The Sweetser laboratory investigates how leukemia and other cancers develop with the goal of developing novel, more effective therapies with fewer side effects. We now know that cancer develops slowly as the result of several sequential mutations that eventually lead to uncontrolled growth and spread. Our group has identified a novel family of tumor suppressor genes, known as the Groucho/TLE family, which appears capable of blocking the effects of almost all known classes of cancer causing oncogenes. This family thus functions as a gatekeeper, protecting cells from turning into cancer. In some types of cancer, these genes are lost, allowing cancer to develop. We are working to understand how these proteins work and the role that they play in the normal function of cells and during development. We have also teamed up with Jing-Ruey Yeh, PhD, Randall Peterson, PhD, and David Langenau, PhD, at Massachusetts General Hospital to use the zebrafish as a model for cancer development and drug discovery. Based on exciting results, we are now developing human clinical trials to test the effectiveness of one of these compounds in treating leukemia.

Genetics of Acute Myeloid Leukemia

Our laboratory is working to elucidate cooperating networks underlying leukemogenesis and to help develop novel targeted therapies for cancer. Current projects are detailed below.

Evaluation of the role of the Groucho/TLE family of corepressors in development and leukemogenesis.

Our laboratory has defined TLE1 and TLE4 as members of a novel family of tumor suppressor genes, the TLE/Groucho proteins, the inactivation of which appears to be a key cooperating event with other oncogenes in the development of a subset of acute myeloid leukemias.

The Groucho/TLE family of corepressor proteins is known to modulate many of the major pathways involved in development and oncogenesis, including Wnt/ß-catenin, Notch, Myc, NFκB, and TGFß. However, researchers are only beginning to understand their potential role in oncogenesis. These genes are involved in the pathogenesis of other myeloid malignancies, lymphomas, and other malignancies including synovial cell sarcomas. Current work in the lab seeks to clarify the role these proteins play in malignancy as well as in normal development. We have shown the ability of these proteins to potently regulate Myc leukemogenesis can be demonstrated in both murine and zebrafish models of leukemia. We are seeking to better understand regulated downstream events related to both gene transcription and chromatin structure.

Our laboratory is also working to understand the role these proteins play in normal development. To assist in this evaluation, we have generated conditional Tle1 and Tle4
Tle4 is not only a tumor suppressor gene in AML, but is critical for normal bone mineralization and bone marrow support.

knockout mice and are currently characterizing role these proteins play in the development of a variety of tissues.

Identification of novel inhibitors of AML1-ETO

We have collaborated with the Yeh and Johnson labs to identify several novel small molecule inhibitors of AML1-ETO using a zebrafish high-throughput biological screen. Our results, published in early 2012, identified several classes of agents capable of inhibiting AML1-ETO. We are currently evaluating the efficacy of these agents in treating mouse models of leukemia.

Selected Publications:


