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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 ultimate aim of each subspecialty group is to supply practical benefits to patients and their families through basic and translational research and clinical study.

Inherited metabolic disease group
In bone marrow transplantation for murine models of mucopolysaccharidosis type II, we clarified the relation between donor chimerism and therapeutic efficacy, in collaboration with hematology and oncology group, and clarified the usefulness of anti-cKit antibody as a preconditioning. We developed an immune tolerance induction method through the oral administration of enzyme in enzyme-replacement therapy for Pome disease. Using cardiomyocytes differentiated from human Pome disease-induced pluripotent stem cells, we demonstrated the feasibility of gene therapy and found that the elevation of oxidized glutathione indicates the presence of oxidative stress. We had certain preclinical results, but we will attempt to apply these results to patients We performed genetic diagnosis with a comparative genomic hybridization array and exome sequencing in patients with congenital anomalies and intellectual disabilities.

Neurology group
We investigated the prognoses in 35 children with hypoxic encephalopathy at more than 1 year since onset. The sequelae were physical disabilities in 28 cases, mental disabilities in 30, epilepsy in 16, and higher brain dysfunction in 12. Continuous performance of the programs based on proper evaluation was a necessary in daily living.
We evaluated the efficacy of fosphenytoin for status epilepticus. Fosphenytoin was effective in 70% of 24 children. Transient hypotension in 1 patient was observed as an adverse effect. Administration of fosphenytoin (22.5 mg/kg) could not maintain the optimal phenytoin level after 15 hours, and maintenance therapy (7.5 mg/kg) could not maintain an optimal level.

Nephrology group
We identified possible risk factors for acute kidney injury following cardiac surgery. We found that postoperative acute kidney injury was associated with age < 1 year, cardiac surgery of the Risk Adjusted Classification for Congenital Heart Surgery grade ≥ 4, and cardiopulmonary bypass time > 90 minutes.

Infectious diseases and Immunologic Disorders group
In this year, we conducted clinical trial of *ex vivo* autologous hematopoietic stem cell gene transfer as salvage therapy for patient with X-linked chronic granulomatous disease (CGD). We showed that gene therapy was able to provide life-saving clinical benefit to patients with CGD lacking a suitable donor.
We also studied human herpes virus (HHV) 6 reactivation in the central nerve system using astrocytoma cell line in collaboration with the Department of Virology. We demonstrated that interleukin 1β and basic fibroblast growth factor are important factors for the propagation and reactivation of HHV-6 and are involved in the pathogenesis of HHV-6 encephalopathy.

Hematology and Oncology group
We performed mutational analyses with the comprehensive Cancer Panel to evaluate the molecular mechanism to develop malignancies associated with congenital anomaly syndrome. We reported on a Japanese boy with phosphoglycerate kinase (PGK) deficiency presenting as chronic hemolytic anemia. The PGK 1 gene (*PGK1*) sequencing showed a novel missense mutation: c. 1180A>G (PGK-Aoto) at exon 10.
Late sequelae, 20 years after onset, in adult survivors of solid tumors during childhood were reported. Even with complete remission of cancer, these survivors had multiple late sequelae or chronic health condition or both.
We studied the pain management and pediatric palliative care. Based on the result of a cross-sectional survey of Tokyo Children's Cancer Study Group, "pain management during bone marrow aspiration and biopsy in pediatric cancer patients" was published.

Cardiology group
The pediatric cardiology group is interested in both basic and clinical cardiology research to improve outcomes for children with congenital or secondary heart disease. Ongoing projects are as follows.
1. Right heart failure and peroxisomal proliferator-activated receptor gamma
2. Hepatic fibrosis and brain mitochondrial deformity in the status of heart failure
3. Right ventricular fibrosis in the status of pulmonary hypertension and pulmonary stenosis
4. Establishment of an aortopulmonary shunt with pulmonary artery banding rats in hypoxia
5. Urocoltin and angiopoietin evaluation in congenital heart disease
Our research on right heart failure and peroxisomal proliferator-activated receptor gamma received the Young Investigator Award at the annual meeting of the Association for European Paediatric Cardiology

Allergy group

The main subjects of our research are as follows: 1) the role of eosinophils, mast cells, and epithelial cells in the pathology of allergic diseases; 2) pediatric asthma; 3) food allergy; 4) atopic dermatitis; and 5) treatments for allergic diseases. We have been organized and performed the following multicenter clinical studies: the ORIMA study (Effect of ORal Immunotherapy in preschool children with Milk Allergy; Trial for the detection of prospective markers for the effectiveness) and the DIFTO study (Daily versus intermittent inhaled fluticasone in toddlers with recurrent wheezing), a multicenter, double-blind, randomized controlled study to investigate the effect of intermittent inhaled fluticasone in treating patients with infantile asthma.

Endocrinology group

To clarify the mechanism of puberty, we analyzed gonadotropin-inhibitory hormone (GnIH)-knockout mice. The onset of puberty of GnIH-deficient mice was slightly earlier than that of wild-type mice. In male mice, body weight of GnIH-knockout models was significantly lighter than that of wild-type models at the onset of puberty. Further analysis is underway.

We investigated 28 boys with precocious puberty. High prevalence of organic diseases in male patients with precocious puberty was confirmed. We especially reported that necessity of paying attention to the progression of precocious puberty at a younger age. On the other hand, we identified 3 novel mutations of the solute carrier family 16, member 2 (thyroid hormone transporter) gene (*SLC16A2*) in 3 patients with suspected deficiency of monocarboxylic acid transporter 8 and found new clinical aspects.

Publications

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