International Symposium

Date: Friday, July 14, 2006 (14:30～18:00)
Venue: Conference Hall of Astellas Pharma Inc., Tokyo

30th Anniversary of
National Research Group on Idiopathic Bone Marrow Failure Syndromes

Bone Marrow Failure Syndromes
from Genomic Analysis to Novel Therapeutics

Cosponsored by

Health and Labour Sciences Research Grants (Research on Measures for Intractable Diseases) of the Ministry of Health, Labour and Welfare

Japan Intractable Diseases Research Foundation

LIST OF SPEAKERS

Hideaki Mizoguchi
Neal S. Young
Shinji Nakao
Peter Hillmen
Kazuya Shimoda
Seishi Ogawa
Alan List

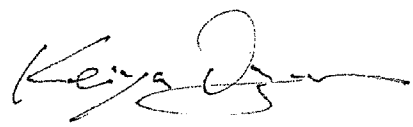
【Secretariat】
Division of Hematology, Department of Medicine, Jichi Medical University
3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan
TEL: +81-285-58-7353 FAX: +81-285-44-5258
URL: http://www.jichi.ac.jp/zoketsushogaihan
E-mail: hematology@jichi.ac.jp

Preface to the International Symposium

The national research group on idiopathic bone marrow failure syndromes is supported by the Health and Labour Sciences Research Grants (Research on Measures for Intractable Diseases) of the Ministry of Health, Labour and Welfare (MHLW). This research group was established in 1977 as a nationwide organization of hematologists with the aim of investigating bone marrow failure syndromes extensively, and since then a large number of important results have been produced. Past principal investigators are Drs. Haruto Uchino, Tadashi Maekawa, Takeo Nomura, Hideaki Mizoguchi, and Mitsuhiro Omine. As a current principal investigator, I have planned to hold an international symposium as a special event on the occasion of the 30th anniversary of this national research group on idiopathic bone marrow failure syndromes, which is held on Friday July 14, 2006. The symposium title is "*Bone Marrow Failure Syndromes: from Genomic Analysis to Novel Therapeutics*". This symposium is cosponsored by the MHLW and the Japan Intractable Diseases Research Foundation.

The main target diseases of this national research group are aplastic anemia, refractory anemia [MDS (myelodysplastic syndromes)], hemolytic anemia [PNH (paroxysmal nocturnal hemoglobinuria) and AIHA (autoimmune hemolytic anemia)], and bone marrow fibrosis. I am delighted to be able to invite leading scientists to the symposium. Among them, we have three distinguished scholars from abroad, namely Dr. Neal S. Young, Dr. Peter Hillmen, and Dr. Alan List. They will give us the latest information on molecular aspects of bone marrow failure syndromes and the innovative molecular targeted therapy. I have great expectations regarding the benefits to our national research group, which will be produced by exchanging knowledge and ideas with the leading scientists in the world.

I hope that the guest speakers from abroad will also enjoy the sightseeing in Japan. Finally, I would like to extend my sincere thanks to all of the participants and hope that you will enjoy the symposium.



Keiya Ozawa, M.D., Ph.D.
Principal Investigator,
National Research Group on Idiopathic Bone Marrow Failure Syndromes
Professor & Chairman,
Division of Hematology, Department of Medicine, Jichi Medical University

Symposium Program

Chairperson: ***Keiya Ozawa****, Principal Investigator*

14:30 – 14:35
Speech on behalf of the Ministry of Health, Labour and Welfare

14:35 – 14:45
History of the National Research Group on Idiopathic Bone Marrow Failure Symdromes
Hideaki Mizoguchi
Saitama Red Cross Blood Center, Japanese Red Cross Society

14:45 – 15:25
Understanding Aplastic Anemia at the Molecular Level
Neal S. Young
Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, USA

15:25 – 15:50
Laboratory Markers for Immune Pathophysiology in Aplastic Anemia (AA): Towards Identification of Autoantigens in AA
Shinji Nakao
Cellular Transplantation Biology, Kanazawa University Graduate School of Medical Science

15:50 – 16:30
PNH - from Biology to Targeted Treatment
Peter Hillmen
Department of Haematology, Leeds Teaching Hospitals NHS Trust, UK

16:30 – 16:55
Primary Myelofibrosis - the Molecular Basis and the Therapy
Kazuya Shimoda
Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences

16:55 – 17:20
Genome-wide Analysis of Copy Number Alterations and Allelic Imbalances in Myelodysplastic Syndromes
Seishi Ogawa
Department of Regeneration Medicine for Hematopoiesis, Graduate School of Medicine, University of Tokyo

17:20 – 18:00
Non-Cytokine Therapeutics for Myelodysplastic Syndromes
Alan List
H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida, USA

Curricula Vitae
&
Abstracts

CURRICULUM VITAE

Hideaki Mizoguchi, M.D., Ph.D.
Director
Saitama Red Cross Blood Center
Japanese Red Cross Society
1370-12 Takahagi, Hidaka-shi, Saitama, 350-1213 Japan
Phone: (+81) 42-985-6111, Fax: (+81) 42-985-6907
E-mail: mizoguchi@saitama.bc.jrc.or.jp

Date of Birth: 1938.10.24

Professional Experience

2004-present	Director, Saitama Red Cross Blood Center, Japanese Red Cross Society, Japan
	Professor Emeritus and Consultant, Tokyo Women's Medical University, Japan
2000-2004	Dean, School of Medicine, Tokyo Women's Medical University, Japan
1991-2004	Chairman and Professor, Department of Hematology, Tokyo Women's Medical University, Japan
1990-1991	Professor, Department of Hematology, Tokyo Women's Medical School
1982-1990	Professor, Department of Medicine, Tokyo Women's Medical School
1980-1982	Associate Professor, Department of Medicine, Tokyo Women's Medical School
1974-1980	Associate Professor, Institute of Hematology, Department of Medicine, Jichi Medical School
1972-1974	Instructor, Central Laboratory, the University of Tokyo, Faculty of Medicine, Japan
1969-1972	Instructor, Department of Medicine, State University of New York, USA
1968-1969	Instructor, the Third Department of Medicine, the University of Tokyo, Faculty of Medicine, Japan
1964-1968	Graduate School of Medicine, the University of Tokyo, Japan
1963-1964	Internship, Tokyo University Hospital, Japan

Education

1964-1968	Ph.D., (Dr. of Medical Science), Graduate School of Medicine, The University of Tokyo
1985-1963	M.D., The University of Tokyo, Faulty of Medicine

Recent Publications

1. Sugimori, C., Chuhjo, T., Feng, X,. Yamazaki, H,. Takami, A., Teramura, M,. Mizoguchi, H., Omine, M., Nakao, S.: Minor population of CD55-CD59- blood cells predicts response to immunosuppressive therapy and prognosis in patients with aplasatic anemia. Blood 107:1308-1314, 2006.
2. Ito, Y., Ohyashiki, K., Hirai, H., Ogawa, S,. Mitani, K., Hotta, T., Bessho, H., Naoe, T., Mizoguchi, H., Uchiyama, T., Omine, M. : Assessment of the internation prognostic scoring system for determing chemotherapeutic indications in myelodysplastic syndrome.: Japanese retrospective multicenter study. Int. J. Hematol. 82: 236-242, 2005.
3. Masuda, M., Teramura, M., Masuda, A., Bessho M., Shimamoto, T., Ohyashiki, K., Omine, M., Motoji, T., Mizoguchi, H.: Clonal T cells of pure red cell aplasia . Am. J. Hematol. 79: 332-333, 2005.
4. Nishimura, J., Kanakura, Y., Ware, RE., Shichishima T., Nakamura, H., Ninomiya, H., Decastro. C.M., Hall, S., Kanamaru, S., Sullivan, K.M., Mizoguchi, H., Omine. M.. Kinoshita, T., Rosse, W.F.: Clinical course and flow cytometeric analysis of paryoxysumal nocturnal hemoglobinuria in the United States and Japan. Medicine 83: 193-207, 2004.
5. Matsuda, A., Misumi, M., Ishikawa, M., Yagasaki, F., Jinnnai, I., Bessho, M., Mizoguchi, H.: Long-term improvement of anaemia in a patient with aplastic aneaemia by short-term administration of pegylated recombinant human meagakaryocyte growth and development factor. Br. J. Haematol. 125: 818-819, 2004.

History of the National Research Group on Idiopathic Bone Marrow Failure Symdromes

Hideaki Mizoguchi
Saitama Red Cross Blood Center, Japanese Red Cross Society, Japan.

The National Research Group on Idiopathic Bone Marrow Failure Syndromes (IBMFS) was started by the Japanese Ministry of Health and Welfare (present Japanese Ministry of Health, Labor and Welfare) in 1977, and the chairman was Dr. Uchino. The aim of this research group is to decide the criteria for diagnosis, to clarify the epidemiology, pathogenesis and prognosis, and to improve the treatment of IBMFS including aplastic anemia, myelodysplastic syndromes, hemolytic anemia and myelofibrosis. Before this research group was established, the national research groups on aplastic anemia, idiopathic thrombocytopenic purpura (ITP) and hemolytic anemia were started in 1972, 1973 and 1974, respectively. In 1977, these research groups were combined into the research group on IBMFS. In 1995, research on myelofibrosis was added to this research group and research on ITP was transfered to another research group on coagulation disorders. Previous chairpersons of this research group were Dr. Uchino, Dr. Maekawa, Dr. Nomura, Mizoguchi, Dr. Omine, and the present chairman is Dr. Ozawa.

This research group has contributed greatly to research on IBMFS by many collaborative studies. Dr. Hara found a decrease in CFU-mix in the case of aplastic anemia. Dr. Hirai found the point mutation of the N-RAS gene in MDS. Dr. Yoshida collected MDS cases from all over Japan and clarified the epidemiology and pathophysiology of MDS in Japan. Dr. Toyama and Dr. Ohyashiki analyzed the chromosome abnormalities of MDS and contributed to the development of the international prognosis scoring system (IPSS). Dr. Motoji reported the usefulness of high-dose methylprednisolone to refractory anemia. Dr. Kinoshita and Dr. Kitani cloned PIG-A gene in PNH.

During the past 30 years, the members of this research group have held several international meetings in Japan supported by the Japanese Medical Research Foundation or the Japanese Intractable Diseases Research Foundation. The 1st international symposium on aplastic anemia was held in September, 1976 in Kyoto with Dr. Hibino as chairman, a meeting "myelodysplastic syndrome : advances in research and treatment" was held in October, 1994 in Tokyo with Dr. Nomura as chairman, a meeting "PNH and related disorders: molecular aspects of pathogenesis" was held in August 2001 in Tokyo with Dr. Omine and Dr. Kinoshita as chairpersons. The 16th annual meeting of ISEH was chaired by Dr. Takaku in 1987 and the 30th annual meeting was chaired by Mizoguchi.

Every year more than 100 researchers, mainly clinical hematologists get together from all over Japan to report new findings on IBMFS and discuss their mutual interest, contributing to the health and welfare of IBMFS patients. I hope this research group will continue to contribute to the health and welfare of the patients with IBMFS.

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CURRICULUM VITAE

Neal Stuart Young, M.D., Ph.D.
Chief, Hematology Branch, NHLBI, NIH
Building 10 CRC 3E-5140,
National Institutes of Health, Bethesda MD 20892-1202, USA
Telephone: 301 496 5093
Telefax: (w) 301 496 8396
E-mail: youngns@mail.nih.gov

Date of Birth: April 13, 1947

Professional Experience

1994-	Chief, Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland
1993-1994	Acting Chief, Clinical Hematology Branch, National Heart, Lung, and Blood Institute
1989-	Head, Clinical Services, Clinical Hematology/Hematology Branch, National Heart, Lung, and Blood Institute
1983-1993	Chief, Cell Biology Section, Clinical Hematology Branch, National Heart, Lung, and Blood Institute
1981-1983	Senior Investigator, Clinical Hematology Branch, National Heart, Lung, and Blood Institute
1976-1981	Visiting Expert, Clinical Hematology Branch, National Heart, Lung, and Blood Institute (Dr. Arthur Nienhuis)
1975-1976	Clinical Fellow, HematologyOncology Division, Barnes Hospital, Washington University, St. Louis, Missouri
1973-1975	Research Associate, Laboratory of Chemical Biology, National Institute of Arthritis, Metabolism, and Digestive Diseases (Dr. Christian Anfinsen)
1971-1973	Medical Resident, Massachusetts General Hospital, Boston, Massachusetts

Recent Publications

1. Risitano, A.M., Maciejewski, J.P., Tarnowka, M.K., Zeng, W., and Young, N.S.: In vivo dominant immune responses in aplastic anemia patients: molecular tracking of putatively pathogenic T cell clones by TCR cell clones by TCR β-CDR3 sequencing. Lancet 364:355-364, 2004.
2. Yamaguchi, H.,* Calado, R.T.,* Ly, H.*, Kajigaya, S. Baerlocher, G.M., Chanock, S.J., Lansdorp, P.M., and Young, N.S.: Mutations in TERT, the gene for human telomerase gene reverse transcriptase, in patients with aplastic anemia. N. Engl. J. Med. 352:1413-1424, 2005.
3. Chen, G., Zeng, W., Miyazato, A., Keyvanfar, K., Billings, E., and Young, N.S.: Differential gene expression profiles in hematopoietic progenitor cells from paroxysmal nocturnal hemoglobinuria patients. Leukemia 19:862-868, 2005.
4. Ogaswara, Y., Nakayama, K., Tarnowka, M., McCoy, J.P., Jr., Kajigaya, S., Levin, B.C. and Young, N.S.: Analysis of mitochondrial DNA spectra in single CD34+ cells, T-cells, B-cells and granulocytes. Blood 106:327184, 2005.
5. Solomou, E.E., Keyvanfar, K., and Young, N.S.: T-bet, a Th1 transcription factor, is upregulated in T cells from patients with aplastic anemia. Blood 107:3983-91, 2006.

Understanding Aplastic Anemia at the Molecular Level

Neal S. Young, Jichun Chen, Rodrigo T. Calado, Elena Solomou, Elaine M. Sloand.
Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda MD, USA.

In aplastic anemia, failure of hematopoiesis leads to an empty bone marrow, pancytopenia, and death. Clinical observations and laboratory studies have implicated immune cell destruction of hematopoietic stem and progenitor cells. Understanding of marrow failure at the molecular level has been achieved by a combination of methods, including genomics using microarrays; genetics with high throughput nucleotide sequencing; immunophenotyping by flow cytometry and spectratyping; fluorescent in situ hybridization; and single cell studies in conventional progenitor assays and for mtDNA sequence. Oligoclonal cytotoxic T cell populations appear to mediate apoptosis via type I cytokines of hematopoietic cells, and their presence fluctuates with immunosuppressive therapy. Abnormal T cell signal transduction (Tbet, SAP, and TCR zeta-chain abnormalities) and related genetic lesions (*PRF1* mutations) may predispose to an aberrant T cell response. The identification of genes responsible for some forms of constitutional bone marrow failure has informed the biology of acquired disease. Mutations in *TERC*, which encodes the RNA template of the telomere repair complex, are present in autosomal dominant dyskeratosis congenita and also in some patients with apparently acquired aplastic anemia; other implicated genes include *TERT*, the telomerase gene itself, a helicase that affects telomere repair, and *SBDS*, the gene affected in the Shwachman-Diamond syndrome. Androgens, long recognized as useful in the treatment of marrow failure in children and some cases in adults, appear to act by upregulating *TERT* expression via the estradiol recptor and increasing telomerase activity in hematopoietic cells. Clonal evolution of aplastic anemia to myelodysplasia is also better understood. For the most common cytogenetic abnormality in this setting, monosomy 7, aberrant proliferation in response to endogenously high or therapeutic G-CSF is due to expression of the short isoform IV of the G-CSFR in monosomy 7 cells. For trisomy 8, which frequently responds to immunosuppression and has a relatively benign prognosis, T cell clones recognize the cytogentically abnormal cells and specifically peptides derived from the WT1 that is overexpressed in these cells; clonal evolution is secondary to escape from the late phase of apoptosis in trisomy 8 cells. Identification of molecular mechanisms in bone marrow failure should be useful in improving treatments and guiding choices among available therapies.

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CURRICULUM VITAE

Shinji Nakao, M.D., Ph.D.
Professor
Cellular Transplantation Biology,
Kanazawa University Graduate School of Medical Science,
13-1 Takaramachi, Kanazawa, Ishikawa 920-8641, Japan
Phone: (+81) 76-265-2274
Fax: (+81) 76-234-4252
E-mail: snakao@med3.m.kanazawa-u.ac.jp

Date of Birth: 1955. 8.20

Professional Experience

2001-present	Professor, Cellular Transplantation Biology, Kanazawa University Graduate School of Medical Science
1999-2001	Professor, Third Department of Medicine, Kanazawa University School of Medicine
1994-1998	Assistant Professor, Third Department of Medicine, Kanazawa University School of Medicine
1989-1993	Instructor, Third Department of Medicine, Kanazawa University School of Medicine
1987-1989	Research Associate, Second Department of Internal Medicine, Fukui Medical School, Japan
1987-1989	Visiting Fellow at Clinical Hematology Branch, National Institutes of Health, USA

Education

1980-1984	Ph.D. (Dr. of Medical Science), Kanazawa University Graduate School of Medicine
1974-1980	M.D., Kanazawa University School of Medicine

Recent Publications

1. Sugimori, C., Chuhjo, T., Feng, X., Yamazaki, H., Takami, A., Teramura, M., Mizoguchi, H., Omine, M., Nakao, S. Minor population of CD55-CD59- blood cells predicts response to immunosuppressive therapy and prognosis in patients with aplastic anemia. Blood, 107, 1308-1314, 2006
2. Takami, A., Mochizuki, K., Okumura, H., Ito, S., Suga, Y., Yamazaki, H., Yamazaki, M., Kondo, Y., Asakura, H., Nakao, S. Mycophenolate mofetil is effective and well tolerated in the treatment of refractory acute and chronic graft-versus-host disease. Int J Hematol, 83, 80-85, 2006
3. Nakao, S., Feng, X., Sugimori, C. Immune pathophysiology of aplastic anemia. Int J Hematol, 82, 196-200, 2005
4. Feng, X., Chuhjo, T., Sugimori, C., Kotani, T., Lu, X., Takami, A., Takamatsu, H., Yamazaki, H., Nakao, S. Diazepam-binding inhibitor-related protein 1: a candidate autoantigen in acquired aplastic anemia patients harboring a minor population of paroxysmal nocturnal hemoglobinuria-type cells. Blood, 104, 2425-2431, 2004
5. Takami, A., Sugimori, C., Feng, X., Yachie, A., Kondo, Y., Nishimura, R., Kuzushima, K., Kotani, T., Asakura, H., Shiobara, S., Nakao, S. Expansion and activation of minor histocompatibility antigen HY-specific T cells associated with graft-versus-leukemia response. Bone Marrow Transplant, 34, 703-709, 2004

Laboratory Markers for Immune Pathophysiology in Aplastic Anemia (AA): Towards Identification of Autoantigens in AA

Shinji Nakao, Chiharu Sugimori, Xingmin Feng, Hideyuki Takamatsu, Hirohito Yamazaki
Cellular Transplantation Biology, Kanazawa University Graduate School of Medical Science

Acquired aplastic anemia (AA) is a syndrome characterized by pancytopenia and bone marrow hypoplasia. Immune-mediated suppression of hematopoiesis contributes to the development of bone marrow failure in many of AA patients but not in all of them. It is therefore desirable to diagnose immune pathophysiology by detecting certain markers in AA patients and treat only the patients who had positive results with immunosuppressive therapy (IST). We have tested blood samples of more than 964 patients over the last 6 years for the presence of several makers such as small populations of PNH-type cells, HLA-DR15, and antibodies specific to DRS-1 and moesin, and studied the correlation of each maker with response to IST. Among these markers, a small population of PNH-type cells is the most reliable predictor of a good response to IST. A small population of PNH-type cells was detectable in 274 of 547 (50.1%) AA patients and 52 of 417 (12.5%) patients with MDS-refractory anemia. The presence of increased PNH-type cells was associated not only with favorable response to IST but also with a higher rate of failure-free survival compared to AA patients not showing a small population of PNH-type cells. Detection of antibodies to DRS-1 and moesin in the serum of AA patients appeared to help diagnose immune pathophysiology, particularly in patients without a small population of PNH-type cells.

With regard to DRB1 alleles corresponding to HLA-DR15 in Japanese, the frequencies of DRB1*1501 and DRB1*1502 were significantly higher in AA patients than in a healthy control population, but only DRB1*1501 was associated with a good response to IST. The frequency of an HLA-class II haplotype, DRB1*1501-DRB5*0101- DQB1*0601 was also higher in Indian AA patients than in a control population. Because DRB1*1501-DRB5*0101 is in linkage disequilibrium with DQB1*0602 in most Japanese individuals, a gene which determines susceptibility to immune-mediated AA is thought to be either DRB1*1501 or DRB5*0101, or other genes which are located in the vicinity of these DR genes. When the influence of several factors including a small population of PNH-type cells and DRB1 alleles on response to IST was examined by multivariate analysis, only the presence of a small population of PNH-type cells was found to be a significant predictor.

These findings seem to be vital not only in managing AA but also in identifying inciting antigens of AA.

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CURRICULUM VITAE

Peter Hillmen, MB ChB, PhD
Consultant Haematologist
Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust, Great George Street, Leeds, LS1 3EX, United Kingdom.
Phone: (+44) 113-392-2974
Fax: (+44) 113-392-6349
E-mail: peter.hillmen@nhs.net

Date of Birth: 21/01/62

Professional Experience

2005.4-present	Consultant in Clinical Haematology, Leeds Teaching Hospitals NHS Trust, Leeds General Infirmary, Leeds.
1996.7-2005.3	Consultant in Clinical Haematology, Pinderfields General Hospital, Wakefield and Leeds General Infirmary, Leeds.
1994.1-1996.6	Senior Registrar in Haematology, Rotation, Leeds, Yorkshire
1991.1-1993.12	Research Training Fellow, Department of Haematology, Royal Postgraduate Medical School, Hammersmith Hospital, London
1989.1-1990.12	Registrar Rotation, Department of Haematology, Hammersmith Hospital, London
1986.8-1988.12	Senior House Officer Medical Rotation, Leeds General Infirmary, Leeds
1985.8-1986.7	Resident House Physician, Leeds General Infirmary Resident House Surgeon, St Luke's Hospital, Bradford

Education

1991-1995	PhD, University of London
1985-1991	MBChB, University of Leeds

Recent Publications

1. Almedia AM, Murakami Y, Layton DM, Hillmen P, Sellick GS, Maeda Y, Richards SJ, Patterson S, Kotsianidis I, Mollica L, Crawford D, Baker A, Ferguson M, Roberts I, Houlston R, Kinoshita T and Karadimitris A. Hypomorphic promoter mutation in the mannosyltransferase-encoding PIG-M?gene causes inherited glycosylphosphatidyl- inositol deficiency. (2006) Nature Medicine, June 11, E-pub.
2. Hill A, Riley SH, Esser D, Oldroyd RG, Cullen MJ, Karelclas P, Gallagher S, Smith GP, Richards SJ, White J, Smith RAG, Hillmen P. Protection of erythrocytes from human complement mediated lysis by membrane-targeted recombinant soluble CD59: A new approach to PNH therapy. (2006) Blood, 107, 2131-7.
3. Parker C, Omine M, Richards S, Nishimura JI, Bessler M, Ware R, Hillmen P, Luzzatto L, Young N, Kinoshita T, Rosse W, Socie G. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. (2005) Blood, 106, 3699-709.
4. Hill A, Hillmen P, Richards SJ, Elebute D, Marsh JC, Chan J, Mojcik CF, Rother RP. Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria. (2005) Blood, 106, 2559-65.
5. Hillmen P, Hall C, Marsh JCW, Elebute M, Bombara MP, Petro BE, Cullen MJ, Richards SJ, Rollins SA, Mojcik CF and Rother RP. Effect of eculizumab on hemolysis and transfusion requirements in paroxysmal nocturnal hemoglobinuria. (2004) New Engl J Med, 350, 552-559.

PNH - from Biology to Targeted Treatment

Peter Hillmen
Department of Haematology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired disorder which is characterized by intravascular haemolysis, ahigh incidence of life-threatening venous thrombosis and an association with aplastic anaemia. PNH results from the clonal expansion of somatically mutated haematopoietic stem cells with a deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins from the surface of blood cells. The biochemical and molecular defect in PNH was elucidated in the early 1990's. The biosynthesis of GPI structures is disrupted by a somatic mutation of the X-linked *PIG-A* gene. The haemolysis and, almost certainly, the thrombotic tendency in PNH result from the unopposed action of terminal complement on PNH red cells and platelets due to their deficiency of the terminal complement inhibitor CD59. Excessive or persistent intravascular hemolysis can result in anaemia, fatigue, thrombosis, pain, pulmonary hypertension, poor quality of life (QoL), and frequently a dependency on transfusions to maintain haemoglobin levels. Therefore the classical disabling symptoms of PNH should be abrogated by the inhibition of complement. An initial Pilot study of a humanized monoclonal antibody against C5 that inhibits terminal complement activation, called eculizumab, revealed very promising responses. Ten patients remain on eculizumab over 3 years since commencing treatment with continued benefit. The pivotal phase III clinical study, TRIUMPH (Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria), evaluated the efficacy and safety of eculizumab, a compared to placebo in a cohort of PNH patients. Patients were randomized to receive either placebo or eculizumab administered intravenously at 600 mg weekly for 4 weeks and then 900 mg every 2 weeks commencing the fifth week for a total of 6 months of therapy. The co-primary endpoints were stabilization of haemoglobin levels and reduction in transfused blood units. Prespecified measures of haemolysis and QoL were assessed. Eighty-seven PNH patients (39 sites, 11 countries) were randomized 1:1 to receive either eculizumab or placebo. Eculizumab therapy was safe and well tolerated in the study. Both primary endpoints were met with statistical significance: 1) stabilization of haemoglobin levels was achieved by 48.8% of eculizumab-treated patients and by 0% of placebo-treated patients (P=0.000000014); 2) median transfused packed red blood cells (PRBCs) were 0 units in the eculizumab-treated group compared with 10 units in placebo (P=0.0000000006). Fifty-one percent of eculizumab-treated patients were completely transfusion-independent through week 26 (study end), while every placebo-treated patient received at least one transfusion by week 14 (P=0.000000005). Eculizumab treatment dramatically reduced intravascular haemolysis, as evidenced by an 85.8% decrease in the lactate dehydrogenase area under the curve relative to placebo (P<0.00000000001). Concomitantly, eculizumab treatment resulted in an increase in the proportion of PNH type III RBCs from 28.1% at baseline to 56.9% by week 26 while the proportion in the placebo group remained constant (P=0.00005). Fatigue, as measured by the FACIT-Fatigue QoL instrument was significantly improved (P=0.000006), and significant improvements were also demonstrated in QoL subscales of the EORTC QLQ-30 instrument including fatigue (P=0.0000006), global health status (P=0.00002), physical functioning (P=0.000003), emotional functioning (P=0.008), cognitive functioning (P=0.002), role functioning (P=0.0001), social functioning (P=0.003), pain (P=0.002), dyspnea (P=0.0008), appetite loss (P=0.00004) and insomnia (P=0.014). The 2 most common adverse events in the trial were headache and nasopharyngitis. Therefore eculizumab stabilized hemoglobin levels, decreased the need for transfusions and provided clinically meaningful improvements in fatigue and other QoL parameters in patients with PNH through reduction of intravascular hemolysis. Long-term eculizumab treatment in PNH is effective and well tolerated. Eculizumab is the first targeted therapy for PNH.

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CURRICULUM VITAE

Kazuya Shimoda, M.D., Ph.D.
Associate Professor
Medicine and Biosystemic Science,
Kyushu University Graduate School of Medical Sciences
3-1-1 Maidashi, Higashi-ku, Fukuoka city, Fukuoka 812-8582, JAPAN
Phone: (+81) 92-642-5230
Fax: (+81) 92-642-5247
E-mail: kshimoda@intmed1.med.kyushu-u.ac.jp

Date of Birth: 1963. 3.13

Professional Experience

1998-present	Associate Professor, The First Department of Internal Medicine, Kyushu University Hospital, Japan
1997-1998	Medical Staff in Internal Medicine, Karatsu Red Cross Hospital, Japan
1994-1996	Research Fellow, Biochemistry, St. Jude Children' s Research Hospital, USA
1994-1997	Fellowship of the Japan Society for the Promotion of Science
1993-1994	Medical Staff in Internal Medicine, Kyushu Kouseinennkinn Hospital, Japan
1990-1993	Senior Resident in The First Department of Internal Medicine, Faculty of Medicine, Kyushu University, Japan
1989-1990	Experimental Training at Kyushu University, Japan
1987-1989	Clinical Training at Kyushu University and Karatsu Red Cross Hospital, Japan

Education

1994	Ph.D., Kyushu University
1981-1987	M.D., Kyushu University

Recent Publications

1. Kawano N, Shimoda K, Ishikawa F, Taketomi A, Yoshizumi T, Shimoda S, Yoshida S, Uozumi K, Suzuki S, Maehara Y and Harada M: ATL development from an HTLV-I carrier after a living-donor liver transplantation. Transplantation (in press)
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Primary Myelofibrosis - the Molecular Basis and the Therapy

Kazuya Shimoda, Kotarou Shide, Haruko Kakumitsu, Kenjirou Kamezaki, Fumihiko Ishikawa, Tetsuya Tanimoto, Noriyuki Saitou, Akihiko Numata, Katsuto Takenaka, Takashi Okamura, Yoshiyuki Niho, and Mine Harada
Medicine and Biosystemic Sciences, Kyushu University Graduate School of Medical Sciences, Japan

Primary myelofibrosis is a clonal stem cell disease which is characterized by fibrosis, osteosclerosis, and angiogenesis of bone marrow stromal cells. When CD34 positive cells from a patient with primary myelofibrosis were transplanted into immunocompromised mice, we found that the mice developed myelofibrosis. Five reports recently demonstrated that 55 of 127 myelofibrosis patients (43%) had a mutation of Jak2 in progenitor cells. On the other hand, the proliferative fibroblasts are polyclonal, and the extensive reticulin and collagen fibrosis in the bone marrow is a reactive event. TPO Tg mice developed myelofibrosis and osteosclerosis as they aged and showed extramedullary hematopoiesis in the spleen. Plasma levels of TGF-?1 and osterprotegerin (OPG), that were directly shown to induce bone marrow fibrosis and osteosclerosis, were higher in TPO Tg mice than in wild-type mice. These results suggest that Jak2 mutations in hematopoietic stem cells constitutively activate Jak2, which transduces pro-proliferation signals. Consequently, the number of megakaryocytes increases, and there is excess production of cytokines such as TGF- β 1 and OPG, which affect bone marrow stromal cells and induce myelofibrosis and osteosclerosis.

According to a prospective survey by the Research Committee for Idiopathic Hematopoietic Disorders, Ministry of Health, Labor, and Welfare, Japan (Principle Investigators: Drs. Mizoguchi, Omine, and Ozawa), the annual incidence of primary myelofibrosis in Japan is 50~60 cases, and the 10-year survival rate was 51.1%. In this cohort, four variables were independently associated with shorter survival: Male sex, Hemoglobin < 10 g/dL, the presence of constitutional symptoms (fever, sweats, and weight loss), and circulating blasts > 1%. A median survival was 292 months in the low-risk group with zero or one adverse prognostic factors, and 66 months in the high-risk group with two or more adverse prognostic factors.

Anabolic steroids are effective for the treatment of anemia in 44 % of primary myelofibrosis patients in Japan. They demonstrated an increase in Hb levels (≥1.5 g/dL) and cessation of transfusion dependence for at least 8 weeks. Allogeneic hematopoietic stem cell transplantation is a possible curative treatment. Engraftment failure was 6%. Some cases showed disappearance of the bone marrow fibrosis following transplantation. However, transplant-related morbidity and mortality were still high, resulting in a 3-year survival of 63% in Japan.

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CURRICULUM VITAE

Seishi Ogawa, M.D., Ph.D.
Associate Professor
Department of Regeneration Medicine for Hematopoiesis, University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655, JAPAN
Phone: (+81) 3-3815-5411
Fax: (+81) 3-5804-6261
E-mail: sogawa-tky@umin.ac.jp

Date of Birth: 1962. 8.12

Professional Experience

2002-present Associate Professor, Department of Regeneration Medicine for Hematopoiesis, Graduate School of Medicine, University of Tokyo, Japan
1996-2002 Assistant Professor, Division of Hematology and Oncology, Graduate School of Medicine, University of Tokyo, Japan
1995-1996 Research Fellow, Japan Society of the Promotion of Science, JAPAN
1993-1995 Clinical Fellow, Third Department of Internal Medicine, University of Tokyo
1988-1989 Resident in Internal Medicine, University of Tokyo Hospital, Japan

Education

1989-1993 Ph.D., University of Tokyo
1985-1988 M.D., University of Tokyo

Recent Publications

1. Hosoya N, Sanada M, Nannya Y, Nakazaki K, Wang L, Hangaishi A, Kurokawa M, Chiba S, Ogawa S. Genomewide screening of DNA copy number changes in chronic myelogenous leukemia with the use of high-resolution array-based comparative genomic hybridization. Genes Chromosomes Cancer. 45, 482-494, 2006.
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Genome-wide Analysis of Copy Number Alterations and Allelic Imbalances in Myelodysplastic Syndromes

Seishi Ogawa, Department of Regeneration Medicine for Hematopoiesis, Graduate School of Medicine, University of Tokyo Japan

Myelodysplastic syndromes (MDS) are intractable disorders caused by neoplastic expansion of hematopoietic progenitors and characterized by ineffective hematopoiesis and propensity to acute myeloid leukemia. A number of chromosomal changes and gene mutations have been implicated in the pathogenesis of MDS but the genetic basis of these syndromes is still to be fully understood. In the current study, we explored genetic abnormalities in MDS genomes using high-density SNP arrays (Affymetrix GeneChip 100K/500K) originally developed for large-scale genotyping. Densely distributed oligonucleotide probes and the robust algorithms to process array signals (CNAG) enabled high resolution copy number analysis of MDS genomes. Moreover, with the use of SNP-specific probes, we were able to accurately detect allele-specific copy number changes, which allowed for sensitive detection of loss of heterozygosity (LOH). The copy number profile of more than 150 MDS cases showed not only typical chromosomal gains and losses previously described in MDS but also disclosed numerous abnormalities involving small chromosomal segments. Breakpoints of unbalanced abnormalities and common overlapping deletions were finely defined due to the high resolution of the analyses. As expected, corresponding to the copy number losses, LOH was inferred from the disappearance of heterozygous SNP calls, but more intriguing is the presence of copy number neutral LOH, or uniparental disomy (UPD) at high frequencies, where allele-specific copy number measurements unmasked the existence of allelic imbalances otherwise undetected due to contamination of normal cell components. In fact UPD represents one of the common features in MDS genomes and was found in 45 of 154 MDS. It recurrently involves 11q, 1p, 7q, 17p, 4q, and other chromosomes, suggesting the presence of the relevant mutations to MDS pathogenesis. Another potential interest is that disappearance of heterozygous SNP calls is constitutive in ~20% of MDS cases, implicating a possible involvement of some genetic background in their pathogenesis.

In conclusion, SNP arrays are powerful tools to dissect complex MDS genomes and successfully revealed novel genetic changes in MDS genomes, which may help to discover genetic signatures to predict clinical outcome as well as new therapeutic targets.

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CURRICULUM VITAE

Alan F. List, M.D.
Professor of Oncology and Medicine,
H. Lee Moffitt Cancer Center and Research Institute
12902 Magnolia Drive SRB 4, Tampa, FL 33612
Phone: 813-745-6086 FAX: 813-745-3727
E-mail: listaf@moffitt.usf.edu

Date of Birth: October 13, 1954

Professional Experience

1986-1988	Chief, Section of Oncology/Hematology, VAMC, Phoenix, Arizona
1988-1991	Staff Physician, Section of Hematology/Oncology, Tucson VAMC, Tucson, Arizona
1989-1991	Acting Director of Clinical Hematology, Arizona Cancer Center and College of Medicine
1988-1994	Assistant Professor of Medicine, Section of Hematology/Oncology, Department of Medicine, College of Medicine, University of Arizona, Tucson, Arizona
1992-1993	Assistant Research Scientist, Arizona Cancer Center, Tucson, Arizona
1993-1996	Clinical Director, BMT Program, University of Arizona Cancer Center, Tucson, Arizona
1994 -2002	Associate Professor of Medicine, Section of Hematology/Oncology, Department of Medicine, College of Medicine, University of Arizona, Tucson, Arizona
1996- 2003	Director, BMT Program, University of Arizona Cancer Center, Tucson, Arizona
2002- 2003	Director, Division of Translational/Clinical Research, Arizona Cancer Center, Tucson, Arizona
2002- 2003	Professor of Medicine, Section of Hematology/Oncology, Department of Medicine, College of Medicine, University of Arizona, Tucson, AZ
2003 -	Professor of Oncology and Medicine, Chief, Malignant Hematology Division, Department of Interdisciplinary Oncology, H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida, Tampa, FL
2005-	Associate Director, Moffitt Cancer Center Infusion Center

Education

1972-1976	Bucknell University, Lewisburg, Pennsylvania (B.S., M.S.)
1976-1980	College of Medicine, University of Pennsylvania (M.D.)
1983-1985	Oncology Fellowship, Vanderbilt University Medical Center, Nashville, Tennessee
1985-1986	Hematology Fellowship, Vanderbilt University Medical Center, Nashville, Tennessee

Recent Publications

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Non-Cytokine Therapeutics for Myelodysplastic Syndromes

Alan List, Gordon Dewald, John Bennett, Kenton Wride, John Patin, Michele Schmidt, Jerome Zeldis, and Robert Knight.
University of South Florida College of Medicine and the H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; and Celgene Corporation, Warren, NJ.

The development of non-cytokine therapeutics with specificity for critical targets implicated in the ineffective hematopoiesis phenotype represents the primary goal for lower-risk MDS. Mechanistically, such agents can be broadly categorized as either anti-angiogenic or survival signal modifiers. Investigations of anti-angiogenic agents in MDS have shown that the predominant responsive lineage is erythroid. Thalidomide and its analogue, lenalidomide, are the most active members of the immunomodulatory drug (IMiD) class. Lenalidomide is a 4-amino glutarimide derivative that lacks the neurologic toxicity and teratogenicity of thalidomide, and is a more potent modulator of ligand-induced responses<<Bartlett et al, 2004, p 318>>. The activity of lenalidomide in MDS was first studied in an open-label, single-center phase I/II efficacy and safety trial. In which all participants had either failed prior treatment with EPO or had low probability of benefit. Twenty?four of 36 evaluable patients (67%) experienced an erythroid response according to the International Working Group criteria, with 21 patients achieving sustained transfusion independence. Response rate was karyotype-dependent with the highest response in patients with a chromosome 5q31.1 deletion (91%), a subset that also had a high frequency of cytogenetic response. A 148 patient multicenter trial (MDS-003) confirmed the activity of lenalidomide in transfusion-dependent patients with Low or Int-1 risk MDS with a chromosome 5q31 deletion. In an intent-to-treat analysis after 24 weeks of treatment, 112 patients (76%) experienced an erythroid response, with 99 patients (67%) achieving transfusion independence while reaching a median hemoglobin of 13.5 mg/dL. Responses are durable, with the median duration of transfusion-independence not reached after a median follow-up of 104 weeks. Cytogenetic responses were observed in 74% of patients, with complete cytogenetic response in 45% and high frequency of resolution of dysplasia resolved (36%). Neutropenia and thrombocytopenia were the most common adverse effects necessitating dose adjustment. Lenalidomide was approved by the U. S. Food and Drug Administration (FDA) December 27, 2005 for the treatment of transfusion-dependent patients with deletion 5q.

Survival Signal Modifiers. The modulation of survival signals by selective inhibition of non-receptor signal intermediates is a strategy that has been exploited initially in higher-risk patients with MDS in an effort to alter the natural history of disease. Two classes of survival signal modifiers are under investigation, i.e., those agents that target hematopoietic inhibitory signals such as p38 α mitogen-activated protein kinase (MAPK), and glutathione S-transferase (GST) P1-1, and those that disrupt anti-apoptotic signals such as the Ras farnesyl transferase inhibitors. TLK199 (Telintra™, Telik) is a liposomal glutathione derivative that promotes granulopoiesis in vitro and in animal models. The compound selectively inhibits GST P1-1, an enzyme that attenuates Jun kinase and MAPK signaling. In a phase II study, 54 patients received TLK199 600 mg/m2 for 3 or 5 days every 3 weeks with multilineage <<Faderl et al, 2003, abstract #1548; Callender et al, 2004, abstract #1428>>hematologic improvement reported in more than 60% of evaluable patients. No dose-limiting toxicities were observed with the liposomal formulation, however, an orally bioavailable analog of TLK199 that offers more convenient dosing has now entered clinical studies.

Preclinical investigations of role of p38 α MAPK, a pivotal effector of external inhibitory stimuli initiated by death receptors or inflammatory cytokines, have shown that the enzyme is activated in MDS precursors and that pharmacologic inhibition enhances survival of marrow progenitor and erythroid fractions<<Mohindru et al, 2004, abstract #470>>. SCIO-469, a selective oral inhibitor of p38 α MAPK, recently completed phase I/II clinical investigations in patients with lower risk MDS. Characterization of cellular targets integral to the disease process is yielding promising new selective therapeutics for MDS. Given the biologic complexity of MDS, such agents should complement existing therapies and permit tailoring of treatment to the biology of disease.

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Ⅱ. 分担研究報告書

厚生労働省科学研究費補助金（難治性疾患克服研究事業）

分担研究報告書

再生不良性貧血、骨髄異形成症候群の前方視的症例登録・セントラルレビュー・追跡調査に関する研究

分担研究者　内山　卓（京都大学大学院医学研究科血液・腫瘍内科学、教授）

研究協力者　松田晃（埼玉医科大学内科学部門血液内科、助教授）
通山薫（川崎医科大学検査診断学、教授）
三谷絹子（獨協医科大学内科学血液）

研究要旨

再生不良性貧血と骨髄異形成症候群に関する疫学統計の作成、両者の鑑別のための形態学的異形成所見のコンセンサス作成、本邦における両疾患の治療成績、臨床像の把握を目的として、再生不良性貧血、骨髄異形成症候群の前方視的症例登録、セントラルレビュー、追跡調査研究が本年度より開始された。研究代表者所属施設と登録ならびにセントラルレビューの事務局がおかれた施設の計 3 施設において、おのおのの倫理審査委員会の承認を得た後、平成 18 年 9 月から 19 年 1 月にかけて、他施設に先行して 11 例の症例登録と 9 例のセントラルレビューを行った。その結果、本研究施行における問題点は指摘されず、今後の参加施設の拡大、参加症例の増加に十分対応可能と判断した。本研究、ならびに本研究とリンクした骨髄異形成症候群に対する画期的治療法に関する研究班による「検体集積事業ならびに遺伝子解析研究」を通じて、再生不良性貧血、骨髄異形成症候群の実態解明がすすみ、両者の境界例の取り扱いが明らかにされ、さらには新規治療法の開発の端緒となることが期待される。

1. 研究目的

本邦における再生不良性貧血(AA)と骨髄異形成症候群(MDS)の前方視的登録により疫学統計を作成すること、セントラルレビューを通じて国際的な形態学的異形成に関するコンセンサスを普及し、従来困難かつ施設間で差の見られた AA と MDS の境界を明らかにすること、ならびに、臨床経過、治療内容、治療反応性を追跡調査することで、これらの疾患の本邦における全体像を把握することを目的とした。また、形態学的異形成基準による AA と MDS の鑑別の妥当性を追跡調査によって確認することも目的の一つである。

2. 研究方法

本研究班参加施設において新規診断された AA と FAB 分類での MDS、ならびにその境界例を前方視的に登録センター（京都大学医学部血液・腫瘍内科）に症例登録する。また、その中で骨髄芽球比率が 5%以下のものに関しては、骨髄塗抹標本（メイギムザ染色、鉄染色）、骨髄生検 HE 標本、