MPDs: Do We Finally Know JAK?

By Ruben Mesa, MD

The 2005 discovery of the JAK2^{V617F} mutation in the BCR-ABL negative myeloproliferative disorders (MPDs) was a watershed event in our understanding, and (hopefully) therapy, of MPDs. Dr. Radek Skoda, from University Hospital in Basel, Switzerland, will present the Ham-Wasserman Lecture today on "The Genetic Basis of Myeloproliferative Disorders." Created in 1984 and named for the late Drs. Thomas H. Ham and Louis R. Wasserman, past presidents of the American Society of Hematology, this award honors an individual from outside the United States who has made a major contribution to the field of hematology. Dr. Skoda's topic is highly relevant, since the lecture partly honors Dr. Louis Wasserman, whose career focused on the MPDs. His *New England Journal of Medicine* paper describing the high prevalence of JAK2^{V617F} in MPD patients joined several other near-simultaneous reports of this mutation from labs in France (Dr. W. Vainchenker), the United Kingdom (Dr. A. Green), and the United States (Dr. D.G. Gilliland).

"The conceptual work of William Dameshek in 1951 laid the basis for understanding the MPDs as a continuum of related diseases," relates Dr. Skoda, whose interest in MPD pathophysiology arose from his early work with c-MPL and hereditary thrombocythemia. Crucial early discoveries in MPD biology included the demonstration of cytokine-independent growth of myeloid colonies and MPD clonal stem cell origin. Subsequently, work on familial MPD cohorts by Drs. Robert Kralovics and Josef Prchal defined loss of heterozygosity on chromosome 9p in polycythemia vera (PV) patients. Scrutiny of this 9p region led to Drs. Skoda and Kralovics' initial report of the JAK2^{V617F}.

The explosion of MPD research that followed this discovery included the recognition of additional disease-associated mutations, such as in 12th exon of JAK2 in JAK2^{V617F} negative PV patients, or c-MPL$^{W515l/K}$ mutations in primary myelofibrosis and essential thrombocythemia. These mutations activate JAK-STAT pathways and alter cell responsiveness to suppressors of cytokine signaling (Socs) proteins, such as Socs3. Murine models have also been created, demonstrating that expression of JAK2^{V617F} is sufficient for a PV-like phenotype. The World Health Organization is currently revising diagnostic criteria for the MPDs to reflect the impact of the new molecular markers.

Dr. Skoda is optimistic about the potential for therapeutic inhibition of JAK2 in MPD patients. Indeed, the focus of the MPD Education Session and various presentations on Monday and Tuesday is the JAK2 inhibitors, which are currently being evaluated in the lab and in pilot clinical trials. Yet, Dr. Skoda cautions that there are many unanswered questions. Why is there such phenotypic variability amongst MPD patients sharing the same mutation? Are there other important genetic determinants of MPD pathobiology? Do JAK2 mutations play a role in disease progression in MPDs to either severe myelofibrosis or blast phase? Despite these unknowns, Dr. Skoda is enthusiastic about the possibilities, in view the relative explosion of knowledge from 2005 to 2007, as opposed to the slow progress from 1951 to 2005. He states, "The current pace of progress raises hopes that many of the key (MPD) questions will be answered soon." This is welcome news for MPD patients, and for those of us involved in their care.