The Sweetser laboratory investigates how leukemia and other cancers develop with the goal of developing novel, safer, and more effective therapies. We are investigating how the Groucho/TLE family of co-repressors function as potent tumor suppressors of acute myeloid leukemia and their roles in normal development and cell function. Knock-out mice for Tle1 and Tle4 have identified critical roles for these proteins in hematopoiesis, bone, lung, and brain development, as well as a critical role in limiting inflammation. We have defined critical inflammatory signaling pathways mediating cell proliferation and synergistic cross talk within the cancer niche. The laboratory is also using whole exome sequencing to characterize underlying cancer predisposition genes in patients with a variety of pediatric malignancies. As the MGH site director for the newly established HMS Undiagnosed Diseases Center and Chief of Medical Genetics and Metabolism at MGH, Dr. Sweetser is also leading a group of clinicians and researchers actively engaged in elucidating the underlying basis of a wide variety of human diseases.

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.


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/β-catenin, Notch, Myc, NFκB, and TGFβ. However, researchers are only beginning to understand their potential role in oncogenesis. These genes appear to behave as tumor suppressor genes in the pathogenesis of other myeloid malignancies and lymphomas. However, the role of this gene family in malignancies is complex, as in synovial cell sarcoma where TLE1 is over-expressed and behaves as an oncogene by pairing with the SS18-SSX fusion oncogene and ATF2 to silence other tumor suppressor genes. Current work in the lab seeks to clarify the role these proteins play in malignancy as well as in normal development. TLE1 and TLE4 are potent inhibitors of the AML1-ETO oncogene in the most common subtype of AML. The mechanism of this inhibition appears to involve both regulation of gene transcription and chromatin structure. In large part this cooperative effect appears to involve regulation of Wnt signaling and...
inflammatory gene pathways. This work has led to the demonstration that anti-inflammatory agents can have potent anti-leukemic effects.

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 knockout mice and are currently characterizing role these proteins play in the development of a variety of tissues. Our studies to date indicate TLE1 is a potent repressor of inflammation via its ability to repress NFKB, while TLE4 is a critical modulator of neuronal and B-cell and T-cell differentiation, and is required for hematopoietic stem cell maintenance, as well as bone development.

**Identification of Novel Inhibitors of AML1-ETO**

We have collaborated with the Yeh laboratory 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, and we have demonstrated the efficacy of these agents in treating mouse models of leukemia.

**Identifying Genetic Predispositions to Cancer**

It is being increasingly recognized that genetic predispositions play a role in the development of many cancers, especially those in children. We are using whole exome sequencing of several cancer types in children to help identify germline mutations that can influence cancer development. Individuals with these mutations may be at higher risk for relapse or the development of additional cancers, and warrant more intensive and extensive surveillance.

**The Undiagnosed Diseases Network**

The Harvard Medical School hospital consortium of MGH, Brigham and Women’s Hospital and Children’s Hospital has been recently selected as one of six new sites comprising a nationwide Undiagnosed Diseases Network. As Chief of Medical Genetics at MGH, and the MGH site director for the UDN, Dr. Sweetser is coordinating a team of expert clinicians and researchers, and is using whole exome/whole genome sequencing, paired with RNASeq and metabolomics profiling, and in collaboration with zebrafish and Drosophila model organism cores to identify the underlying basis of a variety of challenging human diseases.

---

**Selected Publications:**

Shin TH, Brynczka, Dayyani F, Rivera M, Sweetser DA. TLE4 Regulation of Wnt-mediated Inflammation Underlies its Role as a Tumor Suppressor in Myeloid Leukemia. Leuk Res. 2016, 48:46-56.


