



**2012**

**President**

Armand Keating, MD  
Princess Margaret Hospital  
610 University Avenue, Suite 5-303  
Toronto, ON M5G 2M9  
CANADA  
phone 416-946-4595  
fax 416-946-4530  
armand.keating@uhn.on.ca

**President-Elect**

Janis L. Abkowitz, MD  
University of Washington  
Box 357710  
Seattle, WA 98195-0001  
phone 206-685-7877  
fax 206-643-3560  
janabl@u.washington.edu

**Vice President**

Linda J. Burns, MD  
Division of Hematology, Oncology,  
and Transplantation  
420 Delaware Street, SE  
MMC 480/Room 14-154A Moos Tower  
Minneapolis, MN 55455-0341  
phone 612-624-8144  
fax 612-625-9988  
burns019@umn.edu

**Secretary**

Charles S. Abrams, MD  
University of Pennsylvania  
School of Medicine  
421 Curie Boulevard, #912  
Philadelphia, PA 19104-6140  
phone 215-673-3288  
fax 215-673-7400  
abrams@mail.med.upenn.edu

**Treasurer**

Richard A. Larson, MD  
University of Chicago  
5841 S. Maryland Avenue, MC-2115  
Chicago, IL 60637-1470  
phone 773-702-6783  
fax 773-702-3002  
rlarson@medicine.bsd.uchicago.edu

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Martha L. Liggett, Esq.  
mliggett@hematology.org

September 20, 2012

Re: Request for Information (RFI): Building a National Resource to Study Myelodysplastic Syndromes (MDS) – The MDS Cohort Natural History Study (NOT-HL-12-147).

Submitted electronically to: [NHLBI\\_MDScohortstudy@nhlbi.nih.gov](mailto:NHLBI_MDScohortstudy@nhlbi.nih.gov)

Cc: [difronzon@nhlbi.nih.gov](mailto:difronzon@nhlbi.nih.gov)

To Whom It May Concern:

The American Society of Hematology (ASH) appreciates the opportunity to provide input in the deliberations of the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI) in response to the request for information on “Building a National Resource to Study Myelodysplastic Syndromes (MDS) – The MDS Cohort Natural History Study (NOT-HL-12-147),” issued on August 29, 2012.

The American Society of Hematology (ASH) represents more than 14,000 clinicians and scientists worldwide committed to the study and treatment of blood and blood-related diseases. The Society’s members have pioneered the fields of bone marrow transplantation, gene therapy, and stem cell research. MDS represents an important disorder for scientific focus given its epidemiologic link to senescence, its significance as a pre-leukemia model, and its relevance to stem cell biology. With the aging of a large segment of the American population who are at emerging risk for these disorders, the advancement of research and treatment of MDS is one of the Society’s priorities.

Hematology researchers are the scientific engine that will contribute to the accomplishments necessary to delineate pathogenetic features of the disease and are funded by the entire spectrum of National Institutes of Health (NIH) Institutes, including the NHLBI, the NCI, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institute on Aging (NIA); ASH and its members are appreciative of our long-standing collaboration with the Institutes and their support for the science driving new discoveries.

ASH applauds the NHLBI and the NCI for their efforts to build a national resource to better understand MDS disease progression. One of the major challenges for MDS research has always been the lack of a “home” for it within NIH. Because MDS is such a heterogeneous disease, many Institutes, depending on their research affinities, could possibly “house” MDS.

For example, the role of natural aging processes in MDS might be well-suited for study within the context of NIA, while topics that may be of interest to NHLBI, NIDDK, or NCI run the gamut of studies investigating transcriptional dysregulation of hematopoietic cell differentiation in MDS, defects in mature cell function in patients with MDS, iron metabolism, or progression from MDS to AML. However, there has not been a concentrated effort from any of the Institutes in recent years to tackle MDS; instead each Institute has released a limited few requests for applications on MDS each year, resulting in growing concern of MDS “falling through the cracks.” ASH looks forward to the creation of a multi-center, comprehensive, and sustainable program for MDS research at the NIH and believes creating a national MDS resource is an important first step in this endeavor.

ASH welcomes the development of the national MDS resource that will address continuing challenges in MDS research in order to improve our understanding of the biology and pathogenesis of MDS, with the ultimate goal of improving therapeutic approaches to this disease. These challenges include:

1. The lack of a central repository for normal (control) bone marrow specimens representing all decades of life (such as National Cooperative Tissue Network).
2. The lack of corresponding germline specimens from MDS patients (such as from buccal swab) in order to contrast normal and MDS samples.
3. Small cell sample recovery necessitating utilization of limited cell technology.
4. Identification of preferred cell population for analysis.
5. Variable collection/processing/cryopreservation approaches and quality (i.e., need for standardized best practices in these areas).
6. Inadequate stem cell assays/models.
7. Limited relevance and applicability of animal models of MDS.

ASH has identified the most important scientific questions and research priorities that the proposed MDS Cohort Natural History Study should answer; they are listed below in rank order:

**1. Determining the role of stem cell and hematopoietic senescence in MDS predisposition and pathogenesis.**

- Epidemiologic data indicate that predisposition to MDS is age-dependent and is further modified by genotoxic exposures, supporting a link between the disease and hematopoietic stem cell senescence and/or the age-dependent accumulation of genetic abnormalities in hematopoietic stem cells.
- Heritable gene mutations affecting telomere maintenance illustrate the strong connection between replicative stem cell senescence, genomic instability, and a predisposition to MDS. While our understanding of the biology of stem cell senescence is limited, murine models and investigations in solid organ malignancies indicate that age-dependent changes in epigenetic control and patterns of microRNA expression may contribute to stem cell depletion and skewing toward myeloid commitment that merit further study in MDS. Structural and numerical chromosome abnormalities in MDS may reflect deregulation of genomic fidelity arising from acquired changes in the capacity for DNA repair.

- Numerous assays to investigate cellular senescence have emerged that can now be applied to MDS and normal hematopoietic stem cells including genetic, cellular protein, and humoral markers. Predisposition to MDS with age may also reflect interaction of the stem cell with age-dependent changes in the microenvironmental niche and immuno-senescence *per se*, both of which exert selective pressures external to the stem cell and its progeny.
- Emerging evidence from animal models suggests that the introduction of aged stem cells into a young recipient microenvironment restores replicative potential, emphasizing the importance of external cues in stem cell behavior.

## **2. Determining molecular genetics and epigenetics of MDS.**

- MDS is a polygenic disease that will, therefore, benefit from genome-wide analysis for individual genes and genomic patterns that may be pathogenic or predictive of specific disease subtypes.
- Recent application of DNA sequencing technology on MDS bone marrow specimens has revealed that MDS is an oligoclonal disease and that transformation into AML is a result of subclonal proliferation. This important discovery and the future of understanding more about MDS clonal selection will rely on rapid transfer and widespread availability of high-throughput DNA sequencing technology.
- Increasing evidence indicates that epigenetic abnormalities, including both global and gene-specific methylation, play a pathogenetic role in MDS based on data linking tumor suppressor gene inactivation with disease progression and the success of DNA methyltransferase (DNMT) inhibitors in treatment of the disease.
- Recent investigations indicate that only a small fraction of gene promoters are methylated in MDS, raising important questions as to cellular mechanisms directing gene selection, contributions of histone modifications such as acetylation and methylation, and other regulators of chromatin structure.
- Application of sensitive microarray technology such as single nucleotide polymorphism, gene expression, and microRNA arrays has shown that these innovative techniques can identify unrecognized sites of gene deregulation and gene expression signatures that have biological, prognostic, and potentially diagnostic significance.
- Better understanding of these processes will not only improve the diagnosis of MDS, but also provide additional targets for drug design and treatments for patients with MDS. It is expected that molecular profiling will lead to diagnostic and prognostic signatures and assist in understanding genetic predisposition (SNPs, mutations, etc.) to MDS.
- Novel, highly sensitive techniques, such as high-throughput DNA sequencing, whole exome or genome sequencing, microRNA expression arrays, and genomic methylation tiling are priority platforms for molecular discovery to further molecular diagnostic and prognostic characterization, the understanding of the non-epigenetic and epigenetic effects of current therapeutics, and the understanding of the relationship of these processes to senescence, disease predisposition, and MDS stem cell biology.

- Transcriptional repression is believed to be an important contributor to ineffective hematopoiesis in lower risk disease; however, convincing laboratory data are lacking.
- Strategies that integrate the above technologies with assessment of transcriptional control should be prioritized to understand the interaction of molecular processes in disease behavior and the action of novel therapeutics.
- Mutations in the spliceosome machinery constitute another area of interest with specific respect to MDS refractory anemia with ringed sideroblasts. The mutated spliceosomal genes are most likely tumor suppressors; however, more investigation is needed. Moreover, there are several non-hematologic diseases that are caused by mutations in spliceosomal mutations, *e.g.*, familial isolated growth hormone deficiency type II, Frasier syndrome (inactivation of the Wilms tumor suppressor gene), and rare forms of dementia, that would benefit from further investment in spliceosome research.

### **3. Determining the roles of normal and cancer stem cells in MDS.**

- Direct evidence supporting the presence of an MDS stem cell is lacking, reflecting the limitations of current assays.
- Recent work using highly purified murine and human hematopoietic stem cell (HSC) populations have identified stem cell gene expression signatures that can now be interrogated to identify disparities in gene regulation in MDS affecting self-renewal potential, competition with normal HSC, clonal expansion, and cell survival.
- Common convergence signaling pathways involved in terminal differentiation are altered in MDS, creating an opportunity for investigation of novel targeted therapeutics.
- Development of *in vitro* proxy assays for assessment of self-renewal is essential for testing new therapeutics.
- Animal models have proven valuable for candidate gene validation, and new murine models have greater relevance to human disease, creating opportunities for further understanding of disease biology and the actions of novel therapeutics.

### **4. The MDS microenvironment.**

- Emerging data show that an impaired bone marrow microenvironment can give rise to dysplastic hematopoiesis and transformed MDS. This impaired microenvironment may also be implicated in disease progression and disease relapse, such as after hematopoietic cell transplant. A priority should be placed on identifying the extrinsic signals that transform normal hematopoietic stem/progenitor cells to undergo dysplastic and then neoplastic transformation.
- The MDS microenvironment is hyperproliferative and rich in angiogenic signaling, compared to normal bone marrow and even acute myeloid leukemia (AML) transformed bone marrow. More research should be conducted in understanding the full panoply of factors that make up the unique MDS

microenvironment. Targeting the microenvironment is a new strategy for treating MDS.

## **5. Therapy-related MDS.**

- Approximately 5-10% of patient receiving chemotherapy or radiation therapy will develop a therapy-related MDS. As people live longer and undergo treatment for solid tumors, therapy-related MDS is becoming a more significant problem.
- Moreover, therapy-related MDS is usually an aggressive condition with high risk for transforming to AML. Therefore, it is important to understand the mechanisms of how therapy-related MDS originates.
- It would be important to understand the roles of damage to a hematopoietic stem/progenitor cell and/or damage to the bone marrow microenvironment.
- It is also important to develop assays to identify solid tumor patients who are at higher risk of developing MDS after chemotherapy or radiation.
- Alterations in inherited DNA repair mechanisms that may be responsible for predisposing patients to develop MDS after chemotherapy or radiation need to be studied in greater detail.

## **6. MDS epidemiology.**

- The number of MDS cases in the United States may be unreported, as a high rate of uncaptured MDS cases has been seen in at least one state cancer registry (Florida).
- There is a great need for more resources for building better methods of MDS case ascertainment.
- Additionally, more research is needed on disease management decisions and clinical outcomes. Linkages to biospecimens are needed for determining clinical relevancy, case control and hypothesis generation.

The American Society of Hematology looks forward to working with the NHLBI and the NCI on this exciting new endeavor. ASH will be happy to provide further information and be a resource for the Institutes. Please contact ASH Senior Manager for Scientific Affairs, Ulyana V. Desiderio, PhD, at (202) 776-0544 or [udesiderio@hematology.org](mailto:udesiderio@hematology.org) for any additional information.

Sincerely yours,



Armand Keating, MD  
President