

Aplastic Anemia & MDS International Foundation

INSIDER

your resource for
answers
support &
hope.Leading Experts on Future Directions in
BMFD Research

AA&MDSIF asked members of its Medical Advisory Board to share insight based on their expertise by answering several questions about the current status and future promises of bone marrow failure disease research. They are among the best clinicians and researchers in the world on aplastic anemia, MDS and PNH.



Richard Stone, MD
Dana Farber Cancer Center



Mikkael A. Sekeres, MD, MS
Cleveland Clinic Lerner College of
Medicine



H. Joachim Deeg, MD
Fred Hutchinson Cancer Research
Center



Aristotles Giagounidis, MD, PhD
St. Johannes Hospital



Ronald Paquette, MD
UCLA Medical Center



David Steensma, MD
Dana Farber Cancer Center

Q: Given the similar pathophysiologies[Ⓞ] linking aplastic anemia, MDS and PNH, is it important for the research community to study bone marrow failure diseases in general in order to draw connections between them? Please explain why or why not.

A: **Stone:** It is absolutely essential to study bone marrow failure in general in order to gain insight into the molecular mechanisms and thus to develop better therapies for these conditions. In each case, there is evidence that the hematopoietic[Ⓞ] stem cell is disordered. As such, pinpointing how the stem cell thrives or fails will be vital.

Key [Ⓞ] — See glossary on page 14

Deeg: I am not sure the pathophysiologies are that similar—there are major differences (if we have a ‘clean’ diagnosis). I agree, however, that there are overlaps, and studies on the mechanisms in those patients should be of interest, possibly across the board, by revealing ‘transitions’ between the diagnoses.

Sekeres: You make a good point, but I think it would be difficult to solicit grants for a general bone marrow failure project...the biology underlying each of these is sufficiently distinct to make this a difficult challenge.

Paquette: I would argue that the most recent treatment advances in these diseases exploit aspects of each disease that are unique to each. Future advances will likely

target pathogenetic mechanisms not just unique to each disease, but to subpopulations of each disease. This is particularly true for MDS, which is really a heterogeneous group of disorders that share some clinical features.

Giagounidis: Pathophysiology research is always basic research. Many insights that might arise from studying one disease may apply to another one that is more or less closely related. One example is the RPS14 gene in MDS 5q- and ribosomal gene[Ⓞ] in Diamond-Blackfan anemia. Basic research must remain one cornerstone of research funding as this will provide the fundamentals for understanding the disease and identifying target structures for treatment.

▶ Continued on page 12

Executive Director's message

Where Does Hope Come From?

At the Aplastic Anemia & MDS International Foundation (AA&MDSIF), our focus and commitment is to provide *Answers, Support & Hope* to patients, families and caregivers. While each of our programs and services touches all three, research is probably the program that most inspires *Hope*.

Were it not for the advances in treatment and care directly resulting from some of the research over the past two decades described in this newsletter, many bone marrow failure disease patients might not be alive today. It is because of the incredible efforts of those who have dedicated their lives to discovery that we now have better means to test, diagnose and treat patients with bone marrow failure diseases—treatments unheard of only a few years ago, let alone when AA&MDSIF was founded in 1983.

The researcher's task is not an easy one. Research is far more often about failure than success. It is the resilience of the researcher's will that leads to discovery, which translates to care that nurtures the Hope we all hold that we will someday discover the cure for all bone marrow failure diseases.

However, research is far too important to be left only to scientists. All of us have a role to play as...

- ▶ Patients willing to participate in clinical trials (see p. 15).
- ▶ Advocates influencing government funding priorities (see p. 10).
- ▶ Donors providing financial support for research funded by the AA&MDSIF (see p. 6).

It will only be through the partnership and collaboration of researchers, patients, donors and advocates that we will be able to transform Hope into the reality that saves lives.



John M. Huber
Executive Director

Bone Marrow Failure Disease Scientific Symposium:



Aplastic Anemia & MDS International Foundation

Hope Through Research March 11-12, 2010 • Washington, DC

This symposium will bring together physicians treating these diseases and laboratory researchers studying the immunology and cell biology of bone marrow failure to discuss current areas of controversy, share recent research results, and propose specific recommendations for the highest priority directions for basic and clinical research needed to advance the field.

Sponsored by Aplastic Anemia & MDS International Foundation, NHLBI and NIH Office of Rare Diseases



To learn more, contact Alice Houk at houk@aamds.org or 301-279-7202 x101.



www.AAMDS.org

About Us Fighting Bone Marrow Failure Diseases Through Patient Support and Research Since 1983

CONTACT INFO



Aplastic Anemia & MDS International Foundation

100 Park Avenue, Suite 108
Rockville, MD 20850
Phone: 301-279-7202
Fax: 301-279-7205
Toll-Free: 1-800-747-2820
Email: help@aamds.org
Web site: www.AAMDS.org

MISSION

The Aplastic Anemia & MDS International Foundation (AA&MDSIF) is an independent nonprofit organization whose mission is to support patients, families, and caregivers coping with aplastic anemia, myelodysplastic syndromes (MDS), paroxysmal nocturnal hemoglobinuria (PNH), and related bone marrow failure diseases (BMFD).

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20 Years, \$2M+ & 43 Researchers: Catalyst for Scientific Careers Saving Lives

Research has always been an important part of AA&MDSIF's mission. Emerging from its strength as the leading independent nonprofit organization for patients with bone marrow failure diseases, AA&MDSIF funds research and advocates for increased public and private funding. Started as a patient- and family-centered organization in 1983 as the Aplastic Anemia Foundation of America, its founders recognized that supporting patients and families from diagnosis through treatment was matched in importance by providing hope that comes from the new medical and scientific discoveries which research produced. This same dual purpose exists today, clearly stated in AA&MDSIF's mission: "Fighting bone marrow failure diseases through patient support and research since 1983."

In 1983, aplastic anemia patients were given very little chance for survival from the disease. Today, the current success rate of treating aplastic anemia patients is reported in ranges from 75% - 95%¹. For MDS patients, a recent study showed a range of 26.2% to 50.8% as a success rate for treatment over a two-year period². Aplastic anemia and MDS weren't treated as separate diseases until about 30 years ago, even though they are related to each other in their manifestations of stem cell failure in the bone marrow. A closely related bone marrow disease is paroxysmal nocturnal hemoglobinuria (PNH) that until recently had very few treatment options and was difficult to diagnose. When AA&MDSIF was founded, the survival rate was quite low for these diseases and understanding of the causes, development and treatment was limited. There have been tremendous strides in these areas, especially for aplastic anemia. There is still, however, much progress to be made for MDS.

Since then, AA&MDSIF has awarded approximately \$2.2 million in grants to researchers exploring causes and seeking treatments for aplastic anemia, MDS, PNH and similar bone marrow failure diseases. These funds have provided a much needed infusion of capital into bone marrow failure disease research. Often, funds from AA&MDSIF are touted by researchers as the catalyst for their investigating these diseases and to unlocking other sources of research funding. Awarded first in the 1980s as grants of \$30,000, and now as two-year grants totaling \$60,000, these funds encourage research scientists to explore or continue a career dedicated to the study of bone marrow failure diseases.

AA&MDSIF has funded 43 research projects since the late 1980s, covering critical topics for the understanding and treatment of these dangerous diseases and contributing to many key advances in the body of knowledge. AA&MDSIF-sponsored research has resulted in:

- ▶ Findings that contribute to new, effective treatments
- ▶ Deeper understanding of the causes and treatment of bone marrow failure diseases
- ▶ Doctors pursuing a career in bone marrow research and treatment, becoming leaders in the field as both researchers and clinicians
- ▶ Hope for patients and families that progress is being made towards finding a cure

Research scientists who received AA&MDSIF grants have been affiliated or have collaborated with the nation's premier research institutions including Cleveland Clinic, Memorial Sloan Kettering Institute, Fred Hutchinson Cancer Center, UCLA, Dana-Farber Cancer Center, Moffit Cancer Center, MD Anderson, Yale University and many others. Their research has been published in leading scientific journals, and today they are among the leaders in the field who are helping patients live longer and better as they bravely fight these life-threatening diseases.

Behind every research grant are the stories of patients whose bravery in battling their disease inspired them, their loved ones or community to contribute to AA&MDSIF. These grants have been made possible thanks to the generosity of AA&MDSIF patients, families and friends who have established named research funds of \$30,000 - \$60,000 each. Whether their named fund came through personal contributions or proceeds from fundraising events, or whether they were contributed in one year or over several years, each named fund provided a touchstone for the researchers who received them. One researcher recently shared that he kept a photo in his lab of the young woman whose family established the research fund he received; he made sure each of his assistants knew that there was a real patient and a caring family behind their grant.

Awarding New and Established Investigators in Five Basic Categories of Research

AA&MDSIF awards have been given to both new and established investigators, recognizing the importance of supporting the work of those who are already making strides in the field while encouraging a new generation of researchers. As **Dr. David Araten**, a 1996 grant recipient who is now Assistant Professor, Division of Hematology, New York University School of Medicine, says, "The [AA&MDSIF] award I received early in my training was very valuable and had quite positive effects on my career."



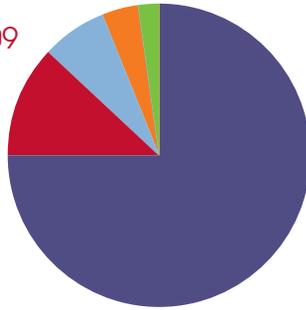
Dr. Araten's work has demonstrated mutant cell populations that expand in patients with aplastic anemia and PNH. This research has served as a cornerstone for his studies on abnormal chromosomes in the marrow and subsequent long term outcome of patients with aplastic anemia. Dr. Araten goes on to say, "These studies inform our understanding of relationships between these 3 disorders [aplastic anemia, myelodysplastic syndrome and paroxysmal nocturnal hemoglobinuria (PNH)]. It is gratifying to answer my patients that this work is supported by AA&MDSIF."

Research supported through AA&MDSIF falls into five main categories according to Medical Advisory Board chair, Dr. Richard Stone of the Dana Farber Cancer Center, and co-chair, Dr. Mikkael Sekeres of The Cleveland Clinic Lerner College of Medicine.

▶ Continued on page 4

AA&MDSIF Sponsored Research by Type: 1989-2009

- 75% Basic Pathophysiology
- 12% Basic Biology
- 7% Drug Treatment/Transplants/Clinical Trials
- 4% Iron Overload
- 2% Epidemiology



Basic Pathophysiology is the Change in Bodily Function as a Result of Disease.

This represents 75% of AA&MDSIF-sponsored research through 2009, the bulk of which has concentrated on understanding the causes of aplastic anemia and MDS and their connections to genetics and chromosomal abnormalities. Key areas of AA&MDSIF-sponsored research in this field include Telomerase, the EV-1 gene, Notch-1 mutations, and GATA-1 gene mutations.



Telomerase: Research on this specialized enzyme has been crucial to understanding how it can be used to maintain chromosomal length and chromosomal integrity. Mutations found in MDS patients may help explain a shortening effect of chromosome ends (known as telomeres) in cells and the exact mechanism by which mutations lead to it. An accelerated shortening of telomeres plays a central role in the pathogenesis of aplastic anemia & MDS. 2004 AA&MDSIF grant recipient, **Dr. Monica Bessler, Professor**, Department of Medicine, Hematology Division, Washington University in St. Louis, feels that results of her study on “Genes, Chromosomes and Bone Marrow Failure” initiated a new area of research in the field of bone marrow failure, promising to have a major impact on how we diagnose, treat, and prevent bone marrow failure in future.

Identification of EV-1: A new pathway to therapy for MDS opened when it was found that overexpression of the gene EV-1 causes disruption in normal bone marrow cellular development. When overexpression of EV-1 can be suppressed, cells become more normal. 2003 grant recipient, **Dr. Archibald Simon Perkins** of Yale University used his award to study “The Role of MDS/EV1 Locus in MDS.”



Notch-1 Mutations are Treatable: Mutations in the Notch1 gene can lead to bone marrow disorder, MDS and on to leukemia. Research has made the important discovery that this mutated gene can be treated with drugs often prescribed to Alzheimer’s patients. **Dr. Lisa Minter** of the University of Massachusetts-Amherst, researched treatment of this mutated gene, thanks to a 2006 grant.



Identifying GATA-1 Gene Mutations: GATA-1 is an important regulator of red and white blood cell development when it functions normally. When GATA-1 and interacting proteins are disrupted in pathological setting, it often manifests itself as abnormal proliferation of red cell precursors that abort in the bone marrow, resulting in anemia and can lead to leukemia. Research helped determine that these mutations were the result of stem cell defects due to chromosomal abnormalities. Research by **Dr. Marianne Greene**, a 2001 grant recipient at the University of Chicago, found that GATA-1 mutations were acquired, not congenital.

Drug Treatment/Clinical Research/Transplants

Another AA&MDSIF-funded research has involved drug treatment; this represents 7% of grants given thus far. The research has included identifying substances that have positive effects on reversing malfunctioning bone marrow cells and exploring tolerance of other treatments such as transplants. Results from this research have been invaluable to continued understanding and treatment of aplastic anemia, MDS and PNH.

Bone marrow transplants replacing defective blood cells in the patient with healthy cells from a matching donor can be quite a successful treatment for some patients. Though it may be the best known treatment, particularly for young aplastic anemia patients, it is by no means without risk and complications. Also, the largest group of patients, those facing MDS in their later years, are generally not candidates at this time. Sponsored research has enabled identification of causes of tissue rejection and has illuminated ways to reduce complications with bone marrow transplants. **Dr. Richard Carter**, recipient of a 1998 AA&MDSIF grant when he was with the Emory University School of Medicine, explored this with his work on “Irradiated Donor Lymphocyte Transfusion, a Novel Approach to Prevent Graft Failure During Allogeneic Bone Marrow Transplantation.”

Basic Biology

Reactions of the immune system are vital to understanding therapies for bone marrow disorders. Research into this area has accounted for 12% of AA&MDSIF research thus far. When immune cells (T-cell receptors) malfunction, they can clone themselves and attack healthy cells. This sequence can lead to rejection of bone marrow transplant tissue and the development of leukemia for those with MDS. A key area of research has been studying how suppressing an over-active immune system can slow or stop the destruction of blood cell production at the stem cell level.

Research found that T-cells (immune lymphocytes) in aplastic anemia patients often target proteins found in marrow stem cells. This phenomenon doesn’t exist in healthy patients. Researchers are not sure what causes T-cells to attack the proteins, but they want to study it further. **Dr. Jaroslaw Maciejewski** of the Cleveland Clinic Taussig Cancer Center, who has been awarded several AA&MDSIF research grants, has conducted extensive research in this area (T-cell receptors) and has published findings in Experimental Hematology (March, 2004).



Dr. Ronald Paquette of UCLA Medical Center, a 1994 grant recipient, has studied the effects and benefits of the growth factor Interleukin-1 on the over-active immune system by regulating rejection.

Epidemiology

Epidemiology is the study of the causes, distribution and control of disease in a population; it represents 21% of AA&MDSIF-funded research projects. Known causes or risks for developing bone marrow failure diseases include exposure to Benzene, radiation and chemotherapy agents. Some inherited bone marrow failure diseases, such as Fanconi's anemia, may develop into aplastic anemia or MDS, and may also have a propensity to transform to leukemia.

AA&MDSIF-sponsored research enabled advances in understanding the connection between bone marrow disorders and factors that regulate cell differentiation as well as molecular mechanisms that induce proliferation of hematopoietic stem cells.



Dr. Surapol Issaragrisil, a 1994 grantee who is now Professor of Medicine at Meadhol University in Bangkok, studied the relationship of pesticides to development of aplastic anemia in Thailand. He concluded that the relationship between developing aplastic anemia and grain farming with agricultural pesticide exposure may partly explain the high incidence of aplastic anemia in Thailand. There does not however appear to be correlation between household pesticide use and aplastic anemia.

Beyond the research grants, AA&MDSIF played a key role in orchestrating a national registry of 150,000 umbilical cord blood units with stem cells that can treat bone marrow diseases.

Iron Overload

Without therapy, lethal amounts of iron can accumulate in patients undergoing bone marrow transplants. This is also a concern for aplastic anemia and PNH patients. The body cannot eliminate the excess iron that is produced so instead, it deposits it in the liver, heart, pancreas and other organs. Death is often the result of cardiac failure. As a treatment, iron chelating for overload is effective, but very unpleasant and takes 8-12 hours. Approximately 4% of AA&MDSIF-funded research addressed this.



Dr. Sujit S. Sheth, a 1999 grant recipient who is an Associate Clinical Professor of Pediatrics at Columbia University Medical Center, studied the study of treatment of iron overload. He looked at a solution called Hbed, which proved to be a major advance.

Influencing Careers that Save Lives

Dr. Richard Stone states that, "These grants to promising research scientists have aided them to further their careers and instill an early interest in research for the field. The work itself as a whole has certainly made contributions in the field and helped serve as a catalyst to advance in their careers."

There have been several research scientists who have won multi-year grants and have made the study of these life-threatening diseases their life's work. Perhaps Dr. Michael Boosalis, 2001 grant recipient who is a Research Associate at the Boston University Medical Center, summed it up best when he said, "I am quite grateful to AA&MDSIF for the research funding so I can pursue this line of discovery and lead myself and others closer to a cure."

AA&MDSIF plays a vital role as a key advocate for patients and their families impacted by this research, offering answers, support and hope. Its role in supporting research in the field has been effective in offering reliable information to patients, identifying expert doctors and research scientists in the field, and championing the search for advances in the treatment and cures for bone marrow failure diseases by public and private institutions.

AA&MDSIF also plays a pivotal role in supporting research to advance knowledge and treatment of Aplastic Anemia, MDS and PNH. Its leadership is highly regarded both through the dollars it raises directly, and those it helps secure through the Department of Defense and other government agencies. Increasingly, AA&MDSIF's role bringing researchers together as collaborators across research institutions and fields of interest will contribute new knowledge for the ultimate benefit of patients. The advances and contributions made by the dedicated scientists who have received AA&MDSIF funding cannot be underestimated. Research in this field is all the richer for AA&MDSIF' vision and the inspired efforts of the scientists.

Endnotes

¹ Medline Plus, Aplastic Anemia, updated 10/30/2006, William Matsui, MD, Assistant Professor of Oncology, Division of Hematologic Malignancies, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD. Review provided by VeriMed Healthcare Network.

² "Relationships between aplastic anemia and MDS," by Dr. Lyle L. Sensenbrenner, AA&MDSIF newsletter, Fall 1998.

2010 Grant Opportunities

Each year, the AA&MDSIF invites researchers to apply for two-year grants of \$30,000 per year to test new ideas and to explore other research leads. The applications are ranked according to merit by a distinguished panel of research scientists and funded by the generosity of families and patients. Established investigators and new investigators in bone marrow failure diseases (aplastic anemia, MDS & PNH) can apply for the awards. Second-year funding is contingent upon progress in the first year. All applications are due on 2/26/10. Payments are awarded to researchers on 7/1/10.

If you are a researcher, news on guidelines and applications is available at www.AAMDS.org/Grants. For specific questions, please contact Alice Houk, Director of Professional Programs, at (301) 279-7202 x101 or email houk@aamds.org.

AA&MDSIF Research Grants 1989 - 2009

1989 • Dr. Winald Gerritsen Memorial Sloan-Kettering Inst. for Cancer Research **1990 • Dr. Hildegard Greinix** Fred Hutchinson Cancer Research Center: *Late Failure of Autologous Marrow Grafts in Lethally Irradiated Dogs Given Anti-Class II Monoclonal Antibody* **1990 • Dr. Stephen R. Paul** Dana-Farber Cancer Institute: *Role of FAC in a Genetic Model of AA* **1991 • Dr. Jeffrey P. Novack** Fred Hutchinson Cancer Research Center: *Signal Transduction of the Ckit Tyrosine Kinase Receptor* **1992 • Dr. Leslie G. Biesecker** University of Michigan Medical Center: *Embryonic Protein Kinase Receptor Cloning* **1994 • Dr. Ronald L. Paquette** UCLA School of Medicine: *Mutations of Interleukin-1 and Stem Cell Factor Receptor Genes in AA; Absence of ckit Point Mutations in Acquired AA: I.D. of New Polymorphisms in Exons 10 and 18* **1994 • Dr. Surapol Issaragrisil** Mahidol University, Thailand **1995 • Dr. Hagop Youssoufian** Bingham and Women's Hospital and Harvard Medical School: *Role of FAC (fanconi anemia) in a Genetic Model of AA* **1995 • Dr. Chaker Nadim Adra** (Mary Elizabeth Clancy*) Beth Israel Hospital: *Molecular and Cellular Biology of a Novel Hematopoietic-Specific Multispanning Protein* **1996 • Dr. David Araten** (Vemille Family*) Memorial Sloan-Kettering Inst. for Cancer Research: *PNH Cells and PID-A Gene Mutations in Normal Donors, Chromosomal abnormalities in PNH* **1998 • Dr. Richard Carter** Emory University: *Irradiated Donor Lymphocyte Transfusion, a Novel Approach to Prevent Graft Failure During Allogeneic Bone Marrow Transplantation* **1998 • Dr. Tatiana Zorina** (Alexandra Jane Greenberg & Tyler David Fica*) Philadelphia & Children's Hospital of Pittsburgh: *Treatment of AA w/Bone Marrow Chimerism Achieved by Facilitating Cell-Mediated Allogeneic Allegheny University Health Sciences, Stem Cell Engraftment* **1999 • Dr. Sherilyn Gross** (Mark Jeska Family*) Ex Vivo Expansion of Bone Marrow Cells from AA Patients **1999 • Dr. Sujit S. Sheth** (**Betsy Lakie*) Columbia University: *Hbed Chelation Therapy for Iron Overload in AA & MDS* **2000 • Jen Chin Wang** (Harold Spielberg*) Maimonides Medical Center, Bookdale University Hospital: *Studies on CMPL Defects fo the Elevated TPO and Fibrosis in MDS* **2001 • Dr. Marianne Greene** (Torry Yahn*) University of Chicago: *Knockout of the GATTA-1-FOG-1 Interaction: Implications for MDS* **2002 • Michael Boosalis** (Donny Schmidt*) Boston University School Medicine: *Molecular Mechanisms of Cell Proliferation Induced by Short Chain Fatty Acid Derivatives* **2003 • Dr. Archibald Perkins** (Harold Spielberg*) Yale University School of Medicine: *Role of the MDS/Evi 1 Locus in MDS* **2003 • Dr. Jaroslaw Maciejewski** (David Homza*) Cleveland Clinic Taussig Cancer Center: *Immune Pathophysiology of MDS-Lessons from the Molecular Analysis of T Cell Receptor Repertoire in AA* **2003 • Dr. Jaroslaw Maciejewski** Cleveland Clinic Taussig Cancer Center: *Exploring T-cell Receptor TCR Utilization Pattern and Identify Immunodominant T-cell Clones and Their Sequences* **2003 • Dr. Russell Ware** (Deb Valchik*) Duke University School of Medicine: *Genetic Analysis of Growth Advantage and Thrombosis in PNH* **2004 • Dr. Jaroslaw Maciejewski** (Pursuing New Hope/Papernick Family*) Clinic Taussig Cancer Center: *Differential Inhibition of Normal Stem Cells in PNH* **2004 • Dr. Monica Bessler** (Florentine Caminisch*) Washington University in St. Louis: *Genes, Chromosomes, and Bone Marrow Failure* **2005 • Dr. Catriona H.M.Jamieson** (Virginia Stephenson*) Stanford University School of Medicine: *Progenitor Profiling in MDS* **2005 • Dr. Elena Solomou** NIH, National Heart, Lung & Blood Institute: *Transcriptional Control of Increased Express of IL-2 and IFN γ in T cells from Patients with AA* **2005 • Dr. Eva Guinan** (Mary-Pat Madden Grieshaber Family*) Dana-Farber Cancer Institute: *Strategies to Improve Immune Reconstitution after Allogeneic Transplant: Development of Class II Tetramers for CMV Epitopes* **2005 • Dr. Gabrielle Meyers** (PNH Group Research Study*) Utah Unversity: *Clonal Evolution and Dominance in PNH* **2005 • Dr. Hyo Seop Ahn** Seoul National University College of Medicine (Korea): *Fludarabine Cyclophosphamide plus Thymoglobulin Conditioning Regimen for Unrelated Bone Marrow Transplantation in Severe AA* **2005 • Dr. Jane L. Liesveld** University of Rochester Medical Center: *Proteasome Inhibition in MDS* (Julia Anderson & Gordon Forgash*) **2005 • Dr. Matthew Walter** (Malama Collingsworth*) Washington University in St. Louis: *Genomics of MDS* **2005 • Dr. Seth Joel Corey** University of Texas-MD Anderson Cancer Center: *Signaling Defects in the MDS of Severe Chronic Neutropenia* **2006 • Dr. Hinh Ly** (Holly Cataldo & Jennifer Walsh-Hawes*) Emory University School of Medicine: *Telomere Maintenance in Patients with AA* **2006 • Dr. Lisa Minter** (Marissa Marie Amuso & Jack Byrne*) University of Massachusetts - Amherst: *Gamma-Secretase Inhibitors as Therapeutic Intervention in Bone Marrow Failure Syndromes* **2006 • Dr. Lukasz Gondek** (PNH Foundation/ Sarah Higgins Famly*) Cleveland Clinic Taussig Cancer Center: *A Novel Approach for the Study of Genetic Predisposition in AA and PNH Using High-Density Arrays* **2006 • Dr. Mario Querido Marcondes** Fred Hutchinson Cancer Research Center: *Dysregulation of Interleukin-32 in MDS* **2006 • Dr. Christine O'Keefe** (Lindsay Minelli*) Cleveland Clinic Taussig Cancer Center: *Genome Stability in MDS* **2007 • Dr. Hiromi Gunshin** (Trinity Ewert*) University of Massachusetts - Amherst: *Studies Toward Alternative Therapies for Iron Overload in Patients* **2007 • Dr. Kay Macleod** (Erwin Umbach/MacGillivray Family*) Ben May Inst. Cancer Research Center: *Oxidative Stress in Etiology of MDS* **2007 • Dr. Lubomiro Sokol** (Harold Spielberg*) H.Lee Moffitt Cancer Center: *Studying Microarray Profiling of Micro RNA in 5Q Minus Syndrome* **2008 • Dr. Antonio Maria Risitano** University of Naples (Italy): *Genetic Fingerprint of Complement and Complement-related Genes in PNH: Relationship with Pathophysiology, Clinical Manifestations (including Thrombosis) and Response to Eculizumab* PNH Foundation **2008 • Dr. Benjamin Braun** (Harold Spielberg*) University of California, San Francisco: *Mechanisms and Therapy of Anemia Caused by Activating Kras Mutuation* **2008 • Dr. Jaroslaw Maciejewski** Cleveland Clinic Taussig Cancer Center: *Identification of Mutations in C-Cbl as Pathogenetic Factors in Patients with MDS* **2008 • Dr. Lisa Minter** (Torry Yahn*) University of Massachusetts-Amherst: *Evaluating PKC θ as a Therapeutic Target in a Mouse Model of Severe AA* **2009 • Dr. Archibald Perkins** (Harold Spielberg*) University of Rochester: *Development of Targeted Therapies for 3q26-positive MDS* **2009 • Dr. Kazuhiko Ikeda** (PNH Foundation*) Washington University School of Medicine: *The Mechanism of Clonal Dominance of PNH Cells* **2009 • Dr. Regis Peffault de Latour** (PNH Foundation*) National Heart, Lung and Blood Institute: *The Role of Unfolded Protein Response in PNH*

Key * Supported by a Named Tribute Fund; AA= aplastic anemia; MDS= myelodysplastic syndromes; PNH= paroxysmal nocturnal hemoglobinuria.

How to establish a tribute fund

Research projects are selected for funding through a competitive process each year; selections are made by AA&MDSIF's Medical Advisory Board of the leading experts in bone marrow failure diseases. Funding of \$60,000 is provided to selected researchers for a two-year period. These funds are donated and raised by patients themselves, as well as family members and friends who use their gifts to honor and remember loved ones.

 Your fund can be designated toward research grants or other AA&MDSIF patient education, advocacy, awareness or general projects. **To learn more, contact our Development Director, Sandra Walter-Steinberg at 301-279-7202 x104 or walter@aamds.org.**

Research Studies Awarded 2009 - 2011



The Role of Unfolded Protein Response in PNH

Regis Peffault de Latour, MD, PhD, NIH-National Heart, Lung and Blood Institute (N)

● AA&MDSIF PNH Foundation Research Grant

Dr. Peffault de Latour's study will examine the role of the Unfolded Protein Response (UPR) in the development of PNH cells. Understanding how the UPR allows for cell adaptation instead of cell self-destruction could lead to the discovery of new therapeutic strategies which target this pathway.

Key (N) New Investigator; (E) Established Investigator

Web exclusives

Research Spotlight: Dr. Leslie Biesecker

For the last twenty years, the Aplastic Anemia & MDS International Foundation (AA&MDSIF) has been awarding research grants to new researchers to inspire these scientists to stay in research and encourage them to work on projects relating to bone marrow failure disease. Recently, Mason Dunham, an AA&MDSIF college intern studying chemistry and economics at the University of Maryland, College Park, wrote this story after meeting with one of AA&MDSIF's first research grantees, Dr. Leslie Biesecker. Currently at the National Institutes of Health (NIH), Dr. Biesecker won a new researcher grant from AA&MDSIF in 1992. In the interview, Dr. Biesecker told the story of how the grant came to him at a key point in his development as a physician-scientist, and the lasting effect it had on his career.

"Clinical research is a funny business," said Biesecker looking back on his transition. "It's not purely what you can do and it's not what you should do, it's a curious hybrid of the two...the people who are most successful and solve the most problems and do the most good are the people who optimize that the best." Still, he is extremely grateful for the grant from AA&MDSIF, noting that without the grant it is unlikely he would ever have had the opportunity to work on bone marrow failure research at all.

Today, Dr. Biesecker is a senior investigator at NIH's Genetic Disease Research Branch and head of the Human Development section, positions earned after a long and successful research career. He also stays involved in helping young researchers in their careers, heading the Physician Scientist Development Program. He remembers his experience with the AA&MDSIF as "extremely positive" and credits some of his success to the AA&MDSIF grant.

The Mechanism of Clonal Dominance of PNH Cells

Kazuhiko Ikeda, MD, PhD, Washington University in St. Louis School of Medicine (N)

● AA&MDSIF PNH Foundation Research Grant

Dr. Ikeda will be studying how PNH blood cells acquire a "growth advantage" through a gene mutation. His findings are likely to provide new insights into the role of gene expression in clonal blood disorders such as PNH and MDS.

Development of Targeted Therapies for 3q26-positive MDS

Archibald Perkins, MD, PhD, University of Rochester (E)

● AA&MDSIF Harold Spielberg Research Grant

This study by Dr. Perkins will focus on a particular protein function believed to cause gene overexpression leading to MDS. Targeting this protein area may lead to the development of a drug, called a polyamide, which represents a new class of agent that has never been tried in the treatment of MDS.

NIH Insights into Bone Marrow Failure Disease Research:

An interview with Pankaj Qasba, Ph.D., Program Director of the Blood Diseases Branch, National Heart, Lung and Blood Institute (NHLBI) at NIH, and Stephen Groft, PharmD, Director of the NIH Office of Rare Disease Research (ORDR).



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Don't have internet access? Send a self-addressed stamped envelope to Newsletter at AA&MDSIF, 100 Park Avenue, Suite 108, Rockville, MD 20850.



From AA&MDSIF Archives 1992: Dr. Leslie Biesecker (far right) is awarded a \$25,000 Post-Doctoral Fellowship by (right to left) Dr. Stephen Emerson, then a member of the Michigan Chapter Advisory Committee; Todd Snider, an aplastic anemia patient; and Todd's mother Susan. Dr. Biesecker is now at the National Institutes of Health; Dr. Emerson is the President of Haverford College in Haverford, PA; Susan Snider and her husband Gary, former member of the AA&MDSIF Board, have a second son battling aplastic anemia today; Todd Snider, an aplastic anemia survivor from the age of 4 when he was diagnosed, passed away in 2005. In a recent conversation Susan Snider says that awareness and research have come a long way since those early days when she and her husband first volunteered with AA&MDSIF.

AA&MDSIF Plays Key Stakeholder Role in DoD Research Program

Advocacy Impacts Funding

AA&MDSIF's leadership involvement in a recently initiated research program run by the U.S. Department of Defense (DoD) demonstrated a complete circle of support throughout the process.

Why is the DoD funding bone marrow failure disease research? In 1992, grassroots advocacy organizations lobbied Congress to expand funding for breast cancer research in ways that were different from those used by traditional medical research entities like National Institutes of Health (NIH). In response, Congress allocated specific funds for this type of research in the DoD budget because the Department had a history of performing medical research studies and its administrative structure was designed for flexibility and quick response.

This funding is administered by the DoD Congressionally Directed Medical Research Program (CDMRP), and the specific disease areas chosen for the research are the result of advocacy by organizations and individual constituents. Since 2007, AA&MDSIF, its patients, families and friends have been reaching out to members of Congress to include funding for bone marrow failure disease research as part of the DoD bill. As a result of this effort, led by Congresswoman Doris O. Matsui (D-CA), the DoD appropriation included \$1 million for bone marrow failure research.

Since 2007, AA&MDSIF, its patients, families and friends have been asking their members of Congress to include funding for bone marrow failure disease research as part of the DoD bill. As a result of this effort, the DoD appropriation included \$1 million for bone marrow failure research. Thanks to continued advocacy led by AA&MDSIF, the DoD appropriation for FY09 was increased to \$5 million. For FY10, \$7.5 million had been requested; however the pending bill includes \$5 million for funding these research projects next year.

Leadership as a Stakeholder

After this successful advocacy for the funding, AA&MDSIF was then invited to be involved in the next step of the CDMRP process—participating in the Stakeholders Meeting to determine the focus areas of the research. AA&MDSIF board president and aplastic anemia survivor Neil Horikoshi, JD, was invited to join this group as a patient representative, and AA&MDSIF research grantee Lisa Minter, MD, was asked to join as a researcher.



Neil Horikoshi, aplastic anemia survivor, chairs AA&MDSIF's Board of Directors.

"Participating in the Stakeholders Meeting was important for me because it allowed me to be a 'voice' for my particular research focus, in so much as I could advocate for those areas which I felt to be underfunded, underdeveloped or underutilized as a means to advancing the state of research in the field," Dr. Minter said of her experience.



AA&MDSIF Torry Yahn Research Grant recipient, Dr. Lisa Minter, whose daughter's battle inspires her work on aplastic anemia, helps patients and families understand the science behind the disease.

Neil Horikoshi felt that his role as a patient and consumer in the Stakeholders Meeting "enabled not only the promotion of and visibility of AA&MDSIF's significant work and leadership to facilitate the advocacy of the DoD funding for the Congressionally Mandated Bone Marrow Failure Research Project (BMFRP), but also insured that its mission statement included the promotion of innovative research for bone marrow failure as well as language that focused on the ultimate goal of finding cures."

Both Minter and Horikoshi were also asked to serve on the Integration Panel, which decided how to incorporate the chosen focus areas into a Request for Proposals sent to researchers. Horikoshi appreciated this opportunity to not only represent AA&MDSIF, but also to learn about the initiatives from related participants. "The top medical practitioners and research professionals, together with patient groups supporting both acquired and inherited bone marrow failure diseases, have all been independently focused on improving the health and lives of their patients," Horikoshi noted.

"Every Stakeholder and Integration Panel member is dedicated and passionate about the common goal of supporting innovative government supported research that contributes to improving the health of both acquired and inherited bone marrow failure disease patients," he continued.

"I am proud of AAMDSIF's leadership and contribution to spearhead the advocacy to insure sustained DoD funding to help support not only our acquired bone marrow failure patients, but also inherited bone marrow failure patients. This is all about our patients!"

Minter noted, "As researchers, we hope to contribute to our fields of study incrementally through novel findings or significant observations. Being invited to sit on the Integration Panel has allowed me the privilege of helping to advance bone marrow research on a much broader front, since members of the panel are actively engaged in crafting the vision of the CDMRP Bone Marrow Failure Research Program, as well as the funding mechanisms to achieve that vision."

Minter added, “As a result of my participation, I have learned that, although funding for bone marrow failure is a small part of the CDMRP, it is a growing part. The Integration Panel has worked hard to create funding opportunities that will encourage new investigators to enter the field, that will reward innovative and creative research ideas, and that will assist collaborative research efforts to enhance networking within the clinical and research communities.”

Patient Participation in the Process

The next phase of the CDMRP process involved the peer review of the submitted research proposals, and again, AA&MDSIF was represented by board member Stephen King as a consumer reviewer. King is also a patient, diagnosed with aplastic anemia in 1988 and then later with PNH. In this role, he was a full voting member of the scientific peer review panel, along with prominent scientists and clinicians.

Consumer Reviewers were asked to represent the collective view of their community, including survivors and patients, family members and persons at risk for the disease. Specifically, they were asked to score and comment on the potential impact of the proposed study on issues such as disease prevention, screening, diagnosis, treatment, and quality of life after treatment. Commenting on his role as a consumer reviewer, King said, “It was a privilege to represent the patients and family members of the bone marrow failure communities” on the CDMRP review panel. “The dedication of panel members and the extraordinary effort to identify promising areas of research that may lead to new treatments and possible cures for these diseases was impressive.”

According to Captain E. Melissa Kaime, MD, Director of the CDMRP, “The Consumer Reviewers on each panel helped the scientists understand the patient’s perspective and provided

valuable insight into the potential impact of the proposed project. Likewise, these important members of the peer review panels have been enriched by learning more about the scientific process through discussing proposals with the other peer review panel members and seeing the future possibilities of successful research outcomes.”

The initial project funded, (out of 20+ submissions), *The Role of TAK1 in the Pathogenesis of Bone Marrow Failure Syndromes*, is being led by Jiwang Zhang at Loyola University in Chicago. The goal of this study is to “uncover the molecular processes by which blood stem cells are maintained in the bone marrow.” Discovering more about these processes could offer a significant new advantage for clinical stem cell transplantation. This research may also help to identify new molecular targets, which could prove useful in the design of new drugs to stimulate blood stem cell survival and thus more effective treatments for bone marrow failure syndrome patients.



Patient Advocate Stephen King meets with his representative, Congressman John Lewis (D-GA) during AA&MDSIF Capitol Hill Day, 2008.

Promoting Innovation & High Impact Research

Thanks again to effective advocacy led by AA&MDSIF, the DoD appropriation for FY09 was increased to \$5 million. The second year of the BMFRP promises to develop more groundbreaking research by offering the “Idea Award”. Cap. Kaime explained how this new mechanism was created: “When the Integration Panel of the Bone Marrow Failure Research Program (BMFRP) met to set the vision for their \$5 million appropriation from Congress, they wanted to fund very innovative research that could leap ahead and support new ideas, not just extensions of existing work. The Idea Award is intended to support innovative ideas and high-impact approaches to bone marrow failure research to move toward the BMFRP vision of understanding and curing bone marrow failure disease.”

Facts about CDMRP Funding for Bone Marrow Failure Disease Research

Next Year FY2010

\$5 Million request pending congressional approval—your action now can help secure these funds.

Big Picture

In FY2009, \$500+ million allocated across 19 disease research areas.



To learn more about CDMRP:
<http://cdmrp.army.mil/aboutus.htm>

To see Stephen King’s Story of Hope:
www.AAMDS.org/youtube.com/user/aamdsif

To read about Dr. Minter’s research:
www.AAMDS.org/Research

To urge your representative and senators to support the \$5 million allocation for CDMRP for FY2010:
www.AAMDS.org/Action

Pending Bills Need **YOUR** Calls & Emails Today!

The U.S. House of Representatives approved the fiscal year 2010 Defense Appropriations Act, which includes \$5 million for the Bone Marrow Failure Disease (BMFD) research program at the Department of Defense (DoD). The Senate has yet to act on its version, but once the bill moves to a House/Senate Conference Committee, it is a real possibility that this amount will be decreased. We need your calls and emails to maintain the current \$5 million funding level.

House Resolution (HR) 1230, the Bone Marrow Failure Disease Research and Treatment Act, introduced by Doris Matsui (D-CA) is currently pending before the House Energy and Commerce Committee. HR1230 would increase the federal government's commitment to researching and treating acquired bone marrow failure diseases.

Action may occur before the end of 2009 on HR1230 to move it out of committee. **Your action now is critical.** HR1230 has picked up the support of key members of Congress and is currently cosponsored by 36 House members, including 11 of the 39 members of the Subcommittee on Health.

Is Your Representative on the House Energy and Commerce Subcommittee on Health?

These members are very important to gaining passage of HR1230.

- Email/Call them today to urge their support as a cosponsor.
- Then, say "thank you" as they sign on. *Indicates cosponsors to date.

AR - Ross	IL - Schakowsky*	OH - Sutton
AZ - Shadegg	IL - Shimkus	PA - Murphy
CA - Capps	IN - Buyer	PA - Pitts
CA - Eshoo*	KY - Whitfield	TN - Blackburn
CA - Harman	MD - Sarbanes	TN - Gordon
CA - Waxman	MI - Dingell	TX - Barton
CO - DeGette*	MI - Rogers	TX - Burgess*
CT - Murphy*	MO - Blunt	TX - Gonzalez*
FL - Castor	NC - Wilkins Myrick	TX - Green*
GA - Barrow*	NJ - Pallone, Jr.	TX - Hall
GA - Deal	NY - Engel*	UT - Matheson
GA - Gingrey	NY - Weiner	VI - Christensen
IA - Braley*	OH - Space	WI - Baldwin*

Is Your Representative Listed Here as a Cosponsor of HR1230? (as of 10/1/09)

- If Yes, then call/email to say "Thank You."
- If Your representative is NOT on this list, then contact them to urge their support because it's important to you and their community!

CA - Eshoo	IA - Braley	NY - King
CA - Honda	IL - Schakowsky	PA - Altmire
CA - Matsui, Bill Sponsor	MA - Frank	PA - Murtha
CA - Stark	MA - McGovern	PA - Platts
CO - DeGette	MD - Van Hollen	PA - Schwartz
CT - Murphy	MI - Conyers	PA - Sestak
GA - Barrow	MI - Miller	TX - Burgess
GA - Bishop	MO - Emerson	TX - Gonzalez
GA - Lewis	NY - Arcuri	TX - Green
GU - Bordallo	NY - Bishop	VA - Wolf
HI - Abercrombie	NY - Engel	WA - McDermott
HI - Hirono	NY - Hinchey	WI - Baldwin

Your Activist Checklist – Making Your Voice Heard Today Helps Find Answers, Saves Lives

- Use our Action Center (www.AAMDS.org/Action) to send a message to your representative. Put a personal face on these diseases by including a few sentences concisely telling your story.
- Spread the word to family and friends around the country. Ask them to email/call/write their representatives urging support for both HR1230 and the DoD funding. Sample letter and talking points are available at www.AAMDS.org/Action or by contacting Benita Marcus, at 301-279-7202 x102 or marcus@aamds.org.



Don't Have Internet Access?
You can still be involved.

- Write a letter to your representative and senators. Due to postal security for Congress, letters can often take weeks, which is why we encourage you to send an email or call.
- Go to your local library where there is probably free computer access. A librarian can help you go online to our Web site www.AAMDS.org/Action.

Our Researchers Report...



To read the complete lay summaries and full reports of these and other AA&MDSIF research award recipients, go to www.AAMDS.org/Research.

Dr. Kay Macleod, University of Chicago
AA&MDSIF Established Researcher Award

● *Erwin Umbach Research Study (2007-2009)*

Oxidative Stress in the Etiology of Myelodysplasia



From Dr. Macleod:

We have built on our findings from year one in which we identified a novel mechanism to explain how blood cells lacking the function of the RB tumor suppressor accumulate increased levels of reactive oxygen species and DNA damage that results in defective blood cell function. We show that pRB interacts with a DNA-damage sensing protein called Parp-1 and that loss of pRB is associated with abnormally high levels of Parp-1 activity that feeds back to induce reactive oxygen species and more DNA damage, thus producing a detrimental positive feedback loop. Chemical inhibition of Parp-1 both prevented accumulation of reactive oxygen species and DNA damage. Importantly, this also promoted normal maturation of RB deficient blood cells in vitro. Based on these novel findings, we examined the effect of treating a mouse model of bone marrow failure and anemia with chemical agents that inhibit the abnormal activity of Parp-1 and showed that this reduced levels of oxidative stress and delayed the onset of anemia in this mouse model of disease. We will also be presenting this data in an oral presentation at the American Society of Hematology Annual Meeting in December 2009 during the Scientific Program Session on "Apoptosis: On Matters of Life and Death."

Funding for Dr. Macleod's work was donated by Jim and Lois MacGillivray in memory of her late father, Erwin Umbach, who died of MDS in 2006. Jim, an AA&MDSIF board member, is approaching his 6year anniversary as an MDS survivor; and marrow transplant survivor.

Dr. Lubomir Sokol, H. Lee Moffitt Cancer Center and Research Institute
AA&MDSIF New Investigator Award

● *Harold Spielberg Research Study (2007-2009)*

Microarray Profiling of Micro RNA in 5q-Syndrome

From Dr. Sokol:

MiRNAs are small non-coding RNAs that post-transcriptionally regulate the expression of many important genes in normal and cancer cells including tumor suppressor genes and oncogenes. The AA&MDSIF Grant supported our initial research in this new field. We studied a role of miRNAs in the pathobiology of

Dr. Jaroslaw Maciejewski, Cleveland Clinic Foundation Taussig Cancer Center
AA&MDSIF Established Researcher Award

● *Pursuing New Hope Papernick Family Research Study (2005-2008)*

Differential Inhibition of Normal Stem Cells in PNH

From Dr. Maciejewski:

PNH as an orphan disease is very difficult to study because the funding sources are very limited and in match with other common and well publicized diseases research applications are not competitive. The grant we have received allowed us to devote time to systematic investigations in PNH. Thanks to the funding obtained, we were able to investigate the mechanisms leading to selective outgrowth of PNH stem cell. Using high density DNA chips, we have demonstrated that there are no genomic differences between the normal and PNH clone derived from the same patient, a finding that suggest mechanisms of clonal selection do not operate in from PNH stem cell but are rather. Through high density genotyping, we have identified a number of genetic polymorphic variants which could explain propensity for PNH evolution in individual patients. Thanks to the funding provided with the help of AA&MDSIF and incredible gifts of the donors, discovery of these variants allowed us to prepare larger studies involving whole genome scanning technology for which are currently await funding from federal sources. If successful, the impact of initial funding will be amplified.

Funding for Dr. Maciejewski's work is made through the generous support of Alan Papernick, his family and friends, in honor of his daughter, Amy Glick, who is a PNH survivor.



MDS. We found that miRNA expression is significantly dysregulated in MDS vs. normal bone marrow cells suggesting that miRNAs could serve as novel biomarkers. We have also discovered a unique miRNA signature that predicted the prognosis in MDS patients. In our future, research we would like to investigate the role of miRNA target molecules in the pathogenesis of MDS and use this knowledge in the development of novel personalized therapies for patients with MDS.

Funding for Dr. Sokol's work is made through the generous support of Mrs. Shizue Spielberg and Vibratex, Inc. in loving memory of her husband, Harold Spielberg, who bravely battled MDS.

Q: AA&MDSIF is sponsoring a Bone Marrow Failure Disease Scientific Symposium March 11-12, 2010, bringing together experts from around the world to provide specific recommendations for the highest priority and direction for future basic and clinical research. Why is this type of collaboration important?

A: **Steensma:** All experts have strengths and limitations – promising insights and also “blind spots” to weaknesses in areas of thinking. The diverse experts in bone marrow failure have differing training, experiences, and skills, and may come up with unique ideas for how best to pursue the important research questions. By talking with one another, being open to the ideas of others, and approaching ideas critically, the most fruitful lines of research can be identified, and concrete plans made to pursue them.

Stone: No one person or group is likely to independently solve the complicated problem of bone marrow failure. The idea exchange allowed by this symposium will synergistically result in a new way of looking at these problems.

Sekeres: Just for the word you use, collaboration, and having people “in the know” all in one place at one time discussing a similar topic bears fruit in future collaborations and research topics.

Deeg: For many patients with these diseases, treatment is still far from optimal. Only new insights into the pathophysiology can identify novel treatment options, possibly more specific for more narrowly defined patient groups.

Paquette: Cutting edge research in this field is conducted worldwide. Collaboration internationally is required to progress in uncommon disorders like the bone marrow failure states.

Giagounidis: It is important to bundle research efforts from different international groups. In times of financial restraints, concentration on certain topics will achieve the highest return on investment. Bringing together faculty from all over the world will allow the participants to identify the most important questions, focus on common research interests, and start collaboration to maximize research efficiency. These effects are best supported by bringing the different participants together.

Q: What are the primary questions that need to be answered as soon as possible in the field of bone marrow failure disease research? Why are these questions so important?

A: **Deeg:** This is too big a question - the primary question is why does the disease develop? If we have a better understanding there, we can possibly try and prevent the development.



Paquette: We need to fully understand the the pathophysiology of each disorder and the heterogeneity[©] that exists between individuals with the same disease.

Steensma: In aplastic anemia, there is suspicion that many cases are virally mediated and initiated by normal or aberrant immune response viruses that have not previously been linked to the disease; identification of these viruses will be helpful. In MDS, the underlying genetic basis is poorly understood, and disease mechanisms are largely obscure. These and other pathobiologic questions are critical to answer in order for improved treatments to be developed.

Giagounidis: For MDS, we need to identify prognostic factors for therapeutic intervention, i.e. subpopulations for which specific treatment strategies exist or may be suitable (e.g. del(5q) -> Lenalidomide; -7 -> Azacitidine; ATG? low-dose chemotherapy?, HDAC-Inhibitors? etc.) We need to ask which patients don't benefit. This would have a major impact on patients benefiting from treatment and would spare unnecessary treatment to all others. As for bone marrow transplants, investigate on conditioning regimens that will allow transplantation for the higher age population of MDS patients most safely.

Sekeres: My bias is to accelerate clinical trials of novel drugs/ combinations to get them to patients as soon as possible.

Q: What is the most promising research underway in bone marrow failure disease (or specifically in aplastic anemia, MDS and/or PNH)? What might this research mean to patients in the next 3 - 5 years? In the next 10 years?

A: **Deeg:** The answer depends upon whom you ask. I think we need to recognize the heterogeneity of the diseases that we call by one name - more specific treatment (or preventive measures) should follow. Patients would be treated more effectively.

Stone: Among many important questions, we need to know a) against what antigens[©] is the immune system directed in aplastic

anemia; b) what is the nature of the inflammatory response in PNH; and c) what are the genetic underpinnings in MDS. If we solve all or part of these issues, more effective therapy might well be developed for patients with these conditions.

Paquette: Molecular profiling of MDS is identifying new genes involved in its pathogenesis. By discovering such new genes and learning how they cause disease, new drugs can be developed to target these mechanisms.

Giagounidis: For MDS, identification of genes involved in certain disease subgroups by snp (single nucleotide polymorphism[®]) analysis. This might lead to novel therapeutic approaches within 5 to 10 years.

Q: In terms of funding, what do you think is needed to truly make an all-out effort to find the answers to these questions? In addition to more funding, what other resources are needed in the field of bone marrow failure disease research?

A: **Paquette:** Patient participation in clinical trials and basic research studies remain critical to advancing the field.

Sekeres: I'll go back to the clinical trials issue - I think we need more funding of Phase I/II studies and easier paths to collaboration - tearing down some of the administrative hurdles to collaborating across centers.

Stone: One important potential, albeit expensive, approach is to perform deep sequencing[®] of a large group of MDS stem cells. Beyond funding, awareness of the issue of anemia in the elderly.

Deeg: We need substantially more money; we need money that can be used without holding the investigator to narrowly defined objectives; we need more exploratory work and must not always expect an answer tomorrow. More exchange of information and biologic samples would be helpful, and I think that could be achieved if these collaborations would be acknowledged when continuation of funding is considered.

Giagounidis: Identify 5 international groups that work on that research. Funding should allow continuous research for at least 5 years.

Steensma: There are many obstacles to successful research in addition to funding: intellectual property issues, incentives for academic promotion that still favor individual efforts rather than collaboration, bureaucratic hassles and administrative distractions, and other claims on experts' time. All of these issues need to be addressed for research to proceed as rapidly as possible.

Q: How can young investigators be encouraged to pursue careers in bone marrow failure disease research? What is the value of attracting young investigators to the field?

A: **Stone:** New 'blood' is needed both in marrow failure syndromes and in bone marrow failure research. Without benefit of young enthusiastic intelligent researchers, the same old out-of-date thoughts might be recycled.

Steensma: Most investigators pursue careers in a given area because of a combination of three factors: innate interest; opportunity; and inspiring mentorship. I am convinced that many young investigators can be encouraged to find marrow failure research interesting. Funding provides opportunity, and inspiring mentorship is dependent on encouraging young investigators.

Deeg: Assure them of sustained support.

Giagounidis: I suppose reading [more about the career impact of grants like those given to new investigators by AA&MDSIF and other organizations like the American Society of Hematologists] might help to see how people can efficiently be involved into hematology research.

Paquette: This is an exciting area of research right now because so much is happening both at the basic research level and in the clinics. Young investigators invigorate the field and make the discoveries of the future.

Q: In your opinion, will researchers be able to find a "cure" for bone marrow failure diseases to prevent them from occurring, or will these always be diseases that require treatment after diagnosis?

A: **Stone:** This is difficult question, but cure should be the goal. In fact, we certainly cure some patients with these conditions today, such as the use of allogeneic[®] stem cell transplant in MDS.

Sekeres: In our lifetime, there will not be one cure, but there will be significant advances in isolated bone marrow failure areas. For example, MDS is not just one disorder - it is nine under the World Health Organization classification, and probably hundreds of disorders genetically. We will make real in-roads in some of those hundreds, but not most.

Paquette: There already is a cure (stem cell transplantation), but it is not appropriate for everyone. We are transplanting much older patients now than we did 10 years ago. Further advances in preventing and managing transplant-related complications are needed to improve the safety of this procedure for older patients.

Giagounidis: Prevention of MDS is difficult as those diseases result from accumulation of mutations of the genome[®], and mutation is a naturally occurring phenomenon that cannot be easily prevented (and was indispensable for the development of life on Earth). In only about 10% of MDS can we find a definitive previous cause or injury that explains its occurrence. In most cases, cure will come through treatment.

Steensma: It is difficult to talk about prevention without a thorough understanding of what initiates the disease process. Therefore, we are restricted to educated guessing. While aplastic anemia might be made less common by vaccination against inciting viruses (if such viruses are identified) and avoidance of precipitating drugs, myelodysplasia seems likely to result from random genetic injuries from ubiquitous environmental exposures and would be very difficult to prevent. I suspect these diseases will always require treatment after diagnosis.

Deeg: I think there will be successful preventive measures—eventually.

Q: Are there any advances on the horizon to improve the outcomes from bone marrow transplantation (including post-transplantation complications), both for patients with matched donors and unmatched donors?

A: **Deeg:** Yes, a lot of work is ongoing, including work with mismatched donors.

Stone: Increasing understanding of the immune system will provide a) better selection of donors which will minimize Graft Vs Host Disease (GVHD[®]) and maximize Graft Vs Leukemia (GVL[®]) and b) less toxic and more effective therapies to prevent and/or treat GVHD.

Paquette: Umbilical cord blood transplantation has been a major development in this field. Its use will likely expand further as we learn to optimize the use of this cell source.

Q: Are community hematologists adequately informed about bone marrow failure disease? How should more information be shared with them so they can stay up-to-date on treatment options for their patients?

A: **Stone:** The Aplastic Anemia and MDS International Foundation can play an important role in the dissemination of information to providers and patients.

Deeg: Well, I actually think that more patients should be referred, and earlier, to specialized centers.

Paquette: Community hematologists need to identify and interact with those of us who have a special interest in bone marrow failure.

Giagounidis: From a European standpoint, more continuing medical education (CME) activities would be helpful to increase

awareness of those diseases to the general hematologists.

Steensma: Continued partnership between academic and community hematologists is essential to provide the best possible care for patients with bone marrow disease. Physicians have many demands on their time, and succinct, infrequent updates on major changes from respected experts go a long way towards making sure all clinicians caring for patients with these uncommon disorders are adequately informed.

Additional members of AA&MDSIF's Medical Advisory Board:

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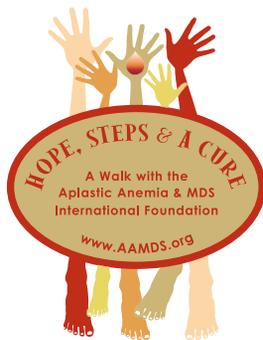
G Glossary (alphabetically)

- ▶ **Antigens:** substance that can cause the production of an antibody, a protein produced by the body's immune system in response to a foreign substance. Once produced, an antibody will later react specifically with the antigen that triggered its formation and inactivate the antigen
- ▶ **Genome:** a full set of chromosomes; all the inheritable traits of an organism
- ▶ **GVHD:** a complication (during a bone marrow transplant) in which the transplanted marrow reacts or rejects normal tissues in the person who has received the transplant
- ▶ **GVL:** the Immunological rejection of leukemia cells following bone marrow transplantation; GVL is also called graft versus cancer
- ▶ **Hematopoietic:** relating to the formation of blood cells
- ▶ **Heterogeneity:** multiple origins causing the same disorder in different individuals
- ▶ **Pathophysiology:** the study of changes in normal mechanical, physical and biochemical functions caused by a disease or resulting from an abnormal syndrome
- ▶ **Ribosomal Gene:** genes which carry ribosome, the protein manufacturing machinery of all living cells
- ▶ **Sequencing:** learning the order of nucleotides (base sequences) in a DNA or RNA molecule or the order of amino acids in a protein allogeneic taken from different individuals of the same species
- ▶ **Single-Nucleotide Polymorphism (SNP, pronounced snip):** a small genetic change, or variation, that can occur within a person's DNA sequence – A,T,C or G

Awareness & Patient Education

Sign-up as a Hope, Steps & A Cure Volunteer for Fall 2009 or Spring 2010!

The Aplastic Anemia & MDS International Foundation's "Hope, Steps & A Cure" is a fun and festive walk that you can participate in with your own community to raise awareness about bone marrow failure diseases while raising much needed funds for AA&MDSIF programs & services to help patients and families. Volunteers and organizers are needed across the globe.



Consider reaching out to your family and friends to join you. Survivors are getting involved as a way to inspire fellow patients. Families and friends are signing up to celebrate and honor their loved ones bravery in facing these diseases. Many are using this volunteer opportunity as a way to "pay forward" all they support they received from AA&MDSIF.

AA&MDSIF professionals are here to help you every step of the way to success! You can design a walk that fits your interests and timeline! Anyone can take part in your walk—children, adults and seniors. Plan a neighborhood or community walk—long or short, outdoors or indoors. Involve family & friends, neighbors and other patients & families. Finish your walk with a picnic or BBQ celebration for everyone.

@ Contact Martha Crews to learn more at crews@aamds.org or 800-747-2820 x103. Ask for information about our Fast Start program that can help you put together a walk in just 6 weeks.

Facts for life

"Should I volunteer for a clinical trial?"

As a patient, it is important to understand what clinical research studies are and how they work, what to expect if you choose to participate in a study, and the risks and benefits to consider so you can make an informed decision that is right for you. A clinical trial is a research study of how a drug, medical device, or treatment approach works in people. Carefully conducted research studies are the fastest and safest way to find treatments that work for patients and new approaches to improve health. If you are considering volunteering to participate in a clinical trial, you should first ask your doctor if he or she knows of any studies that may be a good option for you.

🌐 To learn more, visit www.AAMDS.org/ClinicalTrials for a better understanding and for information on clinical trial opportunities.

🌐 To apply for Patient Travel Funds, get details and an application from www.AAMDS.org/TravelFund. If you are a patient, or parent of a pediatric patient, with significant financial need, AA&MDSIF may be able to reimburse you up to \$500/year for travel costs to be in a clinical trial. Receipts are required.

@ To request your copy of the booklet, *Clinical Trials for Patients with Bone Marrow Failure Disease* or have your personal questions answered, call our Patient Educator, Leigh Clark at 800-747-2820 or 301-279-7202, then choose option 1; or email clark@aamds.org. She can also put you in touch with a Peer Support Network volunteer who as a patient has participated in a clinical trial.



Join the AA&MDSIF *Guardians of Hope*

In addition to the gifts you give today and throughout your lifetime, taking the time to write AA&MDSIF into your will or to make any other planned/estate gift provides an enduring legacy of your personal interest and commitment to providing education, service and research for those facing bone marrow failure diseases.

Ask your attorney to include this paragraph, specified to your gift preferences, in your will:

I give, devise, and bequeath \$ _____ (amount) or ____% (percentage) to the Aplastic Anemia & MDS International Foundation (AA&MDSIF), 100 Park Avenue, Suite 108, Rockville,

MD, 20850, a not-for-profit corporation for its charitable uses as directed by its Board of Directors.

Please let us know if you've included AA&MDSIF in your will or estate plan, and we'll be pleased to recognize you today in our Guardians of Hope Society with a special thank you.

@ To discuss your interests, learn more about making a bequest or other gift, or how to designate your gift for specific use, please call our Development Director, Sandra Walter-Steinberg at 301-279-7202 x104 or email at walter@aamds.org.

Checklist for Fall Follow-up

- Update your Address Book with AA&MDSIF's new address [p.16]
- Request a copy be sent to your treating physician, send us a SASE (size 9x12 with \$2.25 postage) addressed to them with your return address. Mark your envelope "News."
- Ask your representative and senators to support HR1230 and DoD Research funds at www.AAMDS.org/Action [p.10]
- Register for Webinar: *Your Health Insurance: What You Need to Know* www.AAMDS.org/Learn
 - For MDS : 10/15/09 @3pm EDT with Penni Potter-Perez, JD, Patient Services Inc., Access Program
 - For PNH: 10/29/09 @3pm EDT with Kevin Lucia MHP, JD, Georgetown University Health Policy Institute
- Register for Webinar: *Living Well: Tips & Strategies for Staying Healthy* www.AAMDS.org/Learn
 - For MDS : 11/12/09 @3pm EST with Ruben Mesa, MD; Mayo Clinic
 - For PNH: 12/17/09 @3pm EST with Ilene Weitz, MD, Keck School of Medicine of USC
- Read the Web Exclusives on NIH Insights into Bone Marrow Failure Disease Research and Dr. Leslie Biesecker at www.AAMDS.org/News [p.7]
- Volunteer to bring "Hope, Steps & A Cure" to your community by contacting crews@aamds.org [p.15]
- Consider becoming a Guardian of Hope by naming AA&MDSIF as a beneficiary in your will/estate plan. Contact walter@aamds.org [p.15]
- Give in honor/memory of a loved one or dedicate a date on AA&MDSIF's Calendar of Hope at www.AAMDS.org/Dedication or www.AAMDS.org/DonateNow
- Provide your new or updated email address at www.AAMDS.org/Email

*Never received email from AA&MDSIF before?

You are missing out on inspirational and informational news through our monthly eBulletin, as well as timely updates on medical issues and special invitations during the year.

Your Email Address Helps Us! Email has become the fastest and most cost-effective way for us to reach you. Whether you are a patient, family member, friend or supporter, having your email lets us keep you in the know about urgent health information and AA&MDSIF program news. Be assured that we will never sell, rent or share your email address with any other organization, company or direct mailer.



DON'T HAVE AN EMAIL ADDRESS?

- ▶ If you have a computer and online access, get a free email address through providers like www.gmail.com or www.msn.com.
- ▶ Visit your local library. Most have free computer access and a librarian who can help you go online to our Web site.
- ▶ Ask a family member/friend to set-up an email address for you to receive AA&MDSIF information. Ask them to print the emails and give them to you. Or, read your email online when you visit them.

answers
support &
hope.

New Address & Phone!



Aplastic Anemia & MDS
International Foundation

100 Park Avenue, Suite 108 • Rockville, MD 20850
Phone: 301-279-7202 or 1-800-747-2820 • Fax: 301-279-7205
Email: help@aamds.org • Web site: www.AAMDS.org

Return Service Requested



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