We will be able to use what we learn about MRI perfusion, spectroscopy, and diffusion tensor on a daily basis as patients return for follow-up imaging during treatment. By optimizing our imaging protocols, we may learn more about tumor biology and use that information to predict future tumor behavior (e.g., how and when tumors will recur).

Our ultimate goal is to develop individualized radiation therapy plans for each brain tumor patient, based on biological changes rather than structural changes or arbitrary margins. This would permit higher doses to tumor regions and lower doses to normal brain, potentially improving failure rates and patient morbidity.

Bipin Bobby Bhatia

Title: Tumor Suppressor TSC2 Inactivation and p27 Mislocalization in Brain Development and Medulloblastoma

The lack of novel drugs focused on killing tumor cells without damaging healthy nervous tissue has been a problem. We believe we have identified novel targets that play a role in cell metabolism and production of new proteins for tumor cells in medulloblastoma.

When we treat mice with medulloblastoma, our findings provide new insight on target genes that tumor cells specifically depend on, and that normal cells do not, thereby putting us one step closer to finding the right cure. Therefore, it is vital for clinical trials to focus on these new targets in order to prevent survival and aggression of medulloblastoma tumor cells.

Steven Foster

Title: The link between covalent protein-DNA lesion formation and repair in neurons and

medulloblastoma development

The cellular DNA damage response is required to maintain genomic stability and is of vital importance in the prevention of a variety of human pathologies, including cancer and aging. In particular, defects in the repair of DNA damage have been linked to neuropathologies such as neurodegeneration and brain tumor development. We are currently using a variety of DNA-repair-deficient mice as model systems to uncover the important aspects of the DNA damage response in preventing medulloblastoma development, the most common malignant brain tumor in children.

In the work funded by the Brain Tumor Center in 2008, we further highlighted the requirement of a functional DNA damage response for the prevention of brain tumors. Specifically, we have uncovered the importance of particular cell cycle control pathways in the inhibition of medulloblastomas in DNA-repair-deficient mice. These data provide insight into the molecular basis of medulloblastoma development, providing vital information on the genetic causes of this highly malignant childhood tumor. The information obtained could translate into better clinical care through providing a basis for new, improved targeted therapeutic strategies, as well as aiding in the discovery of mechanisms of cellular resistance to current therapies.

Understanding the molecular basis of such pathologies allows for a more accurate prediction of each patient's response to various therapies, thereby allowing for the development of better individual treatment strategies and more accurate prognoses.

Ruimin Huang

Title: Non-Invasive Bioluminescence Imaging of Antiangiogenic Effects on Gliomas in VEGF/VEGFR2 Reporter Mouse Models

Malignant gliomas are highly vascularized; therefore, antiangiogenic agents are increasingly being explored as therapeutic options. Preclinical and clinical studies have demonstrated promising efficacy of antiangiogenic agents in malignant gliomas. However, recent studies show that the benefits from antiangiogenic therapy are at best transitory and are followed by a restoration of tumor growth, progression, and invasion.

Our research project has developed a novel mouse glioma model with a bioluminescence reporter for angiogenesis. We have tested bevacizumab (Avastin), an antibody against vascular endothelial growth factor (or VEGF, a dominant angiogenic mediator) in this model. Using sequential noninvasive bioluminescence imaging, we monitored the dynamics of VEGF activity in tumor angiogenesis and microenvironmental incorporation upon antiangiogenic therapy. Novel antiangiogenic agents and combination with traditional radiotherapy and chemotherapy will also be tested. Successful drug candidates based on this study will be translated into future clinical trials in malignant glioma.

Our project will provide a mouse glioma model with angiogenesis-reporter. It allows us to test and optimize the efficacy of different single-agent and combination antiangiogenic strategies in preclinical trials of malignant gliomas.