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General Summary

We have 9 subspeciality research groups: 1) the Congenital Metabolic Diseases, Endocrinology, Gastroenterology and Medical Genetics group, 2) the Allergy and Immunology group, 3) the Neurology group, 4) the Hematology and Oncology group, 5) the Cardiology group, 6) the Infectious Diseases group, 7) the Neonatology group, 8) the Nephrology group, and 9) the Pediatric Psychiatry group. The ultimate aim of these subspeciality groups is providing practical benefits to patients and their families by means of basic and clinical research. To accomplish this aim, we must have a high motivation for research and cooperate with each other. Regarding our achievements this year, however, we had fewer publications and reviews than usual. Therefore, we must make efforts to increase our academic achievements next year.

Research Activities

Congenital metabolic diseases, endocrinology, gastroenterology and medical genetics

Accomplishments of our group this year are as follows.

1. We used an anti-CD3 antibody to induce immune tolerance to enzymes in enzyme replacement therapy for lysosomal storage diseases (LSDs).
2. We developed a novel gene therapy strategy for LSDs.
3. We found that endoplasmic reticulum stress was a cause of autophagy build-up in LSDs.
4. We surgically prepared rats with left ventricular heart failure and then analyzed the expression of urocortin 1, 2, and 3 and corticotropin-releasing factor receptor type 2α in their brains.
5. We analyzed the effects of drugs for treating inflammatory bowel diseases.
6. We showed the usefulness of a kit for diagnosing Norovirus infections.
7. We are developing methods for the molecular diagnosis of genetic diseases by means of comparative genomic hybridization arrays and multiplex ligation-dependent probe amplification.

Neurology
The outcomes of acute encephalopathy in children who underwent rehabilitation at our rehabilitation center were presented. The main sequelae were motor disturbance (in 25%), mental deterioration (in 90%), higher cortical dysfunction (in 80%), and epilepsy (in 70%). The patients were divided into 5 groups according to the clinical courses at onset: patients with metabolic disorders, patients with cytokine storms, patients with status convulsivus, patients with severe refractory status epilepticus, and patients with the main symptom of decreased consciousness. Typical patients of each group were described along with the results of magnetic resonance imaging of the brain and of single photon emission cerebral tomography. In patients with metabolic disorders and cytokine storms, the sequelae were generally severe. In patients with status convulsivus, the main sequela was mental deterioration. In patients with severe refractory status epilepticus, the most controversial problem was epilepsy. In patients with the main symptom of decreased consciousness, higher cortical dysfunction was the main problem.

Allergy and Immunology
We have organized and performed the following multicenter clinical studies: 1) Preventive effect of tulobuterol patch for the long-term management of infantile asthma (PET study); 2) Effect of tulobuterol patch on exacerbations in the management of childhood asthma (PAMC study); 3) A comparison of continuous inhalation of salbutamol and continuous inhalation of isoproterenol for severe pediatric bronchial asthma: A multicenter, double-blind, randomized study (CIT study); 4) Optimal stepdown therapy for controlled pediatric asthma responded to salmeterol/fluticasone propionate (OSCAR study); and 5) Preventive effect of pranlukast on nasal membrane swelling in Japanese cedar pollinosis (PRAN study). Recently, we finished the PET study and have prepared a manuscript (on submission).
We developed a questionnaire for measuring quality of life in caregivers of children with atopic dermatitis[2]. We are now developing a shorter version of the questionnaire.

Cardiology
For basic research, a rodent model of right heart failure was created to investigate gene expression and physiological changes in right ventricular remodeling. To clarify the effect of right heart failure on each organ, we undertook a collaborative study with the adult cardiology group and pediatric endocrinology group. We also studied the growth of the pulmonary artery in a rodent model of pulmonary artery stenosis created with pulmonary artery banding. For clinical research, we are examining: 1) magnesium kinetics in pediatric cardiology, 2) treatment of pediatric arrhythmia with magnesium, 3) the secretion and kinetics of atrial natriuretic peptide and brain natriuretic peptide in pediatric cardiac diseases, 4) cardiac lesions of Fabry disease, 5) hemodynamics after the Fontan operation, and 6) postoperative antithrombotic therapy in patients with congenital heart disease.

Infectious Diseases
We focus on primary immunodeficiency, infectious diseases, and collagen diseases in

children. We have been studying the new diagnosis and treatment based on our clinical experiences. Our research and development are as follows.

1) Genetic diagnosis of primary immunodeficiency syndrome
2) Retrovirus gene therapy for X-linked chronic granulomatous disease
3) Surveillance of respiratory infection
4) Rapid identification of causative pathogen using polymerase chain reaction techniques
5) Molecular analysis of drug-resistance genes of bacteria
6) Efficacy and safety of vaccines
7) Disease activities and prognosis of juvenile idiopathic arthritis and systemic lupus erythematosus
8) Effect of molecular intervention against of refractory collagen diseases

Hematology and Oncology

We have investigated refractory severe chronic idiopathic thrombocytonpenic purpura (ITP) in collaboration with several major centers in Japan. We performed a survey of the uses of rituximab and could confirm its effectiveness in patients with severe chronic ITP in Japan. In basic research to improve the rate of eye preservation, we investigated the molecular mechanism of the antitumor activity of the cationic porphyrin 5, 10, 15, 20-tetra-(*N*-methyl-4-pyridyl)porphyrin (TMPyP4) in Y79 and WERI-Rb1 retinoblastoma cells. We showed that the antitumor activity of TMPyP4 can be attributed to the phosphorylation of H2AX and p53 (Ser46) and the activation of the mitogen-activated protein kinase signaling pathway. Moreover, TMPyP4 significantly enhanced the susceptibility to irradiation. These findings provide insight into the molecular mechanism of the antitumor effects of TMPyP4. The G-quadruplex structure is a potential therapeutic target in refractory retinoblastoma.

Pediatric palliative care, which is the active, total, and comprehensive care for children with has recently been attracting attention. The principles of pediatric palliative care were reviewed. Challenges in the management of pain for children with cancer in Japan were investigated through a nationwide survey of hospitals and other institutions. The advantages and challenges of providing palliative care in our clinic were reviewed.

Publications

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