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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 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 continue to study gene therapy projects for mucopolysaccharidosis type II. In a project funded by the Japan Agency for Medical Research and Development, the optimal lentivirus vector was selected for hematopoietic stem cell–targeted gene therapy. We started to generate a lentiviral vector for a nonclinical study and to optimize transduction of human hematopoietic stem cells. In another agency-funded gene therapy project for mucopolysaccharidosis type II, significant reductions of accumulated compounds in the brain were observed by intravenous administration of adeno-associated virus vectors in a murine model. In addition, we are developing gene therapy for GM1 gangliosidosis and have started a study of Fabry's disease using artificial intelligence.

Neurology group
We are conducting research on Dravet syndrome and epilepsy related to the protocadherin 19 gene (*PCDH19*) by using disease-specific induced pluripotent stem cells and knockout rats. The aims of our research include clarifying the molecular and cellular pathology and exploring a therapeutic availability of cell transplantation. By using manganese-enhanced magnetic resonance imaging, we have successfully identified a novel finding in the Dravet syndrome rat brain, which might be related to the epileptogenesis of Dravet syndrome. In clinical research, we have found that high frequency oscillation in electroencephalograms of the scalp can be an early sign of atypical evolution of childhood epilepsy with centrotemporal spikes; we have also characterized a developmental alteration of regional cerebral blood flow in childhood.

Nephrology group
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 whether a combination of ACK2, an anti-c-kit antibody, with a low-dose irradiation conditioning regimen is effective for hematopoietic stem cell-targeted gene therapy for mucopolysaccharidosis type II mice; and (4) functional analysis of mutations of laminin subunit beta 2 (*LAMB2*) in children with asymptomatic proteinuria.

Neonatology group
We have developed a new respiratory support device for neonates on the basis of the fluid dynamics theory. We are now assessing the function of this device for its clinical usefulness. The other basic study is time-solved near-infrared spectroscopic measurement of tissue oxygen. This technology is a new way for monitoring oxygen and hemodynamics in live brain tissue. We have studied lectin-like oxidized low-density lipoprotein receptor 1, which is recognized as a biomarker of the severity of hypoxic-ischemic encephalopathy, with the National Center of Neurology and Psychiatry. We are preparing for an international study of the effect of music therapy for neonates with cerebral palsy.

Infectious diseases and Immunologic Disorders group
We investigated the anti-inflammatory treatment for colitis associated with chronic granulomatous disease. Furthermore, we examined the sensitivity and specificity of pathogenic genome sequence analysis in patients with severe infection. Although a culture test of blood is a useful and reliable method of identifying pathogenic bacteria and fungi in patients with sepsis, it has several problems, such as detection sensitivity, a long duration for culture, and the development of an appropriate culture medium.

Hematology and Oncology group
We have prepared to perform a phase II international clinical study for patients who are children, adolescents, or young adults in whom acute promyelocytic leukemia was newly diagnosed. We are starting phase I and II clinical studies of dendritic cell therapy for therapy-resistant pediatric brain tumors. We demonstrated the molecular mechanism of development of esophageal squamous cell carcinoma in the patient with chronic graft-versus-host disease and prolonged administration oimmunosuppressants. Moreover, we demonstrated that therapy targeting the nuclear factor kappa B signaling pathway is effective for enhancing or restoring the sensitivity to bromodomain inhibitor I-BET151 in U937 cells.

Cardiology group
The research studies have included the following: (1) evaluation of the mechanism of reverse remodeling in the status of heart failure during the growth period, (2) calculation of the shunt flow in a rat model of aortopulmonary collateral artery with left pulmonary artery ligation under hypoxia environment, (3) the 2nd group with pulmonary hypertension of a rat model of left atrium stenosis, (4) utility of urine titin to detect pediatric myo-

cardial damage, (5) evaluation of right ventricular fibrosis using 2-dimensional speckle tracking and diffusion tensor imaging in mice with right ventricular pressure overload, (6) the role of hypoxia-inducible factor 1α in the pulmonary artery smooth muscle of mice with hyperoxia-induced neonatal lung injury, (7) the drug stress test utility of long QT syndrome and (8) validation of a pediatric index of a mortality score of 3 in the 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. We are performing some multicenter randomized controlled trials: the Daily versus intermittent Inhaled Fluticasone in Toddlers with recurrent wheezing (DIFTO) study and the Efficacy of a moisturizing cream in the treatment of atopic dermatitis in children (MADEC) study.

Endocrinology group

We conducted the first alanine scanning mutagenesis study, in which 132 alanine variants located in the paired domain of the thyroid-specific transcription factor paired box family protein 8 were created and systematically evaluated *in vitro*. We found that 76 alanine variants (55%) were loss-of-function variants, which were of skewed distribution and were more frequently observed in the N-subdomain than in the C-subdomain. We performed a survey of the present condition of fetal goitrous hypothyroidism in Japan. We found 31 patients in whom fetal goitrous hypothyroidism had been treated with intrauterine injection of levothyroxine in the past 20 years.

Publications

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