Pediatrics and Developmental Biology

1. Staffs and Students (April, 2009)

Professor	Shuki Mizutani	
Associate Professor	Tomohiro Morio	
Junior Associate Professor	Shozaburo Doi,	Masayuki Nagasawa
Assistant Professor	Satoshi Araki,	Masatoshi Takagi,
	Akihito Sasaki,	Makoto Ono,
	Toshihiko Nishida,	Yaeko Motoyoshi,
Tokunin Assistant Professor	Fumiaki Watanabe	
Graduate Student	Naoko ishibashi,	Kimiko Hamano,
	Wakana Furushima,	Daisuke Tomizawa,
	Atsuko Taki,	Takeshi Isoda,
	Masaki Sato,	Junya Unno,
	Fumiko Honda,	Norimasa Ihara,
	Rie Miyata,	Kentaro Miyai,
	Masanobu Takahashi,	Kaori Nakatani,
	Yuuko Ohnishi,	Eriko Tanaka,
	Yuki Aoki,	Fumihiko Takizawa,
	Hideyuki Yokokawa	
Special Study Student	Kouichi Kamei,	Yuuko Komatu,
	Hiromi Kameda,	Yoshihiro Fukawatase
Collaborator	Minoru Asada（Department of Pharmacology, Nippon Medical School）	
	Hatsume Uno（Sony Life Science Laboratories）	
	Naomi Terada（The Japan Health Sciences Foundation）	
	Kimitoshi Imamura（Institute of Biomaterials and Bioengineering, TMDU）	

2. The goal of Education

The Department of Pediatrics and Developmental Biology plays a central role for education of Pediatrics at Medical school. A comprehensive lecture course for 30 themes of main pediatric diseases is provided for 3rd to 4th grade medical students. Opportunities of training in scientific research are provided for elective 4th graders, One month practice in clinical trainings is provided for 5th to 6th graders, where every student belongs to one of the professional clinical teams and studies clinical practice as one of the team members. During this course of clinical training, each student is expected to learn skills for differential diagnosis, planning of examination schedule and description of clinical records. Junior clinical fellows who are in the training course of pediatric practice under the supervision of senior staffs are also expected to supervise these medical students. Another mission of this department is to provide lecture course on general pediatrics for the students of Dental School and School of Health Science.

The main goal of the education provided by us is to support the students to strengthen their knowledge in fundamental pediatrics with the view for total care, which can be achieved only by mutual cooperation with subspecialties in various fields of pediatrics.

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. Defects in DNA repair system and genetic background-environment factors interactions for the development of childhood leukemia.
2. Molecular mechanisms of chromosomal translocation
3. Novel roles of ATM in cellular differentiation
4. Novel roles of Artemis in the DNA repair system
5. Systematic search for genes responsible for primary immunodeficiency diseases
6. Development of innovative techniques for cell therapy and gene therapy

7. Molecular mechanisms of primary pulmonary hypertension

We have been collaborating with Institute of Cancer Research in London (Prof Mel Greaves), Istitute Nazionale Tumori (Dr. D. Delia), 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, Tokai University (Prof. IchikawaTokyo), Metropolitan Institute for Neuroscience, Nihon Medical 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.

Our research interest involves development of a leukemogenesis model that stemmed defective tumor surveillance system *in vitro* and *in vivo* and in-depth analysis of DNA damage response (DDR) cascades. Among the molecules involved in DDR, we currently focus on ATM, Artemis, and Mre11. The functions of those molecules in health and diseases have been studied at molecular, cellular, and individual level. The topics include impaired ATM function and infantile leukemia, role of Artemis in replication fork stall, regulation of Artemis stability by its associated protein. The function of mutant Mre11, XLF1, and LIGIV have been analyzed with using materials obtained from the patients deficient in each molecule. Our approach also led to the work that elucidated the function of ATM in adipocyte differentiation, which would potentially explain the reason why the patients with Ataxia telangiectasia suffer from emaciation and from diabetes mellitus.

In the field immunodeficiency, we work on the role of Btk in production of reactive oxygen species and apoptosis, molecular and cellular mechanism of common variable immunodeficiency, and development of protein therapy with the use of protein transduction domain-based intracellular delivery system. We also work on the protean functions of those molecules in the non-immunological system in collaboration with other laboratories.

Our goal of research is to establish techniques that would directly help children in our clinical field. We have recently developed a novel method to detect DDR by a flow cytometry, and continuously work to develop a novel system to detect multiple microbes rapidly and economically.

●Cardiology Group

1) Elucidation of mechanisms how pulmonary hypertension (PH) occurs and development of concrete evaluation method of PH,
   followed by new therapeutics for PH (by Dr. Imamura, Sasaki and Doi)
2) Establishment of the methods for functional evaluations in left and right ventricles by using 2D speckle tracking echocardiogram (by PhD student Mrs. Onishi and Dr. Doi)
3) Clarification of judgment methodology in severity of fatal arrhythmias (by Dr. Sasaki, Doi and Izumida)
4) Analyses of relationships between changes in ventricular function during cardiac developmental stages, and myocardial intracellular
   Ca^{2+} transient (by Dr. Ishiwata)
5) Analysis of effects of β-blocker under the clinical situations (by PhD student Ms. Ishibashi and Dr. Nishiyama)
6) Interactions between alveolar epithelial cells and vascular endothelial cells in lungs (by PhD student Mr. Wakabayashi in Imperial Collage London)

●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.

In 2009, we identified ANA (abundant in neuroepithelial area) as a suppressor of ectopic bone formation and unique and novel inhibitor of BMP function (collaborated with Department of Molecular Pharmacology, TMDU).

●Neonatology group

1) Relationship between neoangiogenesis in fetuses and complication of preterm infants
2) Effectiveness of Neonatal Cardio-Pulmonary Resuscitation program(NCPR) in JAPAN

●Nephrology Group

1) Efficacy of Rituximab for severe idiopathic nephrotic syndrome: examining correlation of B cells, T cells, and activating markers in those with Rituximab administration and relapse of nephrotic syndrome.
2) Analyses of patients who underwent blood purification therapy: i. e., risk factors, problems and prognosis.
3) Analyses of glomerular epithelial cells (podocytes) unknown function.

We work on these researches in cooperation with National Center of Health and Development (1, 2) , Juntendo University (3), and Division of Nephrology and Hypertension, Miller School of Medicine, University of Miami (3).

●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.

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 3 senior and 3 junior staff, and care both inpatients and outpatients cooperatively.

We follow more than 80 patients with primary immunodeficiency; the largest patient number followed in Japan. We conducted a nation-wide survey for ataxia telangiectasia patients and for common variable immunodeficiency supported by the Ministy of Health Labor and Welfare, and receive consultation on the diagnosis and clinical management of these patients.

In collaboration with international 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.

New inpatients in 2009 include 9 ALL (acute lymphocytic leukemia), 5 AML (acute ,myelogenous leukemia), , 1 malignant lymphoma, one rhabdomyosarcoma, one Ewing' s sarcoma, 2 SCID (severe combined immunodeficiency), one HIM (Hyper IgM syndrome), one bone marrow failure syndrome, two hemophagocytic syndrome, one CAEBV(chronic active EBV infection), one immune thrombocytopenic purpura, three unclassified immunodeficiency and so on. We performed six HSCT, which included two unrelated cord blood, one sibling and three unrelated bone marrow HSCT in 2009.

We have performed more than 120 HSCT so far, which includes more than 40 cases with primary immunodeficiency. With these experiences, we are leading this field in Japan.

●Cardiology Group

Pediatric cardiology group provides an original concrete judgment and evaluation using pulmonary vascular pressure-flow relationships for severe pulmonary hypertensive (PH) patients, which is followed by active treatment such as surgical operation, NO inhalation and another medications for PH patients.

We try an earlier application of percutaneous cardiopulmonary support for fulminant myocarditis patients, and cardiac resynchronization therapy for medication-resistant severe cardiomyopathy patients by utilizing a new method of echocardiogram.

We participate in Raise study for severe Kawasaki diseases, which compares two kinds of treatments, immunoglobulin only or combination of immunoglobulin and prednisolon.

We perform education and medical treatments for patients with severe arrhythmias such as prolonged QT syndrome by examining gene mutations and several kinds of provocation test.

●Neurology Group

Child neurology provides highly specialized diagnostic and medical care for neurological disorders such as epilepsy, neuromuscular disorders, infections of nervous system and other neurodegenerative diseases. In particular, we provide therapeutic approach of xeroderma pigmentosum by using of clinicopathological analysis.

●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, 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.

●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. Nanki T, Takada K, Komano Y, Morio T, Kanegane H, Nakajima A, Lipsky PE, Miyasaka N. Chemokine receptor expression and functional effects of chemokines on B cells: implication in the pathogenesis of rheumatoid arthritis. ***Arthritis Res Ther.*** 2009 ; 11:R149 [Epub].
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7. Uchisaka N, Takahashi N, Sato M, Kikuchi A, Mochizuki S, Imai K, Nonoyama S, Ohara O, Watanabe F, Mizutani S, Hanada R, Morio T. Two brothers with ataxia-telangiectasia–like disorder with lung adenocarcinoma. ***J. Pediatr.*** 2009；155:435-438.
8. Futagami Y, Sugita S, Fujimaki T, Yokoyama T, Morio T, Mochizuki M. :Bilateral anterior granulomatous keratouveitis with sunset glow fundus in a patient with autoimmune polyglandular syndrome. ***Ocul Immunol Inflamm.*** 2009；17:88-90.
9. Takahashi N, Matsukoto K, Saito H, Nanki T, Miyasaka N, Kobata T, Azuma M, Lee S-K, Mizutani S, Morio T. Impaired CD4 and CD8 effector function and decreased memory T-cell populations in ICOS deficient patients. ***J. Immunol.*** 2009；182:5515-5527.
10. Honda M, Takagi M, Chessa L, Morio T, Mizuatni S.: Rapid diagnosis of ataxia-telangiectasia by flow cytometric monitoring of DNA damage-dependent ATM phosphorylation. ***Leukemia.*** 2009；23: 409-414.
11. Minegishi Y, Saito M, Nagasawa M, Takada H, Hara T, Tsuchiya S, Agematsu K, Yamada M, Kawamura N, Ariga T, Tsuge I, Karasuyama H. Molecular explanation for the contradiction between systemic Th17 defect and localized bacterial infection in hyper-IgE syndrome. ***J. Exp. Med.*** 2009 ; 206(6):1291-301.
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13. Tomizawa D, Koh K, Hirayama M, Miyamura T, Hatanaka M, Saikawa Y, Ishii E. Outcome of recurrent or refractory acute lymphoblastic leukemia in infants with *MLL* gene rearrangements: A report from the Japan Infant Leukemia Study Group. ***Pediatr Blood Cancer.*** 2009; 52(7): 808-13.
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19. Hayashi M, Miyata R, Tanuma N. Increase of oxidative stress markers in the urine in patients with xeroderma pigmentosum. p133-5 10th Asian & Oceanian Congress of Child Neurology. –AOCCN-. 10th Asia & Oceanian Congress of Child Neurology. –AOCCN-. Medimond 2009.
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21. Furushima W, Inagaki M, Gunji A, Inoue Y, Kaga M, Mizutani S. Early signs of visual perception and evoked potentials in radiologically asymptomatic boys with X-linked adrenoleukodystrophy. ***J Child Neurol.*** 2009;24:927-35.
22. Sasaki M, Takanashi J, Tada H, Sakuma H, Furushima W, Sato N. Diffuse cerebral hypomyelination with cerebeller atrophy and hypoplasia of the corpus callosum. ***Brain Dev.*** 2009;31:582-7.
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quantitative real-time RT-PCR analysis of gene expression in fetal mouse gonads. ***Sex Dev.*** 2009;3(4):194-204.
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International congress

1. Morio T. ROS induced DNA damage response. Symposium: "ROS and NO", The 46th Meeting of Korean Society of Biochemistry and Molecular Biology. Seoul. Korea. May 2009.
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4. Nishi M, Sadakane Y, Eguchi Eguchi-Ishimae M, Tauchi H, Kawakami S, Tomizawa D, Mizutani S, Sugita K, Ishii E. Suppression of *Let-7b* microRNA and enhanced its target genes in infant acute lymphoblastic leukemia with *MLL* gene rearrangements. 51st Annual Meeting of the American Society of Hematology, New Orleans, USA, Dec. 5-8, 2009.
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8. Wakabayashi K, Wilson MR, O'Dea KP, Takata M. Role of intravascular leucocytes in ventilator-induced lung injury in the isolated perfused mouse lung. British Thoracic Society Winter Meeting; London, United Kingdom, Dec. 2009.
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potentials in radiologically asymptomatic boys with X-linked adrenoleukodystrophy. 10th Asian and Oceanian Congress of Child Neurology. Daegu, Korea, June 2009.

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