“Functions and Mechanisms of E-box-binding Transcription Factors in AML 1-ETO-mediated Leukemogenesis”

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Funding Category: A

Abstract: In many types of acute leukemia, transcription factors are frequently altered through chromosomal translocation, mutation or aberrant expression, thus representing a huge therapeutic potential. The leukemogenic AML1-ETO fusion protein, generated by the t(8;21) translocation, is the most common fusion protein in acute myeloid leukemia. We recently have found that, in leukemic cells, AML1-ETO resides in and functions through a stable protein complex that contains multiple transcription factors and cofactors. The most notable of these are several members of the large family of helix-loop-helix (HLH) transcription factors, which typically form hetero- or homo-dimers and bind to E-box DNA elements. While these E-box-binding transcription factors have been shown to play key roles in a wide variety of developmental processes, their role in AML1-ETO-mediated leukemogenesis is largely unknown. Of special note, we have found that E proteins, a subfamily of HLH transcription factors, interact directly with the dimerized AML1-ETO. The NHR2 dimerization domain of AML1-ETO, previously shown to be critical for leukemogenesis, utilizes a distinct surface of the dimerized alpha-helixes to interact with a novel NHR2-binding (N2B) motif in the E proteins, thus ideally allowing design of peptidomimetic inhibitors to target the specific interaction. This collaborative project will employ biochemistry, crystallography, and both cell-based and mouse leukemic models (i) to clarify the functions and mechanisms by which the interacting proteins, especially the E-box-binding transcription factors, cooperate with AML1-ETO in aberrant gene regulation and (ii) to test the efficacy of the peptidomimetic inhibitors. These studies should provide not only new insights into AML1-ETO-mediated leukemogenesis but also potential therapeutic targets for leukemia treatment.