

# NCI Cancer Bulletin

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## Researchers Discuss State of the Science on Myelodysplastic Syndromes

The National Heart, Lung, and Blood Institute (NHLBI) and NCI recently held a state-of-the-science symposium on myelodysplastic syndromes (MDS) to identify areas of research where investment would improve understanding of these diseases and accelerate the development of better treatments.

MDS is a set of rare diseases in which a patient's bone marrow does not make enough healthy red or white blood cells, leading to severe anemia and infections. In about 30 percent of patients with MDS, the condition eventually progresses to acute myelogenous leukemia (AML), but the genetic changes driving this transformation—as well as those leading to the inevitable worsening of MDS in patients whose disease does not progress to AML—are not well understood.

Dr. Susan Shurin, acting director of NHLBI, described the symposium as a "call to action" to better understand the biology and environmental factors that cause MDS in order to develop new therapies. Participants came from many countries, reflecting "how global a research endeavor the whole area of MDS and bone marrow failure is," said Dr. Shurin. A common theme of the meeting was that international collaboration is vital for MDS research because the diseases are relatively rare.

Speakers at the symposium described what is and what isn't understood in the field of MDS, including how best to treat patients given the limitations of available therapies, the biology and pathophysiology of MDS, and the complex genetic and epigenetic factors driving this set of diseases.

### **A Complex Disease**

Researchers recognized long ago that MDS is genetically complex—patients whose bone marrow cells have identical chromosomal abnormalities can have very different clinical outcomes. But until 3 or 4 years ago, said Dr. Pierre Fenaux of the Hôpital Avicenne University in France, perhaps only three genes were known to play a role in driving MDS.

In the past few years, he continued, the availability of microarrays and high-throughput genetic sequencing has helped experts identify more of the genes found within the most common chromosomal abnormalities in MDS, including those that affect the epigenetic state of cells.

Researchers speaking at the conference expressed hope that having a more complete genetic and epigenetic profile of MDS will help them design new treatments to target specific abnormalities, as well as improve upon current systems for determining prognoses.

Speakers also highlighted areas of current uncertainty: whether MDS is driven by "MDS stem cells," similar to the cancer stem cells postulated to drive leukemia; whether, in some cases, the bone marrow microenvironment or immune system might promote MDS; the role of microRNAs in MDS initiation and progression; and the difference between idiopathic MDS and MDS caused by chemical exposures, such as some chemotherapy drugs (secondary MDS or treatment-induced MDS).

The cellular events that cause disease initiation and progression—and that are, therefore, targets for treatment—may be different for MDS that progresses to AML and MDS that is characterized by worsening blood cell counts (cytopenias), said Dr. Sten Eirik W. Jacobsen of the University of Oxford. The conference participants advocated the importance of studying MDS as a set of distinct diseases.

### **Funding Priorities**

Several areas that would likely benefit from focused funding emerged from the many discussion sessions. One of these, outlined by University of New Mexico Cancer Center Director, Dr. Cheryl Willman, is an urgent need for high-quality tissue banks containing biospecimens and the appropriate control specimens for genetic and epigenetic

studies that are well-annotated and compiled with proper patient consent. Dr. Willman's research group at the University of New Mexico has helped to assemble such a tissue bank for NCI's Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative.

Such a resource is necessary to build a complete biological profile of MDS, including genetic mutations, epigenetic alterations, bone marrow microenvironments, and fates of healthy blood-forming stem cells as disease progression occurs, the speakers said. Better MDS cell lines and more mouse models would also help researchers working to understand the basic mechanisms of these diseases.

The clinical significance of any genetic mutations or epigenetic alterations discovered in MDS will need to be validated in large prospective populations, which will require funding and collaboration. Clinical trials testing new treatments for MDS based on genetic information may need to be restricted to include only patients with the genetic profiles thought to potentially benefit from a new treatment, suggested Dr. Guillermo Garcia-Manero of the University of Texas M. D. Anderson Cancer Center.

And the focus of any research must be to move closer to new treatments, stressed many participants, as few currently exist. The available drugs only slow progression for several months to years, and the only potentially curative treatment—allogeneic stem cell transplantation (SCT)—is a high-risk procedure. Most patients with MDS are older than 70 and have other medical problems, stressed Dr. Garcia-Manero, making SCT an option for relatively few.

"With the great tools [we now have for research], if we had the right resources and the right infrastructure, I think we could really make a huge difference," summarized Dr. Steven D. Gore of Johns Hopkins University.

—*Sharon Reynolds*