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

Research Activities

Inherited metabolic disease group
The phenotype of peripheral neuropathy of murine model of Fabry disease is hypoesthesia. AAV vector expressing alfa-galactosidase A (GLA) was administered into intrathecal space of model mice. GLA activity in dorsal root ganglion was elevated and hypoesthesia was improved.
We previously shown that hematopoietic stem cell targeted gene therapy using lentiviral vector was effective for mucopolysaccharidosis type II mice. This year, to test human hematopoietic stem cell targeted lentiviral gene therapy is also effective, we generated immune deficient mucopolysaccharidosis type II mice which human cell can be transplantable using gene editing technology. The enzyme activity was decreased in organ in 3 strains. Next, we will treat the mice by human hematopoietic stem cell targeted gene therapy using lentiviral vector for future clinical trial.

Neurology group
We are conducting a research on Dravet syndrome by using disease-specific induced pluripotent stem cells and knockout rats. The aims include to elucidate the developmental molecular and cellular pathology and to explore the possibility of cell therapy. In 2006, to anatomically identify epileptogenic brain area/neural circuits in the disease rats, we newly started an experiment to depict hyperexcitable regions by using a manganese-enhanced magnetic resonance imaging technique. This analysis would be helpful to determine regions to be targeted in cell therapy and to assess efficacy of the treatment. In another study, we performed a clinical survey of 70 cases of West syndrome and determined the efficacy and safety of intravenous immunoglobulin therapy in this disease.

Nephrology group
We conducted a nationwide survey for pediatric end-stage kidney disease (ESKD) and examined the level of estimated glomerular filtration rate (eGFR) at the start of renal replacement therapy (RRT). We found a possible association between baseline eGFR and subsequent survival outcome.
We also identified possible risk factors for prolonged hematuria after methylprednisolone pulse therapy combined with tonsillectomy in childhood-onset IgA patients, and found that severe crescents formation was associated with prolonged hematuria.

Infectious diseases and Immunologic Disorders group
We studied human herpes virus-6 (HHV-6) reactivation in the central nerve system. We reported that IL-1β and basic fibroblast growth factor (bFGF) are important factors for proliferation of HHV-6 in astrocyte cell line and are elevated in the cerebrospinal fluid of patients with HHV-6 encephalitis. Our results indicate that IL-1β and bFGF play a key role in the onset of HHV-6 encephalitis.
We investigated early diagnosis and treatment for primary immunodeficiency diseases at Department of Human Genetics in National Research Institute for Child Health and Development. We have prepared for newborn screening to detect treatable severe primary immunodeficiency diseases threatening to life or long-term health, before they become symptomatic.

Hematology and Oncology group
We have performed several clinical studies for hematologic malignancies as a member of Japan Child Cancer Study Group (JCCG) and Tokyo Children's Cancer Study Group (TCCSG) to explore novel therapy and diagnostic tool. We investigated the management of chronic idiopathic thrombocytopenic purpura in children by questionaires to hospitals. Genomic analysis of clonal origin of Langerhans cell histiocytosis (LCH) following acute lymphoblastic leukemia (ALL) was performed. We demonstrated that homozygous deletion of *CDKN2A* at 9p21 of 72 kb was detected in the specimen of LCH following ALL by SNP assay. In addition, *NRAS* c.G34A mutation was found in the specimen.
We studied the molecular effects of GNAS-cAMP-dependent protein kinase A-sonic hedgehog (SHH) coupling on progression of sonic hedgehog-driven medulloblastoma.

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 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, and protein losing enteropathy after Fontan operation, and safety management of congenital heart disease at 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 have been organized and performed following multicenter randomized trials. Recently, olfactory function in children with rhinitis has been investigated, which is the first study in the world as far as we know.

Endocrinology group

We investigated whether thyroid dysfunction affects pubertal onset in female mice via gonadotropin-inhibitory hormone (GnIH). As a result, hypothyroidism showed delayed puberty onset with increased GnIH expression and reduced pituitary gonadal activity. This finding indicates a novel function of GnIH to mediate hypothalamic-pituitary-thyroid axis (HPT) - hypothalamic-pituitary-gonadal axis (HPG) interactions that contribute to proper pubertal development. Moreover, we have performed intervention studies to prevent metabolic syndrome in children by using exercise therapy that was newly developed.

Publications

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