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General Summary

We have 9 subspecialty research groups: the Inherited Metabolic Disease, Endocrinology, and Medical Genetics 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 provide practical benefits to patients and their families through basic and translational research and clinical study.

Research Activities

Inherited Metabolic Disease, Endocrinology, and Medical Genetics group
Accomplishments of our group this year are follows.
1. We clarified the mechanism of the build-up of autophagy in Pompe disease cells and developed a novel method to control autophagy.
2. We found that proteasome inhibitors improve the function of mutant lysosomal alpha-glucosidase in fibroblasts from a patient with Pompe disease.
3. We clarified the effect of antibodies against an infused enzyme in enzyme-replacement therapy for Fabry disease.
4. We developed a novel gene therapy approach using a lentiviral vector.
5. We analyzed the expression in the brain of urocortin 2, urocortin 3, corticotropin-releasing factor receptor 2, and nesfatin 1 in a rat model of left ventricular failure.
6. We studied insulin insufficiency in Rota virus infection.
By using a comparative genomic hybridization array for genome-wide screening, we have detected submicroscopic pathogenic genome imbalances with a diagnostic yield of 12% in patients with congenital malformations.

Neurology group
1. We investigated the development of posttraumatic epilepsy in 142 children with sequelae of traumatic brain injury. Epilepsy developed in 37 patients. The risk factors for posttraumatic epilepsy were child abuse, acute subdural hematomas, severe and long-term loss of consciousness, and such complications as poor mobility and mental deterioration.
2. We evaluated the efficacy of intravenous antiepileptic drugs for treating status epilep-

ticus in children. Of the 189 episodes of status epilepticus, 42.3% were in children with epilepsy and 41.3% were febrile seizures. The most frequently administered agents were diazepam as a first-line treatment and intravenous midazolam or phenobarbital as second-line treatments. Phenobarbital and diazepam were effective in at least 70% of cases. Thiopental was the agent most likely to produce adverse effects. Diazepam as a first-line treatment and phenobarbital and intravenous midazolam as second-line treatments may be practical for status epilepticus in children.

Hematology and Oncology group

Telomerase, a ribonucleoprotein DNA polymerase that elongates the telomeres of chromosomes to compensate for losses during DNA replication, is constitutively expressed in most malignant tumor cells. We have established a human megakaryocytic-erythroid cell line that expresses the erythropoietin receptor. Erythropoietin is a hematopoietic growth factor that regulates cellular proliferation and differentiation in the erythroid lineage. However, the mechanism by which telomerase regulation is modulated by erythropoietin has remained unclear. We demonstrated that erythropoietin activates telomerase in JAS-REN-A cells through dual regulation: *hTERT* gene transcription by JAK2/STAT5/c-Myc and hTERT protein phosphorylation by phosphatidylinositol 3'-kinase/AKT.

Pediatric palliative care programs for children with cancer in university hospitals have unique challenges. We established a pediatric palliative care education program in the undergraduate medical course.

Infectious Diseases and Immunologic Disorders group

We focus on the identification of causative pathogen by means of polymerase chain reaction techniques, genetic diagnosis and treatment of primary immunodeficiency syndrome, and analysis of immune response in pediatric rheumatic diseases.

Our research and development achievements were as follows.

1. Rapid identification of causative pathogens in inflammatory diseases using multiplex polymerase chain reaction

We showed that our assay was more sensitive, more specific, and faster than the gold-standard culture-based method.

2. *Ex vivo* gene therapy for X-linked chronic granulomatous disease

We submitted an application to perform a clinical trial of retroviral gene therapy for X-linked chronic granulomatous disease.

3. Fecal microbial composition of healthy infants and patients with chronic granulomatous disease

We found that in patients with chronic granulomatous disease that the populations of *Bacteroides* and *Bifidobacterium* were significantly smaller in patients with enteritis than in patients without enteritis.

Nephrology

We investigated the clinical characteristics and the efficacy of voiding cystourethrography (VCUG) in infants with febrile urinary tract infection (UTI).

We analyzed the medical records of 115 infants (mean age, 2.84 ± 2.18 months; male:female ratio, 83:32) who were admitted to the hospital with febrile UTI from January 1999 through May 2009. A UTI was diagnosed when a bacterial quantitative culture of catheter-obtained urine was more than 10^4/ml, or 10^3/ml when clinical characteristics and laboratory data were considered. We performed VCUG for boys at the first UTI and for girls at the second UTI.
When urinary organ anomalies, such as vesicoureteral reflux (VUR), were detected with VCUG, we consulted pediatric urologists and continued to follow up the cases.
The bacteria most often identified with urine culture were *Escherichia coli* (n=83) and *Enterococcus* (n=28). A total of 75 patients, of whom 70 were boys, underwent VCUG. Thirteen patients had VUR, and 5 patients had other anomalies. Of these 18 patients, 8 (5 with VUR and 3 with other anomalies) required surgery. Neither the clinical characteristics nor laboratory data differed significantly between cases with or without abnormalities identified with VCUG. In conclusion, VCUG is useful for diagnosing operation adaptive anomalies, including VUR.

Cardiology
The Pediatric Cardiology group is interested in both basic and clinical cardiology research to improve the outcomes of children with congenital heart issues. The results of our research have been presented at the annual meetings of the Japan Pediatric Society and the Japan Pediatric Cardiology Society. Our research projects on right ventricle heart failure and copy number variants in congenital heart disease received funding from the Japanese society for the promotion of science. Specific projects under way in our group are as follows.
1. The effect of telmisartan in right-heart failure
2. Cardiac apoptosis in right-heart failure
3. Clinical outcomes of cardiac morphology involved in congenital metabolic disorders
4. Gene transmutation in patients with noncompunction

We also are interested in clinical research, specifically:
1. A management of fetal cardiac issues
2. Long-term outcomes in patients with total cavopulmonary connection circulation
3. Interventional catheterization (balloon angioplasty and valvuloplasty, coil embolization, transcatheter stenting, and catheter closure of congenital heart defects)

Allergy
The main subjects of our research are as follows: 1) the role of eosinophils and mast 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:
PET study: Preventive effect of tulobuterol patch for the long-term management of infantile asthma study
PARG study: Pediatric Asthma Research for Guideline Update: Add-on use of tulobuterol patch for unstable asthma treated with leukotriene receptor antagonist
CIT study: A comparison of continuous inhalation treatment with salbutamol and isopro-

terenol for severe pediatric bronchial asthma: A multicenter, double-blind, randomized study
OSCAR study: Optimal stepdown therapy for controlled pediatric asthma responding to salmeterol/fluticasone
ORIMA study: Effect of oral immunotherapy in preschool children with milk allergy

Publications

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