

Magic Bullets Target AML

By Robert L. Redner, MD

In yesterday's Scientific Committee session on Myeloid Neoplasia, Chair Steven Grant, MD, got out his six-shooter to target myeloid leukemia transcription factors.

The successes of ATRA in APL and imatinib in CML have energized the leukemia field to seek other molecular pathways unique to leukemias that could be targeted specifically. Jay Hess, MD, PhD, led off yesterday's discussion with a review of potential therapeutic targets in leukemia. The majority of acute myeloid leukemias have recurring chromosomal rearrangements involving transcription factors. The resulting fusion proteins lead to misregulation of downstream target genes important for leukemogenesis. To date targeting transcription factors has proven to be difficult. Dr. Hess outlined the approach his laboratory is taking to develop mechanism-based therapy for leukemias with rearrangements of the mixed lineage leukemia gene, *MLL*, and shared his perspective on the role that academic investigators can play in the development of antileukemic therapeutics.

John Bushweller, PhD, focused on the RUNX1 family of proteins as potential targets. RUNX1, also known as AML1, is a transcription factor that binds to specific well-defined sequence motifs in DNA to regulate gene expression of its targets. The RUNX1 transcriptional pathway may be dysregulated by any of 10 or more chromosomal rearrangements associated with leukemia. One potential strategy for interfering with dysregulated RUNX1 transcription would be to block the heterodimerization between RUNX1 and its heterodimer partner, protein CBF β . As proof of principle, a mutated AML1-ETO fusion protein that is incompetent in binding CBF β loses its ability to immortalize cells and confer leukemia. Using structure-based computational methods and subsequent medicinal chemistry optimization, Dr. Bushweller has identified a series of heterodimerization inhibitors capable of blocking the growth of AML1-ETO cell lines. These compounds represent the first in an exciting array of intelligently engineered compounds that may abrogate the leukemogenicity of the RUNX1 fusion proteins.

In the third presentation of the session, Michael Thirman, MD, discussed strategies for targeting MLL. The *MLL* gene on chromosome 11q23 has been identified as being the partner gene in more than 50 chromosomal translocations in leukemia. Though the exact mechanism of leukemogenesis remains unknown, these *MLL* fusion genes retain the N-terminus of MLL fused to the C-terminus of a partner. Past attempts to target the MLL pathways have focused on downmodulation of the MLL-fusion protein, such as by siRNA that targets the unique sequences formed at the junction of the fused genes or downmodulation of the MLL target HOX proteins. Dr. Thirman discussed experiments in which his group targeted the interaction between MLL and melin, an association that is essential for MLL-leukemias in experimental models. Using a transducible peptide containing sequences of MLL that could bind to melin and inhibit MLL-melin interactions, he has found significant effects on viability of MLL-fusion cell lines.

Those who missed the mark will have another shot at this morning's 7:30 a.m. reprise of this session. Oncogene hunters will no doubt find more ammunition in the Monday morning Scientific Simultaneous Session "Identification of Novel Mutations and Targets in AML" and the Tuesday morning session "Oncogenes and Tumor Suppressors."