Most pediatric patients whose sarcoma or leukemia recurs will succumb to their disease. The focus of the Langenau lab is to uncover the mechanisms that drive progression and relapse in pediatric tumors with the long-term goal of identifying new therapeutic drug targets to treat relapse and refractory disease. One approach we have used is to add drugs to the water of novel zebrafish models of pediatric sarcoma and leukemia that mimic human malignancy. We then imaged tumor growth in the zebrafish and utilize detailed imaging studies to visualize tumor cells in live animals to assess how cellular heterogeneity drives continued tumor growth.

Capitalizing on insights gained from our zebrafish models of cancer, we are now extending our findings to human T-cell acute lymphoblastic leukemia and rhabdomyosarcoma.

"Identifying molecular pathways that drive progression and relapse in pediatric cancer..."

The Langenau laboratory research focus is to uncover relapse mechanisms in pediatric cancer. Utilizing zebrafish models of T-cell acute lymphoblastic leukemia (T-ALL) and embryonal rhabdomyosarcoma (ERMS), we have undertaken chemical and genetic approaches to identify novel modulators of progression, therapy-resistance, and relapse.

Uncovering progression-associated driver mutations in T-cell acute lymphoblastic leukemia

T-ALL is an aggressive malignancy of thymocytes that affects thousands of children and adults in the United States each year. Recent advancements in conventional chemotherapies have improved the five-year survival rate of patients with T-ALL. However, patients with relapse disease are largely unresponsive to additional therapy and have a very poor prognosis. Ultimately, 70% of children and 92% of adults will die of relapse T-ALL, underscoring the clinical imperative for identifying the molecular mechanisms that cause leukemia cells to re-emerge at relapse. Utilizing a novel zebrafish model of relapse T-ALL, large-scale transgenesis platforms, and unbiased bioinformatic approaches, we have uncovered new oncogenic drivers associated with aggression, therapy resistance and relapse. A large subset of these genes exert important roles in regulating human T-ALL proliferation, apoptosis and response to therapy. Discovering novel relapse-driving oncogenic pathways will likely identify new drug targets for the treatment of T-ALL.

Visualizing and killing cancer stem cells in embryonal rhabdomyosarcoma

ERMS is a common soft-tissue sarcoma of childhood and phenotypically recapitulates fetal muscle development arrested at early stages of differentiation. Microarray and cross-species comparisons of zebrafish, mouse and human ERMS uncovered the finding that the RAS pathway is activated in a majority of ERMS. Building on this discovery, our laboratory has developed a transgenic zebrafish model of kRASG12D-induced ERMS.
Visualizing cancer stem cells in live zebrafish affected with embryonal rhabdomyosarcoma. GFP expression is confined to the myf5+ ERMS-propagating cells while differentiated nontumor propagating cells are labeled with a nuclear histone-RFP fusion and membrane associated Cyan that mimics the molecular underpinnings of human ERMS. We used fluorescent transgenic zebrafish that label ERMS cell subpopulations based on myogenic factor expression to identify functionally distinct classes of tumor cells contained within the ERMS mass. Specifically, the myf5-GFP+ self-renewing cancer stem cell drives continued tumor growth at relapse and is molecularly similar to a non-transformed, activated muscle satellite cell. Building on the dynamic live cell imaging approaches available in the zebrafish ERMS model, our laboratory has undertaken chemical genetic approaches to identify drugs that kill relapse-associated, self-renewing myf5-GFP+ ERMS cells. We are currently assessing a subset of drugs for their ability to regulate growth of human ERMS cells and mouse xenografts.

Selected Publications:


