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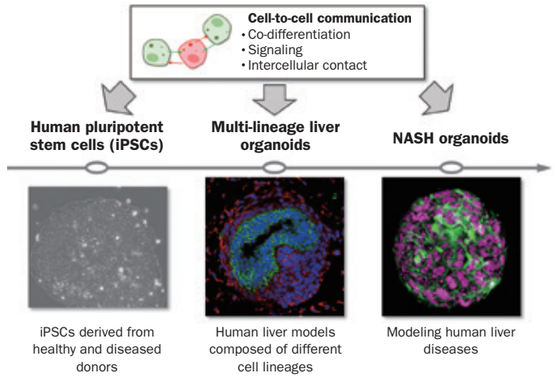
Toward understanding cell-to-cell communication using stem cell and organoid biology

Yosuke Yoneyama
Assistant Professor of Institute of Research at TMDU

I obtained my PhD in 2014 from the University of Tokyo where I completed my thesis work in Shin-Ichiro Takahashi's laboratory and then worked as a postdoctoral fellow there until 2018. During this training period, I focused on insulin-like growth factor (IGF), a peptide hormone that plays a critical role in body growth, metabolism, and aging of animals, including humans. Since IGF induces a variety of bioactivities, I was particularly interested in how IGF tightly controls its activities in target cells. Using molecular and cellular biology techniques, I found some key regulatory nodes in the signaling network that are spatially and temporally organized to control specific bioactivities.

In 2018, I joined Takanori Takebe's laboratory at TMDU as an assistant professor. Our laboratory is focusing on miniature organs *in vitro* called "organoids" that are derived from human stem cells, including induced pluripotent stem cells (iPSCs). Fortunately, I became part of a team studying non-alcoholic steatohepatitis (NASH), a liver disease that causes liver cirrhosis and hepatic carcinomas and is prevalent worldwide. We recently published research on a new human iPSC-derived organoid system that includes multiple lineages of liver cells and recapitulates the complex pathologies of NASH, such as steatosis, inflammation and fibrosis (*Cell Metab.*, doi: 10.1016/j.cmet.2019.05.007). By leveraging this organoid technique, we are trying to elucidate the molecular mechanisms underlying human NASH, focusing on cell-to-cell communication (hepatocytes, stromal cells, immune cells, endothelial cells, etc.), leading to the identification of potential drug targets for NASH. We are also tackling a novel form of cell-to-cell communication observed in pluripotent stem cells, which will eventually contribute to further understanding of human stem cell biology.

Stem cell & organoid technology for understanding cell-to-cell communication and diseases in humans



[Reprinted with permission from *Cell Metabolism*, doi: 10.1016/j.cmet.2019.05.007]

Elucidation of basophil functions in allergic inflammation

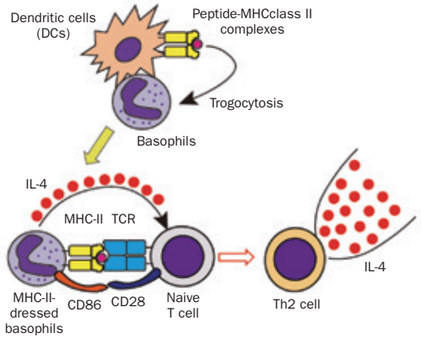
Kensuke Miyake
Specially Appointed Assistant Professor of Immune Regulation at TMDU

I started my research activities as I entered the advanced course for cultivating young researchers in 2012, when I was a fifth-year medical student at TMDU. After obtaining my MD in 2014, I directly entered the PhD course, and I obtained my PhD in 2017. I was then assigned to become the Specially Appointed Assistant Professor of Immune Regulation, and in 2019, was elected as a member of Next Generation Researchers at TMDU.

My research focuses on the functional roles of basophils, especially in the context of allergic inflammation. Basophils are the least common granulocyte, representing less than 1% of peripheral blood leukocytes. Research on basophil functions had been hampered by a lack of tools for investigating basophils. However, the recent development of several tools enables us to understand crucial roles of basophils in chronic allergic inflammation (*Allergol. Int.,* doi: 10.1016/j.alit.2017.04.007). Furthermore, basophils also modulate immune reactions by communicating with other immune cells, including T cells and macrophages. I first focused on the interaction between basophils and T cells, and revealed that basophils present antigens to naive T cells, after interacting with dendritic cells (DCs). Basophils acquire peptide-MHC class II complexes from DCs via a process called trogocytosis (*Proc. Natl. Acad. Sci. USA.*, doi: 10.1073/pnas.1615973114). Antigen presentation together with IL-4 produced by basophils lead to Th2 cell differentiation in the context of allergic inflammation. This work won many awards, including from the Japanese Society of Immunology, and was recommended by F1000 Prime.

In my current research, I focus on the interaction between basophils and macrophages. In the late phase of allergic reactions, basophils induce the differentiation of anti-inflammatory macrophages to suppress excess inflammation. I am now aiming to clarify the suppressive mechanisms of basophils by using transcriptome analysis of anti-inflammatory macrophages. I expect that the outcome of this research will produce novel targets for allergic diseases.

Basophils exert antigen presentation via trogocytosis-mediated acquisition of peptide-MHC class II complexes



Clinical research in geriatric dentistry for a super-aged society

Manabu Kanazawa
Junior Associate Professor of Gerodontology and Oral Rehabilitation at TMDU

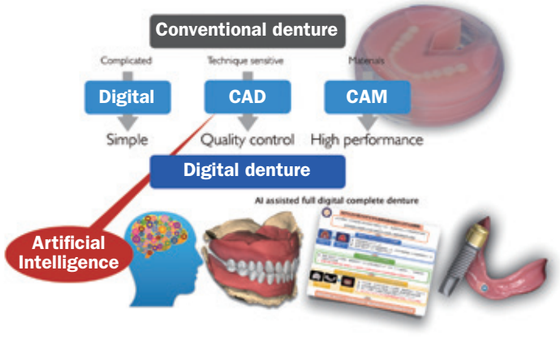
After graduating from TMDU in 2002, I received my PhD in 2006. I worked as clinical staff in TMDU Dental Hospital, and since 2008 as an assistant professor, I have mainly continued clinical studies on complete dentures (CD), implant overdentures (IOD) and computer-aided design/computer-aided manufacturing (CAD/CAM) dentures. In 2013-2014, I had the opportunity to move to McGill University in Canada to pursue research as a visiting professor of Oral Health and Society in the Faculty of Dentistry, under Prof. Jocelyne Fein, a world-famous professor in the field of IOD research.

My current research is focused on the clinical study of edentulous patients who use CDs, IODs and digital CDs. I have been interested in the outcomes and oral function reported by patients. Therefore, we have developed a chewing gum that changes color to assess masticatory performance (Masticatory Performance Evaluating Gum XYLITOL, Lotte) and acquired the patent in partnership with Lotte Corp. More recently, I have focused on nutrition while using a prosthesis, and reported on the importance of providing dietary advice to patients (*Clin. Nutr.*, doi: 10.1016/j.clnu.2017.07.022; *J. Prosthodont. Res.*, doi: 10.1016/j.jpor.2018.12.010). I also have some patents pending for digital CDs (*J. Prosthodont. Res.*, doi: 10.1016/j.jpor.2018.02.001), and am performing specific clinical research.

Additionally, I have signed an open-innovation agreement with Mitsui & Co., Ltd., to develop new artificial intelligence (AI) systems for use in dental diagnosis and treatment. This system also will be linked to studies in geriatric dentistry.

I hope to promote clinical studies based on higher quality evidence and to contribute to society by providing high quality specialized dental treatment.

The digital complete denture system for super-aged society



Analysis of age-related changes in skeletal muscle using progeria model mice

Kyoko Matsuzaki
Assistant Professor of Medical Biochemistry at TMDU

After receiving my PhD from the University of Tokyo, I worked as an assistant professor at the Institute of Medical Science at the University of Tokyo for six years. In 2015, I moved to the Department of Medical Biochemistry at TMDU.

Since I started my career as a researcher, I have been interested in cell biology and have analyzed cellular responses against various stimuli at a molecular level. I have focused particularly on cytoplasmic stress granules (SGs), a major adaptive defense mechanism, investigating the physiological function of SGs and revealing novel relationships between SGs and diseases. After moving to TMDU, I continued working on SG studies, and in 2018, we identified chemical compounds that suppress SG formation.

In my current position working with graduate students, I have broadened my interest to include analysis on an individual level. In particular, we are now focusing on senescence. To accelerate the research, we have established a knock-in model mouse of human Hutchinson-Gilford Progeria Syndrome (HGPS). HGPS is an autosomal dominant genetic disorder caused by mutations of *LMNA*, which encodes Lamin A, a nuclear membrane protein. HGPS patients have a heterozygous *LMNA* mutation and start exhibiting features of premature aging during childhood. Our hetero mice also showed a short life span and started to lose weight from around 24 weeks of age. Above all, the most notable feature in our hetero mice was their muscle atrophy. Thus, we are now focusing on this phenotype and working to figure out the molecular mechanism that induces age-related muscle atrophy.

Characteristics of HGPS model mice