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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.

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.

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.

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.

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.