A Proposal

to

The Gray Matter Foundation

for Support of Brain Cancer Research

at Dana-Farber Cancer Institute

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Introduction: Neuro-Oncology in the Era of Personalized Medicine

Over the course of the last decade, major scientific breakthroughs have redefined the way that we think about the causes, diagnosis, and treatment of cancer. Dana-Farber – because of its unique 50-50 balance of research and clinical care – is in the optimal position to make groundbreaking discoveries in the lab and translate them to the bedside, where patients desperately need them. For instance, recent Biological discoveries have taught us that cancer is not one disease, but a complex set of diseases, each unique in its genetic and molecular character. Thus, to successfully treat and eradicate cancer, medicine must be tailored to each subtype, a concept that is often referred to as personalized medicine. At the most basic level, personalized medicine means that treatment is based on defining which genetic mutations are important in promoting tumor growth, and selecting or developing a drug – or combination of drugs – to counteract that growth. This specific, targeted strategy is a sea change from a "one size fits all" approach to treatment, and Dana-Farber is a leader in this new arena as a result of its investment in key areas, including genomics, proteomics, chemical biology, imaging and computational biology.

While there are a few spectacular successes to date, cancer medicine is only at the beginning of this era. Patrick Wen, MD, director of the Center for Neuro-Oncology at Dana-Farber Cancer Institute, and David Reardon, MD, the Center's new clinical director, are committed to leading neuro-oncology research and care in this new and exciting direction, with the hope and promise of finding *the right drug, for the right patient, at the right time*. This year, significant progress has been made to identify new drug-susceptible targets in tumors, and today, 35 neuro-oncology clinical trials are open to patients at Dana-Farber.

Characterizing Cancer Genomes

In an effort to identify additional genes that drive cancer and new potential therapeutic targets, Principal Investigator Rameen Beroukhim, MD, PhD, and his colleagues have characterized the genomes of more than 3,100 cancer specimens across more than two dozen cancer types – representing the largest data set to date on somatic copy-number variation across specimens of human cancers.

To expand this research and with support from the Gray Matters Foundation support, we have been conducting a screen of several hundred compounds against several dozen glioblastomas cultured *in vitro* as neurosphere cell line models. We are using this screen to identify compounds which prevent growth of subsets of these glioblastoma cell lines. We also have comprehensive genomic information about these cell lines, enabling us to determine whether response to drugs is associated with specific genomic profiles such as the presence of specific mutations or expression of certain genes.

These genomic profiles represent averages over the millions of individual glioblastoma cells in each test. However, variations within these cell populations can be important determinants of drug response. Indeed, glioblastomas are known to exhibit high levels of intratumoral

heterogeneity. Some of this heterogeneity represents a diversity of mutations acquired during tumor evolution. Additional heterogeneity results from differentiation of cancer stem cells to more specialized cells, leading to separate populations of cancer cells within the tumor that can exhibit different growth and drug sensitivity characteristics. These differentiation states can often be indicated by the presence or absence of stem cell markers on the surface of the cells.

We propose to characterize the heterogeneity of the neurosphere models undergoing drug screening. We will evaluate stem cell surface markers including CD133, CD44, and CD15, and intracellular markers previously reported in neural stem cells including Sox2, Nestin and Olig2. We will determine whether the differentiation state of these cells is associated with response to any of the several hundred compounds we are testing. We will also test specific compounds such as histone deacetylatase inhibitors to determine their effect on the distribution of subpopulations for each cell line, and whether the changes these induce confer sensitivity to other compounds.

With a gift of $70,000, these studies will determine if heterogeneity in differentiation states within glioblastoma models determines the response to a large number of compounds, and whether these differentiation states can be effectively modulated to enhance drug sensitivity.

Thank you

The exciting initiatives that continue to develop in the Center for Neuro-Oncology perfectly reflect Dana-Farber's mission to provide excellent care for patients today, and research the most effective treatments for tomorrow. This balance results in extraordinary collaboration between investigators and caregivers so that more patients can overcome brain tumors and lead healthier lives. The exciting work of Dr. Rameen Beroukhim could not continue without the support of critical philanthropic dollars, particularly in such difficult economic times. Your continued generosity would allow us to accelerate the pace of discovery and the translation of these novel scientific techniques into personalized, effective treatments for our patients, establishing new standards of care. On behalf of the staff and patients of the Center for Neuro-Oncology, and all of those served by Dana-Farber Cancer Institute, we thank you for your consideration.