Department of Pediatrics

Hiroyuki Ida, *Professor*
Mitsuyoshi Urashima, *Professor*
Ichiro Miyata, *Professor*
Yoshihiro Saito, *Associate Professor*
Hiroshi Kobayashi, *Associate Professor*
Masaharu Akiyama, *Assistant Professor*
Masahisa Kobayashi, *Assistant Professor*
Kenjiro Kikuchi, *Assistant Professor*
Daishi Hirano, *Assistant Professor*
Toya Ohashi, *Professor*
Yasuyuki Wada, *Professor*
Toshio Katsunuma, *Professor*
Yoko Kato, *Associate Professor*
Hiroshi Tachimoto, *Associate Professor*
Noriko Takahata, *Assistant Professor*
Asako Tajima, *Assistant Professor*
Norimichi Higurashi, *Assistant Professor*

General Summary

We have 10 subspecialty research groups consisting of the Inherited Metabolic Disease group, the Endocrinology group, the Neurology group, the Hematology and Oncology group, the Infectious Diseases and Immunologic Disorders group, the Nephrology group, the Cardiology group, the Allergy group, the Neonatology group, and the Pediatric Psychiatry group. The final aim of each subspecialty groups is supplying practical benefits to patients and their families through basic and translational research and clinical study.

Research Activities

Inherited metabolic disease group
Our main project is clinical development of lentivirus vector mediated hematopoietic stem cell targeted gene therapy for mucopolysaccharidosis type II (MPS II) and this project was funded by Japan Agency for Medical Research and Development (AMED) this year. This funding facilitated translation of this project to clinics. To optimize transduction of hematopoietic stem cell, three lentiviral vectors were developed and tested their ability to transduce hematopoietic stem cell using immune competent and immune deficient MPS II model mice. This year, patent of these vector were applied. In addition AAV vector medicated gene therapy for MPS II was also funded by AMED and its efficacy was also tested. The target disease was extended to GM1 gangliosidosis and Krabbe disease using similar approach to MPS II.

Neurology group
We are conducting a research on Dravet syndrome (DS) and PCDH19-related epilepsy by using disease-specific induced pluripotent stem cells (iPSCs) and knockout rats. The aims include to elucidate the molecular and cellular pathology and to explore a therapeutic availability of cell transplantation. In 2017, we have successfully identified an increased excitability in the DS rat brain by using a manganese-enhanced magnetic resonance imaging. Furthermore, we have started a new research on PCDH19-related epilepsy to examine if somatic mosaicism, a suggested pathomechanism of this disease, affects synapse formation in disease-specific neurons. In another study, we have characterized a developmental change of a gamma-aminobutyric acid receptor expression in developing

human brain by using iomazenil single photon emission computed tomography.

Nephrology group
We have performed several nationwide surveys for pediatric kidney disease such as end-stage kidney disease (ESKD) and anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) as a member of the Japanese society for pediatric nephrology to clarify the epidemiology of them. We investigated whether anti c-kit antibody (ACK2) combination with low dose irradiation (LDIR) conditioning regimen was effective for hematopoietic stem cell targeted gene therapy for mucopolysaccharidosis (MPS) II mice.

Infectious diseases and Immunologic Disorders group
Our group specializes in immune deficiencies caused by autoimmunity, autoinflammatory, immune dysfunction or dysregulation. We investigated the mechanisms of immune deficiencies, diagnostic method for primary immunodeficiency, and treatment for chronic granulomatous disease associated colitis. Furthermore, we performed pathological analysis of human herpes virus-6 (HHV-6) reactivation in the central nerve system. IL-1β and basic fibroblast growth factor (bFGF) are required for HHV-6 proliferation in astrocyte, interestingly, which are elevated in the cerebrospinal fluid of patients with HHV-6 encephalitis.

Hematology and Oncology group
We have performed several clinical studies for hematologic malignancies as a member of Japan Child Cancer Study Group (JCCG) to explore novel therapy and diagnostic tool. We studied the effect of high-dose replacement of enzyme combined with immune-tolerance therapy on the brain tissue of the MPS type II model mouse. Moreover, we evaluated the mechanism of hypereosinophilia associated with acute lymphoblastic leukemia by comprehensive analysis of cytokines/chemokines with the patient's serum samples. We are preparing for recruiting the pediatric patients with therapy-resistant pediatric brain tumor who has the first and second phases of clinical study of dendritic cell therapy for therapy-resistant pediatric brain tumor from 2018.

Cardiology group
We evaluated right ventricular remodeling using right ventricular pressure overload mouse, right ventricular fibrosis in response to pressure overload in rats using two-dimensional speckle tracking echocardiography and MRI, and the mechanism of angiogenesis using the model rat with aorto-pulmonary collateral artery. Moreover, we made model rat with pulmonary hypertension caused by left heart disease and evaluated intrapulmonary venous arterialization. We have performed following studies; technical investigation of intervention catheterization, cardiac function, hepatic fibrosis, protein losing enteropathy after Fontan operation and validation of the Pediatric Index of Mortality (PIM) 3 Score in pediatric intensive care unit.

Allergy group
The main subjects of our research are as follows: 1) the role of eosinophil, mast cells and

epithelial cells in the pathology of allergic diseases, 2) pediatric asthma, 3) food allergy, 4) atopic dermatitis, 5) treatments for allergic diseases, and 6) prevention of allergic diseases.

Endocrinology group

We investigated the possible role of GnIH (Gonadotropin-inhibitory hormone) as a mediator between the HPG (hypothalamic-pituitary-gonadal) and HPT (hypothalamic-pituitary-thyroid) axes involved in the regulation of puberty onset by thyroid status. Finally, we elucidated that GnIH is an important factor to keep the balance of TH-mediated HPG regulation for the proper timing of pubertal onset. On the other hand, we studied the efficacy of IGF-1 therapy for a female patient with Rabson-Mendenhall syndrome having novel insulin receptor mutations. As a result, IGF-1 therapy was effective to a certain degree for the control of her blood glucose. We are now submitting a paper regarding this study to the Journal of the Japan Diabetes Society.

Publications

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