Research Profile:
The McFadden lab is committed to discovering new therapeutic approaches for recalcitrant malignancies including small cell lung cancer, Ewing sarcoma, and advanced thyroid cancers.

Approach:
The lab uses genetically engineered mouse models of cancer (GEMMs) to precisely control the genetics and tissue of origin of cancer development in the mouse. Prior work has demonstrated that these models exhibit very few additional somatic mutations compared to many human cancers.

From these models, we develop high-throughput chemical and genetic screens to identify small molecules with selective toxicity and genes with synthetic lethality to cancer cells based on driver mutation and lineage of origin. Small molecule ‘hits’ from these screens are extensively validated against murine and human cancer cell lines, and in vivo using transplantation models and autochthonous GEMMs. Biochemical and genetic studies of these small molecules are pursued to identify the chemical target and mechanism of action.

We also study well-characterized cancer cell lines derived from pediatric sarcomas, including Ewing sarcoma. These cancers are driven by unique translocations that encode neomorphic oncogenic transcriptional regulators. The molecular mechanisms by which these fusions initiate tumorigenesis remain incompletely defined, and therefore no targeted therapies exist for these malignancies. The McFadden lab is using CRISPR/Cas9 methods to engineer “self-destruct” protein domains into the fusion oncogenes in order to study their mechanism of action and the cellular response to oncogene depletion. High-throughput chemical and genetic screens are subsequently used to identify new entry points for impairing the oncogenic action of these fusions.

Active Projects:
Identifying selective toxins for small cell lung cancer
Targeting the "untargetable": Ewing sarcoma
Re-differentiation of radioiodine-resistant thyroid carcinoma
Selected References:


