David A. Sweetser, MD, PhD

Sweetser Laboratory

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The Sweetser laboratory investigates how leukemia and other cancers form with the goal of developing novel, safer, and more effective therapies. Our lab has identified a novel family of tumor suppressor genes, the Groucho/TLE family of co-repressors and defined how TLE1 and TLE4 function as potent tumor suppressors of acute myeloid leukemia and how they have critical roles in hematopoiesis, bone, lung, and brain development, and limiting inflammation. It is this latter function that appears to underlie their tumor suppressor role. Currently, we are defining a cooperative role of TLE1 in melanoma development. A second line of research seeks to define and target critical signaling pathways within the cancer niche that are required for the proliferation and survival of leukemia. As the Mass General site director for the Undiagnosed Diseases Network and Chief of Medical Genetics and Metabolism at Mass General, 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.

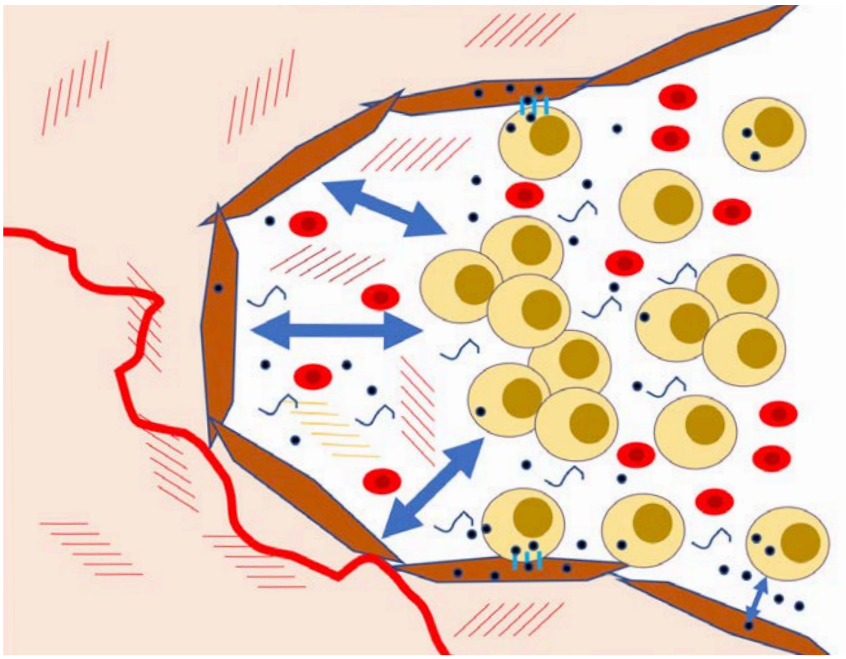
Evaluation of the role of the Groucho/TLE family of corepressors in cancer and development

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 and other cancers.

The Groucho/TLE family of corepressor proteins can modulate many of the major pathways involved in development and oncogenesis, including Wnt/β-catenin, Notch, Myc, NFκB, and TGFβ. These genes appear to behave as tumor suppressor genes in the pathogenesis of other myeloid malignancies and lymphomas, but as an oncogene in synovial cell sarcoma. 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. Our work indicates this cooperative effect appears to involve regulation of Wnt signaling and inflammatory gene pathways. This work has led to the demonstration that specific anti-inflammatory agents can have potent anti-leukemic effects. We are currently studying the role of TLE1 in melanomas using conditional knockout of Tle1 and conditional oncogenicV600E BRAF expression.

The role of the bone marrow niche in nurturing leukemia

The bone marrow niche is remodeled in the process of leukemia development to provide a supportive environment that contributes to leukemic cell proliferation, survival, and resistance to chemotherapy. Leukemia treatments to date have focused on attacking leukemia cells and have largely ignored that fact that the survival of leukemia is critically dependent on the supportive role of a transformed leukemic bone marrow niche. This bone marrow niche is rich in cytokines, growth factors, and various nucleic acids including miRNAs. Using diagnostic bone marrow aspirates from patients with leukemia and controls



Schematic diagram of the leukemic bone marrow niche. *Remodeling of the bone marrow niche creates a necessary and supportive environment for the development and expansion of leukemia. This synergistic cross talk involves a complex milieu of compounds including cytokines, growth factors, miRNAs and other nucleic acids and proteins. Disruption of critical signals in this niche could represent a valuable therapeutic strategy.*

we have characterized many of these dysregulated components in bone marrow stroma, bone marrow plasma and leukemic cells. We are now systematically evaluating these to identify novel therapeutic modalities to block critical signals necessary to sustain leukemic growth and survival.

The undiagnosed diseases network

Dr. Sweetser is also engaged in rare and undiagnosed disease research. The Harvard Medical School Hospital consortium of Mass General, Brigham and Women's Hospital and Children's Hospital together with 11 other clinical sites around the US comprise the NIH sponsored Undiagnosed Diseases Network. As Chief of Medical Genetics at Mass General, and the Mass General site director for the UDN, Dr. Sweetser coordinates a team of expert clinicians and researchers, using comprehensive clinical phenotyping, whole exome/whole genome sequencing, paired with RNASeq and metabolomics profiling, in vitro functional modeling, and collaboration with zebrafish and Drosophila model organism cores to identify the underlying basis of a variety of challenging human diseases. Over three dozen new genetic disorders have been characterized with these efforts. His lab is also developing stem cell models of several inherited neurological disorders to understand alterations in brain development and potential novel therapies.

Selected Publications:

Galazo M, **Sweetser DA**, D. Macklis J. Tle4 controls both developmental acquisition and postnatal maintenance of corticothalamic projection neuron identity. May 2022 *BioRxiv*. https://doi.org/10.1101/2022.05.09.491192

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Ramasamy S, Saez B, Mukhopadhyay S, Ding D, Ahemd AM, Chen X, Pucci F, Yamin R, Pittet MJ, Kelleher CM, Scadden DT, **Sweetser DA**. Tle1 tumor suppressor negatively regulates inflammation in vivo and modulates NF-κB inflammatory pathway. *PNAS* 2016, 113:1871-6.