Pediatrics and Developmental Biology

1. Staffs and Students (April, 2010)

Professor	Shuki Mizutani	
Associate Professor	Tomohiro Morio	
Junior Associate Professor	Masatoshi Takagi,	Mitunori Nisiyama
Assistant Professor	Akihito Sasaki,	Makoto Ono,
	Yaeko Motoyoshi,	Yuuji Sugawara,
	Daisuke Tomizawa,	Toshiaki Ono
Tokunin Assistant Professor	Fumiaki Watanabe	
Graduate Student	Atsuko Taki,	Fumiko Honda,
	Zeynalov Bakhtiyar,	Takeshi Isoda,
	Norimasa Ihara,	Kaori Nakatani,
	Yuuko Ohnishi,	Eriko Tanaka,
	Yuki Aoki,	Fumihiko Takizawa,
	Hideyuki Yokokawa,	Naoko ishibashi,
	Kimiko Hamano,	Wakana Furushima,
	Junya Unno,	Susumu hosokawa,
	Setuko kaneko,	Kei Takasawa,
	Noriko Mituiki,	Takahiro Kamiya,
	Tetsuro Nagasawa,	Yuuko Komatu
Special Study Student	Kouichi Kamei,	
Collaborator	Minoru Asada（Department of Pharmacology, Nippon Medical School）	
	Hatsume Uno（Sony Life Science Laboratories）	
	Masaki Sato（Sony Life Science Laboratories）	
	Naomi Terada	
Professor	Shozaburo Doi,	
Junior Associate Professor	Satoshi Araki,	Toshihiko Nishida
Professor	Masayuki Nagasawa	
Assistant Professor	Akifumi Enndo,	Manabu Sugie,
	Eriko Kikuchi	

2. Educational activities

Field of Education: Education for the 3rd and the first half of the 4th graders of medical students was proposed on the basis of two big standpoints, child developments and pediatric diseases, by the staffs of the Department of Pediatrics and Developmental Biology, Pediatrics, Perinatal and Maternal Medicine, Research for Regional Pediatrics, and the part-time lecturers. The number of lectures was totally 34 and the field of education is widely covered, for example, Hematology, Oncology, Immunology, Cardiology, Neurology, Endocrinology, Neonatology, Nephrology, Allergy, Infection, and Social Medicine and so on. Opportunities of training in scientific research were provided for the four elective latter half of the 4th graders during so-called project semester. The 5th graders were divided into the small groups and started to learn the introduction of Clinical Clerkship, so-called Pre-clerkship, classified by organs. We were engaged in the organs of Blood, Chest and Neuron shared with another departments.. Then one month practice in clinical trainings was provided for the 5th to 6th graders, where every student belonged to one of the professional clinical teams and studies clinical practice as one of the team members. Another mission of this department is to provide lecture course on general pediatrics for the students of Dental School 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. From the last year, the style of clinical training was changed and the 1st year trainee as well as the 2nd year trainee changed to be able to choose the training in the pediatric ward for two months. On the other hand, the 2nd year trainee could select two to eight months depending on the individuals.

Strategy of Educational

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 immunodeficiency
7. Negative regulation of granulocyte activation and apoptosis by Tec family protein
8. Glycobiologic approach for molecular pathogenesis of IgA nephropathy developed in WASP deficiency
9. Involvement of Notch signaling pathway in the process of glomerular sclerosis
10. Molecular mechanisms of primary pulmonary hypertension
11. Lung injury induced by cytokines/monocytes/granulocytes
12. Pathogenesis of periventricular leukomalacia (PVL) and broncho-pulmonary dysplasia (BPD); Development of novel therapy using mesenchymal stem cells for PVL and BPD.
13. Sox family protein in sex differentiation
14. Development of innovative techniques for cell therapy and gene therapy
15. Intrauterine stem cell transplantation for congenital disorders

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), 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 Insititute, 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 includes 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.
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 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
Develepment of innovative technique for quality control and cell profiling for processed cells used in regenerative medicine/cell therapy

●Cardiology Group

In the university, each post-doctoral student was engaged in the basic or clinical researches as follows, ①Analysis of mechanism and development of therapeutics of pulmonary hypertension, ②Analysis of Left/Right ventricular functions of fetuses and neonates, ③Effects of β-blockers for congenital uni-ventricular heart diseases

Since before, the basic research has performed to elucidate the mechanism of pulmonary hypertension by using monocrotaline-induced pulmonary hypertension. We clarified the mechanism of endothelial dysfunction, which was caused by the accumulation of endogenous nitric oxide synthase (NOS) inhibitors, following the decrease in NO production, the increase in endothelin-1 and the acceleration of vascular remodeling as these results. Recently, we moved to be engaged in platelet aggregation in the mechanism of pulmonary hypertension, and presented that annexin-2 not only prevented, but improved the vascular remodeling, pulmonary hypertension and survival curve. Therefore, Farthur experiments could analyze the signal transduction pathway downstream from annexin-2 and propose the more effective new strategy including combination therapies.

The ventricular function in fetuses is almost unclear and not yet correctly evaluated. Therefore, we analyzed LV diastolic and RV functions as well as LV systolic function from the view of localized wall motions and torsions by utilizing new 2D speckle tracking method of echocardiogram.

The effect of β-blockers on heart failure in congenital single ventricle anomaly is not yet elucidated. We examined the effect of β-blockers by analyzing the patients' symptoms, laboratory findings and medications before and after the univentricular repair such as Glenn and/or Fontan operations, in cooperation with Sakakibara Heart Institute where the number of congenital heart surgery was biggest in Japan.

In other facilities, three kinds of basic experiments have been performed. The overall analyses of gene expressions of mouse or zebra fish using the next-generation sequencer were performed to clarify the mechanism of development of normal or abnormal impulse conduction system in the model of myocardial disease. From these results, we analyzed the relationship between the specific genotype and phenotype. Moreover, the functional analyses of myocardial sarcoplasmic reticulum under the process of heart development were achieved by utilizing mice in vivo and in vitro experiments. In another laboratory, interaction of alveolar epithelial cells and pulmonary vascular endothelial cells was examined by using isolated mouse lung preparation to analyze the mechanism of ARDS.

●Neurology Group

1) Mechanism of neurodegeneration and therapeutic approach in xeroderma pigmentosum
2) Role of oxidative stress in childhood neurodegenerative disease

●Endocrinology Group

We investigate molecular mechanisms of pediatric endocrine disorders and genetic control of mammalian sex determination. Currently, a member of our group is working at IMB of Queensland University, Australia as a research fellow, and in 2010, we identified that Foxl2 and BMP2 cooperatively regulate Follistatin, during ovarian fetal development. We also research the role of macrophages in the inflammatory response mechanism with Department of Molecular Medicine and Metabolism, TMDU.

●Neonatology group

1) Analysis of the expression of angiogenesis-related factors in placenta and umbilical vessels in complicated pregnancies
2) Treatment by umbilical cord derived mesenchymal stem cells to lung and brain injury by intra-amnion LPS injection
3) Development of new neonatal cardiopulmonary resuscitation in Japan based on Consensus 2010
4) Survey of light environment in NICUs and development of light environment to prevent developmental injury in preterm babies
5) Feasibility study of quality and safety improvements in perinatal medicine

●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

We work on these researches in cooperation with 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 focus on the regulatory T cells which inhibit Th2 type immune response. 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 toleranc.

4. Clinical Services

●Hematology/Oncology/Immunology Group

Hematology-Oncology-Immunology Group treats the patients with hematological malignancies, hematological disorders, malignant solid tumors, and primary immunodeficiency. Our team consists of 7 staff, including 3 senior and 4 junior staff, and cares both inpatients and outpatients cooperatively.

In collaboration with national co-operative clinical research group, we offer the latest treatment for these patients with malignancy. Furthermore, we perform HSCT (hematopoietic stem cell transplantation) for patients with leukemia, refractory malignant solid tumor, and primary immunodeficiency. We also undergo clinical research for effectiveness of activated T cell therapy against refractory persistent virus infection and graft failure after HSCT in collaboration with institutional cell therapy center. To overcome the life-threatening coagulopathy and microangiopathy during the SCT, we analyzed SCT cases retrospectively, and proposed a simple clinical score system for prognostic evaluation of coagulopathy in SCT. According to this score, we are evaluating the effectiveness of recombinant thrombomodulin in coagulopathy in SCT.

New inpatients in 2010 include 11 ALL (acute lymphocytic leukemia), 4 AML (acute myelogenous leukemia), one rhabdomyosarcoma, 3 primary immunodeficiency (severe combined immunodeficiency), 2 CAEBV (chronic active EBV infection), 3 immune thrombocytopenic purpura, and so on. We performed 9 HSCT, which included two unrelated cord blood, two HLA-identical sibling, two related HLA-mismathced, and three unrelated bone marrow HSCT in 2010. We have more than 40 new outpatients including immunodeficiency, neutropenia, thrombocytopenia, coagulopathy, anemia and so many.

We have performed more than 130 HSCT so far, which includes more than 40 cases with primary immunodeficiency. With these experiences, we are leading this field in Japan.

Our group identified an infant with ras mutation who exhibited both of JMML- and ALPS-like clinical features. From the analysis of several similar cases, we proposed a new clinical concept called "RALD (ras-associated lymphoproliferative disease)" in the international journal.

With the help of pediatric endocrionologists, CLS (child life specialist) and psychotherapists, we are taking care of increasing cancer survivors and supporting their quality of life.

●Cardiology Group

The university has been certified as a training institute for educating the expert of pediatric cardiology by Japanese Pediatric Society of Pediatric Cardiology and Cardiac Surgery. The institution of special pediatric cardiologist will officially start on April 2011. We are chiefly engaged in the diagnosis and treatment of congenital and acquired heart disease such as Kawasaki Disease, myocarditis and Cardiomyopathy etc, cardiac arrhythmia and pulmonary hypertension.

In-patients were chiefly introduced from the affiliated hospitals. We examined several special examinations for the patients with congenital heart diseases, acquired heart diseases (Kawasaki disease, myocarditis and cardiomyopathies), cardiac arrhythmia and pulmonary hypertension. We performed several examination such as cardiac catheterization, cardiovascular angiogram and myocardial biopsy, and offered medical treatments for heart failure, such as drugs, cardiopulmonary support and cardiac resynchronization therapy, moreover catheter intervensions such as balloon valvuloplasty, PDA coil embolization. We especially tried to evaluate the severity of the patients with pulmonary hypertension and then treat them based on the result. We added the originally-developed precise pulmonary vascular characterization measurement, so called pulmonary vascular pressure-flow relationship study, after the routine

examination. As the result, we succeeded in the determination of diagnosis and therapeutic strategy.

We performed the cardiac catheterization on 52 cases (37 for congenital heart disease, 5 for acquired heart disease, 5 for pulmonary hypertension, and 5 catheter ablation therapies for tachyarrhythmia). Twenty five cases were surgically operated after the cardiac catheterization except one case at The Sakakibara Heart Institute.

Out-patients for pediatric cardiology was 1,500 people per year, about 75% of whom we performed echocardiogram. We have participated in the school heart screening program of Tokyo Metropolitan Institute for Preventive Medicine for more than 20 years. This year, 15 students out of 10,000 first screening students finally visited us for the third screening. Holter twenty-four hours electrocardiogram extermination and Treadmill exercise-induced electrocardiogram were regularly were underwent to evaluate the management level of each student during 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 and neurodegenerative diseases. In particular, we provide therapeutic approach of xeroderma pigmentosum by using of clinicopathological analysis. In addition, in cooperation with the department of neurosurgery, we evaluate the indication for surgical treatment and then perfome surgical operation such as focal brain resection to the patient of intractable epilepsy.

●Endocrinology Group

We provide medical care for patients with pediatric endocrine disorders, such as growth disorders, pubertal disorders, hypopituitarism, Turner syndrome, thyroid disorders, adrenal disorders, gonadal disorders, disorders of sex development, problems of calcium and phosphate metabolism, diabetes mellitus and so on.

Our department is one of the neonatal mass-screening centers for congenital adrenal hyperplasia and congenital hypothyroidism in Tokyo Metropolis.

We support a summer camp program for children with type 1 diabetes mellitus in every August.

●Neonatology group

We have started Neonatal and Infantile High Care Unit (NIHCU) for severely ill neonates and infants since July 2008. Intended patients are preterm infants (>32 weeks of gestation, >1500g of birth weights) and sick children who have cardiac diseases, respiratory diseases, hypoglycemia, birth asphyxia, infection and so on. We provide comprehensive care for critically ill newborns and infants, using various medical devices, such as blood gas analyzer, artificial respirators, NO inhalation system, fiberoptic bronchoscopes and brain function monitor.

●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 also participate positively in urinary analysis screening performed at schools. We perform special examination such as kidney biopsy, renogram, MRU, etc. We hold conference together with other 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

1. Asai E, Wada T, Sakakibara Y, Toga A, Toma T, Shimizu T, Imai K, Nonoyama S, Morio T, Kamachi Y, Ohara O, Yachie A, Analysis of mutations and recombination activity in RAG-deficient patient. ***Clin. Immunol***. 2010; 138(2) : 172-7.
2. Takagi M, Shinoda K, Piao J, Mitsuiki N, Takagi M, Matsuda K, Muramatsu H, Doisaki S, Nagasawa M, Morio T, Kasahara Y, Koike K, Kojima S, Takao A, MizutaniS. Autoimmune Lymphoproliferative Syndrome Like Disease With Somatic KRAS Mutation. ***Blood*** 2010; Nov 9, Epub ahead of print.
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differences in the intensity of Fas-mediated intracellular signals determine life and death in T cells. ***Int J. Hematol***. 2010; 92(2) : 262-70.

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11. Nagasawa M, Mitsuiki N, Ono T, Takagi M, Oda H, Yasuhara M, Mizutani S. Pharmacokinetic monitoring is still required for intravenous busulfan in SCT for small children. ***Int J Hematol***. 2010; 91(4) : 728-30.
12. Kawagishi H, Nakamura H, Maruyama M, Mizutani S, Sugimoto K, Takagi M, Sugimoto M. ARF Suppresses Tumor Angiogenesis thorough Translational Control of VEGF mRNA. ***Cancer Res***. 2010; 70(11) : 4749-58.
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transients and functional sarcoplasmic reticulum in beating mouse hearts. ***Circ J***. 2010; 74 : 1442-50.
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International congress

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2. Morio T, Tomizawa D, Atsuta Y, Nagamura T, Kato K, Ariga T, Kawa K, Koike K, Tauchi H, Kajiwara M, Hara S, and Kato S. Unrelated umbilical cord blood transplantation for patients with primary immunodeficiency in Japan. The 52nd ASH Annual Meeting. Orlando, Florida, USA. Dec. 2010.
3. Morio T, Tomizawa D, Atsuta Y, Nagamura T, Kato K, Ariga T, Kawa K, Koike K, Tauchi H, Kajiwara M, Hara S, and Kato S. Unrelated umbilical cord blood transplantation for patients with primary immunodeficiency in Japan. XIVth meeting of the European Society for Immunodeficiencies. Isutanbul, Republic of Turkey.Oct. 2010.
4. Morio T. Btk Controls ROS Production and Apoptosis in Human Neutrophils. XIVth meeting of the European Society for Immunodeficiencies. Isutanbul, Republic of Turkey.Oct. 2010.
5. Morio T. Immunomonitoring and T-cell immunotherapy in CBT. The Second Korea-Japan Cord Blood Transplantation Symposium. Yokohama in Japan. Sep. 2010.
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9. Honda F, Ikeda Y, Takahashi1 N, Lee S, Mizutani S, Morio T. WS/PP-034-04 - Btk controls ROS production and apoptosis in human neutrophil. 14th International Congress of Immunology 2010. Kobe in Japan. Aug. 2010.
10. MorioT.Common variable immunodeficiency(CVID) : Molecular basis of immunedysfunction : The 2nd Symposium for PID in Asia. Chiba in Japan. Feb. 2010.
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12. Feng M, Yang W, Ebihara Y, Nishihama M, Tomizawa D, Kambe N, Nakahata T, Nakauchi H, Tsuji K. Derivation of mature mast cells from human embryonic and induced pluripotent stem cells. International Society for Stem Cell Research (ISSCR) 8th Annual Meeting, San Francisco, USA, Jun. 2010.
13. Koh K, Tomizawa D. Infant ALL. Japanese experience. 21st Annual Meeting of the International BFM Study Group, Antalya, Turkey, Oct. 2010.
14. Tomizawa D, Saito A, Taga T, Adachi S, Nakayama H, Moritake H, Azuma E, Kinosihita A, Takahashi H, Imaizumi M, Kudo K, Hama A, Tsurusawa M, Horibe K, Tawa A. Unexpected high mortality rate due to acute respiratory

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