An in vivo CRISPR Screen for Melanoma Progression in Zebrafish

Principal Investigator:

- Richard White, MD, PhD – Memorial Sloan Kettering Cancer Center

Co-Principal Investigator:

- Leonard Zon, MD – The Broad Institute of MIT and Harvard

Abstract: Successful macrometastatic colonization is a collaborative event between the tumor cells and the microenvironment, but functionally defining those interactions *in vivo* remains a significant obstacle. Using zebrafish models of melanoma, we have observed that: 1) additional genetic events in the melanocyte lineage can promote tumor progression above and beyond BRAFV600E;p53-/- and 2) metastatic melanoma cells acquire a lipid-laden state that is in part due to uptake of lipids from nearby cancer-associated adipocytes. We propose a CRISPR-based screen in the zebrafish model of melanoma that interrogates both of these compartments. In Aim 1, we will develop a melanocyte-specific mitf-Cas9 transgenic. This will be used to functionally test whether genes contained on chromosomes 2q37 and 19p13.3, regions commonly deleted in human melanoma, act as tumor suppressors and promote melanoma progression. In Aim 2, we will develop an adipocyte-specific Cas9 transgenic using the plin2 promoter, which can then be used to inactivate genes that are involved with free fatty acid mobilization and transport from the adipocyte to the melanoma cell. Both of these approaches take advantage of the exceptional imaging techniques and genetic manipulation available in the zebrafish, at a scale that could not be approached in other vertebrate models. Future studies will validate findings from our fish screens using mammalian cell culture systems and pharmacologic manipulation, providing new avenues for therapeutic intervention in advanced disease.