Research in the McGrail lab investigates how disruption of tumor suppressor genes leads to uncontrolled cellular proliferation and cancer. We use CRISPR/Cas9 genome engineering and classical genetics in zebrafish to model human brain cancer caused by inactivation of the tumor suppressor RB. RB regulates cell cycle exit and terminal differentiation, however, the mechanism by which RB induces neural progenitor differentiation and suppresses transformation is not completely understood. Somatic inactivation of RB in zebrafish causes brain tumors that resemble human primitive neuroectodermal tumors, a poorly differentiated and highly proliferative cancer. Transcriptome analysis of the brain tumors identified altered expression of transcriptional regulators, including repressive chromatin remodelers and neurogenic transcription factors. This suggests epigenetic mechanisms controlling transcriptional regulation maintain the tumor cell in a progenitor-like state. Mutant analysis of RB and chromatin regulators HDAC1 and RBBP4 reveals distinct roles in neural progenitor proliferation and survival during zebrafish brain development, providing insight into their role in driving tumor growth. We are currently developing new tools using CRISPR/Cas9 targeted integration for conditional gene inactivation in specific neural cell populations. Through these studies we hope to increase understanding of the mechanisms driving pathogenesis in brain tumors and other RB defective cancers.