1. Staffs and Students (April, 2012)

Professor Shuki Mizutani
Associate Professor Tomohiro Morio
Junior Associate Professor Masatoshi Takagi, Mitunori Nisiyama
Assistant Professor Yaeko Motoyoshi, Yuuji Sugawara,
Daisuke Tomizawa, Kenichi Kashimada,
Taku Ishii,
(Apr~) Takeshi Isoda, Atsuko Taki,
Manabu Sugie, Tomohiro Udagawa,
(Mar~) Keisuke Enomoto

Graduate Student Norimasa Ibara, Kaori Nakatani,
Yuuko Ohnishi, Eriko Tanaka,
Yuki Aoki, Fumihiko Takizawa,
Susumu Hosokawa, Setuko Kaneko,
Kei Takasawa, Noriko Mituiki,
Takahiro Kamiya, Tetsuro Nagasawa,
Keisuke Nakajima, Eriko Kikuchi,
Yohei Matsubara,
(~Mar) Takeshi Isoda, Yuuko Komatsu,
(Apr~) Akifumi Endo, Chikako Morioka,
RinaNishii, Rie Kumaki,
Miko Shigeno

Special Study Student Sayaka Osada,
(~Mar) Kensuke Kojima

Collaborator Minoru Asada (Department of Pharmacology, Nippon Medical School)
Hatsume Uno (Sony Life Science Laboratories)

Medical Fellow Konka Boku

Department of Pediatrics, Neonatal and Maternal Medicine

Professor Shozaburo Doi
Associate Professor Kohsuke Imai
Junior Associate Professor
(~Mar) Atsuko Taki,
(Apr~) Shigeru Takishima

Department of Research for Regional Pediatrics

Professor Masayuki Nagasawa
Assistant Professor
(Apr~) Kengo Moriyama, Tomohiro Watanabe,
Teppei Ookawa
(~Mar) Akifumi Endo, Manabu Sugie,
Tomohiro Udagawa

2. Educational activities

Field of Education: Education for the 3rd and the first half of the 4th graders of Medical students was proposed 34 lectures on the basis of two big standpoints, child developments and pediatric diseases, by the staffs of Department of Pediatrics and Developmental Biology, Department of Pediatrics, Perinatal and Maternal Medicine, Department of Research for Regional Pediatrics, and the part-time lecturers. The field of totally 34 lectures is widely covered, for example, Hematology, Oncology, Immunology, Cardiology, Neurology, Endocrinology, Neonatology, Nephrology, Allergy, Pulmonology, Infection, and Social Medicine and so on. Opportunities of training in scientific research were provided for the elective latter half of three 4th graders during so-called project semester. The 5th graders were divided into the small groups, and started and continued for three months to learn the introduction of Clinical Clerkship, so-called Pre-clerkship, classified by organs. We were engaged in the organs of Blood, Chest(Heart) and Neuron shared with the another Departments. Then one month practice in pediatric clinical trainings was provided for the 5th to 6th graders among 13
months, where every student belonged to one of the professional clinical teams (Hematology/Oncology/Immunology, Cardiology, Neurology, Endocrinology, Neonatology and Nephrology) in the University Hospital or some affiliated hospitals (Tsuchiura Kyodo General Hospital, Kawaguchi municipal Medical Center or North Tokyo Social Insurance Hospital), and studied clinical practice as one of the team members. Another mission of this Department was to provide lecture courses on general pediatrics for the students of Dental and School of Health Science.

Junior clinical fellows who are in the training course of pediatric practice under the supervision of senior staffs were also expected to supervise these medical students. The style of clinical training was maintained and the 1st year trainee as well as the 2nd year trainee could choose the training in the pediatric ward for two months. On the other hand, the 2nd year trainee was in general engaged in the basic training for one month in the pediatric ward in some affiliated hospitals (Musashino Red Cross Hospital, Soka Municipal Hospital or North Tokyo Social Insurance Hospital). Depending on the individuals, they could select the advanced training at the pediatric ward in The University Hospital for two to eight months.

**Strategy of Education**

It is a goal of education for the 3rd and 4th graders (first half) of medical students to learn the whole picture of general pediatric diseases, and for the 4th graders (latter half, so-called project semester) to touch the basic research, get the fundamental way of thinking and skills of experiments. On the other hand, it is a goal for the 5th and 6th graders (so-called pre-Clerkship and Clinical Clerkship), to be in charge of each patient with pediatric staffs and experience the general steps under the clinical medicine, for example, the following steps how to interview the medical history, get the physical findings, plan the laboratory examinations, differentially diagnose by analyzing the personal data, describe the clinical records, and discuss about the treatment planning. Junior clinical trainees, previously started to train the pediatrics from the 2nd year, became to be able to elect the pediatric training for two months from the 1st year, actually however, the fellows who desired to optionally choose the pediatric training did not necessarily perform it because of too many applicants. The 2nd year junior clinical trainees were divided two groups. Those only required pediatric training for one month were generally planned to experience the common pediatric diseases in the affiliated hospitals. On the other hand, those electively selected pediatrics were basically planned to train almost in university hospitals together with at the affiliated hospitals for one month. Senior clinical trainees were rotated among in the university hospitals and chief affiliated hospitals, planned to experience all kinds of pediatric diseases related to oncology, cardiology, neurology, infections and immunology, endocrinology and metabolic diseases, neonatology, nephrology, pulmonology, digestive diseases, and genomics. Moreover, we educate the students of dentistry and health care sciences, who learn not only general pediatric diseases but the importance of pediatrics as playing roles of total coordination and mutual cooperation beyond specialty for children’s care.

### 3. Research Subjects

The final goal of our research is to elucidate the molecular mechanisms of intractable diseases in children and to develop novel measures to cure the diseases. We are interested in a broad spectrum of subjects in life science field as shown below.

1. Stem cells and hierarchy of infantile leukemic cells
2. Molecular mechanism of aberrant T-cell differentiation and lymphoma development in the absence of ATM
3. Molecular mechanism of Purkinje cell loss in Ataxia telangiectasia
4. Novel roles of ATM in cellular differentiation
5. Ras associated ALPS like syndrome
6. Systematic search for responsible gene for a subset of common variable immunodefiency
7. Gene hunting for radiosensitive-hyperIgM syndrome
8. Negative regulation of granulocyte activation and apoptosis by Tec family protein
9. Development of innovative techniques for cell therapy and gene therapy
10. Skin barrier and development of atopic dermatitis and of GI allergy
11. Glycobiologic approach for molecular pathogenesis of IgA nephropathy developed in WASP deficiency
12. Involvement of Notch signaling pathway in the process of glomerular sclerosis
13. Molecular mechanisms of primary pulmonary hypertension
14. Lung injury induced by cytokines/monocytes/granulocytes
15. Pathogenesis of periventricular leukomalacia (PVL) and broncho-pulmonary dysplasia (BPD); Development of novel therapy using mesenchymal stem cells for PVL and BPD.
16. Sox family protein in sex differentitation
17. Intrauterine stem cell transplantation for congenital disorders
18. Coagulopathy in hematopoietic cell transplantation and alteration in membrane protein expression in red blood cells

We have been collaborating with Institute of Cancer Research in London (Prof Mel Greaves), Istitute Nazionale Tumori (Dr. D. Delia), University of Queensland (Prof. Peter Koopman), Erasmus University (Prof. Jacques van Dongen), Yonsei University (Profs. H. Kim, and SK Lee), Sony Life Science Laboratories, Medical Research Institute at TMDU, National Institute for Longevity Sciences, National Research Institute for Child Health and Development, RIKEN Research Center for Allergy and Immunology, Kazusa DNA Research Institute, National Institute of Advanced Industry and Technology, Metropolitan Institute for Neuroscience, Juntendo University, and many other laboratories.

The research projects of each subspecialty group in the department are as follows.

● Hematology/Oncology/Immunology Group (Basic Research)

Our research focuses on the dissection of molecular basis of DNA damage repair response and the analysis of molecules that play important roles in human immune responses. The main projects include the following.

# Development of in vitro and in vivo leukemogenesis model that stemmed from defective tumor surveillance system.
# Involvement of ATM in T-cell differentiation and adipocyte differentiation.
# Molecular pathogenesis of T-cell malignancy in ATM deficiency
# Identification of stem cells of infantile leukemia using leukemic-cell transplanted NOG-SCID mice.
# Lymphoproliferation and leukemia in Ras associated ALPS like disorder (RALD)
# Responsible gene hunting for CVID and for radiosensitive hyperIgM syndrome using next generation sequencing system
# Negative regulation of activation and apoptosis of granulocytes by Btk
# Application of protein transduction strategy for congenital gene defect
# Development of adoptive immunotherapy for immune reconstitution after SCT
# Development of innovative technique for quality control and cell profiling for processed cells used in regenerative medicine/cell therapy
# Dielectric spectrum cytometer for analysis of membrane protein expression in RBC in association with post-transplant coagulopathy

We have achieved two great discoveries in this year. Most remarkable achievement in this year is identification of novel roles of BTK for regulation of reactive oxygen species (ROS) and neutrophil survival done by F Honda and T Morio. Btk is responsible genes for a gamma globulinemia. Only, function in B cell has been explored. This finding opens a window for new filed of neutrophil research. The report was published in Nature Immunology. Second is explication of T cell developmental failure in Ataxia Telangiectasia done by T Isoda, M Takagi and S Mizutani. In this research, we found how ATM deficiency causes T cell developmental failure, and increased susceptibility of chromosomal translocation which leads to tumor development during double negative phase of T cell development. The report was published in Blood.

● Cardiology Group

We performed both the basic and clinical studies.

The basic studies were related to the vascular remodeling in pulmonary hypertension (PH), whose mechanisms are still unknown but thought to be inflammation as one factor. Dipeptidyl peptidase-4 (DPP-4) inhibitors (Algloliptin) are new drugs for type 2 diabetes mellitus and have an important role for cardiovascular protection by its anti-inflammation effect. Therefore we investigated the role of DPP-4 in PH. In vivo study, Algloliptin markedly improved the survival and pulmonary artery pressure of monocrotaline (MCT)-induced PH rats by improving medial hypertrophy. In in vitro experiments, algloliptin dependently inhibited proliferation of PASMCs stimulated with TGF-beta and also suppressed p-Erk 1/2 protein levels induced by TGF-beta. Therefore, DPP-4 inhibitor has potential as a new therapeutic tool for PH because DPP-4 is associated with the progression of PH by causing TGF-beta-induced inflammation. On the other hand, omega-3 fatty acids (FA) such as eicosapentaenoic acid (EPA) were reported to exert potent anti-inflammatory effects through G protein-coupled receptor 120 (GPR120). We investigated the effect of EPA in PH as well. In vivo study, EPA markedly improved survival, PH and medial hypertrophy of small pulmonary arteries. In vitro study, EPA inhibited dose-dependently pulmonary arterial smooth muscle cells (PASMCs) proliferation stimulated with TGF-beta or FGF2. EPA also suppressed nuclear factor-kappa B p65 translocation into the nucleus in PASMCs. We elucidated that EPA had anti-inflammatory effects through GPR120 in PH. EPA has also potential as a new therapeutic tool for PH. Both results were presented in The 77th Annual Scientific Meeting of Japanese Circulation Society.

Secondly, we were engaged in four multi-center-associated clinical studies. All of them were related to The Japanese
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Society of Pediatric Cardiology and Cardiac Surgery. These themes were “Clinical backgrounds of Eisenmenger syndrome”, “Randomized controled trial to assess immunoglobulin plus steroid efficacy for Kawasaki disease (RAISE study)”, “Efficacy of school-based heart examination in early detection of idiopathic pulmonary arterial hypertension” and “Gene mutations in idiopathic pulmonary arterial hypertension”. The result of RAISE study were published in The LANCET and the result of gene mutations in IPAH was published in American Journal of Cardiology.

●Neurology Group
1) Mechanism of neurodegeneration and therapeutic approach in xeroderma pigmentosum
2) Role of oxidative stress in childhood neurodegenerative disease
3) Analysis of multiple malformation disorders with or without intellectual disability using techniques of molecular genetics and cytogenetics (e.g. micro-array CGH) and clinical dysmorphology
4) Derivation of neural stem cell via iPS cell from ataxia telangiectasia
5) Efficacy and safety of very-low-dose betamethasone therapy in ataxia telangiectasia

●Endocrinology Group
Currently, our research is focused on elucidating the molecular mechanisms of congenital diseases of endocrine organs, especially adrenal glands and gonads. We are looking at developing the radical treatment systems for the congenital endocrine diseases by using regenerative medicine as a final target.
Our ongoing projects are bellows
#1: Molecular mechanisms of sexual determination, collaborating with P. Koopman’s lab (IMB. The university of Queensland, Brisbane, Australia) A. Sinclair’s Lab. (Royal Children’s Hospital, Melbourne, Australia) and V. Harely’s Lab (Prince Henry’s Institute, Melbourne, Australia)
#2: Molecular pathological mechanisms in congenital adrenal hyperplasia
Current ongoing projects will be integrated systematically, and be developed further in order to accomplish our final target.

●Neonatology group
1) We are analyzing the expression of angiogenesis-related factors both in placenta and in umbilical vessels in complicated pregnancies.
2) We are investigating a novel therapy with umbilical cord blood derived mesenchymal stem cells for treating periventricular leukomalacia and chronic lung disease using intrauterine infection model.

●Nephrology Group
1) Analyses of the mechanism of pathogenesis for IgA nephropathy in Wiskott-Aldrich syndrome patients
2) Analyses of glomerular epithelial cells (podocytes) unknown function
3) Analyses of the mechanism of tubulointerstitial injury in nephrotic syndrome patients
We work on these researches in cooperation with The National Institute of Advanced Industrial Science and Technology(1), Juntendo University (2), and Division of Nephrology and Hypertension, Miller School of Medicine, University of Miami (2).

●Allergy Group
To elucidate molecular mechanisms for food allergy such as against milk and egg is one of the main projects of our group. In the light of recent progress of immunology, we analyze the function of regulatory T cells which inhibit Th2 type immune response. We also define the roles of innate immune responses in host defense against foreign antigens entering skin and mucosal tissues. We are one of the research members on the epidemiological study of allergic disorder supported by a grant-in-aid from Ministry of Health, Labor and Welfare, Japan. In collaboration with the Japanese Society of Pediatric Allergy and Clinical Immunology, we conduct several clinical studies to refine pharmacologic therapy listed in the Japanese pediatric guideline for the treatment and management of asthma. We collaborate with pharmaceutical companies on the study of clinical efficacy of leukotriene antagonist. Clinical and epidemiological study on food allergy is another major field in our study. We conduct clinical studies of specific oral tolerance induction in food allergy in which the offending food is administered orally in order to achieve tolerance.

4. Clinical Services
Hematology/Oncology/Immunology Group

Hematology/Oncology/Immunology Group treats patients with hematological malignancies, hematological disorders, malignant solid tumors, and primary immunodeficiency diseases. Our team consists of 8 staffs, including 6 senior with diplomate of board of pediatrics and/or hematology and 2 junior staffs. We offer a team-based high-quality and evidence-based clinical care for both inpatients and outpatients. Additionally, we are on our way to establish cooperative system for medical liaison and professional training with other professional facilities such as St. Luke’s International Hospital and Juntendo University Hospital.

1. Participation in multi-center cooperative clinical research group: In collaboration with national co-operative clinical research group, such as the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG), we offer our patients opportunities to participate in the latest clinical trials and contribute to establish both standard and/or novel therapies for childhood cancers and other non-malignant diseases.

2. Participation in industry-based clinical trials for drug approval: In 2012, we participated in two industry-based trials; IgPro20, a subcutaneous immunoglobulin product, and OP-01, an Erwinia L-asparaginase.

3. Hematopoietic stem cell transplantation (HSCT): In 2012, we performed HSCT for 9 cases; related bone marrow transplantation (BMT) (n=2), unrelated BMT (n=2), unrelated cord blood transplantation (n=4), and related peripheral blood stem cell transplantation (n=1). Our experience of HSCT exceeds 140 cases including more than 50 cases with primary immunodeficiency diseases, so far. We are also working on novel HSCT methods, such as transplantation with haplo-identical donor and/or killer inhibitory receptor (KIR) ligand mismatched donor, and use of reduced-intensity conditioning aiming for reduction of late effects in HSCT recipients.

4. Analysis of pathogenesis and establishment of clinical service for rare diseases: Our group have identified a novel disease, “RALD (RAS-associated lymphoproliferative disease),” from an infant with somatic RAS mutation who exhibited both JMML (juvenile myelomonocytic leukemia)-like and ALPS (autoimmune lymphoproliferative syndrome)-like clinical features, and continuing research for this disorder. Not only for RALD, but for ataxia telangiectasia (A-T) and common variable immunodeficiency (CVID), group members are working as chief organizer of nation-wide clinical research projects financially supported by the Ministry of Health, Labour and Welfare of Japan.

5. long-term follow-up for childhood cancer survivors (CSS): In cooperation with pediatric endocrinologists, CLS (child life specialist) and psychotherapists, we are taking care of cancer survivors and supporting their quality of life.

Cardiology Group

The University Hospital has been certified as a training institute to produce the expert in pediatric cardiology by Japanese Society of Pediatric Cardiology and Cardiac Surgery. There are three pediatric cardiology experts (Doi S, Nishiyama M, Ishii T), two general pediatric cardiologists (Watanabe T, Sazuka M) and one senior resident in The University Hospital who were mainly engaged in the diagnosis and treatment for every kind of heart disease patients both in the pediatric ward and the field for pediatric outpatients. On cardiac catheterization performed in every Friday, one postgraduate (Hosokawa S) and three part-time doctors (Tashiro R, Matsumura Y, Sakurai M) were also joined to back up the procedures.

In-patients were 109 and chiefly introduced from the affiliated hospitals and out-patients field in The University Hospital. The diseases we dealt with were 46 congenital heart diseases, acquired heart diseases such as 30 Kawasaki diseases, 15 pulmonary hypertensions and 4 cardiomyopathies, and 14 cardiac arrhythmia. We performed invasive examination of cardiac catheterization, cardiovascular angiogram and myocardial biopsy as well as non-invasive examinations such as nuclear medicine, CT and MRI for differential diagnosis, decision of medication strategy and evaluation of treatments. In 65 cardiac catheterizations per year, catheter intervention included 1 coil embolization for PDA and 3 catheter ablation for arrhythmias. Twenty five cases were radically or palliatively operated at The Sakakibara Heart Institute. The treatment strategy for Kawasaki Diseases (KD) was severity-dependent and active usage of glucocorticoids, urinastatin, infriximab and cyclosporine to protect the complications of coronary aneurysms. Three KD patients were treated by infriximab and one was treated by cyclosporine. 15 patients with pulmonary hypertension (PH) were admitted for diagnosis, evaluation of treatments or decision of treatment strategy. The most important thing is early diagnosis and early initiation of treatment for PH, which is nominated for difficult-cured and progressive disease. Therefore, we decide to positively treat by receiving up-front combination therapy (uCT) with tree kinds of disease targeted drugs and inducing continuous venous infusion of epoprostenol. Four patients were treated with uCT and one patient was induced epoprostenol. As the result, we succeeded in decreasing pulmonary arterial pressure as well as increase in cardiac output and decrease in pulmonary vascular resistance. 14 patients with cardiac arrhythmia was admitted. Among them, six patients was prolonged QT elongation (PQT) and one was Brugada syndrome. They were examined to be diagnosed, on drug provocation test,
exercise-tolerated ECG, face drop in cold water examination or gene mutation evaluation. Moreover, three patients were performed catheter ablation therapy, one was ventricular fibrillation with arrhythmogenic right ventricular cardiomyopathy (ARVC) and two were AVRT with WPW syndrome.

Out-patients for pediatric cardiology were up to 1,500 patients with the 1,400 examinations of echocardiogram. Moreover, Holter 24-hours ECG monitoring examination was performed on about 100 patients, and Treadmill exercise tolerance examination were also performed on the same number patients. We have participated in the school heart screening program of Tokyo Metropolitan Institute for Preventive Medicine and Tokyo Medical Association, and checked more than 10,000 students ECG records in elementary, junior high and senior high schools. The students who were needed the third stage checkup visited The University Hospital, examined at out- or in-patients fields and finally decided the exercise restriction level in school life.

●Neurology Group

Child neurology group provides highly specialized diagnostic approach and medical care for neurological disorders such as epilepsy, neuromuscular disorders, infection of nervous system, neurodegenerative diseases and genetic syndromes. In particular, we provide therapeutic approach of xeroderma pigmentosum by using of clinicopathological analysis, and perform molecular genetic testing for multiple congenital malformation disorders with or without intellectual disability. In addition, in cooperation with the department of neurosurgery, we evaluate the indication for surgical treatment and then perform surgery operation such as focal brain resection to the patient of intractable epilepsy.

●Endocrinology Group

We provide highly specific diagnostic approach and therapy for pediatric endocrine disorders, such as growth retardation, hypogonadism, thyroid diseases, disorder of sex development, disorder of Ca-P-PTH metabolism, type1 diabetes mellitus. In collaborating with the satellite hospitals, we are following more than a thousand patients, and more than 80 children with endocrine disorders hospitalized yearly our university.

Senior physician of our group is an adviser of Tokyo Health Service Association, and leading the newborn screening of congenital adrenal hyperplasia in Tokyo.

Among many pediatric endocrine disorders, we are directing our effort at the disorders of adrenal gland and sex development, and looking at establishing the clinical center for those patients with pediatric-urologist and other co-medical staffs.

Type1 DM is another disease into which we put a great effort. We manage the Type 1 DM patients’ association (Wakamatsu-kai) and organize the summer camp every year. The camp is consisted of more than a hundred participants and provides the valuable educational opportunities for the patients, the medical staffs and the medical students.

●Neonatology group

1) Our NICU (Neonatal Intensive Care Unit) was established on April 2012 with 6 beds, and provide intensive care for preterm infants (> 30 weeks of gestation and/or >1000g of birth weights). We also take care of critically ill newborns, those with congenital heart disease, hematological disorder, etc., in cooperation with other pediatric subspecialty groups.

2) As a designated Perinatal Cooperation Hospital in Tokyo, we accept newborn patients from various areas in Tokyo.

●Nephrology Group

Nephrology Group provides diagnosis and treatment for patients with acute and chronic glomerular diseases, nephrotic syndrome, and congenital abnormality of kidney and urinary tract. We perform special examination such as kidney biopsy, renogram, MRU, etc. We also participate positively in urinary analysis screening performed at schools.

We operate clinical trial to examine the efficacy and safety of eculizumab for treatment of atypical hemolytic uremic syndrome patient.

We participate in multi-institutional joint research of refractory nephrotic syndrome operated by Japanese Study Group of Kidney Disease in Children.

We hold conference together with neighboring institutions regularly to discuss about better treatment for serious kidney diseases and to improve our knowledge. Some members study treatment for serious kidney diseases, kidney transplantation and renal replacement therapy for children at National Research Institute for Child Health and Development.

●Allergy Group
Allergy Group provides diagnostic and medical care for patients with allergic diseases such as asthma, food allergy, atopic dermatitis mainly at outpatient clinic.

5. Publications

Original articles


**International congress**


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