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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 groups is to supply practical benefits to patients and their families through basic and translational research and clinical study.

Inherited metabolic disease group
Current therapies have a limited effect on bone involvement in patients with mucopolysaccharidosis type II (MPS II). We found that radiographic evaluations were extremely useful for monitoring bone involvement in patients with MPS II after gene therapy targeted at hematopoietic stem cell. Moreover, we found a chaperone effect of a certain disaccharide for some mutant enzymes from patients with MPS II. We are preparing for a gene therapy clinical trial for Fabry disease and MPS II under agreement with a company of biotechnology in US.

Neurology group
We are conducting basic research on several types of monogenic epilepsy by using patient-derived induced pluripotent stem cells and gene knockout rats to elucidate pathomechanisms and to establish innovative treatments, including cell therapy. We have refined our strategy for neuronal differentiation to obtain high-quality induced pluripotent stem cell-derived neurons, which are essential for replicating the "true" brain pathology *in vitro* and are to be used for cell therapy. Additionally, we have started a new project with magnetic resonance imaging to identify anatomical and cell biological characteristics of epileptogenesis in the developing brains of knockout rats. Furthermore, we have performed several clinical studies and identified the therapeutic efficacy of corticosteroids in epilepsy related to the protocadherin 19 gene (*PCDH19*) and the difficulty of diagnosing benign infantile seizures.

Nephrology group
We conducted a combined analysis of a nationwide survey for pediatric chronic kidney disease (CKD) and the National Report of Vital Statistics to investigate the effect of birth weight and gestational age on the risk of pediatric CKD. We found that both birth weight

and gestational age are strongly associated with childhood-onset CKD.
We also identified possible risk factors for cyclosporine-induced nephropathy in idiopathic nephrotic syndrome and found that cyclosporine-induced nephropathy is associated with steroid-resistant nephrotic syndrome.

Infectious diseases and Immunologic Disorders group
We reported that gene therapy can provide a life-saving clinical benefit to patients who have X-linked chronic granulomatous disease (CGD) but lack a suitable donor. We also demonstrated that bowel inflammation in patients with CGD was improved by thalidomide without the progression of fungal or bacterial infections, suggesting that thalidomide might be an efficacious therapeutic option for patients with CGD colitis. Moreover, we showed that interleukin 1β and basic fibroblast growth factor are important factors for the proliferation of human herpesvirus (HHV) 6 in an astrocyte cell line and that both were elevated in the cerebrospinal fluid of patients with HHV-6 encephalitis. Our results indicate that interleukin 1β and basic fibroblast growth factor play key roles in the onset of HHV-6 encephalitis.

Hematology and Oncology group
We have performed several clinical studies for hematologic malignancies as a member of the Japan Child Cancer Study Group and the Tokyo Children's Cancer Study Group to explore novel therapies and diagnostic tools. We investigated late effects in survivors of childhood cancers, pediatric palliative care, and pain management in children with cancer. The mutation analysis by comprehensive Cancer Panel was performed to evaluate the molecular mechanism to develop malignancies associated with congenital anomaly syndrome. We demonstrated a novel mutation of the patched 1 gene (*PTCH1*) in medulloblastoma-associated Gorlin syndrome. Moreover, we have studied sequential urine polyamine in patients with retinoblastoma and reported that urine polyamine is a useful tumor marker for the recurrence of retinoblastoma.

Cardiology group
We evaluated the right ventricular remodeling in a mouse model of right ventricular pressure overload and the mechanism of angiogenesis in a rat model of the aortopulmonary collateral artery. Moreover, we produced a rat model of pulmonary hypertension caused by left heart disease. We have performed studies of the following topics: cardiac function and hepatic fibrosis in patients who have undergone the Fontan operation, correlation between stool calprotectin and protein-losing enteropathy, clinical assessment of infectious endocarditis, effectiveness of genetic analysis of ion channel disease, and the safety of congenital heart disease in the pediatric intensive care unit.

Allergy group
The main subjects of our research are as follows: (1) the roles of eosinophil, 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 organized and performed the following multicenter clinical studies: the ORIMA study (Effect of

Oral Immunotherapy in Preschool Children with Milk Allergy) 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. Recently, we have performed a study, which is, to our knowledge, the first in the world to investigate olfactory function in children with rhinitis.

Endocrinology group

We investigated the possible role of gonadotropin inhibitory hormone (GnIH) as a mediator between the hypothalamic-pituitary-gonadal axis and the hypothalamic-pituitary-thyroid axis involved in the regulation of puberty onset by thyroid status. We demonstrated that thyroid status alters GnIH messenger RNA expression *in vivo* and *in vitro* and that GnIH neurons express thyroid hormone receptors. These findings indicate that the effect of thyroid hormone on GnIH expression is mediated by thyroid hormone receptors. Moreover, we identified 3 novel mutations in 3 patients with suspected monocarboxylate transporter 8 deficiency and found new clinical aspects.

Publications

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