some individual mutations, were more likely to occur if the patients smoked, drank alcohol, or were infected with hepatitis B or C. This strongly shows the importance of gene–environment interactions on the development of disease. Using the statistical technique mentioned above, we identified six clusters of patients, with each cluster sharing similarities such as mutations in particular driver genes. When taking into account other factors like age, sex, and whether the patients had undergone surgery, we found that patients in two clusters had a significantly lower chance of survival while those in another cluster had a significantly better chance of recurrence-free-survival than individuals in other clusters. These findings can be used to target patients who will best respond to particular therapies or interventions.

Nat. Genet., doi: 10.1038/ng.3547

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

Natural antibodies identified as potential anti-tumor agents

Shumpei Ishikawa Professor of Genomic Pathology at TMDU

Q Your focus is on B-cell immunity in cancer. Please give us a brief overview of your latest findings

A: I have been working with my TMDU colleagues to clarify the architecture of B-cell immunity in cancers. B cells, together with Tcells, are subsets of lymphocytes within the immune system. There is substantial evidence that these cells play a pivotal role in the immune system's fight against cancers, although B-cell activity remains relatively elusive compared to the well-studied T-cell system.

In our study in *Cell Reports*, we initially investigated the global landscape of anti-tumor immunity through an "immunogenetics" approach where antigen receptor repertoires of B and T cells were clarified by next-generation sequencing. We found: (1) highly clonal infiltration of B cells in cancer tissues; (2) prominent IgG-type B cells in tumor tissues; and, (3) substantially different profiles of B-cell repertoire between individuals. We then paid closer attention to the dominant B-cell clones in each cancer case, and artificially reconstructed the highly clonal immunoglobulins, or antibodies (Abs). By identifying tumor-antigens that correspond to those Abs, we found that, although a portion of B-cell immunity is shaped by abundant cellular auto-antigens, a substantial portion of tumor-resident B cells produce functional Abs. In particular, we identified anti-sulfated glycosaminoglycans (sulfated-GAGs) Abs, which showed robust growth-suppression against gastric cancer cells and a wide variety of other human malignancies. HSGAG (heparan sulfate glycosaminoglycan) is a common type of sulfated GAGs found on cell surface, and its tumor-specific structures and functions are also hypothesized to date.

Q What made you focus on gastric carcinoma and B Cells?

A: Gastric carcinoma (GC) is one of the most frequent malignancies worldwide. Diffuse-type gastric carcinoma (DGC), which accounts for more than 30% of GCs, shows the worst prognosis among gastric tumors. Although we have identified several frequent genetic mutations in DGCs, including RHOA, targeted therapies against such classically non-druggable proteins have not yet been established. Anti-tumor immunotherapy has gained considerable attention recently and GCs might also be good candidates for it. Through an integrative analysis of The Cancer Genome Atlas (TCGA) database, we found higher B-cell infiltration specifically in DGC cases compared to other types of GCs; thus, we were motivated to study precise B-cell immunity in cancers by focusing on DGCs.

Q How does your research align with the focus areas of TMDU?

A: At TMDU, there is a strong focus on cancer research and well-established facilities for supporting translational research. One of TMDU's goals is to expedite the discovery of new diagnostic tools and treatments to contribute to society and humanity.

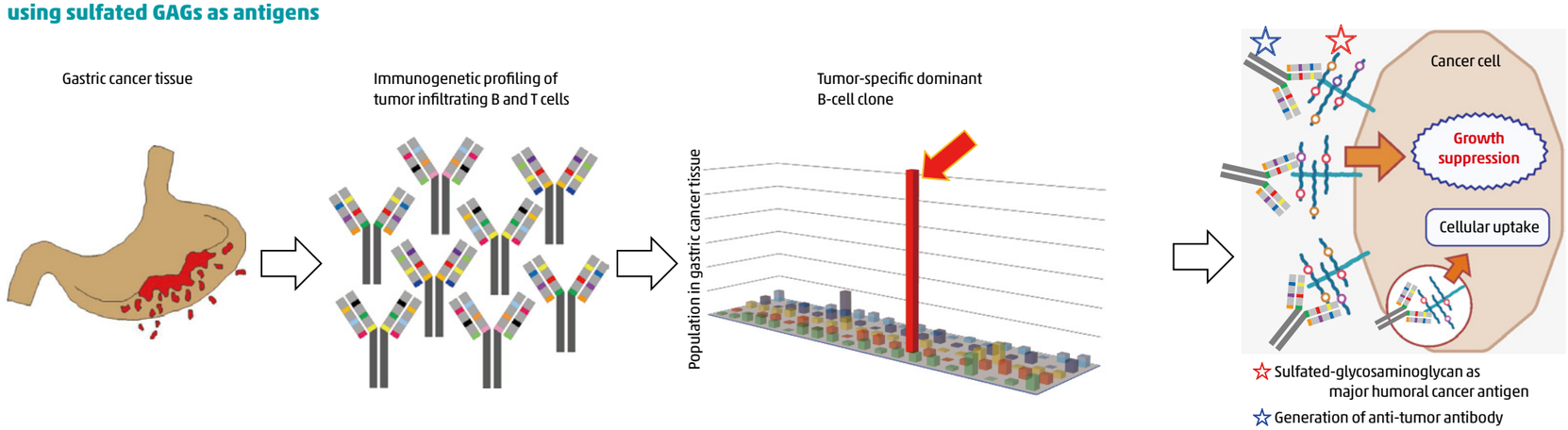
Q What are the future directions and challenges of your research?

A: Although the Abs identified in our study exerted growth-suppressive effects against a wide variety of human malignancies *in vitro*, their molecular functions and behaviors *in vivo* are still open questions. Identification of more specific structures of the HSGAG antigens is one of the most important aims of future research to clarify the precise function and safety of the Abs we identified. Also, it is important to perform in-depth evaluation of the safety and efficacy of the anti-HSGAG Abs in *in vivo* models.

Q What are the clinical implications of your study?

A: One of the most important points of our study is that we identified HSGAGs as the major and functional B-cell antigen in cancer environments. Our findings shed light on the immunologic aspects of HSGAGs and might encourage clinical communities to develop HSGAGs such as heparin as a cancer vaccine. From an optimistic point of view, combined therapies with a state-of-the-art anti-PD-1 immune stimulant and patient stratification based on pre-existing anti-HSGAGs immunity would maximize the efficacies and benefits of the heparin as a cancer vaccine. Going forward, the adoption of more extensive profiling of tumor-infiltrating B cells is expected to pave the way toward understanding tumor immunity, and to help discover tumor antigens and natural anti-tumor Abs to fight against refractory cancers.

Identification of tumor-specific dominant B cells, and immunotherapy using sulfated GAGs as antigens



Dr. Ishikawa graduated from the Faculty of Medicine at the University of Tokyo in 2000 and received his PhD 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 Associate Professor in the Department of Pathology there, and joined TMDU as Professor of Genomic Pathology in 2013.

Cell Rep., doi: 10.1016/j.celrep.2017.07.016

A new graduate program on preemptive and precision medicine launched at TMDU

Hajime Karasuyama
Executive Director / Executive Vice President

TMDU will launch a new graduate program called "Integrative Sciences for Preemptive Medicine" in April 2018.

The new program will offer an innovative academic framework for providing preemptive and precision medicine. In addition to using traditional methods of gathering, managing, and analyzing data from individual genetic or epigenetic profiles and electronic clinical records, researchers will also utilize IoT, ICT, and AI technologies. Using all of these methods, they can gather, manage, and analyze real-time information on an individual's lifestyle and relevant environmental factors in an integrated manner.

It is increasingly clear that researchers today must be able to analyze medical big data in an integrated fashion in order to achieve higher accuracy in preemptive and precision medicine. To that end, this new program will offer critical opportunities to learn about preemptive and precision medicine to interested students of all academic backgrounds – whether medicine, dentistry, or engineering science. Such an approach will bring together faculty and students from diverse academic backgrounds. Through their collaboration, they will be able to discover novel findings heretofore unknown in medical research, and thus create a predictive system that promises to optimize medicine and health.

At a time when death from infectious disease has decreased, yet the number of patients with lifestyle-related diseases is on the rise, we are determined to train healthcare professionals to conduct preemptive and precision medicine capable of predicting disease at the individual level and delivering optimized therapies for each patient.

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

Know your enemy to know your strategy: Identification of genomic signatures and biochemical pathways in precision medicine

Johji Inazawa
Professor of Molecular Cytogenetics at TMDU
Toshihiro Tanaka
Professor of Human Genetics and Disease Diversity at TMDU

Q Dr. Inazawa, you are Director of the TMDU Bioresource Research Center. Can you tell us about the key objectives and focus of the Center?

A: The TMDU Bioresource Research Center aims to discover new causes for diseases and develop precision medicine—a key concept in recent years. Precision medicine is disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle. This enables us to more accurately predict which treatment and prevention strategies for a particular disease will work in which groups of people. Research has already revealed many of the molecular mechanisms that lead to diseases, with some having their own unique genomic signatures and biochemical pathways.

While the concept of precision medicine is not new—blood typing, for instance, has been used to guide blood transfusions for more than a century—the prospect of applying this concept broadly has been dramatically improved by the recent development of large-scale biologic databases, powerful methods for characterizing patients, and computational tools for analyzing large sets of data. At the Center, we have advanced facilities to collect and maintain high-quality data, as well as tissue samples, from patients at TMDU hospitals.

Q Your research has focused mainly on microRNAs associated with the NRF2-KEAP1 pathway in cancer. Can you tell us more?

A: The protein NRF2 plays a key role in cellular antioxidant defenses and maintains redox homeostasis. A substantial body of literature demonstrates the enhancement of NRF2 function as a promising antioxidant strategy. In human cancers, aberrantly stabilized NRF2, either by mutation of the NRF2 or KEAP1 gene, plays a vital role in chemoresistance and tumor cell growth, suggesting that targeted inhibition of NRF2 is a potential therapy for NRF2-stabilized tumors.

MicroRNAs (miRNA), which are small RNAs that are not directing the production of a peptide sequence, can negatively regulate gene expression by interfering with the translation and/or the stability of target transcripts. Cancer cells are thought to upregulate cytoprotective processes (protection of cells by chemical compounds) for their survival. Previously, we reported that overexpression of the miRNA, *miR-634*, activates enhanced chemotherapy-induced cytotoxicity in a model of esophageal cancer, where resistance to chemotherapy remains clinically problematic (*Mol. Cancer Res*. 2014, *Cancer Res*. 2015). More recently, we found that inhibition of another miRNA, *miR-432-3p*, results in increased sensitivity of esophageal cancer cells to chemotherapy drugs, including cisplatin.

Taken together, our findings provide novel insights for regulation of the NRF2 pathway and for miRNAs as targets for overcoming chemoresistance in patients with cancer.

Q Dr. Tanaka, your research interest lies in genetic loci associated with diseases. Please give us a brief overview of your latest findings.

A: To further define the genetic basis of atrial fibrillation, we conducted a meta-analysis of 22,346 individuals with atrial fibrillation and 132,086 referents as international collaborative efforts. We successfully identified 12 new genetic loci, implicating genes involved in cardiac electrical and structural remodeling. We focused on atrial fibrillation because it is a common cardiac arrhythmia condition that can cause serious complications such as stroke, heart failure, dementia, and death. The lifetime risk of atrial fibrillation is one in four, with over 33 million individuals estimated to be affected worldwide today.

Q What are the clinical implications of your study?

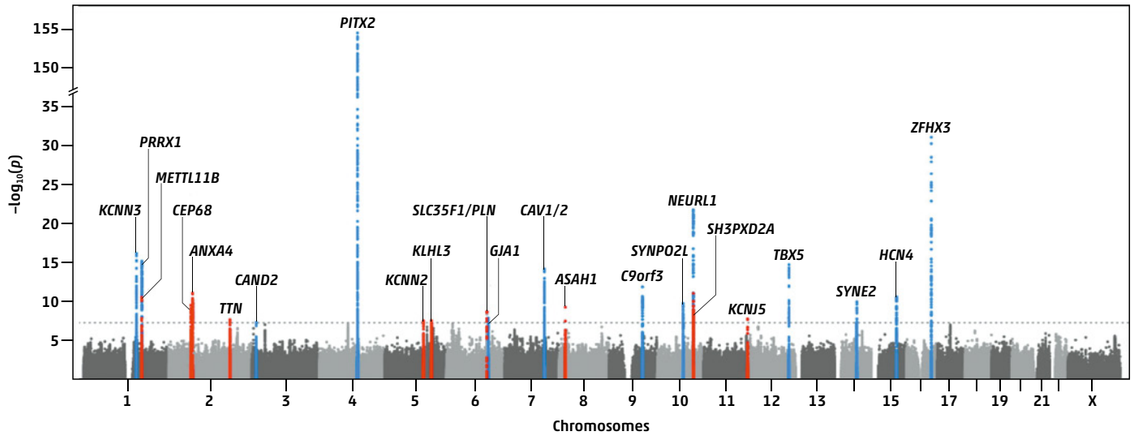
A: Our results nearly double the number of known genetic loci implicated in atrial fibrillation, providing novel insights into the molecular basis of atrial fibrillation. We have identified a series of new atrial fibrillation-associated loci variants, which lie proximal to genes involved in atrial electrical and mechanical function. This is valuable information for future downstream research to establish the mechanistic links between identified genetic loci and atrial fibrillation pathogenesis. Most importantly, our findings may help in the discovery of new therapeutic targets for the treatment of atrial fibrillation.

Dr. Inazawa graduated from Kyoto Prefectural University of Medicine where he received his MD and PhD. He pursued postdoctoral research at Kyoto Prefectural University from 1982 to 1996, when he became Associate Professor at the University of Tokyo. He joined TMDU as Professor of Molecular Cytogenetics at Medical Research Institute in 1998, and assumed the position of Director of the Bioresource Research Center in 2012.

Dr. Tanaka graduated from the University of Tokyo, School of Medicine where he received his MD and PhD. He conducted research as Assistant Professor at the University of Tokyo from 1997 to 1999, then moved to RIKEN in 2000, and took the post of Deputy Director of RIKEN Center for Genomic Medicine in 2009. Since 2013, he has been Professor of Research Division at the Bioresource Research Center of TMDU and Professor of Human Genetics and Disease Diversity at Graduate School of TMDU.

Mol.Cancer Res., doi:10.1158/1541-7786.MCR-17-0232
Nat. Genetics, doi: 10.1038/ng.3843

Manhattan plot of the meta-analysis revealing the genes involved in atrial fibrillation



This plot shows novel (red) and replicated (blue) genetic loci associated with atrial fibrillation. The dotted line represents the threshold of statistical significance (5×10^{-8}). The gene names represent the genes in closest proximity to the most significant variant at each locus. There is a break in the *Y*-axis to increase the resolution of the genetic loci near the genome-wide significance threshold.

Comprehensive survey of blood samples for 73 cancer genes: toward painless and faster cancer medicine

Sadakatsu Ikeda
Specially Appointed Junior Associate Professor, Cancer Center of TMDU

At the Medical Hospital of TMDU, we have initiated the "PROFILE study", a clinical trial focused on cancer genome analysis using patients' blood samples. For the first time in Japan, this study utilizes the comprehensive genetic test of 73 cancer genes called "Guardant360" under contract for consignment of operations with Guardant Health, Inc. (USA).

Although tissue biopsies have been the conventional procedure for cancer genome study, the present test requires only a simple blood draw from patients, offering a non-invasive procedure as compared to tissue biopsies, thereby reducing the patients' pain and shortening sampling time. In this test, a blood sample from a patient yields information on genomic alterations related to cancer by analyzing the DNA originated from dead tumor cells, *i.e.* "cell-free DNA" circulating in the patient's bloodstream. We anticipate that the results from this test will lead to novel cancer treatments, such as precision medicine.

This test procedure, also called liquid biopsy or blood biopsy, is currently regarded as a complement to tissue biopsy rather than as an alternative. However, according to the NCCN Guidelines for Non-Small Cell Lung Cancer (U.S.), liquid biopsy can be considered as an alternative if it is difficult to repeat tissue biopsies. Therefore, in the United States, this procedure is expected to offer a useful screening tool for other types of cancer as well.

In Japan, blood biopsy is currently performed only for detecting EGFR gene alterations using the cobas® EGFR Mutation Test with insurance coverage, while blood biopsy for the comprehensive survey of 73 cancer genes is offered only at the Medical Hospital of TMDU.

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

Nuclear receptors as drug targets

Hiroyuki Kagechika

Professor of Organic and Medicinal Chemistry at TMDU

Q Your focus is on nuclear receptor ligands. Please briefly describe what they are.

A: Nuclear receptors are a family of ligand-regulated transcription factors – proteins that control the transcription of specific genetic information – that are activated by small hydrophobic signaling molecules such as steroid hormones, thyroid hormone and activated vitamin A (retinoid) and D.

Nuclear receptors regulate various biological phenomena, including growth, development, metabolism, the immune system, and homeostasis, and are significant molecular targets for drug discovery in the fields of cancer, metabolic syndromes, autoimmune diseases, and neurodegenerative diseases.

Q Can you give us an overview of your latest findings?

A: We have been extensively studying retinoids (active vitamin A). There are two classes of retinoid nuclear receptors, RARs and RXRs. RXRs play significant roles in nuclear receptor actions by forming heterodimers with various nuclear receptors. We have developed various specific agonists and antagonists for RARs and RXRs. Further, we recently found retinoids with non-classical action mechanisms.

We have also determined the crystal structures of nuclear receptor ligand-binding domains and the ligand-dependent activation mechanism, which enabled us to rationally design selective ligands of nuclear receptors. Further, we have advanced medicinal chemistry of nuclear receptors by successfully developing novel hydrophobic pharmacophores, which have been applied to the development of synthetic steroid hormones and vitamin D analogs with unique structures.

Q Please tell us about your other research interests.

A: We have promoted the collaboration with medical and dental researchers. With my colleagues at TMDU, we have recently identified novel bioactive molecules, such as activators of a transcriptional coactivator TAZ involved in the Hippo pathway, the WNK signaling inhibitors as a new class of antihypertensive drugs, and inhibitors of the Nrf2 signaling pathway that plays a critical role in regulating cellular defenses against electrophilic and oxidative stress.

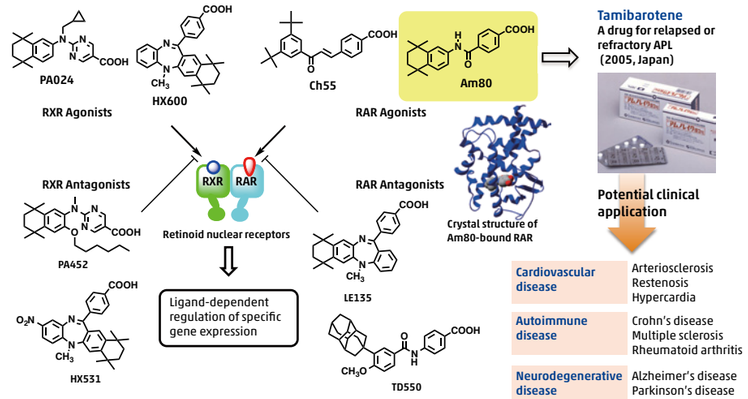
For example, we screened nearly 18,000 molecules in the chemical library of our institute for TAZ activators, and identified one compound that enhanced the myogenesis in mouse C2C12 myoblast cells from 55 hit compounds, which is a promising lead compound for a drug to prevent muscle atrophy and facilitate muscle regeneration after injury.

Q What are the clinical implications of your research?

A: Our synthetic retinoid, Am80 (Tamibarotene) is now clinically used as a drug for acute propyelocytic leukemia (APL). Now, we are trying to use the drug to treat other diseases, including inflammatory bowel disease and Alzheimer's disease.

Synthesis of novel nuclear receptor ligands and their clinical application

[Example: Structures of synthetic retinoids and clinical application of Am80 (Tamibarotene)]



Dr. Kagechika obtained his PhD from the University of Tokyo in 1989, and was employed as an assistant or associate professor there from 1985-2004. Currently, he is Professor in TMDU's Graduate School of Biomedical Sciences, Institute of Biomaterials and Bioengineering, and has been Vice Dean of the Graduate School since 2012. His major research interest is medicinal chemistry of nuclear receptors.

Sci. Rep., doi: 10.1038/s41598-017-04233-3
Sci. Rep., doi: 10.1038/srep22396
Mol.Cell. Biol., doi: 10.1128/MCB.01346-13
Bioorg. Med. Chem., doi: 10.1016/j.bmc.2017.05.034

Uncovering the molecular mechanisms of blood and lymphatic vessel formation

Tetsuro Watabe

Professor of Biochemistry at TMDU

Dr. Watabe graduated from the University of Tokyo and received his PhD at University of California. He became Assistant Professor (2001) and Associate Professor (2009) at the University of Tokyo, then Professor of School of Life Sciences, Tokyo University of Pharmacy and Life Sciences in 2013. He joined TMDU as Professor of Biochemistry in 2015. He has held the office of Special Advisor to the President since 2017.

Q Your research focuses on blood and lymphatic vessel formation. Why are these processes physiologically important?

A: Normal blood vessel development is required for the development of a functioning circulatory system during embryogenesis and also for tissue remodeling and repair in children and adults. In addition, the lymphatic system is necessary for tissue fluid homeostasis; disruption of functional lymphatic vessels results in lymph-edema. We are working with collaborators in Japan and internationally to uncover the molecular pathways that govern blood and lymphatic vessel development and maintenance, both under normal physiological conditions and in disease states such as cancer.

Q Can you tell us about your findings?

A: We have been investigating members of the transforming growth factor (TGF)-ß family. We have shown that TGF-ß inhibits blood vascular endothelial cell proliferation and increases endothelial permeability. We recently found that BMP-9 (bone morphogenetic protein) functions in both blood and lymphatic vessel formation. Activation of this signaling axis promotes blood vessel formation both *in vitro* and *in vivo* (e.g. tumor xenograft model). Conversely, it inhibits lymphatic vessel formation both during normal development and in tumors.

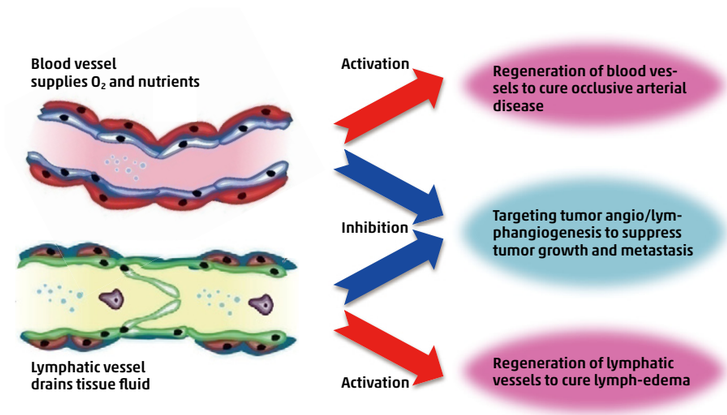
Q Why is an understanding of these molecular pathways important clinically?

A: Both blood and lymphatic vessel formation are of critical interest both in cancer research and regenerative medicine. Progression and metastasis of various types of tumors require growth of new blood and lymphatic vessels, since blood vessels supply oxygen and nutrients to cancer cells and both kinds of vessels provide a pathway for metastasis. We have reported that the inhibition of BMP-9 signals has effectively decreased tumor formation, suggesting that BMP-9 is a potential molecular target for therapeutic interventions. Furthermore, regeneration of blood and lymphatic vessels is urgently required for curing patients of occlusive arterial disease and lymph-edema. Since regulation of signals mediated by TGF-ß and BMPs improves the quality of newly formed blood and lymphatic vessels, a comprehensive overview of the signaling pathways is important for developing novel therapeutic strategies for cancer and regenerative medicine.

Q How does your research align with TMDU's strengths and objectives?

A: TMDU has a strong tradition of translational research, so it is an excellent setting for pursuing this kind of basic research with clinical applicability. In particular, since TMDU recently launched a "Organ and Tissue Neogenesis Consortium", which emphasizes regenerative medicine, our efforts in the bioengineering of blood and lymphatic vessels align with TMDU's mission to contribute to people's well-being.

Bioengineering of blood and lymphatic vessels by TGF-ß family signals



Blood and lymphatic vessels play important roles not only in the maintenance of fluid homeostasis but also in cancer progression. We are trying to activate and/or inhibit angio/lymphangiogensis by modulating TGF-ß family signals for cancer therapy and regenerative medicine of occlusive arterial disease and lymph-edema.

J Cell Biol., doi: 10.1083/jcb.200305147
Proc. Natl. Acad. Sci. U. S. A., doi: 10.1073/pnas.1310479110
Cancer Sci., doi: 10.1111/cas.13103

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Learning from the deceased to help the living

Kana Unuma

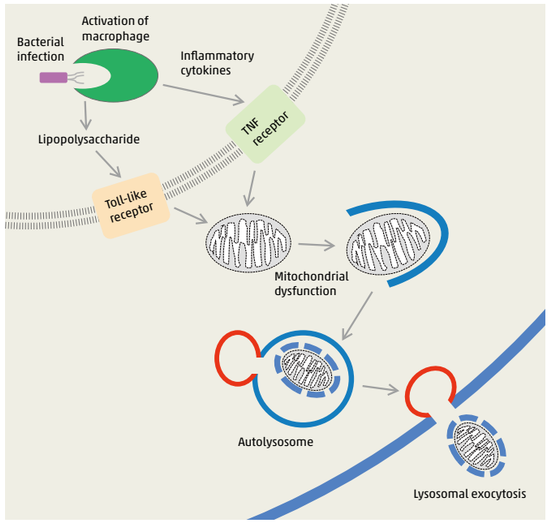
Junior Associate Professor of Forensic Medicine at TMDU

Forensic medicine is an academic discipline in which doctors learn by studying deceased people and make use of the new knowledge for living patients. After completing medical and clinical training, I started my career as a forensic pathologist and received my PhD in 2010.

After I became an assistant professor at TMDU, I began to research sepsis. Sepsis is a state of severe systemic inflammatory response that can progress to multi-organ dysfunction. Although there are many autopsy cases in which sepsis is suspected, their pathophysiology is complicated and it is often difficult to diagnose sepsis. It has recently been reported that there is an increase in mitochondria-derived damage associated molecular patterns (mtDAMPs) molecules in the plasma of sepsis patients and in sepsis animal models. Also, mtDAMPs have been shown to be correlated with the severity of sepsis. However, the mechanism of mtDAMPs release has not been elucidated. In this regard, we showed that lipopolysaccharide stimulation of primary hepatocytes resulted in active extracellular release of mtDAMPs through the exocytosis of autolysosomes (*Autophagy*, doi: 10.1080/15548627.2015.1063765). We also found that inhibition of the autophagy process attenuated mtDAMPs release from the cells. These data demonstrated an active role for autophagy in the secretion of cellular proteins from cells during sepsis and provided important insights into the mechanism of sepsis-induced mtDAMPs release.

The number of autopsies examined totaled around 30 to 40 cases per year in 2010, but that increased to nearly 200 cases in 2016. Facing many complex forensic cases, I often feel myself stretching into new areas and I study every day to keep up with developments in my field. I want to manage a variety of cases, respond to social demands, think about new forensic education, and pursue fulfilling research.

Mechanisms of mtDAMPs release



Targeting intercellular communication between bone cells

Mikihito Hayashi

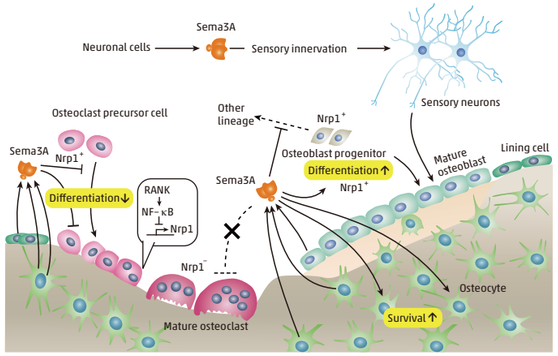
Assistant Professor of Cell Signaling at TMDU

Bone is a constantly renewing organ throughout life. This is characterized predominantly by skeletal growth during development and childhood, and a subsequent continuous turnover, known as "bone remodeling". It is a finely balanced activity and carried out by specialized groups of cells, including osteoclasts, which are multinucleated cells that resorb bone, and osteoblasts, which refill the resorption cavities created by osteoclasts. An imbalance between bone resorption and formation results in metabolic bone disorders such as osteoporosis, a disease of low bone mass with increased susceptibility to bone fractures.

We demonstrated that the essential source of RANKL, a critical factor for osteoclast differentiation, is osteocytes, which are terminally differentiated osteoblasts embedded in bone matrix (*Nat. Med.*, doi:10.1038/nm.2452). We also demonstrated that Sema3A, which was originally identified as a guidance factor for developing axons, plays an important role in the regulation of cell-to-cell communication between osteoclasts, osteoblasts and osteocytes during bone remodeling (Figure; *Nature*, doi:10.1038/nature11000). We are now trying to demonstrate that osteocyte-derived Sema3A, which is under the control of estrogen, acts on osteocyte survival, along with the inhibition of osteoclastic bone resorption and the activation of osteoblastic bone formation.

After completing my PhD at TMDU in 2010, I worked as a postdoctoral fellow of JST(Japan Science and Technology Agency) from 2010 to 2012. In 2012, I became an Assistant Professor at TMDU. The goal of our laboratory's research is to identify the communication factors involved in bone cells and other tissues and organs, in addition to understanding the osteocyte-mediated response to mechanical stress.

Bone homeostasis achieved by osteoprotective Sema3A



Validation of prospectively isolated mesenchymal stem cells

Eriko Grace Suto

Project Assistant Professor of Biochemistry and Biophysics at TMDU

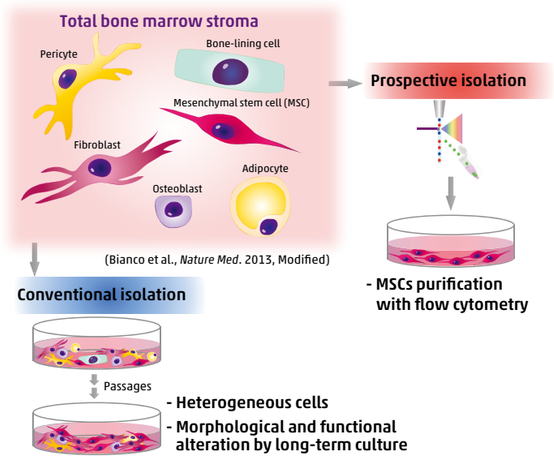
After obtaining my master's degree from TMDU, I started my career in my present position. Although I am qualified as a medical technologist, I have started as a basic researcher because I am fascinated by the mechanisms of regenerative therapy. My research seems to lie at a remove from medical technology, but my ideas are always rooted in what I learned from studying that field.

I've been focusing on somatic cells in the human body, which contribute to homeostasis – in particular, mesenchymal stem/stromal cells (MSCs). MSCs reside in various tissues, such as bone marrow, umbilical cord, synovium, muscle, fat, and dental pulp, to retain the surrounding environment by regenerating tissues or by controlling immune reactions. These days, MSCs are used in clinical practice to regenerate cartilage or prevent graft-vs.-host disease, for example. For clinical materials, MSCs can be harvested from a range of tissues, and the source varies from product to product.

Previously we identified that MSCs can be prospectively isolated using anti-CD73 antibody, which can be used across species such as human, mouse, and rat (*Sci. Rep.*, doi: 10.1038/s41598-017-05099-1). Our finding provided an effective way for harvesting MSCs, and indicated that CD73 could have a role in controlling the function of MSCs.

Now we are trying to compare the characteristics of human MSCs harvested from various tissues. By elucidating MSC behavior depending on the source tissue, we hope to supply suitable MSCs for each disease. Thanks to helpful advice and assistance from many medical doctors, we have been able to pursue our research on human MSCs. I think this cooperative framework is one of the great appeals of conducting research here at TMDU, and I'm honored to do my work here.

MSCs isolation method



Therapeutic applications of supramolecular polymers

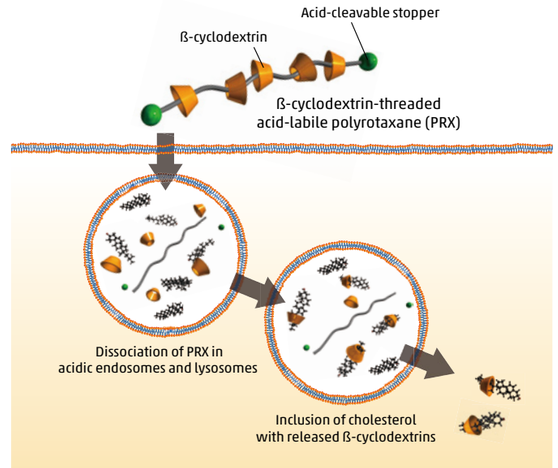
Atsushi Tamura

Assistant Professor of Organic Biomaterials at TMDU

After graduating from the University of Tsukuba in 2010, I worked at the Institute of Advanced Biomedical Engineering and Science at Tokyo Women's Medical University as a postdoctoral fellow. In 2011, I started my career as an Assistant Professor in the Department of Organic Biomaterials at TMDU. My field of expertise is polymer chemistry and materials science, and I have been studying material-based modulation of cellular functions and the treatment of diseases. In particular, my current research interests involve the therapeutic applications of cyclodextrin-threaded biocleavable polyrotaxane, a supramolecular polymer, in which the polymer chain is threaded through numerous cyclodextrin rings.

Recent studies have revealed that cyclodextrins exhibit therapeutic effects against several diseases, such as Alzheimer's disease, atherosclerosis, and lysosomal storage disorders, by the incorporation of lipids and sterols into their hydrophobic cavity. My previous studies revealed that polyrotaxanes act as intracellular delivery carriers of cyclodextrins, and the polyrotaxanes exhibit superior therapeutic effects in Niemann-Pick type C disease compared to cyclodextrins (*Sci. Rep.*, doi: 10.1038/srep04356; *J. Control. Release*, doi: 10.1016/j.jconrel.2017.11.016). Additionally, the methylated ß-cyclodextrin-threaded biocleavable polyrotaxanes are found to induce autophagy and autophagic cell death through the intracellularly released methylated ß-cyclodextrins-mediated induction of organelle stress. Currently, several collaborative studies are being conducted to investigate the therapeutic effects of polyrotaxanes on other metabolic diseases and the modulation of cellular functions by polyrotaxanes. I expect that polyrotaxanes will prove to have a significant role in disease treatment and fundamental research.

Intracellular dissociation of polyrotaxanes and inclusion of intracellular cholesterol



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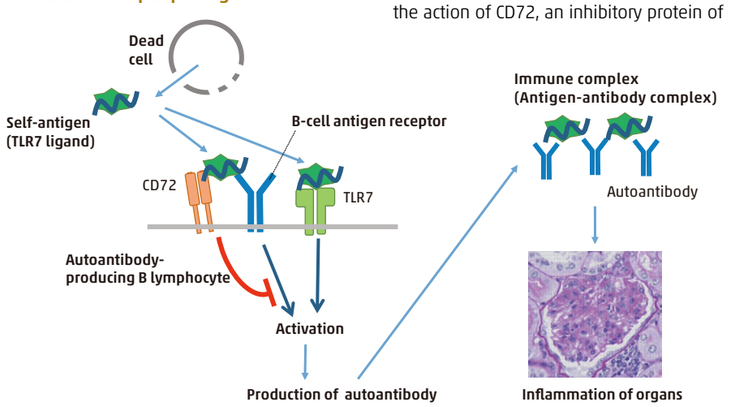
Selective inhibition of lupus autoantibody production provides key to disease control

The immune cells of patients with autoimmune diseases such as systemic lupus erythematosus (known commonly as lupus) are not properly regulated, causing the body to react against its own cells and tissues. In the case of lupus, this occurs in response to the TLR7 protein mistakenly stimulating a type of white blood cell (B lymphocytes, also called B cells) to produce antibodies against a self-antigen (the body's own TLR7 ligand). This results in the inflammation of joints, skin, and internal organs. Lupus development is prevented by the action of CD72, an inhibitory protein of B cells. Takeshi Tsubata and colleagues at TMDU investigated how this occurs, using a recombinant protein composed of a portion of CD72 and B cells from mice that lack CD72. Their work revealed that CD72 selectively binds to the ligand of TLR7, stopping B cells from producing autoantibodies, and preventing lupus symptoms. However, crucially, CD72 did not affect the production of antibodies to other antigens. This suggests that changing the CD72 function may control lupus development without affecting other immune responses. These findings have important implications for understanding the pathophysiology of lupus and the development of novel therapies for this disease.

J. Exp. Med., doi: 10.1084/jem.20160560

Mechanism of lupus pathogenesis



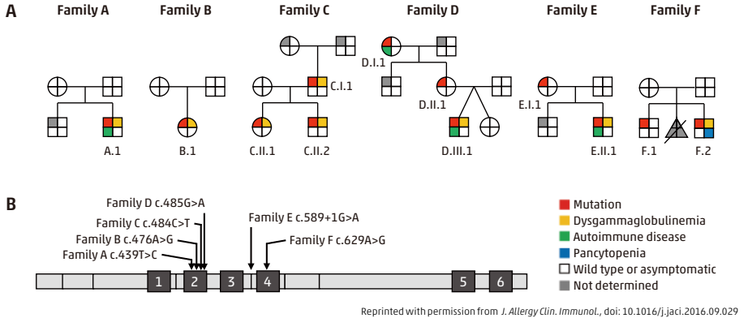
The body's own (self) TLR7 ligand stimulates autoantibody-producing B lymphocytes to produce autoantibody to the self-TLR ligand, which causes tissue damage. This stimulation is mediated by B-cell antigen receptor and TLR7. CD72 interacts with self TLR7 ligand and inhibits cell activation, thereby inhibiting the process of lupus development.

Mutations of blood cell protein cause immune deficiency and autoimmune disorders

Developmental processes in the body are tightly controlled by signaling molecules and transcription factors, which regulate gene expression. The protein IKAROS (encoded by the *IKZF1* gene) is one such transcription factor that controls the development of blood cells. While *IKZF1* mutations are commonly found in leukemic cells in children, heritable *IKZF1* mutations in germ cells are associated with immune disorders. However, the specific effect of these mutations on patient phenotypes remains unclear. Tomohiro Morio of TMDU led research to investigate *IKZF1* mutations in nine patients from six unrelated Japanese families by sequencing all their protein-coding genes. The patients carried various *IKZF1* mutations, but most shared the same immune disorder and a deficiency of B lymphocytes. Several also had autoimmune disorders. Analysis of their mutant IKAROS proteins showed that all were unable to correctly bind DNA, and had an abnormal nuclear localization. This work extends the *IKZF1* mutation spectrum, and reveals a role for IKAROS in human immunology and the development of blood cells.

J. Allergy Clin. Immunol., doi: 10.1016/j.jaci.2016.09.029

Analysis of *IKZF1* mutations in patients with immune disorders



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Heterozygous germline *IKZF1* mutations cause hematopoietic abnormality and autoimmunity. A: Pedigrees of families A to F. B: Schematic of IKAROS protein domain and location of its mutations. Black boxes labelled by number indicate zinc finger (ZF) domains.

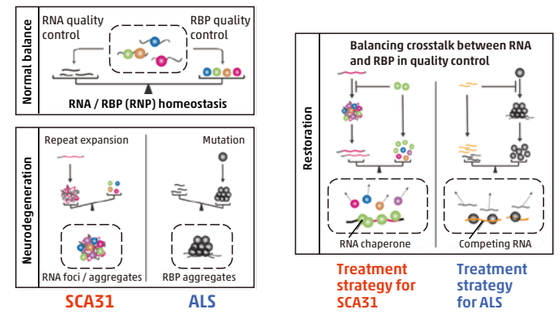
Protein quality-control mechanism limits neurological damage

A number of neurological diseases are caused by an increase in the number of repeats of short lengths of DNA motifs known as microsatellites. One such disease, SCA31, is associated with damage to the cerebellum, which is the part of the brain involved in balance, coordination, and speech. To understand how the repeats cause disease, an international team including TMDU researchers led by Kinya Ishikawa studied their effects in a fruit fly model of SCA31.

The authors demonstrated that TDP-43 and other RNA-binding proteins (RBPs) act as chaperones to regulate the formation of toxic RNA aggregates. Furthermore, these RBPs markedly inhibit expression of toxic proteins derived from SCA31 repeat RNA in fruit fly models. Surprisingly, these RNA/RBP interactions regulated not only the RNA folding but also the aggregation propensity and toxicity of RBPs in fruit fly models of motor neuron disease. Thus, it appears that functional crosstalk of the RNA/RBP network regulates their own quality and balance, suggesting a convergence of pathomechanisms in microsatellite expansion disorders and RBP proteinopathies. It is hoped that controlling this crosstalk could be a therapeutic strategy for various neurological disorders.

Neuron, doi: 10.1016/j.neuron.2017.02.046

Proposed model in neurodegeneration and strategy for treating neurological diseases



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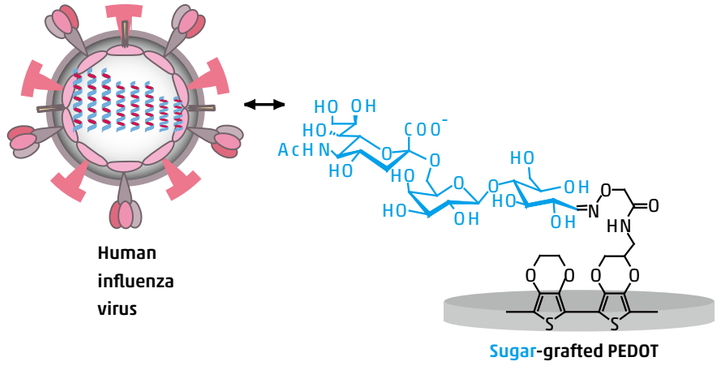
The authors built a new hypothesis that certain RNAs and their binding proteins (RBPs) normally have a balanced state ("homeostasis"), which seemed to be disturbed in some of the devastating neurological diseases such as ALS and cerebellar ataxias (SCA31). Restoring this balance may make these diseases treatable. For example, RNA repeat expansion overload in SCA31 was re-balanced and cured by putting RBP in SCA31 fly model.

Incorporation of sugar into polymer enables specific biosensing of human influenza virus

Conducting polymers conduct electricity, and they have the advantages of low toxicity and flexibility, which make them suitable for use in biological systems as biosensors. Tatsuro Goda and colleagues at TMDU exploited the ability of conducting polymers to chemically receive a "graft" of biomolecules, such as proteins or sugars, into their building blocks to detect human influenza virus. Current influenza virus diagnostic methods are limited by time, sensitivity, cost, and complexity of use. However, early detection is key to the prevention of pandemics, which cause up to 500,000 deaths worldwide each year. The team synthesized conducting polymer films based on the PEDOT polymer. They then used the chemical process glycosylation to introduce a type of sugar that could recognize and specifically bind to human influenza virus. This binding was detected by measuring small electrical changes, enabling the virus to be identified at a level of sensitivity two orders of magnitude higher than conventional techniques. The potential to mass produce this approach could allow on-site viral detection, which would be particularly beneficial in remote areas.

ACS Appl. Mater. Interfaces, doi: 10.1021/acsami.7b02523

Sugar-specific viral recognitions on conducting polymers

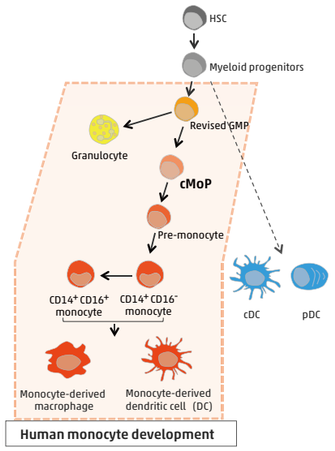


Identification of human clonogenic progenitor provides insight into human myeloid cell differentiation pathways

Monocytes and monocyte-derived macrophages cause a variety of inflammatory disorders, including metabolic syndromes and tumor development. Monocytes, a type of white blood cell, arise from hematopoietic stem cells (HSC) via sequential intermediate progenitors in the bone marrow. Progenitors are biological cells that differentiate into a specific type of cell. In mice, a common monocyte progenitor (cMoP), which is restricted to the monocyte lineage, has been identified. A TMDU research team led by Toshiaki Ohteki found human cMoP as CLEC12A^{hi}CD64^{hi} cells in umbilical-cord blood and bone marrow. The human cMoP can produce both CD14^{+}CD16^{-} and CD14^{+}CD16^{+} monocytes. The presence of cMoP within the conventional granulocyte-monocyte progenitors (GMP) population suggests that conventional GMPs are actually a mixed population of genuine GMPs and other progenitors. This finding not only sheds light on human monocyte differentiation, but also on possible therapeutic applications that target cMoP and monocytes.

Immunity., doi: 10.1016/j.immuni.2017.04.019

Proposed process of human monocyte differentiation



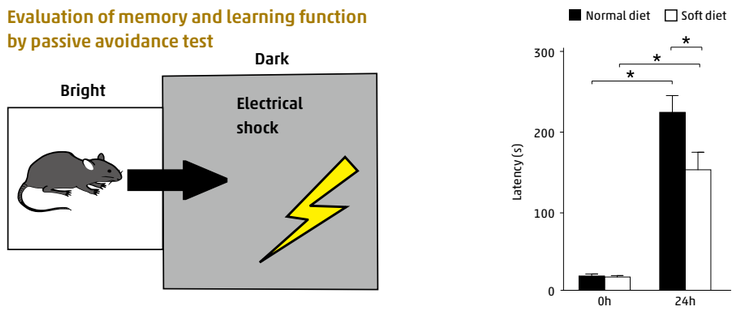
Reprinted with permission from *Immunity.*, doi: 10.1016/j.immuni.2017.04.019

Changes in hippocampus morphology and function explain links between chewing and memory

The action of chewing stimulates the central nervous system and affects cognitive functions such as learning and memory. However, the precise mechanisms underlying these effects have remained obscure. Now, a team led by Takashi Ono and Tomoki Nakashima of TMDU linked reduced chewing during development to reduced neuron formation and activity, and reduced synapse formation in the hippocampus. The researchers created an *in vivo* model of reduced chewing during development by feeding a powdered diet to juvenile mice. The changes in hippocampus morphology and neuronal activity were related to a decrease in levels of a key regulator of neuronal development, brain-derived neurotrophic factor, and were associated with impaired spatial learning and memory in behavioral tests. These findings support a functional link between chewing and cognitive function during development, thus highlighting the importance of addressing, particularly in children, problems such as malocclusion that may make chewing difficult.

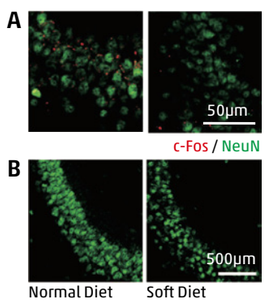
J. Dent. Res., doi: 10.1177/0022034517708771

Evaluation of memory and learning function by passive avoidance test



The passive avoidance apparatus consists of a light and a dark compartment with a hole through which mice can pass. Mice were placed in the light compartment, and the latency to entry into the dark compartment was measured. An electric shock was given to mice in the dark compartment as a conditioning procedure. After 24 hours, the latency of the conditioned mice was measured. Long-term memory, shown in the latency to enter the dark compartment after electric shock conditioning, was lower in the mice fed with soft diet (SD) than normal diet (ND).

Comparison of hippocampus activity in mice fed with SD and ND



A: Neuron activity (c-Fos–positive neurons) in the hippocampus. The number of c-Fos–positive neurons was significantly lower in the hippocampus in mice fed with SD (right) than ND (left). B: The number of neuronal cells (NeuN-positive cells) in the hippocampus. NeuN-positive neuronal progenitor cells in the hippocampus were fewer in mice fed with SD than ND.

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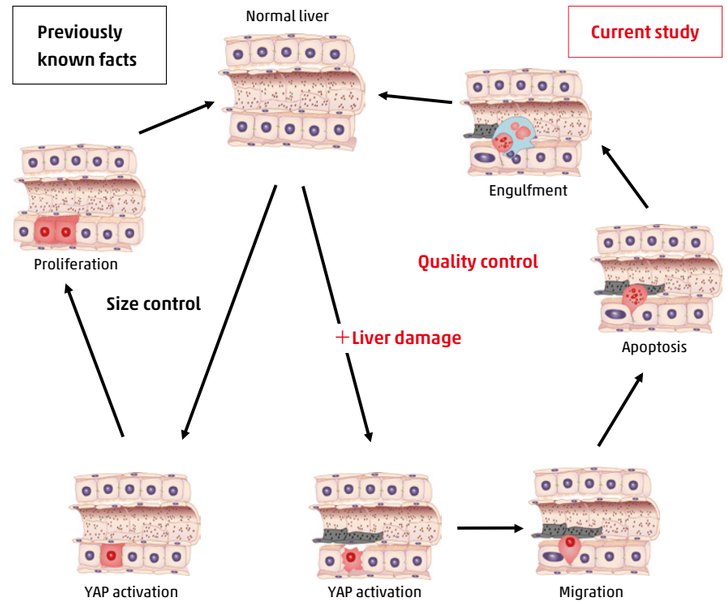
Cell fate of injured mouse hepatocytes *in vivo* determined by the protein YAP

Cellular stress in tissues and organs leads to senescent, transformed or damaged cells, which can impair tissue function or tumorigenesis. However, the molecular mechanisms that act to maintain tissue and organ homeostasis during cellular stress remain largely unknown. Hiroshi Nishina led a TMDU-centered research team which showed that activation of the protein YAP in damaged mouse liver cells promotes their selective elimination. This activation was induced by inactivation of the Hippo pathway, which regulates organ size and cancer formation. The damaged cells migrate into the hepatic sinusoids, undergo apoptosis and are engulfed by Kupffer cells. In contrast, YAP activation in undamaged cells leads to proliferation. The findings indicate that YAP plays a role in emergency stress response by maintaining tissue homeostasis through the elimination of injured cells, highlighting a new role for YAP in tissue dynamics.

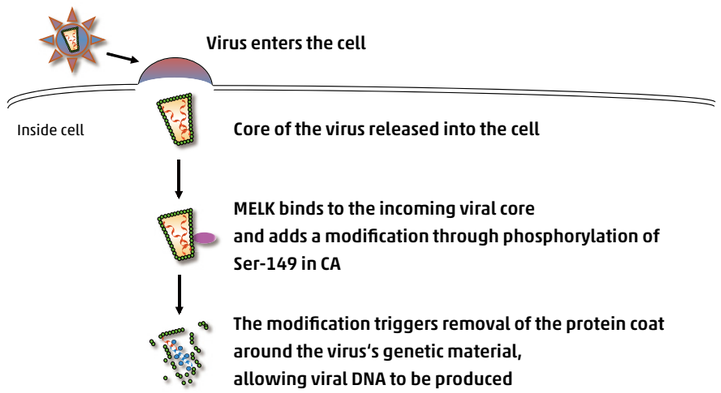
Nat. Commun., doi: 10.1038/ncomms16017

YAP roles in normal and damaged liver tissue



Protein critical for efficient cellular HIV infection identified

Modification of the viral protein coat by MELK regulates its removal to allow viral DNA synthesis



Shortly after HIV-1 entry, MELK produced by the target cell regulates removal of the protein coat (the capsid, CA, which is an important part of the core of the virus) by adding a modification at a specific location. This regulated coat removal promotes optimal production of viral DNA, allowing the infection process to proceed efficiently.

A team led by Hiroaki Takeuchi and Shoji Yamaoka of TMDU identified a protein, MELK, required for the HIV-1 to efficiently infect the cells it attacks. HIV-1 is the most common form of HIV, the virus that causes AIDS. The team found that MELK, which is produced by the infected cell, is necessary for correct removal of the protein coat around the HIV-1, an early stage in the viral life cycle that is essential for infection to proceed efficiently. The study further revealed that MELK alters the protein coat by attaching a chemically active modification through specific phosphorylation of the capsid at serine-149 to promote its removal. These findings not only provide insight into the early stages of the viral life cycle, but also suggest that MELK is a potential new target for anti-HIV treatment.

PLOS Pathog., doi: 10.1371/journal.ppat.1006441

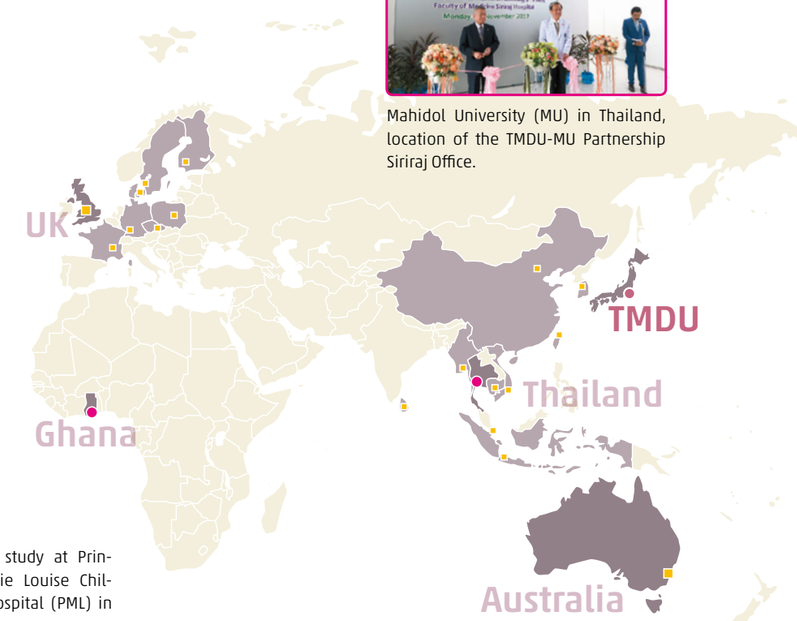
Please contact us »» uraoffice.adm@tmd.ac.jp

Sharing expertise and groundbreaking research around the world

Our international exchange activities in research and education are based in three centers, in Ghana, Thailand and Chile. We further promote educational collaboration with Harvard Medical School, Imperial College London and Australian National University. We also have 108 affiliated schools in 31 countries.

Mahidol University (MU) in Thailand, location of the TMDU-MU Partnership Siriraj Office.

Students join in an oversea program at University of Leeds, UK.

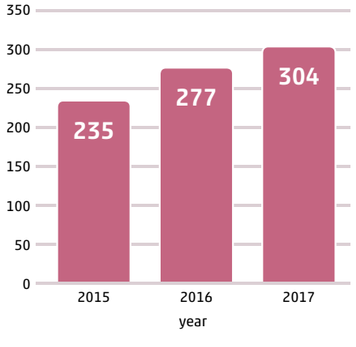


Students study at Princess Marie Louise Children's Hospital (PML) in Ghana.

● Our international collaboration centers
■ Our representative international education partners

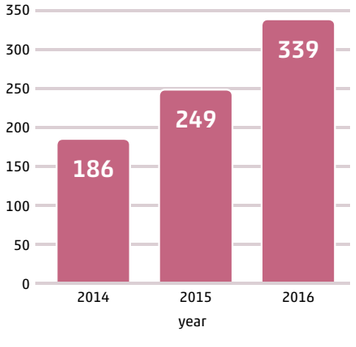
Students participate in exchange program with Australian National University.

International Students



International students comprise about 17% of TMDU's postgraduate student body. May, 2017

Students sent overseas



About 19% of eligible students study abroad. March, 2016

Promoting evidence-based global public health action

Takeo Fujiwara,
Professor, Department of Global Health Promotion

Knowledge generated from scientific research is a strong tool for carrying out effective health policy and practice. There is a great gap, however, between scientific knowledge and practice in today's public health arena. The Master of Public Health in Global Health (MPH) course at TMDU was designed to educate individuals from around the world who want to be leaders in their fields; generating, translating and disseminating public health-related scientific evidence in the real world to make the world a healthier place. TMDU-MPH course offers ambitious people opportunities to gain the necessary knowledge and skills to become global public health leaders.

"*We aim to elucidate how the social environment may be improved to prevent disease and promote overall health throughout the life-course. Furthermore, based on accumulated evidence, we can develop practical health policies and programs to improve our society.*"

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

TMDU's medical students pursue clinical training in the United States at Harvard Medical School, Vanderbilt University and University of Nevada.

How do you like life at TMDU?

Manivong Dasavanh
(Lao PDR)

Not only have I gained knowledge from informative lectures and stimulating seminars by Japanese and foreign experts here, I have also learned about the working processes of mind and service of the university staff and hospital staff, which I will adapt to my work when I return home. Furthermore, I have felt deeply impressed by the sincere help, good advice and beautiful friendship of the teachers and colleagues I have met here at TMDU.

Rajendran Arun Kumar
(India)

It is a great privilege to do my research in one of the world's top universities for dentistry, TMDU. With eminent professors and researchers for guidance, easy access to cutting-edge technology and wide access to scientific literature, it is a great place to acquire advanced scientific knowledge. The friendly staff, sociable students and amenities available for day-to-day life make the living experience especially pleasing for international students.

Human life cannot continue without science and technology. TMDU researchers typically transcend the boundaries of their own specific fields, freely adopting and utilizing diverse areas of scholarship and methodologies for the advancement of research. I have been able to learn from the best researchers and professors and also gained the opportunity to present my research at international academic conferences. During various activities at TMDU, I have realized the importance of team spirit, and how it helps spur me on.

Mieradili Mulati
(China)