Neurosurgical Oncology Laboratory
The neurosurgical oncology laboratory centers on translational cancer medicine. The central objective of our laboratory is to develop innovative and transformative therapeutic strategies for the treatment of glioma and other human cancers. In the pursuit of this goal, our research focuses on frequently mutated oncodrivers, molecules implicated in cancer stem cell biology, as well as emerging epigenetic regulators as cancer drug targets. We use a wide range of molecularly characterized cancer cell lines and patient-derived xenograft tumor lines to model the diseases. We are particularly interested in drug combinations that induce synergistic drug response and circumvent drug resistance.

Personalized medicine for glioma treatment
Our understanding of the molecular pathogenesis of glioma and other brain tumors has been greatly improved over the past decade. It has been demonstrated that glioma is highly heterogeneous at genetic and epigenetic levels. Emerging driver mutations, such as IDH1 and Histone H3.3, define new molecular subtypes of glioma and provide novel therapeutic opportunities. However, driver mutations remain poorly defined in the majority of gliomas. Through multi-institutional collaborations, we are generating a molecularly characterized patient-derived glioma xenograft tumor bank. On the basis of this platform, we are now working to identify novel links between tumor genotypes and phenotypes with a goal to develop molecular-guided treatments for gliomas. This knowledge will then be translated into clinics to improve patient-tailored care.

Cancer stem cells in glioma
Cancer is a remarkably heterogenous disease at all aspects. A small subset of cancer cells with stem cell-like phenotypes have been identified in a wide range of human cancers, including glioma. These cells are termed cancer stem cells or cancer initiating cells. Cancer stem cells have extended capacity of self-renewal and can give rise to multiple lineages of differentiated progenies. In xenotransplantation assays, as low as a few cancer stem cells may give rise to a xenograft tumor. Importantly, cancer stem cells in glioma and several other cancer types exhibit preferential resistance to conventional chemoradiotherapy and targeted therapies. Therefore, these cells are blamed to result in recurrent tumors following initial clinical response. Our laboratory has a specific interest in the mechanisms that mediate resistance to radiation and other therapeutics in glioma stem cells. To this end, we are currently working on the Notch signaling pathway and other targets to develop glioma stem cell-specific targeted strategies.

Epigenetic therapy for human cancers
Epigenetics are heritable modifications of the genome that play critical roles in chromatin activities. It has become increasingly recognized that epigenetic abnormalities are crucially implicated in cancer initiation, progression and therapeutic resistance. The Cancer Genome Atlas (TCGA) project and other studies have identified an increasing number of alterations in epigenetic regulators in human cancers. For example, nearly half of glioblastoma tumors carry at least one mutation that affects an epigenetic regulator. We recently identified crucial functions of the BET family bromodomain proteins in proliferation and survival of glioblastoma with diverse genetic profiles. The BET proteins are epigenetic readers that specifically bind to acetylated histones and direct active transcription. Inhibition of BET proteins by small molecular inhibitors or RNA interference impairs active transcription of many important oncogenes, including some previously undruggable targets, such as MYC. Several BET bromodomain inhibitors have recently entered clinical trials. As such, BET bromodomain proteins are new and important drug targets in
glioma and many other cancer types, particularly those dependent on aberrantly activated oncogenic transcription factors. We have further demonstrated that inhibition of BET proteins significantly improve tumor response to a variety of anti-cancer drugs, potentially due to reduced expression of anti-apoptotic genes. The objective of this project is to develop epigenetics-based novel combination therapy for glioma and other cancers refractory to currently available therapeutics.