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Understanding the Function of the Tyrosine Phosphatase PTPRD, a Frequently Inactivated and Mutated Tumor Suppressor in Glioblastoma

Our research project focused on understanding the function of a widely inactivated tumor suppressor gene in gliomas called PTPRD. A significant part of our work entailed determining the prognostic value of PTPRD inactivation in determining prognosis of patients with gliomas. We determined that patients with grade II and III gliomas who have PTPRD inactivation have a much higher risk of recurrence and death. Therefore, these patients likely require more aggressive therapies. Our data indicates that PTPRD holds promise as a biomarker for aggressive glioma tumors.

A second aim of our research was to investigate the efficacy of targeting the PTPRD/STAT3 axis. Previously, we had determined that PTPRD inactivation results in overactivity of the well known STAT3 oncoprotein. During the course of this funding period, we found that glioma cells that have PTPRD inactivation (and hence STAT3 overactivation) are very sensitive to inhibitors of the STAT3 signaling pathway. This work indicates that the STAT3 pathway is a new target for tumors that have inactive PTPRD. These results may lay the foundation for a new target in gliomas.

Our results may provide a novel biomarker for predicting which patients require more aggressive therapies (PTPRD loss). Furthermore, our work may help elucidate a new target (STAT3 pathway) to help improve the outcomes of patients with malignant glioma.

Jason Huse

Title: Biomarker Development for the Molecular Subclassification of Malignant Glioma

Molecularly subclassifying tumors is essential to the effective implementation of targeted therapeutics and personalized medicine. This research project was focused on developing biomarkers for clinically relevant molecular stratification of malignant gliomas. We hope to apply the systems we have developed to routine patient workup at this institution. In this way, the assignment of patients to appropriate clinical trials will be facilitated.

Andrew B. Lassman

Title: Pulsatile Kinase Inhibitor Therapy for Malignant Glioma: Proof of Concept Clinical Trial

We are addressing whether EGFR kinase inhibitor response in patients with recurrent malignant gliomas is improved using a novel clinical trial design. The project differs from previous EGFR kinase inhibitor trials in this disease by administering the EGFR tyrosine kinase inhibitor erlotinib on an intermittent (pulsatile) “high dose” schedule. This is because we and others are investigating the emerging concept that transient potent kinase inhibition can be sufficient to commit cancer cells irreversibly to cell death. Pulsatile dosing of kinase inhibitors has not been explored previously in gliomas in a clinical trial. In addition, we will restrict enrollment to patients with tumors harboring oncogenic EGFR mutations that are erlotinib sensitive. Therefore, this trial has the potential to change the current paradigm of drug development for malignant glioma. Following input, review, and approval by all collaborating departments, the protocol has been resubmitted to the IRB for final approval and we anticipate it will open to accrual in the next month.

Our trial is unique in its approach to treatment with targeted therapies. If the outcome is positive, this approach could change the current paradigm for clinical trial design and drug development for brain tumors.

Tatsuya Ozawa

Title: The Discovery of the Genetic Events Cooperating with NF1 Inactivation in Gliomagenesis

Mouse models based on the genetic alterations identified in human gliomas are valuable tools for understanding brain tumor biology and exploring novel therapeutic targets and drugs. Given that neurofibromatosis type 1 (NF1) mutation/loss was recently found to be common in sporadic human GBMs, I have established a novel Nf1 loss-mediated glioma mouse model with the RCAS/tv-a system in this proposal. My goal is to identify a molecular mechanism of glioma formation mediated by loss of NF1 using various approaches in this mouse model. This approach will hopefully lead us to explore potential novel drugable targets for brain tumors, specifically those with Nf1 mutation. My project is directly targeted for clinical application, so if a promising drug target is found, it may be translatable to clinical care.

My mouse model differs from previously established-Nf1 mouse models as this model utilizes the RCAS/tv-a system, which allows us to easily examine the functionality between a gene of interest and glioma formation. As such, this model is important for furthering our understanding for the underlying molecular biology behind gliomas, which will be beneficial for glioma patients.

Teodoro Pulvirenti

Title: Wnt Signaling in Gliomas and the Control of Stem-Like Glioma Cell Fate

This project demonstrated that a block of canonical Wnt signaling blocks glioma cell proliferation but is not sufficient to induce differentiation, showing a new important role for the non-canonical Wnt pathway. We found that the knockdown of two major components of non-canonical Wnt signaling, Wnt5a and the tyrosine kinase receptor Ror2, blocks the proliferation of human glioma cells.

Considering that Wnt blockers are small molecules available on the market, it would be ideal to start an animal experiment to see the efficacy and toxicity of these drugs in glioma mouse models. If any Wnt blocker has an effect on mice, the next step could be a clinical trial.

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