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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 group is supplying practical benefits to patients and their families through basic and translational research and clinical study.

Research Activities

Inherited metabolic disease group
We continued research mainly on gene therapy for patients with mucopolysaccharidosis type II and GM1 gangliosidosis. This year, we optimized gene transfer into human hematopoietic stem cells. We purchased the CliniMACS Prodigy (Miltenyi Biotec), a device that can semiautomatically introduce genes into cells. As a result, we have established a protocol that can efficiently introduce a mucopolysaccharidosis type II defective enzyme gene into CD34-positive cells by using a lentivirus vector. We also conducted joint research with JCR Pharma Co., Ltd., developed an adeno-associated virus vector expressing a blood-brain barrier crossing enzyme, tested the vector in GM1 ganglioside-cis model mice, and received promising results. We also created guidelines, constructed a registry, and conducted a questionnaire survey on the latest treatments for patients.

Neurology group
We are conducting basic research on the pathomechanisms of developmental epileptic encephalopathies. In 2019, by using a manganese-enhanced magnetic resonance imaging technique and a rat model, we have successfully characterized a novel pathogenesis of Dravet syndrome. We also found an alteration in a neuronal maturation pattern in cerebral organoids generated from protocadherin 19 gene (*PCDH19*)-related epilepsy-specific induced pluripotent stem cells. In clinical research, we have elucidated a variety of findings on pediatric neurological diseases: risk factors for intravenous immunoglobulin-related adverse effects, clinical predictors of recurrent febrile seizures during the same febrile illness, the neurological outcome of autoimmune encephalitis, and significant

associations between ripple activities in scalp electroencephalograms and absence status epilepticus and between serum levels of matrix metallopeptidase-9 and tissue inhibitor of metalloproteinase-1.

Nephrology group
We have performed several epidemiologic studies for rare renal diseases as a member of the Japanese Society for Pediatric Nephrology. The main subjects of our research are as follows: 1) to estimate human total nephron number using a combination of image analysis and renal biopsy, 2) to investigate the independent risk factors for acute kidney injury after hematopoietic stem cell transplantation, 3) to investigated preventive effect of tonsillectomy on recurrence of Henoch-Schonlein purpura nephritis after intravenous methylprednisolone pulse therapy.

Neonatology group
We conduct the neonatal medical training for young pediatricians working in university hospital and Saitama Children's Medical Center. The training help the high-risk neonate care in the university hospital and the university association institution. The main research is followed: 1) renal glomerulus development in the baby with small-for-date (SFD), 2) respiratory support device CPAP element by the new air flow body mechanism using the clinical model lung, 3) brain tissue oxygen saturation concentrations assay by the transmissive time resolved near infrared spectroscopy, 4) LOX-1 as a severity marker of the neonatal hypoxic-ischemic encephalopathy and 5) the treatment innovative drug development in AMED study with National Institute of Neuroscience.

Infectious diseases and Immunologic Disorders group
Our research projects were associated with infectious diseases, autoinflammatory diseases, autoimmune diseases and primary immunodeficiency diseases. We investigated the mechanisms of primary immunodeficiency diseases including chronic granulomatous disease, and autoinflammatory diseases. Moreover, our group actively undertook the investigator-initiated clinical trial that lead to the development of the anti-inflammatory therapy for chronic granulomatous disease associated colitis. As clinical research, we examine sensitivity and specificity of pathogenic genome sequence analysis in childhood patients with severe infection, and the mechanisms of soluble PD-L1 in induction of immune tolerance. We also contributed to make guidelines for autoinflammatory disease.

Hematology and Oncology group
The use of thrombopoietin analogue for pediatric refractory immune thrombocytopenia purpura (ITP) was investigated as the activity of the platelet committee of The Japanese Society of Pediatric Hematology/Oncology. Moreover, the treatment guide for refractory ITP in children 2019 was proposed. We are conducting a phase I/II clinical trial of a dendritic cell therapy for refractory childhood brain tumors. We and Dr. Nagayoshi of the Department of nursing, The Jikei University, in collaboration with the National Cancer Center, created materials to support long-term follow-up of retinoblastoma.

Cardiology group

We evaluated mechanism of reverse remodeling in the status of heart failure during growth period, calculation of the shunt flow in aorto-pulmonary collateral artery model rat with left pulmonary artery ligation under hypoxia environment, 2nd group pulmonary hypertension of left atrium stenosis model rat, utility of urine titin to detect pediatric myocardial damage, evaluation of right ventricular fibrosis using 2D-speckle tracking and Diffusion tensor imaging in right ventricular pressure overload mouse, the role of HIF-1α in pulmonary artery smooth muscle of hyperoxia-induced neonatal lung injury mice We had performed following studies; drug stress test utility of LQTS.

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. We demonstrated that cow's milk, hen's egg and wheat allergy, even anaphylaxis, could be primarily prevented using simple methods, ie, avoiding cow's milk formula or changing to amino acid-based elemental formula for at least the first 3 days of life in addition of breastfeeding. We are performing some multicenter randomized controlled trials: DIFTO study (Daily versus intermittent Inhaled fluticasone in toddlers with recurrent wheezing), MADEC study (Efficacy of a moisturizing cream in the treatment of atopic dermatitis in children) and ABC II study (Primary prevention of food allergy by restricting maternal intake of processed meat and others during first month after birth).

Endocrinology group

We conducted the first alanine scanning mutagenesis study, in which 132 alanine variants located in the paired domain of thyroid-specific transcription factor PAX8 were created and systematically evaluated *in vitro*. We found that 76 alanine variants (55%) were loss of function variants, and the distribution of LOF variants were skewed, with more frequently observed in the N-subdomain than in the C-subdomain. Twelve out of 13 alanine variants in residues that have been affected in patients with congenital hypothyroidism were actually LOF, suggesting that the alanine scanning data can be used to evaluate the functional importance mutated residues. On the other hand, we reported the first case of a BBS patient with biallelic splice-site BBS1 variants in the Japanese population. In our study, it was suggested that disparity between funduscopic and ERG findings might be a feature of BBS1-associated rod-cone dystrophy.

Publications

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