Our study is focused on understanding the role of the transcription factor MEF (Myeloid ELF-1-like factor), which has been shown to function as an oncogene in previous work done in fibroblasts. We are exploring whether MEF could promote gliomagenesis and trying to elucidate its role in gliomas. The data generated so far, using mouse models in the laboratory of Eric Holland, has shown that in the absence of MEF, gliomas grow at a slower rate and the tumors have less-aggressive histopathological features. Another significant finding is that MEF confers stem-like properties to both primary neuronal cells and glioma cell lines; activation of pluripotent stem-like signatures has been correlated with an increased malignancy in human glioma. It was found that the mechanism behind this phenotype of MEF activates and binds to Sox2, another transcription factor, which is very well known for promoting pluripotency and stemness.

Glioblastoma multiforme (GBM) represents a heterogeneous disease, and recent genomic analyses have quantified the expression level of a wide variety of genes. A study from The Cancer Genome Atlas (TCGA) analyzed the data set for GBMs and found MEF expression significantly elevated in all GBM samples compared with nontumor brain tissue. Moreover, patients with a low level of MEF expression have a better overall survival. Taken together, these data suggest that MEF might potentially be a new therapeutic target in the clinical care of patients suffering from gliomas.

So far, our project has been exploring a potential new therapeutic target for patients suffering from high-grade gliomas. Future studies will analyze whether the modulation of the *MEF* gene in glioma cells directly isolated from patients' tumors will have an impact on the tumors' sensitivity to radiation therapy and chemotherapy.

Michael J. Evans

Title: Noninvasive Measurement of PI3K Pathway Signaling with a Positron-Emitting Radiopharmaceutical That Targets the Transferrin Receptor

The focus of our project is to develop a noninvasive biomarker that could help optimize the dosing of therapies for patients. Biomarkers are a measurable substance found in organisms that indicate the presence of disease. These findings will hopefully allow a better designation and monitoring of brain tumors so we can be more effective with drug dosing for each individual patient.

This project makes use of a clinically validated imaging technology (the PET scan) to better demarcate and monitor brain tumors. The distinguishing feature of the biomarker is how it targets the tumor, exploiting a biological P13K pathway that is often unregulated in certain classes of the disease. In this regard, the biomarker could be used to quantify the effect of drugs targeting this pathway.

This technology would almost certainly streamline the evaluation of experimental targeted therapies in clinical trials, as the inherent risk of endeavoring into phase III studies often justifies invoking exotic diagnostic technologies such as an experimental PET imaging tool to better understand drug pharmacology. More speculatively, the imaging tool could eventually be used as standard of care to optimize the dosing of targeted therapies for more-individualized patient care.

Armida Fabius

Title: The Role of the Parkinson's Disease–Associated Gene *PARK2* in the Molecular Pathogenesis of Glioblastoma

The focus of this project is to make the prognoses of patients with glioblastoma more effective by using the *PARK2* gene as a biomarker. Biomarkers are measurable substances found in organisms that indicate the presence of disease. The *PARK2* gene is one of the largest human genes and produces a protein known as parkin. Parkin can act as a tumor suppressor, preventing cells from growing and dividing too quickly or uncontrollably. The goal here is to help better diagnose those patients with low *PARK2* levels.

This project seeks to determine the role of *PARK2* in the molecular pathogenesis of glioblastoma.

Scientists hypothesize that *PARK2* loss in glioma results in genomic instability. Because it has been observed that low PARK2 mRNA levels correlate with poorer prognosis, the gene has clinical relevance.

This study further examines the relationship between inactivation of the *PARK2* gene and overall survival, tumor grade, and tumor aggressiveness in lower grade gliomas and glioblastomas. These findings may have relevance for using *PARK2* as a biomarker in the clinic. For example, PARK2 mRNA levels could be measured in biopsies and *PARK2* gene expression potentially could be used as a clinical prognostic biomarker, since patients with low PARK2 mRNA levels have a poorer prognosis.

Jason T. Huse

Title: Characterizing the Pathophysiological Significance of Transcriptional Subclass in WHO Grade II and III Diffuse Astrocytoma

The focus of this project is on a subgroup of patients who have lower-grade astrocytomas. Astrocytomas are the most common type of glioma. They develop from star-shaped glial cells known as astrocytes, which are part of the supportive tissue in the brain. Our goal is to be able to better identify and treat patients with this subtype by studying astrocytomas in greater detail and increasing the effectiveness with which we characterize them.

This study has identified clinically distinct subgroups of lower-grade astrocytomas using molecular profiles. Using a stratification system, eventually we will be able to better identify additional important molecular alterations that affect specific patient subgroups and more effectively assign individual patients to appropriate therapies. We have already begun to develop clinical diagnostics based on findings of this study.

Through this work, we have taken an important first step toward more effectively characterizing the molecular landscape underlying lower-grade astrocytomas, and we have set the stage for more-detailed analysis of specific subtypes of astrocytoma, particularly with respect to evolving treatment strategies.

Moritz F. Kircher

Title: A Novel Brain Tumor Imaging Approach Using Surface-Enhanced Raman Spectroscopy

The goal of our project is to improve survival in brain tumor patients by using a nanoparticle brain tumor imaging approach that enables more-accurate tumor removal. Nanoparticles are extremely small particles that can be used to carry antibodies, drugs, imaging agents, and other substances to certain parts of the

body and can also be used to detect, diagnose, and treat cancer.

This project, a preclinical study in mouse models of glioma, seeks to validate a dual-modality MRI-Raman nanoparticle concept to improve the delineation of brain tumors both pre- and intraoperatively. Given that the nanoparticles in our study are based on inert gold and silica materials, and several other nanoparticles composed of gold and/or silica have already entered clinical trials, we expect that this study will be able to complete a data package for an investigational new drug application within the next three years. Hand-held Raman scanners that could be used in the operating room are already commercially available.

This nanoparticle brain tumor imaging approach has the potential to allow for more-accurate intraoperative brain tumor resection, enabling much more accurate image guidance than is currently feasible using intraoperative MRI. Because more-complete resection of brain tumors is a good predictor of outcome, we expect that this approach will improve survival in patients with brain tumors.

Barbara Oldrini

Title: Dissecting the Mechanism of EGFR Signal Termination by the PTEN Tumor Suppressor

The focus of this project is to improve EGFR therapy by examining *EGFR* mutations that make glioblastoma multiforme (GBM) patients resistant to certain treatments. EGFR stands for epidermal growth factor receptor, which is a protein found on the surface of some cells that causes cells to divide. The EGFR protein is typically found at abnormally high levels on the surface of cancer cells, causing cells to divide at an excessive rate.

One focus of our project is to improve EGFR kinase inhibitor therapies by targeting a second vulnerability in the EGFR life cycle (for example, EGFR protein levels). *EGFR* mutations and loss of another gene called *PTEN* are associated with resistance to EGFR kinase inhibitor therapy in GBM patients.

Using a global mass spectrometry approach, our study has characterized the effects of PTEN on EGFR signaling complex, identified a member of the RanGTPase family, and characterized its effect on the EGFR protein. These findings may provide a novel angle to target EGFR in GBM through the regulation of the Ran pathway.